

SFDPH TB Clinic/UCSF TB-Targeted Immunotherapy Group (TB-TIG)*

Recommendations for TB Screening in Persons taking Targeted Immunotherapies (including Tumor Necrosis Factor Inhibitors)

The use of new targeted immunotherapies (or biologics) has radically transformed the available treatment options for many chronic diseases. These targeted immunotherapies work by blocking specific molecules that mediate certain immune responses or by depleting the cells that express them. Some can also increase the risk of progression to active TB disease by downregulating the immunologic functions that contain TB organisms. This risk varies by drug class and mechanism of action¹.

The use of tumor necrosis factor (TNF)-alpha inhibitors has been associated with high risk of progression of TB; active TB infection occurring in the setting of TNF-inhibitor use has a greater likelihood of involving extra-pulmonary sites and of being disseminated at presentation compared with other TB cases². The risk has been reported to be greater with infliximab and adalimumab than with etanercept². Latent TB infection (LTBI) screening and treatment appears to significantly reduce the incidence of progression to active TB in these patients³.

There is growing evidence that other targeted immunotherapies (e.g., PD-1/PDL-1 inhibitors, CTLA-4 inhibitors, JAK kinase inhibitors, and IL-6 and IL-23 inhibitors to name a few) are also associated with increased risk of TB reactivation. These targeted immunotherapies should be treated similarly as for a TNF-inhibitor. Data is rapidly emerging in this area as more targeted immunotherapies are approved. Based mostly on expert opinion, SFDPH recommends that patients with a diagnosis of LTBI should be initiated on treatment for at least 1 month, if possible, prior to starting those targeted immunotherapies where a risk for TB progression has been identified.

The Table lists targeted immunotherapies as of July 2024 where the manufacturer's package insert recommends TB testing⁴. This list may not include all available targeted immunotherapies; check the manufacturer's package insert for details.

References

1. Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2022. Available at URL: <https://www.tbcontrollers.org/resources/tb-infection/clinical-recommendations/>
2. Dixon WG, Hyrich KL, Watson KD, Lunt M, et al. Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). *Ann Rheum Dis.* 2010;69(3):522.
3. Carmona L, Gómez-Reino JJ, Rodríguez-Valverde V, et al. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. *Arthritis Rheum.* 2005;52(6):1766.
4. List of targeted immunotherapies: Murrill MT, Velásquez GE, Louie J, Tahir P, Kim A, D. Szumowski JD, Salazar J, Minter D, Casalegno ML, Phillips A, Ernst J. Latent tuberculosis screening recommendations for targeted immunotherapies. Presented at the 2023 National Tuberculosis Conference. June 12, 2023, Atlanta, United States

***University of California San Francisco TB-Targeted Immunotherapy Group (TB-TIG)**

- Joel Ernst, MD, UCSF Division of Experimental Medicine
 - Annie Kim, Clinical Pharmacist, UCSF-San Francisco General Hospital
 - Janice Louie, MD, MPH, SFDPH TB Clinic/ UCSF Division of Infectious Diseases
 - Matthew Murrill, MD, PhD, UCSF Department of Medicine
 - Allison Phillips, PhD, SFDPH TB Clinic
 - Haiyan Ramirez-Battle, SFDPH TB Clinic
 - John Szumowski, MD, MPH, UCSF Division of HIV, ID & Global Medicine
 - Gustavo Velasquez, MD, MPH, UCSF Division of HIV, ID & Global Medicine
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Targeted Immunotherapies and TB Risk, 2024

University of California San Francisco TB Targeted Immunotherapy Group (TB-TIG)

TB testing with interferon-gamma release assay or tuberculin skin test is recommended for the following targeted immunotherapies (per the manufacturers drug insert)

Drug Name	Mechanism/Target
Abatacept	Selective T-cell co-stimulation modulator, CTLA-4
Abrocitinib	Kinase inhibitor (JAK1)
Adalimumab	Anti-TNF-alpha mAb
Alemtuzumab	Anti-CD-52 mAb
Anakinra	IL-1 receptor antagonist
Baricitinib	Kinase inhibitor (JAK1/JAK2)
Bimekizumab	Anti-IL-17 receptor mAb
Brodalumab	Anti-IL-17 receptor mAb
Canakinumab	Anti-IL-1beta mAb
Certolizumab	Anti-TNF-alpha mAb

Deucravacitinib	Kinase inhibitor (TYK2)
Emapalumab	Anti-IFN-gamma mAb
Etanercept	Soluble TNF-alpha receptor
Golimumab	Anti TNF-alpha mAb
Guselkumab	Anti-IL-23 mAb
Inebilizumab	Anti-CD-19 mAb
Infliximab	Anti-TNF-alpha mAb
Ixekizumab	Anti-IL-17 mAb
Mirikizumab	Anti-IL-23 mAb
Riloncept	Soluble IL-1 receptor
Risankizumab	Anti-IL-23 mAb
Ritlecitinib	Kinase inhibitor (JAK3)
Rituximab	Anti-CD-20 mAb
Ruxolitinib	Kinase inhibitor (JAK1/JAK2)
Sarilumab	Anti-IL-6 receptor mAb
Satralizumab	Anti-IL-6 receptor mAb

Secukinumab	Anti-IL-17 mAb
Spesolimab	Anti-IL-36 receptor mAb
Tildrakizumab	Anti-IL-23 mAb
Tocilizumab	Anti-IL-6 receptor mAb
Tofacitinib	Kinase inhibitor (JAK1/JAK2/JAK3)
Upadacitinib	Kinase inhibitor (JAK1)
Ustekinumab	Anti-IL-12 and IL-23 mAb
Vedolizumab	Anti-integrin (α4β7) mAb

Abbreviations: CTLA-4, Cytotoxic T-lymphocyte associated protein 4; mAb, monoclonal antibody; TNF, tumor-necrosis factor; IL, interleukin; IFN, interferon

Note: While the manufacturers' package insert does not mention risk of active TB for the PD-1 (programmed cell death-1) and PDL-1 (programmed cell death ligand-1) inhibitor class of drugs, use in animal models has demonstrated increased severity of TB infections and enhanced inflammatory response. TB infected PD-1 knockout mice exhibit markedly decreased survival compared to wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 blockage using a primate anti-PD-1 antibody was also shown to exacerbate TB infection in rhesus macaques. Pending further data, the SFDPH TB Clinic recommends TB testing prior to use of these classes of drugs (including atezolizumab, avelumab, cemiplimab, dostarlimab, durvalumab, nivolumab, nivolumab/relatlimab, pembrolizumab, retifanimab-diwr and toripalimab).