


BMJ Open Tuberculosis among patients treated with TNF inhibitors for rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis in Slovenia: a cohort study

Ziga Rotar ^{1,2}, Petra Svetina,³ Matija Tomsic,^{1,2} Alojzija Hočevar,^{1,2} Sonja Prapotnik^{1,2}

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¹Department of Rheumatology, University Medical Centre Ljubljana, Ljubljana, Slovenia
²Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
³University Clinic of Respiratory and Allergic Diseases Golnik, Golnik, Slovenia

Correspondence to

Dr Ziga Rotar;
ziga.rotar@gmail.com

ABSTRACT

Objectives This study aimed to assess the risk of tuberculosis (TB) in patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) treated with any of the commercially available tumour necrosis factor inhibitors (TNFis) in Slovenia.

Design This is a cohort, registry (biorx.si) cross-linked with the Slovenian National TB Registry.

Setting National, involving all Slovenian rheumatology centres (six secondary and two secondary/tertiary).

Participants 2429 patients with RA, AS or PsA exposed to at least one TNFi participated in the study.

Primary and secondary outcome measures The primary outcome measures were age-adjusted and sex-adjusted TB incidence rates (IRs) and the standardised incidence ratios (SIRs) compared with the general population exploring different TNFi exposure windows. The secondary outcome measures were a detailed characterisation of the national latent tuberculosis infection (LTBI) screening and TB chemoprophylaxis protocol implementation.

Results Among the 2429 patients exposed to at least one TNFi for a total of 10 445 (49% RA, 33% AS and 18% PsA) person-years (PY), 99% completed LTBI screening and 6% required TB chemoprophylaxis. Six RA (three adalimumab, three certolizumab), two PsA (two golimumab) and zero AS patients developed TB. Five out of eight had miliary TB, three out of eight had pulmonary TB and two patients died. The age-standardised and sex-standardised TB IR (95% CI) per 100 000 PYs/SIRs (95% CI) compared with the general Slovenian population for the current TNFi exposure were 52 (0 to 110)/6.7 (0.6 to 80), 47 (0 to 110)/6.1 (0.3 to 105), 45 (0 to 109)/5.8 (0.3 to 112) overall, in RA and PsA, respectively.

Conclusions The TB IR in the Slovenian patients with RA, AS and PsA treated with TNFi was comparable with TB IRs in TB non-endemic countries with less than a tenth of the patients requiring TB chemoprophylaxis.

INTRODUCTION

Tumour necrosis factor inhibitors (TNFis), commonly used to treat rheumatoid arthritis (RA), ankylosing spondylitis (AS) and

Strengths and limitations of the study

- The use of the Slovenian national multicentric registry biorx.si which prospectively collects safety and effectiveness data from up to 95% of rheumatoid arthritis (RA) and ankylosing spondylitis (AS), and up to 80% of psoriatic arthritis (PsA) patients treated with targeted disease-modifying antirheumatic drugs (DMARDs), including all commercially available tumour necrosis factor inhibitors since 2008.
- The availability of detailed results of the mandatory national latent tuberculosis (TB) infection screening and TB chemoprophylaxis.
- The cross-link of biorx.si and the mandatory National Tuberculosis Registry that contains data on all TB cases in Slovenia enabled us to identify and describe all TB cases in detail.
- The biorx.si lacks a comparator cohort of targeted DMARD-naïve patients.
- The low count of cases in our cohort precluded the exploration of potential predictors of TB.

psoriatic arthritis (PsA), have been implicated in increasing the risk of tuberculosis (TB), especially in patients with a pre-existing latent tuberculosis infection (LTBI) in both the real-world setting and the randomised controlled trials (RCTs).^{1 2} This risk can be mitigated, but not avoided, by screening the patients for LTBI and initiating TB chemoprophylaxis when needed before starting a TNFi.³

A recent meta-analysis of RCTs in various diseases has shown that TNFi doubled the chance of TB.² The short duration of the RCTs may lead to an underestimation of TB incidence rates (IRs), hence most data on the subject have come from the real-world observational studies and open label extensions (OLEs) of the RCTs. After the recognition of the importance of LTBI screening and TB

chemoprophylaxis, the TB IRs vary from 15 to 780 per 100 000 person-years (PY), which is 12–35 times higher than in the respective general populations and 2–29 times higher than in the respective targeted disease-modifying antirheumatic drug (tDMARD)-naïve patients.^{4–12} Most of the data come from RA cohorts, mostly on infliximab, adalimumab and etanercept. The data on golimumab and certolizumab are scarce. The TB IR observed in RCTs and OLEs per 100 000 PY of golimumab overall for RA, AS and PsA, and of certolizumab for RA were 230 (95% CI 140 to 350) and 470 (95% CI 340 to 640), respectively^{13 14} (table 1). Other factors that may influence TB IR make the generalisability of the results difficult. It is appreciated that the TB IR is higher in TB endemic areas, but also in tDMARD-naïve RA patients, and when TNFis are combined with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs).¹⁵

Most of the above-mentioned studies were unable to ascertain the details of the implementation of LTBI screening protocols and TB chemoprophylaxis. The LTBI screening protocol and chemoprophylaxis recommendations differ and may impact TB IR. Common screening protocols include the TB exposure history, tuberculin skin test (TST) or interferon- γ release assays (IGRA), and chest X-ray (CXR). In most countries, 9 months of isoniazid treatment is used for chemoprophylaxis.

With the availability of IGRA, for example, Quantiferon TB Gold in a tube (QTB), the much cheaper TST, has fallen out of favour due to difficulties with the availability of Bacillus Calmette–Guérin (BCG), because the patients have to return to the clinic for evaluation, problems with interpretation, especially in BCG-vaccinated populations, and due to its high sensitivity, which may lead to the over-prescription of TB chemoprophylaxis. A recent meta-analysis of studies comparing the performance of TST versus IGRA found the methods comparably effective; however, the included studies were probably underpowered to detect the differences.¹⁶ Another recent report also suggested that the combination TST was more cost-effective than QTB in screening for LTBI, at the expense of a 20% increase in TB chemoprophylaxis.¹⁷

The epidemiological impact of TNFi on the IR of TB in Slovenia has thus far not been studied. Our aim was to determine the IR of TB among patients with RA, AS and PsA treated with all commercially available TNFis (adalimumab, certolizumab, etanercept, golimumab and infliximab) following a uniform LTBI screening protocol relying mainly on TST and CXR, using the national biorx.si registry in comparison with the general population.

METHODS

Setting

The biorx.si, established in February 2008, is a mandatory, national registry used to prospectively collect demographic, effectiveness and safety data of patients treated for RA, AS or PsA with tDMARDs (online supplementary table 1).¹⁸ In Slovenia, tDMARDs are selected jointly by

the patient and their attending rheumatologist and are fully reimbursed by the national health insurance. The patients are classified in accordance with the modified 1987 American College of Rheumatology (ACR) criteria, or European League Against Rheumatism (EULAR)/ACR 2010 criteria for RA, the modified 1984 New York criteria for AS and the Classification for Psoriatic ARthritis (CASPAR) criteria for PsA.^{19–22} The data are entered by the attending rheumatologists, the sole prescribers of tDMARDs, from the two secondary/tertiary and six secondary Slovenian rheumatology centres, every 3 months during the first year of treatment, and every 6 months thereafter if the patient is stable on the current therapy. We estimate an over 95% coverage of patients with RA and AS, and over 80% coverage of patients with PsA, because patients with PsA in whom the tDMARD was prescribed by a dermatologist for psoriasis are not included in the biorx.si.

The National Tuberculosis Registry was established in 1954. The reporting of the cases to the registry is obligatory and thus 100% complete. From 2001, the registry also collects data on persons who were in close contact with patients with TB and patients screened for LTBI. All Slovenian newborns prior to 1 January 2005 were vaccinated with BCG. The National Tuberculosis Registry was the source of the data on the annual, and age-specific and sex-specific IRs of TB in the general population. The national annual TB IR in Slovenia steadily declined from 2007 to 2017 from 10.8 to 5.8 cases per 100 000, respectively.

Study population and TB case identification

We included all patients in the biorx.si exposed to at least one TNFi adalimumab (available since 2004), certolizumab (2010), etanercept (2004), golimumab (2010) or infliximab (2000) up to 30 November 2018. We identified cases of TB by exploring the spontaneous adverse event reports in the biorx.si, and, to avoid missing any cases of TB, we cross-matched our records with the mandatory National Tuberculosis Registry. We considered two windows of exposure to identify cases: in the first analysis, we attributed TB to the *most recent TNFi* used before the diagnosis of TB, regardless of the interval between the last TNFi dose and the diagnosis of TB, and in the second analysis, we only considered patients with TB as cases if TB was diagnosed within a 90-day period after the last administered dose (*current TNFi use*).

Exposure to TNFis

We calculated the exposure time expressed in PY for each individual TNFi. The beginning of exposure was the date of the first administration. The end of exposure was determined as (1) the date of the last dose of the TNFi plus a 90-day washout period in patients who discontinued therapy, even for patients who were switched to another tDMARD during the washout period, or (2) the date of the last recorded visit plus 180 days for patients during the first year of follow-up, or plus 270 days for

Table 1 Review of reported tuberculosis incidences

Study	Observation period	Dataset	tDMARD	Patients	Control	TB IR in the general population	Crude IR (95% CI)	Adj IR (95% CI)
Gomez-Reino ¹	1999–2002	BIOBADASER	IFX	RA, AS, PsA	General population	21	2000: 1893 (NR) 2001: 1113 (NR)	2000: 90.1 (58.8 to 146.0) 2001: 53.0 (34.5 to 89.0)
Carmona ³	2000–2004	BIOBADASER	IFX, (ADA, ETA)	RA, AS, PsA, JIA, other	General population		Prescreening: 522 (369–738) Postscreening: 117 (29–470)	Prescreening: 20.9 (12.0 to 36.8) Postscreening: 4.7 (0.5 to 18.9)
Dixon ⁴	<April 2008	BSRBR	ETA, ADA, IFX	RA	csDMARDs	(14)	TNFi 118 (84–160)* ETA 53 (23–105) ADA 217 (132–335) IFX 123 (64–215)	NR
Tam ⁵	2004–2008	Hong Kong cohort	ETA, ADA, IFX	RA	General population csDMARDs	60–84.5	TNFi 2162 (NR)	34.9 (8.9 to 137) 12.5 (3.5 to 44.7)
Tubach ⁶	2004–2007	RATIO, France	ETA, ADA, IFX	RA (58%), AS, PsA, PsO, IBD, Behçet disease	General population	8.7	TNFi 117 (11–223) ETA 9.3 (0.0 to 9.4) ADA 215.0 (0.0 to 521.7) IFX 187.5 (0.1 to 375)	12.2 (9.7 to 16) 1.8 (0.7 to 4.3) 29.3 (20 to 42) 18.6 (13.4 to 26)
Winthrop ⁷	2000–2008	Kaiser Permanente Northern California (KPNC) insurance dataset	ETA, ADA, IFX	RA	KPNC general population	2.8	TNFi 56 (24–111)	NR
Baddley ⁸	1998–2007	Four US insurance datasets—SABER study	ETA, ADA, IFX, new users	RA, PsO, PsA, AS, IBD	csDMARDs		TNFi 40 (20–70)	4.2 (0.5 to 33.5)
Arkema ⁹	2002–2011	Pooled Swedish registries	ETA, ADA, IFX, GOL, CZP, ANA, ABA, TCZ, RTX	RA	csDMARDs	6.8	All tDMARD: 39.4 (23.7 to 61.5) 2002 to 06: 89.9 (NR) 2007 to 11: 24.2 (NR) By tDMARD: ETA 15.7 (3.2 to 46)* ADA 52.4 (19.2 to 114.1) IFX 67.2 (29 to 132.4) GOL 0 (0 to 1074) CZP 0 (0 to 1218) RTX 29 (0.7 to 161.7)	4.4 (2.3 to 8.5) 7.9 (3.3 to 18.9) 2.4 (0.9 to 6.1) NR

Continued

Table 1 Continued

Study	Observation period	Dataset	tDMARD	Patients	Control	TB IR in the general population	Crude IR (95% CI)	Adj IR (95% CI)
de Vries ¹⁰	2002–2013	Pooled Swedish registries	TNFi pooled	PsA, SpA, AS pooled	tDMARD naive	6.8	TNFi: 22 (8.3 to 59)	7.5 (1.9 to 29)
Yonekura ¹¹	2009–2013	BiobadaBrasil	ETA, ADA, IFX	RA	csDMARDs	37.2	TNFi 286 (NR) ETA 192 ADA 443 IFX 182	NR
Wang ¹²	2006–2016	Hong Kong Hospital Authority database	ETA, ADA, IFX	RA, AS, PsA pooled	General population	60–84.5	TNFi: 784 (NR)	11 (7.8 to 14.1)
Kay ¹³		RCTs+OLEs	GOL	RA, AS, PsA pooled	Placebo	Endemic and non-endemic TB populations	GOL 230 (140–350)	NR
Bykerk ¹⁴		RCTs+OLEs	CZP	RA	Placebo	Endemic and non-endemic TB populations	CZP 470 (340–640)	NR

*Most recent TNFis, switchers included. % calculated from the provided data for KPNC population.

ADA, adalimumab; AS, ankylosing spondylitis; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CZP, certolizumab; ETA, etanercept; GOL, golimumab; IFX, infliximab; IR, incidence rate per 100 000 person-years; NR, not reported; OLE, open label extension of the RCT; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RCT, randomised controlled trial; TB, tuberculosis; tDMARD, targeted disease-modifying antirheumatic drug; TNFi, tumour necrosis factor inhibitor.

the patients who were followed up for more than 1 year. The added exposure time was censored on 30 November 2018. The added time windows reflect the usual biorx.si entry pattern as described above and the washout period used in previous studies.

Latent TB screening protocol

The LTBI screening protocol prior to the initiation of any tDMARDs has been mandatory in Slovenia since 2003. It consists of two steps. In the first step, the rheumatologist considers the TB exposure history, TST and CXR report. If there is a low risk of TB exposure, the TST is <5 mm and the CXR report is within normal limits, the rheumatologist prescribes a tDMARD without further testing. If there is a history of a high risk of TB exposure, a TST ≥ 5 mm or a CXR report suggests changes consistent with the active or past TB, we refer the patient to a pulmonologist for further evaluation. The pulmonologist always orders IGRA, cultures of induced sputum or other samples, and sometimes additional tests such as chest CT. Finally, the pulmonologist approves tDMARD based on the additional testing or prescribes and manages TB chemoprophylaxis prior to tDMARD initiation. A 3-month course of rifampin and isoniazid is the standard chemoprophylaxis regimen used in Slovenia. The details of this screening protocol, except for the history of TB exposure, are recorded in biorx.si.

Statistical analysis

Appropriate descriptive statistics were used to describe the cohort. No imputation of missing data was performed. We estimated the crude, and age-standardised and sex-standardised TB IR among subgroups of patients exposed to TNFi assuming the Poisson distribution. Direct method, with Slovenian population's age and sex distribution, and age-specific and sex-specific IRs of TB between 2007 and 2017 divided into 5-year age brackets as the standard population (sources: Statistical Office of Slovenia, National Tuberculosis Registry) was used to estimate the age-standardised and sex-standardised TB IR and TB SIR. Data preparation and statistical analyses were done in the R V.3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

Patient consent

All patients gave a written informed consent to the use of data from biorx.si for research purposes.

Patient and public involvement

Patients and the public were not involved in study design. Data are collected as a part of routine structured follow-up.

RESULTS

Study population

During period under study, 2636 patients were enrolled into biorx.si. Of these, 2429 (92%) were treated with at least one TNFi and they represented our study population.

There were 1355 (55.8%) patients with RA, 661 (27.2%) with AS and 413 (17.0%) with PsA. The baseline characteristics of the cohort are presented in [table 2](#).

Results of latent TB screening

The first screening step, comprising TST and CXR, was completed and recorded in the biorx.si for 98.9% of patients. In 77% of patients, this was the only step performed, as both TST and CXR were not suggestive of LTBI. The second screening step, that is, referral to a pulmonologist for further evaluation, was done in 23% of patients. An IGRA test was done in 466 (19.1%) and was positive in 143/466 (30.7%) of the tested patients. LTBI chemoprophylaxis prior to the TNFi treatment was prescribed by pneumologists to 146 (6.0%) patients. The details of the screening protocol outcomes are presented in [figure 1](#).

TB cases

The reports of TB cases in patients with RA, AS and PsA in biorx.si matched the cases recorded in the National Tuberculosis Registry. There were no cases of TB recorded in the National Tuberculosis Registry among patients with RA, AS and PsA exposed to TNFi before the biorx.si was established. An additional case of TB after exposure to a TNFi was identified in the National Tuberculosis Registry in a patient with a predominantly peripheral spondylarthritis who did not fulfil the enrolment criteria for biorx.si. There were eight cases of TB (six out of eight female) in patients ever exposed to a TNFi. Six out of eight patients had RA, two out of eight had PsA and none had AS. All cases were confirmed using a culture, and all isolated strains of *Mycobacterium tuberculosis* were susceptible to rifampicin and isoniazid. Five out of eight patients had extrapulmonary TB and five out of eight had miliary TB. Two patients with miliary TB died. The time from the first dose of TNFi to the diagnosis of TB ranged from 74 to 724 days. Four out of eight patients were only screened using TST and CXR, the remaining had had the IGRA done, and were also examined by a pulmonologist. One out of eight patients received a 3-month chemoprophylaxis with rifampin and isoniazid prior to the TNFi therapy. Seven out of eight patients developed TB after being exposed to only one TNFi, and one out of eight after three TNFis (adalimumab, infliximab and finally golimumab). One patient developed TB a year after stopping adalimumab, and another a year and a month after stopping adalimumab, having passed a second LTBI screening that included TST, CXR, IGRA and a pulmonologist, and had been treated with the first two doses of rituximab a month prior to developing TB. Six out of eight patients were exposed to glucocorticoids at the time of developing TB, and seven out of eight were exposed to csDMARDs (four out of seven methotrexate, three out of seven leflunomide). None of incident cases were exposed to tDMARDs with other modes of action prior to developing TB. The details of individual cases are presented in [table 3](#).

Table 2 Cohort characteristics

	All	Rheumatoid arthritis	Ankylosing spondylitis	Psoriatic arthritis
N	2429	1355	661	413
TNFi exposure, person-years (% of all)	10 455	5175 (49)	3431 (33)	1849 (18)
Adalimumab	4140 (39)	1891 (37)	1393 (41)	856 (46)
Certolizumab	771 (7)	686 (13)	41 0 (1)	44 0 (2)
Etanercept	3002 (29)	1779 (34)	794 (23)	429 (23)
Golimumab	1217 (12)	375 0 (7)	555 (16)	287 (16)
Infliximab	1325 (13)	444 0 (9)	648 (19)	233 (13)
Exposure, years, median (IQR)	2.3 (0.8–5.7)	1.8 (0.7–4.8)	2.8 (0.9–6.0)	2.0 (0.9–4.9)
% female	63.0	81.2	36.2	46.2
Age at diagnosis, years, median (IQR)	44.1 (34.6–52.9)	49.0 (39.5–56.1)	36.8 (29.0–46.3)	40.4 (33.2–49.0)
Age at first bDMARD, years, median (IQR)	53.1 (44.0–61.0)	56.7 (48.8–64.2)	45.6 (35.7–54.8)	49.4 (41.9–56.1)
Time to first bDMARD, years, median (IQR)	5.8 (2.2–12.5)	5.8 (2.4–12.3)	3.9 (1.0–11.1)	4.8 (1.6–11.5)
% RF positive		78		
% ACPA positive		76		
% HLA B27 positive			79	23
% ever smokers	29	29	37	28
History of comorbidities				
% diabetes	7	7	8	6
% COPD	2	3	1	0
% asthma	4	5	3	4
% cancer	2	3	1	2
Prior csDMARDs, median (IQR)		3 (2–4)	0 (0–1)	3 (2–3)
% on csDMARD	61	78	14	68
% on methotrexate	52	66	11	53
% on leflunomide	10	14	0	15
% on sulfasalazine	3	2	3	5
% on glucocorticoids	25	39	3	7
Baseline CRP, mg/L, median (IQR)	11 (4.1–25)	11 (5.0–25)	9 (2.1–23)	8 (3.0–17)
Baseline ESR, median (IQR)	31 (17–48)	36 (21–52)	22 (11–39)	24 (12–38)
Baseline DAS28, mean (SD)		6.12 (1.09)		5.11 (1.28)
Baseline SDAI, mean (SD)		37.86 (13.24)		28.27 (12.5)
Baseline CDAI, mean (SD)		35.86 (12.65)		26.83 (12.38)
Baseline BASDAI, mean (SD)			6.8 (1.7)	
Baseline BASFI, mean (SD)			5.6 (2.4)	
Baseline ASDAS-CRP, mean (SD)			3.75 (0.89)	
Baseline PromisHAQ, 0–100, mean (SD)	38.48 (24.2)	43.1 (24.1)	34.0 (21.1)	35.14 (22.1)

BASDAI, Bath Ankylosing Spondylitis Activity Index; CDAI, Clinical Disease Activity Index; COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; DAS28, Disease Activity Score based on a 28-joint count; ESR, erythrocyte sedimentation rate (mm in the first hour); n/a, not applicable; SDAI, Simplified Disease Activity Index.

TB IRs per 100 000 patient-years

The crude TB IRs and age-standardised and sex-standardised TB IRs, and SIRs for the two considered TB case definitions for the entire cohort and stratified by indication and TNFi are presented in [table 4](#). There were no TB cases among patients with AS and no cases among etanercept and infliximab users regardless of indication.

DISCUSSION

In the present study, we report the TB IR in a well-defined prospective cohort of patients with RA, AS and PsA exposed to any of the five commercially available TNFis in Slovenia, a country with a low TB incidence in the general population, who underwent a unified mandatory LTBI screening and the TB chemoprophylaxis protocol.

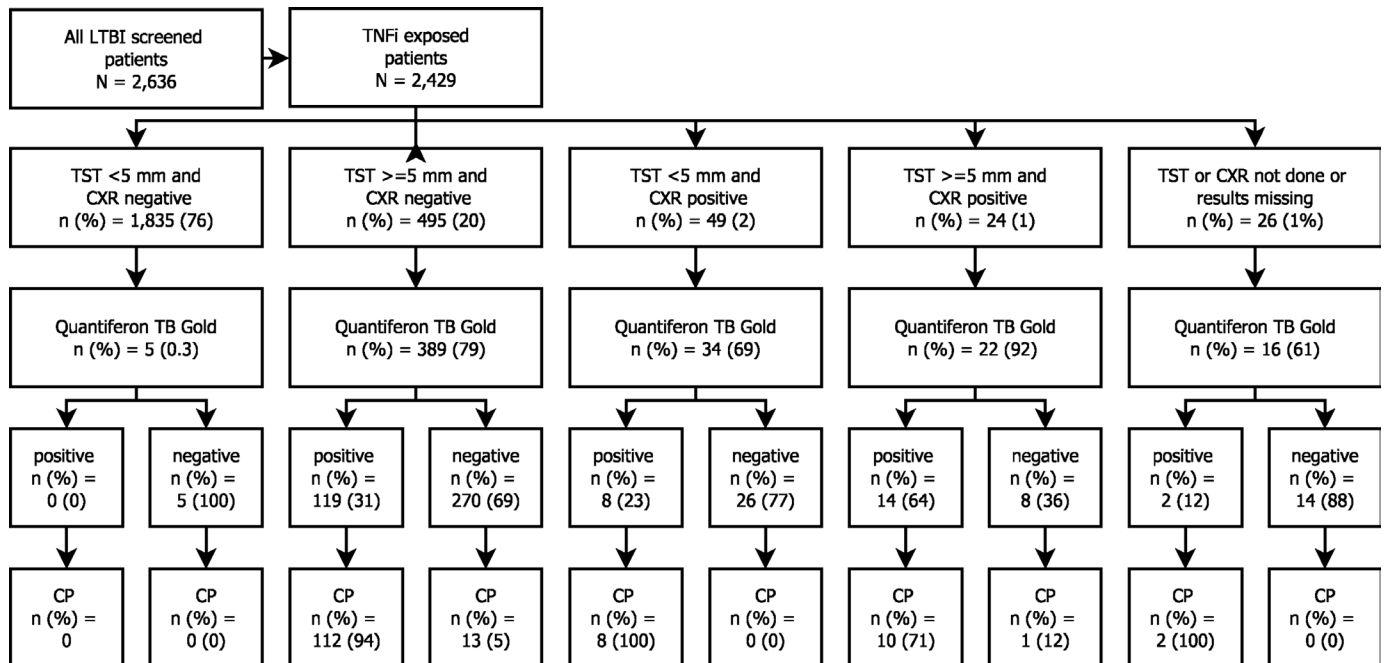


Figure 1 Detailed screening outcomes and latent tuberculosis chemoprophylaxis in patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis ever exposed to TNFis. CP, chemoprophylaxis; CXR, chest X-ray; LTBI, latent tuberculosis infection; TNFi, tumour necrosis factor- α inhibitor; TB, tuberculosis; TST, tuberculin skin test.

Not unexpectedly, the overall age-standardised and sex-standardised TB IR in patients exposed to TNFi was higher than in the general Slovenian population (SIR 7–9), but comparable with reports from other non-endemic countries (table 1). This was achieved without delaying the initiation of TNFi in over three-quarters of patients based on negative TST and CXR, a short delay in less than a fifth of patients who underwent pulmonological testing and an approximately 3-month delay in 6% of patients who were prescribed TB chemoprophylaxis with rifampin and isoniazid. This chemoprophylaxis rate was much lower than in France, where the incidence of TB and population BCG vaccination exposure are similar to Slovenia, and where they have shown that replacing TST with an IGRA halved the share of patients requiring TB chemoprophylaxis prior to the initiation of TNFi from 45.7% to 27.3%, respectively.²³ Unfortunately, but not unexpectedly, the mandatory screening did not prevent TB infections altogether (table 3).³ Even one patient who successfully completed TB chemoprophylaxis developed TB, which, we suspect, may have been due to patient's suboptimal adherence to TB chemoprophylaxis or newly acquired TB infection. Comparable with previous reports, a substantial proportion of the patients had extrapulmonary and disseminated TB.⁴ In four out of eight cases the screening was completed after TST and CXR alone, and we wondered if performing an IGRA could help prevent those cases. However, TST, especially in patients vaccinated with BCG, was shown to be more sensitive than IGRA for the detection of LTBI and should not have led to an underprescription of chemoprophylaxis.^{17 23} We are further reassured that our 'two-step' LTBI screening strategy works well in our setting, by using the recent

French cost-effectiveness analysis that compared eight IGRA-based LTBI screening regimens, which has shown that performing Quantiferon TB Gold only in patients who were TST positive resulted in the most cost-effective LTBI screening regimen and suggested that the French national screening recommendations could be changed on reflection.²⁴ It is clear that the TB IR is higher in TB endemic environments,² and while there is a low incidence of TB in the general Slovenian population, Slovenia is a small country neighbouring TB endemic countries. Slovenians thus do not even have to travel far to get in contact with active TB and potentially acquire TB, which we believe happened to at least one patient in our cohort. A new TB infection rather than the reactivation of LTBI is also suggested by the much longer than expected time from the TNFi treatment onset to the development of TB in seven out of eight patients in our cohort.⁴ Having said that, it may be prudent to consider introduction of systematic TB surveillance and re-screening in patients with an increased risk for TB infection.^{25 26}

There were no cases of TB among patients with AS. Although this may be due to chance, these patients were on average younger, and thus had fewer comorbidities, a lower inflammatory burden of disease and had been less often exposed to csDMARDs and glucocorticoids compared with patients with RA. This was not unexpected, as it has been shown that different inflammatory diseases may have different risks for TB infections, for example, it has been shown that tDMARD-naïve RA patients have an increased TB IR in comparison with the general population,⁹ while those with spondyloarthritis do not.¹⁰

There were no cases of TB among patients treated with infliximab and etanercept. For infliximab, the first

Table 3 Details of patients who developed tuberculosis on TNFi's

Diagnosis	Sex	Age at first TNFi	Disease duration, years	TST, mm	Chest X-ray	Quantiferon TB Gold	Chemoprophylaxis	TNFi	Prior bDMARDs	Ever glucocorticoids	Glucocorticoid dose, mg	cSDMARD	Year of TB diagnosis	Time to TB, days	Tuberculosis presentation
RA	F	66	29	0	Neg	Neg	No	ADA	No	Yes	2	MTX	2009	244	Pulmonary
RA	F	57	5.0	20	Neg	Pos	Yes	CZP	No	Yes	4	MTX	2011	74	Miliary
RA	M	62	3.2	0	Neg	ND	No	ADA	No	Yes	6	LEF	2011	655*	Pulmonary
RA	F	70	2.9	10	Neg	Neg	No	CZP	No	No	/	LEF	2012	308	Miliary†
RA	F	79	12	0	Neg	ND	No	CZP	No	Yes	4	MTX	2014	323	Miliary, died
RA	F	74	2.2	0	Neg	ND	No	ADA	No	Yes	6	LEF	2016	622‡	Miliary, died
PsA	M	48	10	5	Neg	ND	No	GOL	No	No	/	/	2015	724	Miliary
PsA	F	45	2	10	Neg	Neg	No	GOL	Yes§	Yes	4	MTX	2017	645	Pulmonary

*TB onset a year and a month after the last dose of adalimumab, and 1 month after two doses of rituximab 1 g within 14-day interval.

†New TB infection after travelling to a TB endemic country.

‡TB onset 1 year after the last adalimumab dose.

§Adalimumab, infliximab.

ADA, adalimumab; AS, ankylosing spondylitis; CZP, certolizumab; ETA, etanercept; F, female; GOL, golimumab; LEF, leflunomide; M, male; MTX, methotrexate; ND, not done; Neg, negative; Pos, positive; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TB, tuberculosis; TNFi, tumour necrosis factor inhibitor; TST, tuberculin skin test.

Table 4 Incidence rates of tuberculosis by indication and tumour necrosis factor inhibitor, and standardised incidence rates against Slovenian general population

	Most recent TNFi*			Current TNFi exposure†			
	Tuberculosis cases/person-years	Crude IR (95% CI)	Age and sex-standardised‡ IR (95% CI)	Tuberculosis cases/person-years	Crude IR (95% CI)	Age and sex-standardised‡ IR (95% CI)	SIR (95% CI)
All patients							
All TNFi	8/10455	77 (33 to 151)	70 (6 to 133)	6/10455	57 (21 to 125)	52 (0 to 110)	6.7 (0.6 to 80)
Etanercept	0/3002			0/3002			
Adalimumab	3/4140	72 (15 to 212)	59 (0 to 132)	1/4140	24 (1 to 135)	12 (0 to 34)	1.5 (0.1 to 16)
Certolizumab	3/771	389 (80 to 1137)	287 (0 to 697)	3/771	389 (80 to 1137)	287 (0 to 697)	37 (0.2 to 7344)
Golimumab	2/1217	164 (20 to 594)	90 (0 to 214)	2/1217	164 (20 to 594)	90 (0 to 214)	11 (0.3 to 463)
Infliximab	0/1325			0/1325			
Rheumatoid arthritis							
All TNFi	6/5175	116 (43 to 252)	79 (2 to 156)	4/5175	77 (21 to 198)	47 (0 to 110)	6.1 (0.3 to 105)
Etanercept	0/1779			0/1779			
Adalimumab	3/1891	159 (33 to 464)	117 (0 to 269)	1/1891	53 (1 to 295)	14 (0 to 42)	1.8 (0.1 to 25)
Certolizumab	3/686	437 (90 to 1278)	288 (0 to 700)	3/686	437 (90 to 1278)	288 (0 to 700)	37 (0.2 to 7257)
Golimumab	0/375			0/375			
Infliximab	0/444			0/444			
Ankylosing spondylitis							
All TNFi	0/3431						
Etanercept	0/794						
Adalimumab	0/1393						
Certolizumab	0/41						
Golimumab	0/555						
Infliximab	0/648						
Psoriatic arthritis							
All TNFi	2/1849	108 (13 to 391)	45 (0 to 109)	2/1849	108 (13 to 391)	45 (0 to 109)	5.8 (0.3 to 112)
Etanercept	0/429						
Adalimumab	0/856						
Certolizumab	0/44						
Golimumab	2/287	697 (84 to 2517)	244 (0 to 590)	2/287	697 (84 to 2517)	244 (0 to 590)	31 (0.2 to 4744)
Infliximab	0/233						

Standardised incidence ratio compared with the IR of tuberculosis in age-matched and sex-matched Slovenian population from 2007 to 2017.

*All TB cases were associated with most recent TNFi used regardless of the time between last dose and TB diagnosis.

†TB cases diagnosed up to 90 days after the last administered dose were considered.

‡The Slovenian population's age and sex distribution between 2007 and 2017 was used as the standard population.

IR, incidence rate per 100 000 person-years; TB, tuberculosis; TNFis, tumour necrosis factor inhibitors.

available TNFi, this may be due to the low exposure, owing to its route of administration. Between 2010 and 2013, we recorded three cases of TB in patients with RA treated with certolizumab, which made us wonder whether this drug might not increase the risk of TB more than other TNFis. However, although the TB IRs were higher for certolizumab compared with other TNFi, the overlapping CIs suggest the differences are not significant. The data on golimumab from our cohort are also difficult to interpret as both TB cases occurred in patients with PsA, where exposure to golimumab was short, and one of the cases occurred in a patient who was previously exposed to two other TNFis. There are few reports on the TB IR in patients exposed to certolizumab and golimumab, which did not show any unexpected increases in risk for TB IR.^{13 14}

We are aware that the results from various published studies are difficult to compare, because the studies were done in different patient populations, on endemic and non-endemic locations, at different time periods, patients were exposed to different tDMARDs, with different LTBI screening and TB chemoprophylaxis protocols. Due to the relative rarity of the events, the populations with different rheumatic diseases, or even other inflammatory diseases (eg, inflammatory bowel disease and psoriasis) were often pooled even when we know, that therapy is only a part of the patients' risk of TB infection. Few studies deal with other comorbidities that could contribute to the risk of TB, because few registries capture this information in detail. These observations are reflected in our results. Another limitation of our study was the lack of a comparator cohort of tDMARD-naïve patients. The low count of cases in our cohort also precluded the exploration of potential predictors of TB.

The strongpoints of our study were the detailed LTBI screening data, lacking in many similar studies, the use of the national registries biorx.si and the National Tuberculosis Registry to identify and describe TB cases in detail, and exposure to all commercially available TNFi.

At 52 (95% CI 0 to 110) TB cases per 100 000 PY, the TB IR in the Slovenian patients with RA, AS and PsA treated with TNFi was comparable with TB IRs in TB non-endemic countries with less than a tenth of the patients exposed to TB chemoprophylaxis.

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Patient consent for publication Not required.

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ORCID iD

Ziga Rotar <http://orcid.org/0000-0002-9323-9189>

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