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BRIEF REPORT

Association between TNFi anti-drug antibodies, smoking, and disease activity in patients with inflammatory arthritis: Results from a Norwegian cross-sectional observational study

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ABSTRACT

Introduction: We aimed to compare demographics and clinical characteristics between patients with inflammatory arthritis (IA) with vs. without neutralizing anti-drug antibodies (nADAb) against tumor necrosis factor inhibitors (TNFi). A secondary aim of the study was to explore if current smokers were more frequently nADAb-positive.

Methods: TNFi-treated outpatients with IA were recruited and a broad range of disease activity measures were assessed. nADAb were assessed using a reporter gene assay. Comparisons between nADAb-positive and -negative patients were done in unadjusted analyses as well as in adjusted logistic regression and general linear models.

Results: A total of 282 patients with IA currently under treatment with TNFi were included. nADAb were identified in 11 patients (nine treated with infliximab, one with etanercept and one with certolizumab pegol). Patients with nADAb reported significantly worse joint pain, patient's global assessment, Health Assessment Questionnaire, Bath Ankylosing Spondylitis Disease Activity/Functional Index and Short-Form-36 physical functioning scale score than patients without nADAb ($p < 0.04$, adjusted analyses). 28-joint Disease Activity Score, Simplified Disease Activity Index and Maastricht Ankylosing Spondylitis Enthesitis score were also significantly worse in the nADAb-positive patients ($p < 0.04$, adjusted analyses), as were serum calprotectin, C-reactive protein and numbers of circulating peripheral leukocytes ($p \leq 0.001$). A significantly higher proportion of nADAb-positive patients were current smokers (46 vs. 15%), in unadjusted as well as adjusted analyses ($p \leq 0.008$).

Conclusions: nADAb-positive patients were more frequently smokers and had significantly worse disease activity, physical function, and inflammatory markers, than patients without

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nADAb. The association between smoking and nADAb positivity warrants further examination.

Keywords: Rheumatoid arthritis; Psoriatic arthritis; Ankylosing spondylitis; Tumor necrosis factor inhibitors

Key Summary Points

Real-life studies on the clinical impact of neutralizing TNFi anti-drug antibodies (nADAb) including a broad range of disease activity metrics are needed, as well as studies exploring the impact of smoking on formation of nADAb.

The study included patients with inflammatory arthritis treated with TNF inhibitors as part of standard care.

nADAb-positive patients had higher disease activity, including serum calprotectin, and worse physical function than nADAb-negative patients. Furthermore, an association between nADAb positivity and current smoking was found.

nADAb positivity may preclude treatment efficacy in TNFi-treated patients.

INTRODUCTION

Over the course of the last few decades, the tumor necrosis factor inhibitors (TNFi) together with the implementation of a treat-to-target strategy have led to far better treatment outcomes for patients with inflammatory arthritis (IA) [1]. However, some patients still experience treatment failure and in some of these patients this may be related to the development of anti-drug antibodies against TNFi (ADAb) [2]. ADAb formation may not only be associated with reduced clinical efficacy, but also higher risk of adverse events like e.g., infusion reactions [3].

Tobacco smoking is known to have a negative impact on TNFi treatment efficacy, but the underlying mechanism behind this association is unclear [4]. Tobacco smoking impacts both innate and adaptive immunity and is known to increase the production of several pro-inflammatory cytokines including TNFα, decrease levels of anti-inflammatory cytokines, and increase the risk of formation of antibodies against e.g., citrullinated proteins [5, 6].

In this real-life study of patients with IA treated with TNFi, we aimed to explore the differences in demographics and clinical characteristics between patients with and without development of neutralizing ADAb (nADAb). A secondary aim of the study was to explore if current smokers were more frequently nADAb-positive.

METHODS

Patients

We included a convenience sample of patients with IA (including patients with a clinical diagnosis of rheumatoid arthritis [RA], psoriatic arthritis [PsA] and ankylosing spondylitis [AS]) from Sørlandet Hospital Kristiansand, Norway, who were under treatment with TNFi in 2016–2017. All patients were outpatients and treated as part of ordinary care by their regular physician. Demographics and patient-reported outcome measures (PROs) were reported by the patients through the computer system used for standard follow-up (GoTreatIT®) [7], including age, gender, disease duration, currently smoking (yes/no [including previous and never smokers]), current use of snuff (yes/no [including previous and never snuffers]), body mass index (BMI, kg/m^2), years of education, civil status, work status, current and previous treatments, 0–100 visual analogue scales (VAS) for joint pain, back pain, pain, fatigue and patient's global assessment, as well as Short Form-36 (SF-36) physical (PCS) and mental (MCS) component summaries, SF-36 scale scores [8], Health Assessment Questionnaire (HAQ)[8] and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI, range 0–10; AS and PsA patients) [8] and Functional Index (BASFI, range 0–10; AS and PsA patients) [8]; 28 swollen/tender joint

counts (RA and PsA patients), Maastricht Ankylosing Spondylitis Enthesitis Score[8] and physician's global assessment of disease activity were assessed by the treating physician as part of standard care; 28-joint Disease Activity Score with ESR (DAS28) [9] and Simplified Disease Activity Index (SDAI)[9] were calculated (RA and PsA patients).

Ethics Compliance

The study was approved by the Regional Committees for Medical and Health Research Ethics mid-Norway (Ref. 2015/1196/REK midt). Written informed consent was obtained from each patient prior to inclusion in the study. The study was performed in accordance with the Helsinki Declaration.

Laboratory Analyses

The laboratory markers of inflammation C-reactive protein (CRP) and numbers of circulating peripheral leukocytes were measured as part of standard follow-up. Serum samples were stored in a biobank at − 80 °C until analyses of calprotectin and nADAb were performed. Serum calprotectin [10] was analyzed using CalproLabTM (ALP) ELISA kits according to instructions by the manufacturer (Calpro AS, Norway). Neutralizing antibodies against TNFi were assessed in iLiteTM NAb assay kits, using luciferase generated bioluminescence [11]. According to instructions by the manufacturer, the test procedure involved the use of division-arrested TNFα-sensitive cells in a bioassay capable of measuring TNFα bioactivity, where TNFα-induced activation of the firefly luciferase reporter gene construct inversely was proportional to TNFi present. A quantitative estimate of TNFi in serum was determined by detection of firefly luciferase luminescence by Victor^{TM} X (PerkinElmer) luminometer. Renilla luciferase reporter gene construct was used for normalization of the assay. Serum with TNFi levels below 0.65 mg/l was further analyzed for nADAb. A semi-quantitative estimate of the amount of nADAb was determined by titrating the serum samples to a dilution where the neutralizing effect of the antibodies no longer was distinguishable from antibody-negative controls.

Statistics

Demographics and medication were compared across patients with and without nADAb in unadjusted analyses with independent *t* test, Mann–Whitney *U* test or Chi-square test, as appropriate, as well as in age- and gender-adjusted logistic regression analyses. Disease activity measures were compared across patients with and without nADAb in unadjusted analyses with independent *t* test or Mann–Whitney *U* test, as appropriate, as well as in a prespecified general linear model adjusted for age, gender, BMI, diagnosis, and current conventional synthetic disease-modifying antirheumatic drug (csDMARD) comedication. Analyses were performed as completer analyses. Current smokers were compared across nADAb-positive and -negative patients adjusted for age and gender, and additionally also for BMI and concomitant csDMARD use. A p value < 0.05 was considered statistically significant. Statistical analyses were done with SPSS version 26.0.0.1

RESULTS

Patients

A total of 282 patients with IA (114 RA, 99 AS, and 69 PsA) currently under treatment with TNFi were included (Table 1 and supplementary table 1 [clinical assessments across IA diagnoses]).

nADAb were identified in 11 patients: nine patients who were treated with infliximab, one treated with etanercept, and one with certolizumab pegol. Five of the patients with nADAb had RA, three patients had PsA, and three AS. One of the eleven patients with nADAb experienced adverse events (an infusion reaction related to infliximab administration).

Median (IQR) TNFi trough level was 1.6 (1.0, 5.2) mg/l for infliximab, 2.0 (1.7, 8.3) mg/l for etanercept and 4.4 (1.8, 7.7) mg/l for

Table 1 Comparison of demographics and medication in patients with vs. without nADAb

	All patients (*n* = 282)	**Patients without nADAb *n* = 271**	**Patients with nADAb *n* = 11**	***p* value, unadjusted**	***p* value, adjusted[1]**
Age (years), mean (SD)	53.1 (12.7)	53.1 (12.6)	50.7 (15.9)	0.54	0.45
Disease duration (years), mean (SD)	12.4 (9.6)	12.5 (9.5)	9.7 (12.0)	0.36	0.40
Currently smoking, *n* (%)	44 (15.9)	39 (14.7)	5 (45.5)	0.006	0.008[1], 0.004[2]
Currently uses snuff, *n* (%)	17 (7.0)	16 (6.8)	1 (12.5)	0.54	0.59
BMI (kg/m^2), mean (SD)	26.6 (4.1)	26.6 (4.1)	26.8 (4.7)	0.88	0.63
Years of education, mean (SD)	13.2 (3.4)	13.2 (3.4)	12.7 (3.1)	0.64	0.48
Civil status, *n* (%)					
Single	16 (9.6)	16 (10.0)	0 (0.0)	0.02	0.40
Married	100 (59.9)	98 (61.3)	2 (28.6)		
Cohabiter	31 (18.6)	26 (16.3)	5 (71.4)		
Separated	2 (1.2)	2 (1.3)	0 (0.0)		
Divorced	13 (7.8)	13 (8.1)	0 (0.0)		
Widower	5 (3.0)	5 (3.1)	0 (0.0)		
Current TNFi, *n* (%)					
Adalimumab	49 (17.4)	49 (18.1)	0 (0.0)	0.001	0.046
Etanercept	91 (32.3)	90 (33.2)	1 (9.1)		
Certolizumab pegol	64 (22.7)	63 (23.2)	1 (9.1)		
Infliximab	78 (27.7)	69 (25.5)	9 (81.8)		
Previously bDMARD naïve, %	66 (23.4)	62 (22.9)	4 (36.4)	0.30	0.38
Concomitant csDMARDs, %	118 (41.8)	113 (41.7)	5 (45.5)	0.80	0.81
In part-time or full-time work, %	55.6%	56.1%	45.5%	0.49	0.41

BMI body mass index, *bDMARD* biologic disease-modifying antirheumatic drug, *csDMARD* conventional synthetic DMARD, *nADAb* neutralizing anti-drug antibody, *SD* standard deviation, *TNFi* tumor necrosis factor inhibitor

[1]Adjusted for age and gender

[2]Adjusted for age, gender, BMI, and current csDMARD comedication

Table 2 Comparison of disease burden in patients with vs. without nADAb

	Patients without nADAb	Patients with nADAb	*p* value, unadjusted	*p* value, adjusted
Joint pain (0–100 VAS), median (IQR)	26 (10, 45)	40 (20, 74)	0.08	0.04
Back pain (0–100 VAS), median (IQR)	24 (6, 49)	31 (15, 55)	0.32	0.37
Pain (0–100 VAS), median (IQR)	26 (10, 49)	41 (20, 64)	0.21	0.25
Fatigue (0–100 VAS), median (IQR)	36 (14, 65)	52 (19, 71)	0.54	0.63
Patients' global (0–100 VAS), median (IQR)	25 (10, 50)	50 (27, 60)	0.02	0.02
Physician's global (0–100 VAS), median (IQR)	4 (0, 10)	9 (0, 37)	0.28	0.002
HAQ, median (IQR)	0.5 (0.1, 1.0)	0.8 (0.5, 1.6)	0.06	0.02
28 swollen joint count[1], median (IQR)	0 (0, 0)	0 (0, 2)	0.17	0.02
28 tender joint count[1], median (IQR)	0 (0, 2)	0.5 (0, 4.5)	0.54	0.26
BASDAI[2], median (IQR)	2.5 (1.0, 4.4)	5.2 (1.5, 8.6)	0.09	0.02
BASFI[2], median (IQR)	2.1 (0.6, 3.9)	4.3 (2.6, 7.1)	0.04	0.006
DAS28[1], mean (SD)	2.5 (1.0)	3.1 (1.9)	0.13	0.03
SDAI[1], median (IQR)	6.2 (5.6)	10.3 (9.4)	0.05	0.03
MASES, median (IQR)	2 (0, 5)	6 (3, 8)	0.02	0.04
Laboratory markers of inflammation				
CRP (mg/l), median (IQR)	1 (1, 3)	7 (2, 12)	0.001	0.001
Leukocytes (G/l), median (IQR)	7 (6, 8)	9 (6, 11)	0.01	< 0.001
Serum calprotectin (ng/ml), median (IQR)	805 (583, 1110)	874 (672, 2268)	0.17	< 0.001
SF-36 summary scores				
MCS, median (IQR)	50.8 (41.4, 57.5)	47.3 (34.2, 57.1)	0.55	0.57
PCS, median (IQR)	38.0 (29.8, 45.8)	26.9 (22.2, 36.8)	0.04	0.05
SF-36 scale scores				
Mental health, mean (SD)	75.7 (16.6)	69.5 (19.5)	0.30	0.42
Vitality, mean (SD)	45.2 (22.0)	31.9 (26.0)	0.09	0.17
Bodily pain, mean (SD)	55.8 (23.4)	38.1 (24.2)	0.04	0.06
General health, mean (SD)	52.6 (20.7)	45.0 (18.1)	0.30	0.47
Social functioning, mean (SD)	72.7 (23.7)	60.9 (28.7)	0.17	0.24
Physical functioning, mean (SD)	68.8 (22.4)	51.1 (26.6)	0.02	0.01

Table 2 continued

	Patients without nADAb	Patients with nADAb	*p* value, unadjusted	*p* value, adjusted
Role physical, mean (SD)	42.2 (42.3)	25.0 (38.8)	0.26	0.32
Role emotional, mean (SD)	68.1 (39.6)	50.0 (53.5)	0.21	0.28

BASDAI Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *CRP* C-reactive protein, *DAS28* 28-Joint Disease Activity Score, *ESR* erythrocyte sedimentation rate, *HAQ* Stanford Health Assessment Questionnaire, *IQR* interquartile range, *MASES* Maastricht Ankylosing Spondylitis Enthesitis Score, *SDAI* Simplified Disease Activity Index, *MCS* Mental Component Summary, *nADAb* neutralizing anti-drug antibody, *PCS* physical component summary, *SD* standard deviation, *SF-36* Short Form-36, *TNFi* tumor necrosis factor inhibitors
[1]RA and PsA patients
[2]AS and PsA patients

adalimumab. A higher proportion of patients with vs. without nADAb were treated with infliximab and a higher proportion were current smokers. Apart from this, demographics were similar in patients with vs. without nADAb. The association between current smoking and nADAb was confirmed in analyses adjusted for age and gender, as well as in analyses with additional adjustment for BMI and concomitant csDMARD comedication.

Disease burden in patients with vs. without neutralizing anti-drug antibodies

Patients with nADAb reported significantly worse joint pain, patient's global assessment of disease activity, HAQ, BASDAI, and BASFI than patients without nADAb, both in unadjusted analyses as well as in analyses adjusted for age, gender, diagnosis, BMI, and current csDMARD co-medication (Table 2).

Several disease activity metrics (28 swollen joint count, DAS28, SDAI, and MASES) were also significantly higher in patients with vs. without nADAb in adjusted analyses, as were also the laboratory markers of inflammation CRP, number of circulating peripheral leukocytes and serum calprotectin. Although the SF-36 physical functioning scale score was significantly worse in patients with nADAb, the remaining SF-36 measures were similar (Table 2).

DISCUSSION

In this cross-sectional observational study, only a few of the IA outpatients treated with TNFi developed nADAb. Patients with nADAb were more frequently current smokers and had significantly worse disease activity, inflammatory markers, and physical function than patients without nADAb.

This is one of the first reports showing that nADAb-positive patients were more frequently smokers. This was confirmed in unadjusted analyses, in analyses adjusted for age and gender, as well as with additional adjustment for BMI and concomitant csDMARD comedication. Recently, in a study on patients with RA, multiple sclerosis, Crohn's disease, and ulcerative colitis, treated with different biopharmaceuticals (etanercept, infliximab, adalimumab, interferon-beta-1a, interferon-beta-1b, rituximab, and tocilizumab), tobacco smoking was found to increase the rate of ADAb formation [12]. In another recent study that included patients with RA, PsA, spondyloarthritis, ulcerative colitis, Crohn's disease, and psoriasis treated with infliximab, lifetime smoking was reported to be associated with higher risk of ADAb development [13].

It is previously known that smokers may have poorer treatment response to TNFi, due in part to increased systemic inflammation [14]. Of interest, smoking is also linked to the production of anti-CCP in RA and to elevated anti-dsDNA titers in systemic lupus erythematosus

[5]. We may hypothesize that current smoking more often may lead to development of nADAb in patients with IA treated with TNFi. However, as this is a cross-sectional observational study, no causality may be drawn. It will be of interest to further explore the topic in a randomized controlled trial.

The finding of worse disease activity in nADAb-positive patients is in line with previous reports [3]. We found both significantly worse DAS28, BASDAI, BASFI, swollen joint counts, CRP, ESR, and serum calprotectin in the nADAb-positive vs. -negative patients. To our knowledge, we are the first to report calprotectin levels in nADAb-positive vs. -negative IA patients. Previously, other authors have reported calprotectin to be inversely correlated with TNFi trough levels in patients with IA [15].

nADAb positivity may impair clinical response. A relatively small number of patients in our study had nADAb, similar to what was previously reported by other authors using the same type of reporter-gene assay [16]. Of note, nADAb rates vary among TNFi as well as across different types of immunoassays [3, 16]. As is also seen in other studies, infliximab was the TNFi with the highest rate of nADAb [3]. The chimeric mouse-human molecular structure of infliximab may explain the higher rate of nADAb formation for this drug, compared with e.g., fully human TNFi. One patient had nADAb against the soluble dimeric TNF receptor etanercept. Etanercept is known to be less prone to immunogenicity, although this drug may also suffer from nADAb formation [3]. In line with the TNFi tender that applied in Norway during the conduct of the study, most patients were treated with etanercept, which at that time was the most affordable TNFi in the country.

Concomitant use of methotrexate is in previous studies reported to be associated with lower rates of ADAb toward infliximab and adalimumab. The lack of association between csDMARD comedication and nADAb positivity in our study may possibly be partly explained by the high percentage of patients treated with etanercept, for which a benefit from concomitant csDMARD comedication is not generally evident according to current literature [3]. Also contributing to the lack of association could be the overall low proportion of patients using csDMARD comedication. Of note, in recent years, regulatory bodies have favored ADAb assays with very high sensitivity but lower specificity. Low levels of such ADAb are commonly detected but often of little clinical relevance. Hence, in this study, focusing on nADAb was felt to be a more clinically relevant approach.

Limitations of this study include that we did not have information on pack years of smoking and the cross-sectional observational design, as no causality of e.g., the higher frequency of current smokers in the nADAb-positive patients may be drawn. However, observational studies may be hypothesis-generating, which our study has also shown. The major strength of the study is the comprehensive panel of demographics and disease-activity measures assessed, which not so often is reported to this extent in nADAb studies. Furthermore, this is one of the first studies to explore the association between nADAb and smoking.

CONCLUSIONS

In conclusion, in this cross-sectional observational study, IA patients with nADAb were more frequently smokers and had significantly worse disease activity, inflammatory markers, and physical function than patients without nADAb. The association between smoking and nADAb positivity warrants further examination, preferably in a randomized controlled trial, to explore if causality may be established.

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Author contributions All coauthors were responsible for study design. Brigitte Michelsen, Kristine Thomassen Berget, and Glenn Haugeberg were responsible for data acquisition. Brigitte Michelsen analyzed the data and wrote the first version of the manuscript. All authors critically revised the manuscript and approved the final version.

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Compliance with Ethics Guidelines The study was approved by the Regional Committees for Medical and Health Research Ethics mid-Norway (Ref. 2015/1196/REK midt). Written informed consent was obtained from each patient prior to inclusion in the study. The study was performed in accordance with the Helsinki Declaration.

Data Availability All data generated or analyzed during this study are included in this published article/as supplementary information files.

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