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Update on the infection of the immunocompromised patient

Mario Fernández-Ruiz[1,2]

Assessment of latent infections in patients receiving biological therapies

[1]Unit of Infectious Diseases, Hospital Universitario "12 de Octubre", Instituto de Investigación Hospital "12 de Octubre" (imas12), Madrid, Spain
[2]Spanish Network for Research in Infectious Diseases (REIPI RD16/0016/0002), Instituto de Salud Carlos III, Madrid, Spain

ABSTRACT

The use of biological (or targeted) therapies constitutes a major advance in the management of autoinflammatory and malignant diseases. However, due to the selective effect of these agents on the host's immune response, reactivation of certain pathogens that cause latent infection is to be expected. The most relevant concern is the risk of reactivation of latent tuberculosis infection (LTBI) and progression to active tuberculosis among patients treated with agents targeting tumor necrosis factor (TNF)-α. Systematic screening for LTBI at baseline with appropriate initiation of antituberculous treatment, if needed, is mandatory in this patient population as risk minimization strategy. In addition, reactivation of hepatitis B virus induced by B-cell-depleting (anti-CD20) and anti-TNF-α agents should be also prevented among HBsAg-positive patients and those with isolated anti-HBc IgG positivity (risk of "occult HBV infection"). The present review summarizes available evidence regarding the risk of reactivation of these latent infections induced by newer biological agents, as well as the recommendations included in the most recent guidelines.

Keywords: latent infection; tuberculosis; biological therapy; tumor necrosis factor-α; hepatitis B virus.

INTRODUCTION

The advent of the so-called biological (or targeted) agents has revolutionized the therapeutic approach to many inflammatory, autoimmune and malignant diseases. Indeed, biological therapies —both monoclonal antibodies and small-molecule inhibitors— have the ability of directly targeting the soluble inflammatory mediators, cell surface receptors or intracellular pathways implied in the pathogenesis of the condition, thus sparing normal tissues and minimizing the risk of treatment-related adverse events. In contrast to conventional immunosuppressive and cytostatic drugs, biological agents exert a rather selective effect on immune responses and, presumably, host-pathogen interaction. Although direct attribution of causality is often hampered by other contributing factors (such as the nature and activity of the underlying condition, the presence of comorbidities, or the concurrent use of immunosuppressive therapies), the understanding of the precise mode of action may allow for establishing a mechanistic relationship between a given agent and the expected susceptibility to infection [1]. From a clinical and epidemiological perspective, the most relevant and well-established association links the use of available agents targeting tumor necrosis factor (TNF)-α (summarized in table 1) with the risk of reactivation of latent tuberculosis infection (LTBI) and progression to active disease [2]. Therefore, the present review is mainly focused on this serious and preventable complication.

Correspondence:
Mario Fernández-Ruiz
Unit of Infectious Diseases. Hospital Universitario "12 de Octubre". Centro de Actividades Ambulatorias, 2ª planta, bloque D. Avda. de Córdoba, s/n. Postal code 28041. Madrid, Spain.
Phone: +34 913908000 - Fax: +34 914695775.
E-mail: mario_fdezruiz@yahoo.es

REACTIVATION OF LATENT TUBERCULOSIS INFECTION

The role of TNF-α in antituberculous immunity. After the primary infection with *Mycobacterium tuberculosis*, the effective long-term control of LTBI by the host's adaptive immune system ultimately depends on the dynamic equilibrium between pro-inflammatory and anti-inflammatory cytokines. The TNF-α, a pleiotropic cytokine, exerts a major role in the structural maintenance of tuberculous granulomas [3]. Thus, it is to be expected that the therapeutic blockade of TNF-α will result in the progression from LTBI to active tuberculosis. Nevertheless, it is noteworthy that no cases of tuberculosis were reported in the pivotal randomized clinical trials (RCTs) that led to the Food and Drug Administration (FDA) approval of infliximab for rheumatoid arthritis (AR) and Crohn's disease in the late 1990s despite the lack of specific risk-minimiza-

Table 1 **Type, mechanism of action and FDA- and EMA-approved indications of currently available anti-TNF-α agents (modified from ref. [2]).**

Agent	Type	Target	Mechanism of action	Mode of administration[a]	Approved indications
Infliximab (Remicade® and biosimilars)	Human-mouse chimeric IgG1 monoclonal antibody	mTNF-α, sTNF-α	Neutralization, apoptosis, reverse signaling, ADCC, CDC	IV injection every 6-8 weeks	IBD (CD and UC), RA, AS, PsA, plaque psoriasis
Etanercept (Enbrel®)	Fusion protein of the soluble TNFR2/p75 receptor and human IgG1 antibody (hinge, CH2 and CH3 domains of the Fc region)	mTNF-α, sTNF-α, TNF-β	Competitive inhibition, ADCC, CDC (weaker)	SC injection once or twice weekly	RA, AS, JIA, PsA, plaque psoriasis
Adalimumab (Humira®)	Fully human IgG1 monoclonal antibody	mTNF-α, sTNF-α	Neutralization, apoptosis, reverse signaling, ADCC, CDC	SC injection every 2 weeks	IBD (CD and UC), RA, AS, JIA, PsA, plaque psoriasis, hidradenitis, suppurativa, uveitis
Golimumab (Simponi®)	Fully human IgG1 monoclonal antibody	mTNF-α, sTNF-α	Neutralization, apoptosis, reverse signaling, ADCC, CDC	SC injection every 4 weeks	UC, RA, AS, JIA, PsA
Certolizumab pegol (Cimzia®)	PEGylated Fab' fragment of humanized IgG4 monoclonal antibody	mTNF-α, sTNF-α	Neutralization, reverse signaling	SC injection every 2-4 weeks	CD (only FDA), RA, AS, PsA, plaque psoriasis (only EMA)

ADCC: antibody-dependent cell-mediated cytotoxicity; AS: ankylosing spondylitis; CD: Crohn's disease; CDC: complement-dependent cytotoxicity; EMA: European Medicines Agency; FDA: Food and Drug Administration; IBD: inflammatory bowel disease; IV: intravenous; JIA: juvenile idiopathic arthritis; PS: plaque psoriasis; PsA: psoriatic arthritis; RA: rheumatoid arthritis; SC: subcutaneous; sTNF-α: soluble tumor necrosis factor α;mTNF-α: membrane-bound tumor necrosis factor α; UC: ulcerative colitis.

[a]**Maintenance doses once clinical response has been observed; initial doses vary according to the indication.**

tion measures in the study protocols [4, 5]. This circumstance should serve as a reminder of the limited ability of phase 2-3 trials to identify relatively rare but relevant adverse event signals associated with the use of newer biological agents [1]. The relevance of TNF-α in granuloma maintenance is also exemplified by the increased risk of histoplasmosis reported in endemic areas among patients under anti-TNF-α therapy [6].

Clinical evidence and risk factors. Since 2001, when the first cases of infliximab-associated tuberculosis were reported by the FDA Safety Information and Adverse Event Reporting Program [7], a large amount of evidence based on RCTs, open-label extension studies and post-marketing registries allows to delineate the risk of LTBI reactivation in patients receiving TNF-α-targeted therapies [8]. The largest meta-analysis published to date —including 29 RCTs and 11,879 patients— found an overall odds ratio (OR) of 1.94 (95% confidence interval [CI]: 1.10-3.44) for active tuberculosis under anti-TNF-α agents. Subgroup analyses revealed that patients with RA faced an even higher risk (OR: 2.29; 95% CI: 1.09-4.78) [9]. It should be noted that the baseline risk of tuberculosis among RA patients has been found to be higher as compared to the overall population [2]. It is likely that differences in underlying susceptibility to LTBI reactivation according to the condition itself that requires anti-TNF-α therapy may, at least partially, account for the relative lower incidence usually observed in patients with inflammatory bowel disease (IBD).

Such risk increase is not uniform across different agents. The use of etanercept, a dimeric fusion protein consisting of two extracellular ligand-binding portions of the soluble TNF-α receptor linked to the hinge and CH_2 and CH_3 domains of the human IgG1 Fc region, is consistently associated with a lower incidence of LTBI reactivation as compared to monoclonal antibodies targeting TNF-α, such as infliximab or adalimumab (table 1) [10, 11].

Various studies suggest that the previous or concomitant use of conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) and, particularly, corticosteroids has an additive negative impact on the individual susceptibility to tuberculosis [12, 13]. The risk of active tuberculosis also varies according to patient age (with higher incidence in older groups) and the background rate of LTBI in the overall population (with a British registry reporting higher incidence among foreign-born individuals of non-white ethnicity) [14]. The effect of the duration of therapy remains less clear. Some studies have shown that the incidence of associated infection is highest during the first year to gradually decrease thereafter, thus suggesting a progressive reduction over time of the individual risk [2]. However, the observational nature of the data may render such findings prone to misclassification bias due to case mix (i.e. selective treatment switching of patients who are already at an increased risk of infection due to age, comorbidities or prior infectious complications) [15].

Strategies for screening for latent tuberculosis infection. The cornerstone of prevention strategies aimed

at minimizing the risk of tuberculosis in patients receiving TNF-α-targeted agents relies on systematic screening for LTBI at the baseline evaluation, followed by prompt initiation of antituberculous treatment at least one month before the start of biological therapy. In the last few years, various guidelines and position papers have summarized the literature supporting the implementation of such practices, including an official initiative of the ESCMID (European Society of Clinical Microbiology and Infectious Diseases) Study Group for Infections in Compromised Hosts (ESGICH) that performed a comprehensive literature review accompanied by a series of evidence-based recommendations [16].

The diagnosis of LTBI mainly depends on demonstration of a *M. tuberculosis*-specific T-cell-mediated immune response, since by definition the infecting mycobacteria remain in a state of latency and the subject has no attributable symptoms. To this end, two different diagnostic approaches are currently available: the tuberculin skin test (TST) and the more recent interferon (IFN)-γ release assays (IGRAs). In overall terms, the latter approach —that may be based in enzyme-linked immunosorbent assay (ELISA) (QuantiFERON-TB® in different versions, Qiagen, Hilden, Germany) or enzyme-linked immunospot (ELISpot) formats (T-SPOT®.TB, Oxford Immunotec, Oxford, United Kingdom)— has the advantages of better reproducibility and specificity than the TST. This is because a pool of peptides (CFP-10, ESAT-6, TB7.7), which span a specific area (region of difference [RD1]) of *M. tuberculosis* genome, serves as stimulating antigens in IGRAs. Since RD1 is deleted in the Bacillus Calmette-Guérin (BCG) and is not shared by most of non-tuberculous pathogenic and environmental mycobacteria, the use of IGRAs as screening for LTBI would result in a lower false-positive rate. On the other hand, it should be also considered the increased cost of these assays compared to TST and the unexpected rate of reversions and conversions in healthy subjects (i.e. healthcare workers) in which serial IGRA testing was performed over time and no new exposure to *M. tuberculosis* could be apparently identified [17]. Assay variability due to lot manufacturing and pre-analytical and analytical execution defects might explain this finding [8]. Not surprisingly, the concordance rate between IGRA and TST has revealed to be suboptimal.

There is general consensus in performing both tests (TST and IGRA) and, eventually, a chest X-ray examination prior to the initiation of TNF-α-targeted agents to maximize sensitivity [2, 8, 16]. The positivity of any of them should lead to the diagnosis of LTBI and to the administration of antituberculous treatment, regardless of previous history of BCG vaccination. However, the optimal screening sequence to avoid an unacceptable number of false-positive results (and, therefore, unnecessary treatment courses and delays in anti-TNF-α therapy) is still not well established. A 10-year prospective study performed in Spain including 726 patients compared three screening strategies over consecutive periods: two-step TST (either an induration of ≥5 mm in the first test or an increase of ≥5 mm in the second test was considered positive); two-step TST followed by ELISA-based IGRA; and single-step TTS followed by IGRA. The proportion of patients diagnosed with LTBI was lower with the simplified single-step TTS plus IGRA strategy (26.5%) compared with the two-step TST (42.5%) or the two-step TST plus IGRA (38.5%) groups. As expected, BCG-vaccinated subjects had higher positivity rates for TST but not for IGRA. The authors found no significant differences in the incidence of active tuberculosis across the three periods (overall: 2.47 cases per 1,000 patient-years), suggesting that the repeat of TST after a first negative test would be not justified as long as the evaluation is completed with an IGRA [18]. There is also some experience (mostly based on small sized studies performed in low-incidence countries) with the use of a single IGRA as the sole screening, an approach may be particularly useful among patients with psoriasis in which the underlying skin condition often hinders the interpretation of TST [19].

In patients with a baseline negative evaluation for LTBI, the need for periodical retesting during the entire period of anti-TNF-α treatment remains a matter of debate, since the probability of new primary *M. tuberculosis* infection —which is greatly influenced by the background incidence of tuberculosis in the overall population— must be balanced against the risk of false positive results derived from repeated TST and/or IGRA (i.e. single or dual retesting strategy) over time. In the previously mentioned Spanish study, and after a median follow-up of almost 5 years, no cases of active tuberculosis occurred beyond the first year of therapy despite the fact that patients with a negative initial screening were not subsequently retested for LTBI. The authors concluded that retesting should be only considered on the basis of an individual risk assessment for *M. tuberculosis* infection [18]. A prospective study carried out in Greece —with a tuberculosis incidence rate in the overall population lower than that reported in Spain— included 70 RA patients with negative baseline screening (TST, IGRA [QuantiFERON-TB® Gold In-Tube and T-SPOT®.TB assays], and chest X-ray examination) that underwent re-screening following one year of anti-TNF-α treatment. Almost one third of them experienced conversion of at least one of these tests (with conversion rates of 13% for TST and 7% to 10% for IGRAs), despite that no obvious tuberculosis exposure had been recorded within the prior year. Although only 40% of these "converters" received therapy for LTBI, no cases of active tuberculosis were observed during the follow-up [20]. The ESGICH Consensus Document suggests that annual re-screening should be generally considered, acknowledging that clinical significance of test conversions remains unclear [16]. Thus, it seems reasonable that, in low-incidence settings, repeated screening for LTBI would be focused only on those subjects with clinical or epidemiological evidence of new exposure to *M. tuberculosis* since the initial negative evaluation, rather than in a systematic manner [2].

Treatment of latent tuberculosis infection. In patients diagnosed with LTBI, antituberculous treatment is mandatory and the administration of the anti-TNF-α agent should be delayed for 30-60 days [2, 8, 16]. Similar to other high-risk pa-

tient groups with indication for LTBI treatment, active disease must be previously ruled out on the basis of clinical and radiological assessment and, if necessary, sputum smear microscopy. If the patient has active tuberculosis, biological therapy must be postponed for a longer period (at least until sterilization of sputum cultures and clinical improvement have been achieved). In this scenario, it is likely that the subsequent use of etanercept —rather than anti-TNF-α monoclonal antibodies— or other biological agents, such as those targeting interleukin (IL)-6 receptor (certolizumab) or cell adhesion molecules (vedolizumab) should be favored in order to minimize the subsequent risk of tuberculosis relapse.

Isoniazid has potent tuberculocidal activity against intracellular and extracellular micobacteria. A 6- to 12-month course of isoniazid monotherapy (5 mg/Kg [maximum 300 mg] daily) remains as the first-line option for LTBI in patients receiving anti-TNF-α agents [8]. Vitamin B_6 (pyridoxine) supplementation is recommended in adults at risk for isoniazid-induced neuropathy (e.g. diabetes mellitus or alcoholism). The optimal duration of therapy is not well established in the absence of RCTs specifically focused on this population. By analogy with other high-risk groups, such as those with fibrotic pulmonary lesions, it seems that 6- or 9-month isoniazid regimens can be safely compared with 12 months of therapy. In addition, alternative regimens have been successfully tested in recent trials, including 3 months of isoniazid (900 mg) and rifapentine (900 mg) in 12 weekly doses, or 4 months of daily rifampicin (10 mg/Kg [maximum 600 mg] daily) [21, 22]. The available experience with such regimens to prevent LTBI reactivation induced by anti-TNF-α agents is so far limited. A recent single-center non-randomized study compared 41 patients with RA and positive IGRA results that received a 3-month regimen of weekly isoniazid and rifapentine or a 9-month regimen of daily isoniazid. Although not reaching statistical significance, a higher completion rate was found in the former than in the latter group (90.5% versus 78.3%, respectively). Moreover, the occurrence of hepatotoxicity was also lower among patients receiving weekly isoniazid and rifapentine. No cases of active tuberculosis were detected after a two-year follow-up [23]. No experience has been published to date on the use of the 4-month daily rifampicin regimen in patients scheduled to receive anti-TNF-α therapy, although the pivotal trial included about 100 patients per treatment arm with non-HIV-related immunosuppression [22]. Nevertheless, it should be keep in mind that rifampicin acts as a strong liver microsomal enzyme inducer, with the subsequent potential for drug-to-drug interactions [8].

Risk of tuberculosis with other biological therapies. The available evidence points out that the risk of LTBI reactivation and progression to active disease associated to biological therapies appears to be mainly restricted to TNF-α blockade [8]. As noted above, experience derived from pivotal RCTs must be taken with caution since such studies are generally underpowered to detect uncommon adverse events occurring in the mid- and long-term follow-up, as is the case of tuberculosis. Furthermore, most participants in phase 2-3 trials for RA or other rheumatologic conditions, IBD or psoriasis are recruited in low-incidence regions. In addition, and due to the past experience with anti-TNF-α therapy, LTBI screening and treatment is often (but not always) required as per study protocol at patient entry in trials on newer biological agents. Having said this, both the theoretical effect on the antimycobacterial immune response of the targeted pathways and the accumulated clinical experience suggest that anti-IL-17A (secukinumab or ixekizumab) and anti-IL-17 receptor agents (brodalumab) do not meaningfully impact the risk of active tuberculosis [24]. Likewise, the risk of LTBI reactivation under therapeutic blockade of the IL-6/IL-6 receptor pathway (tocilizumab, siltuximab or sarilumab) seems to be lower than that observed with anti-TNF-α agents, although the confounding effect of underlying conditions and prior and concomitant immunosuppressive drugs cannot be ruled out [24]. Finally, it has been shown that the functional abrogation of IL-12 is associated with an increased risk of tuberculosis. This is exemplified by an uncommon condition known as Mendelian susceptibility to mycobacterial disease, which consists of a collection of monogenic disorders. In detail, *IL12RB1* (one of the affected genes) encodes for the common receptor chain whose interaction with IL-12 and IL-23 is inhibited by ustekinumab, a monoclonal antibody targeting the p40 subunit shared by both cytokines. Therefore, the ESGICH Consensus Document recommends LTBI screening before starting treatment with ustekinumab. However, this theoretical risk of active tuberculosis has been not substantiated by clinical experience [24].

REACTIVATION OF HEPATITIS B VIRUS INFECTION

Apart from LTBI, the use of certain biological therapies also poses a risk for reactivation of viral pathogens able to establish chronic or latent infection within the host. Such a concern applies particularly to hepatitis B virus (HBV), not only in patients with chronic HBV surface antigen (HBsAg)-positive infection but also in those who have apparently cleared the virus but remain at risk of "occult" infection (HBsAg-negative, anti-hepatitis B core [HBc] IgG-positive patients, with or without detectable anti-HBs antibodies). In the latter group, HBV DNA may be still detected in the serum and liver tissue in form of episomal covalently closed circular DNA (cccDNA) or integrated into the hepatocyte genome. This balance between the host's immune surveillance and the virus can be disrupted by immunosuppressive therapy, leading to viral replication that can evolve into life-threatening hepatitis, with occasional HBsAg re-seroconversion [25].

The risk of HBV reactivation is clearly associated with the use of B-cell-depleting agents (rituximab and the newer anti-CD20 monoclonal antibodies such as ofatumumab, obinutuzumab or ocaratuzumab), with rates exceeding 30-40% and 10% for HBs-positive and HBsAg-negative/anti-HBc-positive subgroups, respectively [25]. Reactivation of HBsAg-positive infection has been also described with anti-TNF-α agents, although the available evidence is more limited than in the case

of anti-CD20 therapy [2]. A comprehensive literature review that comprised 225 cases published until 2011 revealed that reactivation occurred in 37% of HBsAg-positive patients, substantially lower than the rate observed among HBsAg-negative/anti-HBc-positive patients (5%). Previous immunosuppressive therapy was found to increase the risk of HBV reactivation, and infliximab was associated with a higher rate of liver disease than etanercept. Of note, five patients experienced fatal acute liver failure [26]. However, it is likely that the reactivation rates reported in this study may be overestimated [25]. Anti-TNF-α agents have generally been reported to be associated with a lower incidence of reactivation than that observed with potent immunosuppressive cancer chemotherapy, being most cases restricted to patients with RA rather than IBD or psoriasis.

On the basis of these experiences, systematic screening for HBsAg and anti-HBc IgG is mandatory before initiating anti-CD20 or anti-TNF-α therapy. HBV DNA levels should be determined through PCR-based nucleic acid testing in patients with isolated anti-HBc IgG positivity to exclude the presence of occult infection. There is general consensus to recommend the administration of anti-HBV prophylaxis in HBsAg-positive and HBsAg-negative/anti-HBc-positive patients during the entire duration of anti-CD20 therapy and for at least 12-18 months after the last administration of the monoclonal antibody, since cases of delayed viral reactivation have been reported. Antiviral drugs with high genetic barrier to resistance, such as tenofovir disoproxil fumarate (TDF) or alafenamide (TAF) or entecavir, are usually preferred over lamivudine, particularly for long prophylaxis courses or if baseline HBV DNA level is higher than 2,000 IU/mL [2]. Regarding patients under anti-TNF-α therapy, both the ESGICH [27] and the American Gastroenterological Association [25] support the use of anti-HBV prophylaxis in case of HBsAg or HBV DNA positivity, a recommendation mostly based on non-randomized studies. Due to the lower risk of reactivation among HBsAg-negative/anti-HBc-positive patients (provided that HBV DNA is undetectable at baseline), a preemptive approach with regular monitoring of viral load may be considered with early initiation of antiviral therapy in case of reactivation of an occult HBV infection, although the optimal frequency of monitoring and the threshold for initiating antiviral therapy are not well established.

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