Graduate thesis

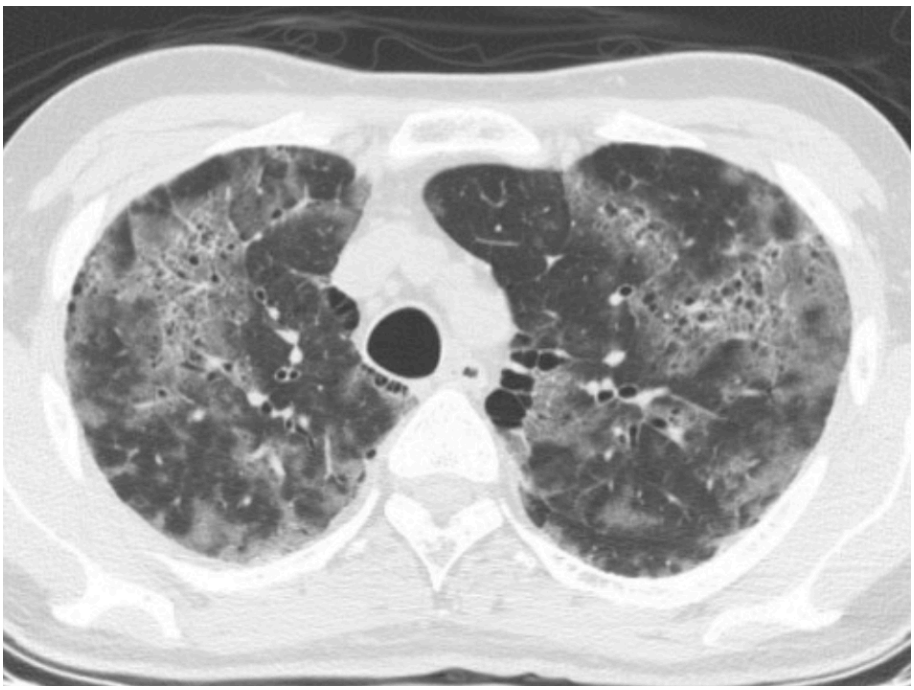
NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
Department of Clinical and Molecular Medicine

Tonje Kristiansen

Pneumocystis jirovecii-pneumonia (PCP) in patients with haematological cancers

Exploring the use of corticosteroids as a risk factor

Graduate thesis in Programme of Professional Study, Medicine
Supervisor: Jan Kristian Damås
Co-supervisor: Jan Egil Afset
June 2021



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Abstracts

Abstract in English

Introduction: Iatrogenic immunosuppression has a revolutionary impact in the treatment of chronic autoimmune disorders, several malignancies and patients in need of organ transplants. Although immunosuppressive drugs have a broad range of effects, like improving lives and life expectancy, they also contribute to the increase in number of people living with increased risk for a secondary immunodeficiency. Opportunistic infections, including Pneumocystis jirovecii-pneumonia (PCP), can be an unfortunate outcome of immunosuppressive drugs. The symptoms of PCP are non-specific, and accurate diagnosis cannot rely on the clinical assessment alone. Polymerase chain reaction (PCR) for molecular detection of microorganisms and high-resolution CT-scans are of essential value in this context.

Objectives: To explore the use of corticosteroids as a risk factor of Pneumocystis jirovecii-pneumonias (PCP) in patients with haematological malignancies.

Methods: We obtained a cohort of 297 patients with verified PCP in at least one respiratory sample by PCR technique during a 12-year period, but herein we focused on the 107 patients with underlying haematological malignancies. We retrieved information from the patient records and sorted various data in excel. The current information was transferred to SPSS where statistical analyses were performed. Standard descriptive statistics was used to summarize the data.

Results: More than half of patients with haematological malignancies had been exposed to systemic corticosteroids in the two months prior to P. jirovecii detection, and only three patients had received primary PCP-prophylaxis. At time of diagnose, anti-PCP treatment was instituted in 93.5 % (n = 100) of the patients. Although the majority in our study population received anti-PCP treatment, all-cause overall mortality <30 days, 30-90 days, 90-180 days and >180 days were 7.5 %, 10.3 %, 7.5 % and 27.1 % respectively.

Conclusions: We found that immunosuppression, especially with corticosteroids, appears to be the main predisposing factor for contamination with the opportunistic fungus P. jirovecii in patients with haematological malignancies. Therefore, those exposed to high doses of

corticosteroids should be considered for prophylactical treatment with Trimethoprim sulfamethoxazole (TMP-SMX).

Abstract in Norwegian

Innledning: Iatrogen immunsuppresjon har hatt en revolusjonerende påvirkning i behandling av en rekke tilstander, blant annet autoimmune lidelser, kreft og etter organtransplantasjon. Selv om immunsuppressive medikamenter har flere positive effekter, blant annet ved å øke livskvalitet og forventet levealder, bidrar de også til økningen i antall mennesker som lever med økt risiko for å utvikle en sekundær immunsvikt. Opportunistiske infeksjoner, inkludert Pneumocystis jirovecii-pneumoni (PCP), kan være et uheldig resultat av immunsuppressive medikamenter. Symptomene på PCP er uspesifikke og nøyaktig diagnose kan ikke stilles kun basert på den kliniske vurderingen. Polymerasekjedereaksjon (PCR) for molekylær deteksjon av mikroorganismer og høyoppløselig CT toraks er av vesentlig verdi i denne sammenhengen.

Mål: Å utforske bruken av kortikosteroider som en risikofaktor for PCP hos pasienter med hematologiske maligniteter.

Materiale og metoder: Vi oppnådde en kohort på 297 pasienter med verifisert PCP i minst en luftveisprøve ved PCR-teknikk i løpet av en 12-års periode, men vi valgte å fokusere på de 107 pasientene med underliggende hematologiske maligniteter. Vi hentet informasjon fra pasientjournalene og sorterte dataene i et Excel-dokument. Aktuell informasjon ble overført til SPSS hvor statistiske analyser ble utført. Standard beskrivende statistikk ble brukt som metode for å oppsummere dataene.

Resultater: Mer en halvparten av pasientene med hematologiske maligniteter hadde blitt utsatt for systemiske kortikosteroider i de to månedene før P. jirovecii ble påvist, og bare tre av pasientene hadde fått primær PCP-profylakse. På diagnosetidspunktet ble anti-PCP-behandling gitt til 93,5% (n=100) av pasientene. Selv om flertallet i vår studiepopulasjon fikk anti-PCP-behandling, var dødeligheten <30 dager, 30-90 dager, 90-180 dager og >180 dager henholdsvis 7.5 %, 10.3 %, 7.5 % og 27.1 %

Konklusjoner: Vi fant at immunosuppresjon, spesielt kortikosteroider, ser ut til å være den viktigste predisponerende faktoren for kontaminering med den opportunistiske soppmikroben

P. jirovecii hos pasienter med hematologiske maligniteter. Derfor bør de som står på høye doser kortikosteroider bli vurdert til å få profylaktisk behandling med Trimetoprim sulfametokazole (TMP-SMX).

Introduction

Iatrogenic immunosuppression has a revolutionary impact in the treatment of chronic autoimmune disorders, malignancies and patients in need of organ transplants. Although immunosuppressive drugs have a broad range of effects, like improving lives and life expectancy, they also contribute to the increase in number of people at increased risk for developing a secondary immunodeficiency. Opportunistic infections once associated with the HIV/AIDS-epidemic, can be an unfortunate outcome of immunosuppressive drugs and chemotherapy. Pneumonia with the atypical fungus Pneumocystis jirovecii (P. jirovecii) represents one of these. P. jirovecii-pneumonia (PCP) may cause severe morbidity and high mortality in affected individuals. At present, it constitutes a serious complication and delineates an important limitation of the modern immunosuppressive treatment.

The symptoms of PCP are non-specific and include fever, dyspnoea and cough, usually characterized as dry and non-productive, in addition to constitutional symptoms like malaise and weight loss (1). Clinical presentation of PCP varies according to the degree of immunosuppression and more markedly depending on the host's HIV-status (1-3). HIV-infected individuals with PCP commonly present with insidious onset of longstanding fatigue, fever, non-productive cough and dyspnoea (2). The symptoms and the clinical course of patients with non-HIV population of PCP-patients have been less characterized. Nonetheless, there is a general assumption that these patients tend to have a more fulminant onset and rapid progression of severe pneumonitis with respiratory failure and acute respiratory distress syndrome (ARDS) (1). However, the literature is scarce when describing the symptoms in patients with haematological malignancies and patients on modern immunosuppressive drugs.

In similarity to the symptomatology, the clinical findings on physical examination are not pathognomonic for PCP and include fever, tachypnoea and tachycardia (3). The presence of hypoxemia, especially on exertion, is a very common finding in PCP (4). PCP may mimic other diseases in this patient population and is often mistaken for pulmonary embolism or

pneumonia of another bacterial, viral or fungal aetiology, malign processes, sarcoidosis, and non-infectious interstitial pneumonitis. Although described in HIV-patients, there is a need for characterization of the clinical findings and course of PCP in patients with various non-HIV immunosuppressive conditions.

Comprehensive history taking, including exposures and epidemiological risk factors, in addition to physical examination and appropriate diagnostic procedures represent the cornerstones in the diagnostic workup of pulmonary complications in immunocompromised patients. Polymerase chain reaction (PCR) for molecular detection of microorganisms and high-resolution CT-scans are of essential value in this context (5). In order to build precise predictive clinical algorithms for PCP in the immunosuppressed patients of today (6), we need to implement comprehensive clinical data from this cohort. Herein, we describe the clinical characteristics of patients with haematological malignancies with PCP in a 12-year-retrospective study from Norway. In particular, we examine the association between premorbid iatrogenic immunosuppression (i.e. chemotherapy and corticosteroid exposure) and PCP in these patients.

Due to underlying malignancy, treatment-related immunosuppression and/or corticosteroid use, there is a different risk of developing PCP. Haematological malignancies constitute a type of cancer at high risk. Especially heavily pre-treated patients (e.g., multiple lines of chemotherapy) and patients receiving high doses of corticosteroid (often in combination with chemotherapy). Prolonged, high-dose corticosteroid treatment (16-25 mg of prednisolone per day or ≥4 mg dexamethasone daily for ≥4 weeks) constitute a high risk of PCP, regardless of underlying malignancy or use of other chemotherapy agents (7). Patients receiving treatment for ALL and for allogeneic haemopoietic stem cell transplant have the highest risk, while those with autologous bone marrow transplant have a moderate risk (7). These patients are offered antimicrobial prophylaxis named Trimethoprim sulfamethoxazole (TMP-SMX), which is well-established for preventing PCP in patients with immunodeficiencies.

Materials and methods

P. jirovecii is an opportunistic pathogen, which almost exclusively cause infection when the host's defence mechanism against infection is impaired. Therefore, PCP is a marker for

immunodeficiencies, and our target population was therefore immunocompromised patients. For this retrospective case analysis, we obtained a cohort of 297 patients with detected P. jirovecii in at least one respiratory sample by PCR (8). These samples were identified through linkage of birth numbers in the Laboratory Information System of the Department of Medical Microbiology of St. Olav's Hospital. This department receives specimens for selected microbiological analyses from the seven community hospitals incorporated in Central Norway Regional Health Authority; Orkdal, Levanger, Namsos, Molde, Kristiansund, Volda and Ålesund hospital. Central Norway Regional Health Authority is one of four regional health authorities in Norway, and with regard to population coverage and representativeness, it is the third largest in the country. Consequently, St. Olav's hospital receives microbiological samples, including detection of P. jirovecii, from the entire region of central Norway (Trøndelag and Møre og Romsdal) consisting of over 700,000 inhabitants (9).

In this particular study, we have chosen to focus on the major predisposing factor for PCP, haematological malignancies, which are present in more than a third of the patients (n = 107). Specifically, we wanted to explore the use of corticosteroid as a risk factor in these patients. The ages range was 19 to 82 years, with an average age (a median ages) of 63 years, and a prevalence of males over females (70 vs 37). We only included alive patients who gave an informed consent to participate in accordance with guidelines made by regional committees for medical health.

We retrieved information from the patient records and sorted various data in excel, such as sex, comorbidities, clinical and radiological findings, laboratory results, prophylaxis status and immunosuppressive and chemotherapeutic agents administrated last 5 years. We used SPSS for statistical analyses. To maintain confidentiality, identification numbers were removed from the final document and replaced with a number code.

Results

In the present retrospective study, we investigated 107 patients with haematological malignancies where at least one respiratory sample resulting positive for P. jirovecii with PCR technique during a 12-year period. It should be mentioned that this quantity was after excluding alive patients who had not given their informed consent to participate. To support

the PCP diagnosis, thoracic CT was performed in most patients with suspected P. jirovecii infection (n = 89). Thoracic CT manifested abnormalities in 87 of 89 cases, with ground glass opacities (GGO), being the most common abnormality present in 62 cases. Not surprisingly, GGO has been shown to be the principal CT-finding in PCP.

Among our 107 patients, non-Hodgkin lymphoma (n = 55) was the dominant underlying haematological malignancy followed by chronic leukaemia, plasma cell diseases, acute leukaemia and Hodgkin's lymphoma (figure 1).

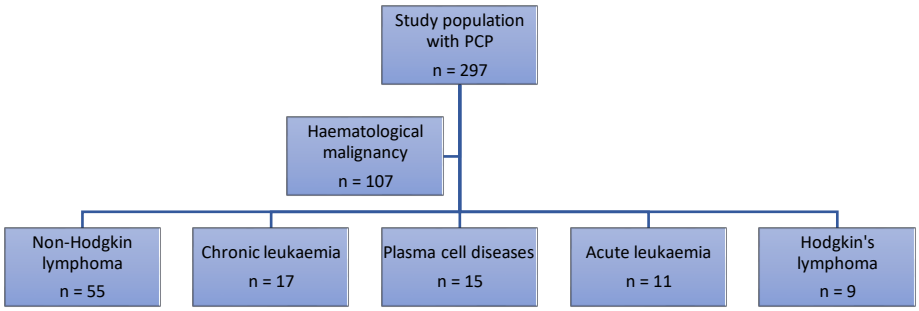

Figure 1. Number of patients with different types of haematological malignancies.

Other immunosuppressive conditions who were particularly prone to P. jirovecii infection were; solid malignancies, immunological disorders, organ transplantations, chronic lung diseases and HIV-infections which constitute a very small proportion after the emergence of anti-retroviral therapy (ART). However, we did not explore these conditions further.

In the interest of describing iatrogenic immunosuppression (especially corticosteroid) in patients with haematological malignancies as a risk factors for developing PCP, we compared various treatment regimens at time of P. jirovecii detection (table 1).

TABLE 1 Iatrogenic immunosuppression exposure in study population	
Total study population	n = 107
No. of patients receiving the following treatment at time of diagnosis (%)	
Chemotherapy for haematological malignancy and adjuvant corticosteroids	67 (62.6)
Chemotherapy for haematological malignancy	12 (11.2)
Steroids only	3 (2.8)

Prophylaxis or treatment for GVHD	3 (2.8)
Chemotherapy for solid malignancy	1 (0.9)
No. of patients not receiving any immunosuppression at time of diagnosis (%)	21 (19.6)

As expected, chemotherapy for haematological malignancy and adjuvant corticosteroids was the category with the highest number of patients (n = 67). Although the most common treatment for patients with haematological malignancies is a combination of these, it unfortunately leads to a severely weakened immune system, which may be available to an opportunistic infection with P. jirovecii. Furthermore, we investigated whether corticosteroids were taken daily, intermittent or not at all, during the last 60 days prior to PCP detection.

TABLE 2 Systemic corticosteroid exposure last 60 days prior to detection (%)	
Daily	11 (10.3)
Intermittent	60 (56.1)
No exposure	34 (31.8)
Unknown (i.e missing)	2 (1.9)
Corticosteroid dose in methylprednisolone at detection	
Mean for daily users, mg (SD)	17.1 (±10.4)
Minimum, maximum, mg	0.60

Remarkably, more than half 66 % (n = 71) of patients with haematological malignancies had been exposed to systemic corticosteroids in the two months prior to P. jiroveciii detection. There was a 56 % predominance of intermittent corticosteroids administration, followed by daily administration in 10 %. For patients with intermittent consumption, average dose in methylprednisolone on time of detection was 3.1 (±9.8) mg, compared with 17.1 mg (± 10.4) in daily takers. Systemic corticosteroids as chemotherapeutic agents led to the high prevalence of corticosteroid usage.

Among all patients with haematological malignancies, only three had received primary PCP-prophylaxis during PCP-investigation (figure 2). 45 initiated secondary prophylaxis for presumed colonization with P. jirovecii. At time of diagnose, anti-PCP treatment was instituted to 93.5 % (n = 100), whereof 90 % (n = 96) received the first-line treatment with TMP-SMX. The mean duration of treatment was 15 days (±3.36). Furthermore, 65 % (n = 69) administrated either adjunctive systemic corticosteroids for PCP or due to their underlying

conditions concomitantly with anti-PCP treatment. At risk of co-infection, the majority received adjunctive treatment with other antimicrobials. Antibiotics were most frequently administered (n = 51), followed by antifungal (n = 22), antiviral (n = 12) and anti-tuberculous drugs (n = 2).

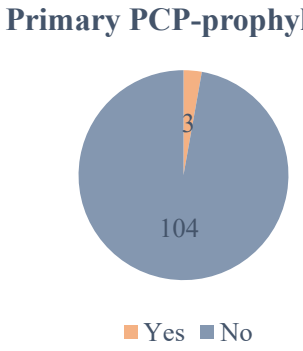

Figure 2. Number of patients on primary PCP-prophylaxis at time of PCP suspicion. Only three patients had received PCP-prophylaxis.

With the purpose of examining patients with PCP infection, we also investigated the outcome of the disease. Overall, 33 patients reported complications in the course of the infection, whereof 25 patients needed ICU admission. The following complications involved; ARDS (n = 20), superinfection (n = 10), hemodynamic failure (n = 5), renal failure (n = 3) or pneumothorax (n = 1). In-hospital mortality for haematological patients was estimated to be 9.3 %. Although the majority in our study population received anti-PCP treatment, all-cause overall mortality <30 days, 30-90 days, 90-180 days and >180 days were 7.5 %, 10.3 %, 7.5 % and 27.1 % respectively.

TABLE 3 Complications and outcome for P. jirovecii infected patients	
Complications	
No. of patients transferred to an ICU (%)	25 (23.4)
No. of patients receiving ventilation support (%)	17 (15.8)
No. of patients developing the following complications (%)	
ARDS	20 (18.7)
Superinfection	10 (9.3)
Hemodynamic failure	5 (4.7)
Renal failure	3 (2.8)
Pneumothorax	1 (0.9)

Outcome, no. of patients (%)	
In-hospital mortality	10 (9.3)
All-cause mortality	
< 30-days	8 (7.5)
30-90-days	11 (10.3)
90-180-days	8 (7.5)
> 180-days	29 (27.1)
PCP-related death	8 (7.5)

Discussion

In our study, we included patients with P. jirovecii infection. The diagnosis was confirmed by positive PCR, and well-supported with HRCT. We found that patients with underlying haematological malignancies are more susceptible to P. jirovecii infection than other immunosuppressed patients, and that exposure to corticosteroids prior to detection appears to be a significant risk factor. Although patients with haematological malignancies were more prone to PCP resulting in high morbidity and mortality, only a minority received prophylactically TMP-SMX.

Retrospectively, 48 of 107 respiratory samples were examined by both immunofluorescence and PCR. 24 of these were positive on microscopy, whereas all PCR results were positive. Given the high sensitivity compared to microscopy, quantitative real-time PCR was used to diagnose P. jirovecii infection. However, the high sensitivity of PCR does not allow distinction between PCP and colonization with P. jiroveciii, hence a “high” and a “low” threshold has been introduced. A “low” threshold would exclude PCR with a high degree of certainty, at least on BAL fluid; sensitivity of PCR on upper respiratory tract samples is lower than on BAL fluid, ergo, sample material also has an impact on the sensitivity of the test (10). HRCT is a valuable supplement to confirm diagnosis or allow exclusion of PCP.

Several studies have reported that patients with ALL and lymphoproliferative disorders which includes non-Hodgkin’s lymphoma, chronic lymphocytic leukaemia and multiple myeloma constitute the vast majority among haematological patients with PCP. (11-14). This is consistent with our findings. Moreover, haematological patients seem to be particularly prone to this infection compared to other immunocompromised hosts. In a study from 2014

conducted by Fillatre et. al (15), the PCP incidence was estimated to be > 45 cases per 100,000 patient year in patients with non-Hodgkin lymphoma, chronic lymphocytic leukeaemia and acute leukaemia, compared to < 25 cases per 100,000 patient year in those with solid tumours. Similarly, haematological malignancies were the major predisposing factor for PCP development in our study. A severely impaired immune system, high doses of chemotherapy and corticosteroid use may be possible reasons for this.

Immunosuppression, especially corticosteroids, appears to be the main predisposing factor for contamination with the opportunistic fungus P. jirovecii (11, 16, 17), and the primary reason for this may be their lymphocytotoxic effects (i.e., reduction of CD4+ T cells). Correspondingly, the majority (n=71) in our study had been exposed to systemic corticosteroids in advance of P. jirovecii detection. Systemic corticosteroids as chemotherapeutic agents are very common among cancer patients, especially due to significant symptom-relieving effect; “They are favoured by their lack of bone marrow toxicity, their ability to reduce fever and sweating in most patients, and, frequently, a subjective sensation of increased well-being» (18 p. 38). The disadvantage of corticosteroid use is the weakened immune system which makes them susceptible to infections such as PCP. Only the minority of those exposed to steroids develop PCP, but this infection can cause life-threatening pneumonia. At the same time, steroids are efficient in alleviating discomfort in cancer patients. Therefore, it becomes difficult to avoid steroids. One possible solution may be adequate prophylaxis for these patients.

Among our patient group, only 3% had received primary PCP prophylaxis. One may wonder why not more of the patients had received prophylaxis when absence of prophylaxis or poor compliance are the main risk factors for PCP development in high-risk populations such as haematology patients. (11) Indeed, Cordonnier et al. argued that “although rare, PCP is a severe, but preventable disease” (11, p. 5). Recent data show incidences as low as 0.28 % in patients treated prophylactically (19), and as low as 0.09 % in treated patients with ALL (11). A Cohcrane review, including 13 trials, indicated that overall TMP-SMX was highly effective in preventing PCP with an 72 % incidence reduction (RR 0.28, 95% CI 0.02 to 4.57) among haematological patients (19). In high-risk populations, it seems to be more beneficial to protect against PCP than to treat this condition when it occurs, due to very high mortality rate among infected patients.

As mentioned, PCP is associated with high morbidity and mortality rates, but the case fatality is dependent on the underlying disease. The mortality among non-HIV patients ranges from 30-40 % compared to 10-20 % in patients with HIV/AIDS. Nevertheless, it may reach higher (up to approximately 80 %) in patients receiving mechanical ventilation support or those with ARDS (5). Respectively, 15.8% and 18.7% among our participants received mechanical ventilation, but without knowing the case fatality of these. Unfortunately, infected haematological patients are among the patients with highest mortality risk (7).

Conclusion

Our primary objective was to examine the association between premorbid iatrogenic immunosuppression (i.e. chemotherapy and corticosteroid exposure) and PCP in patients with haematological malignancies. We found that immunosuppression, especially with corticosteroids, appears to be the main predisposing factor for developing infections with the opportunistic fungus P. jirovecii in these patients. However, since corticosteroids are commonly used in treatment of patients with haematological malignancies, both due to immunomodulatory functions as well as in effective pain relief, it may become difficult to reduce the use of this drug in these patients. Simultaneously, there will be increased life expectancy for patients with haematological cancer in the years to come, due to the development of new immunosuppressants and other drugs. Therefore, a common goal for the future should be to offer patients with haematological malignancies TMP-SMX-prophylaxis for protection against PCP.

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