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Review

Guidance for the management of patients with latent tuberculosis infection requiring biologic therapy in rheumatology and dermatology clinical practice

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ABSTRACT

Since the introduction of biologics for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), and psoriasis (Pso) an increased risk of tuberculosis (TB) reactivation in patients with latent tuberculosis infection (LTBI) has been recorded for anti-TNF agents, while a low or absent risk is associated with the non-anti-TNF targeted biologics. To reduce this risk several recommendation sets have been published over time, but in most of them the host-related risk, and the predisposing role to TB reactivation exerted by corticosteroids and by the traditional disease-modifying anti-rheumatic drugs has not been adequately addressed. Moreover, the management of the underlying disease, and the timing of biologic restarting in patients with TB occurrence have been rarely indicated. A multidisciplinary expert panel, the Italian multidisciplinary task force for screening of tuberculosis before and during biologic therapy (SAFE BIO), was constituted, and through a review of the literature, an evidence-based guidance for LTBI detection, identification of the individualized level of risk of TB reactivation, and practical management of patients with TB occurrence was formulated. The literature review confirmed a higher TB risk associated with monoclonal anti-TNF agents, a low risk for soluble receptor etanercept, and a low or absent risk for non-anti-TNF targeted biologics. Considering the TB reactivation risk associated with host demographic and clinical features, and previous or current non-biologic therapies, a low, intermediate, or high TB reactivation risk in the single patient was identified, thus driving the safest biologic choice. Moreover, based on the underlying disease activity measurement and the different TB risk associated with non-biologic and biologic therapies, practical indications for the treatment of RA, PsA, AS, and Pso in patients with TB occurrence, as well as the safest timing of biologic restarting, were provided.

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1. Introduction

Over the last 15 years biologic drugs have ensured relevant advantages in rheumatology and dermatology for the treatment of rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), and psoriasis (Pso). To date, several agents with pharmacological activity targeted on different levels of immune response are available in clinical practice, including interleukin-6 inhibitor tocilizumab (TCZ), anti-CD20 rituximab (RTX), anti-interleukin-1 anakinra (ANK), anti-CD28 abatacept (ABA), anti-IL12-23 ustekinumab (UTK), and anti-tumor necrosis factor alpha agents (anti-TNF α) including adalimumab (ADA), etanercept (ETN), infliximab (IFX), golimumab (GOL), and certolizumab (CTP).

However, data from clinical trials and from real-life clinical practice have shown that currently used biologics, namely the anti-TNF α and to a lesser extent the non-anti-TNF α targeted agents, may constitute a risk factor for tuberculosis (TB) reactivation in subjects with latent TB infection (LTBI) [1,2]. Hence, LTBI screening and prevention of active TB represent a current worldwide challenge for biologic prescribers.

To reduce the risk of TB reactivation several sets of recommendations and guidelines have been proposed, but none of them may be appropriate for the single country due to the different social and economic conditions and the variable prevalence of TB [3]. The majority of recommendations/guidelines have been prompted for patients to be treated with the oldest anti-TNF α , namely IFX, ETN and ADA, while no policy document is available for the more recently marketed biologics such as GOL, CTP, TCZ, RTX, ABA, and UTK.

In addition, most of the current recommendations raise some concerns because they do not take in account the specific risk related to the host and to the previous or current treatments, and only two sets have been formulated through a multidisciplinary approach [4,5]. Furthermore, although biologics are loaded by a different TB risk, none of the recommendations provide indications for choosing the proper biologic treatment in function of the specific risk associated with the single patient. Finally, details concerning the management of the underlying rheumatic disease or Pso in case of active TB occurrence have been rarely indicated [6].

2. Objective

To provide an evidence-based algorithm for the detection of LTBI and prevention of TB reactivation, to examine the clinical variables, including the host-related, the traditional disease modifying anti-rheumatic drug (DMARD)-related, and the single biologic agent-

related TB risk, that may influence the therapeutic choice in LTBI positive patients with RA, PsA, AS, and Pso requiring biologic therapy, and to suggest practical indications for the management of the patients with active TB complicating the clinical disease course.

3. Methods

3.1. SAFE BIO expert panel purpose

A multidisciplinary expert panel, the Italian multidisciplinary task force for screening of tuberculosis before and during biologic therapy (SAFE BIO), including specialists in rheumatology (FC, CN, LN, FI), microbiology (GD), radiology (GG), pneumology (ASZ), immunology (AM), dermatology (FP), epidemiology (MC), and infectious diseases (DG), was constituted to perform a systematic literature review on the existing recommendations for LTBI screening before biologic starting and overtime follow-up, the TB risk related to different biologics, the host-related risk, the previous therapy-related risk, and to formulate evidence-based practical guidelines for the management of LTBI positive patients with inflammatory rheumatic disorders and Pso.

3.2. Literature search

The literature review was made using PubMed database to identify English-language articles related to the previously mentioned topics. Regarding the TB risk associated with the specific biologic agent, all published clinical trials, data from post-marketing surveillance, and from national registries of currently used biologics for the treatment of RA, AS, and PsA, and Pso were reviewed to identify all cases of TB complicating the underlying rheumatic or dermatologic disease course. Data were extracted from phase III randomized controlled trials (RCTs), their open-label extension phase studies, and from open-label, prospective studies of at least 12-week duration focused on the efficacy and safety of each drug. As an additional selection criterion, we included only the studies published after October 2001, when the recommendations for LTBI detection and TB reactivation prevention were introduced. In addition, available data from biologic national registries, national healthcare databases, and post-marketing surveillance surveys were included. Reviews and meta-analyses were excluded.

The following drugs were investigated: IFX, ETN, ADA, GOL, CTP, RTX, TCZ, ANK, ABA, and UTK. The research was performed by crossing the single drug name with the following key terms: TB, infections,

comorbidities, safety, registry, guidelines, and recommendations. For each biologic were recorded the number of publications, the type of trial, the number of enrolled patients, the number of TB cases and, when possible, the setting where TB occurred. Moreover, the evidence on LTBI detection, TB reactivation prophylaxis, host-related risk, the risk associated with the underlying disease and with previous or concomitant non-biologic therapies was reviewed.

The literature review was extended to December 31, 2014.

4. Results

4.1. SAFEBIO evidence-based guidance for LTBI screening procedures and active TB prophylaxis

LTBI screening procedures are mandatory before biologic starting. A full clinical history and physical examination should be part of the initial assessment. This should include details of ethnicity, country of birth, history of recent exposure to TB, previous active TB and treatment completion, together with any additional risk such as drug or alcohol abuse [7]. Fig. 1 shows the SAFEBIO recommendations in BCG-unvaccinated and -vaccinated subjects. These recommendations have been developed on the basis of current evidence with respect to the sensitivity and specificity of tuberculin skin test (TST), interferon gamma release assay (IGRA), and chest radiograph used for LTBI screening and TB-preventive therapy [8–10].

The panel recommends the use of the IGRA over the TST in patients who had previously received a BCG vaccination, due to the high false positive test rates for TST [11,12]. Due to the discrepancies between TST and IGRA results [13,14], and the recent data on the better performance of combined TST and IGRAs in the detection of LTBI [15], in

those that are not BCG-vaccinated, the panel recommends combined use of TST and IGRA as the initial tests in all patients before starting biologic agents. Since TST may increase IGRA results [16], IGRA determination should precede TST execution.

RA, PsA, AS and Pso patients with a positive TST (≥ 5 mm in BCG-unvaccinated) or IGRA (QFT-GIT ≥ 0.35 UI/ml; T-SPOTB when at least one of the antigens has ≥ 6 spots) should have a chest radiograph and, if suggestive of active TB, a subsequent sputum examination to evaluate the presence of *Mycobacterium tuberculosis*.

Patients with RA, PsA, AS and Pso with a negative screening TST or IGRA may not need further evaluation in the absence of risk factors and/or absence of clinical suspicion for TB in low TB risk countries.

The panel recommends annual testing for LTBI in RA, PsA, AS and Pso patients with a negative screening TST or IGRA at baseline if they live, travel, or work in situations where TB exposure is likely while they continue treatment with biologic agents.

After the screening, if the patient results with active TB, the panel recommends appropriate anti-TB treatment and consideration of referral to a specialist. Oral and written information (education) on TB infection and disease should be provided to the patient.

For those defined as LTBI, treatment with biologic agents can be initiated or resumed after 1 month of LTBI treatment with anti-TB medications (INH for 9 months, or INH + RFP for 3 months or RFP for 4 months) and after completion of the treatment of active TB, as applicable [17,18]. LTBI patients scored positive to TST or IGRA at baseline can remain positive to these tests even after successful TB preventive therapy [19]. These patients need monitoring for clinical signs and symptoms of active TB, since repeating TST or IGRA will not help in the diagnosis of TB reactivation [8].

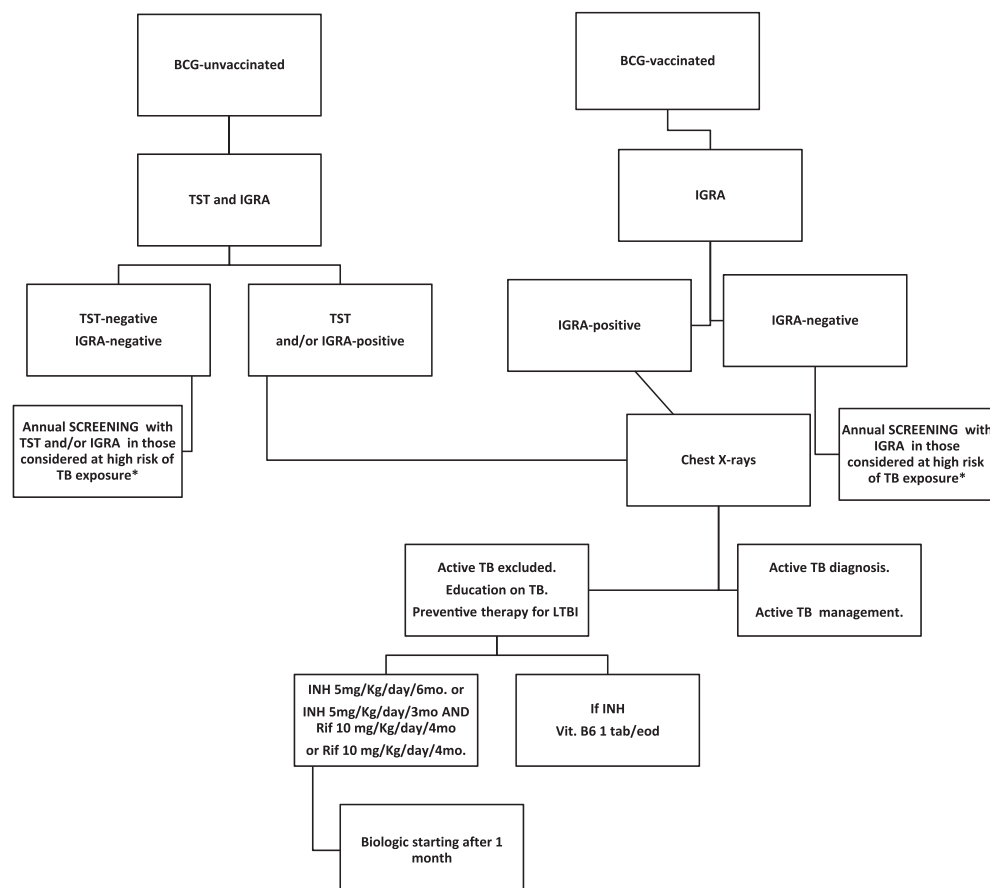


Fig. 1. SAFEBIO recommendations for LTBI detection and active TB prevention in RA patients before biologic therapy starting.

4.2. Evidence on host-related TB risk

In 2005, the Center for Disease Control and Prevention, Atlanta, indicated the persons who are at highest risk of TB infection and those at high risk of progression from LTBI to active TB, including people living in close contact with persons with suspected or active TB, born in high TB-risk countries, travelers who do frequent and prolonged visits in areas with a high prevalence of active TB, people who work in close contact with subjects at increased risk of active TB such as those medically underserved, low-income populations, drug or alcohol abusers, and infants, children, and adolescents exposed to adults at high TB risk [7].

After screening, those defined as LTBI, may have an increased risk of TB reactivation based on age, socioeconomic status, lifestyle, malnutrition, immune-suppression conditions and comorbidities [20]. In addition, the underlying autoimmune disease itself is associated with a higher TB risk, ranging from 2.0 to 8.9 in RA patients not receiving biologic therapies [21,22], and similar results were also reported in PsA and Pso [23,24]. Table 1 reports the host-related TB risk features with indication of the relative risk value.

4.3. Evidence on previous or concomitant therapy-related risk

As recommended [25], the first line therapy for patients with RA and PsA is based on the use of corticosteroids (CS) and traditional disease modifying anti-rheumatic drugs (DMARDs) including methotrexate (MTX), hydroxychloroquine (HCQ), leflunomide (LEF), sulphasalazine (SSZ), azathioprine (AZA), and cyclosporine A (CsA). This approach is also valid for Pso even if the DMARDs prevalently used are MTX and CsA [26], while traditional DMARDs are not recommended for the treatment of AS [27]. It has long been recognized that in patients with LTBI a prolonged CS therapy, or prednisone doses of 15 mg/day, or equivalent, given for 1 month or more predispose to TB reactivation [28]. In a recent British study a 3-fold increase of active TB cases in patients taking a dose of prednisolone <7.5 mg/day has been reported [29]. Similarly, an adjusted relative risk (RR) of 2.4 was found in a large cohort of RA patients receiving CS in Canada [23]. In the same report the traditional DMARD-

related TB risk was assessed. The highest risk resulted for LEF (RR: 11.7), almost equal risk for MTX and CsA (RR: 3.4 and 3.8, respectively), while no increased risk was registered for HCQ, SSZ, and AZA [23]. Table 1 reports the available data of traditional DMARD-related risk of TB reactivation.

4.4. Evidence on single biologic-related risk and individualized biologic choice

As previously reported [30], data from RCTs, national registries [31], and post-marketing surveillance of biologics report a 2–6 fold higher rate of TB reactivation in patients receiving anti-TNF agents, with some differences among the specific drug. Indeed, the risk resulted higher for monoclonal antibody anti-TNF ADA and IFX compared with ETN, while no conclusive data were available for GOL and CTP due to their recent introduction in the market. Since in the above quoted review the literature analysis was limited to May 31st, 2013, we extended the search to December 31st, 2014. Overall, 3 new TB cases were recorded in ADA trials [32–34], 1 case in IFX, CTP, and GOL trials respectively [35–39], while no TB cases were observed in ETN trials, thus confirming the higher TB risk in monoclonal antibody anti-TNF-exposed patients compared to those receiving ETN.

This concept seems to be reinforced by two recent studies of biosimilar infliximab. In the Planetra study [40], a RCT on 606 patients with RA where CT-P13 (biosimilar infliximab) efficacy and safety was compared to the originator IFX, 3 cases of active TB were recorded in CT-P13 treatment arm, and in the Planetas study, conducted on 229 patients with AS, 2 cases of TB were observed in the CT-P13 and 1 case in the originator IFX arms, respectively [41]. The limited data on biosimilar infliximab-related TB risk do not allow drawing of definitive conclusion, and this concern needs to be better addressed in large clinical series from real-life practice [42].

Of note, the combined use of anti-TNF agents and traditional DMARDs exposes to a higher risk of TB reactivation in subjects with LTBI compared to patients treated with anti-TNF monotherapy [43].

As recorded by the national registries of biologics and post-marketing surveillances, data from real-life practice further support the higher risk of TB reactivation associated with monoclonal antibody anti-TNF compared to soluble receptor, with a pooled median incidence rate/100,000/year of 83 cases for ETN, 203 for ADA, and 268 for IFX [30]. Similar data are not available for the recently marketed GOL and CTP.

Relative to non-anti-TNF targeted biologics, data of RTX, as expected due to its action targeted on B-lymphocytes, show no TB cases occurring in thousands of RA patients treated with this biologic [44,45]. Based on this evidence, recently the Rituximab Consensus Expert Committee suggested as unnecessary the screening procedures for LTBI before RTX therapy starting [46]. An absent or low TB risk has been recorded in patients treated with ABA, TCZ, and UTK [44], and the low or absent risk of TB reactivation in patients receiving ANK has been underlined in a recent review [47].

With respect to our previous review [44], the literature update confirms no increased risk of TB reactivation in patients receiving TCZ [48–53], ABA [33,54–56], and UTK [57–59].

4.5. SAFEBIO guidance for biologic starting in subjects requiring TB prophylaxis

There is no clear evidence in the literature concerning the optimal interval between the beginning of the preventive therapy for TB reactivation and biologic therapy starting. Experimental data have shown that 2-month INH therapy prevents the reactivation of LTBI and reduces the bacterial load in Mtb-infected monkeys treated with ADA [60]. In the absence of a similar evidence in humans, a lag time of 4 weeks between INH initiation and anti-TNF starting is considered safe by most experts and the majority of the international recommendations [3]. Data from the Spanish registry BIOBADASER seem to support the

Table 1
Host-and traditional DMARD-related TB risk reactivation.

Host-related		Traditional DMARD-related	
Demographic characteristic and comorbidity	Estimated RR	Drug	Estimated RR
Age <50 years	2	Corticosteroids	2.4
Family history of TB	2.38	Methotrexate	3.4
Recent TB infection (<2 years)	15	Leflunomide	11.7
Former TB disease	2.69		
Exposure to active TB subjects	10.1	Cyclosporine	3.8
Cigarette smoker	2	Other (sulphasalazine, azathioprine, hydroxychloroquine)	1.6
Alcohol abuse	1.84		
Drug abuse	2.83		
Malnutrition, low body weight (BMI ≤ 20)	2		
Pso/PsA [24]	3.1		
Diabetes	3.11		
RA [21]	3.68		
AS [25]	3.9		
Silicosis	30		
Severe kidney disease	25		
Abnormal chest x-ray—with upper lobe fibronodular disease typical of healed TB infection	19		

Except where otherwise indicated, data are quoted from the reference number [20]. Abbreviations. DMARD: disease modifying anti-rheumatic drug; RR: relative risk; TB: tuberculosis; Pso: psoriasis; PsA: psoriatic arthritis; RA: rheumatoid arthritis; AS: ankylosing spondylitis.

Table 3
Panel guidance for the management of RA, PsA, AS and Pso in patients with active TB complicating the disease course.

Disease	Disease activity	Treatment ^a
Rheumatoid arthritis	Low (DAS28: <3.2)	NSAIDs, analgesics, ICLR, SSZ. Restart biologics after 6 months of therapy for active TB.
	Moderate (DAS28: 3.3–5.0)	After 2-month of therapy for active TB, it is possible to use CS (as low as possible dose) + MTX or CsA. Restart biologics after 6 months of therapy for active TB.
	High (DAS28: >5.1)	After 2-month therapy for active TB it is possible to restart a low risk biologic: ANK, TCZ, RTX, and ABA for RA.
Peripheral psoriatic arthritis	Low (DAS28: <3.2)	NSAIDs, analgesics, SSZ. Restart biologics after 6 months of therapy for active TB.
	Moderate (DAS28: 3.3–5.0)	After 2-month therapy for active TB, it is possible to use CS (as low as possible dose) + MTX or CsA. Restart biologics after 6 months of therapy for active TB.
	High (DAS28: >5.1)	After 2-month therapy for active TB it is possible to restart a low risk biologic, preferably UTK and ETN as second choice
Axial psoriatic arthritis Ankylosing spondylitis	Inactive (ASDAS: <1.3)	NSAIDs on demand.
	Moderate (ASDAS: 1.4–2.0)	NSAIDs at full doses.
	High (ASDAS: >2.1–<3.5)	After 2-month therapy for active TB, if no response to NSAIDs, try bisphosphonates or restart anti-TNF, preferably ETN.
Psoriasis	Low (PASI: <5)	Topical therapy.
	Moderate (PASI: 5.1–10.0)	Topical therapy and/or phototherapy.
	High (PASI: >10.0)	After 2-month therapy for active TB restart a low risk biologic, preferably UTK, or ETN as second choice.

^a When necessary, local CS infiltrative therapy is allowed in patients with RA, PsA, and AS.

above mentioned recommendations showing a significant reduction of active TB cases in patients receiving anti-TNF therapy after 1 month from the initiation of the preventive therapy for TB reactivation [61].

As reported in Table 1, several conditions constitute major risk factors for TB reactivation, but in the case of patients with inflammatory rheumatic disorders or Pso, the underlying autoimmune disease itself increases the risk of TB reactivation. In addition, patients with RA, PsA, and Pso who require biologic therapy have a more severe disease and are usually treated with CS and traditional DMARDs that contribute to increase the risk. This therapeutic background is usually absent in AS, therefore these patients should be evaluated only for the host-related risk factors.

In the absence of validated risk score to be applied to the single patient, it may be reasonable to stratify the patients in function of the adjunctive risk factors and of the single biologic-related risk. As shown in Table 1, the RR values of risk factors have a bimodal distribution, below and above 10. Therefore, the host-related risk factors with an associated RR > 10 were arbitrarily categorized as major, and those below this cut-off as minor. In the last category we included the risk factors associated with the socio-economic status, traveling in high-risk country, and working in increased TB risk settings. In addition, patients presenting with two or more minor risk factors were considered as at high risk. In analogy with the validated RABBIT infection risk score [62], LTBI

patients with RA, PsA, AS, and Pso may be stratified in low, intermediate, and high risk as reported in Table 2. On this basis, patients at low risk may be treated with any biologic agent, RA patients with intermediate risk with non-anti-TNF targeted agents or with low TB risk ETN, while ETN and UTK are indicated for PsA. (See Table 2).

Concerning patients at high risk, ABA, TCZ, and ANK represent the drug of choice for RA therapy. Regarding RA therapy, RTX is not included in Table 2 because in Italy the drug has been licensed as second-line therapy.

Since only anti-TNF drugs are licensed for the treatment of AS, in patients at intermediate risk ETN is indicated, while in those at high risk, in view of some evidence of efficacy, bisphosphonates [63,64] may be tried before starting ETN.

In Pso patients at low risk all biologics may be employed, otherwise the drugs of choice are ETN or UTK in those at intermediate risk, and only UTK in high-risk subjects.

4.6. SAFE BIO guidance for the management of RA, AS, PsA and Pso in the case of active TB occurrence

Biologic therapy withdrawn is mandatory in the case of active TB diagnosis. Patients with inflammatory rheumatic disorders may be treated with analgesics, non-steroidal anti-inflammatory drugs (NSAIDs). In

Table 2
SAFE BIO guidance for biologic choice in patients with RA, PsA, AS, and Pso stratified in different categories of TB risk.

Disease	Risk factors	Risk category	First biologic choice
Rheumatoid arthritis	DMARD + CS + no host-related RF	Low	Any
	DMARD + CS + 1 minor host-related RF	Intermediate	ABA, TCZ, ANK, ETN
	DMARD + CS + 2 or >2 minor host-related RFs	High	ABA, TCZ, ANK
Psoriatic arthritis	DMARD + CS + 1 major host-related RF	Low	Any
	DMARD + CS + 1 minor host-related RF	Intermediate	ETN, UTK
	DMARD + CS + ≥2 minor host-related RFs	High	UTK
	DMARD + CS + 1 major host-related RF		
Ankylosing spondylitis	No host-related RF	Low	Any anti-TNF
	≤2 minor host-related RFs	Intermediate	ETN
	>2 minor host-related RFs	High	Try bisphosphonates
	1 major host-related RF		ETN (tight control for TB reactivation)
Psoriasis	DMARD + CS + no host-related RF	Low	Any
	DMARD + CS + 1 minor host-related RF	Intermediate	ETN, UTK
	DMARD + CS + ≥2 minor host-related RFs	High	UTK
	DMARD + CS + 1 major host-related RF		

Abbreviations. RF = risk factor; DMARD = disease modifying anti-rheumatic drug; CS = corticosteroids; ABA = abatacept; TCZ = tocilizumab; ANK = anakinra; ETN = etanercept; UTK = ustekinumab.

more severe cases, low-risk DMARDs such as hydroxychloroquine (HCQ) and sulphasalazine (SSZ) in RA and only sulphasalazine in AS and PsA (due to inefficacy of HCQ in these patients) can be used. Patients with Pso should be treated with local therapy and phototherapy. In collaboration with the local infectious disease specialists or pneumologists, patients with reactivated TB should undergo to monthly evaluation for toxicity of TB drugs and rigorously observe the international schemes for the clinical, radiological and microbiological TB follow-up (months 2 and 6) [65].

However, to date there are no guidelines/recommendations stating the correct management of the underlying rheumatic disease or Pso in patients treated for active TB and when to restart the biologics in case of severe disease flare. As shown in Table 3, according to previous report [66], SAFEbio expert panel suggests modulating the treatment based on the disease activity as measured by DAS28 for RA and PsA [67], ASDAS for AS [68], and PASI for Pso [69].

According to other reports [70,71], biologics may be restarted after at least 6 months of active TB treatment which usually corresponds to treatment completion. In the case of severe flare with high disease activity low risk biologics may be restarted after the 2-month induction therapy for TB.

4.7. SAFEbio guidance for patient monitoring after TB therapy withdrawal

After the successful completion of TB therapy, patient education on symptoms and signs of active TB through given oral and written instructions is recommended. Moreover patients should be referred to the infectologist/pneumologist twice a year over the first 2 years from TB therapy completion. Patients should be also informed to contact an infectivologist/pneumologist in case of TB signs/symptoms recurrence.

5. Conclusion

Biologics are characterized by different molecular structure and pharmacologic target with relevant differentiation concerning the risk of TB reactivation. Hence, clinicians should properly screen for LTBI the patients with RA, PsA, AS, and Pso who are candidates for biologic therapy, and LTBI subjects need to be properly assessed for different risk factors related to the host demographic and comorbidity features and to the previous or current immunosuppressive therapies.

Based on the literature data patients may be divided in different risk categories that may drive the appropriate biologic choice to ensure the safest treatment. The SAFEbio expert panel guidance may represent a useful instrument for the management of LTBI in patients with autoimmune diseases and for the treatment of the underlying disease in case of TB reactivation.

6. Take-home messages

- The risk associated with the demographic characteristics, the presence of comorbidities, the previous or current non-biologic drug exposure, and the different predisposing roles of biologics should be evaluated in patients with RA, PsA, AS, and Pso who are positive for LTBI and require biologic therapies.
- Through an evidence-based approach, LTBI positive patients may be categorized as at low, intermediate, and high risk of TB reactivation, with consequent reflexes on the choice of the safest treatment.
- The underlying disease treatment in patients with Tb occurrence should be guided by the disease activity assessment.

Conflict of interests

The authors declare no conflict of interests.

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