

Tuberculosis in Biologic-naïve Patients With Rheumatoid Arthritis: Risk Factors and Tuberculosis Characteristics

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ABSTRACT. *Objective.* To investigate risk factors and characteristics of active tuberculosis (TB) in biologic-naïve patients with rheumatoid arthritis (RA).

Methods. We conducted a population-based case-control study using the Swedish Rheumatology Quality Register, the National Patient Register, and the Tuberculosis Register to identify RA patients with active TB and matched RA controls without TB between 2001–2014. Clinical data were obtained from medical records. TB risk was estimated as adjusted OR (aOR) with 95% CI using univariate and multivariable logistic regression analyses.

Results. After validation of diagnoses, the study included 31 RA patients with TB and 122 matched RA controls. All except 3 cases had reactivation of latent TB. Pulmonary TB was most prevalent (84%). Ever use of methotrexate was not associated with increased TB risk (aOR 0.8, 95% CI 0.3–2.0), whereas ever treatment with leflunomide (aOR 6.0, 95% CI 1.5–24.7), azathioprine (aOR 3.8, 95% CI 1.1–13.8), and prednisolone (PSL; aOR 2.4, 95% CI 1.0–6.0) was. There were no significant differences between maximum dose of PSL, treatment duration with PSL before TB, or cumulative dose of PSL the year before TB diagnosis between cases and controls. Obstructive pulmonary disease was associated with an increased TB risk (aOR 3.9, 95% CI 1.5–10.7).

Conclusion. Several RA-associated factors may contribute to increased TB risk in biologic-naïve patients with RA, making the risk of TB activation difficult to predict in the individual patient. To further decrease TB in patients with RA, the results suggest that screening for latent TB should also be considered in biologic-naïve patients.

Key Indexing Terms: biologic-naïve, rheumatoid arthritis, risk factors, tuberculosis

Shortly after the introduction of tumor necrosis factor inhibitors (TNFi) in the treatment of rheumatoid arthritis (RA), an increase in the risk of tuberculosis (TB), in particular of reactivation of

latent TB infection (LTBI), was observed.¹ Ensuing guidelines recommending screening and treatment for LTBI before starting treatment with TNFi and other biologic (b) disease-modifying antirheumatic drugs (DMARDs) have been followed by a decrease of active TB among bDMARD-treated patients with RA.^{2,3} However, the TB risk in biologic-naïve patients with RA appears to remain several-fold higher compared to the general population. In a previous study, we showed that the rate of TB in bDMARD-treated patients with RA decreased following the initiation of pretreatment TB screening in Sweden, but no similar decline in risk was observed among the biologic-naïve patients with RA.⁴ The risk in this group remained 4 times higher than the general population in Sweden. Notably, most TB cases in contemporary patients with RA occur in biologic-naïve patients.^{5,6} It is therefore reasonable that efforts to further decrease the TB risk in RA should also incorporate the group of biologic-naïve patients. To do this, a better understanding of TB risk factors and characteristics in this patient group is essential, yet consistent results are largely lacking (studies summarized in Supplementary Table 1, available with the online version of this article).^{7–20}

We aimed to assess risk factors for active TB infection in biologic-naïve patients with RA and to describe the clinical characteristics and outcomes of the clinical TB manifestations. We therefore performed a matched population-based case-control

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study using national registers in combination with data collection from medical records.

METHODS

Patients with RA. We identified a national population-based RA cohort from the National Patient Register (NPR) using registered inpatient care from 1969 to 2014 and outpatient, nonprimary care from 2001 to 2014, and from the Swedish Rheumatology Quality Register (SRQ) between 1997–2014. The registration of inpatient care in the NPR is over 99% complete since 1987 and the outpatient specialist nonsurgical care component is over 80% complete.^{21,22} Patients were included if they were ≥ 18 years old at RA diagnosis and had at least 2 visits with an International Classification of Diseases (ICD) code for RA (ICD-10: M05, M06.0, M06.2, M06.8, M06.9, M12.3; ICD-9: 714A, 714B, 714C, 714W, 719D; ICD-8: 712.10, 712.20, 712.38) in the NPR and/or SRQ. The patients were required to have at least 1 specialist visit to a rheumatology or internal medicine department in the NPR and at least 1 visit in outpatient care. With this definition of RA, it has been shown that $> 90\%$ of the identified patients fulfilled current criteria for RA.²³ The RA diagnoses in the medical records were validated against the American College of Rheumatology (ACR) 1987 or the ACR/European League Against Rheumatism (EULAR) 2010 RA criteria. To identify the patients with RA unexposed to bDMARDs, we used treatment data from SRQ. Data on exposure to bDMARDs are entered by clinicians in the SRQ, and the registry covers approximately 90% of the bDMARD-treated Swedish patients with RA.

Cases with TB. Cases were patients with RA unexposed to bDMARDs with a first TB diagnosis after the second discharge listing RA in the NPR, identified by linking the RA population and the Swedish Tuberculosis Register from 2001–2014. All forms of active TB are notifiable according to Swedish law, and clinicians are obliged to report to the Swedish Tuberculosis Register any individual they start on TB treatment, whether it be for verified or suspected TB. Laboratories report mycobacterial culture–positive patients in the same system, linked to the clinician's report by the patient's unique personal number. If the laboratory report is not followed by a clinical report within a few weeks, the treating physician is asked to complete the report. The coverage of TB cases confirmed by culture for the register is therefore close to 100%.

Controls free from TB. For each bDMARD-unexposed RA case with TB, 4 RA controls without TB were identified from the RA population who were living in Sweden and who had not been exposed to bDMARDs before the TB diagnosis of the corresponding case. Controls had to be free from any registered TB diagnosis in the NPR and the TB register, and were matched on sex, year of birth (± 5 yrs), year of first RA diagnosis in the NPR, and region of residence at the time of the TB diagnosis of their corresponding case.

Exposures. Clinical data of cases and controls were collected from medical records and included information about RA disease, smoking habits, and comorbidities known at any time before TB diagnosis for cases, and before TB diagnosis of the matched case for controls. Data on RA disease activity at visits 6 months (± 1 month) before TB diagnosis and at TB diagnosis (± 1 month) were obtained, together with data on RA disease activity during TB treatment and outcome of TB treatment for the cases. RA disease activity was considered increased if (1) a note in the medical records mentioned increased RA disease activity, such as more affected joints compared to last visit; (2) the patient had received several local corticoid injections; or (3) there was a change in therapy due to increased disease activity.

Data on exposure to corticosteroids and any conventional synthetic (cs)DMARD, including methotrexate (MTX), sulfasalazine, hydroxychloroquine/chloroquine, leflunomide (LEF), cyclosporine, azathioprine (AZA), cyclophosphamide, penicillamine, mycristine, and auranofin, for ≥ 4 consecutive weeks from RA diagnosis until TB diagnosis and at specific timepoints (i.e., 12 months, 9 months, 6 months, and 3 months) before TB diagnosis were obtained, together with treatment duration and maximum

dose. For MTX and prednisolone (PSL), information on cumulative dose the year before TB diagnosis and the exposure to doses ≥ 15 mg of PSL ≥ 1 month at any time during the course of RA, as well as during the 12 months and 6 months preceding TB diagnosis, was also collected.

Established epidemiological risk factors for TB were assessed. These included former TB infection or known exposure to TB in the family (parents or siblings with diagnosed TB), occupational history, and a history of living abroad in high-endemic areas. To be born before 1950 was regarded as a risk factor in descriptive analyses, but not in risk assessments as cases and controls were matched for age. If the patient had been screened for LTBI, the type of screening test and outcome were collected.

Statistical analysis. For comparative analyses between cases and controls, *t* tests and Mann-Whitney *U* tests were used for continuous data, and chi-square and Fisher exact tests were used for categorical data. *P* values < 0.05 were considered statistically significant. Age- and sex-adjusted logistic regression models were used to estimate the relative risk for TB expressed as adjusted OR (aOR) with 95% CI. Analyses of PSL treatment were additionally adjusted for DMARD use. We used a complete case analysis approach, meaning that for each exposure patients with missing values were excluded from the respective analysis. Data analyses were conducted using SPSS version 25 for Windows (IBM Corp.).

This study complies with the Declaration of Helsinki and was approved by the regional ethics committee in Uppsala, Sweden (2015/306). According to the ethical approval, no written informed consent from the patients was needed.

RESULTS

We initially identified 42 biologic-naïve RA patients with TB and 164 matched biologic-naïve RA controls without TB from the register data during the 2001–2014 study period. After exclusions, mainly due to missing or incomplete medical records or because patients did not fulfill RA criteria (Supplementary Figure 1, available with the online version of this article), we finally included 31 cases with verified RA and active TB and 122 matched RA controls without TB. Fifteen (48%) of the cases and 70 (57%) of the controls were women. Table 1 summarizes the RA characteristics and comorbidities of cases and controls.

TB characteristics and screening. The mean age at TB diagnosis was 73.2 years, with TB diagnosed on average 15.8 (0–58) years after the RA diagnosis. Most patients reported typical TB symptoms such as weight loss, cough, fever, and night sweats, followed by a TB diagnosis on average 15 weeks after onset of symptoms. Pulmonary TB was most prevalent (84%). There were no drug-resistant strains, and most patients had unique strains indicating reactivation of LTBI. A possible acquisition of new infection abroad (United States, Thailand, and the Baltic countries) was reported in the Swedish Tuberculosis Register in 3 cases, whereas all other cases were regarded as reactivation of LTBI. The patients tolerated TB treatment well without any reported serious adverse events. Overall, the prognosis of TB was good and 94% of the patients fulfilled the treatment course, whereas 1 patient died of miliary TB and 3 patients died from other medical conditions before completing TB therapy (Table 2).

Early screening for LTBI with tuberculin skin test (TST) was performed in only 2 of the patients—1 case (who later developed active TB) and 1 control—both with identified epidemiological risk factors for TB exposure. Both had negative TST results and were not given preventive TB treatment.

Table 1. Characteristics of TB cases with biologic-naïve RA and matched RA controls.

	TB Cases, n = 31	Controls, n = 122
Sex, female, n (%)	15 (48)	70 (57)
Age at RA diagnosis, yrs, mean \pm SD (min–max)	57.4 \pm 18.1 (17–82)	55.8 \pm 15.8 (13–81) ^a
Age at TB diagnosis, yrs, mean \pm SD (min–max)	73.2 \pm 10.2 (45–87)	–
RA diagnosis and treatment in Sweden	31 (100)	121 (99) ^b
RF positivity	26 (84)	84 (69)
Missing	2 (7)	7 (6)
Anti-CCP positivity	7 (22)	24 (19)
Missing	20 (65)	77 (63)
Treatment during the course of RA ^c		
DMARD	30 (97)	117 (96)
DMARD during the year before TB	26 (84)	97 (80)
CS	23 (74)	63 (54)
CS during the year before TB	11 (50)	52 (44)
CS missing	0 (0)	5 (4)
Comorbidities known at diagnosis of TB ^d		
Cancer	4 (14)	11 (9)
Diabetes	3 (10)	15 (12)
COPD or asthma	9 (29)	11 (9)
Comorbidities missing	0 (0)	5 (4)
Ever smoker	16 (52)	47 (38)
Missing	6 (20)	42 (34)

Values are expressed as n (%) unless stated otherwise. ^a Missing data from 5 patients. ^b One patient diagnosed in the United States. ^c Treatment for ≥ 4 consecutive weeks from RA diagnosis until TB diagnosis. ^d For controls at diagnosis of the corresponding case. CCP: cyclic citrullinated peptide; COPD: chronic obstructive pulmonary disease; CS: corticosteroid; DMARD: disease-modifying antirheumatic drug; RA: rheumatoid arthritis; RF: rheumatoid factor; TB: tuberculosis.

Table 2. Characteristics of TB patients with biologic-naïve RA.

	TB Cases, n = 31
Characteristics of TB	
Duration of symptoms before TB diagnosis, weeks, mean \pm SD (min–max)	15 \pm 9 (2–41) ^a
Pulmonary TB ^b	26 (84)
Extrapulmonary TB ^b	8 (26)
Miliary TB	2 (6)
Diagnosis of TB	
Smear-positive TB ^c	7 (23)
Bacteriologically confirmed TB by culture ^d	20 (65)
Clinically diagnosed TB	6 (19)
Other ^e	5 (16)
Treatment of TB ^f	
Drug resistance	0 (0)
Treatment completed	27 (94)
Died of TB	1 (3)

Values are expressed as n (%) unless stated otherwise. ^a Missing data from 5 patients. ^b Five patients with pulmonary and extrapulmonary localization. ^c All smear-positive tests were confirmed by culture. ^d Includes 7 smear-positive patients. ^e One diagnosed by positive PCR and 4 diagnosed by positive pathological-anatomical diagnosis. ^f Standard treatment in most cases 6 months with isoniazid, rifampicin, pyrazinamide, and ethambutol (at initiation). RA: rheumatoid arthritis; TB: tuberculosis.

RA-associated risk factors for TB. MTX was the most common DMARD, used at any time in 68% of the TB cases and 74% of the controls. Treatment with MTX was not associated with an

increased TB risk (aOR 0.8, 95% CI 0.3–2.0), and there were no significant differences between cases and controls regarding maximum dose, treatment time, or cumulative dose of MTX in the last year before TB onset (Table 3 and Table 4). In contrast, although used in only a minority of the patients, treatment during the last year before TB onset with LEF was associated with increased TB risk (aOR 8.6, 95% CI 1.5–50.5), as well as treatment with AZA (aOR 17, 95% CI 1.6–161). Analyses comparing other DMARDs did not reveal any significant differences between cases and controls (Table 3).

Treatment with oral corticosteroids (PSL) during the course of RA was associated with an aOR for TB of 2.5 (95% CI 1.0–6.0; Table 3). No significant differences were identified between PSL-treated cases and controls in terms of maximum dose ever of PSL, treatment duration before TB, treatment during the last year before TB, or cumulative dose of PSL during the last year before diagnosis of TB. Likewise, there were no associations with TB and PSL treatment ≥ 15 mg with a duration of ≥ 1 month ever or during the last 12 months (Table 5), and 6 months, before diagnosis of TB (data not shown).

An increase in RA disease activity was reported in 20% of cases compared to 7.3% of controls ($P = 0.07$) during the 6 months preceding the TB diagnosis. A majority of these cases also continued to have active RA disease during TB treatment. Obstructive pulmonary disease was linked to an increased TB risk (aOR 3.9, 95% CI 1.5–10.7; Table 3). No other evaluated comorbidity (diabetes, dialysis-dependent chronic kidney disease, HIV infection, primary immunodeficiency, or

Table 3. RA-related risk factors for tuberculosis among biological-naïve patients with RA.

Exposure	TB Cases, n = 31	Controls, n = 122	aOR (95% CI)*
Treatment**			
Antimalarials	6/30 (20) ^a	40/117 (34) ^b	0.5 (0.2–1.4)
AZA	5/30 (17) ^a	6/117 (5) ^b	3.8 (1.1–13.8)
AZA the last year before TB	4/30 (13) ^a	1/117 (0.8) ^b	17 (1.8–161)
LEF	5/30 (17) ^a	4/118 (3) ^c	6.0 (1.5–24.7)
LEF the last year before TB	4/30 (13) ^a	2/118 (2) ^c	8.6 (1.5–50.5)
MTX	21/31 (68)	88/121 (74) ^a	0.8 (0.3–2.0)
PSL	23/31 (74)	63/117 (54) ^b	2.5 (1.0–6.0)***
Sulfasalazine	15/31 (50) ^a	50/116 (43) ^d	1.2 (0.6–2.8)
No. of DMARDs, mean ± SD (min–max)	1.9 ± 1.1 (0–5)	1.9 ± 1.2 (0–6)	1.0 (1.0–1.1)
COPD or asthma	9/31 (29)	11/120 (9) ^e	3.9 (1.5–10.7)
Smoking, n/N	16/31 ^d	47/122 ^f	0.8 (0.3–2.1)

Values are expressed as n/N (%) unless stated otherwise. ^a Missing data from 1 patient. ^b Missing data from 5 patients. ^c Missing data from 3 patients. ^d Missing data from 6 patients. ^e Missing data from 2 patients. ^f Missing data from 42 patients. * Estimated from logistic regression models adjusted for sex and age. ** Treatment for ≥ 4 consecutive weeks from RA diagnosis until TB diagnosis. *** Prednisolone additionally adjusted for concomitant DMARD use. aOR: adjusted OR; AZA: azathioprine; COPD: chronic obstructive pulmonary disease; DMARD: disease-modifying antirheumatic drug; LEF: leflunomide; MTX: methotrexate; PSL: prednisolone; TB: tuberculosis.

Table 4. Relative risk for tuberculosis among MTX-treated biologic-naïve patients with RA.

Treatment With MTX*	TB Cases, n = 21	Controls, n = 88	aOR (95% CI)**
Maximum dose, mg	15.7 ± 5.4 (7.5–25) ^a	14.1 ± 4.9 (7.5–25) ^b	0.9 (0.8–1.0)
Duration of treatment, weeks	200 ± 223 (19–813) ^b	241 ± 1946 (6–812) ^c	1.0 (1.0–1.0)
Cumulative dose the last year before TB diagnosis, mg	575 ± 356 (97.5–1040) ^d	622 ± 283 (120–1300) ^e	1.0 (1.0–1.0)
Weekly dose 1 year before TB diagnosis, mg, mean [n]	14.5 [10]	13.8 [59] ^d	0.97 (0.83–1.12)

Values are expressed as mean ± SD (min–max) unless stated otherwise. ^a Missing data from 4 patients. ^b Missing data from 3 patients. ^c Missing data from 12 patients. ^d Missing data from 5 patients. ^e Missing data from 9 patients. * Treatment for ≥ 4 consecutive weeks from RA diagnosis until TB diagnosis. ** Estimated from logistic regression models adjusted for sex and age. aOR: adjusted OR; MTX: methotrexate; RA: rheumatoid arthritis; TB: tuberculosis.

Table 5. Relative risk for TB among PSL-treated biologic-naïve patients with RA.

Treatment With PSL*	TB Cases, n = 23	Controls, n = 63	aOR** (95% CI)
Maximum dose, mg	14.1 ± 10.8 (5–50) ^a	11 ± 9.1 (2.5–40) ^a	1.04 (0.98–1.10)
Duration of treatment, weeks	306 ± 361 (7–1426) ^a	297 ± 324 (4–1265) ^b	1.0 (1.0–1.0)
Cumulative dose the last year before TB diagnosis, mg, mean ± SD (min–max) [n]	2153 ± 888 (280–3600) ^a [14]	1769 ± 784 (225–3650) ^c [42]	1.00 (1.00–1.00)
≥ 15 mg/d PSL ≥ 1 month ever before TB diagnosis, n (%)	3 (10)	7 (5.7)	0.9 (0.1–8.3)
≥ 15 mg/d PSL ≥ 1 month the last year before TB diagnosis, n (%) ^a	2 (6.5)	1 (0.8)	NA
Mean daily dose 1 year before TB diagnosis, mg [n]	5.78 [14] ^d	5.66 [40] ^d	1.0 (0.8–1.2)
Mean daily dose at TB diagnosis, mg [n]	8.23 [16] ^d	5.12 [41]	1.2 (1.05–1.5)

Values are expressed as mean ± SD (min–max) unless stated otherwise. ^a Missing data from 3 patients. ^b Missing data from 9 patients. ^c Missing data from 14 patients. ^d Missing data from 2 patients. * Treatment for ≥ 4 consecutive weeks from RA diagnosis until TB diagnosis. ** Estimated from logistic regression models adjusted for sex, age, and DMARD medication. aOR: adjusted OR; DMARD: disease-modifying antirheumatic drug; RA: rheumatoid arthritis; PSL: prednisolone; TB: tuberculosis.

malignancies) was associated with increased TB risk, and no patient suffered from a complicating comorbidity leading to discontinuation of RA treatment during the year before TB diagnosis.

There was no association between smoking and risk of TB (aOR 0.8, 95% CI 0.3–2.1) but data were missing from 6 cases and 42 controls (Table 3).

Epidemiological risk factors for TB. Increased risk for TB was associated with a family history of TB (aOR 10.6, 95% CI 2.9–39.3), a history of previous TB (aOR 9.2, 95% CI 2.1–39.4), and being born outside Nordic countries (aOR 5.7, 95% CI 1.2–27.1). Almost 90% of the cases (and the age-matched controls) were born before 1950, which is a known risk factor for TB in general in Sweden. Some epidemiological data were missing in the medical records, in particular for the controls (Table 6).

Taking both RA-associated (treatment with PSL and/or LEF) and epidemiological risk factors (born before 1950, former TB infection, known exposure of TB in the family, occupational history, and a history of living abroad in high-endemic areas) into account, the cases had at TB diagnosis a median of 3 (1–6) noted risk factors for TB compared to a median of 2 (0–4) in controls. The most common combination in cases was being born before 1950, having any suspected exposure of TB, and having been treated with oral corticosteroids for ≥ 4 consecutive weeks during the course of RA.

DISCUSSION

In this population-based case-control study of TB occurring in biologic-naïve patients with RA, we found no association with commonly used csDMARDs and increased TB risk. Importantly, MTX, the most frequently used csDMARD in this study and in contemporary patients with RA in general, was not associated with an increased TB risk, regardless of duration of treatment and dose. Ever use of PSL was associated with a borderline increased TB risk, but we could not confirm previous findings of an association with the use of moderate-to-high doses of PSL (≥ 15 mg).

Table 6. Epidemiological risk factors for TB in TB cases with biologic-naïve RA and matched RA controls.

Risk Factor	Cases, n = 31	Controls, n = 122	aOR* (95% CI)
Born before 1950	27 (87.1)	106 (86.8)	–
History of TB	6 (19.3)	3 (2.4) ^a	9.2 (2.1–39.4)
Family history of TB	8 (25.8)	4 (3.3) ^b	10.6 (2.9–39.3)
Work-related risk	3 (9.6) ^c	10 (8.2) ^d	0.9 (0.2–3.8)
Born in high-incidence country ^e	1 (3.2)	0 (0)	NA
Born outside Nordic countries ^f	4 (12.9)	3 (2.4)	5.7 (1.2–27.1)
Lived/worked > 3 months in high-incidence country ^e	1 (3.2)	0 (0)	NA

^a Missing data from 119 patients. ^b Missing data from 118 patients. ^c Missing data from 9 patients. ^d Missing data from 29 patients. ^e >100 cases/100,000.

^f Includes high-incidence countries. * Estimated from logistic regression models adjusted for sex and age. Values are expressed as n (%) unless stated otherwise. aOR: adjusted OR; NA: not applicable; RA: rheumatoid arthritis; TB: tuberculosis.

So far, results in studies on MTX and TB risk have been contradictory. Brode, *et al*¹¹ reported no increased risk for TB, whereas Brassard, *et al*⁹ found an increased risk for TB (adjusted rate ratio 3.4, 95% CI 1.8–6.4) linked to MTX treatment. Data on treatment duration and dose were, however, missing in both studies, and exposure was based on register information only. More recent studies focus mainly on MTX in combination with bDMARDs, which makes interpretation of the role of MTX difficult, although TB risk appears to be further increased when TNFi is used in combination with MTX or AZA as compared with bDMARD monotherapy regimens.²⁴

Treatment with PSL during the course of RA was associated with a borderline increased risk of TB. We did not find any association between TB risk and maximum dose of PSL, the cumulative dose of PSL the year preceding TB diagnosis, nor with the use of PSL ≥ 15 mg ≥ 1 month, as indicated previously.^{25,26} Thus, our results suggest an increased risk of TB in corticosteroid-treated patients, but a clear cutoff between a safe and an unsafe dose could not be set. However, some other studies have reported a dose-dependent risk of TB with corticosteroids. In a study from Taiwan, the cumulative dose of corticosteroids was associated with an increased risk for TB.²⁰ Similarly, an increased risk of TB associated with prescription of PSL, both for ≥ 7.5 mg/d vs < 7.5 mg, and ≥ 15 mg/d vs < 15 mg, was reported in a study from the UK.¹⁷

Based on few exposed cases, there were signals of increased TB risks in patients treated with LEF or AZA. Treatment with LEF has also been linked to an increased risk of TB in some previous studies,^{9,11,27,28} but the reason for this risk increase has not been specifically studied. One mode of action of LEF is an ability to suppress TNF- α ,^{29,30} and it could be speculated that this effect contributes to its association with TB, in line with the well-described biological effect of TNF on maintenance of granulomas containing *Mycobacterium tuberculosis* in patients with LTBI.^{31,32}

We have not identified other reports about TB risk in patients with RA treated with AZA, a sparsely used drug nowadays in the treatment of RA. In a study from 1975, AZA was reported to cause a depression of specific antimycobacterial resistance and also to affect *in vitro* cell-mediated immunological mechanisms of importance for infectious defense,³³ but it is unclear if this could explain an association with TB and AZA in patients with RA. It should be noted that in our study (as in the previous studies), only a few of the patients had been exposed to LEF or AZA and that these TB cases constitute a small minority of all TB that occurs in biologic-naïve patients with RA. We also cannot exclude that patients with multicomorbidities were treated with these drugs instead of a bDMARD and that the increased risk of TB reflects other patient conditions rather than the exposure of drugs.

Obstructive pulmonary diseases, present in 9 (29%) of the cases, was associated with a 3.9-fold increased risk of TB. An association between obstructive pulmonary disease and other pulmonary diseases (i.e., asthma, emphysema, and bronchitis) and TB has been described previously.^{17,34} In a Swedish population-based study from 2010, a diagnosis of chronic obstructive

pulmonary disease (COPD) increased the risk for TB 3-fold compared to the general population.³⁴ Several mechanisms could contribute to this association. Immunological mechanisms such as dysregulation of phagocytes³⁵ together with inhaled corticosteroid treatment³⁶ may increase the risk for mycobacterial infection. Malnutrition, a common problem in COPD,³⁷ also increases the risk for TB.^{38,39} COPD and TB also share other risk factors such as tobacco smoking^{17,40} and diabetes.³⁵ Additionally, smoking (past or present) is common in patients with RA,⁴¹ and has been identified as an independent risk factor for TB in these patients.¹⁷ We did not find an increased TB risk associated with smoking, but due to missing data on smoking habits, especially among controls, this finding must be interpreted with caution.

We also noted an increase in RA activity before and during TB treatment among cases compared to controls. A higher RA disease activity during TB treatment may reflect a reduced anti-rheumatic treatment during this period, but an effect of the TB infection cannot be excluded, as the RA disease activity increased before TB diagnosis and initiation of TB treatment in many of the cases. Mycobacterial disease affects the immune system in different ways. The upregulation of toll-like receptors can lead to an increased production of proinflammatory cytokines such as TNF and interleukin 6 and 12,⁴² which might induce more RA symptoms.

The majority of patients (84%) presented with pulmonary TB, and the main extrapulmonary site was lymph node. This is consistent with findings of TB in an elderly Swedish population and with 1 RA study from Japan,⁴³ but is different from the increase in extrapulmonary TB reported after TNFi exposure.¹ The TB prognosis was also comparable to TB prognosis in the general population,⁴⁴ with 94% treatment success. Delay from symptom onset to TB diagnosis was close to 4 months. A long delay increases the risk of severe disease⁴⁵ and greater transmission of infection.⁴⁶

Epidemiological risk factors were reported in the medical records typically at TB diagnosis for the cases, but sparsely in the controls (without TB). These data are generally not asked for at the clinic until the patient is considered for bDMARD treatment or is diagnosed with TB. Apart from being born before 1950, half of the cases had reported epidemiological risk factors suggestive of previous TB exposure. Only one of the cases had been screened for LTBI with a TST before onset of TB symptoms. To be born in Sweden before 1950 is a known general risk factor for TB, reflecting the high prevalence of TB and a greater likelihood for TB exposure in Sweden during the first half of the last century.⁴⁷

It is now generally accepted to screen for LTBI in rheumatic patients before the start of bDMARD or targeted synthetic DMARD treatment,⁴⁸ using a combination of data on epidemiological risk factors, chest radiograph, and immune-reactive tests. There is, however, growing support to also consider LTBI screening in biologic-naïve patients.¹⁷ The effect of screening is also dependent on the incidence of TB. Although the overall incidence of TB is low in Sweden, the biologic-naïve patients with RA have a 4-fold increased risk of TB compared to the general population,⁴ and represent a large number of the TB

cases in the RA population. The majority of these TB cases are caused by reactivation of LTBI and thus potentially preventable by TB treatment if identified. It seems that several risk factors contribute to the increased TB risk in biologic-naïve patients with RA and that prediction of TB based on RA-associated factors may be difficult in the individual patient. An important advantage of early screening for TB is to avoid influence of immune-modulating treatment on the test results. A number of studies have reported that immune-modulating drugs such as corticosteroids^{49,50} and MTX⁴⁹ may cause both falsely negative results and indeterminate responses of TST and interferon- γ release assays used to screen for LTBI.

Strengths of our study include the population-based setting using high-quality, nationwide registers for identification of cases and controls, combined with data from medical records for detailed clinical information. TB cases were identified from a large dataset, which enabled the study of this relatively rare outcome. Both RA and TB diagnoses were validated. Limitations include missing data in the medical records, which was more pronounced for controls than cases regarding epidemiological risk factors for TB. Data on socioeconomic risk factors were overall very limited and therefore not included in the analyses. The number of patients with some of the analyzed exposures such as treatment with LEF or AZA was low, making these results less robust and increasing the risk for bias and the chance to affect the results. Further, these patients might represent a cohort of RA patients with multimorbidities with increased risk of TB. With few exposed individuals and risk of confounding factors, there is inherent uncertainty in the quantity and quality of these results and therefore should be cautiously interpreted.

In conclusion, several RA-associated risk factors such as treatment with LEF, AZA, or PSL, and concomitant obstructive lung disease may contribute to the increased TB risk in biologic-naïve patients with RA. We could not find any association with the use of moderate-to-high doses of PSL (≥ 15 mg) or treatment with MTX and an increased risk of TB. TB risk seems difficult to predict with precision in the individual biologic-naïve patient based on RA-associated risk factors. To further decrease the TB risk in patients with RA, we therefore suggest considering TB screening in biologic-naïve patients.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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