U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Teriflunomide. [Updated 2017 Jan 15].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Teriflunomide

Updated: January 15, 2017.

OVERVIEW

Introduction

Teriflunomide is an orally available immunomodulatory agent used to treat relapsing multiple sclerosis. Teriflunomide is associated with transient serum enzyme elevations during therapy and with rare instances of acute liver injury.

Background

Teriflunomide (ter" i floo' noe mide) is the active metabolite of leflunomide, an immunomodulatory agent similar to thalidomide, and is used in the treatment of rheumatoid arthritis. The mechanism of action of teriflunomide appears to be based, at least in part, upon inhibition of the enzyme dihydro-orotate dehydrogenase, which is an important step in pyrimidine synthesis. The activation and proliferation of lymphocytes are dependent upon pyrimidine synthesis and is acutely sensitive to its inhibition, resulting in suppression of ongoing immune reactivity. Teriflunomide has other activities including inhibition of NF-kappa B pathways that may contribute to its immunomodulatory actions. In animal models of multiple sclerosis, teriflunomide was shown to have beneficial effects which led to its critical evaluation in this disease. In several large, randomized controlled trials, teriflunomide was found to reduce relapse rates and improve neuro-radiologic outcomes in adult patients with relapsing-remitting multiple sclerosis. Teriflunomide was approved for use for multiple sclerosis in the United States in 2012 and is now available in tablets of 7 and 14 mg under the brand name Aubagio. The recommended dose in adults is 7 or 14 mg orally once daily. Common side effects are headache, diarrhea, nausea and hair loss (alopecia). Rare, but potentially serious adverse events include increased risk of severe infections, reactivation of tuberculosis and peripheral neuropathy.

Hepatotoxicity

In large randomized controlled trials of teriflunomide, serum ALT elevations occurred in 13% to 15% of teriflunomide compared to 9% of placebo recipients. Elevations above 3 times the upper limit of normal occurred in 6% of teriflunomide versus 4% of placebo recipients, usually within the first 6 months of therapy. The enzyme elevations were usually transient and not associated with symptoms or jaundice, but led to drug discontinuation in 2% to 3% of patients. The abnormalities resolved rapidly with drug discontinuation and resolved spontaneously in at least half of patients without drug modification. During preregistration trials, a single case of severe liver injury with jaundice was described, ALT elevations appearing 5 months after starting teriflunomide. Because of this and the known hepatotoxic potential of leflunomide, teriflunomide was given a "black box" warning regarding hepatotoxicity, and routine monitoring of liver tests is recommended monthly for the first 6 months and intermittently thereafter. Since approval and more wide scale usage, there have been no

cases of clinical apparent liver injury published in the medical literature, although the package label mentions hepatitis and hepatic failure as possible adverse events. Clinically apparent liver injury has been reported with leflunomide, generally presenting with a hepatocellular or mixed pattern of serum enzyme elevations within 1 to 6 months of starting therapy. Immunoallergic and autoimmune features have not been prominent in these cases. Some cases, however, have been severe leading to acute liver failure and death. Whether similar cases occur with teriflunomide is not known.

Likelihood score: D (possible cause of clinically apparent liver injury but experience with its use is limited).

Mechanism of Injury

The mechanism by which teriflunomide might cause liver injury is not known. It is extensively metabolized by the liver largely by the cytochrome P450 system (largely CYP2C8) and is susceptible to drug-drug interactions, particularly with warfarin, oral contraceptives and agents that are metabolized by CYP 2C8 (paclitaxel, pioglitazone) and possibly others.

Outcome and Management

While chronic therapy with teriflunomide can be associated with mild-to-moderate serum aminotransferase elevations, it has only very rarely been linked to cases of clinically apparent liver injury. Nevertheless, the product label for teriflunomide recommends monitoring of liver tests monthly for 6 months and intermittently thereafter. In instances of suspected teriflunomide toxicity, elimination of the drug can be accelerated by cholestyramine or activated charcoal. Teriflunomide is eliminated slowly from the serum probably due to enterohepatic recirculation. Without an accelerated elimination procedure using activated charcoal (50 g every 12 hours for 11 days) or cholestyramine (8 grams every 8 hours for 11 days), drug levels can remain elevated for months. Cross sensitivity to hepatic injury is likely between teriflunomide and leflunomide as well as thalidomide, but there is no reason to believe that there is similar cross sensitivity with other disease-modifying agents used to treat multiple sclerosis such as glatiramer acetate, dimethyl fumarate, fingolimod or interferon beta.

Drug Class: Multiple Sclerosis Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Teriflunomide – Generic, Aubagio®

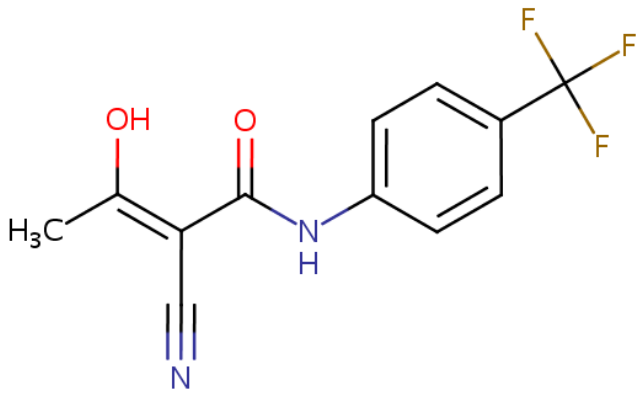
DRUG CLASS

Multiple Sclerosis Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Teriflunomide	163451-81-8	C12-H9-F3-N2-O	

ANNOTATED BIBLIOGRAPHY

References updated: 15 January 2017

Zimmerman HJ. Oncotherapeutic and immunosuppressive agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 697-8.

(Expert review of hepatotoxicity published in 1999 before the availability of teriflunomide).

Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013.

(Multi-authored textbook of hepatotoxicity published in 2013 does not discuss the drugs for multiple sclerosis).

Krensky AM, Bennett WM, Vincenti F. A case study: immunotherapy for multiple sclerosis. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1025-7.

(Textbook of pharmacology and therapeutics).

O'Connor PW, Li D, Freedman MS, Bar-Or A, Rice GP, Confavreux C, Paty DW, Stewart JA, et al.; Teriflunomide Multiple Sclerosis Trial Group; University of British Columbia MS/MRI Research Group. A Phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses. Neurology 2006; 66: 894-900. PubMed PMID: 16567708.

(Among 179 patients with multiple sclerosis treated with teriflunomide [7 or 14 mg daily] or placebo for 36 weeks, ALT elevations occurred in 12-16% of teriflunomide vs 10% of placebo treated patients, but rates of discontinuation because of liver test abnormalities were similar in all groups).

O'Connor P, Wolinsky JS, Confavreux C, Comi G, Kappos L, Olsson TP, Benzerdjeb H, et al.; TEMSO Trial Group. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. N Engl J Med 2011; 365: 1293-303. PubMed PMID: 21991951.

(Among 1088 patients with relapsing multiple sclerosis treated with teriflunomide [7 or 14 mg daily] or placebo for 2 years, relapse rates were lower, but ALT elevations were more common with teriflunomide [54% and 57%] than placebo [36%], although elevations above 3 times the ULN were similar in all groups [~6.5%] and no patient developed clinically apparent liver injury attributable to treatment).

Gold R. Oral therapies for multiple sclerosis: a review of agents in phase III development or recently approved. CNS Drugs 2011; 25: 37-52. PubMed PMID: 21128693.

(Review of oral medications for multiple sclerosis under development, including dimethyl fumarate [BG-12], fingolimod, teriflunomide, laquinimod and cladribine, mentions that ALT elevations are more frequent with teriflunomide than placebo treatment so that monitoring of liver enzymes during therapy is recommended).

Killestein J, Rudick RA, Polman CH. Oral treatment for multiple sclerosis. Lancet Neurol 2011; 10: 1026-34. PubMed PMID: 22014437.

(Review of the clinical usefulness and safety of 5 new oral therapies for relapsing multiple sclerosis mentions that liver enzyme elevations can occur with teriflunomide and fingolimod therapy).

Confavreux C, Li DK, Freedman MS, Truffinet P, Benzerdjeb H, Wang D, Bar-Or A, et al; Teriflunomide Multiple Sclerosis Trial Group. Long-term follow-up of a phase 2 study of oral teriflunomide in relapsing multiple sclerosis: safety and efficacy results up to 8.5 years. Mult Scler. 2012; 18: 1278-89. PubMed PMID: 22307384.

(Among 147 patients enrolled in clinical trials of teriflunomide who were entered into an open label extension study, mild elevations in ALT levels were common occurring in ~63% of patients, but were above 3 times ULN in only 12%, but no elevation was associated with symptoms or jaundice).

New drugs for relapsing multiple sclerosis. Med Lett Drugs Ther 2012; 54 (1403): 89-91. PubMed PMID: 23183318.

(Concise review of efficacy, safety and costs of new disease modifying drugs for multiple sclerosis lists side effects in a table including "transaminase elevations" for interferon beta, fingolimod and teriflunomide, and "hepatotoxicity" for natalizumab, but not for glatiramer or mitoxantrone).

Brunetti L, Wagner ML, Maroney M, Ryan M. Teriflunomide for the treatment of relapsing multiple sclerosis: a review of clinical data. Ann Pharmacother 2013; 47: 1153-60. PubMed PMID: 24259730.

(Systematic review of 6 phase II and III trials of teriflunomide in relapsing multiple sclerosis reports ALT elevations above 3 times ULN in 12-14% of teriflunomide vs 7% of control subjects; no mention of clinically apparent liver injury).

Garnock-Jones KP. Teriflunomide: a review of its use in relapsing multiple sclerosis. CNS Drugs 2013; 27: 1103-23. PubMed PMID: 24198223.

(Review of the structure, mechanism of action, clinical efficacy and safety of teriflunomide in relapsing multiple sclerosis, mentions that ALT elevations are more frequent with teriflunomide than placebo, but are generally mild and asymptomatic with only a few cases having an accompanying elevation in bilirubin, rates being no higher with teriflunomide than with placebo; most ALT elevations occurred during the first year of therapy and, in half, the elevations returned to normal without stopping treatment).

Oh J, O'Connor PW. Safety, Tolerability, and Efficacy of Oral Therapies for Relapsing-Remitting Multiple Sclerosis. CNS Drugs 2013; 27: 591-609. PubMed PMID: 23801528.

(Review of efficacy and safety or oral agents for multiple sclerosis, including fingolimod, teriflunomide, dimethyl fumarate, laquinimod and cladribine, none of which have raised major issues of hepatotoxicity).

Miller AE, Wolinsky JS, Kappos L, Comi G, Freedman MS, Olsson TP, Bauer D, Benamor M, Truffinet P, O'Connor PW; TOPIC Study Group. Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis(TOPIC): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol 2014; 13: 977-86. PubMed PMID: 25192851.

(Among 614 patients with early multiple sclerosis treated with teriflunomide [7 or 14 mg daily] or placebo for up to 2 years, relapse rates were less while ALT elevations above 3 times ULN were more frequent with teriflunomide [12%] than placebo [9.5%], and there were no cases of clinically apparent liver injury).

Confavreux C, O'Connor P, Comi G, Freedman MS, Miller AE, Olsson TP, Wolinsky JS, et al.; TOWER Trial Group. Oral teriflunomide for patients with relapsing multiple sclerosis(TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol 2014; 13 (3): 247-56. PubMed PMID: 24461574.

(Among 1169 patients with relapsing multiple sclerosis treated with teriflunomide [7 or 14 mg daily] or placebo for at least 48 weeks, the relapse rate was decreased, but ALT elevations occurred in 8% of teriflunomide and 6% of placebo-treated subjects; two patients developed jaundice with ALT elevations, and all recovered with discontinuation).

Pawate S, Bagnato F. Newer agents in the treatment of multiple sclerosis. Neurologist 2015; 19: 104-17. PubMed PMID: 25888198.

(Summary of the efficacy and safety of new drugs for multiple sclerosis mentions that fingolimod, laquinimod and teriflunomide have been associated with serum enzyme elevations during treatment, but no specifics given).

Papadopoulou A, Kappos L, Sprenger T. Safety of teriflunomide for the management of relapsing-remitting multiple sclerosis. Expert Opin Drug Saf 2015; 14: 749-59. PubMed PMID: 25687236.

(Review of the mechanism of action, efficacy and safety of teriflunomide in relapsing multiple sclerosis states that ALT elevations were more frequent with teriflunomide [11% to 14%] than placebo [7% to 8%], but that the elevations were mostly mild and asymptomatic, and rates of severe elevations and those accompanied by bilirubin increases were the same with teriflunomide as with placebo).

English C, Aloi JJ. New FDA-approved disease-modifying therapies for multiple sclerosis. Clin Ther 2015; 37: 691-715. PubMed PMID: 25846320.

(Systematic review of efficacy and safety of the newer disease modifying therapies of multiple sclerosis lists ALT elevations as adverse events associated with fingolimod, teriflunomide and dimethyl fumarate, but not peginterferon beta or alemtuzumab).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-1352. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 7 [0.8%] were attributed to interferon beta, but none were linked to teriflunomide or other drugs used for multiple sclerosis).

Feinstein A, Freeman J, Lo AC. Treatment of progressive multiple sclerosis: what works, what does not, and what is needed. Lancet Neurol 2015; 14: 194-207. PubMed PMID: 25772898.

(Commentary on management of progressive multiple sclerosis in which most of the newer disease modifying agents have little effect, mentions that major attention should be paid to management and relief of symptoms such as fatigue, bladder dysfunction, spasticity, pain, depression and cognitive dysfunction; no discussion of liver related adverse effects).

O'Connor P, Comi G, Freedman MS, Miller AE, Kappos L, Bouchard JP, Lebrun-Frenay C, et al.; Teriflunomide Multiple Sclerosis Oral (TEMSO) Trial Group and the MRI-AC in Houston, Texas. Long-term safety and efficacy of teriflunomide: Nine-year follow-up of the randomized TEMSO study. Neurology 2016; 86: 920-30. PubMed PMID: 26865517.

(Among 742 patients with multiple sclerosis treated with teriflunomide for up to 9 years in an extension study after a controlled trial [O'Connor 2011], 25 patients [2.8% to 3.8%] developed ALT elevations above 3 times the ULN and discontinued therapy and 2 had concurrent increases in bilirubin, although other causes were found in both).