Diagnosis of Latent Tuberculosis and Prevention of Reactivation in Rheumatic Patients Receiving Biologic Therapy: International Recommendations

Florenzo Iannone, Fabrizio Cantini, and Giovanni Lapadula

ABSTRACT. ***Objective.*** To review the official international recommendations on the management of latent tuberculosis infection (LTBI) in patients with rheumatic diseases undergoing biologic therapy.

Methods. A systematic search of all clinical practice recommendations on the diagnosis and treatment of LTBI in rheumatic patients eligible for starting biologic drugs published between January 2002 and March 2013.

Results. For the diagnosis of LTBI, based on positivity of tuberculin skin test (TST), interferon-γ release assay (IGRA) is also available. Most recommendations advise using both TST and IGRA, especially in case of Bacillus Calmette-Guérin vaccination, to screen patients before commencing biologic drugs. There is a general consensus that evaluation of the global risk of TB infection is a crucial point and that patients with LTBI must receive chemoprophylaxis prior to biologic therapy. However, recommendations on the need for rescreening for activation of LTBI or new TB infection while patients are being treated are inadequate. Nevertheless, the main concern is poor compliance with TB recommendations of rheumatologists in clinical practice, which seems to be the main cause of the occurrence of active TB in rheumatic patients receiving biologic therapy.

Conclusion. Notwithstanding some differences, mainly related to regional TB incidence, international recommendations strongly suggest careful screening for LTBI before starting biologic therapy. However, the critical point is implementing dissemination and awareness of the recommendations among rheumatologists to improve adherence in real life. (J Rheumatol Suppl. 2014 May; 91:41–6; doi:10.3899/jrheum.140101)

Key Indexing Terms:
MYCOBACTERIUM TUBERCULOSIS
TST
IGRA
ANTI-TUMOR NECROSIS FACTOR-α AGENTS

Since the arrival of biologic drugs targeting tumor necrosis factor-α (TNF-α) for the treatment of rheumatoid arthritis (RA) and spondyloarthritis, the possible reactivation of latent tuberculosis infection (LTBI) has become a major concern for rheumatologists. TNF-α plays a key role in the host defense against *Mycobacterium tuberculosis* (Mtb) and in the formation of granuloma that hamper the dissemination of infection[1]. A strong association between tuberculosis (TB) reactivation and TNF-α blocking was detected in the USA soon after the licensure of infliximab (IFX) for RA[2]. Since then, an increase of incident TB in patients with RA undergoing treatment with TNF-α inhibitors has been reported by several registers worldwide[3,4,5,6,7,8,9]. This unexpected emergency has prompted many scientific societies and national public health agencies to release practical guidelines to reduce the risk of developing active TB during anti-TNF-α therapies, and this need has been felt mainly in those countries, such as Spain, where the prevalence of TB infection is higher. Subsequently, worries of possible activation of LTBI have extended to biologic drugs other than TNF-α blocking agents, notwithstanding that real scientific evidence of their effects on TB granuloma has never been provided.

The aim of this article is to review international recommendations on the diagnosis and treatment of LTBI in patients with rheumatic disease taking biologic drugs (mainly anti-TNF-α), to focus on some critical issues of TB screening, to discuss compliance with guidelines, and to consider unmet needs not yet satisfied by the current recommendations.

METHODS

We conducted a systematic search of all clinical practice recommendations on the diagnosis and treatment of LTBI in rheumatic patients eligible for

From the Department Interdisciplinary of Medicine, Rheumatology Unit, University of Bari, Bari; and Rheumatology Unit, Ospedale di Prato, Prato, Italy.

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F. Iannone, MD, PhD, Associate Professor in Rheumatology, Department Interdisciplinary of Medicine, Rheumatology Unit, University of Bari; F. Cantini, MD, Rheumatology Unit, Ospedale di Prato; G. Lapadula, MD, Full Professor in Rheumatology, Interdisciplinary Department of Medicine, Rheumatology Unit, University of Bari.

Address correspondence to Prof. Iannone, Interdisciplinary Department of Medicine, Rheumatology Unit, P.zza G. Cesare 11, 70124 Bari, Italy; E-mail: florenzo.iannone@uniba.it

starting biologic drugs published between January 2002 and March 2013. Only articles written in English were taken into account. Levels of evidence and strength of recommendation were graded following a simplified system from the Scottish Intercollegiate Guideline Network[10]. Accordingly, the level of evidence was graded as level I when based on metaanalysis of randomized clinical trials (RCT), systematic reviews of RCT, or individual RCT; level II when based on high-quality systematic reviews of observational studies, or well-conducted case-control or cohort studies; level III when based on nonanalytic studies, e.g., case reports and case series; and level IV when based only on expert opinion. The grade of recommendation was judged grade A (strong recommendation) in case of direct level I evidence; B (moderate recommendation) when the body of evidence was rated II; C (weak recommendation) in case of direct level III evidence; and grade D (consensus recommendation) when evidence level was based only on expert opinion.

Each recommendation was examined by comparing the different international guidelines, and questions not covered by the official guidelines were further discussed for each key point.

RESULTS

Screening for LTBI is strongly recommended by all international guidelines (level of evidence II), but some differences may be noted, mainly due to the endemic prevalence of TB infection[11,12,13,14,15,16,17,18,19] (Table 1).

Immunologic tests. Diagnosis of LTBI requires the demonstration of a specific immune response against Mtb, indicating a recall antigen response to Mtb, with or without living bacteria, in absence of clinical or radiological signs of active TB. Two tests are currently available to detect LTBI: the old tuberculin skin test (TST) and IGRA (interferon-γ release assay). TST, performed according to Mantoux method, detects previous infection with Mtb or other mycobacteria and Bacillus Calmette-Guérin (BCG) vaccination, and thus can yield several false positive results. In contrast, IGRA tests are more specific because IGRA detects an immune response against Mtb antigens not present in BCG or other mycobacteria. However, both tests can give false-negative results because of T cell anergy, which may occur in patients receiving treatment with glucocorticoids and immunosuppressants[20]. For this reason, the width of skin induration considered to indicate TST positivity was reduced to below 5 mm in potentially anergic patients[21]. However, IGRA tests can give information on immune reactivity because T cells are also challenged with mitogens. Regarding the diagnosis of LTBI, the American College of Rheumatology (ACR) guidelines recommend screening for LTBI in all patients before starting biologic agents regardless of the presence of risk factors by using TST or IGRA, the latter being preferred in patients with BCG history (level of evidence III)[18]. The guidelines of the Italian Society of Rheumatology recommend using TST, considered positive at > 5 mm, for LTBI screening in patients before initiation of therapy with TNF-α blockers (strength of recommendation B), and IGRA in selected patients with borderline TST and previous BCG vaccination (strength of recommendation C)[17]. Also, the Spanish National Health Service considers patients with TST ≥ 5 mm as having LTBI

Table 1. Summary of international recommendations for diagnosing latent tuberculosis infection (LTBI) in patients with rheumatic conditions before therapy with biologic drugs.

	USA — ACR	Italy — SIR	Spain — NHS, SER	UK — BTS	France	Canada — CRA	Switzerland	Europe — TBNET	Australia — ARA	Japan
Year	2012	2011	2002	2005	2003	2012	2007	2010	2011	2007
TST (Mantoux method)	Yes	Yes	Yes	Yes	Yes	Yes	No	No if BCG history	Yes	Yes
IGRA	Yes if low grade + TST, or BCG history	Yes if BCG history	—	—	—	Yes if BCG history	Yes	Yes if BCG history	Yes	—
Chest radiographs	If TST/IGRA +	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chest CT	—	—	—	—	—	—	—	—	—	Yes[$]
Prophylaxis	—	INH 9 mos	INH 9 mos	INH 6 mos	INH 9 mos, RMP 4 mos	INH 9 mos, RMP 4 mos	INH 9 mos, RMP 4 mos	INH 9–12 mos, RMP + INH 3 mos	INH 6–9 mos, RMP 4 mos	INH 9 mos
Rescreening	In high-risk TB patients[&]	In high-risk TB patients[&]	—	—	—	In high-risk TB patients[&]	In high-risk TB patients[&]	—	—	—
National TB prevalence	2011, 4.7*	2011, 3.5*	2011, 19*	2011, 19*	2011, 13*	2011, 5.6*	2011, 6*	—	2011, 7.6*	2011, 26*
Biologic drugs	All	All	Anti-TNF	Anti-TNF	Anti-TNF	Anti-TNF, ABA, TCZ	Anti-TNF	Anti-TNF	Anti-TNF	IFX, Etan

[$]Whenever possible; [&]If no LTBI at baseline; *Rates per 100,000 population. ACR: American College of Rheumatology; SIR: Italian Society of Rheumatology; NHS: National Health Service; SER: Spanish Society of Rheumatology; CRA: Canadian Rheumatology Association; ARA: Australian Rheumatology Association; TBNET: Tuberculosis network; TST: tuberculin skin test; BCG: Bacille Calmette-Guérin; IGRA: interferon-γ release assay; CT: computed tomography; INH: isoniazid; RMP: rifampicin; IFX: infliximab; Etan: etanercept; ABA: abatacept; TCZ: tocilizumab; anti-TNF: anti-tumor necrosis factor agent; BTS: British Thoracic Society.

without indicating the level of evidence[12]. The British Thorax Society recommends using TST for assessing LTBI in patients set to receive TNF-α therapy, considering TST > 6 mm positive in those without BCG history; however, TST > 15 mm may represent either LTBI or previous BCG vaccination (level of evidence III)[13]. French guidelines recommend a single threshold of 10 mm to consider a TST positive, without indicating the level of evidence[11]. The Canadian Rheumatology Association (CRA) recommends testing for LTBI in patients considered for therapy with anti-TNF-α drugs (level of evidence II) using TST; TST is also recommended preferably before taking other immunosuppressants or prednisolone > 15 mg/day. TST should be considered positive if > 5 mm, and IGRA tests should be used to identify false-positive TST in patients with previous BCG vaccination and without epidemiologic risk factors (level of evidence IV)[19]. The Swiss Lung Association uses an opposite policy: IGRA are the only diagnostic test for LTBI; thus, Swiss recommendations advise using IGRA, and no longer TST, for screening for TB prior to starting anti-TNF-α therapy[15]. The European Respiratory Society recommends using both TST and IGRA tests to diagnose LTBI. Similar clinical data are missing for IGRA and therefore IGRA cannot yet be recommended as the only tool to diagnose LTBI[22]. Also, the Australian Society of Rheumatology recommends performing both TST and IGRA tests[16]. Finally, the Japan College of Rheumatology advises performing TST, which is considered positive when redness is ≥ 20 mm or in the presence of induration, without indicating the diameter[13].

Risk factors. All international guidelines strongly recommend evaluating risk factors of TB infection by accurate clinical history of the patients to identify previous close TB contacts, human immunodeficiency virus (HIV) infection, immunosuppressive drugs, and underlying diseases that predispose to TB reactivation such as diabetes, cirrhosis, and alcoholism[11,13,14,15,17,18,19,21,22].

Chest imaging. The significance of the classic Ghon complex found in a standard chest radiograph as an indicator of previous pulmonary TB infection is incompletely understood and may depend on clinical symptoms and signs. All guidelines recommend a chest radiograph, especially in the presence of high-risk TB factors (level of evidence II), except for the ACR, which advises chest radiograph only in case of positive TB immunologic tests and presence of risk factors[18]. Further, Japanese guidelines recommend carrying out a chest computed tomography whenever possible[13].

LTBI therapy. In all countries the prophylaxis of reactivation of LTBI is recommended. The drug of first choice is isoniazid given for 6 months in the UK[13] or 9 months in Italy[17], Spain[12], France[11], Canada[19], Switzerland[15], Australia[16], and Japan[14]. As an alternative to isoniazid, a course of 4 months with rifampicin is advised[11,15,16,19]. Further, French guidelines recommend giving combined therapy with rifampicin and pyrazinamide for 2 months. However, the efficacy of this regimen for prophylactic treatment has been validated only in HIV-infected patients[11]. In the United States, the ACR recommends referring the patient diagnosed with LTBI to a specialist without indicating the therapeutic regimen[18].

Starting biologic drugs in patients with LTBI. All guidelines recommend starting treatment with biologics 1–2 months after beginning LTBI prophylaxis (level of evidence II; strength of recommendation B). This evidence comes from the observation that initiation of anti-TNF-α therapy after 1 month of TB prophylaxis in patients with RA found positive for LTBI significantly reduced the risk of TB reactivation (level of evidence III)[7,12]. Nevertheless, if the activity of underlying disease and the global status of the patient allow, waiting 1 additional month is preferable because the side effects of the therapy with isoniazid occur mainly within the first 2 months[12].

Rescreening. Another key point is the evaluation of possible TB infection in patients already under treatment with biologic drugs. Annual testing is recommended in US, Italian, Swiss, and Canadian guidelines (level of evidence II in cases of high TB risk, or IV; strength of recommendation B) in patients with high risk of TB infection, especially in those without LTBI prior to treatment. In those patients with positive TST/IGRA tests at entry, because these are not modified by LTBI treatment, the reevaluation is based only on clinical signs and symptoms of recurrent TB[15,17,18,19].

Biologic drugs. Not all biologic drugs share the same risk to reactivate LTBI, i.e., TNF-α blocking being the main mechanism by which mycobacteria may be released from granuloma. Hence, screening for LTBI is strongly recommended in cases of therapy with any TNF-α inhibitor by all the current guidelines, except in Japan, where screening is restricted to IFX and etanercept because their recommendations were issued in 2007 and have not been updated as of 2014[14]. The United States and Italy extended this recommendation to all the biological drugs approved for the treatment of RA[17,18], while the CRA recommends LTBI screening prior to starting anti-TNF-α drugs (level of evidence II) or abatacept and tocilizumab (level of evidence IV), without mentioning rituximab[19].

DISCUSSION

The interest of rheumatologists in TB infection has grown since findings that patients with RA who are receiving therapy with IFX had an increasing incidence of TB because of reactivation of LTBI[2]. This has prompted investigations to elucidate the role of TNF-α inhibition in the pathology of TB granuloma and the need to adopt protocols to screen patients for possible LTBI prior to starting anti-TNF-α

therapy. There is evidence that RA itself is a condition that favors reactivation of LTBI, and this risk is further enhanced by the use of TNF-α drugs[4,5,6,8]. Compared to the general population, Korean patients with RA not exposed to TNF-α inhibitors had a risk of developing active TB 8.9-fold higher and those treated with IFX 30.1-fold higher[8]. Yet, in a large Canadian cohort of biologic-naive patients with RA, the incidence rate of developing overt TB was 10-fold higher than in the general population, and therapy with glucocorticoids and conventional disease-modifying antirheumatic drugs was somewhat related to this risk[4]. Intriguing is the finding that patients with ankylosing spondylitis had a higher risk of TB compared to the general population, but lower than patients with RA, and that anti-TNF-α drugs did not further increase this risk[23], suggesting that RA has an intrinsically heavier burden on TB risk.

The probability of reactivating LTBI is not the same for all biologic drugs. TNF-α blockers pose the greatest risk, and among them the monoclonal antibodies, adalimumab and IFX, have been reported to be more highly correlated to reactivation of LTBI than soluble TNF-α receptor fusion protein[2,3,6,7,8,9,12,24,25].

While many countries and rheumatology associations have released recommendations as guidance to detect and treat LTBI in patients selected to start TNF-α inhibitors, the guidelines have also been extended to some non-anti-TNF-α drugs[11,12,13,14,15,16,17,18,19]. While there is general agreement that all patients must undergo screening for TB before starting biologic drugs and then treatment for 1–2 months of prophylactic therapy if LTBI is diagnosed, there are some differences regarding diagnosis of LTBI and longterm assessment of patients under biologic therapy.

TST is the standard method to identify LTBI but it has low specificity and does not discriminate latent infection sustained by Mtb from an immune response to non-specific mycobacteria or BCG vaccination. On the other hand, IGRA tests are more specific and sensitive for LTBI, and their predictive value for progression of LTBI to TB disease has been demonstrated to be higher than that of TST, as observed in subjects in recent close contact with active TB cases[26], but IGRA tests have not been validated in patients taking anti-TNF-α drugs. Accordingly, current international guidelines recommend TST first, and IGRA in cases of suspected false-negative TST in patients at risk of Mtb exposure, or if a history of previous BCG vaccination is present — except for Switzerland, where TST has been discarded and IGRA is the only test advised[15]. If some aspects of LTBI diagnosis need to be further clarified, an even more intriguing issue is the longterm reevaluation of patients taking ongoing anti-TNF-α therapy and having negative TB screening at entry. Most recommendations neglect this point; only a few consider that TB screening should be performed again in at-risk TB patients, such recommendation having a rather weak strength. This reinforces the relevance of an overall evaluation of possible exposure to Mtb and the intrinsic risks of the patient, as well as RA and anti-TNF-α treatments themselves. It has been shown that serial TST with IGRA may be useful to identify false-negative response to cases of LTBI and new TB infections during longterm anti-TNF-α therapy, especially in areas with intermediate TB burden, such as South Korea, and that the risk of TST conversion significantly increased over 3 years of therapy[27].

When dealing with official guidelines, the most crucial point is evaluation of their outcomes, i.e., adherence to TB recommendations, whether rheumatologists actually comply with guidelines, and finally their effects on TB progression in patients taking anti-TNF-α therapy. Reactivation of LTBI during therapy with TNF-α antagonists is rare nowadays unless there is poor adherence to the official recommendations. A survey of patients with rheumatic disease diagnosed with LTBI and starting anti-TNF-α drugs has shown that 11 patients (8 taking IFX and 3 taking adalimumab) developed active TB; however, 4 of them received none or inadequate chemoprophylaxis[24]. A lack of compliance with official recommendations has been shown to be mainly responsible for new cases of TB reactivation, as reported in a study in Spanish patients taking TNF-α inhibitors. The OR of developing active TB was 7 times higher when recommendations were not fully followed, and 2-step TST was the major failure[7]. A French study collected 69 cases of active TB in patients with different rheumatic diseases treated with anti-TNF-α drugs, and none of them had received correct chemoprophylactic treatment[9]. More recently, a retrospective survey carried out across the West Midlands in England to evaluate TB risk assessment in relation to BTS (British Thoracic Society) guidelines in patients with rheumatic diseases who were commencing TNF-α blockers in clinical practice has provided discouraging results[28]. Of 850 patients surveyed, 84.5% had a chest radiograph within 3 months of commencing anti-TNF-α therapy, and of the 48 patients in whom TST would have been appropriate (according to BTS guidance, TST is not indicated in patients taking immunosuppressants), it was performed on only 45.8%. Further, only 4 of 28 patients who were at high risk for TB because of their ethnicity or birthplace were given chemoprophylaxis[28]. On the other hand, the compliance with TB recommendations has greatly lessened the rate of reactivation of LTBI. In Spain, the likelihood of developing active TB among patients with rheumatic disease who were treated with anti-TNF-α drugs has significantly decreased after release of national recommendations, and the number of active TB cases dropped from 32 to 2, with an incidence rate per 100,000 falling from 523 to 112[12]. The effectiveness in preventing the reactivation of Mtb infection becomes more evident when adherence to official guidelines is absolutely tight, as in RCT. Among 2210 patients under golimumab therapy coming from different phase III clinical

trials, 317 patients were diagnosed with LTBI following complete TB screening and none developed active TB after adequate treatment with isoniazid[29].

Notwithstanding some differences among official recommendations, there is worldwide agreement that patients with rheumatic disease must undergo a comprehensive screening for LTBI prior to commencing biologic drugs, especially TNF-α blockers. There are still some open questions to cover, such as a better understanding of the predictive value of diagnostic tests for LTBI and a careful outlining of the risk of TB infection or LTBI reactivation, but the critical point is to disseminate awareness of the recommendations among rheumatologists to improve adherence in the daily clinical practice.

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