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Review

Tuberculosis and targeted synthetic or biologic DMARDs, beyond tumor necrosis factor inhibitors

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***Abstract*:** Patients with autoimmune rheumatic diseases (ARD) have an increased risk for tuberculosis (TB). The use of tumor necrosis factor inhibitors (TNFi) and glucocorticoids in these patients has been associated with an increased prevalence of latent TB reactivation. Over the last few years, several biologic disease-modifying anti-rheumatic drugs (bDMARDs), other than TNFi (e.g. rituximab, abatacept, tocilizumab, secukinumab) and targeted synthetic DMARDs (tsDMARDs) [e.g. apremilast, Janus kinase (JAK) inhibitors] have been used for the treatment of patients with ARD. For many of these drugs, especially the newer ones like JAK inhibitors or antibodies against interleukin (IL)-23, most data stem from randomized clinical trials and few are available from real life clinical experience. We sought to review the current evidence for TB risk in patients with ARD treated with tsDMARDs or bDMARDs, other than TNFi. It seems that some of these drugs are associated with a lower TB risk, indirectly compared with TNFi treatment. In fact, it appears that rituximab, apremilast and inhibitors of IL-17 and IL-23 might be safer, while more data are needed for JAK inhibitors. As seen in TNFi, risk for TB is more pronounced in TB-endemic areas. Screening for latent TB must precede initiation of any tsDMARDs or bDMARDs. The growing use of non-TNFi agents has raised the need for more real-life studies that would compare the risk for TB between TNFi and other treatment modalities for ARD. Knowledge about the TB-safety profile of these drugs could help in the decision of drug choice in patients with confirmed latent TB infection or in TB endemic areas.

Keywords: autoimmune, biologic DMARDs, rheumatic disease, targeted synthetic DMARDs, tuberculosis, Tumor necrosis factor inhibitor

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Introduction

Tuberculosis (TB) has been recognized as an important opportunistic infection occurring in patients with autoimmune rheumatic diseases (ARD). Data from large nationwide registries have shown that the risk of latent TB reactivation or *de novo* TB cases is increased in ARD patients treated with tumor necrosis factor (TNF) inhibitors (TNFi).[1–10] This seems to be more pronounced in countries that are endemic for TB.[6]

Mycobacterium tuberculosis (MT) contamination can lead to three possible outcomes: eradication of MT, latent or active MT infection. Ideally, successful eradication of the MT can be achieved by the first line of defence, which comprises alveolar macrophages and other phagocytes. Should innate immunity fail to eliminate the pathogen, active TB develops or the infection is limited through the formation of granulomas, which is mainly mediated by T cells. The tuberculous granuloma consists of macrophages and a surrounding layer of lymphocytes acting protectively for the host. On the other hand, granuloma works as a nest for some MT bacilli that survive inside for long period. This is the stage of latent TB infection. Any factor that leads to immunosuppression might disturb the delicate balance of

latent TB and result in active TB infection (TB reactivation).[11] Host responses against TB are mediated through an intricate interplay between innate and adaptive immunity, dominated by macrophages and T cells, respectively. Data regarding humoral immunity are ambiguous, with most studies showing a rather negligible role of B cells.[12] From a cytokine point-of-view, TNFα and interferon gamma (IFNγ), are essential for the effective intra-cell communication and for granuloma formation.[12] Specifically, TNFα is essential in granuloma formation and has been shown to augment phagocytosis of mycobacteria,[13] lead ineffective macrophages to apoptosis[14,15] and aid in the recruitment of inflammatory cells,[16] while IFNγ is vital in preventing TB dissemination, as seen in several cases of defective IFNγ action.[17–19] Several studies have shown that TNFα neutralization might lead to *de novo* TB infection or TB reactivation *via* inhibition of IFNγ-induced phagosomal maturation,[20] granuloma destabilization[21] and alteration of T cell cytokine production and subpopulation distribution.[22,23] A large number of other cytokines have been also implicated in TB immunity, mainly IFNα/β, IL-1, IL-6, IL-12, IL-17 and IL-22.[24]

It is known that in rheumatoid arthritis (RA) glucocorticoids and methotrexate carry a slightly increased risk of TB infection[25,26] while TNFi offer a 4- to 8-fold risk in this population.[1,4,6] This risk seems to be decreased over time as more detailed screening with tuberculin skin test (TST) and interferon gamma release assay (IGRA) is applied to patients who are about to commence treatment with biologic drugs.[1] Of note, it is widely accepted that this risk is significantly lower for soluble receptor of TNF (etanercept) than with monoclonal antibodies against TNF[27,28] (Table 1). This might stem from pharmacokinetic and pharmacodynamic disparities between different TNFi.[29] Significantly, some patients treated with TNFi that had a negative baseline TST or IGRA test might develop a positive test during treatment period (seroconversion).[30]

During the last few years, many new therapeutic modalities have been added to a rheumatologist's arsenal including monoclonal antibodies, anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) [abatacept (ABA)], anti-CD20 [rituximab (RTX)], anti-IL6 receptor [tocilizumab (TCZ), sarilumab], anti-IL-17 (secukinumab, ixekizumab), anti-IL17 receptor (brodalumab), anti-IL-23/IL-12p40 (ustekinumab), anti-IL23p19 (guselkumab) or small molecules like phosphodiesterase 4 inhibitor (apremilast) and, lately, Janus kinase (JAK) inhibitors (tofacitinib, baricitinib, upatacitinib). Other drugs like newer JAK inhibitors (filgotinib, peficitinib), anti-IL-6 (clazakizumab, sirukumab) and other anti-IL23p19 (risankizumab, tildrakizumab) monoclonal antibodies are also in the pipeline for the treatment of patients with ARD. Herein, we aimed to review the current evidence for the TB risk in patients treated with targeted synthetic (apremilast, JAK inhibitors) or biologic disease modifying antirheumatic drugs (DMARDs), other than TNFi, in immune mediated diseases with a focus on inflammatory arthritis.

A literature search using Pubmed and Embase was made. The key words "Apremilast" OR "Tofacitinib" OR "Baricitinib" OR "Upadacitinib" OR "Filgotinib" OR "Peficitinib" OR "Ustekinumab" OR "Guselkumab" OR "Risankizumab" OR "Tildrakizumab" OR "Secukinumab" OR "Ixekizumab" OR "Brodalumab" OR "Tocilizumab" OR "Sirukumab" OR "Clazakizumab" OR "Sirukumab" OR "Abatacept" OR "Rituximab" AND "Tuberculosis" OR "latent TB" OR "latent tuberculosis" OR "TB" were used. Our search review was not limited in RA and articles concerning other immune-mediated diseases were also considered. Randomized clinical trials, their extension studies as well as real-world studies were included. Reference list of the afore-mentioned articles was also reviewed. Case reports, case series and articles not written in English language were excluded. Our search, covered articles published up to 30 August 2019.

Targeted synthetic DMARDs

Apremilast

Apremilast, an oral phosphodiesterase 4 inhibitor, has demonstrated moderate and sustained efficacy in psoriatic arthritis (PsA).[32] Interestingly, in lungs of animal models phosphodiesterase-4 inhibitors CC-3052 and CC-11050 reduced local inflammation and improved the antimicrobial efficacy of isoniazid.[33,34] During PALACE 1, PALACE 2, PALACE 3 and PALACE 4 studies, a total of 1644 patients were exposed to apremilast at a 20 mg or 30 mg dose twice daily for 24 to 52 weeks. No *de novo* TB infection or TB reactivation was

Table 1. Cases of tuberculosis (TB) and incidence rate (IR) in patients receiving TNF inhibitors.

TNF Inhibitors								
Drug	**Disease**	**Study type**	**No~**	**Pt-yrs**	**Active TB cases**	**IR§**	**Rate general population***	**Reference**
Adalimumab	RA, AS, PsA, PsO, CD, UC	LTE	NA	12,757.7	30	184.79	International	Souto *et al.*[27]
Certolizumab	RA	LTE	NA	9277.0	44	474.29	International	Souto *et al.*[27]
Etanercept	RA, AS, PsA, PsO	LTE	NA	7164.8	3	65.01	International	Souto *et al.*[27]
Golimumab	RA, AS, PsA	LTE	NA	3209.1	4	172.13	International	Souto *et al.*[27]
Infliximab	RA, AS, PsA, PsO, CD, UC	LTE	NA	4396.2	13	347.70	International	Souto *et al.*[27]
Adalimumab	RA, AS, PsA, PsO, CD, UC	RLS	NA	NA	28	215.0	8.9 (France)	Tubach *et al.*[28]
Adalimumab	RA	RLS	1190	NA	1	90.0	8.0 (UK)	Dixon *et al.*[9]
Adalimumab	RA	RLS	NA	28,751	24	83.3	8.0 (UK)	Rutherford *et al.*[31]
Certolizumab	RA	RLS	NA	2247	2	88.8	8.0 (UK)	Rutherford *et al.*[31]
Etanercept	RA	RLS	2327	NA	0	NA	3.0 (USA)	Wolfe *et al.*[8]
Etanercept	RA	RLS	3596	NA	2	50.0	8.0 (UK)	Dixon *et al.*[9]
Etanercept	RA	RLS	NA	36.663	17	46.3	8.0 (UK)	Rutherford *et al.*[31]
Etanercept	RA	RLS	NA	NA	4	80.0	5.5 (Sweden)	Askling *et al.*[2]
Etanercept	RA	RLS	103	73.67	0	NA	66.0 (Korea)	Seong *et al.*[6]
Etanercept	RA, AS, PsA	RLS	NA	NA	0	NA	9.4 (Spain)	Gomez-Reino *et al.*[10]
Infliximab	RA, AS, PsA, PsO, CD, UC	RLS	NA	NA	35	187.5	8.9 (France)	Tubach *et al.*[28]
Infliximab	RA	RLS	6460	NA	4	52.5	3.0 (USA)	Wolfe *et al.*[8]
Infliximab	RA	RLS	2878	NA	7	150.0	8.0 (UK)	Dixon *et al.*[9]
Infliximab	RA	RLS	NA	17,670	13	73.4	8.0 (UK)	Rutherford *et al.*[31]
Infliximab	RA	RLS	NA	NA	9	145.0	5.5 (Sweden)	Askling *et al.*[2]
Infliximab	RA	RLS	90	78.17	2	2558.0	66.0 (Korea)	Seong *et al.*[6]
Infliximab	RA, AS, PsA	RLS	NA	NA	17	1113.0	9.4 (Spain)	Gomez-Reino *et al.*[10]

~Number of patients included in the study.
§per 100,000 patient-years.
*IR for TB infection in general population of certain country per 100,000 population.
AS, ankylosing spondylitis; CD, Crohn's disease; LTE, long-term extension; NA, not applicable; PsA, psoriatic arthritis; PsO, psoriasis; Pt-yrs, patient-years; RA, rheumatoid arthritis; RLS, real-life study; TNF, tumour necrosis factor; UC, ulcerative colitis.

reported.[35–38] Patients in PALACE 1 and PALACE 3 did not undergo baseline screening for latent TB. A 4-year extension (a total of 7465 patient-years) pooled analysis from PALACE 1, PALACE 2 and PALACE 3 did not provide specific data for TB infection, but authors concluded

that the long-term risk for opportunistic infections is similar with the first year of apremilast administration and is comparable with placebo group.[32] In addition, data from 1184 patients with psoriasis treated for 3 years with apremilast 30mg twice daily revealed no *de novo* TB infection or TB reactivation.[39] Physicians should keep in mind that pathophysiology of TB infection might differ between patients with psoriasis and patients with PsA. There is a lack of long-term real-life data, but two observational studies with 202 PsA patients treated for 6 months reported no TB cases.[40,41] Collectively, use of apremilast does not appear to be combined with increased risk for TB infection.

JAK inhibitors

JAK inhibitors (also known as Jakinibs) comprise a new class category of DMARDs. These, block the signal mediated through JAK/signal transducers and activators of transcription (STAT) pathway, which is used by many different cytokines and other molecules.[42] JAKs have four members, namely JAK1, JAK2, JAK3 and TYK2. Although Jakinibs have been mainly used in inflammatory arthritis, especially in RA, and in haematological malignancies, it seems that they are efficient in a wide spectrum of immune-mediated diseases such as alopecia areata, inflammatory bowel diseases, dermatomyositis and others.[42] Many different Jakinibs have been developed with various selectivity for specific JAK members. In general, limited data are available regarding their safety profile because most of them have been recently approved or are in phase-III trials.

Regarding the pathophysiologic link between this class category and TB, it has been hypothesized that blockade of IL-12 or IL-23 (which act through JAK2/TYK2)[43,44] might lead to inhibition of IFNγ production by T cells.[45] Besides, mutations in IL-12, TYK2 and STAT1 related genes have been found to associate with inherited susceptibility to mycobacterial diseases.[43,46]

Tofacitinib. Tofacitinib is the most well studied Jakinib inhibiting JAK3 and JAK1 and to a lesser extend JAK2 and TYK2. Tofacitinib has been approved from US Food and Drug Association (FDA) and European Medicines Agency (EMA) for RA and PsA (5 mg twice daily), as well as for ulcerative colitis (UC) (10 mg twice daily). A study examining data from 14 clinical trials [6 phase-III, 6 phase-II and 2 long-term extension (LTE) studies] enrolling 5671 patients followed-up for 12,664 patient-years[47] identified 26 cases of TB with the crude incidence rate (IR) being 210 [95% confidence interval (CI); 140 to 300]/100,000 patient-years. Most of the cases were described in patients receiving high dose tofacitinib (i.e. 10 mg, twice daily). Median time from treatment commencement to TB diagnosis was 64 weeks. Patients aged ⩾65 years-old displayed higher IR compared with younger patients in LTE studies, although this was not the case in data obtained from phase-III studies. Glucocorticoid usage did not seem to alter the risk for TB. It is also noteworthy that in more than half of the patients (58%) TB was extrapulmonary[47] as seen in patients treated with TNFi regimes.[48] Another similarity with the latter population is that cases of TB were more frequent in endemic countries. Of note, from 263 patients diagnosed with latent TB in the phase-III studies and received chemoprophylaxis with isoniazide, none of them developed TB.[47] Similarly, a study assessing the long-term safety of tofacitinib in RA, examining data derived from 6194 patients participating in the phase-I, -II and -III as well as LTE studies, showed that the IR for TB was 200 (100–300)/100,000 person years.[49] IRs did not differ between dosing schemes (i.e. 5 mg or 10 mg, twice a day) although they were numerically lower for the 5 mg groups.[49] In general, although well designed studies are needed so that a safe conclusion can be drawn, it seems that TB risk offered by tofacitinib is similar to that seen in RA patients treated with TNFi.[47]

Beyond RA, no LTE studies exist for tofacitinib in PsA. Data from the phase-III studies assessing the efficacy and safety of this drug in PsA have not reported any cases of TB.[50,51] Similarly, phase-II and phase-III studies for tofacitinib in UC (10 mg twice daily) did not report any TB cases[52–55] while results from open label, LTE studies are awaited [ClinicalTrials.gov identifier: NCT01470612]. In a recently published study analysing data from the aforementioned studies, including 1157 patients with total exposure of 1612.8 patient-years, no TB cases are reported.[54]

Baricitinib. Baricitinib is a more selective Jakinib, inhibiting JAK1 and JAK2. Safety data are derived from studies conducted in patients with RA patients, for which baricitinib has been approved. In the largest study so far, examining data from 8 randomized clinical trials (RCTs) and 1 LTE study, 10 cases of TB were recorded. In a total of 3492 patients with median exposure to the drug

of 2.1 years, the respective IR was 150/100,000 person-years.[56] All cases were reported in regions with a high prevalence of TB. Along the same lines, in a sub-analysis of patients from east Asia, were TB is endemic, the IR for active TB was 230/100,000 patient-years for baricitinib-treated RA patients.[57] However, in a sub-analysis examining Japanese patients enrolled in six of the above-mentioned studies, no case of TB was recorded.[58] Finally, in another open-label, LTE study examining the safety and efficacy of baricitinib for up to 128 weeks with a total exposure of 433.9 patient-years, in patients with RA, no TB cases were recorded.[59]

Newer JAK inhibitors. Fewer data are available for the newer JAK inhibitors. These include filgotinib, upadacitinib, both selective for JAK1 and peficitinib which has some selectivity for JAK3.

For upadacitinib, in all phase-III studies for RA patients published so far, enrolling all together more than 1500 patients, only 1 case of TB has been noted.[60–63] Similarly, for filgotinib and peficitinib that was recently approved in Japan for the treatment of RA, no TB cases have been reported in the published phase-IIb and -III studies.[64–68] LTE studies and real-world data are needed to further characterize the safety profile of the newer generation Jakinibs.

In conclusion, more data, especially from real-world studies, are needed to define whether the risk for TB is comparable with that seen in patients treated with TNFi or other biologic drugs (Table 2),[56] TB screening is *sine qua non* before commencing these drugs. It should be noted that endemic areas are expected to have more cases of TB, as seen with patients treated with TNFi,[47,56] and that many TB cases do not present with the classical manifestations (fever, cough, weight loss) but are extrapulmonary.[47,49] Several questions remain unanswered. For example, is the TB risk the same across different Jakinibs? And are there any differences between the different indications for which these drugs are used?

Biologic DMARDs

IL-12 and IL-23 inhibitors

IL-12 and IL-23 contribute in cellular response to TB, especially in the early phase of the infection, by triggering the expression of IFNγ and TNFα.[69] As briefly mentioned previously, indirect blockade of either IL-12 or IL-23 might lead to inhibition of IFNγ production by T cells,[45] and mutations in IL-12, TYK2 and STAT1 related genes have been associated with susceptibility to mycobacterial infection.[43,46] Of note, it has been shown that the ability to control proliferation of *Mycobacterium bovis* and granuloma formation was not affected in both IL-23p19-deficient mice and in mice treated with a specific anti-IL-23p19 antibody.[70]

Ustekinumab. Ustekinumab is a monoclonal antibody against the shared p40 subunit of IL-12 and IL-23, approved for the treatment of PsA and plaque psoriasis. The 1-year safety data from pivotal studies PSUMMIT 1 and PSUMMIT 2 revealed no cases of active TB in a total of 705 PsA patients treated with 45 mg or 90 mg ustekinumab.[71,72] Moreover, after 2-year follow-up of 598 patients from the same studies no case of active TB was reported.[73] A real-life study with 65 PsA patients treated with ustekinumab for 2 years did not report any data on TB and patients with latent TB were excluded.[74] In an RCT of ustekinumab for Crohn's disease (CD), a patient developed *de novo* active TB ten months after receiving a single intravenous dose of 130 mg.[75] The risk for active TB in RCTs for CD was significantly lower in those treated with ustekinumab, than in those treated with golimumab and infliximab (22, 240 and 390 per 100,000 patient-years, respectively).[76] Notably, ustekinumab dosage in CD is much higher than that used in inflammatory arthritis and one could speculate that opportunistic infections might be more frequent in the former subgroup. However, data are very limited to lead to a safe conclusion.

A plethora of data supports that ustekinumab does not increase the risk of new TB infection or reactivation of latent TB in patients with psoriasis. During a 4-year follow-up of 1482 psoriasis patients treated with ustekinumab, no TB cases were reported.[77] From 167 psoriasis patients with latent TB treated with ustekinumab and isoniazid, no one presented with TB reactivation.[78] A study from Taiwan, an intermediate TB burden country, showed no TB reactivation either with or without chemoprophylaxis after an almost 2-year follow-up in 27 psoriasis and PsA patients with latent TB on ustekinumab.[79] In the same study, the seroconversion rate was 7.3% with ustekinumab (Table 3), which is lower compared with 14.3% reported with TNFi in the same

Table 2. Cases of tuberculosis (TB) and incidence rate (IR) in patients receiving targeted synthetic DMARDs.

Targeted synthetic DMARDs								
Drug	**Disease**	**Study type**	**No~**	**Pt-yrs**	**Active TB cases**	**IR§**	**Rate general population***	**Reference**
Apremilast	PsO	RCT, LTE	1184	3671.3	0	0.0	International	Crowley *et al.*[39]
Apremilast	PsA	RCT	1644	NA	0	0.0	International	Cutolo *et al.*[35]; Edwards *et al.*[36]; Kavanaugh *et al.*[37]; Wells *et al.*[38]
Apremilast	PsA	RLS	202	101.0	0	0.0	7.0 (Italy)	Abignano *et al.*[40]; Favalli *et al.*[41]
Tofacitinib	RA	RCT, LTE	5671	12,664.0	26	210.0	International	Winthrop *et al.*[47]
Tofacitinib	RA	RCT, LTE	6194	19,406.0	36	200.0	International	Cohen, *et al.*[49]
Tofacitinib	PsA	RCT	394	NA	0	0.0	International	Gladman *et al.*[50]
Tofacitinib	PsA	RCT	316	NA	0	0.0	International	Mease *et al.*[51]
Tofacitinib	UC	RCT	1157	1612.8	0	0.0	International	Sandborn *et al.*[54]
Baricitinib	RA	RCT, LTE	3492	6636.7	10	150.0	International	Smolen *et al.*[56]
Baricitinib	RA	RCT, LTE	740	1294	3	230.0	East Asia	Chen *et al.*[57]
Baricitinib	RA	RCT, LTE	540	851.5	0	0.0	14.0 (Japan)	Harigai *et al.*[58]
Baricitinib	RA	LTE	201	433.9	0	0.0	International	Keystone *et al.*[59]
Upatacitinib	RA	RCT	2022	NA	1	NA	International	Burmester *et al.*[60]; Fleischmann *et al.*[61]; Genovese *et al.*[62]; Smolen *et al.*[63]
Filgotinib	RA	RCT	1128	NA	0	0.0	International	Genovese *et al.*[65]; Kavanaugh *et al.*[66]; Westhovens *et al.*[68]
Peficitinib	RA	RCT	545	NA	0	0.0	International	Genovese *et al.*[64]; Kivitz *et al.*[67]

~Number of patients included in the study.
§per 100,000 patient-years.
*IR for TB infection in general population of certain country per 100,000 population.
DMARDs, disease-modifying anti-rheumatic drugs; LTE, long-term extension; NA, not applicable; PsA, psoriatic arthritis; PsO, psoriasis; Pt-yrs, patient-years; RA, rheumatoid arthritis; RCT, randomized control trial; RLS, real-life study; UC, ulcerative colitis.

population.[79,80] Although data from psoriasis and CD patients are reassuring about TB risk and ustekinumab, more real-life data are needed for patients with PsA.

Guselkumab. After ustekinumab, the targeted anti-IL-23p19 monoclonal antibody guselkumab was approved for the treatment of PsA. Recently, a phase-II study in 100 patients with PsA revealed no cases of active TB during a 1-year follow-up.[85] Guselkumab has shown no statistically significant efficacy in RA patients compared with placebo.[86] In the latter trial, no case of TB was reported in 110 guselkumab-treated patients (neither with 50 mg nor with 200 mg dose). In addition, in four phase-III clinical trials in 1283 patients with psoriasis, no increased risk for new TB infection or latent TB reactivation was observed during a 1-year follow-up.[87]

Table 3. Tuberculosis (TB) screening tests seroconversion rates between different biologic DMARDs and cases with seroconversion that developed active TB.

Drug	Disease	Patients	Number of Conversions	Active TB	Rate (%)	Country	Reference
Etanercept	RA	62	6	0	9.7	Italy	Cuomo *et al.*[81]
Etanercept	RA, JIA, AS	27	4	0	14.8	Italy	Cerda *et al.*[82]
Adalimumab	RA	60	11	0	18.3	Italy	Cuomo *et al.*[81]
Adalimumab	RA, JIA, AS	18	3	1	16.7	Italy	Cerda *et al.*[82]
Etanercept, Adalimumab	PsO	91	13	0	14.3	Taiwan	Cheng *et al.*[80]
Infliximab	RA	11	1	0	9.1	Italy	Cuomo *et al.*[81]
Infliximab	RA, JIA, AS	15	0	0	0	Italy	Cerda *et al.*[82]
Certolizumab	RA	19	1	0	5.3	Italy	Cuomo *et al.*[81]
Certolizumab	RA, JIA, AS	1	0	0	0	Italy	Cerda *et al.*[82]
Golimumab	RA	16	2	0	12.5	Italy	Cuomo *et al.*[81]
Golimumab	RA, JIA, AS	3	0	0	0	Italy	Cerda *et al.*[82]
Ustekinumab	PsO	109	8	0	7.3	Taiwan	Hsiao *et al.*[79]
Secukinumab	PsO	96	1	0	1	Taiwan	Wu *et al.*[83]
Tocilizumab	RA	44	7	0	15.9	Italy	Cuomo *et al.*[81]
Tocilizumab	RA, JIA, AS	13	1	0	7.7	Italy	Cerda *et al.*[82]
Abatacept	RA	37	6	0	16.2	Italy	Cuomo *et al.*[81]
Abatacept	RA, JIA, AS	8	0	0	0	Italy	Cerda *et al.*[82]
Rituximab	RA	43	0	0	0	Taiwan	Chen *et al.*[84]

AS, ankylosing spondylitis; DMARDs, disease-modifying anti-rheumatic drugs; JIA, juvenile idiopathic arthritis; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis.

Risankizumab. Risankizumab is a novel anti-IL-23p19 monoclonal antibody approved for the treatment of psoriasis, which is under investigation in PsA and CD and has failed to show efficacy in ankylosing spondylitis (AS). In 185 PsA patients that received risankizumab for 6 months, no active TB cases are reported.[88] As for psoriasis, in two phase-III RCTs (ultIMMa-1, ultIMMa-2) including 588 patients, no opportunistic infection was reported.[87] In a recently published head-to-head 1-year study between risankizumab and adalimumab in psoriasis, no case of active TB occurred in 301 risankizumab-treated patients.[89] No data for TB cases are available for risankizumab use in AS and CD patients.

Tildrakizumab. Another targeted anti-IL-23p19 monoclonal antibody, tildrakizumab, was recently introduced in psoriasis and is under investigation in PsA, AS and non-radiographic axial spondyloarthritis patients. A 6-month phase-IIb study with PsA patients did not present data for TB infection.[90] Of note, in two phase-III clinical trials (reSURFACE 1 and reSURFACE 2) and one phase-II a total of more than 1000 psoriasis patients were exposed to tildrakizumab for about 1000 patient-years and the incidence of severe infections was 1.1–1.6 per 100 patient-years, without specific data for TB.[91]

IL-17 inhibitors

Secukinumab. Secukinumab is a monoclonal antibody that targets IL-17A and has been proved effective in psoriasis, PsA and AS. In TB infection, IL-17 production from neutrophils enhances

host immune response,[92] while increased IL-17 levels has been found in bronchoalveolar lavage fluid from TB patients.[93] Kammüller *et al.* utilized an *in vitro* MT microgranuloma model and administered adalimumab and secukinumab. Microgranulomas treated with adalimumab showed characteristics of MT reactivation in contrast to secukinumab-treated microgranulomas, whose results were comparable with untreated or control-treated microgranulomas.[94] Thus, it is suggested that secukinumab does not influence MT dormancy and does not lead to experimental TB reactivation.

From a clinical point of view, a recent pooled analysis of 21 clinical trials of secukinumab (15 trials in psoriasis, 3 in PsA and 3 in AS) including 7355 patients with an overall exposure of 16227 patient-years, showed no case of TB reactivation and one case of *Mycobacterium avium* infection.[95] In addition, post-marketing surveillance data were presented in the same study; during 96,054 patient-years, five new TB cases were recorded (5 per 100,000 patient-years), but no reactivation.[95] These results are in line with previous report that reviewed safety data from 10 clinical trials of secukinumab only in psoriasis.[96] In the latter, in 3430 patients treated for 2725 subject-years, 146 with latent TB were detected and were given anti-TB chemoprophylaxis; no cases of TB reactivation occurred. In a study from Taiwan with 96 secukinumab-treated patients with psoriasis (40% had PsA also), seroconversion was developed in only one patient (~1%) (Table 3) during a mean follow-up of 12.5 months and no case of active TB was reported.[83] Conclusively, *in vitro* studies, clinical trials and post-marketing surveillance data support that patients on secukinumab are at a low risk for TB infection (Table 4).

Ixekizumab. Another IL-17A antagonist has been recently introduced in the treatment of PsA and AS. Ixekizumab has demonstrated clinical efficacy and safety in two RCTs in PsA patients (SPIRIT-P1 and SPIRIT-P2). Overall, 1118 patients received ixekizumab and were exposed for 1373.4 patient-years, demonstrating no *de novo* TB infection or latent TB reactivation (only two patients had positive IGRA at baseline).[98] In the COAST-V clinical trial, 164 patients with AS received ixekizumab for 16 weeks and no active or latent TB was reported.[97] Notably, the follow-up time in this study was too short and patients with proved or suspected active or latent TB were excluded at the screening. As with other newer bDMARDs, much more safety data is available from clinical trials in patients with psoriasis. An integrated safety data analysis from 11 clinical studies of ixekizumab in psoriasis accounted for 5730 patients exposed for 13479 patient-years.[99] During treatment with ixekizumab, 72 patients (1.3%) developed treatment-emergent latent TB or positive IGRA/TST results, but no cases of active TB.

Brodalumab. An IL-17 receptor-A inhibitor, brodalumab, has been approved for psoriasis and has been shown to be efficacious in PsA and AS. In 168 PsA patients treated for 9–12 months with brodalumab, no case of active TB was reported, although patients with latent TB were excluded if they did not receive prophylactic anti-TB treatment.[101] Moreover, in a 16-week phase-III study of brodalumab in 80 AS patients, no data for TB are available, but the serious adverse events rate was comparable with the placebo group.[100] The experience of brodalumab in psoriasis is richer but data on TB infection from three 1-year phase-III RCTs (AMAGINE-1, AMAGINE-2 and AMAGINE-3) are not available.[102] To be mentioned, patients with a known history of past TB infection or positive screening for TB that did not receive prophylactic anti-TB treatment were excluded from the aforementioned studies. Eventually, data regarding active TB cases in brodalumab-treated patients are inadequate to come to a safe conclusion.

IL-6 inhibitors

Tocilizumab. TCZ is a monoclonal antibody directed against both soluble and membrane IL-6 receptor. It has been approved by the FDA and EMA for the treatment of RA, systemic or polyarticular juvenile inflammatory arthritis (JIA) and refractory giant cell arteritis (GCA). IL-6 appears to play an important protective role against MT, mainly in cases of exposure to high mycobacterial load.[103,104] Nevertheless, Ogata *et al.* showed that TCZ did not hinder IFN-γ production induced by two different MT antigens, contrary to etanercept and infliximab, both of which led to IFN-γ level reduction.[105] The minimal influence of TCZ in IFN-γ production suggests that TCZ-treated patients might not demonstrate false negative IGRA (as TNFi-treated patients) and are at a low risk of latent TB infection reactivation.

A thorough systematic review examined the safety of non-TNFi biologic agents (TCZ, RTX, ABA,

Table 4. Cases of tuberculosis (TB) and relative incidence rate (IR) in patients receiving IL-12, IL-23, IL-17 inhibitors.

IL-12, IL-23, IL-17 Inhibitors								
Drug	**Disease**	**Study type**	**No~**	**Pt-yrs**	**Active TB cases**	**IR§**	**Rate general population***	**Reference**
Ustekinumab	PsA, PsO, CD	RCT	5884	4521	1	22.12	International	Ghosh *et al.*[76]
Ustekinumab	PsA	RCT	705	NA	0	NA	International	Ritchlin *et al.*[72]
Ustekinumab	PsA	LTE	615	NA	0	NA	International	Kavanaugh *et al.*[73]
Ustekinumab	PsA	RLS	65	NA	0	NA	7.0 (Italy)	Chimenti *et al.*[74]
Ustekinumab	CD	RCT	1177	NA	1	NA	International	Feagan *et al.*[75]
Ustekinumab	PsO	LTE	3117	8998	0	0.0	International	Lopez-Ferrer *et al.*[77]
Guselkumab	PsA	Phase II	100	NA	0	NA	International	Deodhar *et al.*[85]
Guselkumab	RA	Phase II	110	NA	0	NA	International	Smolen *et al.*[86]
Guselkumab	PsO	RCT	1283	NA	0	NA	International	Crowley *et al.*[87]
Rizankizumab	PsA	RCT	185	NA	0	NA	International	Mease *et al.*[88]
Rizankizumab	PsO	RCT	588	NA	0	NA	International	Crowley *et al.*[87]
Rizankizumab	PsO	RCT	301	NA	0	NA	International	Reich *et al.*[89]
Secukinumab	AS, PsA, PsO	RCT	7355	16,227	0	NA	International	Deodhar *et al.*[95]
Secukinumab	AS, PsA, PsO	LTE	NA	96,054	1	5.0	International	Deodhar *et al.*[95]
Secukinumab	PsO	RCT	3430	2725	0	0.0	International	van de Kerkhof *et al.*[96]
Secukinumab	PsO	RLS	96	104.5	0	0.0	43.0 (Taiwan)	Wu *et al.*[83]
Ixekizumab	AS	RCT	164	NA	0	NA	International	van der Heijde *et al.*[97]
Ixekizumab	PsA	RCT	1118	1373	0	0.0	International	Mease *et al.*[98]
Ixekizumab	PsO	RCT	5370	13,479	0	0	International	Romiti *et al.*[99]
Brodalumab	AS	RCT	80	NA	0	NA	International	Wei *et al.*[100]
Brodalumab	PsA	RCT	168	NA	0	NA	International	Mease *et al.*[101]

~Number of patients included in the study.
§per 100,000 patient-years.
*IR for TB infection in general population of certain country per 100,000 population.
AS, ankylosing spondylitis; CD, Crohn's disease; LTE, long-term extension; NA, not applicable; PsA, psoriatic arthritis; PsO, psoriasis; Pt-yrs, patient-years; RCT, randomized control trial; RLS, real-life study.

ustekinumab and secukinumab) by collecting data from RCTs, their respective extended-label and open-label studies and national registries.[106] In 15,485 RA patients treated with TCZ no cases of TB were reported, regardless the use of conventional DMARDs (cDMARDs).[106] Similar results were described in previous systematic reviews and meta-analyses; in an earlier report by Cantini *et al.*, which also included 4 JIA clinical trials, no active TB cases were disclosed.[107] Of note, in GCA patients, two clinical studies have shown TCZ efficacy but did not clarify if patients with latent TB were included and if any patient developed active TB during the study period.[108,109] Another previous meta-analysis of RCTs and LTEs enrolling patients with RA, PsA, AS, psoriasis, UC or CD, confirmed the absence of TB associated with TCZ in RCTs of RA patients.[27]

However, in the LTEs in RA patients, there were 9 cases of TB in 12,905.2 patient-years (70/100,000 patient-years) in the TCZ group, though the estimated pooled IR for TB was still considerably lower compared with TNFi.[27]

Data from real-world studies in Japan (REAL registry, $n=302$), Finland (patients with JIA, $n=6$), India ($n=13$) and a TB endemic area in the United Kingdom ($n=17$) showed no cases of active TB in patients under TCZ therapy.[110–113] Two real-life studies from Taiwan, one 15-year retrospective and one 3-year prospective, reported no cases of active TB among 31 and 114 patients, respectively.[114,115] Similarly, a Brazilian retrospective cohort with 336 patient-years follow-up displayed no cases of TB in RA patients treated with TCZ.[116] A big cohort of TCZ-treated patients ($n=16,074$) from USA that used claims data did not present data for TB.[117]

Rutherford *et al.* analysed data from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) in order to reveal the incidence of opportunistic infections in RA patients receiving biologic agents. In the TCZ group there was only one case of TB in 2171 patients, with an IR of 26 per 100,000 patient-years.[31] Lastly, a real-world study from Malaysia, a country with a high TB incidence, included a total of 68 courses of TCZ treatment in RA patients and demonstrated 3 cases of TB development,[118] and a post-marketing safety report of TCZ in RA patients in Japan disclosed a IR of 220 per 100,000 patient-years for active TB infection.[119]

Two studies from Italy investigated the conversion rate of TB screening tests in patients under TCZ treatment. Among 44 patients with negative initial TST or IGRA test, treatment with TCZ resulted in seroconversion in seven patients, during a mean period of 24 months (Table 3). Nevertheless, none of the patients developed active TB infection.[81] In another study, only one out of 13 patients under TCZ treatment experienced TST conversion and received isoniazide as chemoprophylaxis.[82]

To conclude, TCZ does not seem to be linked with a significantly increased risk for TB infection, especially in countries with a low burden of TB (Table 5).

Newer IL-6 inhibitors. Sarilumab, a fully human monoclonal antibody against IL-6 receptor, has been approved by the FDA and EMA for RA. None of 1348 RA patients treated with sarilumab for at least 1 year experienced active TB.[120] Of note, in a 4-month phase-II study in 301 AS patients, sarilumab was not effective, but no cases of TB were reported.[121]

Clazakizumab is a monoclonal antibody that targets IL-6 with high affinity and specificity. Two cases of pulmonary TB were reported during a 6-month phase-III RCT of clazakizumab in 298 RA patients (1340/100,000 patient-years), both of which were in TB endemic countries.[122] On the other hand, no case of TB occurred in 124 clazakizumab-treated PsA patients after a 6-month follow-up.[123]

Sirukumab selectively binds to IL-6 and has been investigated in RA. Four phase-III RCTs with a follow-up of 52 weeks included 2193 RA patients and one TB case was reported (46/100,000 patient-years), although in two of these studies patients with past history of TB or 'chronic or recurrent infections' were excluded.[124–127]

LTE studies and real-life data are still needed to evaluate the TB risk of the newer IL-6 inhibitors.

Abatacept and rituximab

Abatacept. ABA is a fusion protein consisting of the Fc fragment of IgG1 immunoglobulin and the extracellular domain of CTLA-4 that hinders the stimulation of T cells by binding to the co-stimulatory CD80 and CD86 molecules of antigen presenting cells. It has been approved by the FDA and EMA for the treatment of active RA, JIA and adult PsA. A study in animal models has shown that the use of ABA in mice with chronic TB infection did not result in exacerbation of the TB infection, contrary to the use of anti-murine TNF antibody.[136]

Only one case of probable active TB was reported in 17 trials of ABA use in 8539 RA patients,[106] while none were disclosed among 190 JIA and 128 PsA patients.[107] In a meta-analysis of LTEs, ABA displayed a low estimated pooled IR for TB (60/100,000 patient-years).[27] Integrated analyses of intravenous short-term and cumulative use of ABA in 8 clinical trials showed that TB occurred

Table 5. Cases of tuberculosis (TB) in patients receiving IL-6 Inhibitors, abatacept, rituximab.

IL-6 Inhibitors, abatacept, rituximab								
Drug	**Disease**	**Study type**	**No~**	**Pt-yrs**	**Active TB cases**	**Rate§**	**Rate general population***	**Reference**
Tocilizumab	RA	RCT, LTE	15,485	NA	0	0	International	Cantini *et al.*[106]
Tocilizumab	JIA	RCT	205	NA	0	0	International	Cantini *et al.*[107]
Tocilizumab	RA	RCT	3354	NA	0	0	International	Souto *et al.*[27]
Tocilizumab	RA	LTE	NA	12,905.2	9	75.6	International	Souto *et al.*[27]
Tocilizumab	RA	RLS	302	NA	0	0	14 (Japan)	Sakai *et al.*[113]
Tocilizumab	JIA	RLS	4	6.4	0	0	4.7 (Finland)	Tarkiainen *et al.*[111]
Tocilizumab	Various ARD	RLS	16	NA	0	0	199 (India)	Shobha *et al.*[112]
Tocilizumab	RA, JIA	RLS	17	NA	0	0	50 (UK-endemic region)	Nisar *et al.*[110]
Tocilizumab	RA	RLS	31	55.49	0	0	43 (Taiwan)	Lim *et al.*[114]
Tocilizumab	RA	RLS	114	141.38	0	0	43 (Taiwan)	Lin *et al.*[115]
Tocilizumab, Abatacept, Rituximab	RA	RLS	195	NA	0	0	45 (Brazil)	Yonekura *et al.*[116]
Tocilizumab	RA	RLS	2171	3861	1	26	8 (UK)	Rutherford *et al.*[31]
Tocilizumab	RA	RLS	68	NA	3	NA	92 (Malaysia)	Tan *et al.*[118]
Tocilizumab	RA	RLS	3881	1793.5	4	223	14 (Japan)	Koike *et al.*[119]
Sarilumab	RA	RCT	1348	NA	0	0	International	Lee *et al.*[120]
Sarilumab	AS	RCT	251	NA	0	0	International	Sieper *et al.*[121]
Clazakizumab	RA	RCT	298	NA	2	NA	International	Weinblatt *et al.*[122]
Clazakizumab	PsA	RCT	124	NA	0	0	International	Mease *et al.*[123]
Sirukumab	RA	RCT	2193	NA	1	NA	International	Aletaha *et al.*[124]; Takeuchi *et al.*[125,126]; Taylor *et al.*[127]
Abatacept	RA	RCT, LTE	8539	NA	1	NA	International	Cantini *et al.*[106]
Abatacept	RA	RCT	433	433	1	230	International	Souto *et al.*[27]
Abatacept	JIA, PsA, SLE	RCT	535	NA	0	0	International	Cantini *et al.*[107]
Abatacept	RA	RCT, LTE	4149	12,132	8	70	International	Weinblatt *et al.*[128]
Abatacept	RA, JIA, PsA	RLS	1292	NA	0	0	International	Nisar *et al.*[110]; Tarkiainen *et al.*[111]; Shobha *et al.*[112]; Lim *et al.*[114]; Takahashi *et al*[129]; Salmon *et al.*[130]
Rituximab	Various ARD	RCT	5233	NA	0	0	International	Cantini *et al.*[107]

(Continued)

Table 5. (Continued)

IL-6 Inhibitors, abatacept, rituximab								
Drug	**Disease**	**Study type**	**No~**	**Pt-yrs**	**Active TB cases**	**Rate§**	**Rate general population***	**Reference**
Rituximab	RA	RCT, LTE	3194	11,962	2	18	International	Souto *et al.*[27]
Rituximab	RA	RLS	5072	17,154	2	12	8 (UK)	Rutherford *et al.*[31]
Rituximab	RA	RLS	39	NA	2	NA	92 (Malaysia)	Tan *et al.*[118]
Rituximab	Various ARD	RLS	33	NA	0	0	50 (UK-endemic region)	Nisar *et al.*[110]
Rituximab	Various ARD	RLS	42	NA	0	0	199 (India)	Shobha *et al.*[112]
Rituximab	JIA	RLS	9	8	0	0	4,7 (Finland)	Tarkiainen *et al.*[111]
Rituximab	RA	RLS	1303	1629	0	0	9.2 (France)	Gottenberg *et al.*[131]
Rituximab	Various ARD	RLS	370	299	0	0	7.3 (Germany)	Tony *et al.*[132]
Rituximab	RA	RLS	32	NA	0	0	7.3 (Germany)	Xanthouli *et al.*[133]
Rituximab	RA	RLS	2484	NA	1	NA	7.3 (Germany)	Wendler *et al.*[134]
Rituximab	RA	RLS	763	6179	2	32	43 (Taiwan)	Liao *et al.*[135]

~Number of patients included in the study.
§per 100,000 patient-years.
*IR for TB infection in general population of certain country per 100,000 population.
ARD, autoimmune rheumatic diseases; AS, ankylosing spondylitis; JIA, juvenile idiopathic arthritis; LTE, long-term extension; NA, not applicable; PsA, psoriatic arthritis; Pt-yrs, patient-years; RA, rheumatoid arthritis; RCT, randomized control trial; RLS, real-life study; SLE, systematic lupus erythematosus; TCZ, tocilizumab.

in only eight patients (66/100,000 patient-years) and presented after 1–3 years of treatment.[128]

To our knowledge, there have been no cases of active TB reported in several studies conducted in real-life settings in patients with inflammatory arthritis treated with ABA, among 1272 patients.[110–112,114,116,129,130] TST or IGRA conversion occurred in 6 out of 45 patients (13.3%) under ABA; nevertheless, none of them developed active TB.[81,82] In conclusion, it seems that ABA does not significantly increase the risk for *de novo* or reactivated TB infection.

Rituximab. RTX is a monoclonal antibody targeted against the CD20 protein found on B lymphocytes. This regime is marketed for RA, granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). As an anti-B cell agent, it does not inhibit T cell action, which is the primary immune cell involved in the protection against TB. An interesting study examined the effects of RTX therapy on IFN-γ levels in 56 patients with RA. Among them, seven patients had latent TB and 6 had TB associated with TNFi treatment. RTX therapy resulted in no significant changes in IFN-γ levels or IGRA conversion and no active TB cases were reported.[84]

No cases of active TB have been reported in patients receiving RTX in 9 RCTs with RA patients ($n = 3623$) or patients with Sjogren's syndrome ($n = 107$), systematic lupus erythematosus (SLE) ($n = 700$), mixed cryoglobulinemia ($n = 381$) and GPA and MPA ($n = 422$).[107] In two LTEs in RA patients, two cases of active TB have been reported during a follow-up time of 9.5 years (18/100,000 patient-years).[137] In comparison with other biologics, RTX exhibited the lowest pooled IR of TB in a meta-analysis of LTEs (18 per 100,000 patient-years).[27]

Data from national registries and real-world data, including patients with several autoimmune conditions other than RA (JIA, SLE, GPA, MPA, multiple sclerosis, pemphigus and other), have

Table 6. Comparative presentation of active tuberculosis (TB) incidence rates (IR) between different biologic and targeted synthetic DMARDs.

Drug	Disease	Study type	IR§	Reference
Infliximab	RA, AS, PsA, PsO, CD, UC	LTE, RLS	52.5–2558.0	Askling *et al.*[2]; Seong *et al.*[6]; Wolfe *et al.*[8]; Dixon *et al.*[9]; Gomez-Reino *et al.*[10]; Souto *et al.*[27]; Tubach *et al.*[28]
Certolizumab	RA	LTE	474.29	Souto *et al.*[27]
Adalimumab	RA, AS, PsA, PsO, CD, UC	LTE, RLS	90.0–215.0	Dixon *et al.*[9]; Souto *et al.*[27]; Tubach *et al.*[28]
Golimumab	RA, AS, PsA	LTE	172.13	Souto *et al.*[27]
Etanercept	RA, AS, PsA, PsO	RLS, LTE	9.3–80.0	Askling *et al.*[2]; Dixon *et al.*[9]; Souto *et al.*[27]; Tubach *et al.*[28]
Rituximab	RA	RCT, LTE, RLS	0.0–32.0	Rutherford *et al.*[31]; van Vollenhoven *et al.*[137]; Gottenberg *et al.*[131]; Tony *et al.*[132]; Xanthouli *et al.*[133]; Liao *et al.*[135]
Abatacept	RA, JIA, PsA	RCT, LTE, RLS	0.0–230.0	Souto *et al.*[27]; Cantini *et al.*[106,103]; Nisar *et al.*[110]; Tarkiainen *et al.*[111]; Shobha *et al.*[112]; Lim *et al.*[114]; Weinblatt *et al.*[128]; Takahashi *et al.*[129]; Salmon *et al.*[130]
Tocilizumab	RA, JIA	RCT, LTE, RLS	0.0–230.0	Souto *et al.*[27]; Cantini *et al.*[106]; Sakai *et al*[113]; Lim *et al.*[114]; Lin *et al.*[115]; Yonekura *et al.*[116]; Rutherford *et al.*[31]; Koike *et al.*[119]
Apremilast	PsA, PsO	RCT, LTE, RLS	0.0	Cutolo *et al.*[35]; Edwards *et al.*[36]; Kavanaugh *et al.*[37]; Wells *et al.*[38]; Crowley *et al.*[39]; Abignano *et al.*[40]; Favalli *et al.*[41]
Tofacitinib	RA	RCT, LTE	200.0–210.0	Winthrop *et al.*[47]; Cohen *et al.*[49]
Baricitinib	RA	RCT, LTE	150.0–230.0	Smolen *et al.*[56]; Chen *et al.*[57]
Ustekinumab	PsA, PsO, CD	RCT, LTE, RLS	0.0–22.12	Ghosh *et al.*[76]; Lopez-Ferrer *et al.*[77]; Tsai *et al.*[78]; Hsiao *et al.*[79]
Secukinumab	AS, PsA, PsO	RCT, LTE	0.0–5.0	Deodhar *et al.*[95]; van de Kerkhof *et al.*[96]
Ixekizumab	PsA, PsO	RCT	0.0	Mease *et al.*[98]; Romiti *et al.*[99]

§per 100,000 patient-years.
AS, ankylosing spondylitis; CD, Crohn's disease; DMARDs, disease-modifying anti-rheumatic drugs; JIA, juvenile idiopathic arthritis; LTE, long-term extension; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; RCT, randomized control trial; RLS, real-life study; UC, ulcerative colitis.

confirmed the low risk of *de novo* TB infection or latent TB reactivation from RTX treatment as no cases of TB have been reported in most of these,[110,111,116,131–133] even in the presence of latent TB. Only one case of TB was reported in 2484 patients treated with RTX in the German GENIRIS study,[134] while two cases with active TB were found in a retrospective Taiwanese RA study during 6179 patient-years (32/100,000 patient-years), both in patients previously treated

with TNFi.[135] Likewise, data from the BSRBR-RA showed that in the RTX group, only two cases during 17,154 patient-years developed TB (12/100,000 patient-years), which is significantly lower compared with the risk in the TNFi group (65/100,000 patient-years).[31]

In general, it appears that the risk of TB associated with RTX is lower compared with TNFi, but also to most other bDMARDs and tsDMARDs.[27]

Conclusion

Based mainly on the results of RCTs and LTE studies, the TB risk associated with the use of most of the non-TNFi agents is generally lower, compared with TNFi. In fact, it seems that the risk of either *de novo* TB infection or reactivation of latent TB is relatively low with apremilast, ustekinumab, secukinumab and rituximab treatment (Table 6). No safe conclusion can be drawn for Jakinibs yet, but the risk for active TB infection seems comparable with those of TNFi. "Although seroconversion is noted in a small proportion of patients treated with bDMARDs, being lower for those treated with secukinumab and rituximab, this does not lead in increased incidence of latent TB reactivation."

In everyday clinical practice, and bearing in mind that new aspects might be enlightened by long-term post-market surveillance, one could say that when there is latent TB, anti-CD20 therapy would be preferable. In diseases where their role is limited (e.g. PsA, seronegative spondyloarthropathies), drugs targeting cytokines involved in the IL-23/-17 axis or apremilast are the most reasonable options. Jakinibs seem to have the same safety profile, regarding TB, with TNFi.

Risk of TB cannot be definitely assessed by data obtained from RCTs.[27] RCTs generally tend to underestimate the true incidence of latent TB reactivation, possibly due to the strict patient inclusion criteria and the relatively limited observation time. LTE studies or even better, real-world data from big nation-wide registries are thought to be more appropriate to answer this question.[9] The latter are still limited for the most non-TNFi bDMARDs and tsDMARDs. Although TB has been well recognized as an opportunistic infection in the context of RA treated with biologic drugs, it is possibly underestimated in patients receiving non-biologic drugs[25] and in other ARD (e.g. SLE). Moreover, when rheumatologists assess the risk for TB infection, they should take into account concomitant cDMARDs or glucocorticoid usage. Finally, it seems that the risk for TB in biologic-exposed patients has been significantly decreased over the last few years.[1,31] This is probably related to the increased awareness and subsequent screening. Thus, comparison between studies needs to be interpreted with caution.

Studies specifically designed for assessment of opportunistic infections, including TB, are needed to help the clinician safely use the available drugs, especially in countries endemic for TB and for patients diagnosed with latent TB. Screening for latent TB must always precede bDMARD or tsDMARD initiation.

Conflict of interest

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