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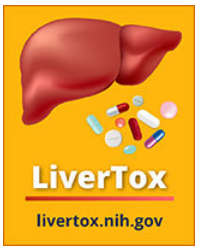

Tildrakizumab

Updated: October 20, 2018.

OVERVIEW

Introduction

Tildrakizumab is humanized monoclonal antibody to interleukin-23 that is used to treat moderate-to-severe plaque psoriasis. Tildrakizumab is associated with a low rate of transient and asymptomatic serum enzyme elevations during therapy, but has not been linked to cases of idiosyncratic, clinically apparent liver injury.

Background

Tildrakizumab (til" dra kiz' ue mab) is a humanized monoclonal IgG1 antibody to interleukin (IL)-23, a cytokine that is an important mediator of autoimmune reactions. IL-23 is found in the skin lesions of psoriasis and in the affected gastrointestinal mucosa of patients with inflammatory bowel disease. Among the monoclonal IL-23 inhibitors, tildrakizumab and guselkumab are directed to the p19 subunit of IL-23, whereas ustekinumab is directed at the p40 subunit which is a component shared by both IL-23 and IL-12. As a consequence, tildrakizumab and guselkumab have a more restricted activity in the Th17 immune pathways which are considered to play a major role in autoimmune reactions. Tildrakizumab has been shown to improve symptoms and signs of plaque psoriasis and was approved for this use in United States in 2017. While current indications are limited to moderate-to-severe plaque psoriasis, tildrakizumab is under active investigation as therapy of several other autoimmune diseases. Tildrakizumab is available in liquid solution in single use prefilled syringes of 100 mg/mL under the brand name Ilumya. The typical regimen is 100 mg subcutaneously initially, 4 weeks later and every 8 weeks thereafter. Side effects are uncommon and are usually mild, but may include injection site reactions, headache, diarrhea and minor infections such as upper respiratory infections. Less common, but potentially severe side effects include serious infections, hypersensitivity reactions and reactivation of tuberculosis.

Hepatotoxicity

Rates of serum aminotransferase elevations during tildrakizumab therapy have not been well defined, but rates of laboratory result abnormalities are said to be similar with tildrakizumab compared to placebo treatment. Neither during premarketing evaluation nor subsequently have there been case reports of clinically apparent, acute liver injury with symptoms or jaundice linked to tildrakizumab therapy, but experience with its use has been limited.

Tildrakizumab has immunosuppressive activity but has not been linked to instances of reactivation of hepatitis B or worsening of hepatitis C. However, patients at risk for these complications are often excluded from preregistration clinical trials, and ustekinumab, a similar biologic agent which is also active against IL-23 and is used to treat psoriasis, has been shown to cause reactivation of hepatitis B in postmarketing studies. HBV

reactivation typically occurs in patients with preexisting HBsAg and relatively inactive disease. Reactivation causes acute hepatocellular injury that can be severe and lead to acute liver failure and death or need for emergency liver transplantation. Screening for hepatitis B before starting tildrakizumab is not recommended in the product label, but screening has been considered "advisable" in guidelines written by academic societies for many monoclonal antibodies used for psoriasis.

Likelihood score: E* (unlikely cause of clinically apparent liver injury but experience with its use has been limited).

Mechanism of Liver Injury

The mechanism of possible liver injury due to tildrakizumab is not known. Reactivation of hepatitis B appears to be due to a brisk immunological response to newly expressed viral antigens caused by suppression of the immune response to hepatitis B antigens. Injury generally arises between courses of immunosuppressive therapy.

Outcome and Management

Tildrakizumab has been linked to minor elevations in serum enzymes during therapy but not to clinically apparent liver injury or with reactivation of hepatitis B. The product label for tildrakizumab does not recommend routine screening for hepatitis B before initiation of therapy. However, guidelines prepared by some academic societies on the management of patients who are to receive biological agents similar to tildrakizumab have recommended routine screening before starting treatment. Screening should include tests for HBsAg and anti-HBc (and perhaps also anti-HBs as this may help in management). Prophylaxis with a potent oral, antiviral agent effective against hepatitis B is recommended for persons who have HBsAg in serum. An alternative approach is careful monitoring for HBV DNA during therapy and early institution of antiviral therapy if levels rise.

Drug Class: Dermatologic Agents, Psoriasis Agents; Monoclonal Antibodies

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Tildrakizumab – Ilumya®

DRUG CLASS

Dermatologic Agents, Psoriasis Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Tildrakizumab	1326244-10-3	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 20 October 2018

Reuben A. Hepatotoxicity of immunosuppressive drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2011, pp. 569-91.

(Review of hepatotoxicity of immunosuppressive agents; does not mention tildrakizumab specifically, but discusses the problems of reactivation of hepatitis B and states that "the biological immunosuppressants are largely free from hepatotoxicity, with the exception of the TNF alpha antagonists").

Chabner BA, Barnes J, Neal J, Olson E, Mujagiv H, Sequist L, Wilson W, et al. Targeted therapies: tyrosine kinase inhibitors, monoclonal antibodies, and cytokines. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1731-53.

(Textbook of pharmacology and therapeutics).

Available at: https://www.accessdata.fda.gov/scripts/cder/daf/

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA scientific review of the new drug application for safety and efficacy which mentions that there were no clinically meaningful changes in laboratory test results in the phase 1, 2 or 3 studies of tildrakizumab).

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Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, Li S, et al.; PHOENIX 1 study investigators. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 2008; 371 (9625): 1665-74. PubMed PMID: 18486739.

(Among 766 patients with psoriasis treated with 1 of 2 doses of ustekinumab or placebo for 12 weeks, response rates were 67% and 66% with ustekinumab vs 3% with placebo, and side effects were similar and "results of laboratory results were much the same" in the 3 groups).

Motaparthi K, Stanisic V, Van Voorhees AS, Lebwohl MG, Hsu S; Medical Board of the National Psoriasis Foundation. From the Medical Board of the National Psoriasis Foundation: Recommendations for screening for hepatitis B infection prior to initiating anti-tumor necrosis factor-alfa inhibitors or other immunosuppressive agents in patients with psoriasis. J Am Acad Dermatol 2014; 70: 178-86. PubMed PMID: 24220724.

(Mentions that little is known about the effects of ustekinumab on HBV infection, but that screening for hepatitis B markers is "advisable" before its use).

Papp K, Thaçi D, Reich K, Riedl E, Langley RG, Krueger JG, Gottlieb AB, et al. Tildrakizumab (MK-3222), an anti-interleukin-23p19 monoclonal antibody, improves psoriasis in a phase IIb randomized placebo-controlled trial. Br J Dermatol 2015; 173: 930-9. PubMed PMID: 26042589.

(Among 355 patients with plaque psoriasis treated with tildrakizumab [5, 25, 100 or 200 mg] or placebo for 52 weeks, clinical improvement response rates were 33-74% vs 4% with placebo and overall and serious adverse reactions were similar in all arms and there were no liver related serious adverse events; no mention of ALT elevations or hepatotoxicity).

Reich K, Papp KA, Blauvelt A, Tyring SK, Sinclair R, Thaçi D, Nograles K, et al. Tildrakizumab versus placebo or etanercept for chronic plaque psoriasis (reSURFACE 1 and reSURFACE 2): results from two randomised controlled, phase 3 trials. Lancet 2017; 390: 276-88. PubMed PMID: 28596043.

(Among 1862 patients with plaque psoriasis enrolled in two 12-week controlled trials, clinical response rates were higher with tildrakizumab [61-66%] than placebo [6-7%] and etanercept [48%], while adverse event rates were similar in all groups; no mention of ALT elevations or hepatotoxicity).

Blauvelt A, Reich K, Papp KA, Kimball AB, Gooderham M, Tyring SK, Sinclair R, et al. Safety of tildrakizumab for moderate-to-severe plaque psoriasis: pooled analysis of three randomized controlled trials. Br J Dermatol 2018; 179: 615-22. PubMed PMID: 29742274.

(Among 2081 patients with moderate-to-severe plaque psoriasis enrolled in 3 placebo-controlled trials, serious adverse event rates, discontinuations due to side effects, major cardiovascular events, and severe infections occurred at similar rates in both groups; no mention of ALT elevations or hepatotoxicity).

Markham A. Tildrakizumab: first global approval. Drugs 2018; 78: 845-9. PubMed PMID: 29752706.

(Review of the mechanism of action, history of development, pharmacology, clinical efficacy and safety of tildrakizumab).