# Tuberculosis Reactivation Risk in Dermatology

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***ABSTRACT.*** The treatment of some dermatological diseases, especially psoriasis, has been revolutionized by the advent of biologic therapies that target various immune cells or cytokines. However, biologic therapies may affect the risk of active tuberculosis (TB). We review the published safety data about TB risk reactivation for biologic agents used in dermatology. According to recent findings, psoriasis itself could represent an independent risk factor for TB; a high prevalence of TB was found in patients with psoriasis (18.0%), even after adjusting for age, work, and other characteristics. Latent TB infection was more common in patients with psoriasis (50%) than in those with inflammatory bowel disease (24.2%). Risk of TB reactivation was also influenced by the type of agent used. Several structural and functional differences among biologic drugs could account for differences in risk of granulomatous infection. Different kinetics of currently available tumor necrosis factor (TNF) antagonists, leading to different TNF bioavailability in granulomatous tissue, may explain differences in TB reactivation among patients treated with biologics. One could argue that etanercept should be the first choice of anti-TNF agent in populations at high risk of TB. Risk of TB reactivation during treatment with other biologics is not yet well defined. (J Rheumatol Suppl. 2014 May; 91:65–70; doi:10.3899/jrheum.140104)

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PSORIASIS LATENT TUBERCULOSIS INFECTION BIOLOGIC DRUGS

In recent decades, the risk of latent tuberculosis (TB) reactivation has been the focus of much interest in dermatology, particularly because of the introduction of biologic agents in the treatment of immune-mediated cutaneous disorders such as psoriasis. These agents target various immune cells or cytokines that play key roles in local and systemic inflammation, such as tumor necrosis factor-α (TNF-α), T cells, B cells, and interleukins.

Psoriasis is a chronic inflammatory immune-mediated skin disease affecting 2.5% of the world's population[1]. While the pathogenic mechanism is not yet completely understood, the pivotal role played by T helper 1 and T helper 17 cells is clear. Biologic drugs target these key steps in the pathogenesis of disease, and can be classified into 3 main categories: TNF-α inhibitors, T cell inhibitors, and interleukin 12 (IL-12)/IL-23 inhibitors. These immune pathways also appear to be crucial in mounting a host defense against bacterial, fungal, and parasitic infections, as well as intracellular pathogens[2,3,4].

TB infection affects almost one-third of the world's population, with 10% of infected people developing active TB in their lifetime[5] and 90% developing latent TB infection (LTBI), a state in which an immune response to *Mycobacterium tuberculosis* (Mtb) is detected in the absence of clinical features of active disease. From 5% to 10% of patients with LTBI will develop reactivation and this risk is increased in immunocompromised patients[6].

An increased risk of infection is related to a general immunomodulatory or immunosuppressive effect and is common to all biologics[7]. The effect of biological therapies on TB risk in dermatology must be initially evaluated against regional differences in exposure to Mtb and the underlying inflammatory disorder treated[8]. Psoriasis could represent an independent risk factor for TB. Psoriatic patients have a high prevalence of TB (18.0%), even adjusting for age, work, and other characteristics[9]. The risk of TB reactivation is also influenced by the type of agent used. Several structural and functional differences among biologic drugs could account for the differences in granulomatous infection risk[10].

We review published safety data about TB risk reactivation for biologic agents used in dermatology, focusing solely on English-language randomized controlled trials and their extension studies. Literature searches were conducted through MEDLINE using the search string (etanercept OR infliximab OR adalimumab OR golimumab OR ustekinumab OR briakinumab OR anakinra OR abatacept OR rituximab) AND (psoriasis OR skin diseases) AND (tuberculosis OR safety OR side effect OR adverse event). The literature review extended to April 31, 2013.

## TB Risk and Anti-TNF-α Agents Used in Dermatology

Biologic TNF-α antagonists including infliximab (IFX), etanercept (ETN), adalimumab (ADA), and golimumab (GOL) represent a novel type of highly selective therapy approved by both the US Food and Drug Administration

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(FDA) and the European Medicines Agency (EMA) for the treatment of plaque-type psoriasis and/or psoriatic arthritis (PsA). The efficacy of TNF-α-targeting agents in treating psoriasis serves as proof of the crucial role played by TNF-α in its pathogenesis[11]. The effects of TNF-α are also important in host defenses against Mtb and specifically in the formation and maintenance of granulomas[12]. Indeed, TNF-α is essential in suppressing the progression and dissemination of mycobacterial infection by activating macrophages, CD4+ and CD8+ T cells, and controlling intracellular mycobacterial growth[13,14]. It is unsurprising, therefore, that the use of TNF-α inhibitors has been associated with an increased rate of TB. And because each has its own structure and mechanism of action, these agents may pose variable risks regarding TB reactivation[15]. In fact, atypical presentations of TB, such as disseminated and extrapulmonary disease, are common in the setting of treatment with anti-TNF-α therapies[16,17,18].

A review of the FDA adverse events database from January 1998 through September 2002 identified 138 cases of TB in patients receiving anti-TNF-α[19,20].

*Infliximab*. IFX is a murine-human chimeric monoclonal antibody neutralizing both soluble and transmembrane TNF-α. Because of its capability in binding transmembrane TNF-α, IFX causes apoptosis of T cells, monocytes, and other TNF-α-bearing cells (TNF-α-producing cells), leading to a highly increased risk of TB reactivation. IFX could also interfere with immune response by inducing both complement-dependent and antibody-dependent cell-mediated cytotoxicity[21,22,23].

Three clinical trials [Study of Psoriasis with Infliximab (REMICADE) Induction Therapy — SPIRIT[24]; European Infliximab for Psoriasis (REMICADE) Efficacy and Safety Study — EXPRESS[25]; and Evaluation of Infliximab for Psoriasis in a (REMICADE) Efficacy and Safety Study — EXPRESS II[26]] evaluated the safety of IFX in moderate-to-severe plaque-psoriasis patients. More than 1400 psoriatic patients were exposed to at least 1 dose of IFX and the safety analysis included data up to 50 weeks. No cases of active TB were observed in the SPIRIT and EXPRESS I studies, whereas there were 2 cases of TB in the IFX group in the EXPRESS II study.

Longterm safety of IFX was also examined in a 78-week phase III study in 54 Japanese patients with moderate to severe plaque psoriasis and PsA. In the 50 patients who received IFX in the study period there was no evidence of LTBI reactivation[27]. Together, these data indicate that IFX is generally well tolerated up to 78 weeks, with a risk of TB reactivation as a significant consideration in using this drug.

*Etanercept*. Another approved TNF-α blocker, ETN, is a dimeric, soluble recombinant fusion protein constituted by the extracellular domain of the human p75 TNF receptor and the Fc fragment of human IgG1[21].

Studies revealed that the risk of TB reactivation induced by antibody-type drugs is significantly greater than for soluble TNF receptor-type drugs[19,28,29]. Although it is still debated which drug feature determines a differential risk of TB reactivation, the ability to bind to membrane-associated TNF, even if unable to induce cell death, seems to be fundamental. Compared to IFX, ETN, which binds only to soluble TNF-α, is less frequently associated with LTBI reactivation, likely because it does not induce apoptosis in TNF-α-expressing cells and shows limited cytotoxicity and reduced interference with the immune granulomatous response[21,30,31].

The longterm safety profile of ETN up to 48 months was examined in a series of connected trials in patients with moderate to severe plaque psoriasis[32]. In total, 108 patients completed 48 months of therapy; there were no reported cases of TB or opportunistic infections. In a recent Spanish multicenter prospective study in 444 patients with psoriatic disease who were receiving ETN treatment at a dose of 50 mg twice weekly, there were no cases of TB at the 12-month followup[33].

These data suggest that ETN is generally well tolerated in patients with moderate to severe plaque psoriasis over a 4-year treatment period with few serious infections. Among the TNF antagonists, ETN has been reported to be associated with the lowest incidence of TB and a longer lag time to reactivation of latent TB[34].

*Adalimumab and golimumab*. ADA and GOL are fully human monoclonal antibodies that bind to both the soluble and transmembrane bioactive forms of human TNF-α; ADA differs from GOL by inducing lysis of human monocytes expressing transmembrane TNF-α in the presence of complement or effector cells[35,36]. Unlike ADA, in dermatology GOL has been approved by the FDA and EMA only for the treatment of PsA.

Three large randomized clinical trials (Randomized controlled EValuation of adalimumab Every other week in moderate to severe psoriasis trial — REVEAL[37], Comparative Study of Humira vs Methotrexate vs Placebo in Psoriasis Patients — CHAMPION[38], and BELIEVE[39]) assessed the safety of ADA in patients with moderate to severe psoriasis. In the REVEAL trial, among the 840 patients who received at least 1 dose of ADA during the 52-week treatment period, 1 case of TB was reported. In a longterm, followup study of REVEAL, in which patients received open-label ADA continuously for 3 years, the adverse event profile was consistent with that of the original REVEAL study[40].

All 3 approved anti-TNF agents indicated for psoriasis therapy have a black box warning required by the FDA concerning development of serious infections, including TB. All 3 can reactivate TB in patients with psoriatic diseases in the relatively short time of 1 year or less, but the real degree of this risk is difficult to estimate[34].

A recent case-control study, not specific for psoriasis,

suggested that the risk of TB attributable to ADA is similar to that of IFX and greater than that of ETN; other studies reinforce these findings, confirming a reduced risk of ETN-associated TB compared with risk associated with TNF-α monoclonal antibodies[10]. Moreover, the 3 currently available TNF-α antagonists are associated with different median times to onset of infectious TB complications (IFX, 6 weeks; ADA, 3–8 months; ETN, 11.2 months, GOL not known)[10,41].

Regarding patients with psoriatic diseases, there are few postmarketing reports on reactivation of LTBI after initiation of anti-TNF therapy, and the frequency varies across different studies[42,43,44]. In a Spanish study of 144 patients receiving 3 anti-TNF agents, 29% showed tuberculin skin test conversion after different periods of therapy[42]. In a study from Taiwan on 147 patients receiving ETN, ADA, or both, 11% showed interferon-γ releasing assay (IGRA) conversion after a median period of 24 weeks of exposure[43]. Likewise, in an Italian study in 50 patients receiving the 3 anti-TNF agents as monotherapy or in combination with methotrexate, 7 (14%) showed IGRA conversion after 1 year[44]. In the same study, 2 cases of IGRA conversion were discovered during an annual examination of anti-TNF therapy maintenance, and 1 case was diagnosed as active pulmonary TB 10 months after starting the biologic agent. A recent survey concerning the evaluation of infectious complications during biologic therapy of psoriasis showed a rate of infection of 12.24%, with only 1 case of pulmonary TB in a patient treated with IFX, out of 988 patients[45].

## TB Risk and T Cell Inhibitors Used in Dermatology

Psoriasis is defined as a T cell-mediated autoimmune disease based on the advanced understanding of its pathogenesis. Because of the primary role that T cells play in this disease, a new class of biologics has been designed to interfere with T cell activation and functions. Currently, alefacept is the only T cell inhibitor drug approved for the treatment of psoriasis. Efalizumab was withdrawn from the market because of the associated risk of progressive multifocal leukoencephalopathy[46]. Two additional T cell modulators are currently being evaluated for their use in psoriasis and PsA[47].

*Alefacept*. There have been no reported longterm, randomized, placebo-controlled trials of alefacept in patients with moderate to severe psoriasis, although several clinical trials have assessed its efficacy and safety in short-term followup[48,49,50]. Adverse events associated with alefacept were mostly infectious in nature, but no case of TB reactivation was reported.

Prolonged, prospective, randomized clinical trials are required to assess the longterm safety of alefacept in patients with moderate to severe psoriasis. It should be noted that alefacept is not licensed for use in Europe.

## TB Risk and IL-12/IL-23 Inhibitors Used in Dermatology

A third class of biologics classified as IL-12/IL-23 inhibitors has been developed for treating psoriasis. Currently, ustekinumab is FDA-approved and EMA-approved for treatment of chronic plaque psoriasis[51], whereas briakinumab recently had its approval application withdrawn in the United States and Europe to conduct further analysis and clinical trials[52].

*Ustekinumab*. Ustekinumab, a fully human monoclonal antibody directed against the shared p40 subunit of IL-12 and IL-23 cytokines, is a recently approved biologic for the treatment of moderate to severe plaque psoriasis[51].

Studies have demonstrated that both IL-12 and IL-23 play important roles in host protection against bacterial and parasitic infections and intracellular pathogens. In particular it seems that individuals with inborn errors in the IL-12/23-interferon-c circuit are particularly vulnerable to infections caused by mycobacteria, especially atypical mycobacterial infections as well as Mtb[53,54].

Two important clinical trials, intended to determine the safety of ustekinumab, are PHOENIX-1[55] and PHOENIX-2[56]. Both are large-scale, randomized, placebo-controlled, phase III trials designed to evaluate the efficacy and safety of ustekinumab in patients with moderate to severe plaque psoriasis over a period of 5 years. A third clinical trial, the ACCEPT study, directly compares ustekinumab to ETN[57]. None of these reported cases of TB reactivation.

Cumulative safety data about TB reactivation risk were recently published. No cases of active TB were described among the 167 patients with psoriasis with newly identified LTBI who were treated concomitantly with isoniazid at, or before, the start of ustekinumab treatment. Only 1 asymptomatic patient, who did not receive anti-TB treatment, experienced reactivation of LTBI[58,59]. This case, however, further supports the critical need to identify and treat patients with LTBI before, or at the time of, initiation of treatment with ustekinumab to minimize the risk of developing active TB.

*Briakinumab*. Briakinumab is a recombinant fully human IgG1 monoclonal antibody directed against the shared p40 subunit of IL-12 and IL-23. Because of its binding to the aforesaid cytokines, briakinumab causes a decrease in secretion of IL-6, IL-12, interferon-γ, and TNF-α. In a phase II study in 180 patients with psoriatic diseases who were treated with briakinumab, there were no cases of TB reactivation in the longterm safety analysis up to 48 weeks[60].

## Tuberculosis Risk and Other Biologics

*Anakinra*. Anakinra is a recombinant IL-l receptor antagonist used primarily to treat rheumatoid arthritis (RA)[61]. Although outside FDA-approved indications, anakinra has also been found to be useful in a variety of immune-mediated and autoimmune skin disorders in which traditional therapy has failed or resulted in side effects.

However, the tolerability of anakinra in the treatment of dermatological diseases is not yet clear[62].

*Abatacept*. Abatacept is a fusion protein composed of an Fc fragment of IgG1 and the extracellular domain of cytotoxic lymphocyte antigen-4, which inhibits T cell costimulation. Abatacept is currently approved for the treatment of RA[63]. A phase II study in patients with PsA has terminated and showed that 10 mg/kg may be an effective and safe treatment[64]. No other safety data are available in dermatology.

*Rituximab*. Rituximab (RTX) is a chimeric human/mouse monoclonal antibody directed at the CD20 antigen expressed on mature B and pre-B cells. It is approved for the treatment of patients with non-Hodgkin lymphoma, chronic lymphocytic leukemia, and moderate to severe RA who have had an inadequate response to TNF inhibitors[65].

In dermatology, RTX is a useful off-label treatment for primary cutaneous B cell lymphoma, pemphigus vulgaris, dermatomyositis, and idiopathic thrombocytopenic purpura, to name a few[66]. The risk of TB associated with RTX is currently unknown. No cases of TB reactivation were observed in clinical trials of RTX used in rheumatology, in which pre-screening for LTBI was not performed[8,67].

Regarding the use of RTX in the treatment of dermatological disorders, very few randomized, controlled, clinical trials are available, so guidelines for the off-label use of this medication come from anecdotal case reports and cohort studies. In the majority of patients, RTX is safe and tolerable, with only mild infectious complications, although strict care and guidance should be followed with each patient treated because longterm safety in dermatological conditions has not been firmly established[68].

The advent of biologics in dermatology has substantially changed the treatment of cutaneous autoimmune inflammatory diseases. However, the fact that these agents involve immunosuppressive activity has raised safety concerns, particularly regarding reactivation of latent infections, most notably that caused by Mtb.

Given the crucial role played by TNF in granuloma formation, the link between drugs directed against this cytokine and predisposition to TB seems obvious. In fact, most cases of TB associated with anti-TNF agents are due to reactivation of LTBI, rather than newly acquired infections. Moreover, atypical presentations of TB such as extrapulmonary and disseminated forms seem to be more common in patients treated with anti-TNF therapy than in those in immunocompetent patients. Most reported cases occurred within 2–4 months after starting anti-TNF therapy, in regions with a low incidence of TB.

Different kinetics of the currently available TNF antagonists, leading to different TNF bioavailability in granulomatous tissue, may explain differences in TB reactivation among patients treated with these biologic drugs. In particular, studies have shown that the soluble TNF receptor ETN seems to be associated with a lower risk of TB reactivation compared to that associated with monoclonal antibodies IFX and ADA. The explanation of this may reflect the reduced ability of ETN to disrupt granuloma. In fact, ETN is also ineffective in the treatment of chronic granulomatous inflammation in Crohn disease, and potentially less effective in other granulomatous diseases such as sarcoidosis and granulomatosis with polyangiitis[69]. For these reasons, one could argue that ETN should be the first anti-TNF used in populations with a high risk of TB.

The risk of TB reactivation during treatment with other biologics is much less known. There is a relative lack of clinical data on this subject in dermatological diseases, and following the experience with anti-TNF-α, because of the introduction of TB screening before starting biologic therapy. However, biologics directed against targets that are not implicated in host defenses against Mtb, such as anakinra and RTX, seem to have a very lower risk of TB reactivation.

The above report on risk of reactivation of LTBI in dermatology can be summarized as follows:

- Biologic therapies used in dermatology specifically for psoriasis are associated with significant risk to reactivate LTBI
- Psoriasis itself could represent an independent risk factor for TB
- Risk of TB is not the same for the currently available biologic agents

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