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Alefacept

Updated: February 19, 2016.

OVERVIEW

Introduction

Alefacept is a recombinant fusion protein of lymphocyte function associated antigen-3 (LFA-3) and immunoglobulin G dimer that acts to inactive T cells, and is an immunosuppressive agent that was previously used to treat moderate-to-severe plaque psoriasis. Alefacept is associated with a low rate of serum enzyme elevations during therapy and to rare instances of clinically apparent acute liver injury.

Background

Alefacept (a lef' a sept) is a recombinant fusion protein that combines the lymphocyte function associated antigen-3 (LFA3) with the heavy chain of immunoglobulin G. The fusion protein inhibits the binding of endogenous LFA3 to CD2 cells interfering with activation of memory T cells which play an important role in the pathogenesis of inflammatory autoimmune diseases. In controlled clinical trials, alefacept therapy improved symptoms and skin lesions in patients with refractory psoriasis. Alefacept was approved for use in the United States in 2003 and was the first biological agent approved for treatment of psoriasis. However, because of the availability of better tolerated and more effective biologics for psoriasis, alefacept was withdrawn from use by its sponsor in 2011. Alefacept had been available as a solution for parenteral administration in single use vials of 7.5 or 15 mg under the brand name Amevive. Alefacept was given once weekly, either intramuscularly in a dose of 15 mg or intravenously in a dose of 7.5 mg for 12 weeks. Repeat courses were recommended for patients who responded to therapy and then relapsed. Common side effects included headache, dizziness, nausea, myalgias, injection site reactions and infections. Rare, but potentially severe adverse reactions included lymphopenia, serious infections, hypersensitivity reactions and an increased risk for malignancy.

Hepatotoxicity

In prelicensure controlled trials, serum ALT or AST elevations greater than 3 times the upper limit of normal (ULN) occurred in <2% of alefacept and a similar proportion of placebo treated subjects. The elevations were usually mild-to-moderate in severity, asymptomatic and self-limited in course. ALT elevations accompanied by jaundice and symptoms were not reported in the premarketing studies. Subsequent to its approval and more wide scale use, however, cases of marked serum enzyme elevations, acute hepatitis and acute liver failure have been reported to the sponsor. These cases have not been reported in the literature and the strength of the association of these episodes with alefacept use has not been evaluated critically. The clinical features, characteristics, course and outcome of these episodes of hepatitis have not been described.

Likelihood score: E* (unlikely but suspected rare cause of liver injury).

Mechanism of Injury

The mechanism of possible liver injury due to alefacept is unknown. Alefacept is a recombinant protein and unlikely to have intrinsic hepatotoxicity. However, because it is a potent immunomodulatory agent, it may be capable of causing reactivation of hepatitis B or autoimmune liver injury.

Outcome and Management

Liver injury attributed to alefacept has ranged from uncommon instances of transient serum enzyme elevations without symptoms or jaundice to rare cases of acute clinically apparent liver injury.

Drug Class: Dermatologic Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Alefacept – Amevive®

DRUG CLASS

Dermatologic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Alefacept	222535-22-0	Recombinant Protein	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 19 February 2016

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 mentions that "the biological immunosuppressants are largely free from hepatotoxicity, with the exception of the TNF alpha antagonists").

Burkhart C, Morrell D, Goldsmith L. Dermatological pharmacology. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1803-32.

(Textbook of pharmacology and therapeutics).

Ellis CN, Krueger GG; Alefacept Clinical Study Group. Treatment of chronic plaque psoriasis by selective targeting of memory effector T lymphocytes. N Engl J Med 2001; 345: 248-55. PubMed PMID: 11474662.

(Among 229 patients with psoriasis treated with various doses of intravenous alefacept or placebo weekly for 12 weeks, clinical responses occurred in 38-53% of alefacept vs 21% of placebo recipients, adverse events were

generally mild and "laboratory tests showed no significant changes in serum chemical... values in any study groups").

Krueger GG, Papp KA, Stough DB, Loven KH, Gulliver WP, Ellis CN; Alefacept Clinical Study Group. A randomized, double-blind, placebo-controlled phase III study evaluating efficacy and tolerability of 2 courses of alefacept in patients with chronic plaque psoriasis. J Am Acad Dermatol 2002; 47: 821-33. PubMed PMID: 12451365.

(Abstract; among 553 patients with chronic plaque psoriasis treated with two 12 week courses of one weekly alefacept or placebo, clinical responses occurred in 28% of alefacept vs 8% of placebo treated subjects and side effects were mild; no mention of ALT elevations or hepatotoxicity).

Ortonne JP. Clinical response to alefacept: results of a phase 3 study of intramuscular administration of alefacept in patients with chronic plaque psoriasis. J Eur Acad Dermatol Venereol 2003; 17 Suppl 2: 12-6. PubMed PMID: 12795770.

(Among 507 patients with psoriasis treated with 10 or 15 mg per week of alefacept or placebo for 12 weeks, clinical responses occurred in 12% and 21% of alefacept vs 5% of placebo recipients, and "minor elevations in serum aminotransferase levels were noted in all 3 groups", but there were no hepatic severe adverse events).

Alefacept(Amevive) for treatment of psoriasis. Med Lett Drugs Ther 2003; 45 (1154): 31-2. PubMed PMID: 12717339.

(Concise summary of the mechanism of action, efficacy, safety and cost of alefacept shortly after its approval for use in psoriasis in the US, does not mention ALT elevations or liver injury as side effects).

Goffe B, Papp K, Gratton D, Krueger GG, Darif M, Lee S, Bozic C, et al. An integrated analysis of thirteen trials summarizing the long-term safety of alefacept in psoriasis patients who have received up to nine courses of therapy. Clin Ther 2005; 27: 1912-21. PubMed PMID: 16507377.

(In a pooled analysis of adverse events from 13 controlled trials of alefacept which enrolled 1869 patients with psoriasis, common side effects were headache and nasopharyngitis and pruritus, but were rarely severe or required discontinuation and there were "no clinically relevant trends with respect to changes from baseline in laboratory parameters"; no mention of ALT elevations or hepatotoxicity).

Scheinfeld N. Alefacept: a safety profile. Expert Opin Drug Saf 2005; 4: 975-85. PubMed PMID: 16255657.

(Review of clinical trials of alefacept mentions that ALT elevations have occurred on treatment "but do not appear to be clinically significant" and that cases of hepatitis with jaundice have been reported; in clinical trials in more than 2000 patients, there have been no cases of exacerbation of hepatitis B or C).

Thaçi D, Pätzold S, Kaufmann R, Boehncke WH. Treatment of psoriasis with alefacept in patients with hepatitis C infection: a report of two cases. Br J Dermatol 2005; 152: 1048-50. PubMed PMID: 15888169.

(Two men, ages 29 and 63 years, with chronic hepatitis C and psoriasis were treated with weekly injections of alefacept for 12 weeks and had no worsening in serum ALT or HCV RNA levels or other adverse reaction).

Mease PJ, Gladman DD, Keystone EC; Alefacept in Psoriatic Arthritis Study Group. Alefacept in combination with methotrexate for the treatment of psoriatic arthritis: results of a randomized, double-blind, placebo-controlled study. Arthritis Rheum 2006; 54: 1638-45. PubMed PMID: 16646026.

(Among 146 patients with psoriatic arthritis and normal liver tests in a 12 week controlled trial, 1 of 93 treated with alefacept and methotrexate vs 1 of 59 on methotrexate alone developed ALT elevations above 3 times ULN, but both patients recovered without intervention or stopping therapy).

Perlmutter A, Cather J, Franks B, Jaracz E, Menter A. Alefacept revisited: Our 3-year clinical experience in 200 patients with chronic plaque psoriasis. J Am Acad Dermatol 2008; 58: 116-24. PubMed PMID: 17997502.

(Analysis of 201 patients with psoriasis treated with alefacept in a total of 296 courses, therapy was stopped early in one patient who was also on methotrexate because of serum enzyme elevations, but no details provided).

Castelo-Soccio L, Van Voorhees AS. Long-term efficacy of biologics in dermatology. Dermatol Ther 2009; 22: 22-33. PubMed PMID: 19222514.

(Review of long term efficacy of various biologics used to treat psoriasis, including alefacept and the anti-tumor necrosis factor agents; no discussion of hepatotoxicity).

Mease PJ, Reich K; Alefacept in Psoriatic Arthritis Study Group. Alefacept with methotrexate for treatment of psoriatic arthritis: open-label extension of a randomized, double-blind, placebo-controlled study. J Am Acad Dermatol 2009; 60: 402-11. PubMed PMID: 19028407.

(Among 160 patients who enrolled in an extension phase study of alefacept for psoriatic arthritis, increased AST levels [1-3 times ULN] occurred in 30% of patients, but were above 3 times ULN in only 2% during the open-label extension phase).

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.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, no cases were attributed to alefacept).