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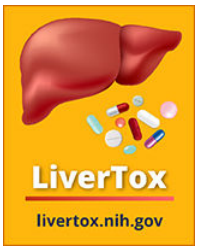

Denileukin Diftitox

Updated: December 27, 2017.

OVERVIEW

Introduction

Denileukin diftitox is a recombinant fusion protein of human interleukin-2 (IL-2) attached to diphtheria toxin fragments A and B that is used as an antineoplastic agent to treat cutaneous T cell lymphomas that express IL-2 receptors. High doses of denileukin diftitox can cause mild-to-moderate elevations in serum enzymes and bilirubin, but rarely result in clinically significant acute liver injury.

Background

Denileukin (den" i loo' kin) diftitox (dif' ti tox) is a fusion protein that combines human interleukin-2 (IL-2) with diphtheria toxin fragments A and B. Denileukin diftitox was approved for use in the United States in 1999 and the indications remain limited to therapy of refractory cutaneous T cell lymphomas that express the CD25 component of the IL-2 receptor on the surface of the malignant cells. Once taken up by the cells expressing the IL-2 receptor, the diphtheria toxin is released into the cytoplasm causing cell death. Denileukin diftitox is available in solution in 2 mL single use vials of 150 µg/mL under the brand name Ontak. The typical dose is 9 to 18 µg/kg given intravenously once daily for 5 consecutive days every 21 days for up to 8 cycles. Side effects are common with denileukin diftitox therapy, and it should be administered in a hospital setting under the supervision of physicians experienced in the use of anticancer agents. Common side effects include fatigue, fever, chills, nausea, diarrhea, arthralgia, headache and rash. Up to 25% of patients develop capillary leak syndrome leading to peripheral edema, hypotension and renal insufficiency and can cause shock, pulmonary edema, renal failure and death. Less common but potentially severe adverse reactions include anaphylaxis, severe infections, thrombotic events and pancreatitis.

Hepatotoxicity

In preregistration clinical trials, serum aminotransferase elevations in occurred in 61% of patients treated with denileukin diftitox, and values were above 5 times the upper limit of normal (ULN) in 15% of recipients. Hypoalbuminemia (less than 3.0 g/dL) was also common during treatment, occurring in 83% of patients but falling to less than 2.0 g/dL in only 14%. However, clinically apparent liver injury with jaundice was not reported in these trials. Since approval of denileukin diftitox there have not been reports of acute liver injury with jaundice associated with its administration, although it has had quite limited clinical use. Thus, denileukin diftitox has been clearly linked to serum enzyme elevations and hypoalbuminemia during treatment, but has not been implicated in cases of idiosyncratic, acute liver injury with jaundice.

Likelihood score: E* (unproven but suspected cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which denileukin diftitox infusions causes liver injury is not well defined, but it is likely taken up by hepatocytes to some degree and might have a direct toxic effect on liver cells. As it is a recombinant human protein, it is unlikely to have direct intrinsic hepatotoxicity.

Outcome and Management

The serum enzyme and bilirubin elevations during denileukin diftitox therapy are generally asymptomatic, self-limited and benign. In situations in which ALT or AST levels rise and remain above 5 times ULN, dose modification or temporary discontinuation of the intravenous infusions is prudent.

Drug Class: Antineoplastic Agents, Cytokines, Biologic Response Modifiers

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Denileukin Diftitox – Ontak®

DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Denileukin Diftitox	173146-27-5	Cytokine	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 27 December 2017

Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999.

(Review of hepatotoxicity published in 1999 before the availability of denileukin diftitox).

Chabner BA, Barnes J, Neal J, Olson E, Mujagic 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. 1731-54.

(Textbook of pharmacology and therapeutics).

Interleukin-2. Med Lett Drugs Ther 1990; 32 (826): 85-6. PubMed PMID: 2202892.

(Concise summary of the mechanism of action, clinical efficacy and safety of recombinant IL-2 mentions side effects of increased capillary permeability with fluid retention, hypotension, renal insufficiency and pulmonary edema as well as severe malaise, fever, nausea, diarrhea, anemia and hyperbilirubinemia).

Olsen E, Duvic M, Frankel A, Kim Y, Martin A, Vonderheid E, Jegasothy B, et al. Pivotal phase III trial of two dose levels of denileukin diftitox for the treatment of cutaneous T-cell lymphoma. J Clin Oncol 2001; 19: 376-88. PubMed PMID: 11208829.

(Among 71 patients with refractory cutaneous T cell lymphoma treated with denileukin diftitox [9 or 18 μg/kg] daily for 5 days every 3 weeks for up to 8 cycles, 30% had a partial or complete response with no differences in the two doses; 61% of patients had elevations in serum ALT or AST, which were above 5 times ULN in 17%).

Dang NH, Hagemeister FB, Pro B, McLaughlin P, Romaguera JE, Jones D, Samuels B, et al. Phase II study of denileukin diftitox for relapsed/refractory B-Cell non-Hodgkin's lymphoma. J Clin Oncol 2004; 22: 4095-102. PubMed PMID: 15353540.

(Among 45 patients with refractory non-Hodgkin lymphoma treated with denileukin diftitox, partial or complete responses occurred in 24% and "overall treatment was well tolerated" with ALT or AST elevations above 5 times ULN in 17 [38%] patients, and toxic epidermal necrosis and capillary leak syndrome in 1 patient each).

Frankel AE, Surendranathan A, Black JH, White A, Ganjoo K, Cripe LD. Phase II clinical studies of denileukin diftitox diphtheria toxin fusion protein in patients with previously treated chronic lymphocytic leukemia. Cancer 2006; 106: 2158-64. PubMed PMID: 16586495.

(Among 22 patients with refractory chronic lymphocytic leukemia treated with denileukin diftitox, 6 [27%] had an objective response and "toxicities were moderate", 32% of patients having ALT or AST elevations above 5 times ULN and 14% vascular leak syndrome, but none required stopping therapy for liver injury).

Gerena-Lewis M, Crawford J, Bonomi P, Maddox AM, Hainsworth J, McCune DE, Shukla R, et al. A Phase II trial of Denileukin Diftitox in patients with previously treated advanced non-small cell lung cancer. Am J Clin Oncol 2009; 32: 269-73. PubMed PMID: 19433964.

(Among 41 patients with advanced non-small cell lung cancer treated with 1 to 6 cycles of denileukin diftitox [18 μg/kg daily for 5 days], none had an objective response, 22% developed ALT or AST levels [all less than 5 times ULN], 5 had vascular leak syndrome and 1 died of drug related myocarditis).

Prince HM, Duvic M, Martin A, Sterry W, Assaf C, Sun Y, Straus D, et al. Phase III placebo-controlled trial of denileukin diftitox for patients with cutaneous T-cell lymphoma. J Clin Oncol 2010; 28: 1870-7. PubMed PMID: 20212249.

(Among 144 patients with refractory cutaneous T-cell lymphomas [CD25 positive] treated with denileukin diftitox [9 or 18 μg/kg daily for 5 days] or placebo infusions every 21 days for up to 8 cycles, objective responses occurred in 44% of those on drug vs 16% on placebo while "continued treatment did not cause worsening of laboratory parameters and was not associated with liver or renal toxicity").

Duvic M, Martin AG, Olsen EA, Fivenson DP, Prince HM. Efficacy and safety of denileukin diftitox retreatment in patients with relapsed cutaneous T-cell lymphoma. Leuk Lymphoma 2013; 54: 514-9. PubMed PMID: 22891708.

(Among 20 patients with cutaneous T cell lymphomas who relapsed after previous therapy with denileukin diftitox and who were then retreated with up to 8 cycles [18 μg/kg daily for 5 days], 40% had an objective response while 55% had serious adverse events, but none died or had severe capillary leak syndrome; no mention of ALT elevations or hepatotoxicity).

Baldo BA. Chimeric fusion proteins used for therapy: indications, mechanisms, and safety. Drug Saf 2015; 38: 455-79. PubMed PMID: 25832756.

(Review of the mechanism of action, efficacy and safety of therapeutic recombinant fusion proteins mentions that serious adverse reactions to denileukin diftitox include infusion and hypersensitivity reactions, skin rash, [including toxic epidermal necrolysis], capillary leak syndrome, shock, renal insufficiency, decreased vision and infections; no discussion of ALT elevations or hepatotoxicity).

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: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, recombinant fusion proteins accounted for only 2 cases [both etanercept], and none were linked to abatacept, alefacept, rilonacept, romiplostim or denileukin-diftitox).