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Serious infections in patients with rheumatoid arthritis and psoriatic arthritis treated with tumour necrosis factor inhibitors: data from register linkage of the NOR-DMARD study

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ABSTRACT

Objectives To estimate the incidence of serious infections (SIs) in patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA) treated with tumour necrosis factor inhibitor (TNFi), and compare risk of SIs between patients with RA and PsA.

Methods We included patients with RA and PsA from the NORwegian-Disease Modifying Anti-Rheumatic Drug registry starting TNFi treatment. Crude incidence rates (IRs) and IR ratio for SIs were calculated. The risk of SIs in patients with RA and PsA was compared using adjusted Cox-regression models.

Results A total of 3169 TNFi treatment courses (RA/PsA: 1778/1391) were identified in 2359 patients. Patients with RA were significantly older with more extensive use of co-medication. The crude IRs for SIs were 4.17 (95% CI 3.52 to 4.95) in patients with RA and 2.16 (95% CI 1.66 to 2.81) in patients with PsA. Compared with the patients with RA, patients with PsA had a lower risk of SIs (HR 0.59, 95% CI 0.41 to 0.85, p=0.004) in complete set analysis. The reduced risk in PsA versus RA remained significant after multiple adjustments and consistent across strata based on age, gender and disease status.

Conclusions Compared with patients with RA, the risk of SIs was significantly lower in patients with PsA during TNFi exposure.

Key messages

What is already known about this subject?

► Previous studies have assessed serious infection (SI) in rheumatoid arthritis (RA) populations treated with tumour necrosis factor inhibitor (TNFi), but data are scarce regarding the risk of SI in patients with psoriatic arthritis (PsA) treated with TNFi and the comparative risk of infection in TNFi treated RA versus patients with PsA.

What does this study add?

► We observed that the risk of SI is significantly lower in patients with PsA compared with patients with RA treated with a TNFi.

How might this impact on clinical practice or future developments?

► Although the results need to be interpreted with caution given the many important differences between the RA and PsA population, our findings indicate that the clinician should consider the rheumatological diagnoses when assessing the risk of future SI in patients starting a TNFi.

INTRODUCTION

Treatment of rheumatoid arthritis (RA) and psoriatic arthritis (PsA) has advanced considerably over the past two decades. Tumour necrosis factor inhibitors (TNFis) are pivotal in the management of RA and PsA.[1–3] Given their immunosuppressive effects, infections related to TNFi treatment is a concern. In patients with RA, TNFi therapy is associated with an increased risk of serious infections (SIs) compared with conventional synthetic disease modifying antirheumatic drugs (DMARDs).[4–7] Few observational studies have addressed incidence rates (IRs) of SIs in PsA[8–11] and studies comparing the risk of SIs between patients with RA and PsA are sparse.[11 12] The future risk of infections should be considered when making treatment decisions.[13]

We aimed to estimate the incidence of SIs in patients with RA and PsA treated with TNFi and compare the risk of SIs between these two disease populations, and across strata.

METHODS

Data sources

Data from the prospective observational multicentre NORwegian-Disease Modifying Anti-Rheumatic Drug (NOR-DMARD) study were used.[14] We included adult patients diagnosed with clinical RA or PsA, starting treatment with a TNFi between January 2009 and December 2018. All were diagnosed by a rheumatologist. In addition, diagnoses were defined according to international classification criteria (American College of Rheumatology/European Alliance Of Associations For Rheumatology (ACR/EULAR)) n=773, ACR n=550, ClASsification criteria for Psoriatic ARthritis (CASPAR) n=597). Each patient could contribute more than one treatment course. Start of

observation was the start of treatment. End of observation was the first occurrence of following; last visit or withdrawal from NOR-DMARD, death, emigration or censor date. A 30-day observation period was added to capture infections registered after the last visit.

Register linkages

To identify events (SIs), we linked NOR-DMARD to the Norwegian Patient Registry (NPR) and Norwegian Cause of Death Registry. Comorbidities were identified through linkage to the Norwegian Control and Payment of Health Reimbursement database and NPR, receiving data from primary and specialist healthcare services respectively. At discharge from hospital stay, diagnoses are reported to the NPR by the attending physician according to the International Classification of Diseases version 10 (ICD-10). The NPR is considered reliable from 2008, and 2009 was thus selected as the first year included in the analyses.[15] Patients signed informed consent.

Outcomes

The outcome, SI, was defined as an infection requiring hospital admission with at least one-night hospital stay and/or as an infection causing death according to a predefined list of ICD-10 diagnoses (online supplemental table 1). The infection had to be listed as the primary diagnosis at discharge, or as the first contributory diagnosis given that the primary diagnosis was RA or PsA. Only the first SI for each treatment course was included in our analyses.

Covariates

Disease activity

At each NOR-DMARD visit, disease activity measures and markers of inflammation were recorded and the Disease Activity Score for 28 joints (DAS28) was calculated. Comprehensive questionnaires including the use of medication and the modified Health Assessment Questionnaire were completed.[14]

Comorbidities

The following were considered potential confounders; diabetes, chronic obstructive pulmonary disease (COPD) or asthma.[16]

Statistical analyses

Baseline demographics are presented as means (SD), medians (IQR) or frequencies (%) and compared between cohorts by appropriate bivariate methods. Crude IRs of SI for RA and PsA were presented as events per 100 person-years and the IR ratio (IRR) of IR between RA and PsA was estimated. Robustness of results was examined in models adjusted for multiple confounders. To ensure comparable models, cases without missing values for included variables were used in the main results. IRs and risk of SI in RA versus PsA were estimated in the stratum. Analyses were made in STATA V.16.

Sensitivity analyses

Baseline variables were compared between patients with complete dataset and those who had missing data for key variables. Cox regressions were performed in cohorts with missing versus not missing for key variables. The linear relationship between time and risk of SI was explored in models censored at 12-month and 24-month follow-up.

Table 1 Baseline characteristics for the treatment courses

Variable	RA (n=1778)	PsA (n=1391)	P value
Age in years, mean (SD)	53.2 (13.8)	48.2 (11.9)	<0.001
Age, n (%)			
<50 years	651 (36.6)	755 (54.3)	<0.001
≥50 years	1127 (63.4)	636 (45.7)	
Female gender, n (%)	1341 (75.4)	797 (57.3)	<0.001
Years on treatment, median (IQR)	1.1 (0.4–2.6)	1.1 (0.5–2.7)	0.65
Disease duration, years, median (IQR)*	6.9 (2.3, 14.5)	5.2 (1.6, 11.8)	<0.001
Current smoking, n (%)	252 (14.2)	225 (16.2)	0.12
DAS28-CRP, mean (SD)†	4.0 (1.3)	3.5 (1.2)	<0.001
MHAQ, median (IQR)‡	0.6 (0.3, 1.0)	0.6 (0.3, 1.0)	0.22
MTX co-medication, n (%)§	1265 (73.2)	798 (59.1)	<0.001
Prednisolone co-medication, n (%)§	976 (56.5)	400 (29.6)	<0.001
Prednisolone dose, n (%)			
>0–5 mg	412 (23)	135 (10)	<0.001
>5–10 mg	264 (15)	68 (5)	<0.001
>10 mg	269 (16)	87 (6)	<0.001
Comorbidities			
COPD and/or asthma, n (%)	180 (10.1)	93 (6.7)	0.001
Diabetes, n (%)	127 (7.1)	116 (8.3)	0.209

Continuous variables presented as mean (SD) or median (IQR), dichotomous variables presented as number (%).
*Disease duration missing in 266 patients with RA, and 286 patients with PsA.
†DAS28-CRP missing in 228 patients with RA and 200 patients with PsA.
‡MHAQ missing in 58 patients with RA and 50 patients with PsA.
§MTX and prednisolone co-medication missing in 50 patients with RA and 41 patients with PsA.
COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; DAS28, Disease Activity Score for 28 joints; MHAQ, Modified Health Assessment Questionnaire; MTX, methotrexate; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor.

RESULTS

Population characteristics

A total of 3169 TNFi treatment courses were identified (RA/PsA 56/44%), in 2359 patients (RA/PsA 1352/1007). Patients with PsA were younger and more frequently male. Patients with RA had significantly longer disease duration, a higher baseline DAS28-CRP (C reactive protein) score, more likely to receive co-medication at baseline and more often had COPD (table 1).

Incidence and risk of SIs

A total of 187 cases of SIs occurred during the study period, 131 with RA versus 56 with PsA. The majority (37%) were respiratory tract infections. The IRR between PsA and RA was 0.52 (95% CI 0.37 to 0.71) (table 2). Patients with PsA had a lower risk of SI (HR 0.59, 95% CI 0.41 to 0.85) compared with patients with RA when adjusted for age and gender, and across subgroups, except in those using methotrexate as sole co-medication (table 3, online supplemental table 2).

Sensitivity analyses

The HR for SI was explored across cohorts of patients with missing versus not-missing data for key variables (online supplemental table 3 and figure 1) and after adjustment for components

Table 2 Incidence of serious infection

	RA	PsA
Treatment courses TNFi, n	1778	1391
Person-years	3139	2590
Serious infection, n	131	56
Crude IR/100 PY (95% CI)	4.17 (3.52 to 4.95)	2.16 (1.66 to 2.81)
Incidence rate ratio (95% CI)	0.52 (0.37 to 0.71)	

IR, incidence rate; PsA, psoriatic arthritis; PY, person years; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor.

of DASs (online supplemental table 4). In sensitivity analyses with 12-month and 24-month follow-up, the risk of SI remained significantly lower in PsA versus patients with RA (HR 0.47, 95% CI 0.28 to 0.78) at 12 months and (HR 0.46, 95% CI 0.30 to 0.71) at 24 months.

DISCUSSION

In this register linkage data study, we found a significantly lower risk of SI for patients with PsA compared with patients with RA receiving TNFi therapy. This result remained significant in the adjusted models with complete cases only, supporting the robustness of our results. Patients with RA were older, more often female, with higher DAS28-CRP and more frequent users of co-medication at baseline. Adjustment for multiple factors, including the above-mentioned differences, were made in multivariate analyses, and did not alter the risk-difference. However, the additive effect of multiple risk factors in the RA population, including more frequent prednisolone use, may explain some of the increased risk of SIs in patients with RA. Another explanation could be the RA disease itself, through disease-related alterations in host defence.[17]

Table 3 Adjusted HRs of serious infection in patients with PsA versus RA treated with tumour necrosis factor inhibitor

	Number	HR (95% CI)	P value
Model A: adjusted for age and gender			
PsA vs RA	2675	0.59 (0.41 to 0.85)	0.004
Model B: adjusted for age, gender, DAS28-CRP, MHAQ			
PsA vs RA	2675	0.58 (0.40 to 0.84)	0.004
Model C: adjusted for age, gender, concomitant MTX, baseline prednisolone			
PsA vs RA	2675	0.69 (0.47 to 1.00)	0.049
Model C1: adjusted for age, gender, concomitant MTX			
PsA vs RA	2675	0.59 (0.41 to 0.85)	0.005
Model C2: adjusted for age, gender, baseline prednisolone any dose			
PsA vs RA	2675	0.69 (0.48 to 1.00)	0.048
Model C3: adjusted for age, gender, baseline prednisolone low dose			
PsA vs RA	2675	0.60 (0.42 to 0.86)	0.006
Model C4: adjusted for age, gender, baseline prednisolone intermediate dose			
PsA vs RA	2675	0.64 (0.44 to 0.92)	0.017
Model C5: adjusted for age, gender, baseline prednisolone high dose			
PsA vs RA	2675	0.62 (0.43 to 0.90)	0.011
Model D: adjusted for age, gender, COPD and/or asthma, diabetes			
PsA vs RA	2675	0.58 (0.40 to 0.83)	0.003
Model E: adjusted for all variables in models A–D			
PsA vs RA	2675	0.65 (0.44 to 0.95)	0.025

COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; DAS28, Disease Activity Score for 28 joints; MHAQ, Modified Health Assessment Questionnaire; MTX, methotrexate; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

While several studies have quantified the risk of SIs in patients with RA treated with biological DMARDs (bDMARDs) with IRs ranging from 2.6 to 5.6/100 person-years,[7 13 16 18] the risk of SIs in patients with PsA has been far less studied. The few observational studies assessing IRs of SIs in patients with PsA treated with biologicals have reported widespread estimates from 2.7 to 19.6/100 person-years.[8–11] The IRs found in our analyses are thus in line with these previously reported estimates.

Few studies have compared the risk of SIs between patients with RA and PsA. A recent case–control study from DANBIO, the Danish rheumatology registry, reported the risk of SIs within the first year after bDMARD initiation in bionaive RA, PsA and axial spondyloarthrtitis compared with matched population controls. The study was not specifically designed to compare the risk of SIs between patient groups, but concluded that the risk is similar.[11] However, in this study, the follow-up period was defined as 12 months regardless of drug discontinuation, and difference in drug retention between patients with RA and PsA were not accounted for. A study using administrative data found no significant difference in risk between patients with RA, PsA and/or severe psoriasis.[12] However, the PsA population was here categorised in the same cohort as patients with psoriasis.[12]

Missing data is a limitation to our analyses. Cases with missing information for disease duration had less severe disease activity, and excluding this population from the analyses may have given a falsely high-risk estimate. Also, smoking could not be adjusted for due to missingness. Another limitation is the possibility of residual confounding. Although the risk estimate was not changed by including disease activity measurements in the model (table 3, online supplemental table 4), we have to consider that disease activity in PsA was not fully captured by variables registered in NOR-DMARD. Further, we cannot exclude the possibility of misclassification of outcomes, as physicians might be more aware of infections among patients with RA than in patients with PsA, resulting in patients with RA being hospitalised for less severe infections more frequently than patients with PsA. However, our definition of SIs limits the risk of non-SIs being misclassified. Stratified analyses over co-medication indicate that differences in prednisolone use between patients with RA and PsA may partly explain the risk difference, and the effects of prednisolone should be further explored. Finally, we cannot account for initiation and discontinuation of co-medication during TNFi exposure, as only baseline co-medication data were accessible, and this limitation needs to be considered when interpreting the results.

Multi-centre high-quality observational prospective register data reflective of real-world clinical practice is a major strength to this study. The outcome (SI) was well defined using ICD-10 registered by the attending physician. Also, our patient population is defined according to international classification criteria.

In conclusion, this study found a significantly lower risk of SIs in patients with PsA than in patients with RA, during exposure to TNFi. The results need to be interpreted with caution given the many important differences between the RA and PsA population, especially with regards to the use of co-medication. Recognising the elevated risk in patients with RA supports the heightened awareness of SIs during follow-up of these patients.

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Contributors IEC: conceived the idea, developed data synthesis, performed data analyses and wrote the paper. SL: contributed to idea development, assisted in data analyses, contributed in writing the paper, revised the manuscript and approved the final version. GB, PM, LL: organised and collected data, critically revised the manuscript and approved the final version. JS: developed data synthesis, assisted in data analyses, revised the manuscript and approved the final version. TU and TKK: established NOR-DMARD, contributed to idea development, assisted in data

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Patient consent for publication Not applicable.

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