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Interstitial Lung Disease in Patients With Rheumatoid Arthritis or Psoriatic Arthritis Initiating Biologics and Controls: Data From 5 Nordic Registries

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ABSTRACT. ***Objective.*** Interstitial lung disease (ILD) is one of the most common pulmonary manifestations of rheumatoid arthritis (RA), but its prevalence has not been investigated in psoriatic arthritis (PsA). The role of methotrexate (MTX) in ILD development remains under debate. This study (1) compares the incidences of ILD in patients with RA or PsA initiating a first biologic disease-modifying antirheumatic drug (bDMARD) to that in the general population, and (2) investigates the role of MTX comedication on ILD incidence.

Methods. Patients were identified in 5 rheumatology registries. Demographics, MTX use, and disease activity were retrieved. Matched subjects from the general population were available from 4 countries. Incidence of ILD during follow-up of up to 5 years was assessed through national patient registries. Subjects with prior ILD were excluded. Adjusted hazard ratios (HRs) were calculated for ILD incidence in patients vs the general population, and for MTX users vs nonusers.

Results. During follow-up of 29,478 patients with RA and 10,919 patients with PsA initiating a first bDMARD and 362,087 population subjects, 225, 23, and 251 cases of ILD were identified, respectively. HRs for ILD (vs population subjects) were 9.7 (95% CI 7.97-11.91) in RA and 4.4 (95% CI 2.83-6.97) in PsA. HRs for ILD with MTX comedication (vs nonuse) were 1.0 (95% CI 0.72-1.25) in RA and 0.9 (95% CI 0.38-2.05) in PsA.

Conclusion. Among patients with RA and PsA initiating a bDMARD, the risk of ILD was higher than in the general population, and was highest in RA. MTX comedication was not a risk determinant for ILD.

Key Indexing Terms: interstitial lung disease, methotrexate, psoriatic arthritis, rheumatoid arthritis

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Interstitial lung disease (ILD) is one of the most common pulmonary extraarticular manifestations of rheumatoid arthritis (RA).[1,2] The clinical prevalence of ILD in RA has been estimated to be approximately 2%,[3,4] whereas studies based on data from high-resolution computed tomography (HRCT) of the chest and/or pulmonary function testing have found a strikingly higher prevalence, in the range of 4% to 15%.[5,6] In contrast, to our knowledge, no studies have systematically and prospectively investigated the risk of ILD in patients with psoriatic arthritis (PsA).

Methotrexate (MTX), a conventional synthetic disease-modifying antirheumatic drug (DMARD), is frequently used for the treatment of both RA and PsA, either in monotherapy or as comedication with biologic DMARDs (bDMARDs) or targeted synthetic DMARDs. The role of MTX in ILD development remains contentious.[7] MTX is associated with a rare form of acute pneumonitis as a manifestation of drug toxicity.[8,9] ILD is, however, a distinct clinical entity with a chronic disease course.

The objectives of this study were to (1) assess and compare the incidences of ILD in patients with RA and PsA initiating a first bDMARD, using the general population as benchmark, and (2) assess the potential role of MTX comedication in ILD development among such patients.

METHODS

Study design and participants. We performed an observational cohort study using prospectively recorded data from 5 Nordic rheumatology registries with high coverage among patients with inflammatory arthritis using bDMARDs (~90%) in the regions covered (see Supplementary Text, available with the online version of this article), and general population subjects. Individuals were linked through unique personal identification numbers to national registries on hospitalization, specialty care, and death, and details were extracted when available. The registries contributing observational prospective data are described in the Supplementary Text.

Among patients included in the abovementioned rheumatology registries, we identified all patients aged ≥ 18 years with a diagnosis of RA or PsA who initiated a first ever bDMARD treatment during the study period. The bDMARDs included in the study were abatacept, adaliumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, ixekizumab, rituximab, sarilumab, secukinumab, tocilizumab, and ustekinumab. An individual could only contribute 1 (ie, their first ever) bDMARD treatment course.

General population subjects drawn from the national population registers were available from 4 countries (see Supplementary Text, available with the online version of this article, for details). The controls were initially drawn to match demographics of the entire cohort in each country with regard to age, sex, and municipality of residence. However, individual patient cases could not be matched to specific controls, therefore all individuals who fulfilled the inclusion criteria of this study were included.

Linkage to national registries and outcome definition. In each country, patients and population subjects were linked by the unique personal identification numbers to information from the national patient registries (NPRs) to identify diagnoses obtained in secondary level healthcare services (inpatient or outpatient diagnoses). Patients and population subjects were also linked to cause of death registers in order to establish date of death and identify cases of ILD on death certificates.

ILD incidence was a priori defined as the first occurrence of an International Classification of Diseases, 10th Revision (ICD-10) code of J70 (respiratory conditions due to other external agents), J84 (other interstitial pulmonary disease), or J99 (respiratory disorder in diseases classified elsewhere) after bDMARD initiation, and required 2 ILD registrations in NPRs, or alternatively, 1 ILD registration in NPR and a second in the cause of death register (see Supplementary Material, available with the online version of this article, for all ICD-10 codes used). There was no standardized screening for ILD. Patients and general population subjects with an ILD diagnosis during the 5 years prior to baseline were excluded.

Study period and follow-up. To allow for a 5-year look-back period to identify prevalent ILD and comorbidities, our study period started on January 1, 5 years after the date when valid data were generally first available from the national patient and death registries in each country (Denmark, 2000; Finland, 2003; Iceland, 2010; Norway, 2014; Sweden, 2006). The censoring date was the last date of available registry linkage data for each country.

Follow-up began on the date of the first ever bDMARD treatment course for patient participants or date of matching for general population subjects (referred to as baseline). Follow-up ended at the first occurrence of ILD, death, end of study period, or 5 years from start of follow-up.

Covariates in patient populations.

- *Baseline characteristics and disease activity.* Among patients with RA or PsA, disease activity, defined as the numbers of swollen and tender joints in 28-joint counts, was recorded at baseline. In addition, information on anticitrullinated protein antibodies (ACPA) and rheumatoid factor (RF) status (dichotomized as positive or negative according to each country's specification), smoking habits (dichotomized as ever vs never), C-reactive protein (CRP) in mg/L, disease duration in years, patient global assessment (PtGA) of disease activity on a 100-mm visual analog scale (VAS), physician global assessment of disease activity on a 100-mm VAS, and self-reported physical function in the Health Assessment Questionnaire (HAQ) were extracted from each registry.[10] The Norwegian Antirheumatic Drug Register (NOR-DMARD) collects the modified HAQ, which was transformed into a HAQ score using a validated equation.[11] The Disease Activity Score in 28 joints with CRP (DAS28-CRP) was calculated.[12]
- *Comedication, including MTX exposure.* Information regarding MTX and oral corticosteroid comedications was extracted from each rheumatology registry. MTX use at baseline was defined as ongoing use of MTX at the time of baseline or starting MTX comedication within 14 days from baseline.

In MTX comedication users, the duration of ongoing MTX treatment

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was calculated and categorized as treatment started at baseline, treatment started within 1 year prior to baseline, treatment started > 1 and ≤ 5 years prior to baseline, and treatment started > 5 years prior to baseline. Corticosteroid comedication data were recorded as the cumulative dose of prednisolone (PSL) during the first 6 months of bDMARD treatment. Cumulative dose above 500 mg (an average of 2.7 mg/day) was defined as the cut-off for oral corticosteroid comedication.

- *Comorbidities.* Comorbidity data were collected from NPRs and identified up to 5 years prior to baseline. We recorded previous diagnoses of diabetes, kidney disease, cardiovascular disease, cerebral disease, and peripheral vascular disease (see Supplementary Text, available with the online version of this article, for ICD-10 codes used). A comorbidity index was calculated as a sum score (0-5) of the comorbidities registered at baseline.

Statistical analysis. Pooled cohort-specific estimates of ILD incidence were calculated. Demographic data were compared between patients who did and did not develop ILD during follow-up using *t* test or Mann-Whitney *U* test according to the parametric distribution, judged by a visual inspection of the distribution. Levene test was performed to test equality of variances. Categorical data were compared across groups using chi-square distribution and Fisher exact test was used if chi-square assumptions were violated. Missingness was assumed to be at random and complete case analyses were performed in the main analysis, whereas multiple imputations were performed in the sensitivity analyses.

The incidence of ILD was compared between patients and general population subjects, and hazard ratios (HRs) were calculated using Cox proportional hazards regression models adjusted for baseline age and sex, and stratified by country and decade of bDMARD initiation. As Finland did not have a general population cohort for comparison, and to accommodate the low number of ILD events in some countries, Norway, Iceland, and Finland were grouped together for these analyses, whereas Denmark and Sweden were analyzed separately. The proportional hazards assumption was examined graphically by plotting log-log survival estimates against time and by the global goodness-of-fit test proposed by Schoenfeld.[13] The HRs for ILD in patients vs the general population subjects were also estimated in cohorts stratified by age (< 50 vs ≥ 50 years of age at baseline) and disease duration (dichotomized at the median).

HRs of ILD comparing patients with vs without MTX comedication at baseline were examined in separate models for RA and PsA adjusted for age and sex. Each model was stratified by country and decade of bDMARD initiation. Directed acyclic graphs were used to identify possible confounders, and HR estimates for MTX were subsequently adjusted by successively adding the following variables to the model: disease duration, DAS28-CRP, HAQ, baseline smoking, comorbidity, and use of PSL. In exploratory analyses, the HRs of MTX for ILD were further examined in models stratified by age (< 50 vs ≥ 50 years at bDMARD treatment initiation), RF/ACPA status (in RA), and duration of MTX treatment at bDMARD treatment initiation.

Sensitivity analyses. The following sensitivity analyses were performed:

1. The incidence of ILD was compared between patients and general population subjects with an ILD event defined as ≥ 1 (instead of ≥ 2) registrations with an ILD diagnosis.
2. The association between use of MTX and subsequent ILD was also investigated in models, in which missing variables were replaced by 10 imputations using chained regression. In addition, the confounders in the model were explored as cubic splines.
3. The associations between use of MTX and subsequent ILD were investigated in an on-treatment model, in which follow-up was censored at 29 days after discontinuation of the bDMARD in question, death, a maximum of 5 years of follow-up, or the end of study period. In this model, the HR for MTX was adjusted by successively adding disease duration, DAS28-CRP, HAQ, baseline smoking, comorbidity, and use of PSL.
4. Analyses examining the effect of MTX comedication during bDMARD treatment were performed with ILD restricted to ICD-10 diagnosis J84 (other interstitial pulmonary disease) and J99 (respiratory disorder in diseases classified elsewhere; ie, ICD-10 diagnoses for respiratory conditions due to other external agents were excluded).

Ethics approval. This study involves human participants and was approved by the following data protection and/or ethical committees in each of the Nordic countries, as required: Denmark (Capital Region Data Protection Office [RH-2015-209, I-suite 04145]; ethical approval not required for registry studies [komitélovens §14, stk 2; www.nvk.dk]; Finland (Helsinki University Hospital Coordinating Ethics Committee [73/13/03/00/2014]); Norway (Regional Ethics Committee of South Eastern Norway [2011/1339 and 2017/243]); Sweden (Ethical Review Board Stockholm [2015/1844-31/2]); and Iceland (National Bioethics Committee of Iceland [17-048-V13 and VSNb2017010049/03.01]).

Informed written consent for the reporting of anonymized registry data for research purposes was not required according to the approval committees, apart from Norway where such approval was required (and collected) for patients included after 2012. Participants gave informed consent to participate in the study before taking part.

RESULTS

We identified a total of 29,478 patients with RA and 10,919 patients with PsA initiating a first ever bDMARD, and 362,087 subjects from the general population, who contributed 117,060, 40,685, and 1,419,511 patient-years [PYs] of follow-up, respectively. Considering follow-up from baseline, 17,522 (59%), 5619 (52%) and 206,133 (57%) controls, patients with RA, and patients with PsA completed 5 years of observation, respectively. Table 1 presents baseline demographic characteristics.

Occurrence of ILD in patients starting a first bDMARD and general population subjects. During follow-up, the RA, PsA, and population cohorts contributed 225, 23, and 251 ILD events, corresponding to an ILD incidence per 1000 PYs of 1.9 (95% CI 1.69-2.19), 0.6 (95% CI 0.38-0.85), and 0.2 (95% CI 0.16-0.20), respectively (Table 2). Compared to the general population subjects, the HR for ILD in RA was 9.7 (95% CI 7.97-11.91), and 4.4 (95% CI 2.84-6.97) in PsA.

There was no significant difference in time between start of bDMARD and first ILD diagnosis between patients with RA and PsA (mean time 1.9 [SD 1.5] vs 1.9 [SD 1.4] years, respectively; $P = 0.99$; Table 2 and Figure). Country-specific baseline demographics and ILD incidence rates are presented in Supplementary Table S1 (available with the online version of this article).

The HR for ILD in RA vs PsA was 2.5 (95% CI 1.61-3.97; Table 2). Patients with RA who developed vs did not develop ILD were older (65 vs 55 years, respectively), more often male (46% vs 25%), and had higher levels of most disease activity variables; on the other hand, patients with PsA who developed vs did not develop ILD were older (61 vs 49 years) and had higher levels of erythrocyte sedimentation rate (ESR) and PtGA at baseline. In RA, the majority of ILD cases occurred in patients who were ACPA- and/or RF-positive (92%) compared to patients negative for both markers (8%; Supplementary Table S2, available with the online version of this article).

Distribution of ILD diagnoses. Other interstitial pulmonary disease (J84.1, J84.8, and J84.9) was the most common first

Table 1. Baseline demographic variables of patients with RA and PsA on their first bDMARD treatment course and individuals from the general population.

	No. of Missing RA/PsA/Controls	RA	PsA	General Population
Demographics				
No. of individuals	0/0/0	29,478	10,919	362,087
Age, yrs, mean (SD)	0/0/0	55.6 (13.6)	48.5 (12.7)	52.5 (13.8)
Female sex, n (%)	0/0/0	22,068 (74.86)	5742 (52.59)	252,541 (69.75)
ACPA/RF positive, n (%)	15,340/9886/NA	11,421 (80.78)	82 (7.94)	–
Smoking, current or past, n (%)	16,688/5761/NA	6584 (51.48)	2630 (50.99)	–
Disease duration, yrs, median (IQR)	991/1019/NA	6 (2-14)	6 (2-13)	–
Comorbidity present, n (%)	0/0/NA	4081 (13.84)	1298 (11.89)	–
MTX comedication at baseline, n (%)	0/0/NA	16,330 (55.40)	4590 (42.04)	–
MTX prior to baseline, yrs, mean (SD)	13,241/6392/NA	2.5 (3.6)	2.1 (3.4)	–
PSL comedication[a], n (%)	0/0/NA	13,166 (44.66)	2431 (22.26)	–
bDMARDs				
Adalimumab, n (%)	0/0/NA	5384 (18.26)	3042 (27.86)	–
Etanercept, n (%)	0/0/NA	10,232 (34.71)	3968 (36.34)	–
Infliximab, n (%)	0/0/NA	6839 (23.20)	2460 (22.53)	–
Other TNFi[b], n (%)	0/0/NA	2849 (9.66)	1048 (9.60)	–
Rituximab, n (%)	0/0/NA	2103 (7.13)	26 (0)	–
Other bDMARDs[c], n (%)	0/0/NA	2071 (7.03)	375 (3.43)	–
Variables of disease activity				
CRP, mg/L, mean (SD)	7415/3533/NA	18.6 (25.2)	12.2 (19.4)	–
ESR, mm/h, mean (SD)	15,203/6117/NA	26.1 (21.7)	18.5 (17.5)	–
TJC28, median (IQR)	8083/3983/NA	6 (3-10)	4 (2-8)	–
SJC28, median (IQR)	8080/4006/NA	5 (2-9)	2 (0-5)	–
DAS28-CRP, mean (SD)	9868/4805/NA	4.6 (1.2)	4.1 (1.2)	–
PtGA, mean (SD)	8099/3680/NA	57 (25)	59 (24)	–
PGA, mean (SD)	18,857/7483/NA	40 (22)	35 (20)	–
HAQ, mean (SD)	8835/4118/NA	1.1 (0.7)	1.0 (0.6)	–

[a] PSL use is defined as a cumulative dose of ≥ 500 mg during the first 6 months of bDMARD treatment. [b] Includes certolizumab pegol and golimumab. [c] Includes abatacept, secukinumab, tocilizumab, ustekinumab, anakinra, apremilast, ixekizumab, and sarilumab. ACPA: anticitrullinated peptide antibody; bDMARD: biologic disease-modifying antirheumatic drug; CRP: C-reactive protein; DAS28-CRP: Disease Activity Score in 28 joints based on CRP; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; MTX: methotrexate; NA: not applicable; PGA: physician global assessment; PsA: psoriatic arthritis; PSL: prednisolone; PtGA: patient global assessment; RA: rheumatoid arthritis; RF: rheumatoid factor; SJC28: swollen joint count of 28 joints; TJC28: tender joint count of 28 joints; TNFi: tumor necrosis factor inhibitor.

recorded ILD diagnosis code in all groups (RA: 199 [88%]; PsA: 19 [83%]; general population: 238 [95%]). There was a considerable change in coding within ILD diagnoses during successive ILD registrations, with 31% of patients (5/16) who received a J70 diagnosis at the first of multiple ILD registration coded as J84 at the second registration.

MTX comedication as a risk determinant for ILD incidence. In RA and PsA disease-specific models, use of MTX at bDMARD initiation was not a risk factor for ILD development. The HR of MTX use was 1.0 (95% CI 0.72-1.25) in RA and 0.9 (95% CI 0.38-2.05) in PsA, both adjusted for age and sex (Table 3). In age-stratified models (< 50 vs ≥ 50 years at bDMARD initiation), we found no association between comedication with MTX and ILD. There was also no indication of an interaction between use of MTX comedication and ACPA/RF positivity in models examining risk of ILD. In models stratified by the duration of MTX treatment prior to bDMARD initiation, MTX was not associated with risk of ILD following bDMARD start (Table 3).

Sensitivity analyses. Defining ILD as ≥ 1 registration of any of the ILD diagnoses did not substantially change the incidence rates or HRs for ILD (Supplementary Table S3, available with the online version of this article). The results from the on-treatment analyses came close to those of the main analysis (Supplementary Table S4). Similarly, restricting the ILD definition to ICD-10 J84/J99, or to on-treatment analyses, confirmed the results of the main analysis (Supplementary Table S5-S7).

When testing the proportional hazards assumption, no departure from the assumption was identified for the comparison of ILD occurrence in patients with RA or PsA compared to the general population subjects. However, for the analyses of MTX comedication as a risk determinant in RA, an inspection of the survival curves indicated a change in HR at around 8 months. We therefore chose to reanalyze the data using a time-varying Cox model in which the HR associated with MTX was allowed to differ between the first 8 months and subsequent follow-up. Using this approach, we found that use of MTX comedication carried a significantly increased HR in the first period (HR 1.6, 95% CI 1.02-2.66) and reduced risk in the second period (HR 0.7, 95% CI 0.51-0.97). In models stratified according to duration of MTX treatment at baseline, the risk of ILD was not increased during the first 8 months of bDMARD treatment in patients

Table 2. Incidence and HR of ILD in patients and general population subjects within 5 years of bDMARD treatment initiation.

	RA	PsA	General Population	*P*	
PYs	117,060	40,685	1,419,511	–	
Observation duration, yrs, median (IQR)	5.0 (3.0-5.0)	5.0 (2.3-5.0)	5.0 (2.9-5.0)	–	
ILD incidence, n (%)	225 (0.76)	23 (0.21)	251 (0.07)	–	
Time from inclusion of bDMARD until ILD, yrs, mean (SD)[a]	1.9 (1.5)	1.9 (1.4)	2.3 (1.4)	–	
IRs and IRRs					
Incidence/1000 PYs (95% CI)	1.9 (1.7-2.2)	0.6 (0.4-0.9)	0.2 (0.2-0.2)	–	
Unadjusted IRR (95% CI), patients vs general population	10.9 (9.0-13.1)	3.2 (2.0-4.9)	Ref	< 0.001	
IRR (95% CI), RA vs PsA	3.4 (2.2-5.5)	Ref	–	< 0.001	
HRs					
HR (95% CI), patients vs general population	9.7 (8.0-11.9)	4.4 (2.8-7.0)	Ref	< 0.001	
HR (95% CI), RA vs PsA	2.5 (1.6-3.9)	Ref	–	< 0.001	
Stratified analyses					
Incidence/1000 PYs (95% CI)					
< 50 yrs at baseline	0.5 (0.3-0.8)	0.2 (0.1-0.5)	0.06 (0.04-0.08)	–	
≥ 50 yrs at baseline	3.0 (2.2-3.0)	1.0 (0.7-1.6)	0.3 (0.2-0.3)	–	
Disease duration < median	2.0 (1.6-2.4)	0.4 (0.2-0.9)	–	–	
Disease duration ≥ median	1.9 (1.6-2.3)	0.6 (0.3-1.0)	–	–	
HRs (95% CI), patients vs general population				RA	PsA
< 50 yrs at baseline	10.4 (5.6-19.0)	4.3 (1.5-12.6)	Ref	< 0.001	0.01
≥ 50 yrs at baseline	9.6 (7.8-11.9)	4.6 (2.8-7.6)	Ref	< 0.001	< 0.001
Disease duration < median	11.4 (8.9-14.7)	4.0 (1.9-8.2)	Ref	< 0.001	< 0.001
Disease duration ≥ median	9.3 (7.2-11.9)	4.3 (2.3-8.0)	Ref	< 0.001	< 0.001

HRs from Cox models are adjusted for age and sex and stratified by country and decade of bDMARD initiation. [a] Mean time to develop ILD within 5-year observation period. HR: hazard ratio; PY: patient-years (of follow-up); ILD: interstitial lung disease; bDMARD: biologic disease-modifying antirheumatic drug; IR: incidence rate; IRR: incidence rate ratio; RA: rheumatoid arthritis; PsA: psoriatic arthritis.

with RA who started MTX and bDMARD at the same time-point (HR 1.1, 95% CI 0.48-2.29 in the first period, and HR 0.6, 95% CI 0.32-1.17 during the second period). We found no violation of the proportional hazards assumptions for the analyses of MTX comedication in the PsA population (data not shown).

DISCUSSION

In this large real-world observational study, we found that the incidence of ILD in patients with RA and PsA with no previous ILD who initiated a first ever treatment with a bDMARD was increased several-fold compared to the corresponding rate in

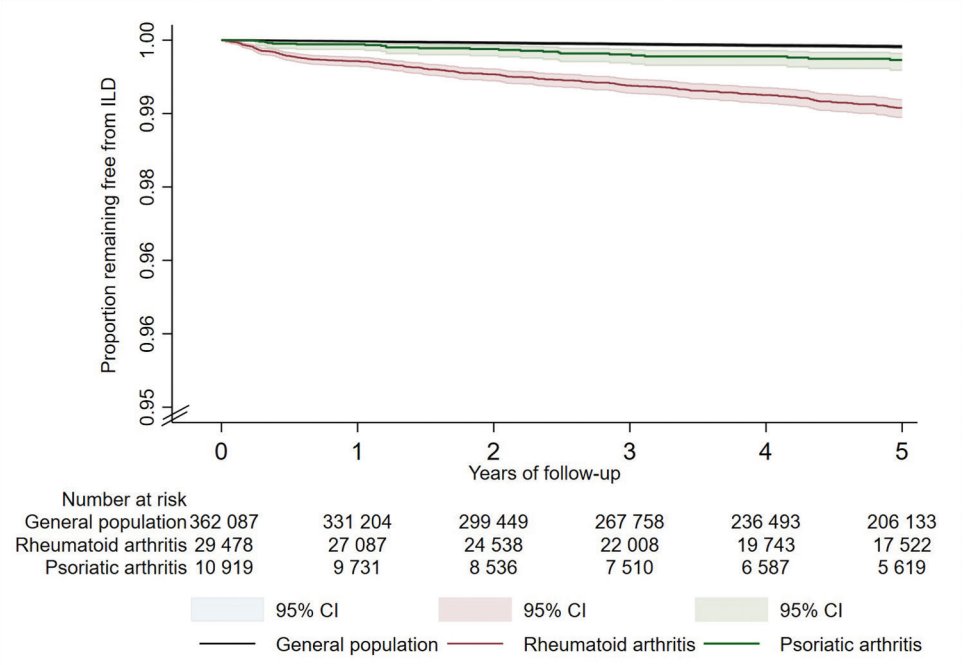

Figure. Kaplan-Meier curves for 5-year risk of ILD in patients with RA and PsA and the general population. Log-rank test, $P < 0.001$. ILD: interstitial lung disease; PsA: psoriatic arthritis; RA: rheumatoid arthritis.

Table 3. Estimated HRs of development of ILD within 5 years after the first registered bDMARD treatment by baseline use of MTX, stratified for RA and PsA, using Cox regression model.

	RA			PsA		
	RA/ILD, n/n	MTX Use vs No Use, HR (95% CI)	*P*	PsA/ILD, n/n	MTX Use vs No Use, HR (95% CI)	*P*
Variables						
Adjusted for age and sex	29,478/225	1.0 (0.7-1.2)	0.72	10,919/23	0.9 (0.4-2.1)	0.78
Adjusted for age, sex, and disease duration	28,487/218	0.9 (0.7-1.2)	0.54	9900/19	0.9 (0.4-2.2)	0.80
Adjusted for age, sex, and DAS28-CRP	19,610/155	1.1 (0.8-1.5)	0.63	6114/11	1.1 (0.3-4.0)	0.83
Adjusted for age, sex, and HAQ	20,004/157	1.0 (0.7-1.4)	0.97	6307/10	0.8 (0.2-2.8)	0.73
Adjusted for age, sex, and smoking	12,790/78	1.2 (0.8-2.0)	0.39	5158/11	0.6 (0.2-2.0)	0.38
Adjusted for age, sex, and comorbidities	29,478/225	1.0 (0.7-1.3)	0.76	10,919/23	1.0 (0.4-2.2)	0.78
Adjusted for age, sex, and PSL	29,478/225	0.9 (0.7-1.2)	0.77	10,564/22	0.9 (0.4-2.1)	> 0.99
Posthoc exploratory analyses						
Age-stratified model						
< 50 yrs at baseline	8854/18	0.6 (0.2-1.5)	0.25	5631/4	1.0 (0.1-7.1)	0.98
≥ 50 yrs at baseline	20,624/207	1.0 (0.8-1.3)	0.99	5288/19	1.0 (0.4-2.5)	0.79
RF/ACPA-stratified model						
Positive	11,421/84	1.1 (0.7-1.7)	0.65	–	–	–
Negative	2717/7	1.8 (0.4-9.6)	0.48	–	–	–
Model stratified according to duration of MTX at baseline						
Did not use MTX comedication at baseline	13,148/107	–	–	6329/13	–	–
Treatment started at the same time as start of bDMARD	2972/17	0.9 (0.5-1.6)	0.72	843/3	1.0 (0.2-4.2)	> 0.99
Treatment started within 1 yr prior to start of bDMARD	4778/33	0.9 (0.6-1.4)	0.80	1589/3	1.1 (0.3-3.8)	0.97
Treatment started > 1 and ≤ 5 yrs prior to start of bDMARD	5812/44	1.0 (0.7-1.4)	0.89	1546/2	0.6 (0.1-2.7)	0.43
Treatment started > 5 yrs prior to start of bDMARD	2768/24	1.1 (0.7-1.7)	0.71	612/2	1.1 (0.2-5.4)	> 0.99

Models stratified for country and period of inclusion. Model for age was adjusted for sex; model for sex was also adjusted for baseline age; and models including DAS28-CRP, HAQ, PSL use, and smoking were also adjusted for baseline age and sex. PSL use was defined as a cumulative dose of ≥ 500 mg of PSL during the first 6 months of bDMARD treatment. ACPA: anticitrullinated peptide antibody; bDMARD: biologic disease-modifying antirheumatic drug; DAS28-CRP: Disease Activity Score in 28 joints based on CRP; HAQ: Health Assessment Questionnaire; HR: hazard ratio; MTX: methotrexate; PsA: psoriatic arthritis; PSL: prednisolone; RA: rheumatoid arthritis; RF: rheumatoid factor.

the general population. The increased incidence of ILD was especially pronounced in RA. Among patients with RA and PsA starting a bDMARD, use of MTX comedication was not associated with an increased incidence of ILD during a 5-year follow-up period.

Our estimated incidence of ILD in patients with RA (1.9/1000 PYs) is lower than the 7.7/1000 PYs identified as incident ILD through retrospective examination of chest CT scans in the Brigham and Women's Hospital Rheumatoid Arthritis Sequential Study (BRASS) cohort,[14] and lower than the 4.1/1000 PYs in the UK Early Rheumatoid Arthritis Study (ERAS) study of incident RA.[15] Importantly, although the mean age of the included populations in these studies is roughly similar to our cohort, the studies are not directly comparable due to differences in the method of ILD identification as well as in the number of patients treated with bDMARDs. In ERAS, the median symptom duration was 6 months; cases of ILD were identified from clinical examination, including by HRCT, of patients who reported pulmonary symptoms; and no patients were treated with bDMARDs. In the North American BRASS study, the median disease duration was 9 years and ILD was determined by a structured review of clinically indicated chest CTs; approximately 50% used bDMARDs. Although we had a high proportion of missing data on smoking status, the proportion of patients who reported current or previous smoking was higher in our cohort compared to both ERAS and BRASS, and our median disease duration was 6 years. It is difficult to compare measures of disease activity between cohorts as different instruments are used, but there are indications of lower disease activity in our cohort compared to others. In ERAS, ESR was a median of 38 mm/h, whereas the mean was 26.1 mm/h for RA in our cohort. In BRASS, 56% had 3-variable DAS28 > 3.2, whereas the mean 4-variable DAS28-CRP in our cohort was 4.6 for RA and 4.1 for PsA, indicating higher baseline disease activity. Our incidence rates are also lower than those estimated from other registry studies. Sparks et al reported an ILD incidence of 7.1/1000 PYs identified from claims databases in a predominately elderly population.[4] Our results may indicate that patients initiating bDMARDs have a lower risk of ILD compared to more heterogeneous patient cohorts. A possible mechanism may be selection of otherwise healthy patients for treatment with a bDMARD. Moreover,

one may hypothesize that bDMARD treatment contributes to lowering the risk of ILD.

Data on ILD in patients with PsA are scarce.[9,16] Although comorbidities of PsA are becoming increasingly recognized, ILD is not mentioned as a comorbidity that the clinician should be aware of in either of the PsA treatment recommendations.[17,18] However, several ILD case reports have been published in patients with PsA[19] and psoriasis.[20] Wong et al investigated the causes of death in 53 patients with PsA and found that respiratory diseases were the second most frequent cause, and were significantly higher than expected.[21] Further, a retrospective study of case records from 387 patients with PsA found 2 cases of apical lung fibrosis.[22]

In our study, incident ILD was associated with older age in both RA and PsA, and in the RA cohort, ILD was also more frequent in male individuals and seropositive patients and was associated with disease activity. Our findings are largely in agreement with the existing literature concerning predictors of ILD, but asthma, pneumonias, and exposure to smoking are also known risk factors.[14,15,23,24] We know from previous studies that patients with psoriasis are more likely to develop chronic obstructive pulmonary disease,[21] and smoking is a common causal factor between these 2 conditions.[25] Thus, the increased risk of ILD in patients with PsA may partly be explained by confounding factors that have not been fully accounted for, such as smoking.

In the present study, MTX comedication was not associated with ILD development in patients with RA or PsA initiating treatment with a bDMARD during a 5-year follow-up. However, the proportional hazards assumption was violated in the RA population and a time-varying Cox regression model indicated an increased risk in the RA population treated with MTX for the first 8 months, followed by reduced risk, compared to patients not treated with MTX. Our sensitivity analyses restricted to J84 and/or J99 confirmed the main results.

Our finding of a lack of association between use of MTX and ILD development agrees with other previous publications,[26] although a previous report on data of adverse events recorded by the US Food and Drug Administration (FDA) found that MTX was among the top 20 most reported drugs associated with ILD.[7] A Danish study did not find an increased risk of ILD in patients with RA from the national quality registry DANBIO who had been dispensed MTX.[27] Use of MTX did also not emerge as a risk factor for ILD in the UK ERAS/Early Rheumatoid Arthritis Network (ERAN) study.[28]

Our study has a number of limitations. Since there are no classification or diagnostic criteria for ILD in patients with arthritic diseases, we identified ILD through registry linkages with a requirement of an ICD-10 diagnosis for ILD at 2 or more timepoints. We were not able to retrieve HRCT thorax examinations. A recent study aimed to verify the registry-derived ILD diagnoses in 80 patients from the Norwegian NOR-DMARD cohort. The study retrospectively collected HRCT thorax and medical records, and the authors were able to retrospectively verify approximately 60% to 75% of the ILD diagnoses derived from the registers using a strategy similar to the one used in the current study.[29] This approach has also been confirmed to have a positive predictive value of 70% to 75% in claims-based Medicare data,[30] but it may not identify mild subclinical ILD. The positive predictive value for registry-derived ILD in patients with PsA has not been explored. Another potential weakness is that the historical exposure to MTX was collected retrospectively at bDMARD initiation, and exposure to MTX was conditioned upon subsequent bDMARD initiation. We also lack information on other pulmonary disease and have a high proportion of missing data for smoking, which, if present, could have resulted in closer surveillance of patients, increased the detection of ILD, and also confounded the results.

Strengths of this study are the use of large and heterogeneous patient cohorts derived from registries in 5 countries with prospective data collections, which include information on the use of MTX and/or bDMARDs; the fact that these cohorts are large enough to evaluate and compare ILD incidences not only in RA, but also in PsA; and the possibility to relate these incidences to those obtained from general population subjects using the same ILD definition. We used a validated method to identify cases of ILD from hospital and death registries, using an approach similar to what has been used in other reports.[4]

To conclude, ILD occurs more frequently in patients with RA and PsA taking bDMARDs than in the general population, especially in those with RA. In this treatment context, MTX is not a risk factor for ILD in the PsA population. In patients with RA who are treated with MTX comedication, we cannot exclude the possibility of an increased risk of ILD during the first 8 months of bDMARD therapy.

DATA AVAILABILITY

Owing to privacy and ethical concerns, any raw data cannot be shared. Aggregated data can be shared upon reasonable request to the authors.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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