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 biologics-naïve rheumatoid arthritis (RA) patients.

Methods Population-based case-control study using the Swedish Rheumatology Quality Register, the National Patient Register and the Tuberculosis Register to identify RA cases with active TB and matched RA controls without TB 2001-2014. Clinical data were obtained from medical records. TB risk was estimated as adjusted (adj) odds ratios (OR) with 95% confidence intervals (CI) using univariate and multivariable logistic regression analyses.

Results After validation of diagnoses, the study included 31 RA cases with TB, and 122 matched RA controls. All except three cases had reactivation of latent TB. Pulmonary TB dominated (84%). Ever use of methotrexate was not associated with increased TB risk (adj OR 0.8; 95% CI 0.3-2.0), whereas ever treatment with leflunomide (adj OR 6.0; 95% CI 1.5-24.6), azathioprine (adj OR 3.8; 95% CI 1.1-13.8) and prednisolone (adj OR 2.4 (95% CI 1.0-5.9) was. There were no significant differences of maximum dose of prednisolone, treatment duration with prednisolone before TB, or cumulative dose of prednisolone the year before TB diagnosis between cases and controls. Obstructive pulmonary disease was associated with an increased TB risk (adj OR 3.9; 95% CI 1.4-10.7).

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

INTRODUCTION

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 treatment start with TNFi and other biologic disease modifying anti-rheumatic drugs (bDMARDs) have been followed by a decrease of active TB among bDMARD-treated RA patients (2, 3). However, the TB risk in biologics-naïve RA patients appears to remain several-fold increased compared to the general population. In a recent study, we showed that the rate of TB in bDMARD-treated RA patients decreased following the initiation of pre-treatment TB screening in Sweden, but no similar decline in risk was observed among the biologics-naïve RA patients (4). The risk in this group remained four times higher than the general population in Sweden. Notably, most TB cases in contemporary RA patients occur in biologics-naïve patients (5, 6). It is therefore reasonable that efforts to further decrease the TB risk in RA also should also incorporate the group of biologics-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, ref 7-20).

We aimed to assess risk factors for active TB infection in biologics-naïve RA patients and to describe the clinical characteristics and outcomes of the clinical TB manifestations. We therefore performed a matched population-based case-control 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 1969-2014 and outpatient, non-primary care 2001-2014, and from the Swedish Rheumatology Quality Register (SRQ) 1997-2014. The registration of inpatient care in the NPR is over 99% complete since 1987 and the outpatient specialist non-surgical care component is over 80 % complete (21, 22). Patients were included if they were ≥18 years old at RA diagnosis and had at least two visits with an International Classification of Diseases (ICD) code for RA (ICD10 M05, M06.0, M06.2, M06.8, M06.9, M12.3; ICD9 714A, 714B, 714C, 714W, 719D; ICD8 – 712.10, 712.20, 712.38) in the NPR and/or SRQ. The patients were required to have at least one specialist visit to a rheumatology or internal medicine department in the NPR and at least one visit in outpatient care. With this definition of RA, it has been shown that >90% of the identified patients fulfill 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 RA patients 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 RA patients.

Cases with TB

Cases were RA patients 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 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, verified or suspected as 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, four RA controls without TB were identified from the RA population who were living in Sweden and not exposed to bDMARDs before 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 years), year of first RA diagnosis in the NPR, and region of residence at the time of TB diagnosis of their corresponding case.

Exposures

Clinical data of cases and controls were collected from medical records, and included information about the RA disease, smoking habits and comorbidities known at any time before TB diagnosis for cases, and for controls before TB diagnosis of the matched case. 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.

Exposure to corticosteroids and any conventional synthetic (cs)DMARD, including methotrexate (MTX), sulfasalazine, hydroxychloroquine/chloroquine, leflunomide, cyclosporine, azathioprine, cyclophosphamide, penicillamine, myocrisine and auranofin for ≥ 4 consecutive weeks ever from RA diagnosis until TB diagnosis and on specific time-points (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, information on cumulative dose the year before TB diagnosis, and the exposure to doses ≥15 mg of prednisolone ≥1 month ever during the course of RA, and 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 of 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 tests 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-tests and Fisher's exact test 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 (adj) odds ratios (OR) with 95% confidence intervals (CI). Analyses of prednisolone treatment were additionally adjusted for DMARD use. We used a complete case analysis approach, i.e., for each exposure patients with missing values were excluded from the respective analysis.

Data analyses were conducted using the Statistical Package for Social Sciences (SPSS) for Windows version 25.

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

RESULTS

We initially identified 42 biologics-naïve RA cases with TB and 164 matched biologics-naïve RA controls without TB from the register data during the study period 2001-2014. After exclusions, mainly due to missing or incomplete medical records or that patients did not fulfill RA criteria (Supplementary Figure 1), we finally included 31 cases with verified RA and active TB and 122 matched RA controls without TB in the study. 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 70.9 years, with TB diagnosed on average 15.8 (0-58) years after the RA diagnosis. Most patients reported typical TB symptoms as weight loss, cough, fever and night sweats, followed by a TB diagnosis on average 15 weeks after onset of symptoms. Pulmonary TB dominated (84%). There were no drug-resistant strains, and most patients had unique strains indicating reactivation of LTBI. A possible acquisition of new infection abroad (USA, Thailand and the Baltic countries) was reported in the Tuberculosis Register in three cases, 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, 94% of the patients fulfilled the treatment course, whereas one patient died of miliary TB and three 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 two of the patients, one case (who later developed active TB) and one control, both with identified epidemiological risk factors for TB exposure. Both had negative TST results and were not given preventive TB treatment.

RA-associated risk factors for TB

Methotrexate was the most common DMARD, ever used in 68 % of the cases and 74% of the controls. Ever treatment with MTX was not associated with an increased TB risk (adj OR 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 methotrexate the last year before TB onset (Tables 3 and 4). In contrast, although used in only a minority of the patients, treatment with leflunomide during the last year before TB was associated with an adj OR for TB of 8.4 (95% CI 1.5-50.5), same with azathioprine with an OR of 17 (95% CI 1.6-144). Analyses comparing other DMARDs did not reveal any significant differences between cases and controls (Table 3).

Treatment with oral corticosteroids (prednisolone) during the course of RA was associated with an adj OR for TB of 2.4 (95% CI 1.0-5.9) (Table 3). No significant differences were identified between prednisolone-treated cases and controls in terms of maximum dose ever of prednisolone, treatment duration before TB, treatment during the last year before TB, or cumulative dose of prednisolone during the last year before diagnosis of TB. Likewise, there

were no associations with TB and prednisolone treatment ≥15 mg ≥1 month ever or during the last 12 months, and 6 months, respectively, before diagnosis of TB (Table 5).

An increase in RA disease activity was reported in 20% of cases, compared to 7.3% of controls (p=0.07) during the six months preceding the TB diagnosis. A majority of these cases continued to have active RA disease also during TB treatment. Obstructive pulmonary disease was linked to an increased TB risk (adj OR 3.9; 95% CI 1.5-10.7). No other evaluated comorbidity (diabetes, dialysis-dependent chronic kidney disease, HIV infection, primary immunodeficiency or 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 with smoking and risk of TB (adj OR 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 (adj OR 10.6; 95% CI 2.9-39.3), a history of previous TB (adj OR 9.2; 95% CI 2.1-39.4) and for patients born outside Nordic countries (adj OR 5.7 95% CI 1.2-27.1). Almost 90% of the cases (and the age-matched controls) were born before 1950, 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 prednisolone and/ or leflunomide) and epidemiological risk factors (born before 1950, former TB infection or 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 to be born before 1950, have any suspected exposure of TB and to have 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 biologics-naïve RA patients 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 RA patients in general, was not associated with an increased TB risk, irrespective of duration of treatment and dose. Ever use of prednisolone 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 prednisolone (≥15 mg).

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 (adj RR 3.4, 95% CI 1.6-6.4) 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 concern mainly 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 azathioprine as compared with bDMARD monotherapy regimens (31).

Treatment with prednisolone 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 prednisolone, the cumulative dose of prednisolone the year preceding TB diagnosis, nor with the use of prednisolone ≥ 15 mg ≥1 month, as indicated previously (32,33). Thus, our results

suggest an increased risk of TB in corticosteroid treated patients, but a clear cut-off 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 prednisone both for ≥7.5 mg/day vs. <7.5 mg and ≥15 mg/day vs. < 15 mg was reported in a study from UK (17).

Based on few exposed cases there were signals of increased TB risks in patients treated with leflunomide or azathioprine. Treatment with leflunomide has been linked to an increased risk of TB also in some previous studies (9, 11, 24, 25), but the reason for this risk increase has not been specifically studied. One mode of action of leflunomide is an ability to suppress tumour necrosis factor (TNF) alpha (26, 27), and it could be speculated that this effect could contribute 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 (28, 29).

We have not identified other reports about TB risk in RA patients treated with azathioprine, a sparsely used drug nowadays in the treatment of RA. In a study from 1973, azathioprine was reported to cause a depression of specific anti-mycobacterial resistance and also affecting in-vitro cell-mediated immunological mechanisms of importance for infectious defense (30), but it is unclear if this could explain an association with TB and azathioprine in the RA patients. It should be noted that in our study (as in the previous studies) only a few of the cases had been exposed to leflunomide or azathioprine and that these TB cases constitute a small minority of all TB that occurs in biologics-naïve RA patients. We also cannot exclude that patients with multi-comorbidities 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 (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 as dysregulation of phagocytes (35) together with inhaled corticosteroid treatment (36) may increase the risk for mycobacterial infection. Malnutrition, a common problem in COPD (37), also increases the risk for TB (38, 39). Chronic obstructive pulmonary disease and TB also share other risk factors such as tobacco smoking (17, 40) and diabetes (35). Additionally, smoking (past or present) is common in RA patients (41), and has been identified as an independent risk factor for TB in RA 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 impact 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 pro-inflammatory cytokines such as TNF and interleukin 6 and 12 (42) which might induce more symptoms of the RA disease.

The majority of patients (84%) presented with pulmonary TB, and the main extra-pulmonary site was lymph node. This is consistent with TB in an elderly Swedish population and with one RA study from Japan (43), but different from the increase in extra-pulmonary 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 disease (45) 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 which reflects that TB was highly prevalent and the likelihood for TB exposure greater in Sweden during the first half of the last century than later (47).

It is now generally accepted to screen for LTBI in rheumatic patients before start of bDMARD or targeted synthetic DMARD treatment (48), using a combination of data on epidemiological risk factors, chest X-ray and immune-reactive tests. There is, however, now growing support to consider LTBI screening also in biologics-naïve patients (17). The effect of screening is dependent also on the incidence of TB. Although the overall incidence of TB is low in Sweden, the biologics-naïve RA patients have a four-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 different risk factors contribute to the increased TB risk in biologics-naïve RA patients and that prediction of TB disease based on RA-associated factors may be difficult in the individual patient. An important advantage with early screening for TB is also 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 MTX (49) may cause both falsely negative results and indeterminate responses of TST and Interferon-Gamma Release Assays used to screen for LTBI.

Strengths of the 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 data set, 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 about 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 leflunomide or azathioprine was low which make these results less robust and increase the risk for biases and chance to affect the results. Further, these patients might represent a cohort of RA patients with multi-comorbidities 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, which therefore should be cautiously interpreted.

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

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Table 1. Characteristics of tuberculosis (TB) cases with biologics-naïve rheumatoid arthritis (RA) and matched RA controls.

Characteristics	**TB Cases n=31**	**Controls n= 122**
Females, n (%)	15 (48%)	70 (57%)
Age at RA diagnosis, mean ± SD (min-max), years	57.4±18.1 (17-82)	55.8 ±15.8 (13-81)[1]
Age at TB diagnosis, mean ± SD (min-max), years	73.2±10.2 (45-87)	-
RA diagnosis and RA treatment in Sweden, n (%)	31 (100%)	121 (99%)[2]
Rheumatoid factor positivity, n (%)	26 (84%)	84 (69%)
Missing, n (%)	2 (7%)	7 (6%)
Anti-CCP positivity, n (%)	7 (22%)	24 (19%)
Missing, n (%)	20 (65%)	77 (63%)
Treatment during the course of RA[3]		
DMARD, n (%)	30 (97%)	117 (96%)
DMARD during the year before TB, n (%)	26 (84%)	97 (80%)
Corticosteroids, n (%)	23 (74%)	63 (54%)
Corticosteroids during the year before TB, n (%)	11 (50%)	52 (44%)
Corticosteroids missing, n (%)	0 (0%)	5 (4%)
Comorbidities known at diagnosis of TB[4]		
Cancer, n (%)	4 (14%)	11 (9%)
Diabetes, n (%)	3 (10%)	15 (12%)
COPD or asthma, n (%)	9 (29%)	11 (9%)
Comorbidities missing, n (%)	0 (0%)	5 (4%)
Ever smoker, n (%)	16 (52%)	47 (38%)
Missing, n (%)	6 (20%)	42 (34%)

[1] Missing data from 5 patients, [2] 1 patient diagnosed in the US, [3] Treatment for ≥ 4 consecutive weeks from RA diagnosis until TB diagnosis, [4]For controls at diagnosis of the corresponding case

RA= rheumatoid arthritis; SD=standard deviation; min=minimum; max=maximum; TB= tuberculosis; CCP = cyclic citrullinated peptide; DMARD=disease modifying anti-rheumatic drug; COPD=chronic obstructive pulmonary disease

Table 2. Characteristics of tuberculosis (TB) cases with biologics-naïve rheumatoid arthritis

Characteristics of TB	**TB Cases** **n= 31**
Duration of symptoms before TB diagnosis, mean ± SD (min-max), weeks	15 ±9 (2-41)[1]
Pulmonary TB, n (%)[2]	26 (84)
Extra-pulmonary TB, n (%)[2]	8 (26)
Miliary TB, n (%)	2 (6)
Diagnosis of TB	
Smear positive TB, n (%)[3]	7 (23)
Bacteriologically confirmed TB by culture, n (%)[4]	20 (65)
Clinically diagnosed TB, n (%)	6 (19)
Other[5]	5 (16)
Treatment of TB[6]	
Drug resistance, n (%)	0 (0)
Treatment completed n (%)	27 (94)
Died of TB, n (%)	1 (3)

[1]Missing data from 5 patients, [2]5 patients with pulmonary and extra pulmonary localization, [3]All smear positive were confirmed by culture, [4]Includes seven smear positive patients, [5]One diagnosed by positive polymerase chain reaction (PCR) and four diagnosed by positive pathological-anatomical diagnosis (PAD), [6] Standard treatment in most cases 6 months with isoniazid, rifampicin, pyrazinamide and etambutol (at initiation)
TB= tuberculosis; SD=standard deviation ; min=minimum; max=maximum

Table 3. Rheumatoid Arthritis-related risk factors for tuberculosis among biological-naïve rheumatoid arthritis patients

Exposure	**TB Cases n=31**	**Controls n= 122**	**Adj. OR (95% CI)***
Treatment**			
Antimalarials, n (%)	6/30 (20)[1]	40/117 (34)[2]	0.5 (0.2-1.4)
Azathioprine, n (%)	5/30 (17)[1]	6/117 (5)[2]	3.8 (1.1-13.8)
Azathioprine the last year before TB, n (%)	4/30 (13)[1]	1/117 (0.8)[2]	17 (1.8-161)
Leflunomide, n (%)	5/30 (17)[1]	4/118 (3)[3]	6.0 (1.5-24.7)
Leflunomide the last year before TB, n (%)	4/30 (13)[1]	2/118 (2)[3]	8.6 (1.5-50.5)
Methotrexate, n (%)	21/31 (68)	88/121 (74)[1]	0.8 (0.3-2.0)
Prednisolone, n (%)	23/31 (74)	63/117 (54)[2]	2.5 (1.0-6.0)***
Sulfasalazine, n (%)	15/31 (50)[1]	50/116 (43)[4]	1.2 (0.6-2.8)
Number 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, n (%)	9/31 (29)	11/120 (9)[5]	3.9 (1.5-10.7)
Smoking	16/31[4]	47/122[6]	0.82 (0.3-2.1)

[1]Missing data from 1 patient, [2]Missing data from 5 patients, [3] Missing data from 3 patients, [4]Missing data from 6 patients, [5]Missing data from 2 patients, [6] 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

OR= odds ratio; CI = confidence interval; Adj= adjusted; SD=standard deviation; min=minimum; max=maximum ;DMARD=disease modifying anti-rheumatic drug; COPD=chronic obstructive pulmonary disease

Table 4. Relative risk for tuberculosis among methotrexate-treated biological-naïve rheumatoid arthritis patients.

Treatment with MTX*	**TB Cases** **n= 21**	**Controls** **n=88**	**Adj.OR** **(95% CI)****
Maximum dose, mean ± SD (min-max), mg	15.7±5.4 (7.5-25)[1]	14.1± 4.9 (7.5-25) [2]	0.9 (0.8-1.0)
Duration of treatment, mean ± SD (min-max), weeks	200±223 (19-813)[2]	241±1946 (6-812) [3]	1.0 (1.0-1.0)
Cumulative dose the last year before TB diagnosis, mean ± SD (min-max), mg	575±356 (97.5-1040)[4]	622±283 (120-1300)[5]	1.0 (1.0-1.0)
Weekly dose 1 year before TB diagnosis, mean, mg	14.5 n=10	13.8[4] n=59	0.97 (0.83-1.12)

[1]Missing data from 4 patients, [2] Missing data from 3 patients, [3] Missing data from 12 patients, [4] Missing data from 5 patients, [5] 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
MTX= methotrexate; OR= odds ratio; CI = confidence interval; Adj= adjusted; SD=standard deviation; min=minimum; max=maximum

Table 5. Relative risk for tuberculosis among prednisolone-treated biological-naïve rheumatoid arthritis patients

Treatment with prednisolone*	**TB Cases** **n= 23**	**Controls** **n=63**	**Adj OR**** **(95% CI)**
Maximum dose, mean ± SD (min-max), mg	14.1±10.8 (5-50)[1]	11±9.1 (2.5-40)[1]	1.04 (0.98-1.10)
Duration of treatment, mean ± SD (min-max), weeks	306±361 (7-1426)[1]	297±324 (4-1265)[2]	1.0 (1.0-1.0)
Cumulative dose the last year before TB diagnosis, mean ± SD (min-max), mg	2153±888 (280-3600)[1] n=14	1769±784 (225-3650)[3] n=42	1.00 (1.00-1.00)
≥15 mg/day Prednisolone ≥1 month ever before TB diagnosis, n (%)	3 (10)	7 (5.7)	0.9 (0.1-8.3)
≥15 mg/day Prednisolone ≥1 month the last year before TB diagnosis, n (%)[1]	2 (6.5)	1 (0.8)	NA
Mean daily dose 1 year before TB diagnosis, mg	5.78[4] n= 14	5.66[4] n= 40	1.0 (0.8-1.2)
Mean daily dose at TB diagnosis, mg	8.234[4] n=16	5.12 n=41	1.2 (1.05-1.5)

[1]Missing data from 3patients, [2]Missing data from 9 patients, [3]Missing data from 14 patients , [4] 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
OR= odds ratio; CI = confidence interval; Adj= adjusted; SD=standard deviation; min=minimum; max=maximum

Table 6. Epidemiological risk factors for tuberculosis (TB) in TB cases with biologics-naïve rheumatoid arthritis (RA) and matched RA controls.

Risk factor	**Cases n= 31**	**Controls n= 122**	**Adj.OR* (95% CI)**
Born before 1950, n (%)	27 (87.1)	106 (86.8)	-
History of TB, n (%)	6 (19.3)	3 (2.4)[1]	9.2 (2.1-39.4)
Family history of TB, n (%)	8 (25.8)	4 (3.3)[2]	10.6 (2.9-39.3)
Work related risk, n (%)	3 (9.6)[3]	10 (8.2)[4]	0.9 (0.2-3.8)
Born in high incidence country[5], n (%)	1 (3.2)	0 (0)	NA
Born outside Nordic countries[6], n (%)	4 (12.9)	3 (2.4)	5.7 (1.2-27.1)
Lived/worked > 3 months in high incidence country[5], n (%)	1 (3.2)	0 (0)	NA