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Efalizumab

Updated: February 10, 2018.

OVERVIEW

Introduction

Efalizumab is a humanized monoclonal antibody to human CD11a subunit of the lymphocyte function-associated antigen 1, which acts as an immunosuppressant agent blocking lymphocyte activation and was formerly used to treat severe plaque psoriasis. Efalizumab has been linked to rare instances of idiosyncratic acute liver injury and may be a rare cause of reactivation of hepatitis B.

Background

Efalizumab (ef" al iz' ue mab) is a recombinant, humanized monoclonal antibody to CD11a, a subunit of the lymphocyte function-associated antigen 1 (LFA-1), which is present on lymphocytes and causes activation and proliferation of lymphocytes. Blocking of CD11a inhibits lymphocyte activation and decreases migration of lymphocytes to sites of inflammation. Efalizumab has been shown to have potent immunosuppressive activity and to lower lymphocyte counts and improve autoimmune conditions. In controlled studies, efalizumab was shown to be effective in inducing clinical responses in 20% to 30% of patients with severe psoriasis. Efalizumab was approved for use in the United States in 2005 as therapy for severe plaque psoriasis, but was withdrawn in 2009 because of several instances of progressive multifocal leukoencephalopathy (PMLE), a severe neurological condition which is believed to be due to reactivation of the JC virus in neural cells. Efalizumab was previously available in 125 mg single use vials under the brand name Raptiva. The recommended initial dose was 0.7 mg/kg subcutaneously, followed by weekly doses of 1 mg/kg, with maximum single dose of 200 mg. Common side effects included headache, fatigue, fever, muscle and back aches, nausea, acne and hypersensitivity reactions. Efalizumab is also capable of causing immune suppression, resulting in an increased susceptibility to opportunistic infections.

Hepatotoxicity

In large clinical trials of efalizumab, serum alkaline phosphatase levels were often reported to be mildly elevated (by 2-3 U/L) compared to baseline, but serum aminotransferase values did not change and there were no reports of marked ALT elevations or clinically apparent liver injury due to the monoclonal antibody therapy. After its approval and wider scale clinical use, there were several reports of liver injury attributed to efalizumab therapy, one case of apparent reactivation of hepatitis B (with concurrent adalimumab therapy) and one case of a self-perpetuating autoimmune hepatitis, arising after 8 weeks of efalizumab therapy and not resolving with stopping the monoclonal antibody and requiring corticosteroid therapy.

Likelihood score: D (possible rare cause of clinically apparent liver injury, including HBV reactivation).

Mechanism of Injury

The mechanism of liver injury caused by efalizumab is probably immunologically mediated, perhaps as a result of its effects on leukocyte function in causing an autoimmune reaction or reactivation of hepatitis B. Efalizumab is a monoclonal antibody and, like other proteins, is metabolized into amino acids and is unlikely to have intrinsic toxicity.

Outcome and Management

The hepatotoxicity of efalizumab is not well established, but in some instances resembles autoimmune hepatitis and warrants corticosteroid therapy. Other cases of liver injury during efalizumab therapy may represent reactivation of hepatitis B and call for antiviral therapy with drugs active against HBV.

Other immunomodulatory monoclonal antibodies used to treat autoimmune diseases include adalimumab, certolizumab, golimumab, infliximab, natalizumab, rituximab and tocilizumab.

Drug Class: Monoclonal Antibodies; Immunomodulatory Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Efalizumab – Raptiva®

DRUG CLASS

Immunomodulatory Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Efalizumab	214745-43-4	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 10 February 2018

Zimmerman HJ. Drugs used to treat rheumatic and musculospastic disease. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 517-54.

(Expert review of hepatotoxicity published in 1999, well before the availability of most monoclonal antibody therapies).

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 rituximab and problems of reactivation of hepatitis B, but also states that "the biological immunosuppressants are largely free from hepatotoxicity, with the exception of the TNF alpha antagonists"; efalizumab not specifically mentioned).

Krensky AM, Vincenti F, Bennett WM. Immunomodulators. In, Brunton LL, Lazo JS, Parker KL, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 11th ed. New York: McGraw-Hill, 2006, pp. 1405-88.

(Textbook of pharmacology and therapeutics).

Efalizumab (Raptiva) for treatment of psoriasis. Med Lett Drugs Ther 2003; 45 (1171): 97-8. PubMed PMID: 14657802.

(Concise summary of efficacy, safety and costs of efalizumab shortly after its approval for use in psoriasis in the US; no mention of ALT elevations or hepatotoxicity).

Lebwohl M, Tyring SK, Hamilton TK, Toth D, Glazer S, Tawfik NH, Walicke P, et al.; Efalizumab Study Group. A novel targeted T-cell modulator, efalizumab, for plaque psoriasis. N Engl J Med 2003; 349: 004-13. PubMed PMID: 14627785.

(Among 597 patients with psoriasis treated with efalizumab [1 or 2 mg/kg/week] or placebo for 12-24 weeks, clinical responses were more frequent with efalizumab [22% and 28% vs 5% at week 12] as were side effects including headaches, chills, fever, nausea, myalgias, and acne; Alk P and GGT levels were slightly and transiently elevated, but there were "no other notable changes" in laboratory values).

Dubertret L, Sterry W, Bos JD, Chimenti S, Shumack S, Larsen CG, Shear NH, Papp KA; CLEAR Multinational Study Group. Clinical experience acquired with the efalizumab (Raptiva) (CLEAR) trial in patients with moderate-to-severe plaque psoriasis: results from a phase III international randomized, placebo-controlled trial. Br J Dermatol 2006; 155: 170-81. PubMed PMID: 16792770.

(Among 793 patients with psoriasis treated with efalizumab or placebo for 12 weeks, Alk P levels increased by ~3 U/L by week 12, but abnormalities of ALT and AST "were generally similar to those present at baseline").

Papp KA, Bressinck R, Fretzin S, Goffe B, Kempers S, Gordon KB, Caro I, et al.; Efalizumab Study Group. Safety of efalizumab in adults with chronic moderate to severe plaque psoriasis: a phase IIIb, randomized, controlled trial. Int J Dermatol 2006; 45: 605-14. PubMed PMID: 16700803.

(Among 686 patients with psoriasis who received efalizumab [0.7 mg/kg initially and then 1 mg/kg weekly] or placebo for 12 weeks, there were "no clinically significant changes in... laboratory parameters and no evidence of end-organ toxicities"; there was a slight increase in Alk P levels but no change in ALT or AST values).

Gordon KB, Papp KA, Hamilton TK, Walicke PA, Dummer W, Li N, Bresnahan BW, Menter A; Efalizumab Study Group. Efalizumab for patients with moderate to severe plaque psoriasis: a randomized controlled trial. JAMA 2003; 290: 3073-80. PubMed PMID: 14679270.

(Among 556 patients with psoriasis treated with efalizumab or placebo for 12 weeks, response rates were 24% on efalizumab vs 4% of placebo, and therapy was "safe and well tolerated" with "no clinically significant laboratory abnormalities").

Kaiser T, Moessner J, Patel K, McHutchison JG, Tillmann HL. Life threatening liver disease during treatment with monoclonal antibodies. BMJ 2009; 338: b508. PubMed PMID: 19224957.

(66 year old man with psoriasis was treated with efalizumab [anti-CD11a] and then adalimumab [anti-TNF], and 11 days later developed jaundice and severe hepatitis [bilirubin 9.1 rising to 52 mg/dL, ALT 549 U/L, Alk P 131 U/L], with HBsAg being detected and slow but eventual recovery).

Primo J, Michavila J, Jiménez I. [Efalizumab-induced autoimmune hepatitis]. Gastroenterol Hepatol 2010 Jan; 33 (1): 69-70. Spanish. PubMed PMID: 19800148.

(55 year old woman with psoriasis developed serum enzyme elevations after 9 doses of efalizumab [50 mg weekly], with bilirubin normal, but ALT 235 U/L, Alk P 428 U/L, ANA rising to 1:1,280 which persisted for 6 months despite stopping therapy, ultimately responding to corticosteroid and azathioprine therapy).

Gadzia J, Turner J. Progressive multifocal leukoencephalopathy in two psoriasis patients treated with efalizumab. J Drugs Dermatol 2010; 9: 1005-9. PubMed PMID: 20684152.

(Two patients, 70 and 73 year old, man and woman, treated for psoriasis with efalizumab for more than 3 years developed progressive neurologic deficits and had JC virus found in spinal fluid compatible with diagnosis of progressive multifocal leukoencephalopathy [PMLE], dying shortly after diagnosis).

Kothary N, Diak IL, Brinker A, Bezabeh S, Avigan M, Dal Pan G. Progressive multifocal leukoencephalopathy associated with efalizumab use in psoriasis patients. J Am Acad Dermatol 2011; 65: 546-51. PubMed PMID: 21514689.

(Analysis of 3 cases of PMLE associated with efalizumab therapy of psoriasis from the FDA Adverse Event Reporting System, 2 men and 1 woman, ages 43-73 on efalizumab for 3 to 4 years, presenting with vertigo, ataxia, paraesthesias and progressive neurologic course, dying 2-6 months after presentation).

Aithal GP. Hepatotoxicity related to antirheumatic drugs. Nat Rev Rheumatol 2011; 7: 139-50. PubMed PMID: 17723920.

(Analysis of spontaneous adverse event reporting of progressive PMLE in the US between 2004-2010 identified 635 cases with higher than expected number of cases from several immunosuppressive monoclonal antibodies, including efalizumab [n=12], rituximab [124] and natalizumab [123]).

Rustin MH. Long-term safety of biologics in the treatment of moderate-to-severe plaque psoriasis: review of current data. Br J Dermatol 2012; 167 Suppl 3: 3-11. PubMed PMID: 23082810.

(Analysis of long term severe adverse events associated with use of biologic agents for psoriasis: "with the exception of efalizumab,..., these biologics are generally well tolerated in long-term studies").

Badavanis G, Pasmatzi E, Monastirli A, Tsambaos D. Biologic agents in systemic dermatotherapy: cutaneous and systemic side effects. Curr Drug Saf 2017 May 18. [Epub ahead of print] PubMed PMID: 28521707.

(Review of the systemic side effects of biologic agents used to treat psoriasis after the withdrawal of efalizumab because of a concern over its serious and fatal side effects).