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Title

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Journal

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Publication Date

DOI

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Tuberculosis and interleukin blocking monoclonal antibodies: Is there risk?

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Abstract

Several new monoclonal antibodies that interfere with interleukin (IL) cascades have come to market in recent years. They follow a generation of drugs that block tumor necrosis factor (TNF). It has been well established that TNF is important in the containment of *Mycobacterium tuberculosis* (*Mtb*) and that blocking this cytokine increases the risk of tuberculosis (TB) infection. Thus, judicious screening for *Mtb* of patients taking TNF blocking drugs has been the standard of care. It remains unclear if the newer monoclonal, interleukin blocking drugs, which affect IL-12, IL-23, and IL-17 pathways are associated with risk of *Mtb* reactivation. Herein we discuss what is known about the immunologic response to *Mtb* and discuss the data that is currently available for the new interleukin monoclonal antibody blocking medications regarding the risk of latent TB reactivation or active TB infection.

Keywords: ustekinumab, ixekizumab, secukinumab, brodalumab, guselkumab, tildrakizumab, risankizumab, tuberculosis, latent tuberculosis, active tuberculosis, interferon gamma release assay, TNF-alpha, interleukin 12, interleukin 23, interleukin 17

Introduction

Mycobacterium tuberculosis characteristics, transmission, infection

Mycobacterium tuberculosis (*Mtb*) is a disease that typically affects the lungs. In up to one-third of cases it may affect other organs, such as skin, lymph nodes, bone, and the central nervous system. The bacterium is aerobic, rod-shaped, and non-spore-forming. *Mtb*

is classically acid-fast owing to the organism's high content of mycolic acid. This structure confers resistance to most antibiotics because of the very low permeability of the cell wall [1]. In 2015, there were an estimated 10.4 million new TB cases worldwide, of which 5.9 million (56%) were among men, 3.5 million (34%) among women, and 1.0 million (10%) among children [2].

Mtb is transmitted by droplet nuclei that are aerosolized by coughing, sneezing, or speaking. If exposed, the risk of acquiring the infection is dependent on the individual's innate immunologic defenses and how the individual's cell-mediated immunity functions. Following deposition, phagocytosis, and antigen presentation via dendritic cells (DC) in the lungs, the *Mtb* bacteria disseminate through the lymphatic vessels.

A few weeks after infection, two host response pathways are involved in controlling and eliminating the bacteria. The first is the macrophage-activating response, a T-cell mediated response, resulting in the activation of naïve macrophages capable of phagocytizing and killing the bacilli. The accumulation of these activated macrophages, which surround and neutralize bacilli, is how granulomas are formed. Importantly, these macrophages contain live and reproducing *Mtb* bacteria. The second response is a tissue damaging response, which is a delayed-type hypersensitivity against various bacterial agents [1]. It is believed that the infection is controlled by both active innate and adaptive immunity. Those unable to control the infection develop active TB [3].
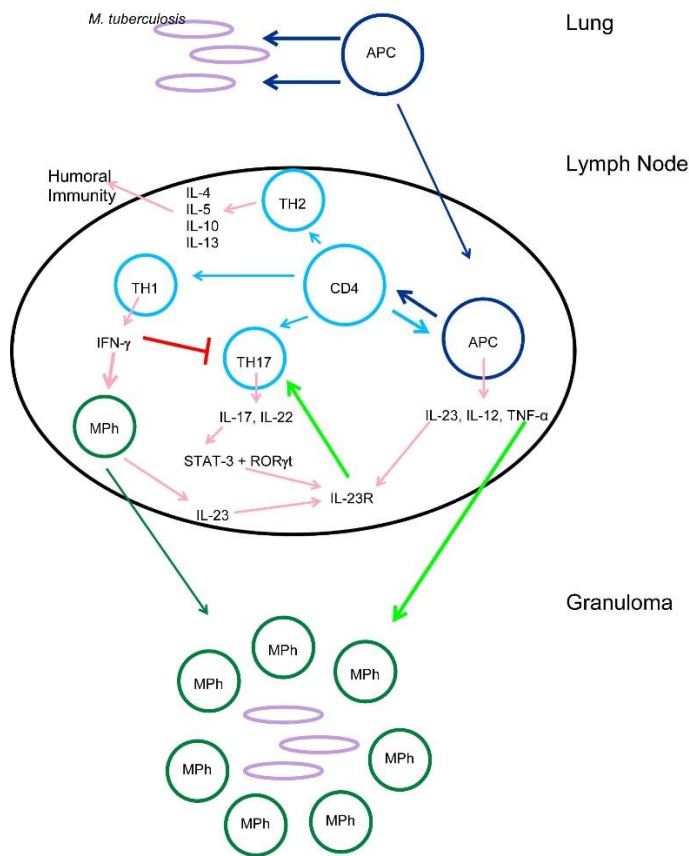
Figure 1. *Mtb (purple ovals) are phagocytosed by APC cells in the lung (dark blue circles). The APC cell then travels to the draining lymph node (dark blue arrow). Here it interacts with CD4 cells (dark blue/light blue interchange). The CD4 cell differentiates into TH2, TH1, and TH17 cells (light blue arrows and circles). Each cell produces signature cytokines, some that interact with transcription factors (i.e., STAT-3). Each cytokine cascade is highlighted with pink arrows. Importantly, TH1 cells produce IFN-γ, which inhibits the TH17 lineage (dark red). However, IFN-γ also enhances macrophage (MPh) cytotoxicity (green circles). These cells migrate back to the lung and form granulomas around the Mtb (dark green arrow). The stimulatory interaction of IL-23 with IL-23R on TH17 cells and the stimulatory action of TNF-α on MPh and granulomas are highlighted with light green arrows.*

The T-cells involved are mainly CD4+ (CD4) cells. These cells interact with antigen presenting DCs in the lymph nodes and initiate a cell-mediated immune response against the bacilli (Figure 1). The CD4 cells can further differentiate into TH1 cells that produce interferon gamma (IFN-γ), which in turn activates macrophages [1, 3]. The antigen presenting cells produce IL-12 and TNF [3]. These CD4 TH1 cells are the primary T-cell subtype in host mitigation of the *Mtb* infection. TH2 cells, on the other hand, produce IL-4, IL-5, IL-10, and IL-13 and are more

involved in humoral immunity. The exact role of these cytokines in promoting intracellular killing of mycobacteria is not fully understood [1]. However, those with mutations in IL-12 or IFN-γ are at risk of developing disseminated infections from BCG and non-tuberculous mycobacteria (NTM), [3].

It has been well established that the cytokine tumor necrosis factor (TNF) is a key bactericidal cytokine [1]. This cytokine plays a role in regulating the production of downstream signaling in both newly formed granulomas and established granulomas [4-6]. In both human and experimental models, changes in TNF levels correlate with disease susceptibility [3]. It is generally well accepted that the mainstream anti-TNF biologic therapies used in the treatment of psoriasis and rheumatologic diseases confer a risk of *Mtb* infection or reactivation.

It remains unclear to many clinicians if the newer anti-interleukin specific monoclonal treatments actually increase the risk of TB infection, which would substantiate routine testing, or if this testing requirement is simply a carryover recommendation from the use of anti-TNF class of biologics.

Testing for Latent Tuberculosis Infection (LTBI)
The decision to test for TB depends on possible prior exposure to *Mtb*, leading to latent tuberculosis infection (LTBI). This occurs when one is infected with the bacilli but has no clinical evidence of the disease. Those who are at increased risk of acquiring the infection are those who reside or are employed in high risk congregate settings (i.e., healthcare workers, those in long term care facilities, prison workers, prisoners), those who immigrate from high disease burden countries (defined as >20/100,000 individuals), mycobacteriology laboratory personnel, and those with household contact or recent exposure to a case of active TB [7].

The risk of developing tuberculosis if exposed to the bacteria depends on additional patient risk factors. Patients at intermediate risk (relative risk 1.3-3) are those with diabetes, chronic renal failure, or intravenous drug use. Patients at high risk (relative risk 3-10) are children less than 5, patients with human immunodeficiency virus (HIV) infection,

patients on immunosuppressive therapy, patients who have a chest X-ray consistent with prior TB, or patients with silicosis [7]. The relative risk of progressing from LTBI to active disease in those undergoing treatment with TNF inhibitors has been reported as 2.0 (1.1-3.5) [8].

Testing for LTBI is accomplished with a tuberculin skin test (TST) or via an interferon-γ release assay (IGRA). A TST must be placed by a healthcare professional and then interpreted by a healthcare professional 48-72 hours later. The TST may be more sensitive in identifying those with a longstanding cell mediated immune response to *Mtb* antigens [9].

An IGRA uses purified antigens from the *M. tuberculosis* bacterium to stimulate lymphocyte production of IFN-γ. Both commercially available tests (QuantiFERON®-TB Gold In-Tube Test, and T-Spot® TBtest) rely on this principle. One advantage is that these tests do not require subsequent evaluation, but they do require a blood draw. Another advantage of IGRA is the lack of false positive findings with repeated testing. This **"booster" phenomenon can be seen with repeated** TST testing. IGRAs also do not cross react with the *M. bovis* bacilli Calmette-Guérin (BCG) vaccine. However, the IGRA tests are typically more expensive than a TST [9]. Importantly, the TST and IGRA tests are all unreliable in immunocompromised populations because of a lack of effective cell mediated immunity [10].

Patients taking immunosuppressive medications are at increased risk of converting to active TB from LTBI and thus must be screened for the infection. If any of the risk factors for acquiring the infection (see above) are present in a patient on immunosuppressive medication, it is recommended that patients be screened for LTBI. Per the Center for Disease Control guidelines, in adults with high likelihood of infection either IGRA or TST is acceptable [7]. It should be stated that the diagnosis of an *active* tuberculosis infection requires an acid-fast bacilli smear and culture [7].

Discussion

IL-17, IL-23, and IL-12

The newer injectable therapies in the treatment of psoriasis include ustekinumab, which blocks the p40 subunit of IL-12 and IL-23, the IL-17 blockers (ixekizumab, secukinumab), an IL-17 receptor blocker (brodalumab), and several sole IL-23p19 blockers (guselkumab, tildrakizumab, and risankizumab).

It is known that activated DCs prime T cells in the draining lymph nodes. IFN-γ and IL-17 producing T-cells are induced via antigen presentation and then migrate to the lung [11, 12]. Here, Th17 cells play an important role in the cellular response and are believed to mature, based on the presence *and* relative expressions of many cytokines including IL-17 and IL-22 [3]. Importantly, downstream signal transducer and activator of transcription 3 (STAT-3) is expressed and couples with RAR related orphan receptor-γt (RORγt) to induce expression of the receptor for IL-23. This signaling is important for stabilizing the Th17 T-cell phenotype (Figure 1), [13, 14]. Additional studies have shown that following BCG vaccination, IL-23 is essential for early cessation of bacterial growth, and the stabilization of IL-17 producing T cells in the lung [15].

Mouse models have shown that mice deficient in IL-23p19 are unable to sustain a Th17 response [11]. Thus, following *Mtb* infection, IL-23 may not be required for initiating the Th17 response but rather for the sustained IL-17 response [13]. Interleukin-12p40, which is blocked by ustekinumab, is required for expression of IL-17 in the lymph nodes but does not appear to have an impact on IL-17 production in the lung [11]. An additional study blocking IL-12 and IL-23 showed that, following immunization with a DNA vaccine expressing *Mtb* antigen 85B there was a limited cell-mediated T cell response and no control of the *Mtb* infection. This further supports that IL-12 and IL-23 expression is required for the expansion of IFN-γ secreting T-cells, which are at the center of controlling an *Mtb* infection [12].

IL-12p40 is also induced by toll like receptors (TLR) following recognition of a pathogen associated molecular pattern. In particular, toll like receptor 9

(TLR-9) has been shown to induce macrophage and DC production of IL-12p40 in vivo. IL-12p40 may then lead to increased production of IL-23 that enhances Th17 T-cells and innate immunity in general. There is also increased production of Th1 cells leading to increased production of IFN-γ [11].

Despite this complex and intricate defense, there was only one case of tuberculosis in all of the clinical trails leading to the approval of ustekinumab, secukinumab, ixekizumab, brodalumab, and guselkumab.

Ustekinumab was associated with the one case of active TB. Leading up to approval there were three clinical trials of which the longest was 2 years in duration. The patient experienced flu-like symptoms 10 months after receiving a single dose of ustekinumab (Table 1). The IGRA and chest x-ray were normal, but a sputum smear and culture were positive for *Mtb*. The patient was treated empirically and symptoms resolved.

Data for secukinumab and ixekizumab from psoriasis, psoriatic arthritis, and ankylosing spondylitis trials incorporating a combined total of 6,257 patients showed no cases of active TB or TB reactivation. Brodalumab had 4,464 patients involved in clinical trials and no cases of active TB or TB reactivation were found (Table 1). Guselkumab was administered to 2,390 patients in clinical trials.

Table 1. *Interleukin blocking monoclonal antibody clinical trials data and LTBI.*

Interleukin	Medication	Trade Name	Manufacturer	# Patients in trials	# Patients positive for LTBI in trials	# Patients with prior treatment	# Patients treated during trials	# Patients converting to positive LTBI during trials	# Cases of TB reactivation
IL-12/23 p40	Ustekinumab	Stelara	Janssen	1275	68	-	68	-	1[*]
IL-17	Ixekizumab	Taltz	Eli Lilly	4213	98	4	-	60	0
IL-17	Secukinumab	Cosentyx	Novartis	2044	132	-	107	1	0
IL-17 Receptor	Brodalumab	Siliq	Valeant	4464	0[+]	14	0	7[+]	0
IL-23 p19	Guselkumab	Tremfya	Janssen	2390[★]	-	-	105	0	0

"-" Indicates this data was not available at the time of publication.
[*]See Ustekinumab below
[+]See Brodalumab below
[★]See Guselkumab below

Ustekinumab: in the maintenance phase of the IM-UNITI trial there was one case of active pulmonary TB that occurred about 10 months after receiving a single induction dose of 130mg ustekinumab IV. The patient previously received the BCG vaccination and at screening had a negative chest radiograph and QuantiFERON test. This patient experienced flu-like symptoms with fever, chills, dysphagia, cough, and yellow sputum production. QuantiFERON results were negative but a sputum smear and culture was positive for Mtb. There were radiographic findings consistent with active TB. The patient was treated empirically with triple anti-TB therapy and his symptoms resolved.

Ixekizumab: Data from pooled analysis from 7 clinical trials. Those with indeterminate IGRA or PPD were excluded from the trials

Secukinumab: Data from a pooled analysis of five Phase III, randomized, double-blind, placebo-controlled studies. 25 patients had h/o TB, LTBI, or positive TB test then tested negative for LTBI and therefore were not treated. Patients who tested positive for LTBI were treated with INH or rifampin per local guidelines. None of these patients discontinued secukinumab. In the six Phase III studies a total of 149 patients (300mg n=55(37), 150mg n=50(34), etanercept n=21(14), and placebo n=23(15)) were diagnosed with LTBI and treated per local guidelines. No reactivation was seen. One patient tested negative at baseline but tested positive on Day 141 after 84 days of placebo and 57 days of secukinumab 150mg. The patient was treated per guidelines, completed the study, entered into the extension period, and did not develop active TB while in the study.

Brodalumab: The inclusions criteria for these trials included negative PPD test or negative Quantiferon test. Of the 7 patients who converted to a positive test for LTBI all of them were in the variable dosing arm. No patients (n= 1204) in the commercial dose arm converted to LTBI. The patients who converted to LTBI had study drug discontinued.

Guselkumab: Includes 1829 patients from VOYAGE 1 and VOYAGE 2, 268 patients from NAVIGATE, and 293 patients from X-PLORE clinical trials.

There were no cases of active TB or TB reactivation (Table 1). Importantly, with the exception of the trials for brodalumab, neither previous LTBI nor current LTBI were exclusion criteria. Some patients received ustekinumab, secukinumab, or guselkumab *while* being treated for LTBI per local guidelines (Table 1).

Conclusion

Clearly all three of these interleukin cytokines are closely linked to the development of a cell-mediated host response against *Mtb* bacilli. Nonetheless, we have yet to see clinical data showing reactivation of TB or new cases of TB in patients with psoriasis or psoriatic arthritis who are taking IL-12/23, IL-17, or IL-23 blocking medications. For the practicing clinician, given what we know today, it is recommended to test for LTBI prior to initiating any biologic therapy.

The challenge going forward will be how to approach patients with indeterminate or positive results. For those clinicians starting anti-TNF therapy, patients would still need to be treated for LTBI prior to initiation of biologic therapy. But for clinicians considering starting IL-12/23, IL-17, or IL-23 blocking medications, perhaps these medications may be safely administered without worry of TB reactivation. The current dilemma is that available studies suggest a role for all of these cytokines in the immunologic cascade and containment of the *Mtb* bacteria but current clinical data does not seem to show an increased risk of reactivation or new active infection. We expect that with time the patient registries will grow and with more accumulated safety data, we may be able to prescribe certain anti-interleukin blocking medications to patients with a history of TB exposure without concern for reactivation of the disease.

References

1. Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, et al. Harrison's principles of internal medicine. New York: McGraw Hill Education, 2015.
2. Organization WH. Global Tuberculosis Report 2017. Switzerland: WHO; 2017. Available: *http://www.who.int/tb/publications/en/*. Accessed on October 30, 2017.
3. Cantini F, Nannini C, Niccoli L, Petrone L, Ippolito G, et al. Risk of Tuberculosis Reactivation in Patients with Rheumatoid Arthritis, Ankylosing Spondylitis, and Psoriatic Arthritis Receiving Non-Anti-TNF-Targeted Biologics. *Mediators Inflamm.* 2017;2017:8909834. [PMID: 28659665].
4. Algood HM, Lin PL, Flynn JL. Tumor necrosis factor and chemokine interactions in the formation and maintenance of granulomas in tuberculosis. *Clin Infect Dis.* 2005;41 Suppl 3:S189-93. [PMID: 15983898].
5. Kindler V, Sappino AP, Grau GE, Piguet PF, Vassalli P. The inducing role of tumor necrosis factor in the development of bactericidal granulomas during BCG infection. *Cell.* 1989;56(5):731-40. [PMID: 2647299].
6. Flynn JL, Goldstein MM, Chan J, Triebold KJ, Pfeffer K, et al. Tumor necrosis factor-alpha is required in the protective immune response against Mycobacterium tuberculosis in mice. *Immunity.* 1995;2(6):561-72. [PMID: 7540941].
7. Lewinsohn DM, Leonard MK, LoBue PA, Cohn DL, Daley CL, et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. *Clin Infect Dis.* 2017;64(2):111-5. [PMID: 28052967].
8. Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, et al. Risk and case characteristics of tuberculosis in rheumatoid arthritis associated with tumor necrosis factor antagonists in Sweden. *Arthritis Rheum.* 2005;52(7):1986-92. [PMID: 15986370].
9. Horsburgh CR, Rubin EJ. Clinical practice. Latent tuberculosis infection in the United States. *N Engl J Med.* 2011;364(15):1441-8. [PMID: 21488766].
10. Pai M, Behr M. Latent Mycobacterium tuberculosis Infection and Interferon-Gamma Release Assays. *Microbiol Spectr.* 2016;4(5). [PMID: 27763261].
11. Khader SA, Pearl JE, Sakamoto K, Gilmartin L, Bell GK, et al. IL-23 compensates for the absence of IL-12p70 and is essential for the IL-17 response during tuberculosis but is dispensable for protection and antigen-specific IFN-gamma responses if IL-12p70 is vailable. *J Immunol.* 2005;175(2):788-95. [PMID: 16002675].
12. Wozniak TM, Ryan AA, Britton WJ. Interleukin-23 restores immunity to Mycobacterium tuberculosis infection in IL-12p40-deficient mice and is not required for the development of IL-17-secreting T cell responses. *J Immunol.* 2006;177(12):8684-92. [PMID: 17142769].
13. Torrado E, Cooper AM. IL-17 and Th17 cells in tuberculosis. *Cytokine Growth Factor Rev.* 2010;21(6):455-62. [PMID: 21075039].
14. Zhu J, Yamane H, Paul WE. Differentiation of effector CD4 T cell populations (*). *Annu Rev Immunol.* 2010;28:445-89. [PMID: 20192806].
15. Khader SA, Bell GK, Pearl JE, Fountain JJ, Rangel-Moreno J, et al. IL-23 and IL-17 in the establishment of protective pulmonary CD4+ T cell responses after vaccination and during Mycobacterium tuberculosis challenge. *Nat Immunol.* 2007;8(4):369-77. [PMID: 17351619].