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Doctoral thesis

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Virkning av norsk farmasøytisk anbud på utgifter og forskrivningsrater for dyre legemidler og begrensningene i ulike remisjonsdefinisjoner ved revmatoid artritt

BAKGRUNN OG FORMÅL

Biologiske og målrettede syntetiske sykdomsmodifiserende antirevmatiske legemidler (b/tsDMARDer) er svært effektive i behandling av revmatoid artritt (RA), men denne behandlingen er forbundet med høye medikamentkostnader. I Norge har man som kostnadsreduserende strategi innført et nasjonalt anbudssystem for disse dyre medikamentene. Denne avhandlingen undersøker endringer i gjennomsnittspris og bruk av de enkelte legemidlene som tas i bruk i behandling av RA i Norge i 10 års perioden 2010 til 2019 under påvirkning av et nasjonalt anbudssystem. Innenfor rammen av denne avhandlingen, beskrives kostnader til de finansielle ressursene som brukes på anskaffelse av b/tsDMARDs, og det legges ingen vekt på de tilknyttede utgiftene, f.eks. lagring, transport, og administrering av disse medikamentene.

I behandlingen av RA pasienter med antinflammatoriske sykdomsmodifiserende legemidler, inkludert b/tsDMARDer, er målet at pasientene skal oppnå stabil remisjon eller lav sykdomsaktivitet. Flere operasjonelle instrumenter og definisjoner for remisjon og lav sykdomsaktivitet er utviklet til bruk i forskning og klinisk oppfølging av RA pasienter. Disse instrumentene er satt sammen av enkeltelementer i form av algoritmer som reflekterer sykdomsaktivitet og består oftest av objektive målinger som laboratorieverdier og klinisk undersøkelse utført av lege, samt pasientens egen opplevelse av sykdomsaktivitet. Denne avhandlingen undersøker hvordan de forskjellige instrumentene analyserer frem andelen av RA pasienter som er i remisjon, og da spesielt hvordan pasientens egen opplevelse av sykdomsaktivitet påvirker denne andelen.

METODE

RA pasientene ble fulgt opp ved ordinære poliklinikker ved ti norske sentre. Data om demografi, sykdomsutfall og behandling ble innsamlet hvert år fra hvert senter. Brukere av b/tsDMARDene ble delt inn i kategoriene naive brukere (de med ny registrering av b/tsDMARD uten tidligere b/tsDMARD bruk), ikke-naive (de med ny registrering av b/tsDMARD men med tidligere b/tsDMARD bruk), og nåværende brukere (de med registrert bruk av b/tsDMARD). Andelen RA pasienter (den relative mengden registreringer av en type b/tsDMARD i forhold til den totale mengden registreringer av alle b/tsDMARD) som bruker de 13 b/tsDMARDer (med undergrupper av subkutane vs. intravenøse, og biotilsvarende vs. ikke-biotilsvarende) ble grundig vurdert og sammenlignet med anbudsrangeringene fra hvert år. Den totale og gjennomsnittlige årlige kostnaden for behandling av RA pasienter med b/tsDMARDer ble beregnet for hele medikamentgruppen og for medikamentundergrupper.

For undersøkelse av hvor mange pasienter som var i remisjon ved bruk av de forskjellige instrumentene, ble det brukt data fra en revmatologisk sykehuspoliklinikk i Norge. Variablene fra disse metodene ble analysert ved bruk av lineær og logistisk regresjon. Alle studiene var tverrsnittstudier.

RESULTATER

Den totale b/tsDMARD behandlingsandelen varierte mellom 40% i 2010 til 45% i 2019. Den gjennomsnittlige årlige kostnaden per b/tsDMARD per naive RA bruker sank fra 13.0 tusen euro i 2010 til 3.2 tusen euro i 2019, som tilsvarer en kostnadsreduksjon på 75%. Den estimerte kostnadsreduksjonen var 64% for ikke-naive brukere og 47% for nåværende brukere. Alle kostnadsreduksjoner var enda større når det ble tatt hensyn til variasjon i norsk valuta. Det anbudsvinnende b/tsDMARDet var enten det høyeste eller nest høyeste i volum i ni av ti år for naive b/tsDMARD brukere, syv av ti år for ikke-naive brukere og to av ti år for nåværende brukere. Det anbudsvinnende legemidlet var et intravenøst legemiddel i åtte av ti år, men gjennomsnittlig volum av intravenøse b/tsDMARDer for de forskjellige brukergruppene var rundt 50% eller lavere. Det anbudsvinnende legemiddelet var et biotilsvarende medikament i fem av seks farmasøytiske anbud. I løpet av årene med biotilsvarende legemidler, utgjorde de biotilsvarende i gjennomsnitt omtrent 40% av det totale b/tsDMARD andelen for naive brukere, omtrent 40% for ikke-naive brukere, og rundt 20% av de nåværende brukerne. I denne perioden med reduserte medikamentkostnader ble det ikke observert forverring av sykdomsaktivitet, pasientrapporterte utfall eller arbeidsevne. Det var en forskjell på omtrent 40% i remisjonsrate (altså andelen av analyserte RA pasienter som oppnår remisjon) mellom den strengeste remisjonsvurderingsmetoden, også kjent som Boolean remisjon, og Boolean remisjonen uten pasientenes subjektive vurdering (uten pasientens globale evaluering (PGA)) da de samme 502 RA pasientene fra et enkelt senter i 2019 ble evaluert. Blant disse pasientene oppnådde mindre enn 30% Boolean remisjon når PGA sin grenseverdi var ≤10 på en skala fra 0-100, mens 75% oppnådde Boolean remisjon når PGA ble utelatt i algoritmen. Metoder for måling av sykdomsaktivitet som inkorporerte PGA likeverdig med de andre variablene i algoritmen hadde lavere remisjonsrater og var mer assosiert med andre pasientrapporterte utfall (f.eks. smerte) enn de som ikke inkluderte PGA eller inkluderte med redusert innvirkning i algoritmen. Uavhengig av målemetode var smerte (standardisert koeffisient $\beta = 0.7$, $p < 0.001$) sterkest assosiert med PGA.

KONKLUSJON

Med et nasjonalt farmasøytisk anbudssystem i Norge ble det i perioden 2010 til 2019 observert store endringer i medikamentkostnader for b/tsDMARDer. For betaleren falt den gjennomsnittlige årlige kostnaden per b/tsDMARD per pasient betraktelig og da spesielt for pasienter som startet b/tsDMARD for første gang. For leverandøren så hadde de farmasøytiske selskapene som leverte det billigste legemidlet hvert år også det høyeste eller nest høyeste andel blant nye b/tsDMARD utskrivelser. Denne

avhandlingen viser også at oppnåelse av remisjon påvirkes i stor grad av hvilke instrumenter som brukes for å definere remisjon. Pasientens subjektive helhetsvurdering av sykdomsaktivitet som er sterkt assosiert med smerte og som ikke skiller mellom inflammatorisk og ikke-inflammatorisk smerte har stor påvirkning på om remisjon oppnås eller ikke ved enkelte instrumenter. Dette er viktig å ta hensyn til når man starter pasienter på b/tsDMARDer for å unngå å gi legemidlene for ikke-inflammatoriske årsaker. Denne avhandlingen setter spørsmål ved bruk av metoder for måling av sykdomsaktivitet som kan påvirkes av pasientens egen vurdering av sykdomsaktivitet i behandling med b/tsDMARDer.

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LIST OF PAPERS

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Brkic A, Diamantopoulos AP, Haavardsholm EA, Fevang BTS, Brekke LK, Loli L, Zettel C, Rødevand E, Bakland G., Mielnik P, Haugeberg G. **Exploring drug cost and disease outcome in rheumatoid arthritis patients treated with biologic and targeted synthetic DMARDs in Norway in 2010–2019 – a country with a national tender system for prescription of costly drugs.** BMC Health Serv Res. 2022;22(1):48

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Brkic A, Diamantopoulos AP, Hoff M, Haavardsholm EA, Fevang BTS, Brekke LK, Loli L, Zettel C, Bakland G., Mielnik P, Haugeberg G. **Exploring the impact of the national tender system on the use of costly drugs treating rheumatoid arthritis patients in ten rheumatology centers in Norway (2010-2019).** BMC Health Serv Res. 2023;23(1):968.

PAPER III

Brkic A, Łosińska K, Pripp AH, Korkosz M, Haugeberg G. **Remission or Not Remission, That'' the Question: Shedding Light on Remission and the Impact of Objective and Subjective Measures Reflecting Disease Activity in Rheumatoid Arthritis.** Rheumatology and therapy vol. 9,6 (2022): 1531-1547

ABBREVIATION

ACR	American college of rheumatology
ANOVA	One-way analysis of variance
BioRheuma project	Biologic treatment of patients suffering from inflammatory rheumatic disorders in Norway project
b/tsDMARD	Biologic and targeted synthetic disease-modifying antirheumatic drug
CDAI	Clinical disease activity index
CDAS	Composite disease activity score
CRP	C-reactive peptide
csDMARD	Conventional synthetic disease-modifying antirheumatic drug
DALY	Disability-adjusted life year
DAS28	Disease activity score 28-joint count
DMARD	Disease-modifying antirheumatic drug
ESR	Erythrocyte sedimentation rate
EU	European Union
EUR	Euro
EULAR	European alliance of associations for rheumatology
GTI	GoTreatIt Rheuma
HIC	High-income country
IGA	Investigator global assessment
iv	Intravenous
LMIC	Low- and middle-income country
NHPT	Norwegian hospital procurement trust
NOK	Norwegian kroner
NorArthritis	Norwegian arthritis registry
PGA	Patient global assessment
po	Per oral
PPP	Pharmacy purchase price
PROM	Patient-reported outcome measures
QALY	Quality-adjusted life-years
RA	Rheumatoid arthritis
REC	Regional ethical committee
sc	Subcutaneous
SDAI	Simple disease activity index
SDG	Sustainable development goal
SJC28	Swollen 28-joint count
SPSS	Statistical program for social sciences
T2T	Treat-to-target
TJC28	Tender 28-joint count
TNFi	Tumor necrosis factor inhibitor
TRS	Tender ranking score
tsDMARD	Target synthetic disease-modifying antirheumatic drug
VAS	Visual analog scale
UN	United Nations
WHO	World Health Organization

SUMMARY

BACKGROUND AND OBJECTIVES

Biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) are highly effective in treating rheumatoid arthritis (RA) but come with a high cost. Within the scope of this thesis, cost refers to the financial resources for the procurement of b/tsDMARDs, and no attention is placed on the associated expenses, e.g., storage, transportation, and administration of these drugs. A recommended cost-reducing strategy for these drugs is pharmaceutical tendering, which has been implemented in Norway for over a decade. Under the influence of a national tender system, this thesis explores the cost and proportion (i.e., the relative amount of given b/tsDMARD registrations compared to the total b/tsDMARDs registrations) of 13 different b/tsDMARDs used in treating RA from 2010 to 2019 in Norway.

The goal of all anti-inflammatory drugs, including b/tsDMARDs, is to treat RA patients into stable remission or low disease activity. Many remission-assessing methods are available and recommended, albeit few are comparable. Therefore, this thesis also evaluates the different remission-assessing methods in-depth and questions the elements causing the discrepancy.

METHODS

The RA patients were monitored at ordinary outpatient clinics across ten Norwegian centers. Data concerning demographics, disease outcomes, and the prescribed treatment were collected from each center for each year. The b/tsDMARD users were subdivided into the categories: naïve users (those registered to receive a new b/tsDMARD without prior b/tsDMARD), non-naïve (those registered to receive a new b/tsDMARD with prior b/tsDMARD but are given a different b/tsDMARD), and current users (those registered on a b/tsDMARD). The proportion of 13 b/tsDMARD (with subgroups of subcutaneous vs. intravenous and biosimilars vs. non-biosimilars) was thoroughly assessed and compared with the tender rankings from each year. The total and average cost (using confidential tender offers) of b/tsDMARDs was calculated and subdivided according to the b/tsDMARD RA user groups.

Complete data from a single center were used to calculate remission rates (i.e., the number of RA patients achieving remission divided by the total number of assessed RA patients) using different remission-assessing methods between 2015 and 2019. The variables from these methods were analyzed using linear and logistic regression. All studies were cross-sectional studies.

RESULTS

The overall b/tsDMARD treatment proportion ranged between 40% in 2010 to 45% in 2019. The average annual cost per b/tsDMARD per naïve RA user decreased from 13.0 thousand euros in 2010 to 3.2 thousand euros in 2019, which resulted in a 75% cost reduction. Non-naïve users had an estimated

cost reduction of 64%, while current users had an estimated cost reduction of 47%. All cost reductions were even more prominent when variation in Norwegian currency was accounted for.

The tender-winning b/tsDMARD was either the highest or second-highest in usage in nine out of ten years for b/tsDMARD naïve users, seven out of ten years for non-naïve users, and twice out of ten years for current users. The tender-winning drug was intravenous in eight out of ten years, but the average proportion of intravenous b/tsDMARDs for the different user groups was approximately 50% or lower. The tender-winning drug was a biosimilar in five out of six pharmaceutical tenders. On average, during the years with biosimilars, the biosimilars accounted for roughly 40%, 40%, and 20% of the total b/tsDMARD proportion for naïve, non-naïve, and current users, respectively.

There was an approximate 40% difference in remission rate between the most stringent remission-assessing method (i.e., Boolean remission) and the Boolean remission without patients' subjective evaluation (i.e., without the variable patient global assessment (PGA)) when the same 502 RA patients from a single center in 2019 were evaluated. Among these patients, less than 30% achieved ≤10 PGA (0-100), while over 75% achieved the other stringent requirements of Boolean remission. Disease activity measuring methods incorporating PGA equally as the other variables in the algorithm had lower remission rates and were more associated with other patient-reported outcomes (e.g., pain) than those that did not include PGA or included it but with reduced impact in the algorithm. Regardless of the measurement method, pain (standardized coefficient $\beta = 0.7$, $p < 0.001$) was most strongly associated with PGA.

CONCLUSION

During the national pharmaceutical tendering in Norway in the period from 2010 to 2019, changes were observed. For the payer, the average annual cost per b/tsDMARD per patient decreased considerably and was most pronounced for patients starting naïve on b/tsDMARD. For the supplier, the pharmaceutical companies that provided the most inexpensive drug each year also had the highest or second-highest proportion among new b/tsDMARD prescriptions. Simultaneously, no findings of worsened disease activity, patient-reported outcome measures, or work capability were observed.

With the saved expenditure (i.e., the total cost spent on acquiring b/tsDMARDs over a given time) and increasing b/tsDMARD treatment proportion, this thesis recommends being vigilant when starting patients on new b/tsDMARDs to avoid administering the medications for noninflammatory causes. As such, the thesis advises against using disease activity measuring methods that can interfere with that judgment. This thesis shows that the instruments used to determine remission substantially influence attaining remission. The patient's overall assessment of disease activity, which is strongly associated with pain and does not distinguish between inflammatory and noninflammatory pain, has a considerable impact on whether remission is achieved with certain instruments. This is important to consider when starting patients on b/tsDMARDs to prevent administering the medications

for noninflammatory reasons. In that perspective, when treating patients with b/tsDMARDs, this thesis calls into question the use of methods for measuring disease activity that is heavily impacted by the patient's own evaluation of their disease activity.

1. BACKGROUND

1.1 THE GLOBAL PERSPECTIVE

1.1.1 A Decade of Action

In 2016, the United Nations (UN) formally announced the 17 Sustainable Development Goals (SDGs) and envisioned them being achieved within 2030 [1]. With less than ten years remaining to achieve the set goals, a *Decade of Action* initiative was announced to encourage further SDG engagement [2]. The World Health Organization (WHO) responded to the Decade to Action call with a list of the 13 most urgent global health challenges (Table 1) [3]. Although these healthcare challenges are considered interlinked, the presented thesis will primarily focus on *expanding access to medicine*.

Table 1: World Health Organization's list of the 13 most urgent health challenges for 2020-2030 [3]

1.	Elevating health in the climate debate
2.	Delivering health in conflict and crisis
3.	Making health care fairer
4.	*Expanding access to medicines* [A]
5.	Stopping infectious diseases
6.	Preparing for epidemics
7.	Protecting people from dangerous products
8.	Investing in the people who defend our health
9.	Keeping adolescents safe
10.	Earning public trust
11.	Harnessing new technologies
12.	Protecting the medicines that protect us
13.	Keeping health care clean

Note: [A] = The primary challenge of this thesis.

1.1.2 Expanding Access to Medicine

While millions of lives have been saved over the last two decades because of the increased access to pharmaceuticals, one-third of the world's population still lacks access to essential medications or other necessary health products (e.g., vaccines and health equipment) [3, 4]. Despite the armamentarium of known and novel drugs for debilitating and life-threatening diseases, many countries continue to struggle with the safety, availability, and affordability of medications — especially the low- and middle-income countries (LMICs) [4-6]. Access to medications and, subsequently, patients' health highly depends on the cost-effectiveness of pharmaceutical procurement policies [4]. In this thesis, cost refers to the financial resources for procuring b/tsDMARDs without considering the associated expenses (e.g., storage, transportation, and administration of these drugs), whereas expenditure is considered as the cumulative cost spent on acquiring b/tsDMARDs over a given period. Cost-effectiveness in this regard is determined by whether the expenditure outweighs the health benefit.

One argument for the steep cost of pharmaceuticals, hence their restricted access, is related to the countries' suboptimal procurement policies [4]. This is particularly observed in the LMICs, where they have to pay a higher cost for many of their essential medications compared to high-income countries (HICs) [4]. A such economic discrepancy of medications is often governed by the minimal or

absent pharmaceutical competition (often in the forms of pharmaceutical monopolies) seen in many LMICs [4].

To improve the cost-effectiveness of pharmaceutical procurements, the WHO advises countries to develop and implement national policies for obtaining medications that are (1) reliable and continuously accessible at healthcare facilities, (2) adequately prescribed and administrated, (3) affordable, (4) possible to be paid from the patient's out-of-pocket salary, and (5) safeguarded in case of catastrophic expenditure [7]. Promoting cost-effective approaches for monitoring, evaluating, and regulating the pricing of medications is, therefore, fundamental for efficient pharmaceutical acquisition [8]. In this regard, the WHO has suggested implementing competitive strategies in the form of pharmaceutical tendering to improve affordability and maintain financial sustainability [9]. The European Commission has similarly advised to implement pharmaceutical tendering across the European Union (EU) countries [5]. For over a decade, Norway has utilized a national pharmaceutical tendering to procure costly and potent medications. This thesis will analyze and report on the expenditure and usage of costly medication (exemplified in rheumatoid arthritis (RA)) under the influence of a Norwegian pharmaceutical tender system in the period between 2010 and 2019.

1.1.3 Rational Use of Pharmaceuticals

Even with an efficiently implemented pharmaceutical tender system, which promotes decreased cost of the obtained medications, the lack of *rational use* of drugs is still considered a serious problem in numerous countries [10]. The WHO (1985) described rational pharmaceutical use as patients who "receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community" [11]. Rational pharmaceutical use can also be expressed as the *five rights,* as illustrated in Figure 1 [12].

Figure 1: The Five Rights of rational pharmaceutical use [12]

Over 50% of all pharmaceuticals are purchased, prescribed, or administrated inappropriately (i.e., irrationally) [10]. The irrational use of medications may result in overuse, underuse, or misuse, contributing to the increased waste of limited and costly medications [10]. To improve the rational use of pharmaceuticals, the WHO has suggested 12 crucial interventions (Table 2) [10].

Table 2: Twelve interventions to promote better rational use of pharmaceuticals according to the World Health Organization [10]

1.	Establishment of a multidisciplinary national body to coordinate policies on medicine use
2.	*Use of clinical guidelines* [A]
3.	Development and use of national essential medicines list
4.	Establishment of drug and therapeutics committees in districts and hospitals
5.	Inclusion of problem-based pharmacotherapy training in undergraduate curricula
6.	Continuing in-service medical education as a licensure requirement
7.	Supervision, audit, and feedback
8.	Use of independent information on medicines
9.	Public education about medicines
10.	Avoidance of perverse financial incentives
11.	Use of appropriate and enforced regulation
12.	Sufficient government expenditure to ensure the availability of medicines and staff
13.	Establishment of a multidisciplinary national body to coordinate policies on medicine use

Note: [A] = The primary focus of this thesis.

The Norwegian Health Authority has, to their best effort, incorporated many of these interventions when regulating and advocating the procurement and prescription of pharmaceuticals (e.g., via a national pharmaceutical tender system for costly drugs). This thesis questions and seeks to investigate the *use of clinical guidelines* as an intervention to promote better rational pharmaceutical usage. To clarify, the thesis does not question the implementation of this intervention, since failing to prescribe according to guidelines may lead to irrational use of medication. However, the thesis questions the reliance on clinical guidelines where there is a possibility of misinterpretation, which can become critically erroneous when using costly, complicated-to-acquire, potent medications.

As it is regarded irrational to use antibiotics to treat non-bacterial infections (e.g., viral infections) [13, 14], this thesis elaborates on how treating noninflammatory pain with costly potent anti-inflammatory medications known to cause serious adverse events should also be considered an irrational use of pharmaceuticals. More specifically, this thesis assesses the discrepancy between various disease activity measuring methods recommended by clinical guidelines for evaluating the disease activity progress of RA and how these methods may lead to overestimation or underestimation of disease activity. The outcome of misestimation may dictate how the treatment is provided and can result in dosage change, new prescription, or medication discontinuation of the costly potent anti-inflammatory drugs.

1.2 ACCURACY OF CLINICAL GUIDELINES FOR RHEUMATOID ARTHRITIS

1.2.1 Introduction to Rheumatoid Arthritis

RA is a prominent chronic inflammatory joint disease with a worldwide prevalence of 0.5–1% [15]. In the period between 1990 to 2017, the age-standardized incidence and prevalence rates increased, accounting for approximately 1.2 million RA incident cases and 20 million prevalent cases worldwide [16]. According to Murray and Lopez (1996), the overall disease burden can be measured in *disability-adjusted life years* (DALYs) [17]. DALYs describe the summation of *life-years lost* due to premature mortality and *years lived with a disability* [17, 18]. Data from the Global Burden of Disease Study report roughly 3.4 million DALYs for RA in 2017, which is about 2.5% of all accumulated DALY for musculoskeletal disorders (i.e., osteoarthritis, gout, neck pain, low back pain and other) [16, 19]. RA can lead to joint stiffness and pain, physical disabilities, fatigue, and diminished quality of life [20-22]. Although less frequent, burdens of RA can also manifest in other organs besides joints, e.g., the heart, lungs, kidneys, and skin [23]. The comprehensive amount of RA-related burdens can, in turn, lead to diminished work capacity and increased work disability, resulting in unemployment or early retirement [24, 25].

1.2.2 Assessing Disease Activity and Remission in Rheumatoid Arthritis

When evaluating RA, it is commonly acknowledged that the measurement of RA disease activity cannot be captured with a single variable because of the wide range of RA symptoms, and there is no uncomplicated way of translating applied variables into clinical practice [26, 27]. The selection of today's validated core variables for assessing RA disease activity became agreed upon over time, going back even before the 1990s [26-29]. The applied RA disease activity measuring methods that are frequently used today are built upon these core variables, e.g., disease activity score 28-joint count (DAS28), clinical disease activity index (CDAI), and simple disease activity index (SDAI) [30-37]. However, when these measuring methods were developed, effective treatment options were limited, poor disease outcome was expected, and remission was not considered a realistic or therapeutic goal [30-37].

An additional method to assess only remission in RA was developed about a decade ago. In the proposal's context by Pinals et al. (1989) on using clinically reliable and convenient measures to determine the absence of inflammation (i.e., complete remission) in RA patients, a boolean-based definition was agreed upon by the American (American College of Rheumatology (ACR)) and European (European Alliance of Associations for Rheumatology (EULAR)) conjoint committee in rheumatology (ACR/EULAR committee), naming the method for the ACR/EULAR Boolean remission criteria (simplified to Boolean remission in this thesis) [29, 35].

1.2.3 Discrepancy in the Definition of Remission in Rheumatoid Arthritis

A recent systematic review, Mian et al. (2019) evaluated 20 treatment guidelines for RA between 2000 and 2017, which recommended remission as a treatment target [38]. Despite having different remission cut-offs, calculation methods, variable components, and discordant remission rates, the various treatment guidelines for RA proposed inconsistently which measuring method should be applied [38-41]. Among the 20 RA guidelines supporting attaining remission as a target in RA, 13 advised using DAS28, nine for SDAI, and five for CDAI [38]. Five guidelines recommended using all three methods to evaluate initial remission, while 13 promoted applying all three to guide RA treatment [38]. Besides EULAR and ACR guidelines, four other guidelines promoted Boolean remission as an initial evaluation of remission [38]. The remission rate, in this thesis, is defined as the number of RA patients achieving remission divided by the total number of assessed RA patients.

The variables used in Boolean remission are similar to those included in DAS28, CDAI, and SDAI, which are tender 28-joint count (TJC28), swollen 28-joint count (SJC28), C-reactive peptide (CRP), and patient global assessment (PGA) [35]. The ACR/EULAR committee decided to omit ankles and feet joints from the Boolean remission yet still recommended evaluating these joints, focusing only on the 28-joint count for tender and swollen joints (similarly to DAS28, CDAI, and SDAI) [35]. In case of misclassification due to singular residual RA disease activity from the ankles or feet or other causes, PGA was considered a protective countermeasure [35].

Table 3: Calculation formula for DAS28(4) and DAS28(3)

	Calculation Formula
DAS28(4)-CRP	$0.56\times\sqrt{(TJC28)} + 0.28\times\sqrt{(SJC28)} + 0.36\times\ln(CRP+1) + 0.014\times PGA + 0.96$
DAS28(3)-CRP	$[0.56\times\sqrt{(TJC28)} + 0.28\times\sqrt{(SJC28)} + 0.36\times\ln(CRP+1)] \times 1.10 + 1.15$

Abbreviations: **TJC28** = Tender 28-Joint Count, **SJC28** = Swollen 28-Joint Count, **CRP** = C-Reactive Protein, **ESR** = Erythrocyte Sedimentation Rate, **PGA** = Patient Global Assessment, **IGA** = Investigators Global Assessment, **DAS28** = Disease Activity Score. *Note*: CRP can be replaced with ESR without changing the formula.

Table 4: Variables making up the various disease activity methods and Boolean remission variants

	SJC28	TJC28	CRP	ESR	PGA	IGA	Remission cut-off score
Composite Disease Activity Scores							
DAS28(3)-CRP	⊕	⊕	⊕	⊖	⊖	⊖	<2.6
DAS28(4)-CRP	⊕	⊕	⊕	⊖	⊕	⊖	<2.6
DAS28(3)-ESR	⊕	⊕	⊖	⊕	⊖	⊖	<2.6
DAS28(4)-ESR	⊕	⊕	⊖	⊕	⊕	⊖	<2.6
CDAI	⊕	⊕	⊖	⊖	⊕	⊕	≤2.8
SDAI	⊕	⊕	⊕	⊖	⊕	⊕	≤3.3
Boolean measures of remission							
4-variable remission (Boolean remission)	⊕	⊕	⊕	⊖	⊕	⊖	≤1 (≤10)
3-variable remission	⊕	⊕	⊕	⊖	⊖	⊖	≤1 (≤10)

Abbreviations: **TJC28** = Tender 28-Joint Count, **SJC28** = Swollen 28-Joint Count, **CRP** = C-Reactive Protein, **ESR** = Erythrocyte Sedimentation Rate, **PGA** = Patient Global assessment, **IGA** = Investigators Global Assessment, **DAS28** = Disease Activity Score, **CDAI** = Clinical Disease Activity Index, **SDAI** = Simple Disease Activity Index.

DAS28 is most frequently used with PGA (DAS28(4)), albeit it can also be used without PGA (DAS28(3)) [42]. Regardless of the components applied in DAS28, the cut-off remission score remains the same, albeit with a different algorithm for assessment (Table 3). In contrast, CDAI and SDAI are summation-based calculations. A detailed overview of the used variables in the different disease activity assessment methods and their corresponding cut-off score for remission is provided in Table 4. To attain the Boolean remission status, the RA patient would require a ≤1 score on the TJC28 (0-28), SJC28 (0-28), CRP (mg/dL), and PGA (0–10 visual analog scale (VAS)) [35] (Table 4).

1.2.4 Treating Rheumatoid Arthritis to Remission

Prior to the 1990s, the goal of RA therapy was limited to pain alleviation and swelling reduction using non-steroidal anti-inflammatory drugs (e.g., ibuprofen, paracetamol) and glucocorticoids (e.g., prednisolone) [43]. This type of therapeutic target was often inadequate, and with suboptimal evaluation methods for disease activity and diagnosis, irreversible joint damage and decreased life expectancy were often a consequence [44]. Upon the introduction of the disease-modifying antirheumatic drugs (DMARDs), today called conventional synthetic DMARDs (csDMARD) according to the new nomenclature, the occurrence of irreversible joint damage (i.e., radiographic joint damage) was diminished, and the RA symptoms improved [43]. This positive outcome was further accomplished following the introduction of the biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs), collectively referred to as b/tsDMARDs [34, 43].

In 2010, the EULAR recognized the need for a standardized treatment and follow-up regime for patients living with RA, naming it the treat-to-target (T2T) strategy [45, 46]. The T2T is a systematized patient-physician treatment protocol using clinical-related measures and patient-reported outcome measures (PROMs) to assess the RA patients' disease activity status [45, 46]. Then, and still

today, the therapeutic goal of the T2T strategy is to attain and keep RA patients in remission or low disease activity (if remission is unachievable, e.g., difficult-to-treat RA) with tight disease control and by administrating recommended DMARDs (with or without glucocorticoids) [47]. Despite the unclarity and accuracy in the formulas of the remission-assessing methods, using one method together with the T2T approach and with b/tsDMARDs has proven instrumental in minimizing the RA's repercussions, resulting in improved disease activity, reduced bone and joint destruction, and better patients' self-evaluation [34, 48-55].

1.2.5 The Potential for Irrational Use of Medication when Utilizing Subjective Perception of Disease Activity to Govern Therapy

While the physicians and the scientific community consider complete remission as the absence of measurable inflammation [29], the patients convey a different perspective of what it means to be in remission. From their viewpoint, attaining remission implies lessening RA's burden on their life, "eventually leading to a feeling of normality" [56]. For RA patients, the remission condition is impaired by pain, fatigue, and losing autonomy in the self-management of their own disease [57, 58]. However, normality and autonomy can be complicated to acquire when prolonged disease activity in RA patients results in irreversible joint damage and disabilities [59, 60].

When examining and providing care to the patient, regardless of the healthcare provider and specialty, it is therefore equally crucial to understand the patient's perception of their disease (i.e., their experience of illness) as it is to address the patient's biological disease processes to provide good holistic care [61]. That said, clinicians need to carefully navigate the comorbidities and conditions unrelated to the inflammatory mechanisms of the disease when understanding how to counteract the undesired outcome of inflammation. This matter is no different in rheumatology nor when treating patients with RA.

Health issues with the likelihood of occurring together with RA, e.g., fibromyalgia [35, 62], depression [63], and noninflammatory pain [64], should be addressed by the treating physician or rheumatologist. However, incorporating these health problems into the evaluation of RA-related inflammation can cause a false analysis of the RA patient's disease activity [62, 65]. Treating noninflammatory pain and symptoms of depression with potent anti-inflammatory medication (e.g., b/tsDMARDs) should be deemed worrisome, especially since b/tsDMARDs can often come with a high cost and serious complications [66, 67]. While PGA (i.e., the subjective numerical score on how much the RA disease impacts the patient's overall health) is thought necessary to evaluate the absence of remission [35], integrating this variable in Boolean remission when assessing RA patients who may also have other conditions or comorbidities can instead cause misclassification and, consequently, the possibility of mistreatment. This matter can also be regarded for the other remission-assessing methods that give PGA equal value compared to the other variables in the calculation (i.e., CDAI and SDAI).

DAS28(4) also incorporates PGA but applies an algorithm that decreases the PGA value while increasing the value of the other variables (Table 3).

Considering the WHO's urgency related to the affordability and availability of pharmaceuticals, it stands to reason that when these drugs are eventually prescribed or changed in dosage, they should not be administered or altered because of irrational indications.

1.2.6 Overall Cost of Rheumatoid Arthritis

The repercussions of RA contribute directly and indirectly to the expenditure of illness, which can negatively impact the financial status of patients (and their family members), the healthcare system, and society [24, 25]. When various cost-effective approaches are implemented for RA (and other diseases), their cost-effectiveness is usually measured using the cost per quality-adjusted life-years (QALYs) [68, 69]. The cost per QALY can be an excellent way to illustrate economic effectivity in conjunction with the patient's quality of life, as shown in multiple studies comparing the cost-effectiveness of different treatments for RA [70-73]. However, this thesis will instead primarily focus on reporting on the cost expenditure and usage of treatment for RA during an implemented cost-reducing strategy (i.e., pharmaceutical tendering) and not on comparative cost analysis between different treatments for RA.

1.3 ACHIEVING REMISSION USING COST-EFFECTIVE TREATMENT

1.3.1 Costly Treatment for Rheumatoid Arthritis

A growing number of RA patients are being initiated on new b/tsDMARDs in various countries [67, 74-78] and, as such, require continuous follow-up at outpatient clinics [34, 45, 46]. With effective therapy and tight follow-up control, increasing numbers of patients have attained remission or low disease activity and may no longer require in-hospital treatment [53, 55, 79, 80]. Healthcare expenditures are now reduced by the diminished need for in-hospital treatment of RA, albeit requiring spending more on costly advanced medication via outpatient clinics [24]. Although b/tsDMARDs are now available on the market, their high cost limits their usage, adding to a global disparity in access to treatment [81-83].

1.3.2 Norwegian Pharmaceutical Tendering for Rheumatoid Arthritis

Tendering of pharmaceutical procurements (similar to any other tendering) is a formal and regulated competition among the participating pharmaceutical companies where the regulators aim for the availability and cost reduction of medication, which is thought to benefit the patients and society [84-87]. Since 2007, the Norwegian Hospital Procurement Trust (NHPT) has actively facilitated annual national tendering in Norway [67, 88]. While this thesis addresses the tendering related to b/tsDMARDs for RA, NHPT applies the same principles in other rheumatological diseases and other medical disciplines, such as oncology, gastroenterology, and dermatology.

There are three main criteria in the Norwegian principles for priority-setting in healthcare, (1) the health-benefit criterion that emphasizes on the expected health and quality of life improvements, (2) the resource criterion that underscores the importance of attaining health benefits with few resources, and (3) the severity criterion that focuses on the severity and complexity of conditions [89, 90]. Each of these criteria is applied when a new medication undergoes a comprehensive cost-effectiveness approval assessment before being allowed (or not allowed) into the Norwegian market. During this evaluation process, both the drug's maximum cost and its effectiveness (i.e., its benefits relative to the cost) are established [91]. The maximum cost for the new drug is calculated from the average of the three lowest registered costs among selected European countries (Austria, Belgium, Denmark, Finland, Germany, Ireland, the Netherlands, Sweden, and the United Kingdom) [92]. Once approved, the new drug does not require further cross-evaluation in regard to the three main criteria to partake in the Norwegian pharmaceutical tendering. However, during the annual pharmaceutical tendering, other elements are assessed, including the offered discounts, delivery reliability, clinical safety, and (recently applied) the environmental impact (e.g., carbon footprint) [91, 93].

The NHPT receives confidential offers from competing pharmaceutical companies each year for selected b/tsDMARDs. The offer to the NHPT must be lower than the maximum cost for that given medication [92]. The cost reductions pharmaceutical companies offer on their b/tsDMARD products during tendering take various forms and typically apply to their standard b/tsDMARD packages. Several pharmaceutical companies offered cost reduction in means such as reduced starting dosage or interval-based discounts. If no cost reduction is offered, the b/tsDMARD packages will be sold at maximum cost. In Norway, this cost is known as the *maximum pharmacy purchase price* (PPP), which is the cost without the value-added tax [94]. In this thesis, the cost-reduced amount resulting from pharmaceutical tendering is referred to as *tender PPP*. It is important to note that the negotiation for the discounted cost of a pharmaceutical is also somewhat influenced by other cost-related factors, such as the cost of logistics (e.g., transport and storage of the drug) and the cost of delivery by the Norwegian pharmacies. When the tendering is completed, a cost rank-based report of the recommended b/tsDMARDs based on the best offers is released by the NHPT to selected stakeholders and clinicians [88, 95]. These offers are presented as tender PPP *per patient per year*, albeit the publicly known cost is the maximum PPP *per package*. Following the tendering, the NHPT converts the pharmaceutical company's offered cost reduction on their given b/tsDMARD package (i.e., their tender PPP per package) into *tender PPP per mg* and then to tender PPP per patient per year using a standard dosage (of the given b/tsDMARD) and standard body weight. Although rheumatologists are advised to adhere to the annual rank-based report and prescribe the top-ranked b/tsDMARD (given its clinically appropriate), no law dictates their choice.

The NHPT regulates pharmaceutical tendering under confidentiality, allowing pharmaceutical companies to give high discounts to countries without disclosing the information to other competitors and procuring countries [96]. Disclosure of these confidential tender offers may lead to distrust between

the pharmaceutical companies and the regulating agency, which can further result in unwillingness or delays in the supply of current and novel drugs. However, it can also be argued that this strict confidentiality of tender offers allows various pharmaceutical companies to keep market control by allowing them to sell their pharmaceuticals at high prices in different countries without disclosing the information to other procuring countries [96]. The procuring countries have restricted autonomy in this agreement since they must obtain essential medication for their citizens on the premises established by pharmaceutical companies [97].

National pharmaceutical tender systems worldwide differ significantly due to factors such as the representation of pharmaceutical companies in a country, the variability of pharmaceuticals negotiated annually in a country, the number of years a tender system has been established in a country, and the country's characteristics (e.g., wealth, demographics, and infrastructure). Additionally, each tender system varies depending on its procurement strategy, which ranges from a decentralized approach where the tendering is conducted at individual facilities and institutes (e.g., at the hospitals) to a centralized approach where the tendering is conducted on regional, national, or even international level [98]. While countries (e.g., Cyprus, Estonia, Denmark, Italy, and Norway) with a centralized tender system exhibit similar strategies amongst themselves, there are also distinct differences in their approaches [98]. Norway, having a centralized tender system that aligns most with Denmark's system, has all major pharmaceutical companies partaking in their tendering and is the leading net importer of pharmaceuticals [98, 99].

1.3.3 Biosimilars versus Reference Agents

The emergence of the unique drug group called biosimilars in pharmaceutical tendering has substantially contributed to the decrease in medication costs [100, 101]. Biosimilars are equivalent drugs of their reference agents (bDMARD in RA) and are usually offered for a lower cost when they receive market approval (after the reference agent's patent expiration). Four types of biosimilars were introduced for RA in Norway from 2010 to 2019, infliximab (CT-P13) in 2013, etanercept (SB4) in 2016, and rituximab (GP2013) and several other adalimumab biosimilars in 2019 [67]. Since adalimumab reference outcompeted the adalimumab biosimilars during the pharmaceutical tendering in 2019, only adalimumab reference was recommended that year. From September 2021, there were 80 biosimilars approved for all indications to be used in EU countries [100].

The approval of reference agents and biosimilars follows strict policies to ensure their intrinsic molecular microheterogeneity does not impair quality, safety, or efficacy [102]. The requirements for approving biosimilars mandate the same posology and route of administration (with minor exceptions) as their corresponding reference agents [102]. Also, due to minor variations between biosimilars and reference agents, approval of biosimilar development entails additional pharmacovigilance studies [102]. However, upon approval, since biosimilars exhibit the required similarity with their

corresponding reference agents, biosimilars can utilize reference agents' studies on efficacy and safety to extrapolate one approved therapeutic indication to other indications without further trials [102]. This entire process, before the novel biosimilars can reach the pharmaceutical market, including the reference agents' patent expiration time of market protection, usually takes ten years [102].

Since the development and approval costs for biosimilars are lower than those for reference agents, biosimilars can be sold at a lower cost and subsequently stimulating market competition. In turn, this may reduce the overall cost of all pharmaceuticals, contributing to better affordability, availability, and accessibility to care for all EU countries with an implemented tender system [100, 102, 103]. Positive changes were reported in Norway (NOR-SWITCH study) [104, 105] and Denmark (DANBIO registry) [106, 107] when patients were switched (even non-medically) from reference agents to less expensive biosimilar options.

The implementation of the Norwegian pharmaceutical tender system with the goal to ensure better affordability and availability can therefore be considered in alignment with the UN's Decade of Action initiative as it addresses the WHO's urgent challenge of expanding access to medicine (Table 1).

2. GENERAL AIMS AND SPECIFIC RESEARCH QUESTIONS

The primary aims of this thesis were: 1, to analyze the Norwegian pharmaceutical tender system for costly medications used in the treatment of RA and explore changes in patient disease outcomes during an examined tender period among Norwegian RA patients. 2, to evaluate remission as an outcome when using different remission-assessing methods (i.e., disease activity measuring methods) to define remission in RA.

Specific research questions from Papers I-III

- In Norway, during a 10-year period (2010 to 2019) with a pharmaceutical tender system in effect:
    - What was the change in total and in the average annual cost per b/tsDMARD per current RA patient (**Paper I**)?
    - What was the change in total and the average annual cost per b/tsDMARD per naïve RA patient (without prior b/tsDMARD) (**Paper I**)?
    - What was the change in total and in the average annual cost per b/tsDMARD per non-naïve RA patient (prior b/tsDMARD but starting on a new b/tsDMARD) (**Paper I**)?
    - What was the change in remission rate when using DAS28 in current RA patients treated with b/tsDMARDs (**Paper I**)?
    - What was the change in the PROMs (e.g., PGA, pain, and fatigue) in current RA patients treated with b/tsDMARDs (**Paper I**)?
    - What was the change in work-enabled current RA patients treated with b/tsDMARDs (**Paper I**)?
    - What was the impact of winning the tendering for the naïve b/tsDMARD users, non-naïve users, and current users? (**Paper II**)
    - How was the treatment proportion pattern between subcutaneous and intravenous b/tsDMARDs affected (**Paper II**)?
    - How was the treatment proportion pattern between the biosimilar and non-biosimilar b/tsDMARDs affected (**Paper II**)?
- In Norway, in 2019, from the same RA outpatient clinic cohort (Sørlandet Hospital, Kristiansand):
    - What were the remission rates when using different remission-assessing methods, especially those with PGA (**Paper III**)?
    - What were the associations between RA-related variables with PGA (**Paper III**)?
    - What were the associations of different RA-related variables with remission status acquired from different remission-assessing methods (**Paper III**)?

3. MATERIAL AND METHODS

3.1 ETHICS

The Biologic treatment of patients suffering from inflammatory rheumatic disorders in Norway (BioRheuma) project's approval was obtained from the Regional Committee for Medical Health Research Ethics (REC); 2010/3078 4.2008.2673, the use of biological and disease-modifying drugs (DMARD) in the treatment of rheumatic inflammatory joint diseases in Norway. The description of the BioRheuma project is the following and was approved under these conditions: *This project is primarily a quality-assuring project using pharmaceuticals, especially biological drugs, to treat patients with rheumatic joint diseases in Norway. The research aims to gain an overview of the volume of biological treatment for various rheumatological diagnoses. Furthermore, map the treatment effect, and evaluate drug survival side effects. The data is retrieved through queries at the hospitals' IT record/patient systems. All analyzed data files are anonymized for patient information.*

Henceforth, all studies in this thesis are approved by the REC. The studies in Papers I-III follow the Declaration of Helsinki ethical guidelines for medical research involving human subjects. The REC required no consent from patients, as all data in Papers I-III were anonymized and collected retrospectively as part of routine clinical care. Approval from NHPT was given to evaluate the tender ranking and confidential offers on the premises not to disclose the confidential offers.

3.2 STUDY DESIGN AND STUDY POPULATION

The data for Papers I and II were acquired from the BioRheuma project over a ten-year period (2010 to 2019) with data collection from ten outpatient clinics. Data from the study in Paper III were obtained from the same project, albeit from 2015 to 2019, and only recruited patients from one outpatient clinic. Studies from Papers I-III are all observational retrospective cross-sectional studies.

3.2.1 BioRheuma Project

The BioRheuma project began in 2010 with the goal of making it easier to employ recommended and validated outcome measures to follow patients with inflammatory joint disorders (e.g., RA) as part of routine care at rheumatological outpatient clinics across Norway. The project's clinical objectives were to disclose yearly changes during follow-ups in demographics, disease activity, PROMS, and treatment with csDMARDs and b/tsDMARDs. The software GoTreatIT® Rheuma (GTI) (www.diagraphit.com) facilitated standardized monitoring of a selected minimum collection of variables from the examined RA patients at each participating rheumatology outpatient clinic (BioRheuma center). Rheumatologists at these centers were encouraged, albeit not mandated, to adhere to the standardized patient monitoring protocol, which aimed to collect minimum data on demographics, disease activity, and PROMs (see 3.3.1 – 3.3.3 for further detail).

3.2.2 BioRheuma Center Selection

Initially, this thesis aimed to include data from 13 BioRheuma centers. However, three of these centers (BioRheuma centers in Bodø, Drammen, and Levanger) provided treatment data for four or fewer years out of the ten-year study period, which was deemed insufficient for the data analysis and were consequently excluded from further assessment. The remaining ten BioRheuma centers were included on the premise of providing eight or more years with treatment data out of the ten years. These centers were distributed across Norway, including Bergen, Bærum, Førde, Haugesund, Kristiansand, Lillehammer, Oslo, Skien, Tromsø, and Trondheim. Unless specified otherwise, all RA patients registered in the GTI system from these BioRheuma centers were included in the thesis analysis. In other words, the inclusion criteria of the thesis were all RA patients registered in the GTI system at each included BioRheuma center. While the data from the ten included BioRheuma centers were used for assessment in Papers I and II, only data from Kristiansand was evaluated for Paper III. Following the initial inclusion in each study in Papers I-III, a selected number of patients were excluded for various reasons specified in each paper. Figure 2 shows a geographical overview of the ten included BioRheuma centers, while Figure 3 presents the specifics regarding the inclusion and exclusion of the BioRheuma centers and which years are missing among the included centers (equivalent of Figure 1 in Paper II).

It is important to point out that while all RA patients at each participating center were included, not all rheumatology outpatient clinics in Norway were designated as BioRheuma centers during the ten-year study period. Furthermore, the presence of a GTI system at a center did not necessarily imply complete coverage of that center's service area (5.1.5 Representativeness).

Figure 2: Overview of BioRheuma centers included in the papers (2010-2019)

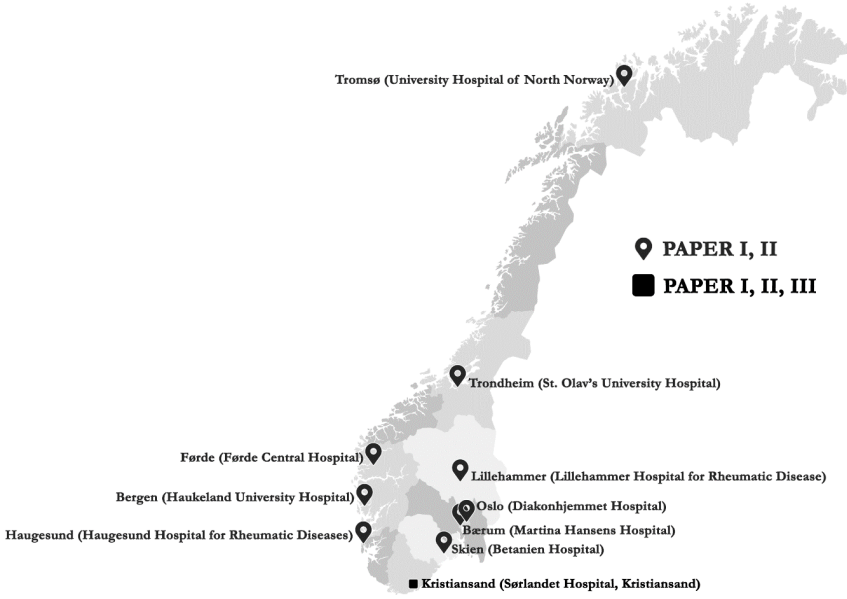
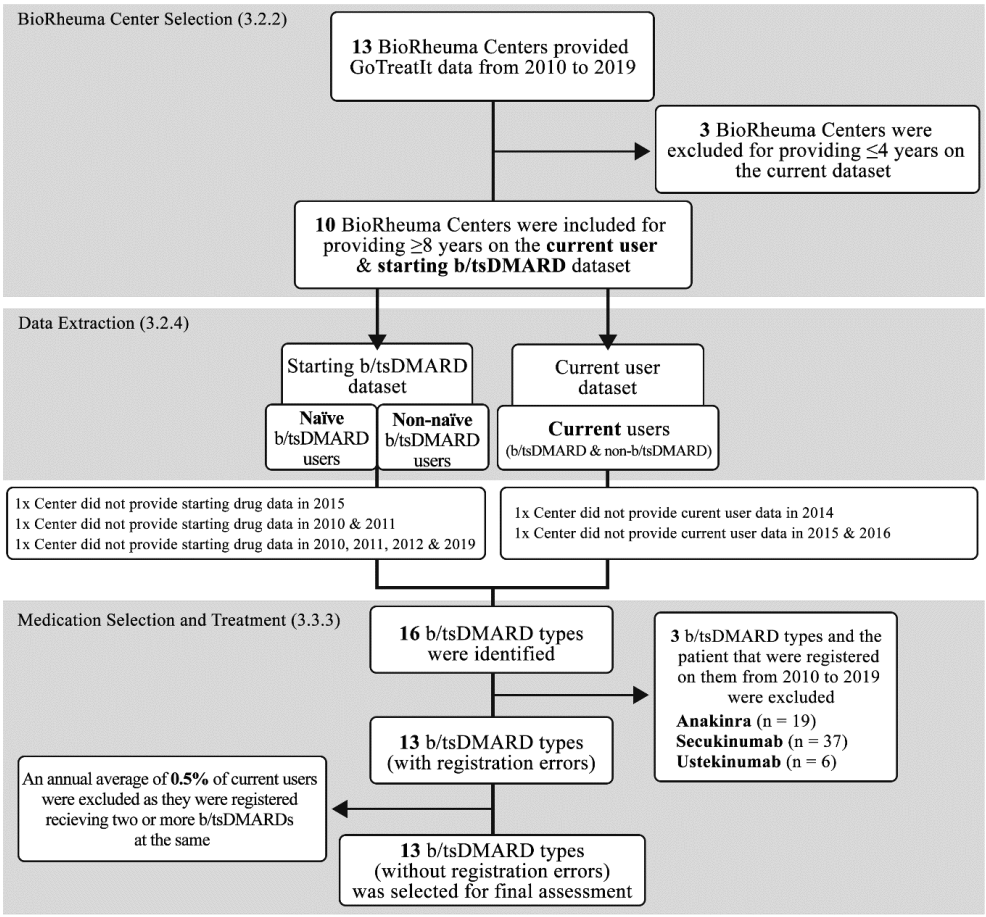


Figure 3: Overview of the inclusion and exclusion of BioRheuma centers and the registered b/tsDMARDs



Abbreviation: **b/tsDMARDs** = biologic and targeted synthetic disease-modifying antirheumatic drugs.

3.2.3 Data Validity

The validity of the study population from each center was determined by comparing them to previously reported RA prevalence in Norway [108, 109]. The RA prevalence from the BioRheuma data was calculated by dividing the included number of RA patients from each participating center by the number of citizens each corresponding center is covering for each given year. A summary of the estimated prevalence is reported in Table 5, with a more detailed version in Paper I (ref. Supplementary Table 2, Paper I).

Table 5: Estimated mean with range prevalence of rheumatoid arthritis registered patients (≥20 years) shown for all participating BioRheuma centers between 2010 to 2019

	Mean	Range
Prevalence of all included BioRheuma centers	0.30%	0.24-0.33%
Patient (≥20 years) from the BioRheuma Project	97.7%	90.3-99.9%
Norway's national population (≥20 years)	3864412	3618442-4072755
Service area for rheumatoid arthritis coverage of BioRheuma centers in Norway	68.6%	53.6-78.8%
Individual Centers		
Bergen (Haukeland University Hospital)	0.34%	0.12-0.40%
Bærum (Martina Hansen Hospital)	0.22%	0.19-0.21%
Førde (Førde Central Hospital	0.38%	0.24-0.46%
Haugesund (Haugesund Hospital for Rheumatic Disease	0.23%	0.11-0.28%
Kristiansand (Sørlandet Hospital, Kristiansand)	0.47%	0.36-0.54%
Lillehammer (Lillehammer Hospital for Rheumatic Diseases)	0.35%	0.31-0.37%
Oslo (Diakonhjemmet Hospital)	0.23%	0.20-0.27%
Skien (Betanien Hospital)	0.31%	0.26-0.34%
Trondheim (St. Olav's University Hospital)	0.32%	0.27-0.41%
Tromsø (University Hospital of North Norway)	0.41%	0.30-0.49%
Previous Studies		
Tromsø (University Hospital of North Norway), **1989** (≥20 years) [108]	0.39%	
Tromsø (University Hospital of North Norway), **1994** (≥20 years) [108]	0.47%	
Oslo (Diakonhjemmet Hospital), 1994 (20-79 years), **1994** [109]	0.44%	

Note: The prevalence is estimated using the BioRheuma age group ≥20 years and the rheumatoid arthritis service area from the corresponding centers for the same age group.

3.2.4 Data Extraction

Each year, each participating center sent anonymized Excel data files for merging and statistical analysis. This data were extracted from each participating center's database using two specified queries for each year between 2010 and 2019. The first query collected all RA patients who had at least one visit in the analyzed year in the selected GTI system and was used to generate the *current user dataset*. The second query was used to obtain all RA patients who initiated either bDMARD or tsDMARD in the various assessed years and was used to create the *starting b/tsDMARD dataset* (Figure 3). If numerous visits transpired during the given year, data from the most recent visit was utilized; otherwise, patients who visited only once in the selected year were included. In other words, it was not possible to determine if a RA patient was receiving treatment initiated at the beginning or the end of the year.

The frequency of patient visits was usually aligned with the need for consultation or follow-up, which was less frequent for RA patients with stable remission or low disease activity. Since each BioRheuma center provided anonymized data files and the frequency of patient follow-ups varied (i.e., not all follow-ups were annual), it was not possible to identify and monitor any RA patients longitudinally. The anonymized data files extracted from the participating centers were merged and examined using Microsoft Excel and the Statistical Program for Social Sciences (SPSS).

3.3 DATA ANALYSIS

The extracted BioRheuma data were used to analyze demographic variables, diagnosis-related variables, PROMs, disease activity measures, and RA treatment medications for each consecutive year. Paper I reports the complete overview of the demographic and clinical data from all participating BioRheuma centers, Paper II reports a summary of the preceding paper but categorization based on the

b/tsDMARD treatment category, and Paper III demonstrates similar reports as Paper I, albeit for a single center (Kristiansand) between 2015 to 2019.

3.3.1 Demographics and Clinical Data

In Paper I, the included demographic variables were patient age, sex, body mass index (kg/m2), current smoking status, years of education, disease duration, and occupational status. The timepoint between the diagnosis date and the latest recorded visit at the outpatient clinic for each given year was used to calculate the disease duration. Similar variables were evaluated in Paper II and III, except for occupational status. The reported occupational data were stratified into enabled or disabled workers (Table 6). For the purpose of assessing occupational health, participants ≥65 years were considered pensioners and therefore omitted from the assessment. A few very extreme outliers from the demographic data were excluded. Rheumatoid factor and anti-cyclic citrullinated peptide were considered diagnosis-related variables and were included in Papers I-III. The PROMs included were pain (VAS; 0-100 mm), PGA (VAS; 0-100 mm), fatigue (VAS; 0-100 mm), morning stiffness (15-minute units), and Modified Health Assessment Questionnaire [110]. PGA in the GTI system is formulated as follows: "*We kindly ask you to assess the activity of your rheumatic disease over the past week. Considering all symptoms, how do you think your condition is*?". The RA patient can respond by marking on a horizontal line with "*Good, no symptoms*" (0 VAS) on the very left side of the line and "*Very bad*" (100 VAS) on the very right side of the line.

Table 6: A dichotomized overview of occupational status among RA patients

Enabled Workers	Disabled Workers
Full-time job	Part-time job/disabled pensioners
Students	Disabled pensioners
Maternity/ Paternity leave	Disabled pensioners due to RA
Sick leave	Medical rehabilitation
Unemployed	Occupational rehabilitation
Early retirement	
Part-time job/sick leave	
Part-time job/unemployed	

Note: Patients ≥65 years were considered pensioners (not workers) and therefore omitted from this variable.

3.3.2 Disease Activity and Remission Definitions

In Papers I-III, clinical measures reflecting disease activity include ESR, CRP (mg/L), SJC28 (0-28 joints), TJC28 (0-28 joints), IGA (VAS; 0-100 mm), and DAS28 with CRP and PGA (DAS28) [30]. In Paper III, SDAI [31], CDAI [32], DAS28(4) (DAS28 CRP with PGA), and DAS28(3) (DAS28 CRP without PGA) [30] are also analyzed. Remission cut-off values for SDAI, CDAI, DAS28(4), and DAS28(3) were ≤3.2 [31], ≤2.8 [32], <2.6, and <2.6 [30], respectively. All evaluated RA patients in all papers were stratified for either having remission or non-remission.

In Paper III, the data was analyzed using the ACR/EULAR Boolean remission, which states that the variables TJC28, SJC28, CRP (mg/dL), and PGA (VAS 0-10 mm) must be ≤1 to achieve remission status [35]. However, the retrieved CRP and PGA from the BioRheuma data are reported in

mg/L and VAS 0-100 mm. Therefore, the cut-off for the Boolean remission criteria in this thesis was re-defined at ≤10 for CRP and PGA. In this thesis, ACR/EULAR Boolean remission is also referred to as 4-variable remission, and a 4-variable remission without the variable PGA is termed 3-variable remission.

In Paper III, further subdivision of the Boolean remission criteria is provided, including subjective 2-variable remission (≤1 TJC28 and ≤10 PGA) and objective 2-variable remission (≤1 SJC28 and ≤10 CRP). Paper III also shows individual variable cut-offs, i.e., ≤1 TJC28, ≤1 SJC28, ≤10 CRP, ≤10 PGA, ≤20 PGA, and ≤10 IGA. Since the remission rate variation across the examined years was only minimally statistically significant, most of the analysis in Paper III is reported for 2019 only.

3.3.3 Medication Selection and Treatment

In Papers I-III, the overview of current b/tsDMARD, csDMARD, and glucocorticoid usage is reported. Data on these medications were directly recorded in the GTI system by either the treating physician or the nurse. The recorded data on treatment encompassed various details, including the medication type, dosage, administration form, and dosing intervals. However, due to the limitation of the GTI query and the scope of the thesis, the current b/tsDMARD dataset and starting b/tsDMARD dataset were limited to only determining whether the RA patient was registered under a specific medication. The evaluated treatment data were presented into three treatment user groups: (1) current b/tsDMARD users, acquired from the current user dataset, (2) naïve and (3) non-naïve b/tsDMARD users (both registered on a new b/tsDMARD), obtained from the starting b/tsDMARD dataset (Figure 3).

Naïve b/tsDMARD users were identified as the RA patients registered to receive a b/tsDMARD for the first time. This was determined by examining the non-chronological drug order list of previous drugs for each registration in the starting b/tsDMARD dataset. If no previous b/tsDMARDs were listed, the patient was classified as a naïve b/tsDMARD user. On the other hand, non-naïve b/tsDMARD users were those registered as receiving a specific b/tsDMARD after previously being on a different b/tsDMARD. While the starting b/tsDMARD dataset does not provide information on the chronological sequence of treatment or duration, any b/tsDMARD in the non-chronological drug order list indicated previous b/tsDMARD use. Despite the absence of longitudinal data, this approach distinguished between naïve and non-naïve users. In Papers I and II, the overview of naïve and non-naïve users are also shown. For clarification, while each b/tsDMARD user group (i.e., current users, naïve users, and non-naïve users) are evaluated independently, there are possibilities where the same "user registration" would be counted in both current and either naïve or non-naïve group.

The data handling concerning the discontinuation of b/tsDMARDs in this thesis occurs when a RA patient ceases their current b/tsDMARD treatment without being paused. In other words, a RA patient would not be discontinued if, e.g., they were on "treatment vacations" or the treatment was paused to prevent complications during ongoing infections (or any other reasons necessitating less

immunosuppression). Being on pause does not change the data entry in the GTI, and as such, the RA patient will be registered as taking a specific b/tsDMARD despite being on hiatus for an undefined time. In other words, regardless of the undefined time length, this type of pause will not trigger a "switch" in the GTI system, either from first-time use (naïve) to non-naïve or within the non-naïve group. However, if a RA patient is discontinued from one b/tsDMARD and initiated on a new one, regardless of the timespan between the discontinuation and the new b/tsDMARD, it will be regarded as a new registration into or among the non-naïve b/tsDMARD users. This new registration will also be present in the current user dataset. There is no registration in the assessed data of when the RA patient discontinued or initiated a b/tsDMARD, only whether the registration is present. If a b/tsDMARD is registered twice, it could indicate that the discontinuation and new registration occurred during the same visit or that the previous b/tsDMARD registration was not removed for some reason. Due to the inability to distinguish between the discontinued and the new registration in such instances, these cases were termed registration errors, resulting in the exclusion of the entire RA patient from further analyses. Such registration errors (Figure 3) were minimal (accounted for 0.5% of all b/tsDMARD current users on average annually) and were not considered significant (see Supplementary Table 1, Paper II for further detail on the registration errors).

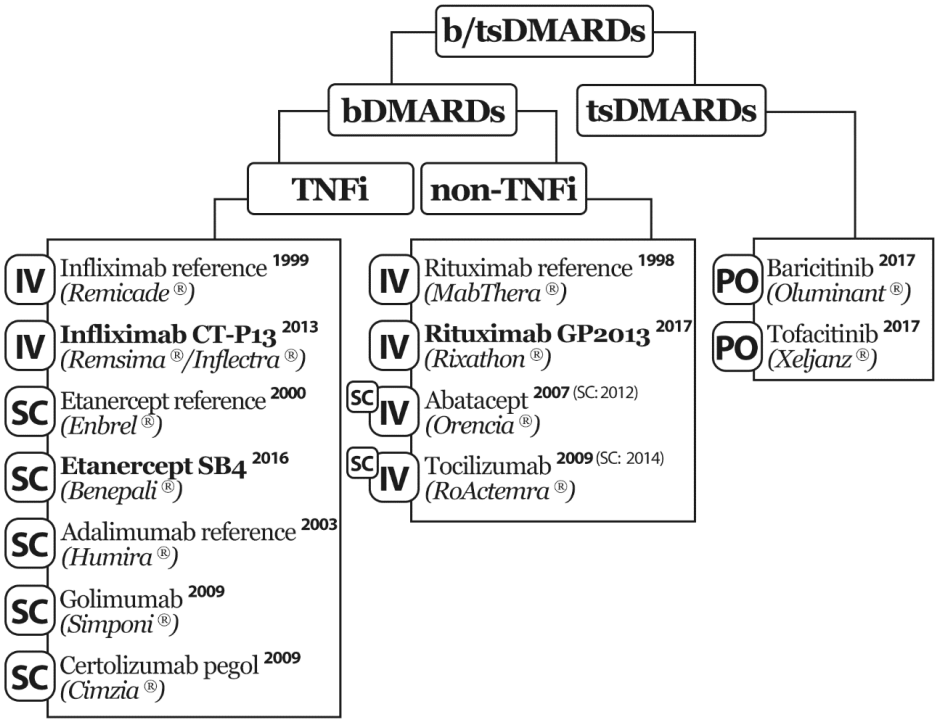
Among the current registered b/tsDMARDs users, 16 b/tsDMARDs were identified. 13 were included, while three b/tsDMARDs (i.e., anakinra, secukinumab, and ustekinumab) were excluded for either lacking indication or registrations. All 13 b/tsDMARDs were in the annual tendering for RA, while none of the three excluded were in the annual tendering for RA. The excluded b/tsDMARD accounted for roughly 0.2% of the total b/tsDMARD. In the starting b/tsDMARD dataset, the number of cases involving one of these excluded b/tsDMARDs was negligible. Although some of these excluded b/tsDMARDs were in the non-chronological drug order list in the starting b/tsDMARD dataset, none were the sole registrations on this list. In other words, when these single cases were omitted from the starting b/tsDMARD dataset, it did not affect the balance between naïve and non-naïve users.

The b/tsDMARD is an umbrella category for medication groups Tumor Necrosis Factor inhibitors (TNFi), non-TNFi (which combined constitute the bDMARDs), and target synthetic DMARDs (tsDMARD). In Papers I-III, the included drugs in the TNFi category were infliximab reference, infliximab CT-P13 (biosimilar), etanercept reference, etanercept SB4 (biosimilar), adalimumab reference, golimumab, and certolizumab pegol. The included non-TNFi were abatacept, rituximab reference, rituximab GP2013 (biosimilar), and tocilizumab. Baricitinib and tofacitinib were included in tsDMARDs. An overview of the included b/tsDMARDs, as well as their trade name, year of reaching the market, and route of administration (intravenous, subcutaneous, and per oral), is displayed in Figure 4. Tocilizumab and abatacept were initially introduced to the market as intravenous (iv) drugs, albeit in 2014 for tocilizumab and 2012 for abatacept, they were also approved for

subcutaneous (sc) use (information obtained from personal communication with representatives from Roche and Bristol-Myers Squibb, respectively, 2022). The adalimumab biosimilars, which were outcompeted by adalimumab reference in 2019, had no registered prescriptions and were omitted from the thesis studies (Papers I-III). The relative amount of given b/tsDMARD registration compared to the total registration is, in this thesis, defined as a treatment proportion.

The collected data also contained supportive information on prednisolone and csDMARDs. In Papers I and III, the four main csDMARDs included were methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine. Less frequently used csDMARDs were also evaluated (i.e., azathioprine, auranofin, ciclosporin, IM gold, mycophenolate mofetil, and reumacon). Papers I and III also report combination therapy between b/tsDMARD, csDMARDs, and prednisolone.

Figure 4: Overview of the b/tsDMARDs available for treatment 2010-2019 in Norway



Abbreviation: **IV** = intravenous, **SC** = subcutaneous, **PO** = per oral, **TNFi** = Tumor Necrosis Factor inhibitors, **b/tsDMARD** = biological and targeted synthetic disease-modifying antirheumatic drug, **tsDMARD** = target synthetic DMARDs, **bDMARD =** biological DMARD. *Note*: Biosimilars are marked in bold. The year of reaching market approval is superscripted next to the drug name. Squared IV, SC, and PO illustrate the route of administration. The trade name is shown in parentheses.

3.3.4 Medication Cost Analysis

In Paper I, the annual total and average cost per b/tsDMARD (of included b/tsDMARDs) per patient per year was determined separately for all current, naïve, and non-naïve b/tsDMARD users. These costs

were calculated using confidential tender offers for various b/tsDMARDs during the annual pharmaceutical tendering. Due to the established confidentiality agreement, drug-specific costs could not be disclosed. The COVID-19 pandemic restricted the collection of data for 2020. In Paper I, simulated costs were provided using the pharmaceutical tender offers from 2020 together with the b/tsDMARD proportion from 2019. In 2020, the adalimumab (GP2017) biosimilar won the tendering, and its cost offers were used with the 2019 adalimumab reference proportion to simulate further cost changes. Similarly, this pattern was conducted for infliximab, where infliximab GP1111 cost offers were used with the 2019 infliximab reference and CT-P13 treatment proportion.

The costs were displayed using euros (EUR) and EUR with the adjusted Norwegian kroner (NOK). For the EUR conversion, an average NOK-to-EUR exchange value between 2010 and 2020 was used (1 NOK = 8.839 EUR). For the adjusted NOK, the Norwegian consumer price index for medication from 2010 NOK was used [111].

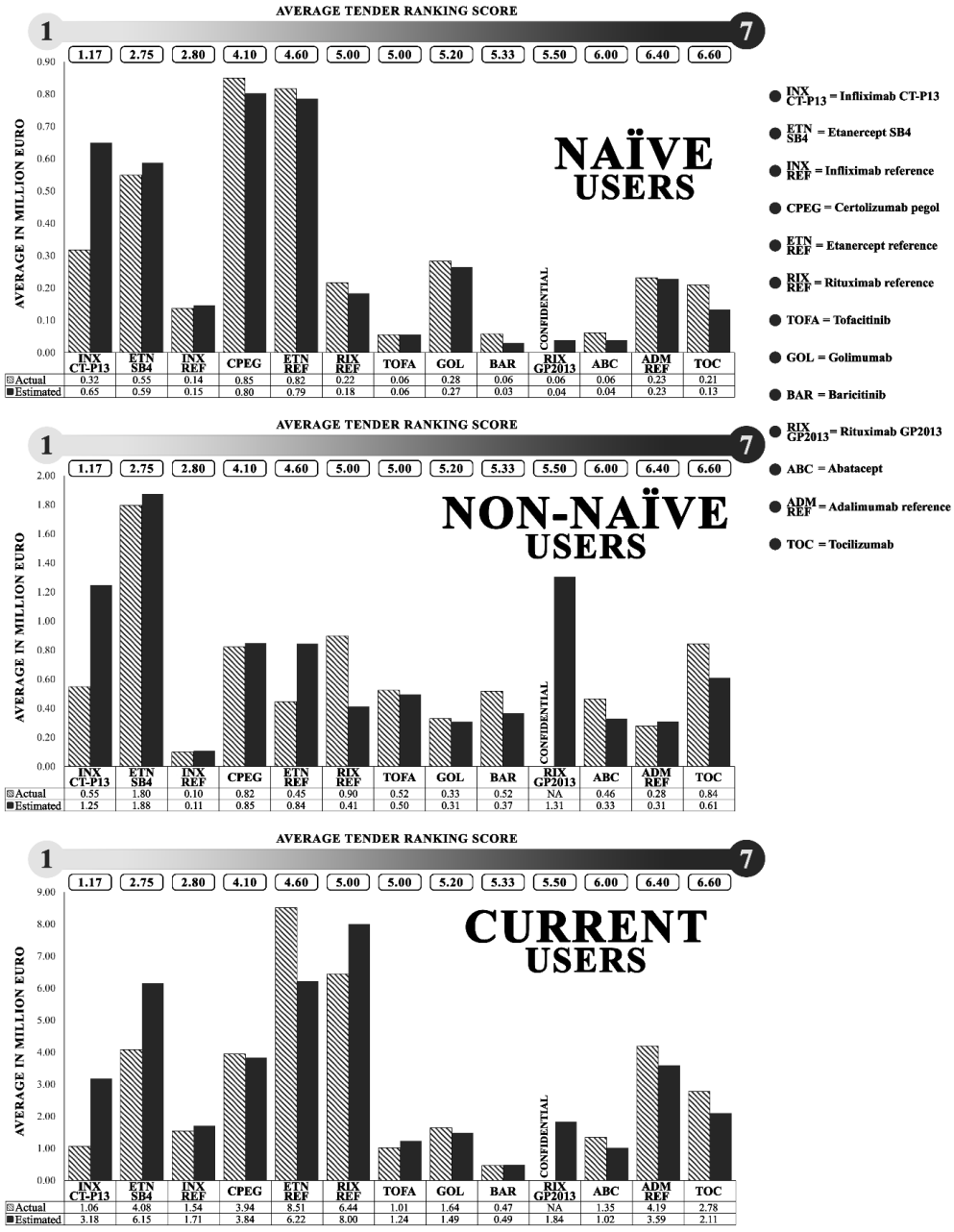
3.3.5 Tender Ranking and Medication Usage Analysis

While the drug costs from annual tendering are confidential for the public, the ranks from the pharmaceutical tendering for b/tsDMARDs in RA were permitted to be shared. Rank 1 represents the winner and, henceforth, the least expensive drug that given year. Ranks 2-6, above 6, no offers, and biosimilar equivalents are also reported. In Paper II, this overview is presented together with the usage of the different b/tsDMARDs. The graphical comparison of current, naïve, and non-naïve users is shown in Paper II using a stacked histogram. An overview comparing the sc vs. iv b/tsDMARDs and biosimilars vs. non-biosimilars b/tsDMARDs is also provided.

3.3.6 Actual and Estimated Average Cost for Individual b/tsDMARDs Arranged by Average Tender Ranking Score

This thesis provides an additional figure (Figure 5) that combines the average cost for individual b/tsDMARD calculated using the treatment proportion from Paper II with either the actual tender cost or the estimated cost from Paper I. The *actual average cost* per selected b/tsDMARD is calculated by multiplying its annual amount with the corresponding confidential tender cost for that year, then summarizing each year's total cost of all participating years, followed by dividing the overall cost by the number of participating years. The *estimated average cost* for selected b/tsDMARD is calculated similarly, but using the average cost per b/tsDMARD per patient for the given year (taken for Paper I) instead. The individual b/tsDMARDs are classified according to the user subgroup and arranged according to their average tender ranking score (TRS). The TRS is calculated by summarizing the tender rank from each year divided by the number of participating years. Ranks above six and no offers were rounded down to tender rank 7. Biosimilar equivalent status was implemented according to their offer. This figure's (Figure 5) confidentiality is verified and approved by NHPT.

Figure 5: Comparison between the actual and estimated average cost for individual b/tsDMARD arranged according to the average tender ranking score for each user subgroup



Note: Each average cost for the individual b/tsDMARD is calculated either by using the actual tender cost or the estimated cost from Paper I (average cost per b/tsDMARD). The actual average cost is calculated by summarizing the total of the selected b/tsDMARD and dividing it by the amount of participating years. The b/tsDMARDs are classified according to the user subgroup (i.e., current users, naïve users, and non-naïve users) and arranged according to their average tender ranking score. Current users encompass all registrations, including those that are new (i.e., naïve and non-naïve) and those that are ongoing. The tender ranking score is calculated by the tender rank divided by the number of participating years. A low tender ranking offer illustrated that the b/tsDMARD offered a good discount consistently, while a high average tender ranking score illustrates that the b/tsDMARD offered a minimal offer.

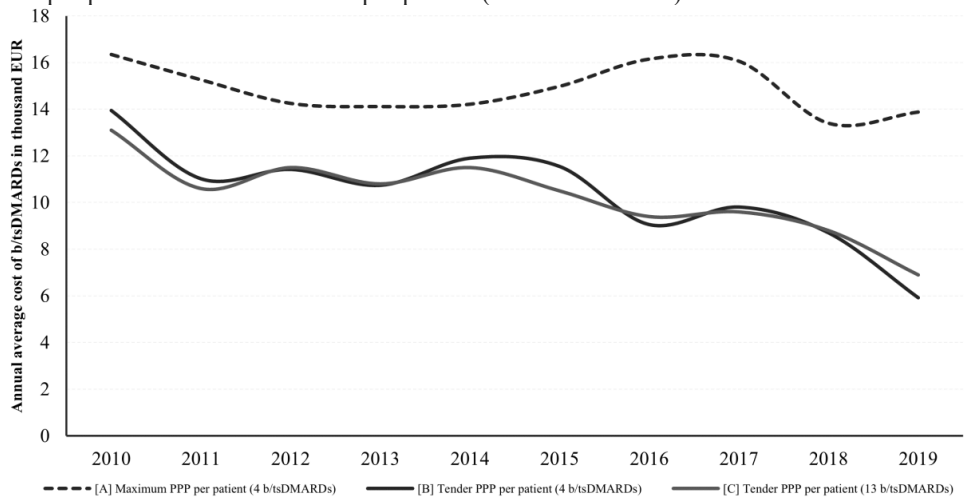
3.3.7 Annual Overview of the Reduced and Maximal Cost of b/tsDMARD per Year per Patient

This thesis provides a comparative assessment between the maximal PPP per patient and tender PPP per patient. Figure 6 in this thesis illustrates the average cost of a b/tsDMARD per patient per year, calculated using four specific b/tsDMARDs; adalimumab reference, etanercept reference, etanercept SB4, and certolizumab pegol, which is compared with the average cost of a b/tsDMARD per patient per year calculated using all 13 b/tsDMARD. The latter values are the same as in Table 4 and Figure 1B in Paper I. The four b/tsDMARD were selected based on their variety in the tender rankings, usage, and cost, but also because the other b/tsDMARDs were challenging to assess from the acquired data in matters of calculation and in the complexity surrounding the tender offers. The average treatment proportion of the four mentioned b/tsDMARDs compared to the 13 b/tsDMARDs was 54% (ranging from 46% to 60%) across the ten years. The two comparisons illustrated in Figure 6, i.e., the average cost of four b/tsDMARDs vs. the average cost of 13 b/tsDMARDs, utilize data on *tender PPP per patient* collected from the confidential annual tender reports on b/tsDMARDs.

Data from the Norwegian Medicines Agency's database on *maximum PPP per package* were collected for the same four aforementioned b/tsDMARDs [94] and recalculated into maximum PPP per patient. Utilizing this data on maximum PPP per patient and the data on annual registration for the same four b/tsDMARDs (ref. Table 4, Paper II), collected from the current b/tsDMARD dataset, an average maximum PPP per patient was calculated for each year for the ten-year period and illustrated in Figure 6. As such, the average cost of a b/tsDMARD was calculated separately for three assessments [A, B, and C] by dividing the combined total (maximum and tender, individually) PPP per patient for all given b/tsDMARD (4 for maximum and tender, and 13 for tender) by the total registered users for all given b/tsDMARDs (4 and 13, separately) in a given year. This produced the graph lines [A] maximum PPP per patient (4 b/tsDMARDs), tender PPP per patient (4 b/tsDMARDs), and tender PPP per patient (13 b/tsDMARDs), describing the average b/tsDMARD per patient per year for each assessment. In-depth details on how these calculations were conducted are provided in the legend section of Figure 6. To ensure better comparability, since the annual average cost of the 13 b/tsDMARD in Figure 1B in Paper I is presented in thousand euros, Figure 6 in this thesis also shows all costs in thousand euros using the same average NOK-to-EUR exchange value for all ten years (1 NOK = 8.839 EUR).

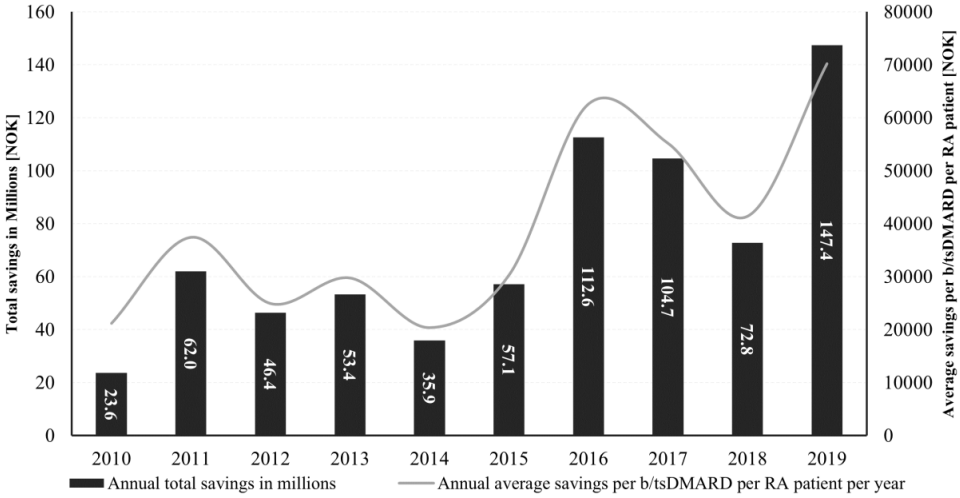
Figure 7 of this thesis was added to show the total cost savings when using the pharmaceutical tender system to procure b/tsDMARDs. As such, the combined total maximum PPP per patient of the four b/tsDMARDs was subtracted from the combined total tender PPP per patient for the same four b/tsDMARD for each given year during the ten-year period and illustrated in a histogram (Figure 7). The same figure also shows the average cost savings by subtracting the annual average cost of the four b/tsDMARDs between the average maximal and the tender-reduced costs (i.e., subtracting data presented in graph line A from graph line B in Figure 6). In-depth details on how these calculations were performed are provided in the legend section of Figure 7. Figure 7 displays the cost in NOK.

Figure 6: Comparing the average cost of b/tsDMARDs per RA patient per year using tender PPP per patient and maximal PPP per patient (in thousand EUR)



Note: **b/tsDMARD** = biologic and targeted synthetic disease-modifying antirheumatic drugs, **PPP** = Pharmacy Purchase Price, **Tender PPP per package** = Tender-reduced cost per given b/tsDMARD package, **Maximum PPP per package** = Maximal cost without any cost reduction per given b/tsDMARD package, **PPP per patient** = PPP per package × PPP per mg (calculated from standard dosage and body weight), **EUR** = Euros, **NOK** = Norwegian kroner. Tender PPP per package was collected from the confidential annual report on b/tsDMARDs. Maximum PPP per package was collected from the Norwegian Medicines Agency's database on b/tsDMARDs. The four b/tsDMARDs were adalimumab reference, etanercept reference, etanercept SB4, and certolizumab pegol. See Figure 4 for a complete overview of the 13 b/tsDMARDs. The PPP per patient for a given b/tsDMARD was multiplied by the registered users of the same b/tsDMARD for a given year (collected from the current b/tsDMARD dataset), generating the **total PPP per patient** for a given b/tsDMARD for a given year (i.e., **total maximum PPP per patient** when using maximum PPP per package, and **total tender PPP per patient** when using tender PPP per package). The **combined total PPP per patient** was calculated by adding the total PPP per patient for all the given b/tsDMARDs, i.e., adding the total PPP per patient for the four b/tsDMARD (both tender PPP and maximum PPP) and adding the total tender PPP per patient for the 13 b/tsDMARDs. This generates **combined total tender PPP per patient (4 b/tsDMARDs)**, **combined total maximum PPP per patient (4 b/tsDMARD)**, and **combined total tender PPP per patient (13 b/tsDMARDs)** – each for a given year. The **average total** (maximum, tender) **PPP per patient** was calculated by dividing the combined total (maximum, tender) PPP per patient by the annual total registrations of the given b/tsDMARDs (4, 13) for a given year, generating **average maximum tender PPP per patient (4 b/tsDMARDs)** [termed Maximum PPP per package (4 b/tsDMARDs) in the figure], **average total tender PPP per patient (4 b/tsDMARDs)** [termed Tender PPP per package (4 b/tsDMARDs) in the figure], and **average total tender PPP per patient (13 b/tsDMARDs)** [termed Tender PPP per package (13 b/tsDMARDs) in the figure]. All costs were converted from NOK to EUR using the average exchange value for the ten-year period (1 NOK = 8.839 EUR).

Figure 7: Overview of the total and average annual cost savings when using tender PPP instead of maximal PPP for four b/tsDMARDs



Note: **b/tsDMARD** = biologic and targeted synthetic disease-modifying antirheumatic drugs, **PPP** = Pharmacy Purchase Price, **Tender PPP per package** = Tender-reduced cost per given b/tsDMARD package, **Maximum PPP per package** = Maximal cost without any cost reduction per given b/tsDMARD package, **PPP per patient** = PPP per package × PPP per mg (calculated from standard dosage and body weight), **NOK** = Norwegian kroner. Tender PPP per package was collected from the confidential annual report on b/tsDMARDs. Maximum PPP per package was collected from the Norwegian Medicines Agency's database on b/tsDMARDs. The four b/tsDMARDs were adalimumab reference, etanercept reference, etanercept SB4, and certolizumab pegol. The PPP per patient for a given b/tsDMARD was multiplied by the registered users of the same b/tsDMARD for a given year (collected from the current b/tsDMARD dataset), generating the **total PPP per patient** for a given b/tsDMARD for a given year (i.e., **total maximum PPP per patient** when using maximum PPP per package, and **total tender PPP per patient** when using tender PPP per package). The **Combined total PPP per patient** was calculated by adding the total PPP per patient for all the four b/tsDMARDs for a given year, generating the **combined total tender PPP per patient (4 b/tsDMARDs)**, and **combined total maximum PPP per patient (4 b/tsDMARD)** – each for a given year. The **average total** (maximum, tender) **PPP per patient** was calculated by dividing the combined total (maximum, tender) PPP per patient by the annual total registrations of the four b/tsDMARDs, generating the **average maximum tender PPP per patient (4 b/tsDMARDs)**, and **average total tender PPP per patient (4 b/tsDMARDs)** for each given year. The **annual total savings** were calculated by subtracting the combined total maximum PPP per patient (4 b/tsDMARD) from the combined total tender PPP per patient (4 b/tsDMARD) for each year and displayed as a histogram in the presented figure. The **annual average savings** were calculated by subtracting the average maximum PPP per patient (4 b/tsDMARD) from the average tender PPP per patient (4 b/tsDMARD) for each year and displayed as a line graph in the presented figure.

3.4 STATISTICAL ANALYSIS

The evaluation of the variable variations over a ten-year period for Papers I and II and the five-year period for Paper III were assessed using SPSS. Categorical variables (reported in numbers and percentages) were analyzed using the chi-square test, and continuous variables (reported in mean with standard deviation or mean with range) were analyzed using a one-way analysis of variance (ANOVA). In some cases, a student t-test was required instead of ANOVA. Unless specified in the papers, all available data were analyzed without imputation of missing data.

In Paper III, linear regression (univariable and multivariable) evaluated the association between PGA and other variables, and logistic regression evaluated the association between disease activity measuring methods and other variables. Standardized coefficient β (β) and unstandardized coefficient B (B) with confidence intervals of 95% were reported using linear regression assessment, and odds ratios with confidence intervals of 95% were used to report on logistic regression assessment. Since there were minimal statistical changes between the five years, both regression assessments were provided for 2019 only. In all papers (I-III), a p-value of <0.05 was regarded as statistically significant. The visual presentation of the findings from all papers (I-III) was developed with Microsoft Excel and supplemented with Adobe Photoshop.

4. SUMMARY OF RESULT

4.1 PAPER I

Exploring drug cost and disease outcome in rheumatoid arthritis patients treated with biologic and targeted synthetic DMARDs in Norway in 2010-2019 — a country with a national tender system for prescription of costly drugs

Background: With excellent treatment strategies and the usage of modern medication such as b/tsDMARDs, clinical outcome improvement for RA is observed. The b/tsDMARDs are becoming increasingly available on the market, albeit sold at a high cost that contributes to inequality in care. Cost-effective strategies, such as the pharmaceutical tender system, are one of the potential approaches that can reduce the cost without impairing the disease outcome. The objective of this study was to explore annual b/tsDMARDs costs and disease outcomes in Norwegian RA patients between 2010 and 2019 under the influence of the pharmaceutical tender system.

Results: During the ten-year period, the percentage of current b/tsDMARD users increased from 40% to 45% (estimated from 4909 to 9335 registered RA patients). Among them, an improvement was seen for disease activity measures and other variables except for pain, PGA, morning stiffness, and enabled workers, which remained statistically unchanged. The remission rate for current b/tsDMARD users increased from 42% to 67% during the assessed ten-year period. The disease activity increased for naïve and non-naïve b/tsDMARD users as well. Overall, no relevant differences were seen when comparing b/tsDMARDs and non-b/tsDMARDs users, except for longer disease duration and lower work capability for the b/tsDMARD users. Simultaneously, with these reported clinical data across ten years, the average annual cost of treating a current b/tsDMARD user decreased by 47% (13.1 to 6.9 thousand EUR). The average reduction cost was even greater for naïve and non-naïve users, with 75% and 64%, respectively. In all cases, the cost improvement was even more considerable when adjusting for the increased value of the 2010 NOK currency.

Conclusion: With real-life data from registered Norwegian RA patients across ten years under the influence of a pharmaceutical tender system, this study shows observations of a reduction in b/tsDMARD treatment cost and, in tandem, a noticeable increase in RA remission rate. The largest cost reduction over this period was seen for patients starting naïve on b/tsDMARD.

4.2 PAPER II

Exploring the impact of the national tender system on the use of costly drugs treating rheumatoid arthritis patients in ten rheumatology centers in Norway (2010-2019)

Background: While Paper I examine the cost changes of b/tsDMARDs for RA treatment in Norway under the influence of a pharmaceutical tender system, the objective of this study was to evaluate the tender system's impact on the usage of b/tsDMARD during the same ten-year period (2010-2019).

Result: In this study, the tender-winning b/tsDMARD was observed in nine out of ten years for naïve b/tsDMARD users, seven out of ten years for non-naïve users, and twice out of ten years for current users, while simultaneously also being either the highest or second-highest in usage. The average accumulated highest and second-highest proportions were 75% for naïve users, 53% for non-naïve users, and 50% for current users. The average accumulated proportion of sc and per oral b/tsDMARDs was roughly 70%, 50%, and 60% for naïve, non-naïve, and current users, respectively. However, the tender-winning drug was iv in eight out of ten pharmaceutical tenders. During the biosimilar years (2016-2019), the average proportion of biosimilars was approximately 40% for naïve b/tsDMARD users, 40% for non-naïve users, and 20% for current users.

Conclusion: Based on observed data, the tender-winning b/tsDMARDs were often observed with one of the highest proportions among naïve and non-naïve b/tsDMARD users. However, in most cases, sc b/tsDMARD resulted in a higher proportion, despite being offered at a lower tender ranking. An implemented pharmaceutical tender system in Norway seems to endorse the pharmaceutical company offering the most inexpensive drugs. While this was most pronounced for patients starting naïve on b/tsDMARD, the currently treated b/tsDMARD RA patients were influenced to a lesser extent by the tender system.

4.3 PAPER III

Remission or not remission, that's the question: Shedding light on remission and the impact of objective and subjective measures reflecting disease activity in rheumatoid arthritis

Background: While the RA guidelines advocate aiming for remission when treating RA patients, there is no unified agreement on an operational definition of remission. The different measuring methods of disease activity and remission incorporate subjective and objective measures in their calculation to various degrees. The objective of this study was to calculate remission rates using various evaluation methods for the same RA patient from a single outpatient clinic. In addition, the goal was to investigate the different variables which constitute the different measuring methods.

Result: Upon evaluating the same 502 RA patients, a 50% discrepancy in remission rate between the least stringent (73%) and most stringent (23%) measuring methods was discovered. The most stringent method, the original Boolean Remission criteria (4-variable remission), incorporates SJC28, TJC28, CRP, and PGA. Using a similar evaluation method (3-variable remission) without PGA, the remission rate increased to 65%. The PGA, i.e., the patient's self-evaluation of their own RA condition, contributed to the lowest remission rate and was strongly associated with pain.

Conclusion: This study points out the flaws of not having a unified agreement on the definition of remission. It also illustrates the possible outcome of including the PGA variable, which can often be influenced by noninflammatory pain or other comorbidities, in assessing remission. Attempting to treat patients into remission with the possibility of misevaluation can result in treating noninflammatory causes with costly potent anti-inflammatory medications (e.g., b/tsDMARD) that can lead to serious adverse events.

5. DISCUSSION
5.1 METHODOLOGICAL CONSIDERATION
5.1.1 Study Design and Data Collection
This thesis is comprised of three cross-sectional studies (Papers I-III). Two are multicenter studies across a ten-year period (Papers I and II), and one single center study across a five-year period. The research questions were formulated after the BioRheuma data collection had been performed prior to variable selection in 2020. The objective of the BioRheuma project was to collect real-life data from ordinary Norwegian outpatient clinics where patients with inflammatory joint disorders (e.g., RA) were being treated. Patient monitoring, hence the data collection, at the participating outpatient clinics (i.e., BioRheuma centers) was conducted using the software GTI (www.diagraphit.com). Variables not incorporated into the GTI were, therefore, consequently unavailable. This was not a limitation for the three studies in this thesis, albeit the large amount of missing data (either partially or entirely of variables) was considered a limitation.

It is essential to clarify that there are no missing variables per se but that the thesis analyses were performed from a set of collected variables (minimal variable collection). Although numerous other less recorded variables were available from the collected GTI data, they had extensive missing data that made them insufficient for further consideration. Even the presented data from the minimal variable collection had considerable missing data in many variables. The specificity of these variables is addressed in 3.3.1-3.3.3. Given that the entry of these variables was encouraged rather than mandated, rheumatologists may have forgotten or deprioritized to provide the data entry on these variables – especially if the information was expected to be recorded twice (once in the GTI and once in the local medical journal system). The rheumatologists or nurses could also be under time constraints or stress, dealing with easy-to-treat RA patients, unfamiliar with the GTI system, or the GTI system was not fully integrated at their BioRheuma center. These factors could have contributed to incomplete data entry individually or in conjunction. Over time, BioRheuma centers and rheumatologists new to the GTI system increased their data entry on the minimal variable collection. This also has likely explanatory factors. For example, early on, the GTI system was adjusted so double data entry was no longer required, and eventually, an effective system to remind the treating rheumatologists of missed variable entries was implemented. Regardless of the cause, missing data reported in the thesis are shown to have a decreasing tendency over time, indicating that whatever direct or indirect strategy was applied had a likely meaningful impact.

The primary purpose of the studies from Papers I and II was to analyze medication usage, where the medication data was complete except in those years when some centers did not provide any data (Figure 3). The secondary goal of these studies was to assess the clinical variables used at the BioRheuma centers, which, unfortunately, had significant discrepancies in missing data (especially during the first year of the studies). However, these missing data are not considered to hinder the central message of the studies. As such, all available data were used in Papers I and II without imputation of

missing data. There were fewer missing data for the single center (Sørlandet Hospital, Kristiansand) study in Paper III, likely because Sørlandet Hospital was the first center to implement the GTI software. Also, the early phase with higher missing data (2010-2014) was not necessary to include to answer the research question posed in Paper III. Nevertheless, the low missing data still became problematic as this study relied more on complete data from selected variables than in the other two studies. Since it was imperative to have complete data from the variables related to disease activity measurements (i.e., SJC28, TJC28, CRP, PGA, and IGA), the patients lacking these data were excluded from the study in Paper III. These excluded patients are elaborated on below and in Paper III.

Missing data should not be unexpected. Implementing a novel digital health platform can often result in variability in the thoroughness among the users (patients and workers) when filling in the data. The overall data collection in real-life clinical scenarios is ultimately left to the doctor's discretion, which frequently deviates from the ideal standard. The discrepancy between real-life and optimal research data reflects the difficulties encountered in uniformly implementing structured data collection across all centers. It also highlights the practical implementation barriers and the complexities associated with real-life clinical scenarios at rheumatology outpatient clinics.

Since the collected data was anonymized and extracted for each year individually, the patients and the b/tsDMARDs could not be followed longitudinally without any identifiers. In other words, it could not be distinguished whether RA patients were consulted for a flare-up or not, if RA patients received consultation only once in the selected year or multiple times, nor if they were seen annually or perhaps only once during the study period. The studies could also not evaluate the change in treatment or treatment time, and it could not be determined when during the year the treatment was initiated or discontinued. As such, there could be rare cases where a RA patient would receive a b/tsDMARD in December and change treatment to another b/tsDMARD in January (a month later) but would be counted fully in terms of cost for both years. Despite these limitations, attempts were made in this thesis to draw assumptions based on trends across the cross-sectional data. The presented data should therefore be interpreted with caution, taking into account that any observed trends do not imply causation due to the cross-sectional nature of the data. After all, these cross-sectional analyses provide only a year's snapshot with no cause-effect comparison. However, the purpose of the two studies in Papers I and II was to show the cost and usage of b/tsDMARDs under the influence of a tender system, where a snapshot view was justified. Paper III's main purpose was to illustrate a snapshot of disease activity using different disease activity measuring methods to define remission.

5.1.2 Disease Outcome Definition

In a sense, Papers I and Paper III contradict each other. While Paper I demonstrated cost reduction with a disease activity reduction and remission rate increase, it was only illustrated with one remission-assessing method. Paper III showed a discrepancy between the methods that define remission status and exemplified the discrepancy in remission rate using a selected number of most established remission-

assessing methods (e.g., DAS28, CDAI, SDAI, and Boolean Remission). While the exact improvement in disease activity may be disputed, the remission rate in the study from Paper III was observed to increase across the evaluated years for all other remission-assessing methods. Given that findings in Paper III at Sørlandet Hospital are similar to the other BioRheuma centers, it can be assumed that the disease activity from the study in Paper I at least did not decrease.

5.1.3 Cost and Usage of b/tsDMARDs

Papers I and II aimed to illuminate the b/tsDMARD cost and b/tsDMARD treatment proportion under the influence of a national pharmaceutical tender system. The annual total and average cost provided in Paper I and the thesis figures were conducted using the tender PPP per patient acquired from the annual confidential rank-based report on tender PPP per patient for each b/tsDMARD. Paper I and the thesis should have provided a more optimal description of the cost outcome to offer better inferences on the cost findings. However, a more detailed description of the calculation and data presentation could let the readers backtrack to the actual tender PPP per patient for the individual b/tsDMARD, which would breach the confidentiality bestowed upon the author of this thesis. At the same time, this is also a major limitation that prevents the reader from evaluating the validity of the cost outcomes – a conundrum that comes with the assessment and the presentation of confidential numbers. Another limitation related to the cost outcome is that this thesis stems from using tender PPP per patient to calculate the current cost. While the tender PPP per patient was necessary to multiply with the registered RA patients taking b/tsDMARD to calculate the annual total and average cost, it is built upon standard dosage and average body weight. This limitation would be present even if the tender PPP per patient were not confidential. The way to bypass this limitation would be to recalculate the tender PPP per package into PPP per mg and multiply it by the actual amount of milligrams used by each individual RA patient of a given b/tsDMARDs throughout the whole year. A third limitation is that the cost data in this thesis is somewhat unique in its presentation, making it challenging to compare with other databases and registries as other registries usually report their cost outcome differently, e.g., using the defined daily dose. The uncertainty of not knowing if the tender PPP per patient decreased simultaneously and equally with the maximum PPP per patient for a given b/tsDMARD is also a limitation affecting the interpretation of whether the national tender system was influential in the cost reduction. While Figure 6 shows a non-similarity between the tender PPP and maximum PPP, this illustration is only for four b/tsDMARDs without any supporting statistical calculation. Figure 6 adds to the overall assumption that the national tender system offered a cost-reduced outcome, albeit a more thorough assessment is necessary to confirm the non-similarity in reduction between the maximum and the tender-reduced cost.

Regarding the treatment proportion of b/tsDMARD, there are several limitations, where multiple will be covered in the 5.1.5 Representativeness paragraph. A few registrations had to be excluded due to multiple registration errors. The excluded drugs from the study were about 1.5% of the total proportion each year, and consequently, the excluded annual average current b/tsDMARD users

was 0.5% of all b/tsDMARD. While the small amount of excluded b/tsDMARD seemed to have little impact on total and average cost, it is crucial to recognize that these drugs were administered at the maximum cost. While the expenditure of non-tender-related drugs was outside the scope of the thesis, it should be pointed out that the small percentage of the excluded drugs likely contributed to more than 1.5% of the overall cost.

5.1.4 Bias

Systematic error, or bias, may have occurred in the thesis's studies, resulting in incorrect measures of association or improper selection of variables [112, 113]. This section will cover the potential biases throughout the thesis studies.

5.1.4.1 Selection Bias

Selection bias may occur when inaccurate methods or procedures are used to determine the selection of the study population [113]. In the case of this thesis, all evaluated patients are assumed to have RA. If a selection error had occurred, it would have been related to the erroneous diagnostic procedures by the rheumatologist (diagnostic bias) or incorrect input of data into the GTI software. The error could also be on the programming level of the software. Neither of these cases is likely, and if there are incidences of misdiagnosis among recently diagnosed RA patients, they are expected to be very minimal. It is also believed that the likelihood of RA diagnosis is higher among the patients treated with csDMARDs or b/tsDMARDs (i.e., proxy to determine diagnosis). The studies in this thesis do not distinguish between recent, very early, or established RA among the study population. The potential of attrition bias is not accounted for as the data did not provide an overview of the patient who no longer participated in being followed up with the GTI system.

The overall assessment of the current users (Paper I) may contain selection bias due to the influence of the increased number of included RA patients. The increase in included RA patients translates into an increased number of annual consultations, where those receiving multiple consultations in a year are only counted once. This increase can be attributed to better GTI enrollment, a sudden increase in the prevalence of RA in Norway (which would be highly unlikely), and a higher need to provide RA-related consultations. The first option is the most likely scenario with an underlying variation frequency of follow-up consultation related to RA patients' health status. The difficult-to-treat RA patients are more likely to receive more frequent follow-ups, while healthier RA patients are more likely to be less often followed up. This results in more follow-ups for those requiring b/tsDMARDs due to unstable disease activity, but also among those with sustainable remission that require consultations due to other unknown reasons. Such a selection bias can affect the credibility of this thesis's reported disease outcome data. As such, the changes in the variables over time, particularly the "improved" disease activity measured with DAS28, which was one of the key points of the study in Paper I, may be an outcome of selection bias and, instead, misinformative.

It is also important to note that the increase in RA patient registration was not constant over time. Overall, across all BioRheuma centers, it increased between 2010 to 2014 and then was relatively stable between 2015 to 2019. Despite this, there was substantial variability in the increase-plateau-decrease pattern across the different centers. The increase-plateau-decrease pattern supports the assumption that the primary force of inclusion was related to GTI enrollment but that there is an underlying variation based on the need for a follow-up consultation. In other words, each BioRheuma center first had an increasing enrollment of RA patients into the GTI that was substantially higher than the non-annual consultation tendency. This period was followed by a plateau, where there was a balance between the enrolment and the non-annual consultation. Lastly, a decreasing period was observed, where it is assumed there are fewer enrollments compared to the number of RA patients requiring annual consultation, which would lead to a decreasing trend at the given BioRheuma center. While this trend will be further elaborated upon in the 5.1.5 Representativeness paragraph, it is worth noting that the b/tsDMARD treatment proportion had a steady slight increase despite this variation. This suggests that the frequency of annual consultation is less likely impacted by a selection bias related to those needing b/tsDMARD.

Another selection bias may have occurred related to the study in Paper III, where the study population from Sørlandet Hospital in 2019 (n = 871) was thoroughly evaluated. Only those with a complete dataset were included (n = 502). Hence, 42% was excluded in 2019. This excluded selection could have caused bias by distorting the results assessed by the included population. For the purpose of clarity, a supplementary table was added to Paper III (ref. Supplementary Table 3, Paper III), which compares the included with the excluded RA patients. The table illustrates that across the five years, none of the variables showed a consistent divergence between included and excluded, except for treatment. A few had some repetitive occurrences of a discrepancy, i.e., ESR, CRP, and DAS28(3).

ESR was significantly different between included and excluded populations on multiple occasions, albeit the average highest vs. lowest value was incoherent, which likely translates the occurrence as random. The average CRP was significantly lower in three years (including 2019) and likely reflected in the significant DAS28(3) difference in the same years. SJC28 and TJC28, which should correspond with the CRP, are not significantly different in included vs. excluded. However, the DAS28(3) score (and CRP) for the excluded had roughly 75% missing data. Hence, around n = 90 showed a 2.5 score for DAS28(3), albeit it was excluded because of missing data on either IGA or PGA. This is in comparison to the included 502 RA patient with a 2.2 DAS28(3) score. Both a DAS28(3) score of 2.2 and 2.5 is within the classification of remission status. This bias may have caused some impairment of results for the DAS28(3) and 3-variable remission. Nevertheless, the excluded n = 90 would not be comparable with other remission-assessing methods due to the missing data in the other required variables for the calculation.

Across the five years, the included patient was significantly more likely to receive treatment. This may indicate that the RA patients that did not receive treatment (DMARD) were more likely to have missing data, which supports the assumption presented in 5.1.1. In turn, this can mean that the likelihood of inserting data about the RA patient into the GTI depends on the necessity of a thorough follow-up; patients receiving DMARD require more vigilant follow-up and data registration than those that do not receive DMARD.

5.1.4.2 Information Bias

Another systematic error type, known as information bias, may have occurred in the studies of this thesis. Information bias can result from an erroneous collection of information for the study or from participants included in the study [113]. Most of the inputted data occur on the same day as the clinical evaluation by the rheumatologist or nurse. Therefore, recall bias is less likely to occur. Although, the clinical information bias may have occurred as a random error by the evaluators.

As a consequence of misinformation during a dialog with the patients or misunderstanding by the patient, an error in the self-reported patient information could also have occurred. The misunderstanding can occur either due to a faulty explanation by the informer or inaccurate self-perception. Most PROMs where patients report using VAS, including PGA, are potential sources of incorrect reports in this manner. The application of PGA is straightforward, albeit its subjective and heterogeneous formulation can present several challenges. The inquiry for PGA occurs by providing the RA patient a single unstandardized question, which is either formulated to question the *general health* or the *disease activity* of RA patients. The evaluator may ask open-ended questions or use specific phrases to which the RA patient responds on a scale of 0-10 or 0-100. Tick marks, horizontal or vertical lines, which graphically illustrate 0-10 or 0-100, can also be used [114]. The discrepancy in how the question is phrased and replied to may facilitate a variety of interpretations and, therefore, can cause information bias. Furthermore, PGA is also linked to other noninflammatory causes, making it a potential confounding bias (discussed below). Since PGA is a pivotal component to evaluate disease activity, which in turn can dictate treatment, there should not be so much possibility of information bias related to this variable (nor other biases). The information bias could also have occurred similarly in other variables that use a 0-100 scale to evaluate the PROM, i.e., pain and fatigue. However, they are less critical for the disease activity and more relevant for the disease impact of RA.

Some longitudinal conclusions may have been misleadingly drawn by interpreting the analyses from the ten BioRheuma centers' cross-sectional data over time. Any statements implying improved outcomes over time should be interpreted cautiously as they may be potential sources of information bias. The observed trends do not explicitly imply causation and are limited by available data. The inability to follow each patient yearly limits the inferences drawn from the outcome data. Despite non-causal implications and data limitations, analyzing real-life cross-sectional data can still provide

valuable insights when observed trends are understood as descriptive rather than definitive outcome changes over time.

5.1.4.3 Confounding Bias

Confounding may occur when the outcome of a result is governed by another factor, and bias occurs when this factor is not adjusted for [113]. While there are possibilities of unknown confounding (residual confounding) throughout all studies in this thesis, in Paper III, some direct confounders are identified.

A large portion of the study in Paper III relies on the assessment of PGA. Clinical guidelines for RA, which suggest using the variable PGA to assess disease activity in RA, imply that the patient's self-evaluation of the impact of the RA disease (i.e., the patient's experience of illness) reflects the RA disease activity status (i.e., biological disease process). While this may be true, other generalized comorbidities have been linked to increased PGA (e.g., depression, noninflammatory pain) [114-117], which may distort the value and the true purpose behind PGA. This is a complex dilemma, where it can be expected that the RA guidelines suggesting using disease activity measures with PGA appear not to account for other generalized comorbidities as potential confounders. It can also be that the guidelines do not consider the potential confounders as highly impactful on PGA on such a scale that it reflects disorderly on the actual function of PGA, i.e., to cloud the evaluation of RA disease activity. In Paper III, other comorbidities were not identified and, therefore, not adjusted for. Inflammatory vs. noninflammatory pain was not adjusted for either. Consequently, if believing that noninflammatory pain and generalized comorbidities such as depression can impact PGA, these unadjusted conditions cause a clear confound bias in the study in Paper III. However, the purpose of the study in Paper III was to illuminate the difference between the remission-assessing methods that incorporate and do not incorporate PGA and to show that there is a strong potential for confounding surrounding PGA (in addition to information bias, as mentioned above).

An additional possibility of confounding in Paper III is related to the usage of multivariant regression. Given that the models are not fully explainable, illustrated with an adjusted $R^2 \neq 1$ (linear regression) or Nagelkerke $R^2 \neq 1$ (logistic regression), residual confounding is possible. Overall, the adjusted R^2 and Nagelkerke R^2 explained approximately 80% of the models, indicating a relatively good model.

5.1.5 Representativeness

The validity of a study is another way of expressing the accuracy of the information obtained from the study [118]. Internal validity is the capacity to assume an association between the observed data and the studied population, while external validity is the degree to which the observed result is represented in other populations, i.e., generalizability [112, 113, 118].

The studies from this thesis used real-life data from ten ordinary rheumatology outpatient clinics (BioRheuma centers) spread across various geographical areas in Norway. It is assumed that the RA patients evaluated and treated at these clinics were consulted similarly to any other rheumatology outpatient clinic, including those not included in the studies.

An in-depth analysis of the estimated RA prevalence of the ten included BioRheuma centers can be found in Table 5, with a more detailed overview in Paper I (ref. Supplementary Table 2, Paper I). Across the ten years, the included BioRheuma centers' average crude prevalence was 0.3% (range 0.2-0.3%), with 0.5% as the highest at Sørlandet Hospital (Kristiansand). These prevalences were relatively similar to those roughly 30 years ago in Norway (Tromsø 1989, 0.4%; Tromsø 1994, 0.5%; Oslo 1994, 0.4%) [108, 109]. While the prevalence for Diakonhjemmet Hospital, Oslo, was higher 30 years ago compared to the data used in this thesis, their previous study only included patients up to 80 years old [109]. A recent study by Kerola et al. using the Norwegian Patient Registry estimated a point prevalence for 2017 in Norway (age ≥18 years) as 0.8% [119]. While the prevalence in the referenced study appears to align better with the worldwide prevalence of 0.5-1% [15, 120], it should be noted that the data from that study on the RA patients were not thoroughly cross-validated with the Norwegian Patient Registry [121].

When the annual registrations from this thesis were compared with the Norwegian Arthritis Registry (NorArthritis) [121], which collects its data mainly from the GTI system and has its data thoroughly cross-validated by the Norwegian Directorate of Health in conjunction with the Norwegian Patient Registry, a similar amount of RA patients was observed when the same BioRheuma centers were compared [122]. In 2019, slightly above nine thousand RA patients were registered from both the ten BioRheuma centers in this thesis and the same centers in the NorArthritis registry (shown in Table 5.1 in the 2019 NorArthritis Report) [122]. However, this comparison may be somewhat misleading as NorArthritis reports only the total included arthritis registrations and not the actual number of included RA patients. The reported number of RA from NorArthritis is obtained by recalculating the overall arthritis numbers using an average estimation provided elsewhere in the NorArthritis report, where around 45% of the arthritis registrations were reported as RA. In contrast, this thesis reports on the exact number of RA patients, albeit only if the patient was consulted during the given year. Also, despite this similar total number of registered RA patients in 2019, a detailed comparison of the same centers between the NorArthritis report (shown in Table 5.1 in the 2019 NorArthritis Report) and the thesis Paper I (ref. Supplementary Table 2, Paper I), shows there is a substantial discrepancy (only five centers have less than 20% discrepancy) when the centers are evaluated individually. The two most considerable differences among these two aforementioned tables were observed in Betanian Hospital, which was registered with 1005 arthritis patients in the NorArthritis report while 1052 RA patients in this thesis, and in St. Olav's University Hospital, which was registered with 2371 arthritis in NorArthritis report while 672 RA patients (far less than 45%) in this thesis. The underreported amount of RA patients

can be explained by a high non-annual consultation follow-up. On the other hand, the overreported amount of RA patients at individual BioRheuma centers from this thesis is likely related to a higher registration accuracy compared to the NorArthritis registry. This can be explained by the fact that this thesis uses all registered cases in the GTI, albeit anonymous, while the NorArthritis registry is formed based on patient consent. In other words, fewer registrations than those reported in the thesis can indicate underreporting numbers in the NorArthritis registry due to various reasons related to incomplete consent coverage. This assumption can be supported by the 2020 NorArthritis report, where the Betanien Hospital's arthritis registration increased to 1648 (shown in Table 5.1 in the 2020 NorArthritis Report) [123], while the Betanian Hospital's annual RA registries in this thesis remained around a thousand RA patients each year throughout the study period. A mismatch in the balance of different arthritis can also explain the discrepancy in registration between the mentioned tables among the individual centers. While there should be no reason for a difference in the prevalence among the different types of arthritis, some centers may have obtained more consent from some arthritis groups compared to others or have a higher focus on one particular type of arthritis, leading to a skewed balance and, consequently, misleading RA comparison.

To recapitulate, there appears to be a somewhat low external validity present in this thesis as the overall 0.3% and Sørlandet Hospital's 0.5% average crude prevalence (2010-2019) was lower than Norway's 0.8% point prevalence (2017). That said, the average prevalence of 0.3% is less discrepant compared to the estimated prevalence from Tromsø (1989, 1994) and Oslo (1994) at 0.4-0.5%. Since the GTI software was initially developed and implemented in concordance with Sørlandet Hospital, and the BioRheuma project was actualized at the hospital, it can explain why the center had a higher prevalence on average. The large difference in the overall inclusion of RA patients between the thesis and the study from Kerola et al. can also be a potential cause of the prevalence discrepancy. The included RA patients in Paper I in 2017 were three times lower (n = 9225 vs. 31885) than the included RA patient in the Norwegian Patient Registry in 2017 [67, 119]. Given the relative similarity in the number of registered RA patients between the thesis and the NorArthritis registry, as well as the slightly lower thesis prevalence compared to previously reported Norwegian prevalence, it can be inferred that this thesis has good external validity. To this extent, it can also be inferred that the overall increase in RA registration in this thesis is likely due to improvement in enrollment into the GTI and other factors that will be elaborated below rather than changes in the prevalence or incidence of RA. In fact, it appears that the incidence of RA is actually decreasing [124]. The RA incidence in this thesis was not provided due to difficulties in calculation and inaccuracy. Technically, the RA incidence could have been estimated by analyzing the anonymized original dataset and identifying cases where the visit date coincided with the verified diagnosis date, but unfortunately was not possible at this stage of the thesis. Even if possible, this method would not provide an accurate incidence as it would be calculated based on the annual RA registration within incomplete area coverage. The incidence accuracy is further

impeded without actual comparative verification of the RA diagnoses with other registries. The potential inaccuracy in the prevalence reported in this thesis can also be explained by its crude calculation (ref. Supplementary Table 2, Paper I) and incomplete area coverage.

While the registration of RA patients included in this thesis aligns with the registration from the 2019 NorArthritis report, it is worth noting that the NorArthritis registry reported only about 60% average coverage among the assessed 20 centers (shown in Table 5.2 in the 2019 NorArthritis Report) [122]. From the same table, when only the ten BioRheuma centers were evaluated, the average coverage area was 64%, which is somewhat lower in comparison to the crude calculation provided in Supplementary Table 2 in Paper I. The NorArthritis coverage percentage of the ten centers ranged from 44% at Diakonhjemmet Hospital to 84% at Haukeland University Hospital. Overall, this supports relatively good representativeness of the studied population in this thesis, especially at centers with high coverage area percentages and similar registrations, e.g., Lillehammer Hospital with 79% area coverage and near the same RA registration (1105 vs. 1068).

Nonetheless, all these assumptions and comparisons raise questions concerning the reasons for the discrepant coverage across the centers, the reduction in the numbers of RA patients at centers following a plateau of inclusion (ref. Supplementary Table 2, Paper I), the difference between the covered and uncovered RA patients, and the interpretation of the annual inclusion trend and its impact on the disease outcome presented in the thesis.

The discrepancies in coverage across BioRheuma centers can be explained by, but not limited to, the following factors. Rheumatologists were not mandated to enroll RA patients into the GTI system, only encouraged. Consequently, there may have been varying degrees of enthusiasm to comply with this request considering elements such as time constraints, stress levels, unfamiliarity with the GTI system, and the availability of a more familiar local digital health journal system. A possible indication of this can be seen in Supplementary Table 2 in Paper I, which shows a gradual increase in enrollments across different centers over time. As such, the aforementioned elements could all have played a role in the enrollment variability. It also stands to reason that not all RA patients in a given BioRheuma center's coverage area could be enrolled during the same year, e.g., due to logistical reasons or the RA patient did not require an annual follow-up schedule.

The assumption of non-annual follow-up tendency can also be observed in Supplementary Table 2 in Paper I, where there is a decreasing tendency in the number of registered RA patients at the centers that obtained a plateau of enrolled RA patients. Sørlandet Hospital has been reporting its GTI data since 2004 [55]. In association with this thesis, one can trace their annual registration trend over a span of 16 years, where the initial six years showcase an ascending trend, followed by a plateau, before observing a decrease from 2016. That said, no co-occurring trend was observed across the different BioRheuma centers. In fact, the accumulated number of RA patients across the centers was relatively stable during the last five years of the ten-year study period, despite a constant decrease in annual

consultation among many of the centers. The increase-plateau-decrease pattern is also explained in 5.1.4.1. This supplies the notion that rheumatologists followed many of their RA patients non-annually.

The standardized approach to treating RA patients during the study period in this thesis, similar to clinical practice elsewhere, was to give the right DMARD with the right dosage to the right RA patient in order to attain remission or low disease activity. Over time as better DMARDs were introduced, follow-up schedules were adjusted according to patient needs, flare-ups, and complications. Patients who managed to obtain and remain in target disease activity without difficulties were followed up with a need-based practice, hence not requiring annual consultation and resulting in fewer annual registrations into the GTI system. While a majority of non-annual registrations can be attributed to need-based follow-up consultations of RA patients with complex disease cases, other causes could have influenced the possibility of annual follow-ups. Staffing challenges linked to logistics and financial constraints, both at the hospital, municipal and national levels, were also substantial contributors.

It is difficult to assess the difference between the patients not covered in this thesis, and even though NorArthritis can provide an estimated coverage percentage, the similarity in coverage is only assumptive. As such, only general assumptions regarding the patient not covered by the GTI in this thesis can be made. One assumption is that those RA patients not included in the thesis analyses in the given area of the BioRheuma center were treated only with glucocorticoids or csDMARDs, or even without any RA medications. These RA patients could have been consulted by general practitioners or via private practicing rheumatologists (without GTI) instead of at the BioRheuma centers in the same area, which would result in fewer annual GTI entries. This assumption is supported by a trend in reducing methotrexate, overall csDMARDs, and glucocorticoid treatment proportion observed in Paper I (Table 4). It can also be suspected, especially based on the missing data reasoning elaborated above (5.1.1 Study Design and Data Collection), that those with established RA diseases and more in need of treatment were registered and followed using GTI. As such, as mentioned previously, the healthier RA patients not requiring DMARD treatment were likely not registered as frequent. There is also a likelihood that very complex and frail patients or those that struggled to self-reported their PROMs into the GTI were also omitted from the software, resulting in further skewness of actual RA patients.

Another issue concerning generalizability arises from the high b/tsDMARD treatment proportion of 42% on average across the study period (ref. Table 4, Paper I), which was substantially higher than the 27% reported in the Kerola et al. study in 2017 [119]. That said, this thesis includes a broader range of b/tsDMARDs, provides only registration from the latest consultation of the given year, and does not compare the treatment proportion with the Norwegian Prescription Database. Comparing the data on annual b/tsDMARD treatment proportion from this thesis with other national registries, such as the Norwegian Prescription Database, is very difficult as this database lacks the possibility to differentiate the b/tsDMARD prescription by indication. However, when the thesis b/tsDMARD treatment proportion was compared with the NorArthritis (shown in Figure 3.21 in the 2019

NorArthritis Report) [125], a similar trend was observed. Even though the b/tsDMARD treatment proportion was not evaluated across the different Norwegian geographical locations, the average of the ten BioRheuma centers was similar to that of Sørlandet Hospital (Paper III). Considering the lack of area coverage, given that this thesis has similar coverage to that of NorArthritis, the generalizability of the studies in this thesis is still suboptimal. It may reflect more on those treated explicitly with b/tsDMARD instead of the whole RA population. However, this matter is not directly of issue, as the objective of the thesis is closely related to the RA patient using b/tsDMARDs.

The question of internal validity investigates if the observed data can be linked with the assessed RA patients, meaning, are the observed results from the b/tsDMARD-treated RA patients applicable to the other RA patient in the studies? Also, can those included patients in Paper III also represent the whole patient group (without exclusion)?

In Paper I, a supplementary table was provided showing the comparison between the b/tsDMARD-treated RA patient and the non-b/tsDMARD-treated RA patients (ref. Supplementary Table 1, Paper I). The comparison shows minimal discrepancy except for a longer disease duration (14 vs. 9 years) and lower enabled workers (60% vs. 70%) for those treated with b/tsDMARDs. This can further add to the assumption that the b/tsDMARD-treated patients have a more established disease and are less likely to work because of the sequela of RA. Interestingly, these two groups had a minimal difference in disease activity, PGA, and pain.

The comparison between the included RA patients and the rest of the Sørlandet Hospital's RA population registered into the GTI (Paper III) shows a difference in the amount of DMARD administration. The difference can indicate that the remission rate assessment provided in the study does not have optimal internal validity. If all those excluded RA patients had complete data, albeit receiving less treatment, the overall remission rate across the different remission-assessing methods would perhaps be different. That said, looking at the tables between excluded vs. included data for Paper III, there is very little difference in the actual value for the various variables used to assess the different remission-assessing methods. Hence, the possible suboptimal internal validity appears only a minor concern in this case.

In Paper I, the average cost per b/tsDMARD per patient is calculated for each user group without disclosing the confidential offers. However, this average cost is calculated using each year's accumulated costs, undistinguishing the highest vs. the lowest offers. In other words, the cost per b/tsDMARD could be overestimated for those who provided the least expensive offer and underestimated for those who provided the most expensive offers. The internal validity can be questioned regarding whether the estimated average cost in Paper I represents the actual cost and to which degree. Figure 5 and Figure 6 were developed to resolve this matter. Figure 5 shows how the average cost per individual b/tsDMARD is calculated using both actual and estimated offers (i.e., the cost per b/tsDMARD per patient provided in Paper I). This figure also reports various discrepancies

between the average actual cost and the average estimated cost for most of the b/tsDMARDs. While multiple b/tsDMARD across the different user groups are either overestimated or underestimated, many are also quite similar. A large gap indicates a low internal validity for the cost of selected b/tsDMARD in the specific user group compared to what was reported in Paper I. Among the 13 b/tsDMARDs, one b/tsDMARD for naïve users, four b/tsDMARDs for non-naïve users, and four b/tsDMARDs for current users appear to have low internal validity. This reduced internal validity regarding the cost is expected when the tender offers cannot be disclosed. Figure 6 illustrates how the average of four b/tsDMARDs was comparable with the average of the 13 b/tsDMARD across ten, indicating a good internal validity of the presented average cost in Paper I. However, it is important to highlight that the average treatment proportion for the selected four b/tsDMARDs was approximately half (54%) compared to the treatment proportion for the entire set of 13 b/tsDMARDs across the ten-year period.

Incomplete area coverage, annual variability in the inclusion of RA patients, and the absence of longitudinal follow-ups are limitations of Paper I (and to a degree Paper II and III) that potentially make the inference of the reported cost outcomes challenging. RA patients who did not require and did not receive an annual follow-up did not have any registered data for the given year. Thus, the cost outcome in Paper I may be more lenient to represent patients who need an annual consultation, such as those needing care or experiencing treatment difficulties. Consequently, for RA patients who did not require a consultation during the assessed year, the cost spent on their b/tsDMARDs was not observed or included in the presented calculation. This limitation may also have impacted the actual b/tsDMARD treatment proportion explained in Paper II, underrepresenting the b/tsDMARDs that were effective enough to keep the RA patient in sustained remission with good satisfaction, negating the need for annual follow-up. It is also worth pointing out that it may be erroneous to assume sustained remission and good patient satisfaction alone can negate annual follow-ups. Various biopsychosocial (and cultural) factors beyond the GTI variables could influence the patient's subjective need to attend annual follow-ups despite having clinical outcomes that are considered "ideal". Nevertheless, overall these factors undermine the validity of the thesis.

Another limitation of Paper I, which also underscores the issues of representativeness related to the study's cross-sectional nature, influences the inference of the outcome data about the remission rate. Although Paper I report an increase in DAS28 remission rates among b/tsDMARD-treated patients from 42% in 2010 to 67% in 2019, it is crucial to interpret these results carefully. Similarly, as mentioned above, RA patients who respond well to treatment and achieve sustained remission relatively quickly may not be registered annually into the GTI system within the given year. Consequently, the reported data on remission outcome primarily represent the RA population portion encompassed by the GTI system that necessitates annual follow-up and less of those not covered by the GTI system or those covered that do not require regular follow-up (i.e., stable health status). A closer look at the 2019 NorArthritis data on DAS28 (shown in Figure 3.17 in the 2019 NorArthritis Report) [122], which in

this case also uses data from the last follow-up but from 20 centers instead of 10, shows a similar remission rate as in Paper I. This suggests good representativeness between the thesis data and the NorArthritis registry (and by extension the Norwegian Patient Registry) and suggests good external validity, albeit it also supports the notion that the assessed outcome data on remission is collected from a cohort that required consultation that year. Conducting regression analyses where various variables (e.g., age, sex, disease duration, and the number of included RA patients) are tested to explain the DAS28 remission would be a good supplement, albeit it would also entail comprehensive data analysis. Such an endeavor would not just fall outside the scope of Paper I; it would likely necessitate a separate study. That said, a variant of this type of regression analysis was performed in Paper III, albeit specifically of the cohort of 2019 from Sørlandet Hospital (ref. Supplementary Table 1, Paper III).

Another validity issue, and one of the more notable biases in selecting RA patients, stems from the increased attention given to RA patients with more complex health conditions. As pointed out previously, difficult-to-treat RA patients receive more frequent follow-ups (annual GTI registration) compared to healthier RA patients, which in turn impacts the credibility and validity of the reported cross-sectional disease outcome data. Although the improvements in disease activity outcomes (with relatively stable PROMs) presented in this thesis for the RA patients are noteworthy, they may not comprehensively represent the entire RA population as those RA patients with more favorable health status are being underrepresented. However, this simultaneously may offer a more precise picture of the improved trend in health outcomes among RA patients with health conditions requiring more frequent follow-ups and b/tsDMARD treatment. One can argue against this assumption by pointing out that the disease activity data for those RA patients who did not receive b/tsDMARD treatment are similarly well-regulated compared to those who received b/tsDMARD (ref. Supplementary Table 1, Paper I). However, it is crucial to remember that rheumatologists aim to use the safest treatment possible to obtain target disease activity. As such, rheumatologists would not prescribe b/tsDMARDs to easily treatable RA patients. Therefore, those patients not requiring b/tsDMARDs likely achieved optimal disease activity without more potent medication in contrast to the b/tsDMARD patient.

Despite these limitations and drawbacks in the validity, the thesis analyses present an essential assessment of the usage of b/tsDMARDs in real-life rheumatology outpatient clinics in Norway. These limitations, which derive primarily from the disparity between the actual outpatient clinical practice and ideal research design, highlight the challenges, complexities, and barriers that arise when translating research methodologies into real-life clinical settings. Instead of viewing this as the disadvantage of the thesis, it should be acknowledged as a realistic depiction of healthcare practices and clinical decisions, emphasizing the rheumatologist's clinical discretion on the frequency of patient follow-ups, data collection, and treatment. In light of the mentioned limitations and drawbacks, this thesis is still believed to retain considerable external and internal validity. The thesis outcome, despite the aforementioned

biases and methodological limitations, can be used to underscore the importance of real-life data in shaping future research and guiding healthcare policy decisions.

5.2 DISCUSSION OF RESULTS AND COMPARISON WITH OTHER STUDIES

5.2.1 Challenges of a National Tender System Upon Access to Medicine

Paper I reports that the average b/tsDMARD cost per current user was about 13 thousand EUR in 2010 and around seven thousand EUR in 2019. Similarly, it was 13 thousand and three thousand for naïve users and 13 thousand and five thousand for non-naïve users. Depending on the user group, this resulted in a 50% to 75% cost reduction, with an even more prominent reduction when accounting for the increased value of the Norwegian currency over time. In Figure 6 of this thesis, the findings on the average cost per b/tsDMARD per patient per year among current users are compared using the exact calculation of only four b/tsDMARDs (adalimumab, etanercept, certolizumab pegol, and etanercept SB4). Intriguingly, even though the four b/tsDMARDs cover half of the 13 b/tsDMARDs in registration amount, the reported average cost from the four b/tsDMARDs was similar to those reported in Paper I. When the same four b/tsDMARDs were compared where one group was calculated based on the maximum cost and the other group based on tender-reduced cost; it was possible to observe that the tender-reduced cost was not likely due to reduction in maximum cost. Figure 7 of this thesis illustrates how the total cost savings achieved by using the reduced cost via the tendering instead of the maximum cost resulted in a savings of about 81 million EUR (715 million NOK) across the ten years for only these four drugs. Figure 7 also shows how the saving per average b/tsDMARD per patient per year gradually improved across the ten-year period.

Paper I also reported a reduction in disease activity and an increase in remission rate in all user groups during the same period. However, this observation is discussable since only one disease activity measure was presented, not all patients were included across Norway, there was a considerably high increase in the included patient over time, and there was a higher b/tsDMARD treatment percentage than those registered elsewhere in Norway [119]. Simultaneously with the cost reduction, there was also minimal observed change among the PROM variables and the work capabilities of the RA patients. Furthermore, Paper I (ref. Supplementary Table I, Paper I) shows that the difference in disease activity between the assessed b/tsDMARD users and the non-b/tsDMARD users was quite similar. It is worth pointing out that these findings can be influenced by the various limitations presented in the 5.1 Methodological Consideration section.

In summary, the study's concrete finding in Paper I shows that there was about a 50% to 75% cost reduction per b/tsDMARD per patient across the different user groups, and it occurred without worsened disease outcomes, PROMs, or work capability. This observation was seen simultaneously during a period when a national tender system was implemented strategically to lower the cost of costly

b/tsDMARDs. While these two events appear to be related, the causality between the reduced b/tsDMARDs cost and the Norwegian pharmaceutical tender system remains assumptive.

Other mechanisms could also have impacted the cost reduction of b/tsDMARDs, either in conjunction with the competition stimulated by the pharmaceutical tendering or independently. These include: (1) The expiration of patents for reference bDMARDs that allowed the introduction of biosimilars into the market. A biosimilar's overall expenditure is much lower than that of reference agents; as such, making a profit from lowering the biosimilar's market cost is a more achievable task [100, 103]). (2) The possibility of a mandatory non-medical switch to a less costly alternative of the same substances, such as between reference agent and biosimilar or between biosimilars. The NOR-SWITCH study and DANBIO registry exemplify how switching patients from reference agents to the less costly biosimilar alternative can result in positive outcomes [104-107].

Regardless of the assumed impact of the tender system upon the cost reduction, another set of developments simultaneously occurred from the treatment proportion perspective, benefiting the providers of b/tsDMARD. Paper II describes how providing a reasonable offer could be linked with increased b/tsDMARD usage that year. In the Paper II study, it was observed that nine out of ten pharmaceutical tenders were both tender-winning drugs and either the highest or second-highest in treatment proportion among naïve users, seven out of ten for non-naïve users, and two out of ten for current users. Hence, not only would the payer benefit from the cost reduction via competing offers, but the providers could also earn more by selling more.

However, is the increased acquisition with a lower cost a cost-effective outcome for pharmaceutical providers? It would be complicated to answer this question accurately without disclosing the confidential cost and without knowing the exact cost of producing each given drug during each year (based on the cost of developing and producing the drugs). Instead, a different overview was constructed using the outcome from both Papers I and II (Figure 5).

In Figure 5, several interesting observations are present. As mentioned in section 5.1.5., there is a distinct difference between the average actual and estimated costs for some of the b/tsDMARDs in some user subgroups. The large gap can indicate low internal validity, but it also illustrates that the cost reduction is even lower among the best offers. Figure 5 also illustrates the average amount of EUR the Norwegian government has used on each of the different b/tsDMARDs. High TRS with a high expenditure means that the government spent a substantial amount of EUR on b/tsDMARDs with minimal cost-reducing offers. High TRS with high expenditure can be exemplified with the adalimumab reference among current users or tocilizumab among non-naïve users. In contrast, the government spent wisely on those with high expenditure and low TRS, e.g., etanercept SB4.

Some of the investments are difficult to assess, e.g., the b/tsDMARDs with TRS 4-5 and very high expenditure. Etanercept reference for naïve and current users and certolizumab pegol for naïve users are among such examples. The Norwegian government gave about 8.5 million EUR on average

per year for etanercept reference to treat (average tender rank 4-5) an average of 734 Norwegian RA per year. This assumption can also be seen from a different perspective. In the early years of the studied period, drugs such as etanercept reference and certolizumab pegol were in high demand and provided reasonable offers during those years, but the cost was still high compared to the cost in 2019. This may indicate that the Norwegian government spent a lot in the early years on these two drugs compared to the expenditure of a similar proportion in 2019. It is also important to recognize that the early years of Norwegian pharmaceutical tendering transpired with limited drug options and without the introduction of biosimilars.

It can be assumed that the supplier has the best profit when the expenditure is high with a high TRS. This is to say that the pharmaceutical company's cost-effective strategy is the Norwegian government's non-cost-effective investments (i.e., high expenditure and high TRS). Such examples may occur when a pharmaceutical company acquires a large group of loyal users by offering them a low-cost and reliable treatment, followed by high costs over consecutive years. This example was observed for certolizumab pegol (Paper II), where certolizumab pegol was provided with the best cost offers between 2013 and 2016 and above rank six offers the next three years. One can also argue that this pattern for certolizumab pegol transpired because the demand for lowering the drug's cost was cost-ineffective for the pharmaceutical company, resulting in their new strategy. Nevertheless, the outcome remained the same—the Norwegian government spent a large amount of money on loyal certolizumab pegol users between 2017-2019 to pay for their above rank six offers.

The sustainability of the ever-changing pharmaceutical market has led to discussions on regulatory adjustments [126]. Suggested initiatives aim to guarantee an uninterrupted supply of reference and biosimilar drugs through potential changes to pharmacy laws that, e.g., allow the interchange of biological pharmaceuticals [126]. These adjustments are intended to improve the use of biosimilar medicines, maintain market equilibrium, and uphold patient safety. This highlights the intricate considerations needed to balance cost-effectiveness and the sustained availability of medications. The author of this thesis believes that an effective tender system needs to adjust for both the payer and the supplier because if the procurement is too expensive, the payer will not procure, and the suppliers will not have a market to sell their products. Simultaneously, the suppliers will withdraw from the market if the cost-effectivity is too weak, a tactic that appears only beneficial for the payer in the short term. With this reasoning, both scenarios are disadvantageous for both parties, and the best outcome is to find a balance where both sides can benefit (nearly) equally.

Therefore, it is crucial for the NHPT and any other governing body attempting to regulate pharmaceutical tendering to recognize that even though there are reports stating pharmaceutical tendering can result in cost-effective outcomes; these will not be long-lasting if the potential pitfalls of cost-effectivity imbalance are not addressed adequately [67, 86, 127]. In Paper II, one can already observe some pharmaceutical companies withdrawing or providing no offers. In a scenario where the

market becomes unfavorable for all suppliers except those providing biosimilars, it can be assumed that the cost of biosimilars will start rising as there will be no new competitors to challenge the costs [127]. These possible events may decrease the availability, affordability, and development of novel medical drugs [128]. One possible countermeasure that is considered to be implemented by the NHPT is to apply a maximum lower-end cost offer during the tenders. This strategy of restricting the competition may keep more pharmaceutical companies in the competition, which in turn may increase the availability of drugs but at the cost of optimal affordability. While this strategy is still speculative in Norway, the Swedish government has already taken a stand on the matter [129]. The Swedish government considers the approach of implementing a maximum lower-end cost against the law and the principle of equal treatment [129].

5.2.2 The Use of Clinical Guidelines and Subjective Interpretation

The overarching RA guidelines advise treating RA patients until a target of remission (if possible) is attained [34]. However, the American, European, and national guidelines worldwide do not unanimously agree on which method to assess the disease activity and remission status [38]. The most reported methods include DAS28(3), DAS28(4), CDAI, SDAI, and Boolean remission criteria (i.e., 4-variable remission), albeit not 3-variable remission [38]. Paper III shows how the different recommended remission-assessing methods (including 3-variable remission) are discordant with each other and that attaining remission depends on the assessment method. Similarly, other studies have also reported discrepancies in remission and disease activity when using different measuring methods [39-41, 130-132].

In simpler terms, difficult-to-achieve (i.e., stringent) measuring methods result in fewer RA patients in remission, while easy-to-achieve (i.e., liberal) measuring methods result in more RA patients in remission—compared to each other. Both types can be erroneous, where misestimation can result in mistreatment. These measuring methods either omit patient-subjective perception of disease activity (i.e., PGA) completely (e.g., 3-variable remission, DAS28(3)), reduce the impact of PGA (e.g., DAS28(4)), or count PGA equal to the other included variables (e.g., 4-variable remission, CDAI, SDAI). An overview of the formula and the variables included in these measuring methods are shown in Tables 3 and 4. Those methods with reduced impact of PGA have also made it possible to attain remission status while simultaneously reporting multiple swollen or tender joints, which in turn has been linked to radiographic joint damage [133]. In contrast, those methods focusing equally on PGA as other variables are more likely to be influenced by other noninflammatory conditions since increased PGA is linked to depression, noninflammatory pain, and other conditions unrelated to RA's biological disease process [114-117, 134, 135]. Furthermore, since PGA lacks a homogenous formulation in how it is questioned, the RA patients are invited to respond based on their own interpretations [114, 136, 137].

In Paper III, the study reports a variation of approximately 40% in remission rate between 4-variable remission and 3-variable remission (23% vs. 65%). The 3-variable remission is the equivalent of the most stringent remission-assessing criteria, albeit without the need to score ≤10 (out of 100) on PGA. Hence, 65% out of 502 Norwegian RA patients had ≤1 tender joint, ≤1 swollen joint, ≤10 in CRP (mg/L), and a >10 PGA. However, if the same 502 patients were re-assessed, where the requirement was ≤10 PGA, only 23% would fulfill the criteria. Meaning approximately 40% could not attain the treatment target (i.e., remission) because they scored a >10 PGA while simultaneously fulfilling the clinical remission criteria. Many other studies have reported this variation, albeit to varying degrees [130, 138, 139]. The considerably higher remission rate in nearly all remission-assessing methods among the RA patient from Sørlandet Hospital (2019) can be explained by their high usage of b/tsDMARDs and low disease activity values. While this may be good for RA patients in Norway, it questions the study's generalizability. One-variable cut-offs can be an additional way of illustrating the discordance of PGA compared to the clinical variables, where the percentage achieving the ≤1 TJC28, ≤1 SJC28, and ≤10 CRP ranged from 74% to 86% while only 23% achieved ≤10 PGA (Paper III). Paper III also shows how the PGA-lenient remission-assessing methods are frequently associated with PROMs, while the non-PGA-lenient remission-assessing methods are not associated (ref. Supplementary Table 1, Paper III).

The reasoning behind the inclusion of PGA in assessing disease activity and remission (in 4-variable, CDAI, SDAI) stems from the documented effect showing it to be effective in predicting radiographic outcome and its effect as a safeguard against symptoms in the joints of ankles and feet (not included in any of the recommended measuring methods) [35]. Later, other studies have documented that only swollen joints and acute phase reactants (CRP or ESR) are adequate to predict radiographic outcomes and synovitis [133, 140-143]. Two recent studies, by Sundlisæter et al. and by Brites et al., did not observe any significant alternation in inflammation on imaging when comparing 4-variable remission, 3-variable remission, and those who failed to attain 4-variable remission but achieved 3-variable remission [144, 145]. Nowadays, modern imaging techniques are practical tools to assess subclinical signs of inflammation and, as such, potentially effective in evaluating true remission in RA [146-149]. In light of all this information, and from the very recent validation study by Studenic et al. (2022), the collaboration of ACR and EULAR has agreed to change the PGA cut-off in Boolean Remission Criteria from ≤1 to ≤2 (≤10 to ≤20) [150, 151]. Nevertheless, following clinical guidelines that promote PGA without careful consideration may still make room for misestimation, resulting in the possibility of irrational use (i.e., misuse) of b/tsDMARDs by administrating them for non-inflammatory causes. In order to avoid the irrational use of b/tsDMARDs, the author of this thesis agrees with Inanc et al. (2014) in the suggestion to assess (and treat) RA patients who fail to attain 4-variable remission for underlying conditions, e.g., fatigue, anxiety, fibromyalgia, and depression that can cause false non-remission status [65].

5.2.3 Perception of Pain and the Patient-Reported Outcome

Since culture may vary across and within nations and change with time, the perceptions of pain and how to address it can change alongside it. According to Morris's description, pain is always historical, constantly reshaped by a particular time, place, culture, and the individual psyche [152]. At the end of the 18th century, Western culture gradually shifted out of the *Age of Pain* and into a period of developing analgesics, a period where pain was no longer just a part of life but an absurdity that should be eased [153]. In contrast, in the early 19th century, it was unethical to attempt to alleviate pain if it had a potential risk to life [154]. Now, and since the arrival of constant improvement in analgesia and research related to pain, we have become more liberal in treating pain with potent pharmaceuticals (i.e., stating pain is a vital sign [155]) under various risk-evaluated scenarios [152-154]. An exemplary scenario of our newfound liberality to the unhindered distribution of very potent pharmaceutical analgesics has resulted in an opioid crisis in the USA, Canada [156-158], and (to a much lesser degree) in European countries [159, 160]. Nearly all pharmaceutical analgesic opioid consumption is accounted for in the developed countries of North America and Europe [161]. Then the question can be asked; why are some countries overly reliant on pain medication while others still view pain as a part of life and consume much less (potent) pain medication? The answer is too complex to address in this thesis, albeit it likely depends on the national economy and culture [162]. If the country cannot afford potent medications, the government and culture may be less inclined to fixate on what they cannot have and instead accept what is possible (e.g., ibuprofen, paracetamol, codeine, or even non-pharmaceuticals for late-stage cancers) [162].

How does this then translate to RA remission? Remission, so far explained, is a set of cut-offs in variables used in various remission-assessing methods. However, RA patients do not necessarily agree with that definition. For them, as mentioned in the introduction, the absence of normality is the absence of remission. Hence, to attain remission, they need to attain the feeling of normality [56]. Such normality is often impaired by chronic fatigue, chronic pain, and decreased autonomy of self-management of own disease [57, 58].

Many studies have reported an association between PGA and pain [65, 114, 163-166], as have the single center study in Paper III with univariant and multivariant linear regression. In Paper I (ref. Supplementary Table 1, Paper I), the average pain and PGA for the ten years of all included patients from all included BioRheuma centers were VAS 34 (range 32-36) and VAS 33 (range 33-35), respectively (despite low disease activity). These VAS values for pain and PGA are similar to those analyzed in Paper III from the single center, indicating that a similar association between pain and PGA may occur in Norway's other included geographical areas. Also, in the same table, the difference in PROMs (PGA, pain, fatigue, MHAQ, and morning stiffness) across the ten years and between the b/tsDMARD-treated group and non-b/tsDMARD-treated group were minimal despite an approximate 40% b/tsDMARD treatment proportion in the former group (ref. Supplementary Table 1, Paper I). That

said, the clinical variables, including DAS28, were also indistinguishable between the two treatment groups. The relatively high and unchanging PROM values and work inability percentage, as well as the high use of b/tsDMARDs despite the high remission rate among the cohort of this thesis, can be explained by the possibility of RA patients' absence of normality and subjective feeling of not being in remission.

The pathogenesis of RA is known to cause irreversible joint damage, often resulting in noninflammatory pain and disability; as such, it becomes difficult to attain the requirement of remission status set by RA patients [59, 60]. Since most guidelines incorporate the RA patients' self-evaluation, and when RA patients are inquired about their general health or disease activity-specific health (asked interchangeably in PGA), it is not unreasonable to consider that pain (physical or emotional) will affect their answer.

Suppose pain perception can depend on the patient's country and culture, particularly if the country has a high usage of potent analgesics and the mentality that all pain should be alleviated or, in contrast, if the country has a low economy and believes pain is part of living. Wouldn't self-reports of PGA, which is strongly associated with pain, deviate from PGA's assumed association with RA's actual disease activity processes vary between country and culture? Then, is following treatment recommendations from generalized clinical guidelines, independent of country and culture, aligned with promoting rational use of medication when we translate pain or the different experience of illness into the same unanimous disease activity status and cut-off values? Is the WHO's description of rational use of medication applied in this case: to receive medications *appropriate to their clinical needs*, in *doses* that meet their *own individual requirements*, for an adequate period of time, and at the *lowest cost to them and their community* [11]? Is it rational use of treatment when clinical objectivity is obscured by potentially unrelated subjectivity? Is it rational to use b/tsDMARDs or csDMARDs when administrated as a response to change in PGA (with or without the presence of objective inflammatory signs) without inquiring about the biopsychosocial aspect of their changed PGA?

The author of this thesis thinks that clinical disease activity should be oriented only around objective clinical variables that measure biological disease activity processes, while the subjective variables should be applied to understand the disease impact from a holistic point of view. These two aspects should occur interchangeably during the consultation with the physician, where both sides count equally when attempting to treat the whole patient. If PGA (or any other PROM) should be elevated, regardless of the presence or absence of the objective variables, a biopsychosocial care approach should be integrated to supplement the biomedical care approach by the treating physician, rheumatologist, or healthcare provider. Distinguishing between the subjective and objective variables in this manner, especially when there is a growing need for standardization, may reduce the error in clinical assessment and, consequently, improve the rational use of medication. However, this will likely require more time from the examining healthcare provider. The question remains whether the time spent on correcting the

errors of standardization is more or less health- and cost-beneficial compared to dedicating the time needed to address both patients' biomedical and biopsychosocial issues in the long run.

5.2.3 Work Capabilities in Rheumatoid Arthritis

Increased work disability and early retirement among the adult (65 years and younger) RA population, along with RA's economic consequences and deterioration of quality of life, are deemed crucial burdens related to the RA disease [24, 25, 167]. In Paper I (ref. Supplementary Table 1, Paper I), the only observable differences between the b/tsDMARD group and the non-b/tsDMARD group were the disease duration (14 years vs. 8 years) and the enabled worker frequency (60% vs. 70%). The disease duration of RA appears to be linked to the need to receive b/tsDMARD and the inability to work. Perhaps it is because those with more severe or long-lasting cases of RA receive more potent treatment, i.e., b/tsDMARDs. These two factors are also perhaps related to the number of previously attempted b/tsDMARDs (e.g., due to difficult-to-treat RA), where there is an observable difference between the naïve and non-naïve group (ref. Table 2 and 3, Paper I); approximately 6 years vs. 12 years of disease duration, and approximately 70% vs. 60% in enabled workers.

Several observations were drawn from a worldwide multinational study on work disability among RA patients (QUEST-RA) [167]. The average work disability from the 32 evaluated countries between 2005 to 2009 was 53% (n = 5493) [167]. Norway's work capability was not assessed in the QUEST-RA study. While the criteria for disabled and enabled workers were likely different, the average work disability percentage in the study from Paper I was 35% for all BioRheuma RA patients (ref. Supplementary Table 1, Paper I). However, clear distinctions could be observed when the countries were stratified based on high and low income [167]. On average, in low-income countries (LICs) compared to HICs, RA patients had higher disease activity, a higher score on clinical variables, and a higher score on PROMs (pain 47 vs. 32, PGA 48 vs. 32, fatigue 50 vs. 38; all on a VAS 0-100). The LICs were treated with a substantially lower amount of bDMARDs compared to HICs (9% vs. 31%), they had a higher percentage of erosive joints (67% vs. 59%), and similar disease duration (11 years vs. 11 years). However, despite the poorer disease outcome among RA patients in LICs, they had a relatively similar work disability percentage (56%) compared to the HICs (48%) [167]. QUEST-RA study adds to the notion that the b/tsDMARDs have a positive impact in improving disease activity and PROMs, albeit the country's income; hence the RA patient's economic health support can potentially dictate if the RA patients can afford to reduce their work capacity [34, 54, 167]. Consequently, the LICs' affordability to acquire b/tsDMARDs for their RA patients appears to result in high disease activity and low remission rate [81-83, 167].

One can therefore argue that an effective cost-reducing strategy, such as a well-established and regulated tender system for b/tsDMARDs, is even more required in LIC (or LMIC). These countries do not just struggle to pay for the b/tsDMARDs; they also struggle to provide economic support for RA

patients with higher disease activity. This may, in turn, push the RA patients to continue working despite the high PROM and disease activity. Affordability and accessibility to b/tsDMARDs will likely not provide economical health support to RA patients from LICs, but at least they will not be required to work while having high inflammation or developing erosive joints.

6. CONCLUSION AND FUTURE ASPECTS

6.1 ANSWER TO RESEARCH QUESTION

The specific research questions are addressed in 2.0 General Aims and Specific Research Questions are answered below.

In Norway, during a 10-year period (2010 to 2019) with a pharmaceutical tender system in effect

- The change in total and the average cost per b/tsDMARD per current RA patient was 25.6 to 28.9 (39.6 as the highest) million EUR and 13.1 to 6.9 thousand EUR (47% cost reduction), respectively (**Paper I**).
- The change in total and the average cost per b/tsDMARD per naïve RA patient was 4.9 to 1.3 (4.9 as the highest) million EUR and 13.0 to 3.2 thousand EUR (75% cost reduction), respectively (**Paper I**).
- The change in total and the average cost per b/tsDMARD per non-naïve RA patient was 5.9 to 4.9 (9.6 as the highest) million EUR for total and 12.9 to 4.6 thousand EUR (64% cost reduction), respectively (**Paper I**).
- When using DAS28, the remission rate increased significantly ($p < 0.05$) from 42% in 2010 to 67% in 2019 among current RA patients treated with b/tsDMARDs. The mean remission rate during the 2010-2019 period was 56% for the same patients (**Paper I**).
- Among current RA patients treated with b/tsDMARDs, there was a non-significant VAS change from 33, 32, and 38 in 2010 to 32, 32, and 40 in 2019 for PGA, pain, and fatigue, respectively. The mean PGA, pain, and fatigue during the 2010-2019 period were 33, 33, and 39 in VAS, respectively (**Paper I**).
- Among current RA patients treated with b/tsDMARDs, the enabled worker percentage changed non-significantly from 63% in 2010 to 59% in 2019, with a mean of 59% during the ten years (**Paper I**).
- The tender-winning drug also had the highest or second-highest treatment proportion of all b/tsDMARDs in nine out of ten pharmaceutical tenders for naïve users, seven out of ten pharmaceutical tenders for non-naïve users, and twice out of ten pharmaceutical tenders for current users (**Paper II**).

- The tender-winning drug was an iv b/tsDMARD in eight out of ten pharmaceutical tenders while only acquiring 30%, 49%, and 40% on average of the whole b/tsDMARD treatment proportion for naïve, non-naïve, and current users (**Paper II**).
- The tender-winning drug was a biosimilar b/tsDMARD in five out of six pharmaceutical tenders (between 2014 to 2019), while the average biosimilar treatment proportion of all b/tsDMARDs during those six years was 42% for naïve b/tsDMARD users, 42% for non-naïve users, and 23% for current users (**Paper II**).

In Norway, in 2019, from the same RA (n = 502) outpatient clinic cohort (Sørlandet Hospital, Kristiansand)

- There was a remission rate of 23%, 37%, 38%, 65%, 67%, and 73% for 4-variable remission (Boolean remission), CDAI, SDAI, 3-variable remission, DAS28(4) and DAS28(3), respectively. The 4-variable remission, CDAI, and SDAI are equally reliant on PGA as the other variable in the calculation. The 3-variable remission and DAS28(3) do not include PGA, and DAS28(4) includes PGA but diminishes its effect in the algorithm calculation compared to the other variables (**Paper III**).
- Of all RA-related variables, pain had the strongest association (standardized coefficient $\beta = 0.7$, $p < 0.001$) with PGA (**Paper III**).
- Of all RA-related variables, pain, fatigue, and morning stiffness were substantially associated with the remission-assessing methods incorporating PGA. No PROMs were associated with the remission-assessing methods that did not include PGA (**Paper III**).

6.2 CLINICAL IMPLICATION AND FUTURE RESEARCH

The UN's call to action (Decade of Action) has prompted the WHO to advocate their most pressing health-related challenges that should be addressed to actualize the 17 SDGs. How to expand access to medicines is among these challenges and the primary target of this thesis. Since this access is closely related to the availability and affordability of medications, the WHO and the EU have vouched for implementing pharmaceutical tendering as a cost-reducing strategy. While numerous countries have incorporated tender systems in various formats to regulate the expenditure of expensive and essential medications (and other medical products), this thesis analyzed 13 different b/tsDMARDs used to treat RA in Norway during a pharmaceutical tender system between 2010 and 2019. In Papers I and II, the economic outcome and the usage of these 13 b/tsDMARDs are reported.

After ten years under the influence of a pharmaceutical tender system in Norway, the average cost per b/tsDMARD per RA patient decreased between 50% to 75% (depending on naïve, non-naïve or current users) without observed worsening of disease activity, decrease in PROM variables, or an impact on work capability. Simultaneously, the best annual offers were observed to have the highest or second-highest treatment proportion of new b/tsDMARD prescriptions. Many other mechanisms

occurred behind the scene that potentially played a role in this observation, namely the economic possibility of a high b/tsDMARD treatment proportion, the patent expiration of reference agents and the introduction of biosimilars, the possibility of conducting a mandatory cost-saving non-medical switch between reference agents and their corresponding biosimilar, and the intrinsic competition between subcutaneous and intravenous b/tsDMARDs.

RA is a chronic joint disease with various symptoms, burdens, and economic challenges for the patient and society. Cost reduction of effective treatment is a great way to provide affordability and availability of b/tsDMARD, albeit it is also necessary to distribute and administrate the b/tsDMARDs rationally. The irrational use of medication can be seen as a misuse of the acquired access to medication. Similarly, as treating a viral infection with antibiotics is regarded as irrational, the use of potent anti-inflammatory medication to treat noninflammatory causes is questioned in this thesis. Especially when these drugs, i.e., b/tsDMARDs, are costly and can lead to serious adverse events.

The author of this thesis, through Paper III, supports the WHO's suggestion for the rational use of pharmaceuticals and their recommendation to use clinical guidelines to achieve it. However, Paper III also points out that guidelines may not always be adaptable to everyone, and elements may lead to misinterpretation. This may become crucial if the misinterpretation can lead to potentially fatal errors when treating using costly, potent drugs. Hence, overly relying on the guidelines without considering the potential for deviation can lead to irrational treatment use. The discrepancy and doubt surrounding clinical guidelines for RA lie in their various ways of assessing remission and using patient subjectivity to dictate clinical objectivity. While translating the patients' own experiences of illness into biological disease processes through the medical theoretical lens is a custom practiced by physicians, the problem may lie in the eagerness for standardization and generalization of these translations. As described previously, the translation that increased PGA is related to a higher disease activity may be misguided, as many confounding factors can contribute to an elevated PGA despite RA being in clinical (objective) remission. In addition, this translation is likely not adjusted for the difference in self-evaluation of the RA patients based on their country of origin (HIC vs. LIC) or their cultural differences.

The pharmaceutical tender system is showing great promise (if potential pitfalls are avoided) and might treat more RA patients with potent b/tsDMARDs (or allocate the saved expenditures elsewhere in the healthcare system), albeit a long road with further research lies ahead. Particularly the need to compare the different pharmaceutical tenders in different countries and stratify them based on income and b/tsDMARD usage.

The current RA guidelines will remain suboptimal until a unanimous remission (disease activity) assessment method is implemented. Preferably one that utilizes today's modern imaging capability and omits subjective interpretations when treating using DMARDs but simultaneously addresses patient self-evaluation when evaluating and treating the RA patient holistically.

While this thesis and the corresponding articles are conducted using anonymized data, the author is fascinated by the potential results one could find if the same data were analyzed without anonymization. Such data could provide a more in-depth understanding of the PROMs upon switching and by following the previous usage and causalities related to each specific b/tsDMARD switch. One could also assess which b/tsDMARD would provide the best disease outcome. If cost confidentiality was not of issue, one could also report on which b/tsDMARD at which cost could provide the best disease outcome. Hence, one could demonstrate cost analysis using cost per QALY between the different b/tsDMARDs. This way, one could paint a much better picture of the Norwegian pharmaceutical tender system's advantages or perhaps disadvantages. Similar studies could also be conducted for other chronic inflammatory joint diseases and diseases from other medical disciplines that use monoclonal antibodies (biologics and biosimilars).

Building on this foundation, potential future research areas could include:

- **International comparative analysis of pharmaceutical tender systems:** Given the success of the pharmaceutical tender system in reducing costs and maintaining effectiveness in Norway, future research could compare the implementation and outcomes of pharmaceutical tender systems in different countries. This comparison could be further stratified based on income level and b/tsDMARD usage, providing a comprehensive picture of how pharmaceutical tenders work worldwide.
- **Advanced cost analysis using cost per QALY and PPP**: Future research could consider a sophisticated cost analysis using cost per QALY and actual patient dosage and weight to evaluate PPP per package for different b/tsDMARDs. If cost confidentiality is not a barrier, this approach will provide an accurate picture of the cost-effectiveness of various treatments. It may improve our understanding of the real-world impact of cost on treatment options, contributing to a better understanding of the benefits and potential improvements of the pharmaceutical tender system.
- **Investigating decentralized vs. centralized areas in Norway:** A comparison of treatment administration between decentralized and centralized areas based on intravenous versus subcutaneous treatment could yield important insights. It would allow for a better understanding of the differences between these areas, as well as the impact of the healthcare delivery system on treatment outcomes and preferences.
- **A comprehensive longitudinal study on b/tsDMARDs in RA:** Similar types of studies as those presented in the thesis, albeit using longitudinal data and more accurate measures on cost and dosage. Also, taking into consideration other factors such as comorbidity and frailty and regression analysis of the tender ranking.
- **Psychosocial and cultural factors influencing annual follow-ups**: A study could investigate the various biopsychosocial and cultural factors influencing the patient's perceived need for annual

follow-ups despite clinical remission. This study could seek to understand the differences between RA patients in remission who believe they need annual check-ups and those who do not, despite having similar health statuses.

- **Redefinition of remission criteria with modern imaging techniques:** Research aimed at redefining remission criteria in RA using modern imaging techniques could be highly beneficial. This research could focus on developing a new method for remission criteria that relies on objective variables and ultrasound imaging. One could also incorporate elements of artificial intelligence and automated ultrasonography in this study.

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8. PAPERS I-III

PAPER I

BMC Health Services Research

RESEARCH

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Exploring drug cost and disease outcome in rheumatoid arthritis patients treated with biologic and targeted synthetic DMARDs in Norway in 2010–2019 – a country with a national tender system for prescription of costly drugs

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Abstract

Background: In Norway, an annual tender system for the prescription of biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) has been used since 2007. This study aimed to explore annual b/tsDMARDs costs and disease outcomes in Norwegian rheumatoid arthritis (RA) patients between 2010 and 2019 under the influence of the tender system.

Methods: RA patients monitored in ordinary clinical practice were recruited from 10 Norwegian centers. Data files from each center for each year were collected to explore demographics, disease outcomes, and the prescribed treatment. The cost of b/tsDMARDs was calculated based on the drug price given in the annual tender process.

Results: The number of registered RA patients increased from 4909 in 2010 to 9335 in 2019. The percentage of patients receiving a b/tsDMARD was 39% in 2010 and 45% in 2019. The proportion of b/tsDMARDs treated patients achieving DAS28 remission increased from 42 to 67%. The estimated mean annual cost to treat a patient on b/tsDMARDs fell by 47%, from 13.1 thousand euros (EUR) in 2010 to 6.9 thousand EUR in 2019. The mean annual cost to treat b/tsDMARDs naïve patients was reduced by 75% (13.0 thousand EUR in 2010 and 3.2 thousand EUR in 2019).

Conclusions: In the period 2010–2019, b/tsDMARD treatment costs for Norwegian RA patients were significantly reduced, whereas DAS28 remission rates increased. Our data may indicate that the health authorities' intention to reduce treatment costs by implementing a tender system has been successful.

Keywords: Rheumatoid arthritis, Economics, Biological therapy, Biosimilar pharmaceuticals

Background

The introduction of biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs), early intervention, and treat to target strategies represents a paradigm shift in the treatment of patients with

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inflammatory joint disorders, e.g., rheumatoid arthritis (RA), where remission is now an attainable treatment goal [1–4]. However, the high cost of b/tsDMARDs has caused restrictions on the usage of these drugs, contributing to inequality of care worldwide [5–7].

In some countries (e.g., Norway and Denmark) with a public tax-funded healthcare system, tender systems, and the possibility of a mandatory switch to potentially cheaper biosimilar drugs have been implemented to reduce the drug expenditure (particularly for costly drugs). To our knowledge, this is the first study to explore changes in b/tsDMARD treatment costs set against changes in disease outcomes in RA following the implementation of a tender system. This study aimed to explore treatment cost and disease outcomes in RA patients treated with b/tsDMARDs in Norway during a 10-year period (2010 to 2019) with a tender system in effect.

Methods

Patient inclusion and data collection

Data were obtained from the BioRheuma project (BIOlogic treatment of patients suffering from inflammatory RHEUMAtic disorders in Norway) that started in 2010. The objective of the BioRheuma project was to facilitate the use of recommended and validated outcome measures to monitor patients with inflammatory joint disorders as part of ordinary care in Norwegian outpatient clinics. Patient monitoring at the participating centers was standardized using the computer tool GoTreatIT® Rheuma (www.diagraphit.com). The clinical expectations of the project were to reveal annual changes in the usage of conventional synthetic DMARDs (csDMARDs) and b/tsDMARDs, viewed against changes in demographics, disease activity, and patient-reported outcome measures (PROMs) during follow-up.

The 10 BioRheuma centers providing data for this study were located across the country (Bergen, Bærum, Førde, Haugesund, Kristiansand, Lillehammer, Oslo, Skien, Tromsø, and Trondheim). We estimated the completeness of included patients from each center by comparing with published prevalence figures for RA in Norway [8, 9]. BioRheuma prevalence figures were calculated using the number of included RA patients at each center divided by the background population the various centers were covering.

For each of the 10 years, data was extracted from each participating center's database using predefined queries. One query retrieved RA patients registered with at least one visit in the examined year. Data from the latest visit was used if multiple visits occurred in that year. Another query retrieved all patients starting on either bDMARD or tsDMARD for the different years. Anonymized data files from the 10 participating centers were merged and analyzed using EXCEL and the Statistical package for social sciences (SPSS).

Data collection for each year included demographic variables, diagnosis-related variables, disease activity measures, PROMs, and RA treatment medications. Demographic variables include patient age, sex, body mass index (BMI, kg/m2), current smoking status, years of education, disease duration, and occupational status. The occupational status of participants younger than 65 years was categorized as enabled workers or disabled workers. Patients who reported their occupational status as a full-time job, part-time job, student, maternity leave, paternity leave, sick leave, unemployed, early retirement, part-time job/sick leave, part-time job/unemployed were defined as "enabled workers." In contrast, patients who reported part-time job/disabled pensioner, disabled pensioner, disabled pensioner due to RA, medical rehabilitation, and occupational rehabilitation were defined as "disabled workers." Participants $\geq$ 65 years were omitted and defined as pensioners. Disease duration was calculated from the date of diagnosis until the latest visit at the outpatient clinic for the examined year.

Diagnosis-related variables include rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP). Measures reflecting disease activity encompass laboratory measures (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), the clinical measures 28 swollen and tender joint count (28SJC/28TJC), investigator global assessment (IGA) scored on a visual analog scale (VAS; 0–100 mm), and composite 28 joint count Disease Activity Score using CRP (DAS28) [10]. The PROMs included were pain, patient global assessment (PGA), and fatigue scored on a VAS-scale (0–100 mm), as well as morning stiffness (reported in 15-min units) and Modified Health Assessment Questionnaire (MHAQ) [11] to evaluate the physical function of the RA patients.

Among available composite scores, DAS28 was used to define the disease activity status with the following cut-off values; remission $\leq$2.6, low disease activity between $>$2.6 and $\leq$3.2, moderate disease between $>$3.2 and $\leq$5.1, and high disease activity for those $>$5.1 [10].

Drug costs analysis

For each of the 10 years, the annual total cost for b/tsDMARDs as well as mean b/tsDMARD cost per patient was calculated for all patients receiving ongoing b/tsDMARDs (current b/tsDMARD users), for those who started on their first b/tsDMARD (naïve b/tsDMARD users) and for those who started on a new b/tsDMARDs but were previous users of b/tsDMARDs. The cost was calculated based on price offers given for the separate drugs at the annual tender process for the given year. Adjusted cost was also calculated using the Norwegian

consumer price index (CPI) for pharmaceuticals from 2010 Norwegian Kroners (NOK) [12]. Only average prices (no drug-specific prices) are presented due to an agreement between the pharmaceutical companies and the Norwegian authorities to keep the costs for individual drugs confidential and exempt from the public. Due to the challenging COVID-19 pandemic situation, clinical data for 2020 was not collected, but the cost for 2020 was calculated using 2019 population data. All costs were converted to euros (EUR) based on the average NOK-to-EUR conversion rate between 2010 and 2020 (1 NOK = 8.839 EUR).

The b/tsDMARDs included were Tumor Necrosis Factor inhibitors (TNFi) (etanercept reference, etanercept SB4, infliximab reference, infliximab CT-P13, adalimumab, golimumab, certolizumab pegol), non-TNFi (rituximab reference, rituximab GP2013, abatacept, and tocilizumab), and tsDMARDs (baricitinib and tofacitinib). For 2020 the biosimilars infliximab GP1111 and adalimumab GP2017 won the tender and were used in the cost analysis for 2020. Data collection also included the use of csDMARDs and prednisolone**.**

Statistical analysis

Categorical variables are reported as numbers and percentages and continuous variables as mean with standard deviation (SD), or mean with range. Change and association between variables over the 10-year period were analyzed with SPSS using one-way analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables. Only available data were used without imputation of missing data. A p-value of < 0.05 was considered statistically significant.

Ethics

The study was approved by the regional ethical committee (REC) (Regional etisk komite Midt-Norge 2010/3078) and follows the Declaration of Helsinki ethical principles of medical research involving human subjects. No consent from patients was required by the REC, as all data were anonymized and collected as part of routine clinical care.

Results

Demographics, disease activity, and patient-reported outcomes

The number of RA patients registered in the BioRheuma project in the 10-year period ranged from 4909 patients in 2010 to a maximum of 9335 in 2019, and the percentage of patients registered as b/tsDMARD users increased from 40% ($n = 1959$) to 45% ($n = 4209$), respectively. In Table 1, annual results are shown for demographics, biomarkers, disease activity, and PROM variables for current users of b/tsDMARDs. The percentage of patients currently treated with b/tsDMARDs increased from 39% in 2010 to 45% in 2019. An improvement was seen for disease activity measures, MHAQ, and fatigue, but not for PGA, pain, and morning stiffness. The proportion of patients in DAS28 remission who received a b/tsDMARD increased from 42% in 2010 to 67% in 2019. The percentage of enabled workers did not change significantly, ranging from 63% in 2010 to 59% in 2019.

A supplementary table (see Additional file 1) compares mean values and range for the 10 years between b/tsDMARD-treated patients and non-b/tsDMARDs RA patients. In general, no relevant differences for disease activity measures and PROMs were seen between b/tsDMARDs and non-b/tsDMARDs treated RA patients. However, more b/tsDMARDs treated patients were RF and CCP positive. Numerically only minor, yet statistically significant differences were found for most demographic variables. However, disease duration was markedly longer for b/tsDMARDs than non-b/tsDMARDs treated patients (14.0 vs. 8.9 years, $p = < 0.001$).

Baseline values for demographics, disease activity, and PROMs are shown in Table 2 for naïve b/tsDMARDs users and in Table 3 for patients starting subsequent b/tsDMARD. For patients naïve to b/tsDMARDs, disease duration was the only demographic variable with a significant change during the 10 years. In contrast, significant changes were found for all demographic variables apart from work status in the non-naïve group.

Both in naïve and non-naïve treatment groups, the disease activity level at the start of a new b/tsDMARD treatment decreased from 2010 to 2019. For naïve users, the mean DAS28 was 5.0 in 2010 and 3.8 in 2019, whereas DAS28 fell from 5.3 in 2010 to 3.8 in 2019 in the non-naïve group. A statistically significant difference was found for all PROM variables for non-naïve patients. However, in RA patients naïve to b/tsDMARDs, there were non-significant changes in VAS for pain and fatigue.

Cost

The total treatment expenditure for b/tsDMARDs was lowest in 2010 (treating 1959 RA patients) with 25.6 million EUR, highest in 2014 (39.6 million EUR for treating 3448 patients), and second lowest in 2019 (28.9 million EUR for treating 4209 patients). Detailed information is shown in Table 4 for current users of b/tsDMARDs and the subgroups TNFi, non-TNFi, and tsDMARDs for the different 10 years. Table 4 also shows the numbers treated, the cost of b/tsDMARDs drugs started in the different years (for all and those naïve to b/tsDMARDs), and the subgroup TNFi non-TNFi and tsDMARDs.

Table 1 Demographic and disease characteristics in Norwegian RA patients currently using b/tsDMARDs during 2010–2019

Ten year period	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Mean	Missing Data Mean, Range	*P*-value
The annual number of patients													
BioRheuma patients, N	4909	7256	7993	7278	8023	9057	9176	9225	9102	9335			
b/tsDMARDs users, N (%)	1936 (39)	2855 (39)	3136 (39)	3060 (42)	3419 (43)	3688 (41)	3770 (41)	3869 (42)	3869 (43)	4154 (45)	41%		
Demographics													
Age (years)	60 (13)	60 (14)	59 (14)	59 (14)	59 (14)	59 (14)	59 (14)	59 (14)	60 (14)	60 (14)	59.3	1.1%, 0–11%	0.044
Female	74%	73%	72%	72%	73%	73%	73%	73%	73%	72%	73%	1.1%, 0–11%	0.938
BMI (kg/m2)	26 (4.9)	26 (4.6)	26 (4.6)	26 (4.6)	26 (4.6)	26 (4.7)	26 (4.8)	26 (4.8)	26 (4.6)	26 (4.9)	26	9.9%, 2–57%	< 0.001
Education (years)	13 (3.6)	12 (3.8)	12 (3.7)	12 (3.7)	12 (3.7)	12 (3.7)	12 (3.7)	13 (3.7)	13 (3.7)	13 (3.7)	12	9.3%, 1–55%	< 0.001
Current Smokers	23%	22%	20%	19%	18%	17%	16%	15%	14%	14%	18%	8.2%, 1–50%	< 0.001
Disease Duration (years)	13 (10)	13 (11)	14 (11)	14 (11)	14 (11)	14 (11)	15 (11)	14 (11)	15 (11)	15 (11)	14	0.0%, 0–0%	< 0.001
Enabled Workers	63%	59%	59%	60%	57%	58%	59%	59%	59%	59%	59%	7.4%, 1–45%	0.393
Biomarkers													
CCP Positive	82%	82%	81%	81%	80%	80%	81%	81%	81%	81%	81%	27%, 14–42%	0.900
RF Positive	75%	75%	74%	73%	73%	73%	72%	73%	73%	72%	73%	45%, 29–61%	0.798
Disease Activity													
ESR (mm/h)	19 (16) [14 (17)]	18 (16) [13 (16)]	16 (15) [12 (15)]	16 (14) [12 (14)]	15 (15) [11 (14)]	15 (15) [11 (14)]	14 (14) [10 (13)]	14 (14) [9 (13)]	14 (15) [9 (13)]	14 (15) [9 (12)]	16	26%, 20–32%	< 0.001
CRP (mg/L)	8.4 (17) [4 (7)]	7.8 (14) [4 (7)]	6.6 (12) [3 (5)]	6.2 (10) [3 (5)]	6.2 (11) [3 (5)]	6.4 (13) [3 (6)]	6.4 (17) [3 (4)]	5.7 (11) [2 (4)]	5.9 (11) [2 (4)]	6.0 (11) [2 (4)]	6.6	19%, 15–27%	< 0.001
TJC28 (0–28)	3.4 (4.7) [2 (5)]	3.1 (4.5) [1 (4)]	2.7 (4.4) [1 (3)]	2.5 (4.1) [1 (3)]	2.4 (3.9) [1 (3)]	2.1 (3.7) [1 (3)]	2.1 (3.7) [1 (2)]	1.9 (3.7) [0 (2)]	1.9 (3.6) [0 (2)]	1.7 (3.4) [0 (2)]	2.4	15%, 9–19%	< 0.001
SJC28 (0–28)	2.3 (3.4) [1 (3)]	2.0 (3.1) [1 (3)]	1.9 (3.1) [1 (2)]	1.5 (2.6) [0 (2)]	1.2 (2.3) [0 (2)]	1.1 (2.2) [0 (1)]	1.1 (2.1) [0 (1)]	1.1 (2.2) [0 (1)]	0.9 (2.0) [0 (1)]	0.8 (2.0) [0 (1)]	1.4	15%, 9–19%	< 0.001
IGA (VAS, 0–100 mm)	18 (16)	18 (16)	17 (16)	16 (15)	16 (15)	15 (15)	14 (15)	14 (15)	13 (15)	12 (14)	15.2	40%, 35–50%	< 0.001
DAS28(4)-CRP	3.1 (1.2)	3.0 (1.2)	2.8 (1.2)	2.7 (1.1)	2.6 (1.1)	2.6 (1.1)	2.6 (1.1)	2.5 (1.1)	2.5 (1.1)	2.4 (1.1)	2.7	30%, 26–34%	< 0.001

Table 1 (continued)

Ten year period	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Mean	Missing Data Mean, Range	*P*-value
DAS28 Remission	42%	46%	51%	56%	57%	59%	60%	63%	64%	67%	56%	30%, 26–34%	< 0.001
DAS28 LDA	18%	17%	17%	17%	16%	16%	16%	15%	16%	14%	16%	30%, 26–34%	0.034
Patient-Reported Outcome Measures													
PGA (VAS, 0–100 mm)	33 (24)	33 (25)	33 (25)	32 (25)	32 (25)	33 (25)	33 (25)	32 (26)	32 (26)	32 (26)	33	10%, 8–11%	0.270
Pain (VAS, 0–100 mm)	32 (25)	34 (25)	33 (24)	32 (25)	32 (25)	33 (25)	32 (25)	32 (26)	32 (25)	32 (26)	33	20%, 14–53%	0.204
MHAQ (0–3)	0.5 (0.5)	0.5 (0.5)	0.5 (0.5)	0.5 (0.5)	0.5 (0.5)	0.5 (0.5)	0.5 (0.5)	0.5 (0.5)	0.5 (0.5)	0.5 (0.5)	0.5	15%, 10–37%	0.001
Fatigue (VAS, 0–100 mm)	38 (29)	37 (29)	38 (29)	37 (29)	38 (30)	39 (30)	39 (30)	39 (30)	40 (310)	40 (31)	39	37%, 15–54%	0.006
Morning Stiffness (hr)	0.9 (1.2)	0.9 (1.3)	0.9 (1.2)	0.9 (1.2)	0.8 (1.2)	0.9 (1.2)	0.9 (1.3)	0.9 (1.2)	0.9 (1.2)	0.9 (1.2)	0.9	42%, 16–59%	0.614

Note: Categorical variables are presented as percentages and continuous variables as mean with standard deviation (SD). Variables ESR, CRP, TJC28, and SJC28 also show median with interquartile range [Median (Interquartile Range)] below their Mean (SD). Missing data are presented as mean with range. χ^2 test for categorical variables and one-way ANOVA for continuous variables was used to test for differences during follow-up of ten years

Occupation Status: Enabled Workers (< 65 years old) = Full Job, Part-time Job, Student, Maternity Leave, Paternity leave, Sick Leave, Unemployed, Early Retirement, Part-time job/Sick Leave, Part-time job/Unemployed), Disabled Workers (< 65 years) = Part-time Job/Disabled Early Retirement, Early Retirement due to Disability, Early Retirement due to RA, Medical Rehabilitation, Occupational Rehabilitation

Abbreviations: *RA* Rheumatoid Arthritis, *b/tsDMARDs* biologic and target synthetic Disease-Modifying Antirheumatic Drugs, *BMI* Body Mass Index, *CCP* Anti-cyclic citrullinated peptide, *RF* Rheumatoid Factor, *ESR* Erythrocyte Sedimentation Rate, *CRP* C-Reactive Protein, *TJC28* Tender 28-Joint Count, *SJC28* Swollen 28-Joint Count, *IGA* Investigators Global Assessment, *VAS* Visual Analog Scale (Measured 0–100), *DAS28* Disease Activity Score, *LDA* Low Disease Activity, *PGA* Patient Global assessment, *MHAQ* Modified Health Assessment Questionnaire

Table 2 Demographic and disease characteristics in Norwegian RA patients starting naïve on b/tsDMARDs during 2010–2019

Ten year period	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Mean	Missing Data Mean, Range	*P*-value
The annual number of patients													
All b/tsDMARDs starters	832	887	875	857	852	946	1671	1342	1068	1475			
Naïve starters, N (%)	378 (45%)	424 (48%)	421 (48%)	386 (45%)	356 (42%)	367 (39%)	400 (24%)	418 (31%)	408 (38%)	409 (28%)	39%		
Demographics													
Age (years)	57 (15)	56 (15)	57 (14)	55 (15)	55 (15)	55 (14)	56 (15)	54 (16)	55 (15)	55 (15)	55	0.3%, 0–2%	0.212
Female	71%	76%	68%	71%	69%	71%	75%	69%	69%	70%	71%	0.1%, 0–1%	0.152
BMI (kg/m2)	25 (4.3)	26 (4.3)	26 (4.7)	26 (4.5)	26 (4.7)	26.1 (5.1)	26 (4.5)	26 (5.1)	27 (5.3)	26 (5.3)	26	23%, 11–66%	0.256
Education (years)	13 (3.7)	12 (3.6)	13 (3.6)	12 (3.9)	13 (3.7)	13 (3.7)	13 (3.9)	12 (3.5)	13 (3.8)	13 (3.7)	13	25%, 18–64%	0.683
Current Smokers	25%	22%	20%	17%	15%	17%	20%	16%	17%	18%	19%	24%, 17–64%	0.175
Disease Duration	4.6 (5.6)	7.2 (9.3)	7.8 (9.9)	5.9 (7.9)	6.4 (8.5)	6.4 (9.0)	7.1 (9.4)	5.8 (8.9)	4.9 (7.2)	5.2 (7.0)	6.1	28%, 0–78%	< 0.001
Enabled Workers	71%	73%	73%	76%	74%	70%	73%	72%	69%	73%	72%	24%, 16–63%	0.922
Disease Activity													
ESR (mm/h)	26 (22) [20 (24)]	26 (22) [20 (23)]	22.6 (20) [16 (21)]	22 (18) [16 (19)]	22.1 (18) [19 (20)]	23 (19) [17 (22)]	22(21) [15 (21)]	22 (18) [17 (21)]	20 (19) [13 (18)]	20 (18) [14 (18)]	23	23%, 15–30%	< 0.001
CRP (mg/L)	17 (24) [8 (16)]	16.9 (29) [7 (16)]	14.2 (20) [7 (14)]	14 (21) [7 (12)]	15.2 (22) [6 (14)]	11 (14) [6 (11)]	15 (26) [5 (13)]	12.9 (16) [6 (17)]	11 (17) [5 (10)]	12 (18) [5 (13)]	14	16%, 8–26%	< 0.001
TJC28 (0–28)	8.3 (6.8) [7 (8)]	7.4 (6.6) [5 (9)]	6.5 (5.9) [5 (8)]	5.8 (5.3) [5 (6)]	6.7 (6.0) [5 (8)]	6.4 (5.8) [5 (7)]	5.6 (5.5) [4 (7)]	6.2 (6.2) [4 (7)]	5.3 (5.4) [4 (6)]	5.1 (5.6) [3 (7)]	6.3	13%, 7–21%	< 0.001
SJC28 (0–28)	6.8 (5.0) [6 (6)]	6.0 (4.9) [5 (6)]	5.4 (4.5) [4 (6)]	4.8 (4.2) [4 (5)]	4.9 (4.5) [4 (6)]	4.8 (4.9) [3 (6)]	4.1 (4.4) [3 (5)]	4.0 (3.9) [3 (5)]	4.0 (4.5) [3 (5)]	3.5 (4.2) [2 (6)]	4.8	13%, 7–21%	< 0.001
IGA (VAS, 0–100 mm)	39 (18)	40.2 (20)	39.1 (19)	38 (18)	38 (18)	37 (18)	38 (20)	36 (18)	33 (19)	32 (20)	37	32%, 19–45%	< 0.001
DAS28	5.0 (1.4)	4.6 (1.3)	4.5 (1.3)	4.3 (1.3)	4.5 (1.4)	4.4 (1.5)	4.3 (1.5)	4.3 (1.5)	4.1 (1.4)	3.8 (1.4)	4.4	29%, 19–35%	< 0.001
Patient-Reported Outcome Measures													
PGA (VAS, 0–100 mm)	54 (25)	50 (25)	51 (26)	48 (25)	53 (26)	49 (26)	50 (26)	50 (26)	49 (26)	47 (26)	50	13%, 8–21%	0.014
Pain (VAS, 0–100 mm)	51 (27)	46 (25)	49 (25)	47 (25)	48 (25)	47 (24)	47 (27)	47 (25)	45 (26)	45 (27)	47	22%, 10–57%	0.357

Table 2 (continued)

Ten year period	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Mean	Missing Data Mean, Range	*P*-value
MHAQ (0–3)	0.7 (0.6)	0.7 (0.5)	0.7 (0.5)	0.6 (0.5)	0.7 (0.5)	0.6 (0.5)	0.6 (0.5)	0.7 (0.5)	0.6 (0.5)	0.6 (0.5)	0.6	18%, 9–39%	0.007
Fatigue (VAS, 0–100 mm)	50 (29)	48 (30)	49 (29)	46 (30)	51 (30)	50 (30)	46 (31)	49 (30)	48 (30)	48 (33)	49	36%, 17–51%	0.725
Morning Stiffness (hr)	1.7 (1.5)	1.6 (1.6)	1.6 (1.5)	1.6 (1.6)	1.8 (1.8)	1.5 (1.5)	1.5 (1.6)	1.7 (1.5)	1.3 (1.5)	1.4 (1.4)	1.6	38%, 17–53%	0.040

Note: Categorical variables are presented as percentages and continuous variables as mean with standard deviation (SD). Variables ESR, CRP, TJC28, and SJC28 also show median with interquartile range [Median (Interquartile Range)] below their Mean (SD). Missing data are presented as mean with range. χ^2 test for categorical variables and one-way ANOVA for continuous variables was used to test for differences during follow-up of ten years

Occupation Status: Enabled Workers (< 65 years old) = Full Job, Part-time Job, Student, Maternity Leave, Paternity leave, Sick Leave, Unemployed, Early Retirement, Part-time job/Sick Leave, Part-time job/Unemployed), Disabled Workers (< 65 years) = Part-time Job/Disabled Early Retirement, Early Retirement due to Disability, Early Retirement due to RA, Medical Rehabilitation, Occupational Rehabilitation

Abbreviations: *RA* Rheumatoid Arthritis, *b/tsDMARDs* biologic and target synthetic Disease-Modifying Antirheumatic Drugs, *BMI* Body Mass Index, *CCP* Anti-cyclic citrullinated peptide, *RF* Rheumatoid Factor, *ESR* Erythrocyte Sedimentation Rate, *CRP* C-Reactive Protein, *TJC28* Tender 28-Joint Count, *SJC28* Swollen 28-Joint Count, *IGA* Investigators Global Assessment, *VAS* Visual Analog Scale (Measured 0–100), *DAS28* Disease Activity Score, *LDA* Low Disease Activity, *PGA* Patient Global assessment, *MHAQ* Modified Health Assessment Questionnaire

Table 3 Demographic and disease characteristics in Norwegian RA patients starting non-naïve on b/tsDMARDs during 2010–2019

Ten year period	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Mean	Missing Data Mean, Range	*P* value
The annual number of patients													
All b/tsDMARDs starters	832	887	875	857	852	946	1671	1342	1068	1475			
Non-naïve starters, N (%)	454 (55)	463 (52)	454 (52)	471 (55)	496 (58)	579 (61)	1271 (76)	924 (69)	660 (62)	1066 (72)	61%		
Demographics													
Age (years)	59 (14)	57 (14)	58 (14)	57 (15)	55 (14)	578 (15)	59 (14)	58 (14)	58 (15)	59 (14)	58	0.3%, 0–3%	< 0.001
Female	75%	79%	78%	75%	790%	79%	71%	76%	75%	74%	76%	0.0%, 0–0%	0.002
BMI (kg/m2)	26 (5.5)	25 (4.6)	26 (4.8)	26 (5.1)	26 (4.4)	26 (5.1)	26 (4.7)	26 (4.7)	26 (5.1)	27 (5.0)	26	19%, 6–65%	< 0.001
Education (years)	12 (3.4)	12 (3.9)	12 (3.6)	12 (3.8)	13 (4.0)	12 (3.7)	12 (3.6)	13 (3.8)	13 (3.8)	13 (3.7)	13	29%, 18–59%	0.019
Current Smokers	27%	26%	22.0%	17%	14%	19%	18%	16%	12%	14%	18%	28%, 18–58%	< 0.001
Disease Duration	11 (10)	11 (9.8)	10 (8.6)	13 (11)	12 (9.7)	13 (10)	14 (11)	13 (10)	13 (11)	13 (11)	12	28%, 0–81%	0.001
Enabled Workers	54%	51%	52%	63%	57%	54%	60%	59%	59%	58%	57%	26%, 15–54%	0.106
Disease Activity													
ESR (mm/h)	32 (24) [25 (33)]	28 (25) [21 (27)]	28 (23) [21 (27)]	30 (25) [21 (30)]	27 (22) [21 (28)]	24 (20) [19 (23)]	22 (21) [16 (20)]	22 (19) [15 (22)]	24 (23) [16 (25)]	20 (20) [13 (19)]	26	23%, 15–41%	< 0.001
CRP (mg/L)	21 (23) [12 (24)]	18 (27) [8 (19)]	16 (21) [7 (17)]	17 (24) [7 (16)]	16 (27) [6 (14)]	14 (20) [5 (13)]	12 (19) [5 (11)]	12 (21) [5 (11)]	14 (22) [5 (15)]	11 (16) [5 (10)]	15	19%, 11–37%	< 0.001
TJC28 (0–28)	9.3 (6.8) [8 (10)]	8.3 (7.0) [7 (9)]	7.3 (6.6) [5 (9)]	7.2 (6.4) [5 (8)]	6.7 (5.9) [5 (8)]	6.1 (6.3) [4 (8)]	4.6 (5.5) [2 (7)]	5.2 (5.5) [4 (7)]	5.7 (5.7) [4 (8)]	4.8 (5.8) [3 (7)]	6.5	15%, 7–37%	< 0.001
SJC28 (0–28)	7.3 (5.3) [6 (8)]	6.2 (5.1) [5 (6)]	5.7 (5.1) [4 (6)]	5.2 (4.7) [4 (5)]	4.4 (4.5) [3 (5)]	4.0 (4.7) [3 (5)]	3.1 (4.1) [2 (5)]	3.6 (4) [3 (6)]	3.7 (4.0) [3 (5)]	2.9 (4.1) [1 (4)]	4.6	15%, 7–37%	< 0.001
IGA (VAS, 0–100 mm)	45 (21)	40 (21)	38 (20)	40 (21)	37 (19)	37 (21)	27 (21)	32 (21)	31 (19)	28 (21)	36	34%, 22–50%	< 0.001
DAS28	5.3 (1.4)	5.0 (1.4)	4.8 (1.4)	4.7 (1.5)	4.6 (1.4)	4.3 (1.5)	3.8 (1.6)	4.0 (1.5)	4.2 (1.6)	3.8 (1.6)	4.4	29%, 18–47%	< 0.001
Patient-Reported Outcome Measures													
PGA (VAS, 0–100 mm)	62 (22)	58 (25)	58 (25)	56 (24)	55 (24)	51 (26)	47 (28)	49 (28)	55 (27)	49 (28)	54	16%, 9–35%	< 0.001
Pain (VAS, 0–100 mm)	57 (24)	54 (26)	54 (25)	53 (24)	51 (26)	48 (26)	45 (27)	47 (28)	52 (27)	47 (28)	51	23%, 13–52%	< 0.001

Table 3 (continued)

Ten year period	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Mean	Missing Data Mean, Range	*P* value
MHAQ (0–3)	1.0 (0.6)	0.9 (0.6)	0.9 (0.5)	0.8 (0.5)	0.8 (0.6)	0.6 (0.6)	0.7 (0.6)	0.7 (0.6)	0.8 (0.6)	0.7 (0.6)	0.8	20%, 12–38%	< 0.001
Fatigue (VAS, 0–100 mm)	58 (29)	55 (28)	57 (29)	53 (28)	56 (27)	51 (29)	48 (31)	52 (31)	54 (30)	51 (31)	54	38%, 15–56%	< 0.001
Morning Stiffness (hr)	2.1 (1.7)	1.9 (1.7)	1.9 (1.7)	1.7 (1.6)	1.7 (1.7)	1.5 (1.6)	1.5 (1.6)	1.6 (1.6)	1.6 (1.7)	1.4 (1.6)	1.7	40%, 16–59%	< 0.001

Note: Categorical variables are presented as percentages and continuous variables as mean with standard deviation (SD). Variables ESR, CRP, TJC28, and SJC28 also show median with interquartile range [Median (Interquartile Range)] below their Mean (SD). Missing data are presented as mean with range. χ^2 test for categorical variables and one-way ANOVA for continuous variables was used to test for differences during follow-up of ten years

Occupation Status: Enabled Workers (< 65 years old) = Full Job, Part-time Job, Student, Maternity Leave, Paternity leave, Sick Leave, Unemployed, Early Retirement, Part-time job/Sick Leave, Part-time job/Unemployed), Disabled Workers (< 65 years) = Part-time Job/Disabled Early Retirement, Early Retirement due to Disability, Early Retirement due to RA, Medical Rehabilitation, Occupational Rehabilitation

Abbreviations: *RA* Rheumatoid Arthritis, *b/tsDMARDs* biologic and target synthetic Disease-Modifying Antirheumatic Drugs, *BMI* Body Mass Index, *CCP* Anti-cyclic citrullinated peptide, *RF* Rheumatoid Factor, *ESR* Erythrocyte Sedimentation Rate, *CRP* C-Reactive Protein, *TJC28* Tender 28-Joint Count, *SJC28* Swollen 28-Joint Count, *IGA* Investigators Global Assessment, *VAS* Visual Analog Scale (Measured 0–100), *DAS28* Disease Activity Score, *LDA* Low Disease Activity, *PGA* Patient Global assessment, *MHAQ* Modified Health Assessment Questionnaire

Table 4 B/tsDMARDs treatment and cost in Norwegian RA outpatient clinic patients shown during 2010–2019

	2010 (*n* = *4909*)	2011 (*n* = *7256*)	2012 (*n* = *7993*)	2013 (*n* = *7278*)	2014 (*n* = *8023*)	2015 (*n* = *9057*)	2016 (*n* = *9176*)	2017 (*n* = *9225*)	2018 (*n* = *9102*)	2019 (*n* = *9335*)	Mean (Range) (2010–2019)
Number of treated patients with b/tsDMARDs and number of patients with double or multiple b/tsDMARDs registration errors (RE)											
b/tsDMARD users, N	1936	2855	3136	3060	3419	3688	3770	3869	3869	4158	
b/tsDMARD RE, N [%]	23 [1.2]	27 [0.9]	23 [0.7]	28 [0.9]	29 [0.8]	45 [1.2]	139 [3.7]	96 [2.5]	54 [1.4]	51 [1.2]	1.5% (0.7–3.7%)
Number of registered b/tsDMARDs (Percentage of n) [Percentage of the corresponding medication group]											
b/tsDMARDs (%)	1959 (40)	2882 (40)	3159 (40)	3088 (42)	3448 (43)	3733 (41)	3909 (43)	3965 (43)	3923 (43)	4209 (45)	42% (40–45%)
TNFi [%]	1485 [76]	2134 [74]	2319 [73]	2262 [73]	2469 [72]	2544 [68]	2696 [69]	2668 [67]	2462 [63]	2689 [64]	70% (64–76%)
Non-TNFi [%]	474 [24]	748 [26]	840 [27]	826 [27]	979 [28]	1189 [32]	1213 [31]	1262 [32]	1183 [30]	1084 [26]	28% (24–32%)
tsDMARD [%]	NA	NA	NA	NA	NA	NA	NA	35 [0.9]	278 [7.1]	436 [10.4]	6.1% (0.9–10%)
Number of b/tsDMARD users treated with csDMARDs, Methotrexate, and Glucocorticoids (percentage of b/tsDMARD users)											
csDMARD, N (%)	1430 (74)	2086 (73)	2256 (72)	2208 (72)	2415 (71)	2596 (70)	2630 (70)	2676 (69)	2568 (66)	2706 (65)	70% (65–74%)
Methotrexate, N (%)	1309 (68)	1885 (66)	2035 (65)	1983 (65)	2163 (63)	2282 (62)	2288 (61)	2327 (60)	2243 (58)	2357 (57)	62% (57–68%)
Glucocorticoids, N (%)	816 (42)	1123 (39)	1181 (38)	1136 (37)	1210 (35)	1277 (35)	1208 (32)	1189 (31)	1144 (30)	1199 (29)	35% (29–42%)
Naïve Starting b/tsDMARD users vs. Non-Naïve starting b/tsDMARD users (percentage of starting b/tsDMARD users) [Percentage of the corresponding medication group]											
All starting b/tsDMARDs	832	887	875	857	852	946	1671	1342	1068	1475	
Naïve to b/tsDMARDs	378 (45)	424 (48)	421 (48)	386 (45)	356 (42)	367 (39)	400 (24)	418 (31)	408 (38)	409 (28)	39% (24–48%)
Naïve to TNFi [%]	326 [86]	382 [90]	384 [91]	350 [91]	310 [87]	308 [84]	362 [91]	372 [89]	327 [80]	355 [87]	88% (80–91%)
Naïve to Non-TNFi [%]	52 [14]	42 [9.9]	37 [8.8]	36 [9.3]	46 [13]	59 [16]	38 [9.5]	46 [11]	51 [13]	23 [5.6]	11% (5.6–16%)
Naïve to tsDMARDs [%]	NA	NA	NA	NA	NA	NA	NA	NA	30 [7.4]	31 [7.6]	7.5% (7.4–7.6%)
Non-naïve to b/tsDMARDs	454 (55)	463 (52)	454 (52)	471 (55)	496 (58)	579 (61)	1271 (76)	924 (69)	660 (62)	1066 (72)	61% (52–76%)
TNFi [%]	213 [50]	252 [54]	282 [62]	281 [60]	278 [56]	364 [63]	1053 [83]	637 [69]	337 [51]	518 [49]	60% (49–83%)
Non-TNFi [%]	241 [53]	211 [46]	172 [38]	190 [40]	218 [44]	215 [37]	218 [17]	232 [25]	133 [20]	321 [30]	35% (17–53%)
tsDMARDs [%]	NA	NA	NA	NA	NA	NA	NA	55 [6.0]	190 [29]	227 [21]	19% (6.0–29%)
The annual mean cost of b/tsDMARDs in thousand Euro [Adjusted consume price index price for 2010 NOK value]											
Current b/tsDMARD cost	13.1 [13.1]	10.6 [10.5]	11.5 [11.1]	10.8 [10.3]	11.5 [10.7]	10.5 [9.7]	9.4 [8.3]	9.6 [8.4]	8.2 [7.1]	6.9 [5.8]	
Naïve b/tsDMARD cost	13.0 [13.0]	10.3 [10.2]	11.0 [10.6]	10.1 [9.6]	9.1 [8.4]	6.6 [6.1]	6.4 [5.7]	6.9 [6.0]	5.3 [4.6]	3.2 [2.7]	
Non-Naïve b/tsDMARD cost	12.9 [12.9]	10.9 [10.7]	11.7 [11.3]	10.8 [10.3]	10.5 [9.8]	8.1 [7.5]	7.6 [6.7]	7.6 [6.7]	5.9 [5.1]	4.6 [3.9]	
The annual total cost of b/tsDMARDs in Million Euro [Adjusted consume price index price for 2010 NOK value]											
Current b/tsDMARD cost	25.6 [25.6]	30.7 [30.3]	36.4 [35.0]	33.4 [31.7]	39.6 [36.8]	39.2 [36.1]	36.6 [32.5]	38.1 [33.3]	32.3 [28.0]	28.9 [24.4]	
Naïve b/tsDMARD cost	4.9 [4.9]	4.4 [4.3]	4.6 [4.5]	3.9 [3.7]	3.2 [3.0]	2.4 [2.2]	2.6 [2.3]	2.9 [2.5]	2.1 [1.9]	1.3 [1.1]	
Non-Naïve b/tsDMARD cost	5.9 [5.9]	5.0 [5.0]	5.3 [5.1]	5.1 [4.8]	5.2 [4.8]	4.7 [4.3]	9.6 [8.5]	7.1 [6.2]	3.9 [3.4]	4.9 [4.2]	

Note: Data are shown for current users b/tsDMARDs and patients starting a b/tsDMARDs both naïve and not naïve to previous use of b/tsDMARDs

Drugs included in TNFi: etanercept, etanercept SB4, infliximab, infliximab CT-P13, adalimumab, golimumab, certolizumab pegol. Drugs included in Non-TNFi: rituximab, rituximab GP2013, abatacept, and tocilizumab. Drugs included in tsDMARDs: baricitinib and tofacitinib

Abbreviations: *RA* Rheumatoid Arthritis, *b/tsDMARDs* biologic and target synthetic Disease-Modifying Antirheumatic Drugs, *tsDMARDs* target Synthetic DMARDs, *csDMARDs* conventional synthetic DMARDs, *TNFi* Tumor Necrosis Factor inhibitor (TNFi and Non-TNFi are subcategories of biologic DMARDs), *NA* Not available, *NOK* Norwegian Krones

The mean cost to treat a current RA user with b/tsDMARDs decreased by approximately 47% from 13.1 thousand EUR in 2010 to 6.9 thousand EUR in 2019 (Table 4). For both naïve and non-naïve b/tsDMARD users, the annual mean cost was markedly reduced from 2010 to 2019 by approximately 75 and 64% (13,0 thousand to 3.2 thousand and from 12.9 thousand to 4.6 thousand, respectively). Adjusted for CPI as displayed in Table 4, the reduction from 2010 to 2019 was even higher: for mean current users 56%, naïve users 80%, and non-naïve users 70%. When applying the tender results from 2020 on the 2019 population, the reduction was even higher with the estimated annual mean cost for current b/tsDMARDs users 5.8 thousand EUR and for naïve users 2.4 thousand EUR, which yields a cost reduction from 2010 of 56 and 82% and adjusted for CPI 64 and 85%, respectively.

Figure 1A visualizes the change in total costs for treating RA patients with b/tsDMARDs for current users and for naïve and non-naïve starters of b/tsDMARDs and numbers of treated patients. Figure 1B shows the mean cost to treat one patient in the three groups.

Completeness of patient recruitment

The estimated RA-prevalence based on BioRheuma data for each year and center is shown in a supplementary table (see Additional file 2). In 2019 the estimated overall prevalence (≥20 years old) was 0.3%, ranging at the single centers from 0.2 to 0.5%.

Discussion

The main finding in this study is an estimated 47% reduction (56% CPI-adjusted) in the annual per-patient cost of b/tsDMARD from 2010 to 2019 in Norway. During this period, a national tender system for the prescription of b/tsDMARDs was implemented. The estimated annual cost reduction for naïve b/tsDMARD users was 75% (79.5% CPI-adjusted). Cost simulation using 2020 tender results on the 2019 population treatment data found that reduction increased further to 82% (85% CPI-adjusted) from 2010 for naïve patients.

The findings in our study suggest that the implemented tender system for b/tsDMARD procurements in Norway for the last 10 years may have facilitated positive competition between pharmaceutical companies and thus served as a market mechanism to reduce prices. The Norwegian Pharmaceutical Procurement Cooperation, a subdivision of the Norwegian Hospital Procurement Trust, has annually released lists of their recommendation for b/tsDMARDs use based on the results of the tender. The prescribing physicians are not obliged by law to follow the annual recommendations and may therefore choose another drug in case of individual reasons. However, the regional health trusts strongly advise and monitor the adherence to the annual (tender-based) recommendations. Since the original cost on specific b/tsDMARD is confidential, we can only report the total average cost of the assessed b/tsDMARDs. However, among the current b/tsDMARDs users, many patients are also using more expensive b/tsDMARDs on the tender list, which is reflected in the slower drop in prices shown in Table 4 and Fig. 1B.

The expiration of patents for reference bDMARDs has enabled the development and production of biosimilar bDMARDs, reaching the market at lower costs. In 2014 infliximab CT-P13 was the first biosimilar to reach the Norwegian market, followed by etanercept SB4 in 2016 [13, 14]. In 2016, a high increase was observed in prescription among RA patients who started on a b/tsDMARDs not being naïve to b/tsDMARDs compared to the steady rate years before. This is explained by the mandatory switching from reference agent to etanercept SB4, which in this study is defined as non-naïve starters on b/tsDMARDs.

In the 2019 Norwegian tender process, several companies manufacturing biosimilar adalimumab drugs gave price offers. However, the reference adalimumab won the tender by offering a lower price than what was offered for the biosimilars. The same was seen for etanercept in 2020, where the reference and not a biosimilar drug won. This shows that biosimilars influence the competition between pharmaceutical companies by influencing producers of reference bDMARDs to reduce their prices in order to win the tender. In 2020 however, the biosimilar GP2017 adalimumab won the tender process.

In Denmark, estimated accumulated price and quantitative data have been published for infliximab, etanercept, and adalimumab after the expiration of a patent [15, 16]. When the adalimumab biosimilar reached Denmark's market in October 2018, the price for adalimumab dropped by 83% within 3 months. Whereas between September 2018 to September 2019, the use of adalimumab increased by approximately 35% [15].

The third mechanism used in Norway and Denmark to promote rapid cost reduction for bDMARDs is the recommended switch to the cheapest available substance when generics or biosimilars are available. In Norway, this switch has to be done by the treating rheumatologist and cannot be performed by the pharmacist, e.g., at the pharmacy.

As shown in our study, the impact of a tender system to reduce drug cost is a mechanism that may increase the availability of b/tsDMARDs to treat inflammatory arthritis, e.g., RA. This may be particularly important for low-income countries where RA patients have been

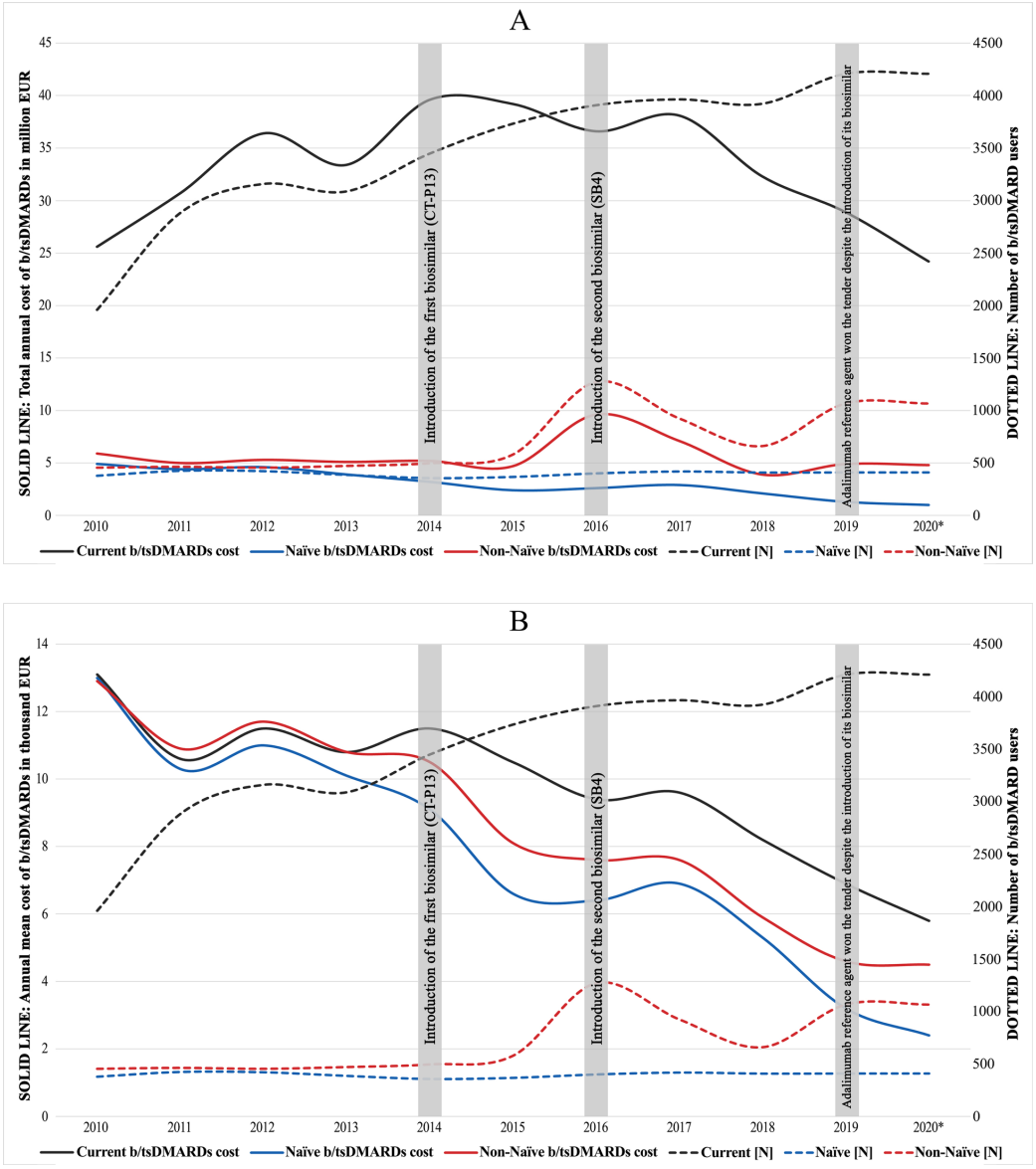

Fig. 1 **A** and **B**: Number of Norwegian RA patients and treatment cost for current b/tsDMARDs users, those starting on a new b/tsDMARD for the first time (naïve), and those starting on a new b/tsDMARD not the first time (non-naïve). *Note*: In Fig. **A** the total cost is shown. Naïve = starting on a new b/tsDMARD for the first time, Non-Naïve = starting on a new b/tsDMARD not for the first time, 2020* = The 2020 tender results are applied in the 2019 population. *Abbreviations*: N = Number of patients with rheumatoid arthritis in the BioRheuma project, EUR = Euros, RA = Rheumatoid Arthritis, b/tsDMARDs = biologic and target synthetic Disease-Modifying Antirheumatic Drugs. *Note*: In Fig. **B** the mean cost to treat one patient is shown for the three groups. Naïve = starting on a new b/tsDMARD for the first time, Non-Naïve = starting on a new b/tsDMARD not for the first time, 2020* = The 2020 tender results are applied in the 2019 population. *Abbreviations*: N = Number of patients with rheumatoid arthritis in the BioRheuma project, EUR = Euros, RA = Rheumatoid Arthritis, b/tsDMARDs = biologic and target synthetic Disease-Modifying Antirheumatic Drugs

shown to have higher disease activity than higher-income countries [5–7, 17, 18].

The previously documented improvement in clinical outcomes for RA patients in the new millennium in Norway [2, 3] and other countries [19–24] was also found in our study. Aga et al., in the NOR-DMARD multicenter study, found that remission rates in RA patients after 6 months of TNFi (and methotrexate) treatment had increased from 17% in the period 2000–2002 to 46% in the period 2009–2010 [3]. Disease duration before starting a TNFi had decreased from a median of 8.0 years (2000–2002) to 3.8 years (2009–2010) [3]. In comparison, in our study, the percentage of patients in DAS28 remission increased from 42% in 2010 to 67% in 2019, whereas disease duration in RA patients who started naïve on b/tsDMARDs did not change substantially.

Treatment with b/tsDMARDs in randomized clinical trials has been shown to improve occupational outcomes [25–27]. From the Swedish bDMARD registry, 35% of work-disabled RA patients with a disease duration of fewer than 5 years were found to regain their work ability within 3 years after starting a TNFi. With a disease duration of 5 years or more, the work recovery proportion was only 14% [28]. In our study, we did not see a significant change in the proportion of enabled workers across the 10 years. However, we saw a significant difference of roughly 10% (59% vs. 70%) among enabled workers when comparing those who were b/tsDMARD users vs. non-b/tsDMARD users (supplementary Table 1). Respectively, their average disease duration was 14 years vs. 9 years. When comparing the mean of naïve b/tsDMARDs users (Table 2) with non-naïve b/tsDMARDs users (Table 3) in the same manner, we observed 72% enabled workers with a six-year disease duration vs. 57% enabled workers with 12 years disease duration.

In the QUEST-RA study with data collected between 2005 and 2009 from 32 countries, 37% of previously work-enabled RA patients aged 65 years and younger reported occupational disability at the onset of RA symptoms (median observation period of 9 years) [29]. Despite the major differences in disease activity in their study, there was no significant difference in the proportion of work-enabled RA patients between countries with high and low gross domestic product (GDP). RA patients in low-GDP countries remained working despite high levels of disability and disease activity, suggesting that cultural and economic differences between societies also impact work disability rates in RA patients [29].

Our study's major strength is that the data collected is standardized for all RA outpatients independent of treatment using the same hospital computer system. This is in contrast to some registry-based studies that either only included selected patient groups using b/tsDMARDs or patients who initiated treatment with csDMARDs and/or b/tsDMARDs (e.g., the Norwegian NOR-DMARD registry) [30]. Another strength is that the included patients come from 10 centers spread across Norway. Selection bias, if present, would most likely affect the first years of the 10-year period as the number of registered patients was lower than at the end of the period. However, no significant changes were seen between the RA patients for age, sex, CCP, and RF status.

Furthermore, comparing the estimated mean prevalence for RA of 0.3% in 2019 (single centers range 0.2 to 0.5%) in our study with a population-based prevalence of 0.4% in Oslo (1994) for the age group 20–80 years and 0.5% in Tromsø (1994) for the age group 20 years and older indicate a low grade of selection bias, at least in some centers [8, 9]. RA patients followed by privately practicing rheumatologists have not been included in the analysis and may partly explain lower prevalence estimates in some centers. However, we have reason to believe that both internal validity for each center and external validity for Norway are satisfactory.

The relatively high rate of missing data for disease activity measures is a limitation. Nevertheless, as argued above, we find this less likely to be caused by a systematic bias and is most likely based on random. Another limitation is the reduced effort of including patients in the BioRheuma projects during the early phase of the 10-year period. Therefore, the increasing percentage of included patients may be strongly affected by the examining physician's interest in including the patient into the GoTreatIt Rheuma database. Also, it cannot be excluded that the improved disease outcome across the 10 years may have improved due to other factors such as earlier diagnosis, starting b/tsDMARDs at a lower disease activity, improved self-management, fewer comorbidities, and other aspects that may have reduced the patient global assessment (a key component of DAS28) besides the effect of b/tsDMARDs.

Conclusions

In conclusion, our data shows that the average annual costs of treating a Norwegian RA patient with b/tsDMARD over the 10 year period 2010–19 were reduced by 47% for any user, and by 75% for naïve b/tsDMARD users. When adjusting for CPI, the percentage reduction was even higher. In Norway, with a tax-based healthcare system, we show that treatment with b/tsDMARDs has become more available at a lower cost, and the threshold for starting b/tsDMARDs has decreased significantly. Although not confirming causality, there is strong reason to believe that the national tender system has contributed

significantly to this favorable price reduction for b/tsDMARDs in Norway.

Abbreviations

ANOVA: Analysis of variance; BioRheuma: BIOlogic treatment of patients suffering from inflammatory RHEUMAtic disorders in Norway; BMI: Body mass index; b/tsDMARDs: Biologic and targeted synthetic disease-modifying antirheumatic drugs; CPI: Consumer price index; CRP: C-reactive protein; csDMARDs: Conventional synthetic DMARDs; ESR: Erythrocyte sedimentation rate; EUR: Euros; GDP: Gross domestic product; IGA: Investigator global assessment; MHAQ: Modified Health Assessment Questionnaire; NOK: Norwegian Kroners; PGA: Patient global assessment; PROMs: Patient-reported outcome measures; RA: Rheumatoid arthritis; REC: Regional ethical committee; RF: Rheumatoid factor; SJC28: 28 swollen joint count; SPSS: Statistical package for social sciences; TJC28: 28 tender joint count; SD: Standard deviation; TNFi: Tumor Necrosis Factor inhibitors; VAS: Visual analog scale; DAS28: Composite 28 joint count Disease Activity Score.

Supplementary Information

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Additional file 1: Supplementary Table. Aggregated data for demographic, disease outcome, and treatment during 2010–2019.

Additional file 2: Supplementary Table. RA prevalence of BioRheuma registered patients (≥20 years) shown for all participating centers.

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Authors' contributions

All authors have contributed with critical components to enable the delivery of the study and manuscript. These include: patient recruitment and/or data generation and/or analysis, as well as writing or critically revising the present manuscript and/or raising infrastructure to support the study. All authors read and approved the final manuscript.

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Availability of data and materials

Data are available on reasonable request and must be approved by all participating centers. Please contact the corresponding author by email to request the data from this study.

Declarations

Ethics approval and consent to participate

The study was approved by the regional ethical committee (REC 2010/3078). No consent from patients was required by the REC as we only use anonymized data.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests. The authors have no financial interests that could create a potential conflict of interest or the appearance of a conflict of interest concerning the submitted work.

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Publisher's Note

Supplementary table 1: Aggregated data for demographic, disease outcome, and treatment during 2010-2019.

	All BioRheuma patients (b/tsDMARDs, csDMARDs, Glucocorticoids); 2010-2019				b/tsDMARDs treated patients; 2010-2019				Non-b/tsDMARDs treated patients (2010-2019)				
	Mean	Range	Missing Data Mean, Range	P-value	Mean	Range	Missing Data Mean, Range	P-value	Mean	Range	Missing Data Mean, Range	P-value	P-value*
Demographics													
Age (Years)	61.4	60.7-62.4	1%, 0-10%	<0.001	59.3	58.7-59.8	1.1%, 0-11%	0.044	62.8	62.1-64.2	0.9%, 0-9%	<0.001	<0.001
Female	70.6%	71.0-71.8%	1%, 0-10%	<0.001	72.6%	71.7-73.5%	1.1%, 0-11%	0.938	70.4%	70.0-70.6%	0.9%, 0-9%	0.997	<0.001
BMI (kg/m^2)	26.0	25.7-26.3	12%, 3-49%	<0.001	25.9	25.5-26.3	9.9%, 2-57%	<0.001	26.0	25.7-26.3	13.5%, 4-44%	<0.001	0.022
Education (Years)	12.0	11.6-12.4	11.7%, 2-46%	<0.001	12.3	11.9-12.7	9.3%, 1-55%	<0.001	11.7	11.4-12.1	13.4%, 3-41%	<0.001	<0.001
Current Smokers	18.4%	14.1-23.7%	10.2%, 2-41%	<0.001	17.7%	13.7-22.6%	8.2%, 1-50%	<0.001	18.9%	14.5-24.2%	11.5%, 3-35%	<0.001	<0.001
Disease Duration (Years)	10.9	10.5-11.5	0.0%, 0-0%	<0.001	14.0	12.9-14.6	1.1%, 0-11%	<0.001	8.9	8.6-9.0	0.0%, 0-0%	0.348	<0.001
Enabled Workers (<65 years)	64.6%	62.6-68.9%	9.1%, 2-37%	0.001	59.1%	56.6-62.7%	7.4%, 1-45%	0.393	69.6%	68.2-73.2%	10.5%, 3-31%	0.055	<0.001
Biomarkers													
CCP Positive	74.8%	74.1-75.5%	31.4%, 19-47%	0.808	80.9%	80.1-82.0%	27.0%, 14-42%	0.900	70.0%	68.8-70.9%	34.5%, 22-49%	0.813	<0.001
RF Positive	67.4%	66.7-68.9%	45.4%, 32-59%	0.701	73.1%	72.1-74.7%	44.7%, 29-61%	0.798	63.4%	62.2-65.4%	46.0%, 36-58%	0.705	<0.001
Disease Activity													
ESR (mm/h)	16.4	14.6-19.0	30.6%, 26-38%	<0.001	15.5	13.5-18.6	26.4%, 20-32%	<0.001	17.1	15.5-19.1	33.6%, 28-43%	<0.001	<0.001
CRP (mg/L)	7.3	6.6-8.7	21.7%, 19-26%	<0.001	6.6	6.0-8.4	18.8%, 15-27%	<0.001	7.9	7.2-8.9	23.8%, 21-29%	<0.001	<0.001
TJC28 (0-28)	2.4	1.7-3.3	15.9%, 12-20%	<0.001	2.4	1.7-3.4	14.5%, 9-19%	<0.001	2.3	1.7-3.3	16.8%, 14-21%	<0.001	0.728
SJC28 (0-28)	1.4	0.9-2.2	15.9%, 12-20%	<0.001	1.4	0.8-2.3	14.5%, 9-19%	<0.001	1.5	1.0-2.2	16.8%, 14-21%	<0.001	<0.001
IGA (VAS, 0-100 mm)	14.7	11.9-17.1	38.6%, 31-51%	<0.001	15.2	12.0-18.1	40.2%, 35-50%	<0.001	14.4	11.8-16.6	37.6%, 24-52%	<0.001	<0.001
DAS28	2.7	2.5-3.1	33.7%, 30-39%	<0.001	2.7	2.4-3.1	30.4%, 26-34%	<0.001	2.7	2.5-3.1	36.0%, 33-42%	<0.001	<0.001
DAS28 Remission	55.6%	41.0-65.4%	33.7%, 30-39%	<0.001	56.4%	41.6-66.8%	30.4%, 26-34%	<0.001	54.9%	40.6-64.2%	36.0%, 33-42%	<0.001	<0.001
DAS28 LDA	16.2%	14.1-18.8%	33.7%, 30-39%	<0.001	16.3%	14.1-18.4%	30.4%, 26-34%	0.034	16.2%	14.0-19.0%	36.0%, 33-42%	<0.001	0.991
Patient-Reported Outcome Measures													
PGA (VAS, 0-100 mm)	33.3	32.3-35.8	11.2%, 9-12%	<0.001	32.5	31.9-33.3	10.0%, 8-11%	0.270	33.9	32.7-37.4	12.0%, 10-13%	<0.00	<0.001
Pain (VAS, 0-100 mm)	33.5	32.6-35.1	21%, 14-45%	<0.001	32.5	31.7-33.5	20.4%, 14-53%	0.204	34.1	32.9-36.4	21.5%, 14-40%	<0.00	<0.001
MHAQ (0-3)	0.45	0.43-0.49	14.2%, 12-23%	<0.001	0.47	0.45-0.51	14.9%, 10-37%	0.001	0.42	0.40-0.48	13.7%, 12-16%	<0.00	<0.001
Fatigue (VAS, 0-100 mm)	37.6	36.5-38.7	33.9%, 16-52%	0.001	38.5	37.1-40.1	37.1%, 15-54%	0.006	37.1	35.8-38.4	31.7%, 14-51%	0.023	<0.001
Morning Stiffness (hr)	0.9	0.8-0.9	37.4%, 16-56%	0.092	0.9	0.8-0.9	41.7%, 16-59%	0.614	0.9	0.8-0.9	34.5%, 15-53%	0.179	0.528
Supplementary Treatment Overview													
csDMARD users, N (%)	73.7%	70.9-75.6%	0%, 0-0 %	<0.001	70.2%	65.1-73.9%	0.0%, 0-0 %	<0.001	76.3%	70.3-81.3%	0.0%, 0-0 %	<0.001	<0.001
Methotrexate users, N (%)	64.5%	62.4-65.8%	0%, 0-0 %	<0.001	62.4%	56.7-67.6%	0.0% ,0-0 %	<0.001	66.2%	60.7-71.4%	0.0%, 0-0 %	<0.001	<0.001
Glucocorticoid users, N (%)	35.6%	30.1-42.7%	0%, 0-0 %	<0.001	34.7%	28.8-42.1%	0.0%, 0-0 %	<0.001	36.3%	31.1-43.1%	0.0%, 0-0 %	<0.001	<0.001

Note: The table includes all RA patients registered in the BioRheuma at the participating centers, b/tsDMARDs treated patients, and non-b/tsDMARDs treated patients during 2010-2019. Categorical variables are presented as a percentage and continuous variables as mean with range. Missing data presented as mean and range. χ^2 test for categorical variables and one-way ANOVA for continuous variables was used to test for differences during follow-up of ten years. *Abbreviation*: **RA** = Rheumatoid arthritis, **b/tsDMARDs** = biologic and target synthetic Disease-Modifying Antirheumatic Drugs, **BMI** = Body Mass Index, **CCP** = Anti-cyclic citrullinated peptide, **RF** = Rheumatoid Factor, **ESR** = Erythrocyte Sedimentation Rate, **CRP** = C-Reactive Protein, **TJC28** = Tender 28-Joint Count, **SJC28** = Swollen 28-Joint Count, **IGA** = Investigators Global Assessment, **VAS =** Visual Analog Scale (Measured 0-100), **DAS28** = Disease Activity Score, **LDA** = Low Disease Activity, **PGA** = Patient Global assessment, **MHAQ** = Modified Health Assessment Questionnaire, **csDMARDs** = conventional synthetic Disease-Modifying Antirheumatic Drugs. Occupation Status: **Enabled Workers** (<65 years old) = Full Job, Part-time Job, Student, Maternity Leave, Paternity leave, Sick Leave, Unemployed, Early Retirement, Part-time job/Sick Leave, Part-time job/Unemployed), Disabled Workers (< 65 years) = Part-time Job/Disabled Early Retirement, Early Retirement due to Disability, Early Retirement due to RA, Medical Rehabilitation, Occupational Rehabilitation. ***** = Shows the p-value between the mean of b/tsDMARDs treated patients (2010-2019) and non-b/tsDMARDs treated patients (2010-2019).

Supplementary table 2: RA prevalence of BioRheuma registered patients (≥20 years) shown for all participating centers.

	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Mean (Range)
All Centers	0.24%	0.31%	0.33%	0.32%	0.33%	0.30%	0.29%	0.29%	0.29%	0.29%	0.30%
(Range)	(0.11-0.54%)	(0.15-0.54%)	(0.21-0.54%)	(0.21-0.51%)	(0.20-0.51%)	(0.20-0.49%)	(0.21-0.45%)	(0.20-0.45%)	(0.19-0.45%)	(0.20-0.46%)	(0.24-0.33%)
[N/SA]	[4696/1.94^{M}]	[7205/2.36^{M}]	[7810/2.40^{M}]	[6849/2.14^{M}]	[7243/2.18^{M}]	[9044/2.99^{M}]	[9166/3.11^{M}]	[9213/3.14^{M}]	[9092/3.18^{M}]	[9323/3.21^{M}]	
Individual Centers											
UNN	0.30%	0.40%	0.45%	0.49%	0.42%	0.45%	0.43%	0.40%	0.37%	0.38%	0.41%
[N/SA]	[348/116165]	[465/117408]	[536/118850]	[596/120936]	[519/122724]	[562/124571]	[544/125752]	[503/127085]	[481/128272]	[487/129427]	(0.30-0.49%)
STO	0.27%	0.34%	0.34%	0.37%	0.41%	0.34%	0.30%	0.30%	0.27%	0.27%	0.32%
[N/SA]	[581/217240]	[743/220443]	[768/224504]	[838/228995]	[959/232344]	[810/236020]	[715/239088]	[720/242669]	[669/245920]	[672/249670]	(0.27-0.41%)
Førde	*	0.24%	0.30%	0.33%	0.37%	*	0.45%	0.45%	0.45%	0.46%	0.38%
[N/SA]		[183/77328]	[230/77947]	[260/78630]	[289/79142]		[359/80115]	[360/80851]	[365/81098]	[370/81022]	(0.24-0.46%)
HUS	0.12%	0.35%	0.37%	0.37%	0.38%	0.40%	0.38%	0.35%	0.37%	0.34%	0.34%
[N/SA]	[381/ 310279]	[1110/316175]	[1187/321659]	[1222/327905]	[1278/334155]	[1370/339543]	[1307/344043]	[1228/347150]	[1307/349990]	[1191/352635]	(0.12-0.40%)
Haugesund	0.11%	0.15%	0.21%	0.23%	0.28%	0.28%	0.27%	0.26%	0.23%	0.23%	0.23%
[N/SA]	[381/350860]	[545/358166]	[771/364895]	[840/373236]	[1052/380021]	[1096/386638]	[1053/390468]	[1020/392742]	[926/394673]	[929/397717]	(0.11-0.28%)
SSHF	0.54%	0.54%	0.54%	0.51%	0.51%	0.49%	0.41%	0.42%	0.36%	0.38%	0.47%
[N/SA]	[1097/203926]	[1123/207093]	[1130/210197]	[1091/213187]	[1107/215997]	[1066/219319]	[906/222085]	[951/224221]	[825/227349]	[870/229252]	(0.36-0.54%)
Betanien	*	0.33%	0.34%	0.32%	0.34%	0.28%	0.26%	0.30%	0.33%	0.32%	0.31%
[N/SA]		[1011/303902]	[1055/307582]	[1000/311026]	[1061/313848]	[887/316642]	[831/319921]	[960/322895]	[1062/325476]	[1052/327955]	(0.26-0.34%)
MHH	*	*	*	*	*	0.21%	0.21%	0.20%	0.19%	0.20%	0.22%
[N/SA]						[1180/562221]	[1228/572096]	[1157/582441]	[1132/592542]	[1213/602860]	(0.19-0.21%)
DS	0.22%	0.22%	0.22%	0.21%	0.20%	0.20%	0.22%	0.24%	0.25%	0.27%	0.23%
[N/SA]	[1006/457327]	[1033/467318]	[1073/479214]	[1002/487975]	[978/496866]	[1033/507474]	[1115/516365]	[1230/523007]	[1342/528676]	[1471/535980]	(0.20-0.27%)
LHR	0.31%	0.34%	0.36%	*	*	0.35%	0.37%	0.36%	0.32%	0.35%	0.35%
[N/SA]	[902/286619]	[992/288855]	[1060/291644]			[1040/297656]	[1108/298896]	[1084/300722]	[983/302508]	[1068/303694]	(0.31-0.37%)
Patient (≥20) from the BioRheuma Project											
	95.7%	99.3%	97.7%	94.1%	90.3%	99.9%	99.9%	99.9%	99.9%	99.9%	
Norway's national population (≥20)											
	3618442	3674972	3737305	3797822	3852406	3906903	3953206	3995587	4034726	4072755	
SA coverage of BioRheuma centers in Norway											
	53.6%	64.1%	64.1%	56.4%	56.5%	76.5%	78.6%	78.7%	78.7%	78.8%	68.6%

Note: The prevalence is estimated using BioRheuma age group ≥20 years and RA service area from the corresponding centers for the same age group. The prevalence that did not reach 0.1 was excluded from the further assessment due to a very low number (presented with *). Only prevalence above the cut-off value of 0.1 was analyzed for the mean across the ten years for each area, and to calculate prevalence for all hospitals and the total service area coverage. *Abbreviation*: **RA** = Rheumatoid Arthritis, **N** = Number of patients with rheumatoid arthritis in the BioRheuma project from individual centers, **SA** = Service Area (for rheumatoid arthritis patients) **UNN** = University Hospital of North Norway, **STO** = St. Olav's university hospital, **HUS** = Haukeland University Hospital, **SSHF** = Hospital of Southern Norway, **MHH** = Martina Hansen Hospital, **DS** = Diakonhjemmet Hospital, **LHR** = Lillehammer Hospital for Rheumatic Diseases, **M** = Millions.

PAPER II

BMC Health Services Research

RESEARCH

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Exploring the impact of the national tender system on the use of costly drugs treating rheumatoid arthritis patients in ten rheumatology centers in Norway (2010–2019)

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Abstract

Background Biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) are highly effective in treating rheumatoid arthritis (RA), albeit high drug cost has restricted their use in many countries. As a countermeasure, Norway implemented pharmaceutical tendering as a cost-reducing strategy. The aim of this study was to assess the annual proportion of different b/tsDMARDs registered to treat RA patients under the influence of a Norwegian pharmaceutical tendering between 2010 and 2019.

Method The data is collected from ten Norwegian outpatient centers. The included patients are categorized as naïve, non-naïve, and current b/tsDMARD users. 13 individual b/tsDMARDs are assessed and compared with the tender rankings from each year. Overview of subcutaneous (sc) with per oral vs. intravenous (iv) and biosimilars vs. non-biosimilar are also described.

Result The tender-winning b/tsDMARD was the most or second most used drug in nine out of ten years for naïve users, seven for non-naïve users, and twice for current users. The average sum of the highest and second highest proportion among naïve, non-naïve, and current b/tsDMARD users were 75%, 53%, and 50% during the ten years, respectively. The tender-winning drug was iv in eight out of ten years. However, the average total proportion of sc and per oral b/tsDMARDs was about 70% for naïve b/tsDMARD users, 50% for non-naïve b/tsDMARD users, and 60% for current b/tsDMARD users. The main contributors to sc and per oral b/tsDMARD were etanercept (reference and biosimilar) and certolizumab pegol. The main contributors to iv b/tsDMARD were rituximab reference and infliximab biosimilar. Despite low-ranking offers, rituximab reference (offered as a second-line drug) often achieved a high proportion among non-naïve and current b/tsDMARD users. After the introduction of biosimilars, their average proportion was about 40%, 40%, and 20% for naïve, non-naïve, and current b/tsDMARD users, respectively.

Conclusion Based on observed data, a higher tender rank was associated with a higher proportion among naïve and non-naïve b/tsDMARD users. However, in most cases, sc b/tsDMARDs achieved a higher proportion with lower tender ranks than iv b/tsDMARDs with higher tender ranks.

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Keywords Pharmaceutical tendering, Biosimilars, Biologics, Subcutaneous, Intravenous

Background

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease with a reported prevalence of 0.5–1% [1]. RA causes joint stiffness and pain, fatigue, physical impairments, and reduced quality of life [2–4], which can further lead to reduced work capacity and work disability (unemployment or early retirement) [5, 6]. This may contribute both directly and indirectly to the cost of illness, financially affecting the patients and their families, the healthcare system, and society [5, 6].

Major improvements in clinical outcomes during the last twenty years can be attributed to the usage of biologic and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) and treatment strategies focusing on treating RA patients into remission [7–11]. Despite today's wide availability of b/tsDMARDs, their high cost limits their use in many countries, contributing to a worldwide discrepancy in access to care [12–14]. As a countermeasure, the Norwegian Hospital Procurement Trust (NHPT) has vigorously promoted annual national pharmaceutical tendering with the intention to lower drug costs [15, 16].

In a recently published paper, we examined the cost changes of b/tsDMARDs for RA treatment between 2010 and 2019 in Norway under the influence of this national pharmaceutical tendering [16]. In the present study, the aim was to assess the annual proportion of different b/tsDMARD used to treat RA patients under the influence of the Norwegian pharmaceutical tendering between 2010 and 2019.

Methodology

Data and patient collection

Data were collected using the software GoTreatIT ® Rheuma (www.diagraphit.com) (GTI) from ten BioRheuma centers with standardized patient monitoring of the minimum dataset of variables presented below. Further details on the BioRheuma project and the BioRheuma centers have been described in another paper [16]. In short, from each participating center, anonymized Excel data files were for every year sent for merging and statical analysis. Due to the anonymized data from each center for each year, the collected data was assessed cross-sectionally to describe annual trends in a descriptive format. The data were extracted from each participating center's GTI database using two predefined queries for each year between 2010 and 2019. The first query retrieved RA patients registered with at least one visit in the evaluated year, generating the *current user dataset*. Data from the latest visit was used if multiple visits occurred during that year. The second query retrieved all patients starting annually on a b/tsDMARD for each year of the ten years, generating the *starting b/tsDMARD dataset*.

For included patients, collected data for each year encompassed demographic variables, biomarker variables, disease activity measures, and patient-reported outcome measures (PROMs). Demographic variables include patient age, sex, body mass index (BMI, kg/m2), current smoking status, and disease duration (calculated from the date of diagnosis until the latest visit at the outpatient clinic for the examined year).

Biomarker variables include rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP). Measures reflecting disease activity encompass laboratory measures (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)), the 28 swollen and tender joint count (SJC28 and TJC28), investigator global assessment (IGA) scored on a visual analog scale (VAS; 0-100 mm), and the composite 28 joint count Disease Activity Score using CRP (DAS28) [17].

The PROMs included were pain, patient global assessment (PGA), and fatigue scored on a VAS scale (0-100 mm). For each variable, the mean and average values were computed and presented separately for those treated with any b/tsDMARD as well as for TNFi-, non-TNFi-, and tsDMARD-groups.

Treatment user categorization

The evaluated data on the treatment user groups were divided into three categories: current b/tsDMARD users collected from the *current user dataset*, and naïve and non-naïve b/tsDMARD users (both registered on a new b/tsDMARD) collected from the *starting b/tsDMARD dataset* (Fig. 1). Naïve b/tsDMARD users are those registered receiving their first b/tsDMARD, and non-naïve b/tsDMARD users are those registered receiving the given b/tsDMARD after previously being on a different b/tsDMARD. Although the *starting b/tsDMARD dataset* does not specify the sequence or treatment duration, a non-chronological drug order of previously used b/tsDMARD for each b/tsDMARD was documented.

The proportions of each b/tsDMARD, defined as the number of individual drug registrations divided by the total number of drug registrations of the given drug for a given year, were calculated and presented annually. A cross-sectional trend assessment of the proportions of

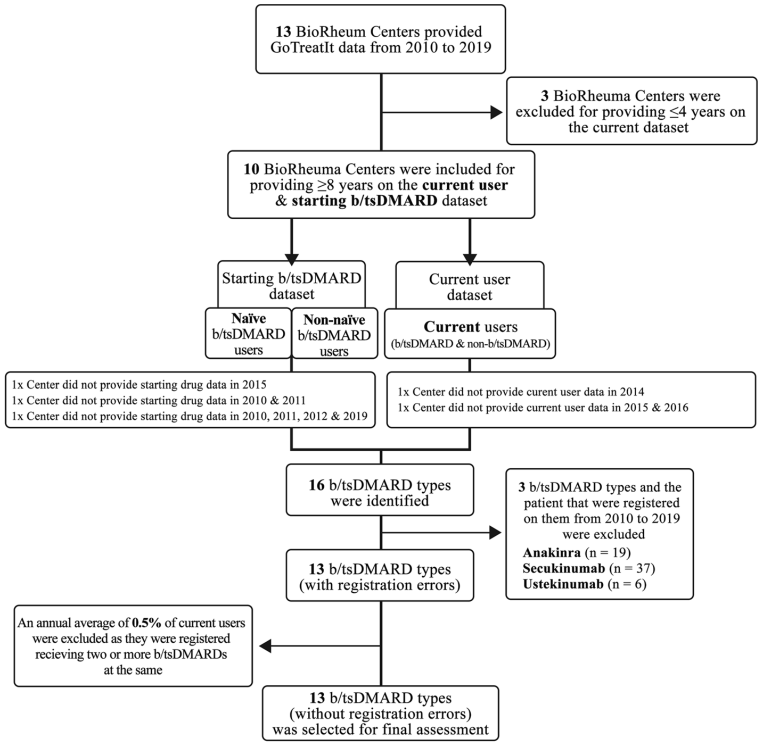

Fig. 1 Overview of the inclusion and exclusion of BioRheuma centers and the registered b/tsDMARDs. *Abbreviation*: b/tsDMARDs = biologic and targeted synthetic disease-modifying antirheumatic drugs

each distinct group was conducted independently. All evaluated registrations were collected from the GTI system and not compared to any other prescription registry.

BioRheuma centers selection

There were 13 BioRheuma centers initially planned for this study. However, three centers provided data (for the current dataset) for four or fewer years and were excluded from our analysis due to data deficiencies. The final current dataset consists of ten centers, each providing data for at least eight out of ten years. Details on these missing years are provided in the paper's flowchart (Fig. 1). Unless stated otherwise, all patients were included from the included centers.

Medication selection and analysis

A total of 16 b/tsDMARD types were identified, of which 13 were included in this study. Anakinra ($n=19$), secukinumab ($n=37$), and ustekinumab ($n=6$) were excluded due to either lack of indication or very few registrations and were prescribed outside the tendering. On average, the excluded b/tsDMARDs accounted for roughly six patients (0.2% of b/tsDMARDs) each year.

The included bDMARD Tumor Necrosis Factor inhibitors (TNFi) were intravenous (iv) infliximab reference (Remicade®) [1999] (presented with the trade name in parenthesis and the year of reaching the market in brackets), iv infliximab CT-P13 (Remsima®/Inflectra®) [2013], subcutaneous (sc) etanercept reference (Enbrel®) [2000], sc etanercept SB4 (Benepali®) [2016], sc adalimumab reference (Humira®) [2003], sc golimumab (Simponi®) [2009], and sc certolizumab pegol (Cimzia®) [2009]. The bDMARD non-TNFi were iv abatacept (Orencia®) [2007, and sc from 2012], iv rituximab reference (MabThera®) [1998], iv rituximab GP2013 (Rixathon®) [2017], and iv tocilizumab (RoActemra®) [2009, and sc from 2014]. The included tsDMARDs were per oral (po) baricitinib (Olumiant®) [2017] and po tofacitinib (Xeljanz®) [2017]. The distinction between iv and sc variants of tocilizumab and abatacept was not registered in GoTreatIt. As they arrived initially to market as iv, they were labeled iv throughout this study.

Patients who received double or multiple b/tsDMARDs (Fig. 1) were assessed as registration errors due to inconsistencies with our treatment guidelines and, as such, excluded from the study as it was not possible to distinguish the correctly registered b/tsDMARD. These errors are typically caused by record overlap when a new b/tsDMARD is added before a previous one is removed. These patients with registration errors were omitted from the study and accounted for 0.5% of the annual average of current users receiving b/tsDMARDs during the study period. See Supplementary Table 1 for further details.

Among non-naïve users, a few of the previous b/tsDMARD administration was attributed to either anakinra, secukinumab, or ustekinumab, but none of these non-naïve users were treated only with one of these drugs. Hence, their previous use did not impact the amount for naïve and non-naïve users.

Tender ranking, medication analysis

Each year the NHPT provides a report of the outcome of the Norwegian pharmaceutical tender, including a ranked list of b/tsDMARDs where rank 1 (highest rank) represents the least expensive drug offered. While the rank list is publicly available, the drug cost is confidential and only available for those with a need-to-know, e.g., prescribing rheumatologists, health economists, or certain health administrators. This study presents these recommendations with permission, albeit without details on the specific drug cost. The terms cost, price, and expenditure are used interchangeably in this paper with no distinction in context.

Statistical analysis

Continuous variables are presented as mean with range and categorical variables as percentages with range. The variables for the ten-year period were calculated with an average of the mean from individual years. Change and association between variables over the ten-year period were analyzed with a one-way analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables (independent for the b/tsDMARD overall, TNFi, non-TNFi, and tsDMARD groups). Although Table 1 displays each group's average size (N), the annual N used for preliminary calculations was derived from the current dataset. Details on the annual N can be found in Table 4. The proportion computations (in percentage) in Tables 2, 3 and 4 are derived from the total annual count (N) for each user group. Detailed explanations of the calculations are provided in the footnotes. No imputations were used for missing data. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 28.0 and Microsoft Excel. The graphical elements were developed using Microsoft Excel and supplemented using Adobe Photoshop.

Ethics

The study was approved by the regional ethical committee for medical health research ethics (REC) (Regional etisk komite Midt-Norge 2010/3078) and consequently follows the Declaration of Helsinki ethical principles of medical research involving human subjects. The study was also approved by the Institutional Review Board (Research Unit Sørlandet Hospital) and met the requirements of the Health Research Act [Helseforksningsloven] from 2009. The protocol used anonymized data, which did not require confirmed consent from the patient and was approved by the regional ethical committee for medical health research ethics. All data was collected as part of routine clinical care.

Results

Demographics and disease characteristics

Table 1 displays aggregated data on demographics, disease activity, and patient-reported outcomes based on treatment groups to contextualize the b/tsDMARD data assessments better and understand the evaluated RA population. The aggregated average values among current b/tsDMARD users were 59 years of age, 73% females, 26 kg/m^2 in BMI, 18% smokers, 14 years disease duration, 2.7 in DAS28, and 32 VAS in PGA. Table 1 shows further details of the aggregated overall b/tsDMARDs users and the three subgroups TNFi, non-TNFi, and tsDMARDs. Annual data on current, naïve, and non-naïve b/tsDMARD users is presented elsewhere [16].

The proportion of b/tsDMARDs

Table 2 shows an overview of b/tsDMARD prescriptions among naïve users, while Fig. 2 displays the annual tender ranking and percentage visualization of naïve prescriptions. Over the ten years, the total number of annual b/tsDMARD prescriptions for naïve users increased from 378 to 409 (highest in 2017 with 418). A proportion change from 86.2% to 2010 to 86.8% in 2019 (highest in 2012 with 91.2%) for TNFi and a proportion decrease from 13.8% to 2010 to 5.6% in 2019 (highest in 2015 with 16.0%) for non-TNFi was observed. An increase of 7.6% for tsDMARDs was observed in the last three years. No tsDMARD use was registered prior to 2017.

Table 3 shows an overview of b/tsDMARD proportion among non-naïve users, while Fig. 3 displays the annual tender ranking and percentage visualization for the non-naïve users. Over the ten years, the total annual b/tsDMARD proportion for non-naïve users increased from 452 to 1065. A proportion change from 47.1% to 2010 to 48.5% in 2019 (highest in 2016 with 82.8%) for TNFi and

Table 1 Demographic and disease characteristics in Norwegian rheumatoid arthritis patients currently using b/tsDMARDs during 2010–2019

	b/tsDMARDs 2010–2019 Average *N* = 3322			**TNFi 2010–2019 Average *N* = 2292**			**Non-TNFi 2010–2019 Average *N* = 961**			**tsDMARDs 2017–2019 Average *N* = 234**		
	Average of Mean, Range of Mean	Missing Data *Mean, Range*	*P*	Average of Mean, Range of Mean	Missing Data *Mean, Range*	*P*	Average of Mean, Range of Mean	Missing Data *Mean, Range*	*P*	Average of Mean, Range of Mean	Missing Data *Mean, Range*	*P*
Demographics												
Age (years)	59, 59–60	1%, 0–11%	0.035	58, 58–59	1%, 0–12%	0.064	62, 61–63	1%, 0–8%	0.057	58, 57–60	0%, 0–0%	0.129
Female	73%, 72–73%	1%, 0–11%	0.946	71%, 71–72%	1%, 0–12%	0.994	76%, 74–78%	1%, 0–8%	0.753	75%, 72–79%	0%, 0–0%	0.138
BMI (kg/m2)	26, 26–26	10%, 2–57%	< 0.001	26, 25–26	11%, 2–58%	< 0.001	26, 26–26	8%, 1–51%	0.616	27, 26–27	1%, 0–2%	0.218
Current Smokers	18%, 14–22%	8%, 1–49%	< 0.001	18%, 13–22%	9%, 1–51%	< 0.001	18%, 13–22%	7%, 1–44%	< 0.001	12%, 10–15%	1%, 0–2%	0.553
Disease Duration (years)	14, 13–15	0%, 0–0%	< 0.001	13, 12–14	0%, 0–0%	< 0.001	16, 15–17	0%, 0–0%	< 0.001	15, 13–17	0%, 0–0%	0.183
Biomarkers												
aCCP Positive	81%, 80–82%	27%, 14–42%	0.921	79%, 77–81%	27%, 15–42%	0.283	87%, 84–88%	27%, 15–42%	0.875	78%, 73–83%	12%, 8–16%	0.184
RF Positive	73%, 72–75%	45%, 28–61%	0.745	71%, 69–74%	44%, 29–60%	0.558	79%, 76–83%	47%, 30–66%	0.232	72%, 67–78%	22%, 20–24%	0.106
Disease Activity												
ESR (mm/h)	15, 13–19	26%, 21–32%	< 0.001	16, 14–18	26%, 21–32%	< 0.001	14, 11–19	27%, 21–32%	< 0.001	22, 19–25	32%, 29–37%	0.316
CRP (mg/L)	6.5, 5.7–8.4	19%, 16–27%	< 0.001	5.9, 5.1–7.5	19%, 15–27%	< 0.001	7.8, 6.2–11	19%, 13–26%	< 0.001	11, 8–15	19%, 16–22%	0.029
TJC28 (0–28)	2.4, 1.7–3.4	15%, 9–19%	< 0.001	2.0, 1.5–2.9	12%, 7–18%	< 0.001	3.3, 1.8–5.2	20%, 13–25%	< 0.001	4.0, 2.3–6.1	13%, 10–16%	< 0.001
SJC28 (0–28)	1.4, 0.8–2.3	15%, 9–19%	< 0.001	1.2, 0.7–1.9	12%, 7–18%	< 0.001	1.9, 0.8–3.9	20%, 13–25%	< 0.001	2.3, 1.2–3.4	13%, 10–16%	< 0.001
IGA (VAS 0-100 mm)	15, 12–18	40%, 35–50%	< 0.001	14, 11–16	40%, 34–51%	< 0.001	18, 12–25	41%, 34–49%	< 0.001	24, 15–35	28%, 23–36%	< 0.001
DAS28	2.7, 2.4–3.1	30%, 26–34%	< 0.001	2.5, 2.3–2.9	28%, 22–34%	< 0.001	3.0, 2.5–3.7	36%, 32–42%	< 0.001	3.3, 2.7–3.9	31%, 26–38%	< 0.001
Patient-Reported Outcome Measures												
PGA (VAS 0-100 mm)	32, 32–33	10%, 8–12%	0.333	30, 30–31	8%, 6–10%	0.652	38, 34–42	15%, 12–16%	< 0.001	43, 36–50	11%, 8–14%	0.003
Pain (VAS 0-100 mm)	32, 32–33	20%, 14–53%	0.329	30, 29–31	19%, 12–55%	0.351	37, 34–41	24%, 17–47%	< 0.001	41, 36–49	15%, 12–20%	0.025
Fatigue (VAS 0-100 mm)	38, 37–40	37%, 15–54%	0.002	36, 35–38	36%, 13–53%	0.041	44, 42–46	41%, 20–57%	0.604	48, 47–49	55%, 49–61%	0.921

Categorical variables are presented as percentages and continuous variables as mean. The presented data are average values from the displayed year within the shown drug category. Missing data are presented as mean with range. χ^2 test for categorical variables and one-way ANOVA for continuous variables was used to test for differences during follow-up of ten years

Abbreviations: *b/tsDMARDs* Biologic and target synthetic disease-modifying antirheumatic drugs, *TNFi* Tumor Necrosis Factor Inhibitor, *tsDMARDs* Target synthetic DMARDs, *BMI* Body Mass Index, *aCCP* Anti-cyclic citrullinated peptide, *RF* Rheumatoid Factor, *ESR* Erythrocyte Sedimentation Rate, *CRP* C-Reactive Protein, *TJC28* Tender 28-Joint Count, *SJC28* Swollen 28-Joint Count, *IGA* Investigators Global Assessment, *VAS* Visual Analog Scale (Measured 0-100), *DAS28* Disease Activity Score, *PGA* Patient Global assessment

Table 2 Overview of annual naïve b/tsDMARD prescriptions shown in numbers and percentages

	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Total (N)	378	424	421	385	356	368	400	418	408	409
TNFi	326 (86.2)	382 (90.1)	384 (91.2)	349 (90.6)	310 (87.1)	309 (84.0)	362 (90.5)	372 (89.0)	327 (80.1)	355 (86.8)
Infliximab R[a]	**63 (16.7)**	20 (4.7)	**14 (3.3)**	14 (3.6)	7 (2.0)	11 (3.0)	0 (0)	0 (0)	2 (0.5)	0 (0)
Infliximab[CT–P13]	NA	NA	NA	NA	**45 (12.6)**	**140 (38.0)**	**145 (36.3)**	**106 (25.4)**	**156 (38.2)**	24 (5.9)
Etanercept R[a]	47 (12.4)	295 (69.6)	273 (64.8)	62 (16.1)	26 (7.3)	18 (4.9)	25 (6.3)	5 (1.2)	5 (1.2)	0 (0)
Etanercept[SB4]	NA	NA	NA	NA	NA	NA	22 (5.5)	208 (49.8)	138 (33.8)	13 (3.2)
Adalimumab R[a]	63 (16.7)	18 (4.2)	10 (2.4)	5 (1.3)	7 (2)	1 (0.3)	3 (0.8)	1 (0.2)	5 (1.2)	**313 (76.5)**
Certolizumab	12 (3.2)	21 (5.0)	69 (16.4)	**249 (64.7)**	215 (60.4)	134 (36.4)	166 (41.5)	52 (12.4)	19 (4.7)	5 (1.2)
Golimumab	141 (37.3)	28 (6.6)	18 (4.3)	19 (4.9)	10 (2.8)	5 (1.4)	1 (0.3)	0 (0)	2 (0.5)	0 (0)
Non-TNFi	52 (13.8)	42 (9.9)	37 (8.8)	36 (9.4)	46 (12.9)	59 (16.0)	38 (9.5)	46 (11.0)	51 (12.5)	23 (5.6)
Abatacept[a]	8 (2.1) §	4 (0.9)	0 (0)	3 (0.8)	2 (0.6)	8 (2.2)	4 (1.0)	9 (2.2)	9 (2.2)	1 (0.2)
Rituximab R[a]	29 (7.7)[b]	**34 (8.0)**[b]	19 (4.5)[b]	16 (4.2)[b]	21 (5.9)[b]	19 (5.2)[b]	22 (5.5)	18 (4.3)	26 (6.4)[b]	7 (1.7)[b]
Rituximab[GP2013]	NA	NA	NA	NA	NA	NA	NA	NA	0 (0)	12 (2.9)[b]
Tocilizumab[a]	15 (4.0)	4 (0.9)	18 (4.3)	17 (4.4)	23 (6.5)	32 (8.7)	12 (3.0)	19 (4.5)	16 (3.9)	3 (0.7)
tsDMARDs	NA	NA	NA	NA	NA	NA	NA	0 (0)	30 (7.4)	31 (7.6)
Tofacitinib	NA	NA	NA	NA	NA	NA	NA	0 (0)	30 (7.4)	3 (0.7)
Baricitinib	NA	NA	NA	NA	NA	NA	NA	0 (0)	0 (0)	28 (6.8)
∑ 1st + 2nd HV	54%[c]	78%[c]	81%	81%[c]	73%[c]	74%[c]	78%[c]	75%[c]	72%[c]	83%[c]
∑ SC + PO	70%	85%	88%	87%	73%	43%	54%	64%	49%	89%
∑ Biosimilar	0%	0%	0%	0%	13%	38%	42%	75%	72%	12%

Annual naïve treatment of rheumatoid arthritis patients in Norway for the period 2010–2019 showing the prescription of specific b/tsDMARDs. Total (N) is the amount of naïve b/tsDMARD prescriptions each year. All values are the annual numbers of prescribed drugs (or subcategories) with a percentage (%) of the Total (N). ∑ 1st + 2nd HV = The sum of the first and second Highest Proportion of b/tsDMARDs. ∑ SC + PO = The accumulated amount of subcutaneous and per oral b/tsDMARD of all naïve b/tsDMARD users. ∑ Biosimilar = The sum of the total amount of biosimilars

Abbreviation: *b/tsDMARDs* Biologic and targeted synthetic disease-modifying antirheumatic drugs, *TNFi* Tumor Necrosis Factor inhibitor, *tsDMARDs* Target synthetic DMARDs, *NA* Not available, *R* Reference agent

[a] Infliximab, etanercept, adalimumab reference, abatacept, and rituximab had their first recommendation in 2008 and tocilizumab in 2009

[b] Illustrates which drug was recommended on the condition of being a second-line drug

[c] Indicate the tender winner is also either the highest or second highest in proportion. The annual tender winner is marked in bold

a proportion decrease from 52.9% to 2010 to 30.1% in 2019 (highest in 2010) for non-TNFi was observed. The tsDMARDs increased to 21.3% in 2019 (29.0% in 2018).

During the ten-year study period, the number of registered RA patients in the databases increased from 4885 to 2010 to 9280 in 2019. Table 4 reports the number of current users of b/tsDMARDs, while Fig. 4 shows the annual tender ranking and visualizes the current b/tsDMARD proportion. The percentage of annual individual b/tsDMARD use increased from 39.1% ($n=1910$) in 2010 to 44.2% ($n=4098$) in 2019. Across the study period, the TNFi proportion decreased from 76.1% to 2010 to 64.4% in 2019 (highest in 2010), non-TNFi increased from 23.9% to 2010 to 25.5% in 2019 (highest in 2017 with 32.9%), while tsDMARDs increased to 10.1% in 2019.

The average sum of the highest and second highest proportions among naïve, non-naïve, and current users were 75%, 53%, and 50% during the ten years, respectively. In Figs. 2, 3 and 4, the ranks are arranged from 1 to 6 ((1), (2), (3), (4), (5), and (6)), ranks > 6 (> 6), those that did not give any offers (NO), and those that were outcompeted by their equivalent biosimilar (BE). The annual winner for each year is emboldened in Tables 2, 3 and 4.

Individual b/tsDMARD proportion observations

Rituximab reference (iv) was approved in 1998 and included in the Norwegian pharmaceutical tendering. Initially, rituximab reference remained relatively stable across all user categories, then decreased over six years among naive and non-naive but not current users. Despite this pattern, rituximab reference was either the highest or second highest in proportion in eight out of ten years for current users, five for non-naïve users, and once for naïve users.

During the first four years (2010–2013), iv infliximab reference (approved in 1999) was observed to have a low prescription proportion compared with all other b/tsDMARDs. In 2014 its biosimilar infliximab CT-P13 gave its first offer (ranking first). In the following years (2014 to 2016), infliximab reference fell close to zero in all categories, while infliximab CT-P13 rapidly increased. Infliximab CT-P13 decreased drastically in 2019 for both

Table 3 Overview of annual non-naïve b/tsDMARDs prescription shown in numbers and percentages

	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Total (N)	452	463	454	471	496	578	1270	921	656	1065
TNFi	213 (47.1)	252 (54.4)	282 (62.1)	281 (59.7)	278 (56.0)	363 (62.8)	1052 (82.8)	635 (68.9)	333 (50.8)	517 (48.5)
Infliximab R[b]	**23 (5.1)**	11 (2.4)	**24 (5.3)**	17 (3.6)	12 (2.4)	10 (1.7)	0 (0)	0 (0)	1 (0.2)	0 (0)
Infliximab[CT–P13]	NA	NA	NA	NA	**29 (5.8)**	**159 (27.5)**	**355 (28.0)**	**213 (23.1)**	**173 (26.4)**	122 (11.5)
Etanercept R[b]	60 (13.3)	98 (21.2)	62 (13.7)	44 (9.3)	43 (8.7)	37 (6.4)	37 (2.9)	4 (0.4)	2 (0.3)	1 (0.1)
Etanercept[SB4]	NA	NA	NA	NA	NA	NA	494 (38.9)	360 (39.1)	127 (19.4)	57 (5.4)
Adalimumab R[b]	36 (8.0)	41 (8.9)	22 (4.8)	10 (2.1)	17 (3.4)	6 (1)	5 (0.4)	3 (0.3)	8 (1.2)	**320 (30.0)**
Certolizumab	32 (7.1)	77 (16.6)	138 (30.4)	**152 (32.3)**	137 (27.6)	118 (20.4)	144 (11.3)	42 (4.6)	17 (2.6)	14 (1.3)
Golimumab	62 (13.7)	25 (5.4)	36 (7.9)	58 (12.3)	40 (8.1)	33 (5.7)	17 (1.3)	13 (1.4)	5 (0.8)	3 (0.3)
Non-TNFi	239 (52.9)	211 (45.6)	172 (37.9)	190 (40.3)	218 (44.0)	215 (37.2)	218 (17.2)	231 (25.1)	133 (20.3)	321 (30.1)
Abatacept[b]	43 (9.5)[c]	38 (8.2)	15 (3.3)	10 (2.1)	51 (10.3)	59 (10.2)	47 (3.7)	57 (6.2)	32 (4.9)	11 (1.0)
Rituximab R[b]	125 (27.7)[c]	**117 (25.3)**[c]	83 (18.3)[c]	94 (20.0)[c]	101 (20.4)[c]	87 (15.1)[c]	91 (7.2)	90 (9.8)	65 (9.9)[c]	10 (0.9)[c]
Rituximab[GP2013]	NA	NA	NA	NA	NA	NA	NA	NA	3 (0.5)	284 (26.7)[c]
Tocilizumab[b]	71 (15.7)	56 (12.1)	74 (16.3)	86 (18.3)	66 (13.3)	69 (11.9)	80 (6.3)	84 (9.1)	33 (5.0)	16 (1.5)
tsDMARDs	NA	NA	NA	NA	NA	NA	NA	55 (6.0)	190 (29.0)	227 (21.3)
Tofacitinib	NA	NA	NA	NA	NA	NA	NA	39 (4.2)	179 (27.3)	29 (2.7)
Baricitinib	NA	NA	NA	NA	NA	NA	NA	16 (1.7)	11 (1.7)	198 (18.6)
∑ 1st + 2nd HV	43%	47%[a]	49%	52%[a]	48%	48%[a]	67%[a]	62%[a]	54%[a]	57%[a]
∑ SC + PO	42%	52%	57%	56%	48%	34%	55%	52%	53%	58%
∑ Biosimilar	NA	NA	NA	NA	6%	28%	67%	62%	46%	44%

Annual non-naïve treatment of rheumatoid arthritis patients in Norway for the period 2010–2019 showing the prescription of specific b/tsDMARDs. Total (N) is the amount of non-naïve b/tsDMARD prescriptions each year. All values are the annual numbers of prescribed drugs (or subcategories) with a percentage (%) of the Total (N). ∑ 1st + 2nd HV = The sum of the first and second Highest Proportion of b/tsDMARDs. ∑ SC + PO = The accumulated amount of subcutaneous and per oral b/tsDMARD of all naïve b/tsDMARD users. ∑ Biosimilar = The sum of the total amount of biosimilars

Abbreviation: *b/tsDMARDs* Biologic and targeted synthetic disease-modifying antirheumatic drugs, *TNFi* Tumor Necrosis Factor inhibitor, *tsDMARDs* Target synthetic DMARDs, *NA* Not available, *R* Reference agent

[a] Indicate the tender winner is also either the highest or second highest in proportion. The annual tender winner is marked in bold

[b] Infliximab, etanercept, adalimumab reference, abatacept, and rituximab had their first recommendation in 2008 and tocilizumab in 2009

[c] Illustrates which drug was recommended on the condition of being a second-line drug

naïve and non-naïve users. That same year iv biosimilar rituximab GP2013 was introduced, and sc adalimumab reference won the tendering. While rituximab GP2013 was negligible for the naïve and current users, it acquired a quarter of the non-naïve proportion in 2019 (rank 4).

Etanercept reference (sc) was also one of the b/tsDMARDs that participated in the early years of pharmaceutical tendering, and in contrast to most other b/tsDMARD, etanercept reference managed to acquire a large proportion prior to 2010. In 2010, it constituted 36% of the total current proportion. This pattern remained stable at around one-third of the total and as the highest proportion until the introduction of etanercept SB4 in 2016, after which etanercept reference gradually decreased (3% in 2019) while etanercept SB4 increased. While not equally stable but overall high in proportion, the same turnover between etanercept reference and its biosimilar was observed among naïve and non-naïve users.

The second observably high sc b/tsDMARD was certolizumab pegol. While it did not reach high numbers initially nor ever managed to reach the highest proportion among current users (2–18%), its proportion was relatively stable, even after the introduction of biosimilars. It was most prescribed between 2012 and 2016 for naïve and non-naïve users, acquiring the highest or second highest proportion in almost all those years. Between 2013 and 2016, it provided either the best or second-best offer during the tendering. Interestingly, from 2017 to 2019, its offers were above rank six each year, but it still managed to keep relatively stable current users.

Golimumab (sc) never acquired a large proportion and never came first or second on the tender ranking (three times rank 3). Adalimumab reference (sc), which had even worse-ranked offers (all above rank six, except 2019), had a higher proportion among current users but lower among naïve and non-naïve compared to golimumab. In 2019 adalimumab reference was priced lower than its corresponding biosimilar adalimumab GP2017, Hyrimoz®, and ranked first in the pharmaceutical tendering (resulting in an exclusion of Hyrimoz from the Norwegian tendering). During the same year, a slight

Table 4 Overview of annual current b/tsDMARD use shown in amount and percentage

	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
	n = 4885	*n* = 7230	*n* = 7970	*n* = 7248	*n* = 7993	*n* = 9010	*n* = 9037	*n* = 9129	*n* = 9048	*n* = 9280
Total (N)	1910 [39.1]	2829 [39.1]	3111 [39.0]	3029 [41.8]	3388 [42.4]	3639 [40.4]	3631 [40.2]	3771 [41.3]	3813 [42.1]	4098 [44.2]
TNFi	1454 (76.1)	2099 (74.2)	2279 (73.3)	2212 (73.0)	2430 (71.7)	2470 (67.9)	2442 (67.3)	2498 (66.2)	2394 (62.8)	2639 (64.4)
Infliximab R[b]	**234 (12.3)**	274 (9.7)	**252 (8.1)**	242 (8.0)	238 (7.0)	152 (4.2)	63 (1.7)	38 (1.0)	27 (0.7)	18 (0.4)
Infliximab[CT–P13]	NA	NA	NA	NA	**60 (1.8)**	**269 (7.4)**	**435 (12.0)**	**448 (11.9)**	**510 (13.4)**	438 (10.7)
Etanercept R[b]	688 (36.0)	1130 (39.9)	1242 (39.9)	1104 (36.4)	1078 (31.8)	977 (26.8)	620 (17.1)	226 (6.0)	164 (4.3)	113 (2.8)
Etanercept[SB4]	NA	NA	NA	NA	NA	NA	255 (7.0)	874 (23.2)	948 (24.9)	878 (21.4)
Adalimumab R[b]	396 (20.7)	430 (15.2)	428 (13.8)	315 (10.4)	313 (9.2)	295 (8.1)	262 (7.2)	225 (6.0)	200 (5.2)	**713 (17.4)**
Certolizumab	29 (1.5)	94 (3.3)	188 (6.0)	**374 (12.3)**	553 (16.3)	611 (16.8)	660 (18.2)	571 (15.1)	444 (11.6)	394 (9.6)
Golimumab	107 (5.6)	171 (6.0)	169 (5.4)	177 (5.8)	188 (5.5)	166 (4.6)	147 (4.0)	116 (3.1)	101 (2.6)	85 (2.1)
Non-TNFi	456 (23.9)	730 (25.8)	832 (26.7)	817 (27.0)	958 (28.3)	1169 (32.1)	1189 (32.7)	1242 (32.9)	1169 (30.7)	1047 (25.5)
Abatacept[b]	68 (3.6) §	85 (3.0)	79 (2.5)	68 (2.2)	97 (2.9)	126 (3.5)	129 (3.6)	147 (3.9)	125 (3.3)	99 (2.4)
Rituximab R[b]	329 (17.2)[c]	**533 (18.8)**[c]	589 (18.9)[c]	558 (18.4)[c]	617 (18.2)[c]	753 (20.7)[c]	777 (21.4)	788 (20.9)	781 (20.5)[c]	456 (11.1)[c]
Rituximab[GP2013]	NA	NA	NA	NA	NA	NA	NA	NA	4 (0.1)	266 (6.5)[c]
Tocilizumab[b]	59 (3.1)	112 (4.0)	164 (5.3)	191 (6.3)	244 (7.2)	290 (8.0)	283 (7.8)	307 (8.1)	259 (6.8)	226 (5.5)
tsDMARDs	NA	NA	NA	NA	NA	NA	NA	31 (0.8)	250 (6.6)	412 (10.1)
Tofacitinib	NA	NA	NA	NA	NA	NA	NA	24 (0.6)	233 (6.1)	227 (5.5)
Baricitinib	NA	NA	NA	NA	NA	NA	NA	7 (0.2)	17 (0.4)	185 (4.5)
∑ 1st + 2nd HV	57%	59%[a]	59%	55%	50%	48%	40%	44%	45%	39%[a]
∑ SC + PO	64%	65%	65%	65%	63%	56%	54%	54%	55%	63%
∑ Biosimilar	NA	NA	NA	NA	2%	7%	19%	35%	38%	39%

Annual current treatment of rheumatoid arthritis patients in Norway for the period 2010–2019 showing the use of specific b/tsDMARDs. Total (N) is the amount of current b/tsDMARD use each year. All values are the annual numbers of used drugs (or subcategories) with a percentage (%) of the Total (N). Percentages in brackets [%] are estimated from the total registered patients (n). ∑ 1st + 2nd HV = The sum of the first and second Highest Proportion of b/tsDMARDs. ∑ SC + PO = The accumulated amount of subcutaneous and per oral b/tsDMARD of all naïve b/tsDMARD users. ∑ Biosimilar = The sum of the total amount of biosimilars

Abbreviation: b/tsDMARDs Biologic and targeted synthetic disease-modifying antirheumatic drugs, *TNFi* Tumor Necrosis Factor inhibitor, *tsDMARDs* Target synthetic DMARDs, *NA* Not available, *R* Reference agent

[a] Indicate the tender winner is also either the highest or second highest in proportion. The annual tender winner is marked in bold

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[c] Illustrates which drug was recommended on the condition of being a second-line drug

increase (5–17%) in proportion was observed among the adalimumab reference current users, and a substantial increase was observed among both the naïve (1–77% increase in proportion) and non-naïve users (1–30% increase).

Tocilizumab (iv) proportion increased during the first four years but gradually decreased during the next six years for naïve and non-naïve users. For current users, it remained stable after the initial increase. Between 2010 and 2019, abatacept (iv) had a low yet stable prescription proportion for all categories, with offers in the tendering ranking above fifth for most years. Both tocilizumab and abatacept were initially offered as iv drugs, but from 2014 (tocilizumab) and 2012 (abatacept), they were also approved for subcutaneous use.

Rituximab reference was only recommended as a second-line drug during the ten years, except those years when no offers were provided. Abatacept in 2010 and rituximab GP2013 in 2019 were also recommended as second-line drugs. In other words, these drugs were recommended to be used only when another b/tsDMARD showed inadequate effect or resulted in adverse effects. Second-line drugs are marked in Tables 2, 3 and 4.

Tofacitinib and baricitinib were introduced in 2017 as po (tablet) b/tsDMARDs (tsDMARDs). Non-naïve users in 2018 for tofacitinib and 2019 for baricitinib acquired about 30% and 20% of the total proportion, respectively. The tsDMARDs did not acquire more than 10% combined proportion in the other user subgroups and years.

Subcutaneous and oral vs. intravenous b/tsDMARD proportion

On average, across the ten years, the sum of subcutaneous and per oral (sc/po) b/tsDMARDs accounted for 70.0% (range 42.9–88.5%) among all naïve b/tsDMARD users, 50.7% (range 33.6–58.4%) among non-naïve users, and 60.4% (range 53.5–62.2%) among current users (Fig. 5).

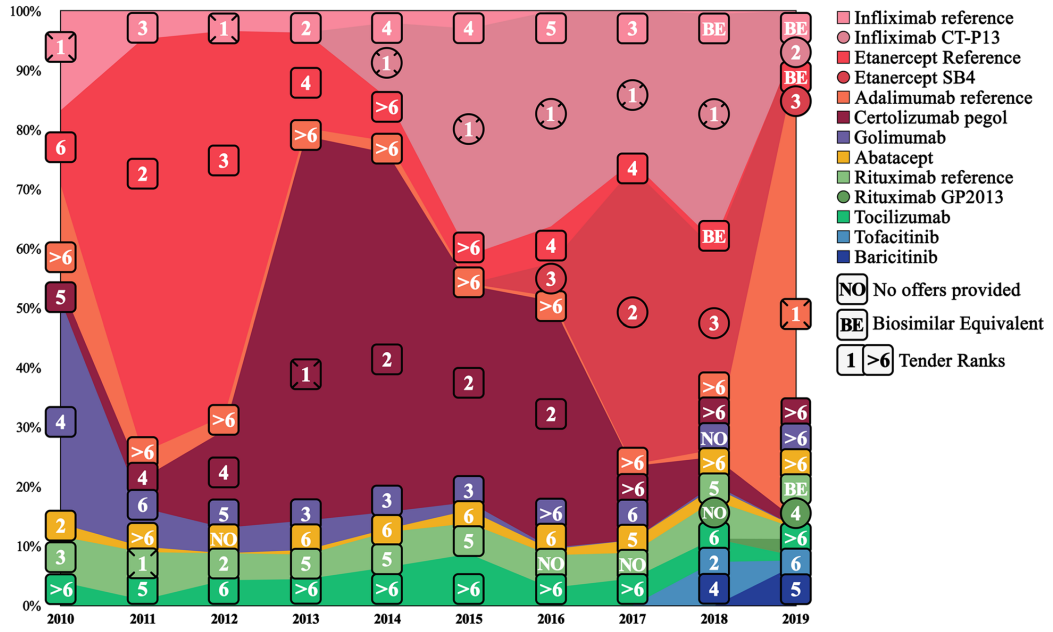

Fig. 2 Overview of annual naïve b/tsDMARD prescriptions illustrated with tender rankings in a stacked area graph. *Note*: Annual naïve treatment of rheumatoid arthritis patients in Norway for the period 2010–2019 showing the prescription of specific b/tsDMARDs drugs with corresponding tender rankings for the b/tsDMARDs drugs displayed using a stacked area graph. The specific values are shown in Table 3. Each b/tsDMARD has a unique color, shown on the right. Biosimilars are marked with circles. No offers indicate b/tsDMARD refrained from participating in the annual tender. Only the best offer was recommended among participating equivalent biosimilars and their corresponding reference agents. Those that provided an offer but were not recommended are marked as Biosimilar Equivalents. *Abbreviation*: b/tsDMARDs = biologic and targeted synthetic disease-modifying antirheumatic drugs

Etanercept reference and its biosimilar SB4 combined and certolizumab pegol constituted about 40% on average each of the sc/po b/tsDMARD proportion among naïve users and around 35% on average among non-naïve users. The combined proportion of etanercept reference and its biosimilar were highest for the current users, where it constituted 52% on average of the sc/po b/tsDMARD proportion. While adalimumab reference achieved 11–18% on average among the different subgroup users, it constituted 86%, 51%, and 28% of the sc/po b/tsDMARD proportion for naïve, non-naïve, and current users in 2019, respectively.

The iv b/tsDMARDs accounted for an average of 30.0% (range 11.5–57.1%) among all naïve b/tsDMARD users, 49.3% (range 41.6–66.4%) among non-naïve users, and 39.6% (range 53.5–62.2%) among current users (Fig. 5). For naïve users, the combined proportion of infliximab reference and infliximab CT-P13 constituted 54% on average of all iv b/tsDMARDs. In comparison, the rituximab reference and rituximab GP2013 combined covered less than 2% on average. For non-naïve users, the infliximab combination and the rituximab combination were relatively similar on average (29% vs. 37%, respectively). Among non-naïve iv b/tsDMARD users, Rituximab reference dominated until infliximab CT-P13 started gaining market in 2014–2015, with another shift in 2019 in favor of rituximab GP2013. For current users, the combination difference was more prominent, with 49% for the rituximab combination and 28% for the infliximab combination.

While sc/po b/tsDMARD were consistently higher or similar in proportion compared to iv b/tsDMARDs across all three user subgroups, the tender-winning drug was iv in eight of ten pharmaceutical tenders. For iv current and non-naïve users, the rituximab combination was favored over the infliximab combination, despite the infliximab combination winning the tender seven out of ten times, while the rituximab combination won once. The accumulated sc/po b/tsDMARDs are shown separately in Tables 2, 3, and 4.

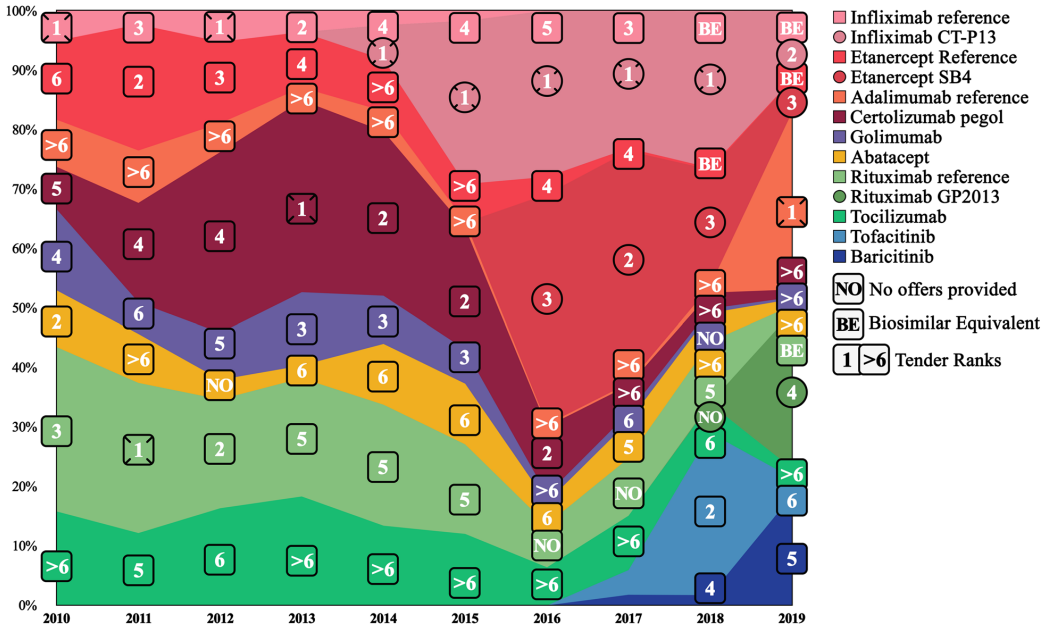

Fig. 3 Overview of annual non-naïve b/tsDMARD prescriptions illustrated with tender rankings in a stacked area graph. *Note*: Annual non-naïve treatment of rheumatoid arthritis patients in Norway for the period 2010–2019 showing the prescription of specific b/tsDMARDs drugs with corresponding tender rankings for the b/tsDMARDs drugs displayed using a stacked area graph. The specific values are shown in Table 4. Each b/tsDMARD has a unique color, shown on the right. Biosimilars are marked with circles. No offers indicate b/tsDMARD refrained from participating in the annual tender. Only the best offer was recommended among participating equivalent biosimilars and their corresponding reference agents. Those that provided an offer but were not recommended are marked as Biosimilar Equivalents. *Abbreviation*: b/tsDMARDs = biologic and targeted synthetic disease-modifying antirheumatic drugs

Biosimilars vs. non-biosimilar proportion

During the last six years of the study period, biosimilars were observed to have either the highest or second highest proportion six out of six years for naïve b/tsDMARD users, five for non-naïve b/tsDMARD users, and three for current b/tsDMARD users. The average total biosimilar proportion was 41.9% (range 12.0–75.1%), 42.0% (range 5.8–66.9%), and 23.4% (range 1.8–38.6%) for naïve, non-naïve and current b/tsDMARD users, respectively (Tables 2, 3 and 4). The tender-winning b/tsDMARD was biosimilar infliximab CT-P13 in five out of six tenders. Observations of the turnover between the reference agent (infliximab and etanercept) and their corresponding biosimilars in all user subgroups can be found in Figs. 2, 3 and 4. The difference between biosimilars and non-biosimilar is displayed in Fig. 6.

Discussion

The main finding of this study shows that b/tsDMARD procurements during the ten-year period, guided by the Norwegian pharmaceutical tendering, appeared to influence the choice of treatment among RA patients registered on a new b/tsDMARD, especially among those without prior b/tsDMARD registration (naïve users). This was determined by observing a tender-winning b/tsDMARD also being the highest or second highest in registration in nine out of ten years for naïve users, seven out of ten for non-naïve users, and only twice among current users. While the iv b/tsDMARDs were the tender-winning drug in seven out of ten years, the sc/po b/tsDMARDs acquired a higher proportion on average among naïve and current users and equally among non-naïve users. Based on these observations, generalized assumptions can be made. A better offer (i.e., higher tender rank) appears to be linked with increased new registrations for the given b/tsDMARD. However, the highest tender rank may not always correspond with changes in b/tsDMARD registration pattern among the current b/tsDMARD users. This may be due to the high number of loyal b/tsDMARD users or prescribers, i.e., those patients who wish to remain or are kept by their rheumatologist on the same b/tsDMARD despite better economic alternatives.

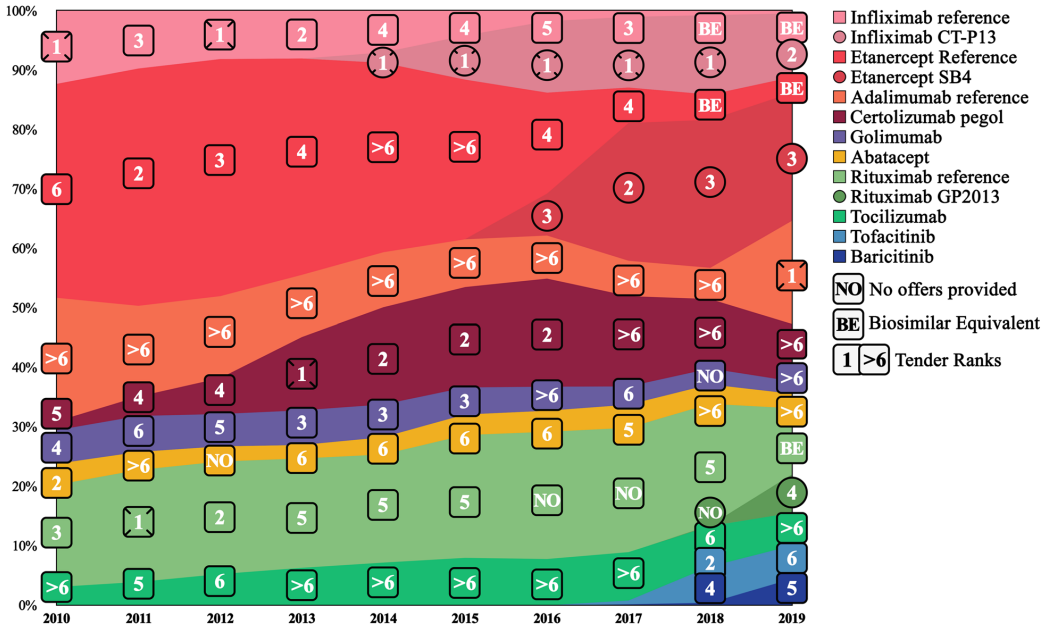

Fig. 4 Overview of annual current b/tsDMARDs use illustrated with tender rankings in a stacked area graph. *Note*: Annual current treatment of rheumatoid arthritis patients in Norway for the period 2010–2019 showing the use of specific b/tsDMARDs drugs with corresponding tender rankings for the b/tsDMARDs drugs displayed using a stacked area graph. The specific values are shown in Table 2. Each b/tsDMARD has a unique color, shown on the right. Biosimilars are marked with circles. No offers indicate b/tsDMARD refrained from participating in the annual tender. Only the best offer was recommended among participating equivalent biosimilars and their corresponding reference agents. Those that provided an offer but were not recommended are marked as Biosimilar Equivalents. *Abbreviation*: b/tsDMARDs = biologic and targeted synthetic disease-modifying antirheumatic drugs

One may argue that if the loyalty of either the user or the prescriber to the given b/tsDMARD is established, e.g., via consistent low cost and/or treatment satisfaction, it is more likely that the RA patient will remain on their current b/tsDMARD, regardless of less costly alternatives available. Such an example can be observed with certolizumab pegol, which gained the proportion benefit among naïve and non-naïve users with first- and second-rank offers in the period between 2013 and 2016. Thereafter, during the three following years, certolizumab pegol remained relatively stable in proportion among current users despite only providing tender offers above rank six. This loyalty is further endorsed by the lack of available evidence or recommendations to promote a cost-beneficial non-medical switch between various b/tsDMARDs with different substances (e.g., within TNFi, or between TNFi and non-TNFi) [18]. Norwegian rheumatologists generally follow the "do not change from the winning team" principle. However, switching non-medically between a reference agent and its biosimilar (or between biosimilars) is now generally recognized and is usually conducted to achieve lower costs in Norway. Some may argue that there is inconclusive data on the safety of conducting this type of non-medical switch and advocate for not switching between reference agent and biosimilar; however, no consistent evidence suggests it is unsafe either [19]. Results from Norway (NOR-SWITCH study) [20, 21] and Denmark (DANBIO registry) [22, 23] have shown positive outcomes when switching (even non-medically) patients from reference agents to the cheaper biosimilar alternative. Since 2018, the Norwegian pharmaceutical tendering has decided to only recommend the best offer among the reference agents and its biosimilars and considered the respective others as bioequivalent.

While iv b/tsDMARD generally provided better offers, they were almost consistently lower in proportion than sc/po b/tsDMARDs. The low interest in iv drugs compared to sc/po may be related to the iv drugs' additional cost and less favorable patient satisfaction [24, 25]. In Norway, by our understanding, the overall cost of iv b/tsDMARD entails higher additional healthcare expenditure due to medical materials, training of anyone

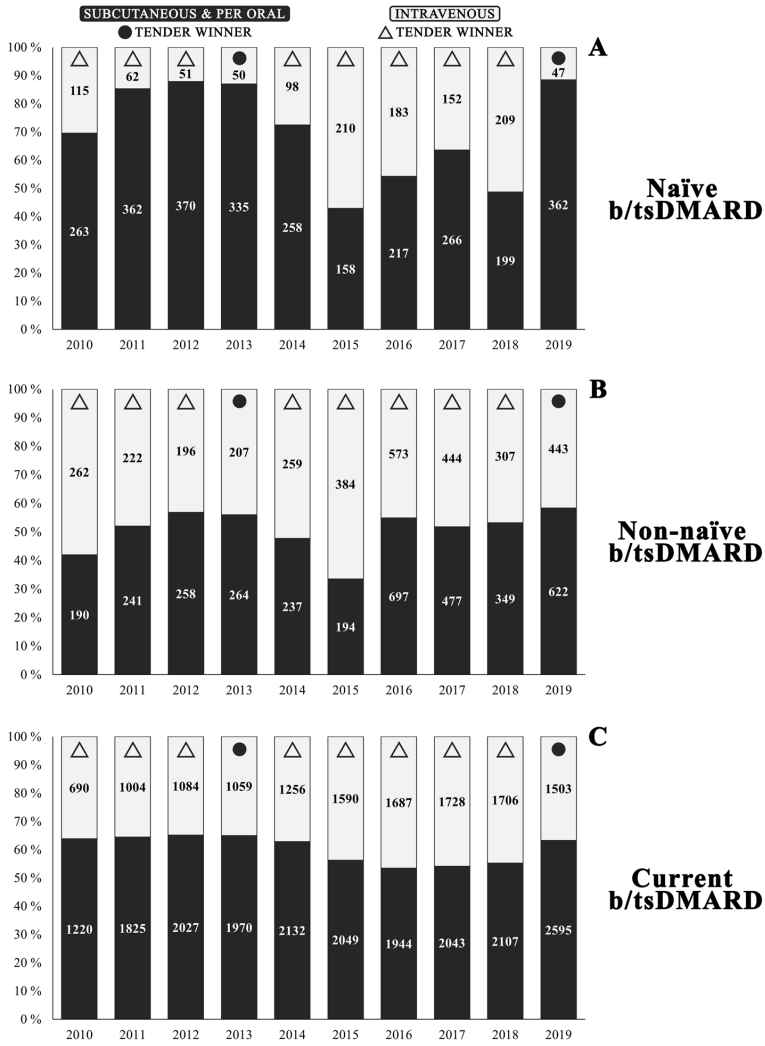

Fig. 5 b/tsDMARD route of administration comparison for naïve (**A**), non-naïve (**B**), and current (**C**) treatment. *Note*: Overview comparison between intravenous and subcutaneous and tablet b/tsDMARDs for the subcategories naïve (**A**), non-naïve (**B**), and current (**C**) treatment of rheumatoid arthritis patients in Norway for the period 2010–2019. Circular icons illustrate if a subcutaneous or per oral b/tsDMARD was the tender-winning drug. Triangle icons illustrate if an intravenous b/tsDMARD was a tender-winning drug. The specific values are shown in Tables 2, 3, and 4. *Abbreviation*: b/tsDMARDs = biologic and targeted synthetic disease-modifying antirheumatic drugs

involved in administrating the iv b/tsDMARD, the cost of implementing a working staff to administrate the drug, and patient transportation (either out of pocket or governmentally paid). In Norway, in decentralized areas, some patients have to travel up to 200–300 km to their nearest rheumatologist. The iv rituximab reference is an exception to the aforementioned observation. Rituximab reference was either the highest or second highest in proportion in eight out of ten years for current users, five for non-naïve, and once for naïve, albeit it was the tender-winning drug only once. An important clarification is that rituximab was only offered as a second-line drug, albeit not exclusively as the only second-line option. Despite being offered on the premises as a backup drug

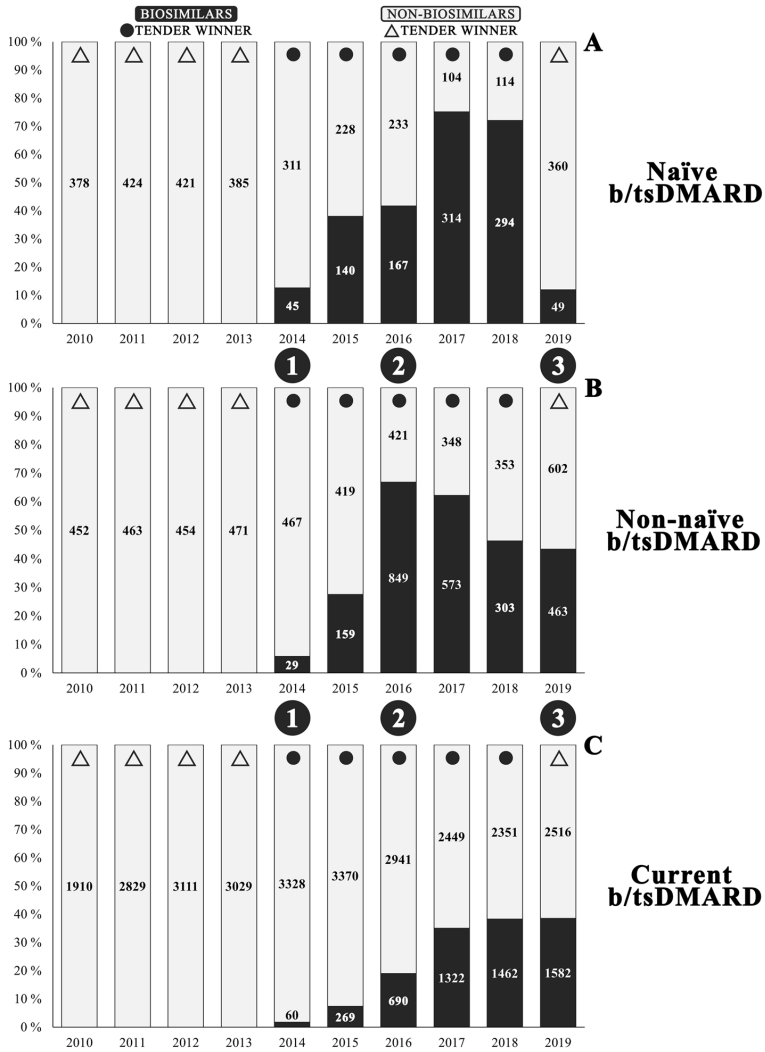

Fig. 6 b/tsDMARD biosimilar vs. non-biosimilar comparison for naïve (**A**), non-naïve (**B**), and current (**C**) treatment. *Note*: Overview comparison between intravenous and subcutaneous and tablet b/tsDMARDs for the subcategories naïve (**A**), non-naïve (**B**), and current (**C**) treatment of rheumatoid arthritis patients in Norway for the period 2010–2019. Circular icons illustrate if a biosimilar was a tender-winning drug. Triangle icons illustrate if a non-biosimilar was a tender-winning drug. The large circles with numbers 1, 2, and 3 mark the introduction of the first, second, and third biosimilar, respectively. The specific values are shown in Tables 2 and 3, and 4. *Abbreviation*: b/tsDMARDs = biologic and targeted synthetic disease-modifying antirheumatic drugs

and advised only under certain circumstances as a first-line drug [26], it still acquired 5% on average across the ten-year period among naïve users. Provided the use of rituximab was not contraindicated, a positive outcome was documented when treating seropositive RA with rituximab [26, 27], which can explain the small, yet unexpected, proportion among naïve b/tsDMARD users.

While it can be argued that the NHPT's effort to manage the Norwegian tender system for costly pharmaceuticals resulted in a reduced b/tsDMARD cost, it is also likely that the introduction of biosimilars played a central role [16]. Since the biosimilars' development and approval expenditure is lower than that of reference agents, biosimilars can be sold for a lower cost and

consequently stir market competition. This may reduce the overall pharmaceutical expenditure for the payers in European Union countries and, in turn, increase the availability of medications and improve access to care [28–30]. Similarly, as illustrated in this study, the biosimilars' introduction into the Norwegian pharmaceutical market may have influenced the overall b/tsDMARD proportion, especially the proportion of corresponding reference agents. Following the introduction of the first biosimilar in 2014, the iv infliximab CT-P13, the iv b/tsDMARDs were able to compete with the sc b/tsDMARDs despite iv's less favorable patient satisfaction and higher cost [24, 25]. The iv b/tsDMARDs reached their proportion peak in 2015, where their usage surpassed the sc/po b/tsDMARDs and acquired 57% and 66% of the total b/tsDMARDs proportion for naïve and non-naïve users, respectively. Infliximab CT-P13's favor started to wane in 2016 when the sc/po b/tsDMARDs' gained a biosimilar of their own, the sc etanercept SB4. Yet, among non-naïve users, these two biosimilars accounted for 67% of the 1270 new biosimilar switches, the highest proportion of switches overall. While the sc etanercept SB4 gained a higher proportion, the iv infliximab CT-P13 kept the high competition active. In 2017 and 2018, the two biosimilars acquired more than 70% of the total b/tsDMARD proportion among naïve users.

Although the NHPT's goal was to achieve the lowest possible b/tsDMARD cost, health outcomes were still prioritized. As such, the prescribing physicians were urged to be vigilant and careful when considering the NHPT's recommendations, especially when dealing with novel b/tsDMARDs [31]. Under the NHPT's recommendation (i.e., the Norwegian pharmaceutical tender system) between 2010 and 2019, the observed health outcomes among RA patients in Norway did not worsen [16]. In fact, the observed remission rate increased from 42 to 67% using DAS28 [16].

Pharmaceutical tendering can be cost-beneficial in the short term, as reported on multiple occasions [16, 32, 33]. However, unless the potential pitfalls of long-term pharmaceutical tendering are adequately handled, its high competition can also lead to unwanted impacts on patient healthcare quality, government budgets, pharmaceutical supply and capacity, novel pharmaceutical development, and sustainability of affordable prices [33–35]. In highly cost-reducing (i.e., highly competitive) pharmaceutical tendering, the offers required to compete can be detrimental for pharmaceutical companies and consequently result in a disinterest in providing any offer [33]. This can also be observed in the current study, where some companies decided not to give any offers, presumptively due to the high offers required to partake. If companies do not renew contracts when they expire, patient treatment options may be reduced. Furthermore, if multiple competitors withdraw, the remaining b/tsDMARDs may face little competition, potentially increasing costs [33]. Reduced competition can also impact pharmacies, resulting in supply instability [35]. Furthermore, if the tender-winning pharmaceutical company cannot supply as agreed, other companies that did not win the tender may not serve as backup suppliers, affecting patient treatment availability [35].

The NHPT is now addressing these potential concerns by considering establishing lower-end cost limits to prevent too low b/tsDMARDs costs. The NHPT has also implemented risk-distributing strategies to ensure better availability. For the risk distribution, NHPT recommends different b/tsDMARDs with the same bioequivalence for different geographical areas in Norway, e.g., infliximab SB2 (Flixabi®) and infliximab GP1111 (Zessly®) in 2020 and adalimumab SB5 (Imaraldi®) and adalimumab GP2017 (Hyrimoz®) in 2022.

The issue concerning confidentiality is an additional potential pitfall. Confidential offers allow pharmaceutical companies to give high offers without disclosing the information to other buyers (e.g., countries) [36]. Releasing these offers can result in mistrust between the pharmaceutical companies and the governing body purchasing the medications, leading to delays in the supply of known and novel drugs. Data release of pharmaceutical tender offers has occurred three times in Norway [37]. That said, pharmaceutical companies maintain market control by keeping the offers secret, benefiting while having the wiggle room to sell medications at high prices in each country without the other countries knowing about it [36]. In turn, the buyers have reduced autonomy as they are still bound to acquire essential medication for their region or nation on the pharmaceutical company's premises [38].

There are several limitations to this study. Firstly, it is a cross-sectional study with no statistical assessment, only interpretations of descriptive data. Our findings reflect population-level trends rather than individual patient trajectories. While this approach may help understand broad patterns and associations, it may overlook individual differences in treatment responses and disease progression, which could provide more nuanced insights into the impact of Norway's pharmaceutical tendering system on RA treatment patterns. Also, as a cross-sectional study, specific trends in change and order of b/tsDMARDs among non-naïve users are unknown. Longitudinal studies may provide more detailed insights into these aspects in the future.

In accordance with the national arthritis registry (NorArtritt) [39], which has cross-validated data with the Norwegian Patient Registry [40], data from our included

centers demonstrates a comparable number of included RA patients and a similar b/tsDMARD treatment ratio.

Although our study's external validity is comparable to that of NorArtritt, both our study and the NorArtritt registry only cover about 60% of the national RA population (2019 NorArtritt report) [39]. As a result, our study does not represent the entire demographic of RA patients and b/tsDMARD RA users in Norway, especially since some centers do not use or have only recently implemented the GTI system. As such, the increase in the patient population during our study period is more likely due to inclusion quantity registrations rather than due to an increase in the incidence of RA. In fact, there seems to be a decreasing trend in the incidence of RA [41]. This highlights the difficulty in interpreting trends in observational data and that it should be done cautiously. Despite these limitations, we believe our study has acceptable external validity and provides valuable, real-world insights into the use of b/tsDMARDs in Norway and how this usage may align with the national tender system.

An in-depth assessment of each drug from each center is not provided. The regional depot was also not accounted for, or the regional b/tsDMARD proportion. The geographical aspect also presents a challenge as there is a much longer travel time for RA patients in northern Norway compared to centralized areas like Bergen and Oslo. The impact of these geographical differences on treatment selection, especially the difference between decentralized and centralized areas based on iv vs. sc treatment, was not evaluated.

An additional potential limitation is our assumption that all patients receive their prescribed medication throughout the year. Given the design of our study, we used the most recent data entry from each year, leaving it unclear if a patient discontinued the drug during the year and the precise start date of treatment. Also, while all centers are expected to follow a standardized patient monitoring process, the reality of clinical practice often deviates from this standard due to various factors, e.g., doctors' clinical decisions, logistical constraints, and practical implementation barriers. Disparities in data, as evidenced by missing data, reflect these complexities and the challenges of achieving uniform structured data collection across all centers. Lastly, while the highest and second highest proportions were outlined and presented as core elements of tendering being impactful, there were some cases where the difference between the second highest and the third highest proportion was only a few percentages apart.

The study also has multiple strengths. It is a unique study exploring the proportion of 13 different b/tsDMARDs across ten years, providing an overview of current, naïve and non-naïve b/tsDMARD users using real-life data from ten rheumatological outpatient clinics in Norway. It distinguishes between sc/po and iv b/tsDMARDs and between biosimilars and non-biosimilars b/tsDMARDs. Visual interpretation of the tender ranks compared with the proportion of the different user groups is also provided. To our awareness, this is the first study providing such a thorough assessment of b/tsDMARD tendering in Norway.

Conclusion

The study's observative finding of the pharmaceutical tendering process from 2010 to 2019 reveals a possible link between tendering outcomes and the use of b/tsDMARDs among various patient groups. According to the data, winning the tender appears to have an impact on b/tsDMARD usage in naive users and non-naive users and a less pronounced impact on current users. While this was a general observation taken from multiple annual tenders, sc/po b/tsDMARDs were generally favored over iv b/tsDMARDs despite higher-ranked offers for the iv b/tsDMARDs. These interpretations, however, are based on observed descriptions.

We also observed that the current b/tsDMARD proportion for several drugs remained high despite a relatively low ranking. This observation may be explained based on the "do not switch from a winning team" principle but also due to the lack of available data or recommendations to promote a cost-beneficial non-medical switch between b/tsDMARDs with different substances.

Building a solid market foundation appears to be an effective strategy for resisting proportion decrease when the necessary offers are not cost-effective for the individual pharmaceutical company. The foundation for some b/tsDMARDs, e.g., etanercept reference, was built prior to initial tendering resulting in a clear advantage. However, the dynamic between etanercept reference and its biosimilar etanercept SB4 is also a great example of how a solid foundation can be challenged and disrupted upon the introduction of corresponding biosimilars.

The pharmaceutical tender system implemented in Norway appears to favor the pharmaceutical company that provides a good offer by increasing their b/tsDMARD proportion among naïve and non-naïve users. Biosimilars contributed substantially to the competition by likely increasing market proportion.

Abbreviations

ANOVA	One-way analysis of variance
anti-CCP	anti-cyclic citrullinated peptide
BE	Biosimilar equivalent
BMI	Body mass index
b/tsDMARD	biologic and targeted synthetic disease-modifying antirheumatic drugs
CRP	C-reactive protein

DAS28	Composite 28 joint count Disease Activity Score using CRP
ESR	Erythrocyte sedimentation rate
IGA	Investigator global assessment
iv	intravenous
NHPT	Norwegian hospital procurement trust
NO	No offer
PGA	Patient global assessment
po	per oral
PROM	Patient-reported outcome measures
RA	Rheumatoid arthritis
REC	Regional ethical committee
RF	Rheumatoid factor
sc	subcutaneous
sc-po	subcutaneous and per oral
SJC28	28 swollen joint count
SPSS	Statistical package for social sciences
TNFi	Tumor necrosis factor inhibitors
TJC28	28 tender joint count
VAS	Visual analog scale

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12913-023-09975-7.

Additional file 1: Supplementary Table 1. Overview of excluded patients and registration errors within the BioRheuma data

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Authors' contributions
All authors have contributed with critical components to enable the delivery of the study and manuscript. These include: patient recruitment and/or data generation and/or analysis, as well as writing or critically revising the present manuscript and/or raising infrastructure to support the study. A. B. had the main responsibility for drafting the manuscript and analyzing data with contributions from G.H. All authors read and approved the final manuscript.

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Availability of data and materials
Data are available on reasonable request and must be approved by all participating centers. Please contact the corresponding author by email to request the data from this study.

Declarations

Ethics approval and consent to participate
The study was approved by the regional ethical committee for medical health research ethics (REC) (Regional etisk komite Midt-Norge 2010/3078) and consequently follows the Declaration of Helsinki ethical principles of medical research involving human subjects. The study was also approved by the Institutional Review Board (Research Unit Sørlandet Hospital) and met the requirements of the Health Research Act [Helseforksningsloven] from 2009. The protocol used anonymized data, which did not require conformed consent from the patient and was approved by the regional ethical committee for medical health research ethics. All data was collected as part of routine clinical care.

Consent for publication
Not applicable.

Competing interests
Two authors declare competing interests. A.B. has provided some consulting to DiagraphIt. A.P.D is employed by DiagraphIt. The authors have no financial interests that could create a potential conflict of interest or the appearance of a conflict of interest concerning the submitted work.

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Publisher's Note

Supplementary Table 1: Overview of excluded patients and registration errors within the BioRheuma data

	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Registered BioRheuma patients										
Total registered BioRheuma patients	4909	7256	7993	7278	8023	9057	9176	9225	9102	9335
Included BioRheuma patients	4885 (99.5%)	7230 (99.6%)	7970 (99.7%)	7248 (99.6%)	7993 (99.6%)	9010 (99.5%)	9037 (98.5%)	9129 (99.0%)	9048 (99.4%)	9280 (99.4%)
Excluded BioRheuma patients	24 (0.5%)	26 (0.4%)	23 (0.3%)	30 (0.4%)	30 (0.4%)	47 (0.5%)	139 (1.5%)	96 (1.0%)	54 (0.6%)	55 (0.6%)
Registration of the 13 b/tsDMARD										
Total registrations	1934	2855	3134	3059	3418	3686	3770	3867	3867	4153
b/tsDMARDs prescriptions	1910 (98.8%)	2829 (99.1%)	3111 (99.3%)	3029 (99.0%)	3388 (99.1%)	3639 (98.7%)	3631 (96.3%)	3771 (97.5%)	3813 (98.6%)	4098 (98.7%)
Registration Errors	24 (1.2%)	26 (0.9%)	23 (0.7%)	30 (1.0%)	30 (0.9%)	47 (1.3%)	139 (3.7%)	96 (2.5%)	54 (1.4%)	55 (1.3%)
Overview of excluded registration errors										
In bDMARDs and tsDMARDs	0	0	0	0	0	0	0	4	24	16
In tsDMARDs	0	0	0	0	0	0	0	0	2	4
In bDMARDs	10	10	6	5	13	14	16	9	10	2
In TNFi	11	13	17	23	13	30	119	79	21	18
In non-TNFi	4	4	1	2	4	3	4	5	0	16
Overlapping registration errors	1	1	1	0	0	0	0	1	3	1

Abbreviations: **b/tsDMARDs** = biologic and target synthetic Disease-Modifying Antirheumatic Drugs. **bDMARDs** = biological DMARDs. **tsDMARDs** = target synthetic DMARDs. **TNFi** = Tumor Necrosis Factor Inhibitor.

PAPER III

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ORIGINAL RESEARCH

Remission or Not Remission, That's the Question: Shedding Light on Remission and the Impact of Objective and Subjective Measures Reflecting Disease Activity in Rheumatoid Arthritis

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ABSTRACT

Introduction: The inclusion of certain variables in remission formulas for rheumatoid arthritis (RA) may give rise to discrepancies. An increase in patient global assessment (PGA), a variable showing the patient's self-evaluation of their disease activity, may alone tilt a patient out of remission when using certain remission-assessing methods. This study aimed to explore differences in remission rates among various formulas and the impact of PGA and other clinical variables on the calculation of remission.

Methods: Data were collected from RA patients monitored during the years 2015–2019 at an outpatient clinic in southern Norway. Linear and logistic regression assessed associations between PGA, other RA-related variables, and remission-assessing methods.

Results: Remission rates were 23%, 65%, and 73% in 2019 when assessing the same 502 RA patients using Boolean remission, Boolean remission without PGA, and the disease activity score (DAS) with C-reactive peptide [DAS28(3)-CRP] method, respectively. Among the same population that year, 27% reported PGA ≤ 10, 74% had a tender joint count of ≤ 1, 85% had a swollen joint count of ≤ 1, and 86% had CRP ≤ 10. Pain (standardized coefficient $\beta = 0.7$, $p < 0.001$) was most strongly associated with PGA. Pain, fatigue, and morning stiffness were substantially associated with the remission-assessing methods that incorporated PGA.

Conclusions: Since PGA is strongly associated with the patient's perception of pain and may not reflect the inflammatory process, our study

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challenges the application of remission-assessing methods containing PGA when monitoring RA patients in the outpatient clinic. We recommend using measures that are less likely to be associated with noninflammatory pain and psychosocial factors.

Keywords: Rheumatoid arthritis; Disease activity; Remission; Patient global assessment; Real-life data

Key Summary Points

Why carry out this study

Several composite measures are recognized to define remission status in rheumatoid arthritis, but they do not provide comparable scores

Most measures incorporate patient self-evaluation, which, while elevated, can be solely responsible for not reaching remission even though the remaining variables reflect an absence of inflammation

This study seeks to assess the comparability of remission rates calculated using different remission-assessing methods in a rheumatoid arthritis outpatient clinic cohort

What was learned from the study

Remission rates calculated for the same group of rheumatoid arthritis patients differ when using various remission-assessing measures, particularly as patient self-evaluation is integrated into their calculation

Patient self-evaluation is important when assessing disease burden; however, this study challenges the applicability of the patient self-evaluation variable when utilizing potent and costly anti-inflammatory drugs for a noninflammatory status

INTRODUCTION

In 1981, the American College of Rheumatology (ACR) defined rheumatoid arthritis (RA) remission as the absence of any inflammatory RA disease activity [1]. According to the European League Against Rheumatism (EULAR) recommendations for managing RA, treatment should aim for remission or low disease activity [2]. An analysis by Mian et al. of 22 RA treatment guidelines (2000–2017) found the disease activity score-28 (DAS28) to be the most frequently recommended parameter to guide RA treatment and assess remission [3], despite the possibility of having multiple swollen joints while in DAS28 remission [4].

A less frequently recommended [3] and more stringent alternative for assessing remission (defined by the ACR/EULAR committee) is Boolean remission, which has the criteria of a score of ≤ 1 for the tender 28-joint count (TJC28), the swollen 28-joint count (SJC28), C-reactive peptide (CRP) (mg/dl), and the patient global assessment (PGA) [visual analog scale (VAS) 0–10] [4]. However, a recent meta-analysis of randomized clinical trials by Ferreira et al. has questioned the importance of using PGA in Boolean remission, as it places greater emphasis on the patient's perception of disease burden, which may be influenced by noninflammatory mechanisms [5]. The incorporation of PGA scoring into other remission-assessing methods should also be questioned, as it may potentially lead to misestimation of inflammatory remission rates and consequently to overtreatment.

The primary aim of this study was to compare remission rates using different remission-assessing methods in a RA outpatient clinic cohort, in particular, to reveal the impact of PGA. The second aim was to examine associations of RA-related variables with PGA, and the third was to explore associations of different RA-related variables with remission status in various measures.

METHODS

Patient Inclusion and Data Collection

Data for this cross-sectional study were obtained (2015–2019) from a rheumatological outpatient clinic in southern Norway. Patient monitoring at the outpatient clinic was standardized using the computer tool GoTreatIT® Rheuma (www.diagraphit.com). Data were extracted from the clinic database using predefined queries. One query extracted RA patients data who had at least one registered visit in the analysed year. The most recent visit was extracted if there were multiple visits during the same year. The anonymized data files were analysed using EXCEL and the Statistical Package for the Social Sciences (SPSS).

Descriptive variables included age, sex, body mass index (kg/m^2), current smoking status, years of education, disease duration, rheumatoid factor (RF), and anti-cyclic citrullinated peptide (aCCP). Variables reflecting disease activity encompassed erythrocyte sedimentation rate (ESR) (mm/h), CRP (mg/L), SJC28 (0–28 joints), TJC28 (0–28 joints), and investigator global assessment (IGA) (VAS 0–100 mm). The patient-reported outcome measures (PROMs) included PGA, pain (VAS 0–100 mm), fatigue (VAS 0–100 mm), morning stiffness (reported in 15-min units), and the modified health assessment questionnaire (MHAQ) [6].

Composite Disease Activity Score and Remission Definitions

The composite disease activity scores (CDASs) included in this study cover the addition-based methods, the simple disease activity index (SDAI) (TJC28, SJC28, CRP, PGA, IGA) [7] and the clinical disease activity index (CDAI) (TJC28, SJC28, PGA, IGA) [8], and the algorithm-based DAS28(3) (TJC28, SJC28, CRP) [9] and DAS28(4) (TJC28, SJC28, CRP, PGA) [9]. Among the assessed CDASs, remission cutoff values were ≤ 2.6 for both DAS28(3) and DAS28(4) [9], ≤ 2.8 for CDAI [8], and ≤ 3.2 for SDAI [7]. Patients were stratified for analysis as having either remission or non-remission.

ACR/EULAR Boolean remission (4-variable remission) is defined as scores of ≤ 1 for TJC28, SJC28, CRP, and PGA [4]. However, since the extracted CRP is measured in mg/L and the PGA by a VAS of 0–100 mm, the Boolean remission CRP and PGA were redefined as ≤ 10. Modified 4-variable remission rates were examined using different PGA cutoffs of ≤ 20, ≤ 30, ≤ 40, ≤ 50, ≤ 60, ≤ 70, ≤ 80, and ≤ 90 (Fig. 1). PGA ≤ 100 was not included, as only 11 patients (2%) scored a PGA of 91–100. A 3-variable remission was defined as Boolean remission without PGA (i.e. TJC28 ≤ 1, SJC28 ≤ 1, and CRP ≤ 10). Subjective 2-variable remission (TJC28 ≤ 1 and PGA ≤ 10) and objective 2-variable remission (SJC28 ≤ 1 and CRP ≤ 10) were also reported (Table 2). RA patients in the study were also assessed with single-component cutoffs: TJC28 ≤ 1, SJC28 ≤ 1, CRP ≤ 10, PGA ≤ 10, PGA ≤ 20, and IGA ≤ 10. Since the difference in the remission rates between the assessed years was only minimally statistically significant, the comparison in Fig. 1 is for 2019 only.

Treatment

The annual data collection (2015–2019) from the RA patients included information on biological and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs), which comprised tumour necrosis factor inhibitors (TNFi) (etanercept reference, etanercept SB4, infliximab reference, infliximab CT-P13, adalimumab, golimumab, certolizumab pegol), non-TNFi (rituximab reference, rituximab GP2013, abatacept, and tocilizumab), and tsDMARDs (baricitinib and tofacitinib). The collected data also contained information on prednisolone and conventional synthetic DMARDs (csDMARDs) such as methotrexate (MTX). Monotherapy for b/tsDMARDs and TNFi, as well as no treatment, i.e. neither b/tsDMARD, csDMARDs, nor prednisolone, was also reported.

Statistical Analysis

Categorical variables are reported as numbers and percentages, and continuous variables as

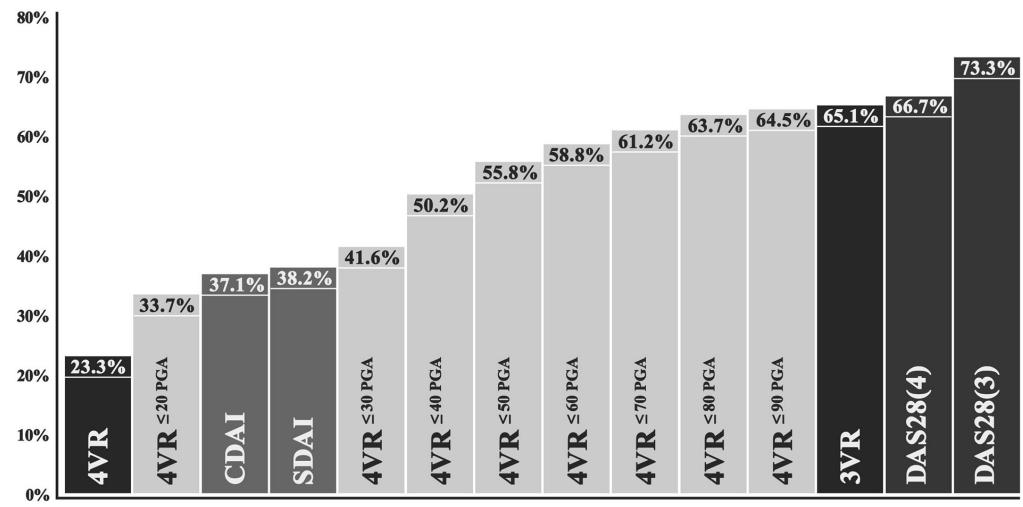

Fig. 1 Comparing composite measures of disease activity and variants of Boolean remission in 2019. *Note*: data are presented as percentages of $n = 502$ in 2019. The figure compares various cutoffs of the patient global assessment in Boolean remission with the remission of composite measures of disease activity and 3-variable remission in rheumatoid arthritis patients in an ordinary outpatient clinic in southern Norway. 4-variable remission is achieved when C-reactive peptide (CRP) ≤ 10, tender 28-joint count (TJC28) ≤ 1, swollen 28-joint count (SJC28) ≤ 1, and PGA ≤ 10. 3-variable remission is achieved when CRP ≤ 10, TJC28 ≤ 1, and SJC28 ≤ 1. *4VR* 4-variable remission, *PGA* patient global assessment, *CDAI* clinical disease activity index, *SDAI* simple disease activity Index, *3VR* 3-variable remission, *DAS28* disease activity score with CRP

means with standard deviations (SDs) or means with ranges. Changes in and associations between variables over 5 years were analysed with SPSS using a one-way analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables. Only patients with a complete dataset for TJC28, SJC28, CRP, PGA, and IGA were analysed. To examine bias due to missing data, the included patients were compared with those without a complete dataset. A p-value of < 0.05 was considered statistically significant.

Univariable and multivariable linear regression with stepwise variable selection was used to assess the association between demographic and disease characteristic variables and PGA. Logistic regression was used to assess the association between demographic and disease characteristic variables and various remission-assessing methods. The variables responsible for the different calculations or assessments of the various remissions were omitted in the logistic regression analysis. For linear regression, the standardized coefficient β and unstandardized coefficient B were reported along with the 95% confidence intervals. For logistic regression, the odds ratios (OR) were reported along with the 95% confidence intervals. Due to the minimal differences in the assessed demographics, disease activity measures, and patient-reported outcomes among the 5 years of the study period, we decided to report only the 2019 regression analysis for clarity purposes. Supplementary Table 2 shows a variant of the multivariate regression analysis, albeit subgrouped based on the 3-variable remission and moderate–high disease activity in RA patients with DAS28(4), CDAI, and SDAI.

Ethics

The study was approved by the Regional Ethics Committee (REC) of Middle Norway (2010/

3078) and followed the ethical principles of medical research involving human subjects of the 1964 Declaration of Helsinki (and its later amendments). No consent from the patients was required by the REC of Middle Norway, as all data were anonymized and collected as part of routine clinical care.

RESULTS

Demographics, Disease Activity, and Patient-Reported Outcomes

Table 1 presents the demographic variables, RF, aCCP, disease activity variables, PROMs, and treatment for the years 2015–2019. The number of RA patients in the included dataset ranged from 613 to 502 (2015–2019). Over the 5 years, no significant change in the mean values of the demographic variables, PROMs, aCCP positive rate (73.8%), RF positive rate (68.8%), TJC28 (1.3), SJC28 (0.9), and CRP (6.1 mg/L) was observed. The mean changes in ESR (14.6, range 12.6–18.0 mm/h) and IGA (9.6, 7.8–10.6) across the 5 years were significant; however, no significant change was noted for DAS28(3) (2.3), DAS28(4) (2.4), CDAI (6.4), or SDAI (7.0).

Approximately 40% of the patients did not have a complete dataset and were excluded from the analysis. As shown in Supplementary Table 3, there were only minor differences between the excluded and included patients.

Comparison of Remission Rates and the Impact of PGA

Table 2 presents the remission rates based on DAS28(3), DAS28(4), CDAI, SDAI, ACR/EULAR Boolean remission, various subgroups of Boolean remission, and individual measures. Over the 5 years, none of the mean remission rates were significantly different except for IGA ≤ 10. The average remission rates ordered from lowest to highest are shown in Fig. 1. A gradual increase in the PGA cutoff in Boolean 4-variable remission was linked to an observable increase in the remission rate. When comparing these different remission rates using an increasing PGA cutoff in 4-variable remission (Fig. 1), the remission rates based on SDAI and CDAI were similar to Boolean 4-variable remission with PGA cutoffs of ≤ 20 and ≤ 30. In comparison, the 3-variable, DAS28(3), and DAS28(4) remission rates were located beyond a cutoff of ≤ 90 PGA.

Treatment

The mean 5-year percentage of RA patients who received any type of b/tsDMARD was 41.3%, and it was 10.1% for those who received b/tsDMARDs as monotherapy. Among the same analysed study population, the 5-year average percentage of patients who received TNFi (no csDMARDs or prednisolone) was 21.5%, and it was 5.0% for those who only received TNFi. Also, an average of 65.7% of the patients were registered as receiving csDMARDs, 56.2% were registered as receiving MTX, and 47.5% were registered as receiving prednisolone. An average of 7.3% did not receive either b/tsDMARDs, csDMARDs, or prednisolone. Both TNFi and b/tsDMARD monotherapy showed statistically significant changes over the 5 years. Supplementary Table 3 includes a treatment comparison between the examined and excluded patients.

Associations of Relevant Variables with Patient Global Assessment

Table 3 shows the associations of different variables (univariate and multivariate models) with PGA in 2019 according to a linear regression. For a univariable linear regression, only PROM variables achieved $\beta \geq 0.5$ with a p-value < 0.001; these variables included pain ($\beta = 0.9$), MHAQ ($\beta = 0.7$), fatigue ($\beta = 0.7$), and morning stiffness ($\beta = 0.5$). In a multivariable regression model with all covariates included, only pain ($\beta = 0.7$), fatigue ($\beta = 0.2$), and MHAQ ($\beta = 0.1$) were significantly associated with PGA, with pain having the strongest association. Similar outcomes were observed for the multivariable regression model after stepwise variable selection. Interestingly, similar findings were observed for the association between pain

Table 1 Demographics, disease characteristics, and treatment of rheumatoid arthritis patients during 2015–2019

	2015	2016	2017	2018	2019	Mean (SD/%) [range]	Missing data Median, mean, range	*P*-value
Original dataset, *N*	1067	908	953	825	871			0.502
Included dataset, *N*	613 (57.5%)	554 (61.0%)	555 (58.2%)	490 (59.4%)	502 (57.6%)	543 (58.7%) [57.5—61.0%]	0%, 0%, 0–0%	
Demographics								
Age (years)	62.8 (12.6)	61.2 (13.5)*	62.0 (13.1)*	60.8 (13.8)*	61.8 (14.0)*	61.7 (13.4) [60.8–62.8]	0%, 0%, 0–0%	0.102
Female	410 (66.9%)*	377 (68.1%)	362 (65.2%)*	334 (68.2%)	335 (66.7%)	364 (67.0%) [65.2–68.2%]	0%, 0%, 0–0%	0.847
BMI (kg/m^2)	26.5 (4.7)*	26.2 (4.4)	26.2 (4.4)	26.3 (4.4)	26.4 (4.5)	26.3 (4.5) [26.2–26.5]	1.8%, 1.7%, 1–2%	0.780
Education (years)	11.6 (3.4)	12.0 (3.6)*	12.0 (3.6)	12.1 (3.5)	12.2 (3.5)	12.0 (3.5) [11.6–12.2]	1.4%, 1.1%, 0–2%	0.090
Current smokers	118 (19.3%)	101 (18.3%)	90 (16.4%)	82 (16.9%)	78 (15.7%)	94 (17.3%) [15.7–19.3%]	1.0%, 0.8%, 0–1%	0.503
Disease duration (years)	11.7 (10.0)*	11.6 (9.9)	12.1 (10.4)	11.3 (11.1)	10.8 (10.9)*	11.5 (10.5) [10.8–12.1]	0%, 0%, 0–0%	0.376
Biomarkers								
aCCP positive	421 (72.2%)	393 (74.6%)	380 (72.1%)	356 (76.4%)*	357 (73.6%)	381 (73.8%) [72.1–76.4%]	4.9%, 4.6%, 3–5%	0.507
RF positive	409 (69.1%)	374 (70.3%)	370 (69.5%)	311 (68.1%)	318 (67.1%)	356 (68.8%) [67.1–70.3%]	4.1%, 4.8%, 3–7%	0.803
Disease activity variables								
ESR (mm/h)	18.0 (15.1)*	14.8 (14.0)*	13.5 (13.4)	14.2 (14.6)*	12.6 (12.2)*	14.6 (13.9) [12.6–18.0]	14.8%, 14.4%, 9–21%	**< 0.001**
CRP (mg/L)	6.5 (10.5)	5.9 (11.4)*	6.2 (14.4)	6.0 (10.4)*	5.8 (10.2)*	6.1 (11.4) [5.8–6.5]	0%, 0%, 0–0%	0.860
TJC28 (0–28)	1.4 (2.9)	1.4 (2.9)	1.2 (2.6)*	1.3 (2.9)	1.4 (2.8)*	1.3 (2.8) [1.2–1.4]	0%, 0%, 0–0%	0.837
SJC28 (0–28)	0.9 (1.8)	1.0 (2.3)	0.9 (2.3)*	0.9 (2.1)	0.7 (1.9)	0.9 (2.1) [0.7–1]	0%, 0%, 0–0%	0.320
IGA (VAS, 0–100 mm)	10.1 (11.9)	10.1 (12.6)	9.2 (13.1)*	10.6 (13.7)	7.8 (12.2)	9.6 (12.7) [7.8–10.6]	0%, 0%, 0–0%	**0.004**

Table 1 continued

	2015	2016	2017	2018	2019	Mean (SD/%) [range]	Missing dataMedian, mean, range	*P*-value
Clinical-reported outcome measures								
DAS28(3) score	2.3 (0.9)	2.3 (0.9)*	2.2 (0.9)*	2.3 (0.9)*	2.2 (0.9)*	2.3 (0.9) [2.2–2.3]	0%, 0%, 0–0%	0.294
DAS28(4) score	2.5 (1.0)	2.4 (1.0)	2.4 (1.0)	2.4 (1.1)	2.4 (1.1)	2.4 (1.0) [2.4–2.5]	0%, 0%, 0–0%	0.255
CDAI value	6.6 (6.5)	6.5 (6.9)	6.1 (6.9)	6.5 (6.7)	6.1 (6.6)	6.4 (6.7) [6.1–6.6]	0%, 0%, 0–0%	0.555
SDAI value	7.2 (6.8)	7.1 (7.3)	6.7 (7.5)	7.2 (7.0)	6.7 (7.0)	7.0 (7.1) [6.7–7.2]	0%, 0%, 0–0%	0.571
Patient-reported outcome measures								
PGA (VAS, 0–100 mm)	33.4 (26.4)	31.9 (25.0)	30.2 (24.4)	32.5 (25.5)	32.7 (25.7)	32.2 (25.4) [30.2–33.4]	0%, 0%, 0–0%	0.284
Pain (VAS, 0–100 mm)	32.5 (25.5)	31.6 (24.7)*	32.1 (25.1)	33.1 (25.6)*	32.6 (26.0)	32.4 (25.4) [31.6–33.1]	7.4%, 7.9%, 7–9%	0.917
MHAQ (0–3)	0.5 (0.5)	0.4 (0.5)*	0.4 (0.5)	0.4 (0.5)	0.4 (0.5)*	0.4 (0.5) [0.4–0.5]	6.5%, 5.9%, 3–8%	0.263
Fatigue (VAS, 0–100 mm)	36.7 (30.3)	36.4 (29.9)	37.8 (29.4)	38.1 (30.8)	37.6 (29.6)	37.3 (30.0) [36.4–38.1]	6.7%, 6.6%, 4–9%	0.872
Morning stiffness (h)	1.0 (1.3)	0.9 (1.3)	0.8 (1.1)	0.9 (1.2)	0.9 (1.3)	0.9 (1.3) [0.8–1.0]	9%, 8.3%, 7–9%	0.390
Treatment								
b/tsDMARDs	255 (41.6%)*	247 (44.6%)*	216 (38.9%)	199 (40.6%)*	206 (41.0%)	225 (41.3%) [38.9–44.6%]	0%, 0%, 0–0%	0.421
TNFi	155 (25.3%)	153 (27.6%)*	129 (23.2%)	102 (20.8%)	102 (20.3%)	128 (23.5%) [20.3–27.6%]	0%, 0%, 0–0%	**0.026**
Monotherapy b/tsDMARDs	40 (6.5%)*	51 (9.2%)	52 (9.4%)	61 (12.4%)*	65 (12.9%)	54 (10.1%) [6.5–12.9%]	0%, 0%, 0–0%	**0.002**
Monotherapy TNFi	19 (3.1%)*	30 (5.4%)*	26 (4.7%)	31 (6.3%)*	28 (5.6%)	27 (5.0%) [3.1–6.3%]	0%, 0%, 0–0%	0.125
csDMARDs	405 (66.1%)*	362 (65.3%)*	366 (65.9%)*	325 (66.3%)*	325 (64.7%)*	357 (65.7%) [64.7–66.3%]	0%, 0%, 0–0%	0.985

Table 1 continued

	2015	2016	2017	2018	2019	Mean (SD/%) [range]	Missing dataMedian, mean, range	*P*-value
Methotrexate	346 (56.4%)*	302 (54.5%)*	315 (56.8%)*	275 (56.1%)*	286 (57.0%)*	305 (56.2%) [54.5–57%]	0%, 0%, 0–0%	0.932
Prednisolone	311 (50.7%)	265 (47.8%)*	266 (47.9%)	226 (46.1%)	227 (45.2%)	259 (47.5%) [45.2–50.7%]	0%, 0%, 0–0%	0.405
No treatment	53 (8.6%)*	44 (7.9%)*	42 (7.6%)*	31 (6.3%)*	31 (6.2%)*	40 (7.3%) [6.2–8.6%]	0%, 0%, 0–0%	0.467

All data were collected from an ordinary outpatient clinic in southern Norway. Categorical variables are presented as percentages (%) and continuous variables as means with standard deviations (SDs). Missing data are presented as the median and the mean with the range. The X^2 test was used for categorical variables and one-way ANOVA was used for continuous variables to test for differences during a follow-up of 5 years. The asterisk symbol (*) represents a significant *p*-value when compared with excluded data (see Supplementary Table 3). *BMI* body mass index, *aCCP* anti-cyclic citrullinated peptide, *RF* rheumatoid factor, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *TJC28* tender 28-joint count, *SJC28* swollen 28-joint count, *IGA* investigators global assessment, *VAS* visual analog scale (measured 0–100), *DAS28* disease activity score with CRP, *CDAI* clinical disease activity index, *SDAI* simple disease activity index, *PGA* patient global assessment, *MHAQ* modified health assessment questionnaire, *b/tsDMARDs* biological and target synthetic disease-modifying antirheumatic drugs, *TNF* tumour necrosis factor, *csDMARDs* conventional synthetic disease-modifying antirheumatic drugs, *No treatment* implies that the patient did not receive b/tsDMARDs, csDMARDs, nor prednisolone

Table 2 Remission rates in rheumatoid arthritis patients during 2015–2019

	2015 (*n* = 613)	**2016 (*n* = 554)**	**2017 (*n* = 555)**	**2018 (*n* = 409)**	**2019 (*n* = 502)**	**Mean (%) [range]**	***P*-value**
Remission rates							
DAS28(4) remission	62.8%	64.4%	66.8%	65.1%	66.7%	353 (65.2%) [62.8–66.8%]	0.581
DAS28(3) remission	70.1%	72.0%	71.7%	70.4%	73.3%	388 (71.5%) [70.1–73.3%]	0.786
CDAI remission	34.4%	33.6%	39.8%	36.1%	37.1%	196 (36.2%) [33.6–39.8%]	0.214
SDAI remission	34.3%	33.9%	39.5%	34.5%	38.2%	196 (36.1%) [33.9–39.5%]	0.178
Boolean-remission-based remission rates (PGA $\leq$ 10, SJC28 $\leq$ 1, TJC28 $\leq$ 1, CRP $\leq$ 10)							
4vRemission (Normal)	22.2%	19.7%	23.4%	23.1%	23.3%	121 (22.3%) [19.7–23.4%]	0.546
4vRemission (PGA $\leq$ 20)	30.8%	31.4%	34.2%	33.3%	33.7%	177 (32.7%) [30.8–34.2%]	0.688
3vRemission (SJC28, TJC28, CRP)	61.3%	62.8%	64.0%	63.1%	65.1%	343 (63.3%) [61.3–65.1%]	0.753
Objective 2vRemission (SJC28, CRP)	72.4%	73.5%	73.2%	71.6%	75.7%	398 (73.3%) [71.6–75.7%]	0.660
Subjective 2vRemission (TJC28, PGA)	25.1%	23.3%	26.1%	25.5%	25.1%	136 (25.0%) [23.3–26.1%]	0.858
Proportion rates of 1-variable cutoffs							
SJC28 (0–28) $\leq$ 1	81.7%	82.1%	82.3%	81.0%	85.3%	448 (82.5%) [81.0–85.3%]	0.449
CRP (mg/L) $\leq$ 10	85.2%	87.0%	86.8%	84.7%	86.1%	467 (86.0%) [84.7–87.0%]	0.764
TJC28 (0–28) $\leq$ 1	75.0%	76.7%	77.5%	74.3%	74.1%	410 (75.5%) [74.1–77.5%]	0.626
PGA (0–100) $\leq$ 10	26.8%	25.3%	27.9%	26.7%	26.9%	145 (26.7%) [25.3–27.9%]	0.907
PGA (0–100) $\leq$ 20	39.6%	41.3%	42.9%	40.4%	40.2%	222 (40.9%) [39.6–42.9%]	0.829
IGA (0–100) $\leq$ 10	65.1%	66.6%	71.4%	65.1%	74.3%	371 (68.5%) [65.1–74.3%]	**0.002**

DAS28 disease activity score with CRP, *CRP* C-reactive protein, *CDAI* clinical disease activity index, *SDAI* simple disease activity index, *PGA* patient global assessment, *SJC28* swollen 28-joint count, *TJC28* tender 28-joint count. All data were collected from an ordinary outpatient clinic in southern Norway. All remission percentages (compared to non-remission) were estimated from the total (*n*). There are no missing data. *4vRemission* is achieved when CRP $\leq$ 10, TJC28 $\leq$ 1, SJC28 $\leq$ 1, and PGA $\leq$ 10. *3vRemission* is achieved when CRP $\leq$ 10, TJC28 $\leq$ 1, and SJC28 $\leq$ 1. *Objective 2vRemission* is achieved when CRP $\leq$ 10 and SJC28 $\leq$ 1. *Subjective 2vRemission* is achieved when PGA $\leq$ 10 and TJC28 $\leq$ 1

and PGA in other disease activity subgroups, including moderate–high disease activity and 3-variable remission (Supplementary Table 2).

Association of Variables with Remission Status

Supplementary Table 1 reports the associations as ORs between different variables and remission assessed through logistic regression. TJC28 had a significant association with objective 2-variable remission, and IGA had significant associations with all except subjective 2-variable remission. Among the PROMs, pain had significant associations with DAS28(4), CDAI, SDAI, 4-variable remission, 4-variable-remission with a PGA cutoff of ≤ 20 (4-variable remission^{PGA20}), and subjective 2-variable remission. Fatigue had significant associations with CDAI remission, SDAI remission, 4-variable remission, 4-variable remission^{PGA20}, and subjective 2-variable remission. Morning stiffness had significant associations with CDAI remission, SDAI remission, and 4-variable remission^{PGA20}. PGA had no significant associations with scores that did not incorporate the variable [3-variable remission, DAS28(3) remission, objective 2-variable remission].

DISCUSSION

The main finding of our study is the large variation in RA remission rate between the remission-assessing methods: rates ranged from 23% for Boolean remission to 73% for DAS28(3) remission (in 2019). For Boolean remission in particular, we should highlight the impact of PGA, which is strongly associated with pain, on the remission rates.

In Fig. 1, among the remission-assessing methods incorporating PGA, 4-variable remission (23%), CDAI (37%), and SDAI (38%) had substantially lower remission rates than DAS28(4) (67%). A discrepancy in remission rate when using different remission-assessing methods has been reported previously across Europe [10]. The DAS28(4) calculation differs as it uses an algorithm that gives PGA much weaker power, giving it a reduced impact compared to the other variables. In contrast, 4-variable (Boolean) remission, CDAI, and SDAI all give equal power to their variables. The remission-assessing methods without PGA produced remission rates of 65% and 73% for 3-variable remission and DAS28(3), respectively. Similar discrepancies between methods have been demonstrated elsewhere [11, 12]. We confirmed that attaining remission is dependent on the method of assessment [12–16].

While DAS28 deprioritizes PGA, the same algorithm allows remission to be attained with multiple swollen joints, which can consequently lead to radiographic joint damage despite the patient being "in remission" [17]. As a reciprocal, a patient must have TJC28, SJC28, CRP, and PGA ≤ 1.0 to attain a 4-variable remission [4]. However, this approach may overemphasize subjectivity, as patients without active joints and normal CRP levels can still report elevated PGA scores, which shift disease activity above the remission threshold due to noninflammatory causes, e.g. fibromyalgia, osteoarthritis, depression, psychological pain and distress, and other comorbidities [18–21]. A study by Inanc et al. observed an increase in anxiety, fatigue, and depression among RA patients who did not attain 4-variable remission but achieved a DAS28-ESR remission [22]. Among these measures, PGA and depression were the most important contributors to nonconcordance between DAS28-ESR and Boolean remission rates. In order to avoid false nonremission and possibly improper targeted treatment, Inanc et al. proposed the implementation of separate supplementary assessments for anxiety, fatigue, fibromyalgia, and depression among RA patients who do not attain 4-variable remission [22].

Solutions to lessen the restrictiveness of 4-variable remission include threshold modification [23] and 3-component variant remission definition [24]. The latter is exemplified by excluding PGA from Boolean remission when assessing disease activity, albeit restricting it to disease impact [5]. We evaluated the threshold modifications, Boolean 3- and 2-variable remission and the individual Boolean components. Figure 1 shows that the remission rates for 3-variable remission, DAS28(4), and

Table 3 Associations between PGA and the patient variables in rheumatoid arthritis patients using linear regression

	Univariate			Multivariate								
	Enter			Enter			Forward			Backward		
	β	*B* (95% CI)	*P*	*β*	*B* (95% CI)	*P*	*β*	*B* (95% CI)	*P*	*β*	*B* (95% CI)	*P*
Demographics												
Age (years)	0.1	0.1 (0.1, 0.3)		0	0 (− 0.1, 0.1)							
Female	**0.1**	**5.9 (1.1, 10.7)**	*	0	−1.4 (−4.2, 1.4)							
BMI (kg/m^2)	**0.1**	**0.5 (0, 1.0)**	*	0	0 (−0.3, 0.3)							
Education (years)	**−0.2**	**−1.1 (−1.8, −0.5)**	***	0	0.2 (−0.1, 0.6)							
Smoker	0.1	5.2 (−1.1, 11.4)		0	−0.9 (−4.5, 2.7)							
Disease duration (years)	**0.1**	**0.3 (0.1, 0.5)**	*	−0.1	−0.1 (−0.3, 0)							
Biomarkers												
aCCP positive	0	−1.1 (−6.3, 4.1)		0	−1.6 (−5.5, 2.3)							
RF positive	0.1	2.6 (−2.4, 7.5)		0	1.9 (−1.7, 5.6)							
Disease activity variables												
ESR (mm/h)	**0.3**	**0.5 (0.3, 0.7)**	***	**0.1**	**0.2 (0, 0.3)**	*	**0.1**	**0.1 (0, 0.2)**	*	**0.1**	**0.1 (0, 0.2)**	*
CRP (mg/L)	**0.2**	**0.5 (0.3, 0.7)**	***	0	−0.1 (−0.2, 0.1)							
TJC28 (0–28)	**0.4**	**3.8 (3.0, 4.5)**	***	0	0.1 (−0.5, 0.6)							
SJC28 (0–28)	**0.3**	**3.5 (2.3, 4.6)**	***	0	0.1 (−1.0, 1.1)							
IGA (VAS, 0–100 mm)	**0.4**	**0.8 (0.7, 1.0)**	***	0.1	0.2 (0, 0.3)		**0.1**	**0.2 (0.1, 0.3)**	**	**0.1**	**0.2 (0.1, 0.3)**	**
Patient−reported outcome measures												
Pain (VAS, 0–100 mm)	**0.9**	**0.9 (0.8, 0.9)**	***	**0.7**	**0.7 (0.6, 0.7)**	***	**0.7**	**0.7 (0.6, 0.7)**	***	**0.7**	**0.7 (0.6, 0.7)**	***
MHAQ (0–3)	**0.7**	**40.7 (37.1, 44.2)**	***	**0.1**	**4.9 (0.5, 9.4)**	*	**0.1**	**4.1 (0.0, 8.1)**	*	**0.1**	**4.5 (0.5, 8.6)**	*
Fatigue (VAS, 0–100 mm)	**0.7**	**0.6 (0.6, 0.7)**	***	**0.2**	**0.2 (0.1, 0.2)**	***	**0.2**	**0.2 (0.1, 0.2)**	***	**0.2**	**0.2 (0.1, 0.2)**	***

Table 3 continued

	Univariate			Multivariate							
	Enter			Enter			Forward			Backward	
	β	*B* (95% CI)	*P*	*β*	*B* (95% CI)	*P*	*β*	*B* (95% CI)	*P*	*β*	*B* (95% CI)	*P*
Morning stiffness (h)	**0.5**	**10.6 (9.0, 12.2)**	***	0	0.1 (−1.2, 1.3)							
Adjusted *R* square		0.8		0.8	0.8							

β standardized coefficient *β*, *B* unstandardized coefficient *B*, *BMI* body mass index, *aCCP* anti-cyclic citrullinated peptide, *RF* rheumatoid factor, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *TJC28* tender 28-joint count, *SJC28* swollen 28-joint count, *IGA* investigators global assessment, *VAS* visual analog scale (measured 0–100), *PGA* patient global assessment, *MHAQ* modified health assessment questionnaire. All data were collected from an ordinary outpatient clinic in southern Norway. All values marked in bold have significant *p*-values: *** < 0.001, ** < 0.01, and * < 0.05

DAS28(3) remained highest regardless of the PGA threshold used in 4-variable remission.

In a meta-analysis by Ferreira et al. (2020) [25], which included 12 studies reporting indirect 3-variable remission rates, a paper by Furu et al. [26] reported the highest 3-variable remission prevalence of 51% in a Japanese cohort in 2014. The average 3-variable remission prevalence from the 12 studies in the meta-analysis was 31% [25]. In other non-single-timepoint studies, Studenic et al. reported a 3-variable remission rate of 30% after 12 months of treatment for early RA [23]. Interestingly, a study of DMARD-naïve patients with early RA showed a similar remission rate when they were only treated with csDMARDs and prednisolone [27]. Our high 3-variable remission rate may be explained by the lower disease activity in our outpatient RA cohort (mean DAS28 2.4 and CDAI 6.4), where a high proportion of the patients ($\sim$ 40%) were treated with b/tsDMARDs.

When the 4-variable remission was divided into subjective (PGA, TJC28) and objective (CRP, SJC28) categories, only 25% of patients achieved subjective remission, whereas 76% reached objective remission. During the same year, among the one-variable cutoffs, PGA $\leq$ 10 had the lowest rate, 27%, the rate for TJC28 $\leq$ 1 was 74%, that for SJC28 $\leq$ 1 was 85%, and that for CRP $\leq$ 10 was the highest: 86%. We believe that these numbers reflect two valuable issues: (1) despite considering tender joints to be subjective, similar rates are reported for the objective SJC28 and CRP, and (2) there are considerable differences in rate between patients expressing PGA $\leq$ 10 and TJC28 $\leq$ 1, SJC28 $\leq$ 1, and CRP $\leq$ 10 (27% vs 74–86%).

Based on these numbers, remission-assessing methods that use PGA, at least for Boolean criteria, CDAI, and SDAI, do not appear favourable. The argument for including PGA was its ability to help differentiate active treatment from control treatment, which in turn meant a significant contribution to defining remission. Together with CDAI and SDAI, 4-variable remission was also considered to predict good radiographic outcomes [4]. In addition, PGA and CRP were considered a safeguard when

using the standardized 28 joint count, which omits ankle and feet joints [4].

However, studies have shown that only swollen joints and acute phase reactants, not PGA, are robustly associated with radiographic progression [17, 23, 28]. This may further weaken the rationale for incorporating PGA into remission assessments, since stopping the progression of joint damage is one of the most important goals of RA treatment. With the introduction of modern imaging techniques, subclinical signs of inflammation have been demonstrated, highlighting the challenges of defining true remission in RA [29–32].

Moreover, RA patients in remission by any established criteria can experience radiographic progression [33]. A recent study showed that the increase in tender joints correlated best with other subjective variables (i.e. pain) but not with ultrasonographic synovitis, whereas swollen joints correlated significantly with ultrasonographic synovitis [34]. Furthermore, Hensor et al. found that a score based on SJC28 and CRP alone had a stronger association with ultrasonography synovitis and radiographic progression than the original DAS28 in early RA [35]. A recently published paper by Sundlisæter et al. (2022) observed no increase in inflammation measured with ultrasound and MRI in patients who failed to attain 4-variable remission due to PGA and/or TJC compared to those who achieved 4-variable remission [36]. Brites et al. (2021) did not observe any significant changes in inflammation on ultrasound either when comparing 4-variable remission and 3-variable remission [37]. This again supports the view that objective measures reflect inflammatory disease status better than subjective measures, which may also be impacted by noninflammatory mechanisms.

To distinguish between patients with treatment failure with and without the presence of objective inflammation, Buch and colleagues recently introduced the terms "persistent inflammatory refractory RA" (PIRRA) and "noninflammatory refractory RA" (NIRRA) [38]. Distinguishing between PIRRA and NIRRA from a clinical perspective is important, as the two require different treatments and treatment strategies. It is particularly relevant in patients who only fail to attain a 4-variable remission because PGA > 10 [38]. Real-life data, as collected in our study, are thus of great importance, as they reveal the strength and weaknesses of the present remission criteria when they are used to treat patients to remission in ordinary clinical practice.

In addition, the use of PGA in RA comes with numerous challenges due to its subjective and heterogeneous formulation. PGA is often a single unstandardized question with global-health-oriented or disease-activity-oriented wording. In our study, we used PGA with a more general description. Khan et al. showed that disease activity and general PGA could be used interchangeably for the calculation of RA activity when using CDAI, DAS28, and Routine Assessment of Patient Index Data 3 [39]. However, Gossec et al. reported discordance between the global-health-formulated and disease-activity-formulated PGA in Boolean remission for early arthritis patients [40]. PGA can also be expressed using various phrases or with an open question, where the answer is transformed to either a 0–10 or a 0–100 scale. Graphics can also be used, such as lines (horizontal or vertical) or tick marks with intervals [20]. In summary, numerous possible results increase the chance of generating various interpretations.

In the multivariable regression analyses, pain had the strongest and fatigue the second strongest association with PGA. When the analysis was based on disease activity, the strong association between pain and PGA was very similar for the subgroups. In the logistic regression assessment, these two variables were also only significant when compared with PGA-incorporated remission-assessing methods. Pain and fatigue are considered the leading sources of discomfort among RA patients and key contributing factors for reporting elevated PGA levels [20, 22, 41–44], especially in near-4-variable remission cases, i.e. in those who only failed to attain 4-variable remission because PGA > 10 [18, 24, 45]. The three most essential domains for achieving patient-perceived remission are pain, fatigue, and independence [46, 47]. From the patient's perspective, being in remission means reducing the impact of RA on

their life, "eventually leading to a feeling of normality" [48].

Since PGA is strongly associated with the patient's perception of pain, using remission methods impacted by PGA to guide medical treatment decisions when monitoring RA patients in an outpatient clinic may not reflect the inflammatory disease process. However, a less restrictive variant in which PGA has only a weak impact (DAS28 remission) can also cause the misestimation and omission of swollen joints.

This study should be seen in the context of its limitations. Like all observational studies, there are issues related to a certain level of missing data, confounding factors, and attrition bias. Only a selected group of patients without missing data were included. As shown in Supplementary Table 3, differences between the included and excluded patients were small and mostly nonsignificant, indicating a high grade of internal validity. Another limitation is the lack of radiographic data. The study's strengths are its real-life setting, the application of a spectrum of RA remission measurements, and the evaluation of PGA associations for relevant RA-related variables and remission definitions.

CONCLUSION

In conclusion, our study challenges the value of the currently used remission-assessing methods. Based on our results and available data, we suggest using methods without measures impacted by noninflammatory pain and psychosocial factors such as PGA when treating patients to remission with DMARDs. Interestingly, among all the variables used to assess the remission rate, only the IGA (used in both CDAI and SDAI) improved significantly, while the rest of the variables remained stable over the 5-year period.

Based on growing evidence, as supported by our study, we suggest that it may be time for a paradigm shift to develop new remission criteria and a new definition for use in ordinary clinical practice, with objective variables and imaging favoured to avoid treating noninflammatory pain with DMARDs.

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Data Availability. Data are available on reasonable request and must be approved by all participating centres.

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SUPPLEMENTARY MATERIAL

Remission or not remission, that's the question. Shedding light on remission and the impact of objective and subjective measures reflecting disease activity in rheumatoid arthritis

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Supplementary Table 1: Association between variables and remission among rheumatoid arthritis patients during 2019 using multivariable logistic regression.

	DAS28(4) Remission	DAS28(3) Remission	CDAI Remission	SDAI Remission	4vRemission (Normal)	4vRemission (>20 PGA)	3vRemission (Without PGA)	2vRemission (Subjective)	2vRemission (Objective)
Age (years)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.1)	1.0 (1.0, 1.0)
Female	0.9 (0.4, 1.9)	0.8 (0.4, 1.5)	1.0 (0.5, 2.0)	1.2 (0.6, 2.4)	1.1 (0.5, 2.6)	0.7 (0.3, 1.5)	0.8 (0.4, 1.4)	1.4 (0.5, 3.2)	0.9 (0.5, 1.9)
BMI (kg/m^2)	1.0 (0.9, 1.0)	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)	0.9 (0.9, 1.0)	1.0 (0.9, 1.0)	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)
Education (years)	1.0 (0.9, 1.1)	1.1 (1.0, 1.1)	0.9 (0.8, 1.0)	1.0 (0.9, 1.1)	1.0 (0.9, 1.2)	1.0 (0.9, 1.1)	1.0 (1.0, 1.1)	1.0 (0.9, 1.1)	1.1 (1.0, 1.2)
Smoker	0.8 (0.3, 1.9)	1.1 (0.4, 2.7)	0.7 (0.3, 1.8)	1.0 (0.4, 2.4)	1.0 (0.3, 3.2	0.4 (0.1, 1.2)	0.6 (0.3, 1.3)	1.5 (0.4, 5.2)	0.9 (0.4, 2.0)
Disease Duration (years)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (0. 1.0, 1.1)	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)
aCCP Positive	2.5 (0.9, 7.2)	**2.8 (1.0, 7.4)** *	2.2 (0.8, 6.1)	2.0 (0.8, 5.4)	1.7 (0.5, 5.7)	3.5 (1.2, 10.8)	2.2 (0.9, 5.2)	1.2 (0.3, 4.1)	2.0 (0.7, 5.4)
RF Positive	0.7 (0.3, 2.1)	0.6 (0.2, 1.6)	0.7 (0.3, 1.7)	0.8 (0.3, 2.0)	0.5 (0.2, 1.5)	0.7 (0.3, 1.8)	0.6 (0.3, 1.5)	0.6 (0.2, 2.0)	1.0 (0.4, 2.5)
ESR (mm/h)	**1.0 (0.9, 1.0)** *	**1.0 (0.9, 1.0)** *	1.0 (0.9, 1.0)	**0.9 (0.9, 1.0)** **	1.0 (0.9, 1.0)	1.0 (0.9, 1.0)	**1.0 (0.9, 1.0)** **	1.0 (0.9, 1.0)	**0.9 (0.9, 1.0)** ***
Pain (VAS, 0–100 mm)	**1.0 (1.0, 1.0)** **	1.0 (1.0, 1.0)	**0.9 (0.9, 1.0)** ***	**0.9 (0.9, 1.0)** ***	**0.9 (0.9, 0.9)** ***	**0.9 (0.9, 1.0)** ***	1.0 (1.0, 1.0)	**0.9 (0.9, 0.9)** ***	1.0 (1.0, 1.0)
M-HAQ (0–3)	1.0 (0.3, 3.2)	0.5 (0.2, 1.5)	0.7 (0.2, 3.1)	1.0 (0.3, 4.1)	0.3 (0.0, 2.3)	0.5 (0.1, 2.4)	1.1 (0.4, 2.9)	0.2 (0.0, 1.7)	1.2 (0.4, 3.3)
Fatigue (VAS, 0–100 mm)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	**1.0 (1.0, 1.0)** ***	**1.0 (1.0, 1.0)** **	**1.0 (1.0, 1.0)** *	**1.0 (1.0, 1.0)** **	1.0 (1.0, 1.0)	**1.0 (1.0, 1.0)** **	1.0 (1.0, 1.0)
Morning stiffness (h)	0.7 (0.5, 1.0)	0.9 (0.7, 1.2)	**0.5 (0.3, 0.9)** *	**0.5 (0.3, 0.9)** *	0.9 (0.5, 1.6)	**0.6 (0.3, 1.0)** *	0.8 (0.6, 1.0)	1.1 (0.6, 2.1)	0.9 (0.6, 1.1)
IGA (VAS, 0–100 mm)	**0.9 (0.8, 0.9)** ***	**0.9 (0.9, 0.9)** ***	NA	NA	**0.9 (0.8, 1.0)** *	**0.9 (0.8, 0.9)** ***	**0.9 (0.9, 0.9)** ***	1.0 (0.9, 1.0)	**0.9 (0.9, 1.0)** ***
PGA (VAS, 0–100 mm)	NA	1.0 (1.0, 1.0)	NA	NA	NA	NA	1.0 (1.0, 1.0)	NA	1.0 (1.0, 1.0)
TJC28 (0–28)	NA	NA	NA	NA	NA	NA	NA	NA	**0.8 (0.8, 1.0)** **
SJC28 (0–28)	NA	NA	NA	NA	NA	NA	NA	0.8 (0.4, 1.6)	NA
CRP (mg/L)	NA	NA	1.0 (0.9, 1.0)	NA	NA	NA	NA	0.9 (0.8, 1.0)	NA
Nagelkerke R Square	0.6	0.5	0.6	0.6	0.7	0.7	0.4	0.7	0.4

Abbreviations: **BMI** = Body Mass Index, **aCCP** = Anti-cyclic citrullinated peptide, **RF** = Rheumatoid Factor, **ESR** = Erythrocyte Sedimentation Rate, **CRP** = C-Reactive Protein, **TJC28** = Tender 28-Joint Count, **SJC28** = Swollen 28-Joint Count, **IGA** = Investigators Global Assessment, **VAS =** Visual Analog Scale (Measured 0–100), **DAS28** = Disease Activity Score, **PGA** = Patient Global Assessment, **MHAQ** = Modified Health Assessment Questionnaire. **DAS28** = Disease Activity Score, **CDAI** = Clinical Disease Activity Index, **SDAI** = Simple Disease Activity Index, **NA** = Not Available. *Note*: All data are collected from an ordinary outpatient clinic in southern Norway. All values represent the Exp(B) (Odds Ratio) for remission with its confidence interval of 95% in parentheses. Variables constructing the given remission-assessing methods are omitted. **4vRemission** is achieved when ≤10 CRP, ≤1 TJC28, ≤1 SJC28, and ≤10 PGA. **3vRemission** is achieved when ≤10 CRP, ≤1 TJC28, and ≤1 SJC28. **2vRemission (Objective)** is achieved when ≤10 CRP and ≤1 SJC28. **2vRemission (Subjective)** is achieved when ≤10 PGA and ≤1 TJC28. **Categorical Variables**: **Sex** (Female, Male), **Smoking Status** (Smokers, Non-Smokers), **aCCP Evaluation** (Positive, Negative), **RF Evaluation** (Positive, Negative). **Significance**: All values marked bold have significant p-value with *** <0.001, ** <0.01, and * <0.05.

Supplementary table 2: Multivariant (enter) association between PGA and the patient's variables in rheumatoid arthritis patients using linear regression reported in different disease activity subgroups (2019)

	3-variable Remission *N = 327 (65%)*			*DAS28(4) m-hDa N = 105 (21%)*			*CDAI m-hDa N = 99 (20%)*			*SDAI m-hDa N = 92 (18%)*		
	β	B (95% CI)	P	β	B (95% CI)	P	β	B (95% CI)	P	β	B (95% CI)	P
Demographics												
Age (years)												
Female												
BMI (kg/m^2)												
Education (years)												
Smoker												
Disease Duration (years)												
Biomarkers												
aCCP Positive												
RF Positive												
Disease Activity Variables												
ESR (mm/h)				0.2	0.2 (0, 0.4)	*				0.2	0.2 (0, 0.4)	*
CRP (mg/L)				-0.2	-0.2 (-0.4, 0)	*						
TJC28 (0–28)												
SJC28 (0–28)												
IGA (VAS, 0–100 mm)												
Patient-Reported Outcome Measures												
Pain (VAS, 0–100 mm)	0.7	0.7 (0.5, 0.8)	***	0.7	0.7 (0.5, 0.9)	***	0.7	0.7 (0.5, 0.8)	***	0.7	0.7 (0.5, 0.8)	***
MHAQ (0–3)	0.1	6.9 (0.5, 13.3)	*									
Fatigue (VAS, 0–100 mm)	0.2	0.2 (0.1, 0.3)	***	0.2	0.1 (0, 0.3)	*	0.2	0.1 (0, 0.3)	*	0.2	0.1 (0, 0.3)	*
Morning stiffness (h)												
Adjusted R Square		0.8			0.8			0.8			0.8	

Abbreviations: **3v-Remission** = 3-variable remission (≤1 SJC28, ≤1 TJC28, ≤10 CRP), **CDAI** = Clinical Disease Activity Index, **SDAI** = Simple Disease Activity Index, **m-hDa** = moderate-high Disease Activity, **β** = Standardized Coefficient Beta, **B** = Unstandardized Coefficient B, **BMI** = Body Mass Index, a**CCP** = Anti-cyclic citrullinated peptide, **RF** = Rheumatoid Factor, **ESR** = Erythrocyte Sedimentation Rate, **CRP** = C-Reactive Protein, **TJC28** = Tender 28-Joint Count, **SJC28** = Swollen 28-Joint Count, **IGA** = Investigators Global Assessment, **VAS** = Visual Analog Scale (Measured 0–100), **PGA** = Patient Global Assessment, **MHAQ** = Modified Health Assessment Questionnaire. *Note*: All data are collected from an ordinary outpatient clinic in southern Norway in 2019 using a complete dataset (N=502). **Significance**: All values marked bold have significant p-value with *** <0.001, ** <0.01, and * <0.05.

Supplementary Table 3: Comparison between excluded and included rheumatoid arthritis patients recruited for the period 2015 and 2019

	2015			2016			2017			2018			2019		
	Excluded (n = 454)	Included (n = 613)	P	Excluded (n = 354)	Included (n = 554)	P	Excluded (n = 389)	Included (n = 555)	P	Excluded (n = 335)	Included (n = 409)	P	Excluded (n = 369)	Included (n = 502)	P
Demographic															
Age (years)	63 (15) [0%]	63 (13) [0.0%]	0.756	65 (14) [0%]	61 (14) [0%]	**<0.001**	64 (14) [0%]	62.0 (13) [0.0%]	**0.023**	64 (15) [0%]	61 (14) [0%]	**0.001**	64 (14) [0%]	62 (14) [0%]	0.053
Female	330 (73%) [0%]	410 (67%) [0%]	**0.042**	260 (73%) [0%]	377 (68%) [0%]	0.083	284 (71%) [0%]	362 (65%) [0%]	**0.046**	233 (70%) [0%]	334 (68%) [0%]	0.673	245 (66%) [0%]	335 (68%) [0%]	0.917
BMI (kg/m^2)	25 (4.2) [6.8%]	27 (4.7) [2.0%]	**<0.001**	26 (5.1) [8.8%]	26 (4.4) [0.9%]	0.830	26 (5.4) [7.3%]	26.2 (4.4) [2.0%]	0.715	26 (5.4) [7.5%]	26 (4.4) [1.6%]	0.947	26 (5.2) [6.5%]	26 (4.5) [1.8%]	0.867
Education (y)	12 (3.7) [5.3%]	12 (3.4) [0.5%]	0.526	11 (3.7) [7.6%]	12 (3.6) [0.4%]	**0.036**	12 (3.8) [6%]	12 (3.6) [1.6%]	0.226	12 (3.8) [6.9%]	12 (3.5) [1.4%]	0.184	12 (3.8) [6.2%]	12 (3.5) [1.6%]	0.179
Current Smokers	82 (19%) [3.5%]	118 (19%) [0.5%]	0.806	65 (20%) [5.9%]	101 (18%) [0.2%]	0.643	52 (14%) [5%]	90 (16%) [1.3%]	0.268	51 (16%) [6.3%]	82 (17%) [1%]	0.805	63 (18%) [4.6%]	78 (16%) [1.0%]	0.395
Disease Duration (y)	13 (11) [0%]	12 (10) [0%]	**0.021**	13 (11) [0%]	12 (9.9) [0%]	0.065	13 (11) [0%]	12 (10) [0%]	0.160	12 (11) [0%]	11 (11) [0%]	0.490	13 (11) [0%]	11 (11) [0%]	**0.005**
Biomarkers															
aCCP Positive	297 (70%) [6.2%]	421 (72%) [4.9%]	0.388	222 (69%) [8.8%]	393 (75%) [4.9%]	0.065	263 (72%) [8%]	380 (72%) [5%]	0.940	211 (68%) [7.5%]	356 (76%) [4.9%]	**0.013**	245 (70%) [5.4%]	357 (74%) [3.4%]	0.309
RF Positive	285 (66%) [4.8%]	409 (69%) [3.4%]	0.292	217 (66%) [7.6%]	374 (70%) [4.0%]	0.226	237 (65%) [8.5%]	370 (70%) [4.1%]	0.163	209 (67%) [7.5%]	311 (68%) [6.7%]	0.854	227 (66%) [6.2%]	318 (67%) [5.6%]	0.657
Disease Activity Variables															
ESR (mm/h)	15 (13) [67%]	18 (15) [8.8%]	**0.045**	18 (19) [57%]	15 (14) [9.2%]	**0.014**	15 (16) [58%]	14 (13) [15%]	0.197	20 (20) [68%]	14 (15) [18%]	**0.001**	19 (21) [68%]	13 (12) [21%]	**<0.001**
CRP (mg/L)	6.3 (11) [67%]	6.5 (11) [0%]	0.857	11 (22) [55%]	5.9 (11) [0%]	**<0.001**	8.7 (17) [51%]	6.2 (14) [0%]	0.051	9.4 (17) 6 (10) [0%]		**0.004**	8.5 (18) [58%]	5.8 (10) [0%]	**0.017**
TJC28 (0–28)	1.5 (3.1) [38%]	1.4 (2.9) [0%]	0.447	1.8 (3.4) [40%]	1.4 (2.9) [0%]	0.072	2.3 (4.0) [40%]	1.2 (2.6) [0%]	**<0.001**	1.8 (3.5) [30%]	1.3 (2.9) [0%]	0.058	1.8 (3.6) [31%]	1.4 (2.8) [0%]	**0.045**
SJC28 (0–28)	1.0 (2.0) [38%]	0.9 (1.8) [0%]	0.247	1.2 (2.5) [40%]	1.0 (2.3) [0%]	0.162	1.5 (3.0) [40%]	0.9 (2.3) [0%]	**0.003**	1.1 (2.3) [30%]	0.9 (2.1) [0%]	0.122	0.9 (2.1) [31%]	0.7 (1.9) [0%]	0.134
IGA (0–100)	9.4 (11) [37%]	10 (12) [0%]	0.381	9.6 (12) [44%]	10.1 (13) [0%]	0.625	12 (15) [45%]	9.2 (13) [0%]	**0.045**	9.8 (12) [41%]	11 (14) [0%]	0.484	8.0 (11) [36%]	7.8 (12) [0%]	0.908
Composite Disease Activity Scores															
DAS28(3) score	2.4 (0.8) [85%]	2.3 (0.9) [0%]	0.595	2.7 (1.1) [75%]	2.3 (0.9) [0%]	**<0.001**	2.9 (1.2) [75%]	2.2 (0.9) [0%]	**<0.001**	2.6 (1.0) [73%]	2.3 (0.9) [0%]	**0.001**	2.5 (1.1) [77%]	2.2 (0.9) [0%]	**0.005**
DAS28(4) score	2.5 (1.0) [94%]	2.5 (1.0) [0%]	0.963	2.9 (1.3) [94%]	2.4 (1.0) [0%]	0.065	2.6 (1.1) [93%]	2.4 (1.0) [0%]	0.285	2.8 (1.1) [91%]	2.4 (1.1) [0%]	0.060	2.7 (1.1) [94%]	2.4 (1.1) [0%]	0.078
CDAI	7.0 (6.4) [62%]	6.6 (6.5) [0%]	0.476	5.3 (5.2) [80%]	6.5 (6.9) [0%]	0.156	6.9 (7.3) [74%]	6.1 (6.9) [0%]	0.271	6.9 (7.2) [70%]	6.5 (6.7) [0%]	0.652	5.9 (6.7) [66%]	6.1 (6.6) [0%]	0.764
SDAI	NA	7.2 (6.8) [0%]	NA	NA	7.1 (7.3) [0%]	NA	NA	6.7 (7.5) [0%]	NA	NA	7.2 (7.0) [0%]	NA	NA	6.7 (7.0) [0%]	NA
Patient-Reported Outcome Measures															
PGA (0–100)	36 (26) [20%]	33 (26) [0%]	0.110	34 (28) [42%]	32 (25) [0%]	0.274	33 (26) [34.2%]	30 (24) [0%]	0.148	36 (27) [36%]	32 (26) [0%]	0.999	34 (26) [34%]	33 (26) [0%]	0.587
Pain (0–100)	36 (26) [22%]	33 (26) [7.2%]	0.084	36 (27) [42%]	32 (25) [7.4%]	**0.032**	33 (27) [37%]	32 (25) [6.8%]	0.491	39 (27) [39%]	33 (26) [8.6%]	**0.011**	34 (27) [36%]	33 (26) [9.4%]	0.403
MHAQ (0–3)	0.5 (0.5) [21%]	0.5 (0.5) [3.6%]	0.364	0.6 (0.6) [40%]	0.4 (0.5) [3.4%]	**0.000**	0.4 (0.5) [34%]	0.4 (0.5) [6.5%]	0.792	0.5 (0.5) [37%]	0.4 (0.5) [8.4%]	0.128	0.5 (0.5) [34%]	0.4 (0.5) [7.6%]	**0.038**
Fatigue (0–100)	40 (30) [22%]	37 (30) [4.7%]	0.142	40 (31) [42%]	36 (30) [4.2%]	0.163	40 (33) [36%]	39 (29) [6.7%]	0.387	41 (32) [38%]	38 (31) [8.2%]	0.253	40 (31) [36%]	38 (30) [9.2%]	0.265
Morning Stiffness	0.9 (1.2) [22%]	1.0 (1.3) [9.0%]	0.573	1.0 (1.4) [41%]	0.9 (1.3) [7.8%]	0.191	0.9 (1.4) [36%]	0.8 (1.1) [6.7%]	0.170	1.0 (1.2) [39%]	0.9 (1.2) [9%]	0.292	0.8 (1.2) [20%]	0.9 (1.3) [9.0%]	0.774
Treatment															
b/tsDMARDs	155 (34%) [0%]	255 (42%) [0%]	**0.011**	116 (33%) [0%]	247 (45%) [0%]	**<0.001**	139 (35%) [0%]	216 (39%) [0%]	0.208	106 (32%) [0%]	199 (41%) [0%]	**0.009**	154 (42%) [0%]	206 (41%) [0%]	0.836
TNFi	93 (21%) [0%]	155 (25%) [0%]	0.066	62 (18%) [0%]	153 (28%) [0%]	**<0.001**	83 (21%) [0%]	129 (23%) [0%]	0.382	55 (16%) [0%]	102 (21%) [0%]	0.141	86 (23%) [0%]	102 (20%) [0%]	0.296
Mono	45 (9.9%) [0%]	40 (6.5%) [0%]	**0.042**	27 (7.6%) [0%]	51 (9.2%) [0%]	0.408	40 (10%) [0%]	52 (9.4%) [0%]	0.726	26 (7.8%) [0%]	61 (12%) [0%]	**0.031**	47 (13%) [0%]	65 (13%) [0%]	0.923
b/tsDMARDs	26 (5.7%) [0%]	19 (3.1%) [0%]	**0.035**	8 (2.3%) [0%]	30 (5.4%) [0%]	**0.021**	26 (6.5%) [0%]	26 (4.7%) [0%]	0.210	10 (3.0%) [0%]	31 (6.3%) [0%]	**0.006**	22 (6.0%) [0%]	28 (5.6%) [0%]	0.810
Mono TNFi	258 (57%) [0%]	405 (66%) [0%]	**0.002**	192 (54%) [0%]	362 (65%) [0%]	**0.001**	223 (56%) [0%]	366 (66%) [0%]	**0.002**	198 (59%) [0%]	325 (66%) [0%]	**0.034**	208 (56%) [0%]	325 (65%) [0%]	**0.012**
csDMARDs	213 (47%) [0%]	346 (56%) [0%]	**0.002**	154 (44%) [0%]	302 (55%) [0%]	**0.001**	181 (46%) [0%]	315 (57%) [0%]	**0.002**	160 (48%) [0%]	275 (56%) [0%]	**0.018**	177 (48%) [0%]	286 (57%) [0%]	**0.008**
Methotrexate	228 (50%) [0%]	311 (51%) [0%]	0.861	197 (56%) [0%]	265 (48%) [0%]	**0.021**	204 (51%) [0%]	266 (48%) [0%]	0.311	175 (52%) [0%]	226 (46%) [0%]	0.084	174 (47%) [0%]	227 (45%) [0%]	0.571
Prednisone	56 (12%) [0%]	53 (8.6%) [0%]	**0.045**	46 (13%) [0%]	44 (7.9%) [0%]	**0.013**	55 (14%) [0%]	42 (7.6%) [0%]	**0.002**	40 (12%) [0%]	31 (6.3%) [0%]	**0.005**	38 (10%) [0%]	31 (6.2%) [0%]	**0.026**
No Treatment															

Note: All data are collected from an ordinary outpatient clinic in southern Norway. Categorical variables are presented as numbers and percentages (%) and continuous variables as mean with standard deviation (SD). Missing data are presented as mean in percentage [%]. χ^2 test for categorical variables and one-way ANOVA for continuous variables was used to assess the differences between included and excluded datasets for each consecutive year. *Abbreviations*: **BMI** = Body Mass Index, **aCCP** = Anti-cyclic citrullinated peptide, **RF** = Rheumatoid Factor, **ESR** = Erythrocyte Sedimentation Rate, **CRP** = C-Reactive Protein, **TJC28** = Tender 28-Joint Count, **SJC28** = Swollen 28-Joint Count, **IGA** = Investigators Global Assessment, **VAS** = Visual Analog Scale (Measured 0-100), **DAS28** = Disease Activity Score with CRP, **CDAI** = Clinical Disease Activity Index, **SDAI** = Simple Disease Activity Index, **PGA** = Patient Global Assessment, **MHAQ** = Modified Health Assessment Questionnaire, **b/tsDMARDs** = biological and target synthetic Disease-Modifying Antirheumatic Drugs, **TNF** = Tumour necrosis factor, **csDMARDs** = conventional synthetic Disease-Modifying Antirheumatic Drugs, No Treatment = Implies patient is not receiving either b/tsDMARDs, csDMARDs or Prednisolone.

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