

EPIDEMIOLOGICAL SCIENCE

Tuberculosis in biologic users for rheumatic diseases: results from the South African Biologics Registry (SABIO)

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ABSTRACT

Objectives To evaluate the rate of tuberculosis (TB) in biologic users for rheumatic diseases in South Africa, the effectiveness of our latent TB infection (LTBI) programme, risk factors and outcome.

Methods TB cases were collected from the South African Biologics Registry (SABIO), rheumatologists and pharmaceutical companies. Demographics, LTBI screening and treatment, biological and disease modifying antirheumatic drug (DMARD) therapies, TB diagnosis and outcomes were recorded.

Results 96 TB cases were collected from 1999 to June 2017: rheumatoid arthritis 55, ankylosing spondylitis 27, psoriatic arthritis 4, and juvenile inflammatory arthritis 10. The TB rate was 1240/100 000 person years for biologic users (n=96) versus the biologic naive cohort of 0/100 000 years with an incidence rate difference of 0.0124 (p<0.0001). 60/96 had pulmonary and 36/96 had extra-pulmonary TB. Reactivation TB occurred in 45/96 cases. TB occurred in all biologics licenced in South Africa, the majority in monoclonal inhibitors (1683/100 000 person years) compared with etanercept (861/100 000 person years) and non-tumour necrosis factor (TNF) inhibitors (681/100 000 person years). The incidence rate ratio for monoclonal inhibitors compared with etanercept was 1.96 (p=0.005) and 2.47 (p=0.002) compared with non-TNF inhibitors with no significant difference between non-TNF inhibitors and etanercept (p=0.336). From those (12.9%) who screened LTBI positive, 14 developed TB, while the majority (77) screened LTBI negative. Black race, male sex, younger age and residence in the Western Cape were statistical risk factors. Two drug resistant TB cases and six deaths occurred.

Conclusion Reactivation and new onset TB is a significant risk for all biologics users in SA. Screening for LTBI is an imperative preventative strategy.

BACKGROUND

TB is a leading cause of morbidity and mortality in the world, accounting for about 10.4 million new cases and 1.4 million deaths annually.¹ More than two thirds of the global TB burden is reported in Africa and Asia, and six countries account for 60% of new cases: India, Indonesia, China, Nigeria, Pakistan and South Africa. Latent TB infection (LTBI) is defined as a state of persistent immune response to Mycobacterium tuberculosis antigens detected either by the tuberculin skin test (TST) or by interferon gamma release assay (IGRA) without evidence of clinical tuberculosis.² LTBI subjects have

Key messages

What is already known about this subject?

- There is an increased risk of tuberculosis (TB) in patients using TNF inhibitors.
- Monoclonal TNF inhibitors are consistently reported to have higher TB infection rates than etanercept, a soluble TNF receptor.
- Screening and treatment of latent TB infection (LTBI) reduces the risk.

What does this study add?

- All biologics increase the risk of TB, especially monoclonal inhibitors, but importantly also non-TNF inhibitors with a risk not statistically different to etanercept.
- In South Africa, the TB incidence rate among biologic users is around ten times higher than in European countries.
- Black race, male sex, younger age and residence in the Western Cape were statistical risk factors for TB.
- Reactivation TB occurred in around 50% of cases.

How might this impact on clinical practice or future developments?

- Risk stratification, screening and treatment for LTBI are important mitigating strategies in preventing TB infection.

an increased risk of progression to TB, augmented by immune impairment such as HIV coinfection, therapies with TNF inhibitors and other immune regulators used for inflammatory diseases, transplantation and diseases such as type 2 diabetes.^{3–10} The use of biologics in our country is an obvious concern.

The incidence rate of TB in anti-TNF users has been reported from registries in Europe and strategies for prevention of reactivation TB have been proposed.¹¹ Monoclonal TNF inhibitors are consistently reported to have higher TB infection rates than etanercept, a soluble TNF receptor; however, non-TNF inhibitors have not been evaluated.^{11–15} Screening for LTBI was not mandatory in some countries and rheumatic disease other than rheumatoid arthritis (RA) were not always considered.^{12–13} The South African Biologics Registry (SABIO) was started in 2008 and upgraded in 2013, with special



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emphasis on evaluating screening for LTBI, patient demographics and drug-related risk factors for acquiring TB.^{16 17}

Most patients accessing biological treatment in SA are from the private sector funded by medical aids, with the minority from state institutions, clinical trials or self-funding. Affordability of biologics has resulted in restricted access in the public health sector and even in the private sector to more expensive medical aid plans.

Application for funding requires registration with SABIO with informed consent and approval by a peer-reviewed biologics panel, consisting of experienced rheumatologists. Screening for LTBI is strongly advocated by the South African Rheumatism and Arthritis Association (SARAA). The primary aim of this study was to evaluate the TB rate of biologic users for rheumatic diseases in South Africa, and secondary aims to evaluate our LTBI programme, risk factors for TB (age, race, sex, rheumatic disease, geographic location, comorbidities and concomitant medications) and outcome.

METHODS

SABIO, a national prospective observational registry, was established in 2008, recruiting all patients starting their first ever biologic.^{18 19} The initial purpose of the registry was to monitor biologic use and collect TB data including LTBI screening and treatment in RA, ankylosing spondylitis (AS), psoriatic arthritis (PsA) and juvenile inflammatory arthritis (JIA). Eligibility was based on SARAA criteria for the use of biologics. Those commenced on a biologic prior to 2008 including all TB cases were also encouraged to be registered. In January 2013, the registry was upgraded to optimise data quality and included six monthly patient telephonic calls to document the biologic start date and serious adverse events in RA, AS and PsA. In addition a biologic naive cohort was started in January 2013 consisting of patients fulfilling criteria for recruitment onto the registry but declining biologic treatment for reasons including funding, side effect concerns, pregnancy and logistical reasons. A total of 4982 patients from 2008 to July 2017 were included in the analysis to assess the TB incidence rate, LTBI screening and treatment. A subset of 1587 patients derived from the upgraded registry was used to determine baseline characteristics and TB risk factors in biologic exposed cases. In this subset we excluded JIA. Confirmation and evaluation of TB diagnosis, time lines between the start of a biologic and acquiring TB, treatment, outcomes and subsequent biologic use were recorded. Diagnosis was based on microbiological (culture, Gen Probe PCR or smear acid fast bacilli (AFB)), histological or radiographic confirmation or on clinical suspicion (constitutional symptoms of fever, weight loss, night sweats, elevated erythrocyte sedimentation rate, suspicious X-ray findings and response to TB therapy). Treatment of active TB was as per standard protocols with isoniazid (INH), rifampicin, ethionamide and pyrazinamide for 2 months and INH with rifampicin for the remaining four. TB is a notifiable disease in SA.

Reactivation TB was defined as TB diagnosed within 18 months of starting a biologic and new infections as TB cases after 18 months. Screening and treatment for LTBI was based on SARAA recommendations and included a chest X-ray (CXR) and TST or IGRA. TST of ≥ 5 mm induration, positive IGRA, granulomas on CXR or radiographic presence of TB was considered a positive test. Retesting was not undertaken in LTBI negative screens or contact with active TB. LTBI treatment with INH monotherapy for 9 months or combined with rifampicin for 3 months, starting at least 1 month before biologic initiation is

recommended if any of the screening tests are positive or if the patient has a high TB exposure risk. LTBI treatment failure was defined as developing reactivation TB despite INH/rifampicin therapy and LTBI screen failure as those who screened negative for LTBI but developed reactivation TB.

There was no patient and public involvement in the design, conduct, publishing or dissemination of this research.

Baseline

All patients provided written consent to be entered onto the registry and to have their data analysed for study purposes. A standardised baseline form was completed by the rheumatologist. Data included demographics, rheumatic disease, rheumatoid factor, anti-cyclic citrullinated peptide, simple disease activity index, human leukocyte antigen B27 (HLAB27), comorbidities, LTBI screening tests and treatment, concomitant DMARDs and corticosteroid.

Follow-up

A standardised follow-up questionnaire on disease activity, adverse events and treatment changes was completed 6 monthly by the rheumatologist. Both biologic exposed and naive cohorts had telephonic follow-up 6 monthly from 2013, specifically addressing adverse events and treatment changes. Patient reported side effects including TB were only included if verified by the rheumatologist. In addition TB cases were also cross-referenced with pharmaceutical companies.

Statistical methodology

The number of patient years was calculated per biologic. The total sum of exposure was calculated from the first to the last day of biologic use which was assumed to be 1 June 2017. The total number of years that a patient used a biologic was referred to as the exposure, in patient years, to that drug. If a patient switched biologics, the actual time each biologic was used was attributed to that specific biologic.

On starting a biologic (biologic naive), TB was attributed to the drug if diagnosed any time from start to 6 months after stopping. The same rule applied to subsequent biologics used (except if starting within 6 months of the preceding biologic, in which case the former biologic would be deemed causative).

The TB incidence rate was calculated by dividing the number of TB cases per biologic, by the sum of exposure, in years, for each biologic. To get the rate per 100 000 person years, the incidence rate was multiplied by 100 000. The incidence rate ratio (IRR) was calculated by dividing the relevant incidence rates by each other. The Fisher exact test was used to calculate the corresponding 95% CI and p-values. Significance was tested at 0.05.

A general linear model, with binomial distribution and log-odds (or logit) link function, was used to determine the risk factors associated with acquiring TB in biologic patients. Univariate and multivariate analysis was performed. Patients with disease category JIA were excluded from all univariate and multivariate analyses. During multivariate analysis, stepwise backward elimination was used to predict the final model using the Akaike information criterion to choose the best fitting model. Patients with missing or unknown data points were removed from the data set before performing multivariate analyses. Patients with race indicated as Asian were removed from multivariate analyses, as no patients in the TB group had race specified as Asian. Certain data sets from the new registry (starting 2013) were extrapolated to the upgraded registry (starting 2008) to obtain

Table 1 Diagnosis of TB cases (n=96)

Microbiologic (n=49)		Histological (n=17)		Radiographic (n=23)		Constitutional (n=6)
Sputum/washings		Lung		Miliary		Constitutional symptoms
Culture +ve	15	Pleura		Fibrocavitation		PPD +ve, elevated ESR
PCR +ve	7	Synovium		Pleural effusion		response to treatment
Smear+ve	18	Lymph node		ADA* +ve		
Lymph node	2	Bone		ADA* -ve		
Synovium	1	Bowel		Pleuro-pulmonary		
Pleura	2	Peritoneum		Pott's disease		
Peritoneum	1					
Liver	2					
CSF	1					Unknown (n=1)

*Adenosine deaminase.

CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; PPD, purified protein derivative; TB, tuberculosis.

total percentages. The p-value for the proportions switching biologics was calculated using a test of equal proportions.

RESULTS

A total of 4830 (7742 person years) were included in the biologic cohort and 152 (463 person years) in the biologic naïve cohort. There were 95 patients in the TB cohort (two separate events in one patient) with a total of 96 events: RA 55 (57%), AS 27 (28%), PsA 4 (4%) and JIA 10 (10%). Reactivation TB occurred in 45/96 (47%) cases, new onset TB in 50/96 (52%) cases and 1 was undetermined due to insufficient data. Pulmonary TB occurred in 60/96 (62.5%) cases while 36/96 (37.5%) had extra-pulmonary, including disseminated (7/96) disease. The diagnosis was proven microbiologically in 49, histologically in 17, radiographically in 23 and clinically in 6, while the exact details in one could not be verified (table 1). The rate of TB was 1240/100 000 person years for all biologic users combined, compared with the biologic naïve arm of 0/100 000 years (n=0) with an incidence rate difference of 0.0124 (95% CI 0.007 to 0.018, p<0.0001). TB occurred in all seven biologics: adalimumab 48, infliximab 15, golimumab 3, etanercept 19, tocilizumab 2, abatacept 5 and rituximab 4. The incidence rate was highest for monoclonal TNF inhibitors (1683/100 000 person years) compared with etanercept (861/100 000 years) and non-TNF inhibitors (681/100 000 years). The IRR for monoclonal inhibitors compared with etanercept was 1.96 (95% CI 1.16 to 3.45, p=0.005) and 2.47 (95% CI 1.29 to 5.19, p=0.002) compared with non-TNF inhibitors. There was no significant difference between non-TNF inhibitors and etanercept (IRR 0.79; 95% CI 0.34 to 1.75, p=0.336). TB rates of individual biological agents are represented in table 2. The incidence of TB cases peaked in 2011/2012 and subsequently declined over the ensuing years (figure 1). More cases of reactivation TB occurred

with monoclonal anti-TNF agents compared with other biologics whereas new TB cases are associated with all biologic DMARD's (online supplementary figure 1).

Outcome

From the 96 TB events, 86 recovered fully including two with drug resistant TB. Two recovered with sequelae (deafness, pulmonary aspergillosis), while six died. There was insufficient data to determine outcome in 2. After TB treatment, 17 patients continued on their original biologic, 46 switched and 25 stopped completely.

LTBI screening results

LTBI screening was undertaken in 98.3% of cases with CXR combined with TST (n=3719; 77%) and/or IGRA (n=1526; 32%). Adherence to SARAA treatment recommendations was 71%. TST was positive in 7% (n=260) and IGRA in 25% (n=387). In total 647 (12.9%) from 4830 screened LTBI positive. From 14 that developed TB infection despite screening LTBI positive, 13 took INH/rifampicin treatment; however, 4 failed to complete the course. Of the 13 patients, 9 developed reactivation TB (treatment failure) and 4 new onset TB. Seventy seven TB cases screened negative, of which 33 developed reactivation TB (screen failures). Empiric INH was prescribed for 7 of the 77 due to high background risk; yet three still developed reactivation TB (treatment failure). LTBI screening was not done in 5/96 cases. LTBI treatment failure therefore occurred in 12 cases (figure 2). The overall TB risk for all biologic users with a rheumatic disease was 2%. The risk of developing reactivation TB was 1.4% if LTBI screened positive (despite treatment) and 0.7% if screened negative. The negative predictive value for both TST and IGRA was 99%, and the positive predictive value, although numerically superior for TST, was not statistically different. LTBI screening with CXR was unhelpful with 84 X-rays reported as normal, 6 showing chronic non-specific changes and 6 reports not available. No granulomas signifying LTBI were reported.

Tb risk factors

Table 3 shows baseline characteristics of the TB cohort, biologic exposed and biologic naïve cohorts, used to evaluate TB risk factors. Table 4 compares baseline characteristics of monoclonal TNF inhibitors, soluble receptor and non-TNF inhibitors.

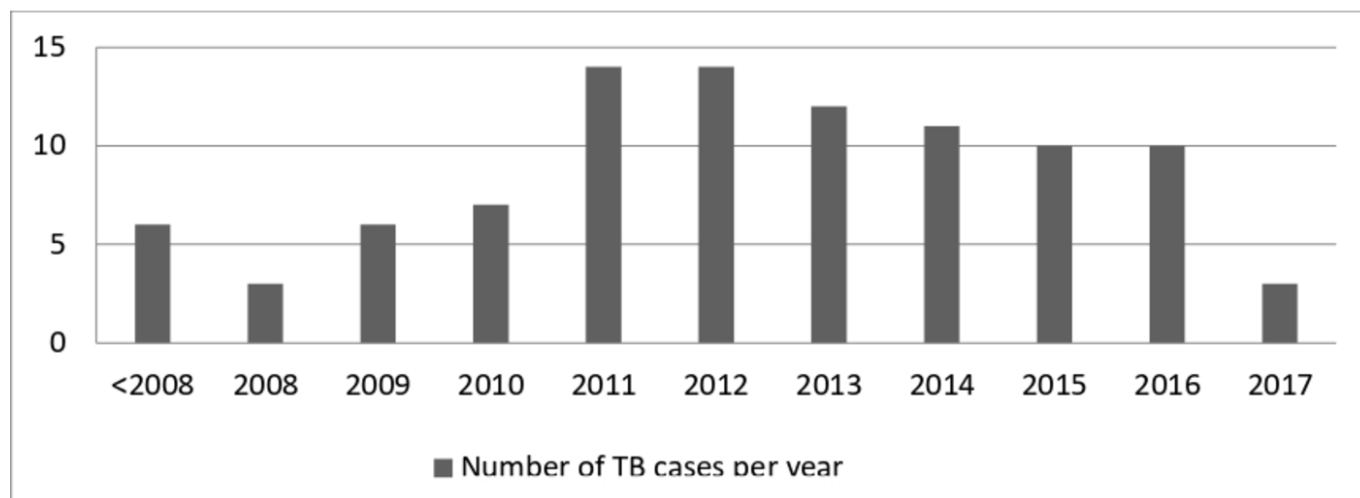
Both univariate and multivariate analysis of risk factors for TB infection showed black race (p=0.029, OR 2.13), younger

Table 2 TB rates of individual biologic agents (SABIO)*

Biologic	Sum of exposure (years)	TB cases/drug (n=96)	TB rate/100 000 person years
Adalimumab	2954	48	1625
Infliximab	694	15	2160
Golimumab	273	3	1099
Etanercept	2207	19	861
Abatacept	546	5	916
Rituximab	803	4	498
Tocilizumab	265	2	754

*South African Biologics Registry.

TB, tuberculosis.



*South African Biologics Registry

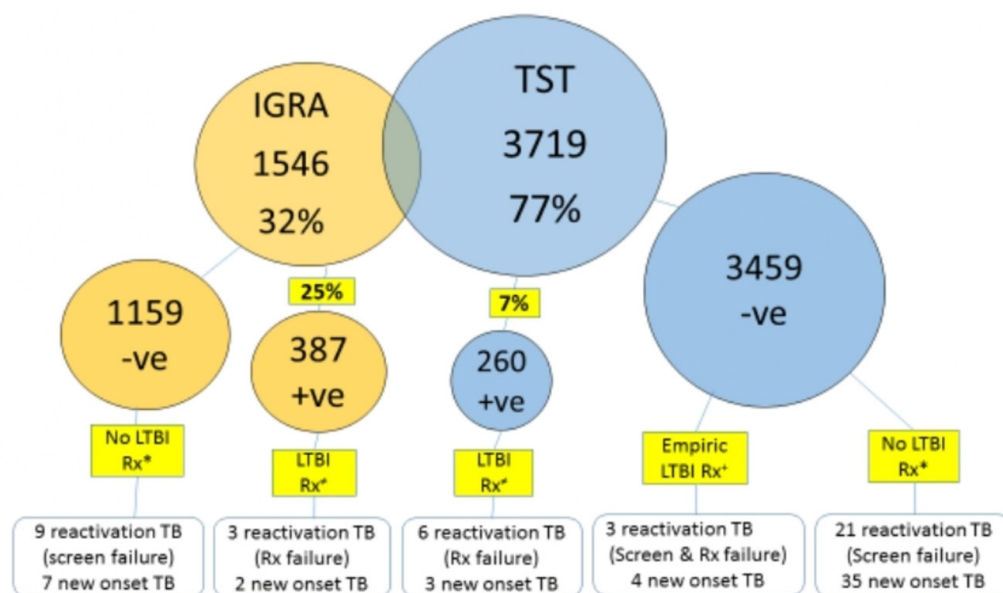
Figure 1 Annual incidence of TB (SABIO)*.

age ($p < 0.001$) and male sex ($p = 0.03$, OR 1.93) to be statistically significant. Multivariate analysis showed residence in the Western Cape to have an increased risk ($p = 0.045$, OR 3.05) compared with other provinces. Underlying rheumatic disease and comorbidities showed no statistical difference (table 5 and online supplementary table 1). Methotrexate use at the time of TB diagnosis (76%) was statistically less ($p < 0.001$) than at baseline (90%) and approximates real life registry data from biologic registries and US claims databases, indicating that 30% of patients take biologics as monotherapy.^{20–28} Similarly steroid use at time of TB diagnosis (53%, median 9.45) was numerically less than at baseline (60%, median 9.6) and equates well with the Australian Rheumatology Association

Database which reports steroid attrition from 55% to 39% over a 10-year period ($p < 0.001$).²⁹ The association with methotrexate and steroid use and risk of acquiring TB is therefore unlikely. Use of more than one biologic prior to TB diagnosis occurred in 29% (25/86) of TB cases compared with 26.5% in the SABIO registry with no statistical difference ($p = 0.597$).

DISCUSSION

This study highlights differences to other registries and adds new insight from our active LTBI screening programme and large TB cohort. We showed that all biologics increase the risk of TB, especially monoclonal inhibitors, but importantly also



*Patients screened IGRA / TST negative and did not receive treatment for latent TB infection

*Patients screened IGRA / TST positive and received treatment for latent TB infection

*Patients screened TST negative and received empiric treatment for latent TB infection

5 TB patients were not screened (3 reactivation TB, one new infection and one not determined). 2 patients (both new onset TB) screened both TST and IGRA negative

Figure 2 Relative tuberculin skin test and IGRA usage and outcome (n=4830).

Table 3 Baseline characteristics

Characteristics	TB cohort (n=86)	Biologic exposed (n=1587)	Biologic naïve (n=152)
Mean age (years)	45.2	52.0	50.7
% female	56	71	67
RA, n (%)	55 (64)	1085 (68)	103 (68)
AS, n (%)	27 (31)	379 (24)	37 (24)
Psoriatic arthritis, n (%)	4 (5)	123 (8)	13 (8)
Geographic area, n (%)			
Gauteng	38 (44)	935 (59)	74 (49)
Western Cape	31 (36)	364 (23)	38 (25)
Kwazulu Natal	12 (14)	192 (12)	32 (21)
Free State, E. Cape	5 (6)	96 (6)	8 (5)
Ethnicity, n (%)			
White	60 (70)	1069 (67)	97 (63)
Black	11 (13)	92 (6)	21 (14)
Coloured	5 (6)	102 (6)	5 (3)
Indian	10 (12)	135 (9)	17 (11)
Asian	0 (0)	73 (5)	13 (9)
Unknown	0 (0)	116 (7)	0 (0)
RF/ACPA in RA (%)	72	62	42
HLAB27 in AS (%)	78	65	88
SDAI, mean (range)	N/A	45.4 (1.3–88.5)	40.9 (2–80)
BASDAI, mean (range)	N/A	6.6 (0.5–9.75)	6.1 (3.1–9.1)
BASFI, mean (range)	N/A	6.6 (0.5–9.7)	6.5 (2.85–10)
CXR (% abnormal)	7	3.7	2
TST +ve, n (%+ve)	9 (10)	260 (7)	104 (12)
IGRA +ve, n (%+ve)	5 (6)	387 (25)	64 (23)
MTX* % (mean dose; range)	N/A	90 (19.4; 5–40)	88 (20.2; 20–25)
Steroid % (mean dose; range)	N/A	60 (9.6; 5–60)	67 (10.3; 7.5–15)

*Methotrexate.

ACPA, anti-citrullinated protein antibody; AS, ankylosing spondylitis; BASDAI, bath ankylosing spondylitis disease activity index; BASFI, bath ankylosing spondylitis functional index; CXR, chest X-ray; HLAB27, human leukocyte antigen B27; IGRA, interferon gamma release assay; RA, rheumatoid arthritis; RF, rheumatoid factor; SDAI, simple disease activity index; TB, tuberculosis; TST, tuberculin skin test.

Table 4 Baseline characteristics of biologic subsets

Characteristics	Monoclonal's (n=703)	Soluble receptor (n=498)	Non-TNF (n=386)
Mean age in years	49.9	51.1	56.5
% female	66	68	82
% ever smoked	22	21	20
% employed	79	81	74
Mean comorbidities	1.3	1.4	2
Ethnicity (%)			
White	77	79	64
Black	6	4	13
Coloured	4	7	7
Indian	10	8	10
Asian	3	2	6
% Rheumatoid arthritis	54	64	100
% RF/ACPA+ve	56	57	72
Mean SDAI	41.5	43.0	46.7
Mean HAQ	1.6	1.9	1.9
% ankylosing spondylitis	35	26	0
BASDAI (mean)	6.9	6.4	N/A
% psoriatic arthritis	11	11	0
Methotrexate % (mean dose)	88 (19.2)	89 (19.6)	95 (19.8)
Steroid % (mean dose)	61 (9.7)	53 (9.6)	67 (9.3)

ACPA, anti-citrullinated protein antibody; BASDAI, bath ankylosing spondylitis disease activity index; HAQ, health assessment questionnaire; RF, rheumatoid factor; SDAI, simple disease activity index; TNF, tumour necrosis factor.

non-TNF inhibitors with a risk not statistically different to etanercept. South Africa is a TB endemic country with the 2010 WHO report showing a prevalence rate of 798/100 000, one of the highest in the world.^{30 31} Therefore it is not surprising that the TB incidence rate among biologic users is around ten times higher than European countries (table 6). LTBI is much more prevalent than active TB and LTBI screening rates from SABIO (12.9%) are not reflective of the broader SA population. The highest prevalence of LTBI estimated at 88% has been found among people in the age group 30–39 years old living in townships and informal settlements.^{32 33} SABIO LTBI screening data account for an economically privileged population subset and the rate in the general rheumatology population is still to be determined, but is estimated to be far in excess.

Post-marketing surveillance studies from Japan and a study from Taiwan have reported on the increased risk of TB associated with anti-TNF.^{34–36} The Brazilian Registry (Registro Brasileiro de Monitoração de Terapias Biológicas—BiobadaBrasil) reported the incidence rate of tuberculosis was 287/100 000 patient years among anti-TNF users (adalimumab: 443/100 000; etanercept: 192/100 000 and infliximab: 182/100 000) while no cases of tuberculosis occurred in the non TNF group (abatacept, rituximab and tocilizumab).³⁷

The number of patients accessing biological therapies in South Africa is increasing yearly (online supplementary figure 2) and so too is the annual incidence of TB in the general population (online supplementary table 2). The recent annual decline in

Table 5 Risk factors for TB using univariate analysis

	Registry data		TB cases		Univariate analyses	
	N	%	N	%	P-value	OR
Gender	1587		86			
Female	1126	71	48	56	Reference	1
Male	461	29	38	44	0.003	1.93
Disease category	1587		86			
AS	379	24	27	31	Reference	1
PsA	123	8	4	5	0.151	0.46
RA	1085	68	55	64	0.160	0.71
Race	1587		86			
White	1069	67	60	70	Reference	1
Coloured	102	6	5	6	0.776	0.87
Black	92	6	11	13	0.029	2.13
Indian	135	9	10	12	0.433	1.32
Asian	73	5	0	0	Excluded from univariate analyses due to 0 cases in TB arm	
Unknown	116	7	0	0		
Region	1587		86			
E.Cape and Free State	96	6	5	6	Reference	1
Gauteng	935	59	38	44	0.611	0.78
Kwazulu-Natal	192	12	12	14	0.739	1.20
Western Cape	364	23	31	36	0.321	1.64
Comorbidities	1587		86			
0	494	31	38	44	Reference	1
>=1	857	54	47	55	0.133	0.71
Unknown	236	15	1	1	0.004	0.06
Age	1351		83			
Mean	52.01		45.20		<0.001	

AS, ankylosing spondylitis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; TB, tuberculosis.

the TB rate among biological users was therefore not expected, but is perhaps due to greater vigilance in LTBI screening, judicious biologic selection and empiric LTBI treatment for high risk patients.

Screening and treatment of LTBI prior to biologic commencement markedly reduces reactivation TB.¹¹ The British registry, British Society for Rheumatology Biologics Register (BSRBR), recorded 40 TB cases with no data on LTBI screening.¹² From the 69 TB patients recorded in the French registry, French Research Axed on Tolerance of Biotherapies (RATIO), TST was done in 45 and was positive (>5 mm) in 15. There was a history of TB exposure in 10 and past history in 4. None of the patients received correct treatment according to French recommendations (9 months of INH or 3 months with two TB drugs including rifampicin).¹³ The Spanish registry, BIOBADASER, recorded 15 cases of TB infection and used a two step skin test as their protocol for detection of LTBI. They concluded that the probability of developing TB was seven times higher when recommendations were

not followed.¹¹ Despite our LTBI programme, approximately 50% developed reactivation TB mainly due to LTBI screen failures (33/77). Poor intradermal injection technique, inaccuracies in reading the TST and under-reporting of granulomas on CXR may be some of the reasons. We were unable to demonstrate any statistical advantage of TST over IGRA as a screening tool. LTBI treatment failure occurred in 12, possibly due to poor adherence, drug resistance or starting a biologic too soon after initiating LTBI treatment. Importantly, the remaining 50% of TB cases were new infections for which LTBI screening will not impact. Continuous INH treatment, avoiding high TB risk spaces such as public transportation and institutions and tapering biological therapy where clinically appropriate may be mitigating factors.

There were differences across registries concerning clinical presentation. Our data show 40% were extra-pulmonary and 60% pleuro-pulmonary, compared with BSRBR: 25/40 (62%) extra-pulmonary, 11 disseminated and RATIO: 42/69 (61%) extra-pulmonary.^{12 13}

Table 6 Comparison of TB rates in biologic users across registries

National registry	SABIO*	BSRBR†	BIOBADASER‡	RATIO§	US National Data Bank
Total number of patients	4830	10 712	5198	N/A	6460
Number of TB cases	96	40	15	69	4
TB rate for anti-TNF per 100 000 patient years	1387	106	172	116	5
TB rate for non-TNF per 100 000 patient years	681	N/A	NA	N/A	N/A

*South African Biologics Registry.

†British Society for Rheumatology Biologics Register.

‡Base de Datos de Productos Biológicos de la Sociedad Española de Reumatología.

§French Research Axed on Tolerance of Biotherapies registry.

TB, tuberculosis; TNF, tumour necrosis factor.

Most patients responded well to TB treatment including two drug resistant cases. We recorded 6 deaths from 96 cases (6%) compared with BSRBR: 10 from 40 (25%) and RATIO: 2 from 57 (3.5%) with missing data in 12.^{12 13} After treatment completion, 63/96 (66%) of our patients elected to continue on a biologic.

Univariate analysis of risk factors for TB in biologic users showed that male sex, black race and younger age were statistically significant risk factors, all possibly attributable to exposure in the workplace. Multivariate analysis showed that residence in the Western Cape increases TB risk ($p=0.045$, OR 3.05) coinciding with a higher prevalence of TB in the province.³⁸ There was no increased risk for underlying rheumatic disease (RA, AS, PsA) despite RA having an inherent risk.^{39 40} The use of methotrexate, corticosteroids and previous biologic therapies were also not risk factors. Twenty five from 86 cases (29%) received more than one biologic prior to acquiring TB compared with BSRBR: 7 from 40 (17.5%) and RATIO: 11 from 69 (16%).^{12 13}

A limitation of this study is that our registry data capture the economically advantaged who have the least exposure and risk of developing TB and cannot be extrapolated to the general rheumatology population. Even in this privileged cohort however, the risk of TB remains high. Further limitations include the assumption that early onset TB, defined as occurring within the first 18 months of starting a biologic, is reactivation TB and late onset TB occurring after this time period are new infections. Other limitations are those inherent to registries including missing data (confounding variables such as disease activity and duration, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), cumulative steroid dose, smoking and pre-existing pulmonary disease) and reliance on data accuracy from treating rheumatologists. Rheumatologists in private practice make use of the registry as a prerequisite to gain access to funding, whereas rheumatologists in the state sector are not incentivised as funding can be obtained from government hospitals, although limited.

CONCLUSION

Patients on biological therapies for rheumatic diseases have a considerable risk of developing reactivation and new onset TB in South Africa (2%), compared with other countries. All biologics evaluated, particularly monoclonal therapies but also non-TNF inhibitors were implicated. Reactivation of latent TB is driven at large by monoclonal anti-TNF therapies whereas new TB cases are associated with all bDMARDs. Black race, male sex, younger age and residence in the Western Cape are risk factors for acquiring TB while concomitant steroids, methotrexate, multiple biological use and underlying rheumatic disease were not. TB risk stratification prior to commencement, screening for LTBI and adherence to SARAA treatment recommendations are strongly advocated. Benefits of continuous INH therapy require further study, considering that 50% of cases are new infections.¹¹ The majority of biologic users in SA are socioeconomically advantaged; however, prescribing these agents in higher TB risk communities is concerning and therefore managing their disease remains an unmet need.

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