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Vedolizumab

Updated: June 18, 2015.

OVERVIEW

Introduction

Vedolizumab is a humanized monoclonal antibody to integrin α4β7 which is used in the treatment of inflammatory bowel disease. Vedolizumab has been linked to a low rate of serum enzyme elevations during therapy, but has not been linked to cases of idiosyncratic, clinically apparent liver injury with jaundice. Because vedolizumab is a potent inhibitor of lymphocyte function, it may cause reactivation of chronic hepatitis B in susceptible patients.

Background

Vedolizumab (ve" doe liz' ue mab) is a humanized monoclonal immunoglobulin G1 antibody to integrin α4β7 (also known as lymphocyte Peyer's patch adhesion molecule 1: LPAM-1), a cell surface molecule that plays a role trafficking inflammatory cells to sites of injury in the gastrointestinal mucosa. Vedolizumab is one of several inhibitors of integrin α4β7 that have been evaluated in autoimmune conditions. In controlled clinical trials, vedolizumab has been shown to decrease inflammation and improve symptoms in patients with refractory or relapsing inflammatory bowel disease. Vedolizumab was approved for use in the United States for both ulcerative colitis and Crohn colitis in 2014 and is recommended only for patients with moderate-to-severe inflammatory bowel disease who have not responded to corticosteroids, immunosuppressants or TNF antagonists. Vedolizumab is available as a lyophilized power in single use vials of 300 mg under the brand name Entyvio. Vedolizumab is given intravenously in a dose of 300 mg over approximately 30 minutes at 0 and 2 weeks, followed by every 4 weeks thereafter. Common side effects include injection site reactions, chills, fever, skin rash and fatigue. Less common, but potentially severe side effects include hypersensitivity reactions and anaphylaxis, opportunistic infections, reactivation of tuberculosis or hepatitis B, congestive heart failure, lymphoma and other malignancies and demyelinating diseases.

Hepatotoxicity

In prelicensure controlled trials, rates of serum ALT elevations during vedolizumab were not reported, although instances of serum enzyme elevations were described. ALT elevations above 5 times the upper limit of normal (ULN) were said to occur in <2% of vedolizumab and in a similar proportion of placebo recipients, and only rare patients had to stop therapy because of serum enzyme elevations. In the prelicensure trials, 3 patients were reported to have a severe adverse reaction of hepatitis, but the specific details were not given and there have been no case reports of clinically apparent, acute liver injury with symptoms or jaundice attributed to vedolizumab, but experience with its use has been limited.

However, vedolizumab is a potent immunomodulatory agent and may be capable of causing reactivation of hepatitis B. To date, however, neither vedolizumab nor natalizumab (another monoclonal antibody to integrin α4β7) have been linked to instances of reactivation of hepatitis B. Nevertheless, because of the possibility of reactivation of hepatitis B with vedolizumab therapy, screening for markers of HBV infection before starting therapy is prudent. Patients with HBsAg or anti-HBc in serum should be monitored for evidence of reactivation and treated with antiviral therapy if HBV DNA or HBsAg appear.

Finally, vedolizumab may reactivate other viral infections and acute hepatitis due to an opportunistic viral infection.

Mechanism of Injury

Why a monoclonal antibody would cause hepatic injury is unclear. The mechanism of liver injury in reactivation of hepatitis B appears to be a brisk immunological response to newly expressed viral antigens. Injury generally arises after the immunosuppressive therapy has stopped or between courses of treatment.

Outcome and Management

Current guidelines for management of patients who are to receive vedolizumab do not recommend routine screening for hepatitis B before starting treatment. If screening is planned, it should include tests for HBsAg and anti-HBc (and perhaps also anti-HBs as this may help in management). An appropriate approach for patients with markers of hepatitis B is careful monitoring for HBV DNA during therapy and early institution of antiviral therapy if levels rise. While reactivation of tuberculosis has been reported after vedolizumab therapy, instances of reactivation of hepatitis B have not, although experience with the agent has been limited and patients with preexisting hepatitis B were typically excluded from prelicensure studies.

Drug Class: Gastrointestinal Agents, Inflammatory Bowel Disease Agents, Monoclonal Antibodies

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Vedolizumab – Entyvio®

DRUG CLASS

Gastrointestinal Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Vedolizumab	**943609-66-3**	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 18 June 2015

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").

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).

Feagan BG, Greenberg GR, Wild G, Fedorak RN, Paré P, McDonald JW, Cohen A, et al. Treatment of active Crohn's disease with MLN0002, a humanized antibody to the alpha4beta7 integrin. Clin Gastroenterol Hepatol 2008; 6: 1370-7. PubMed PMID: 18829392.

(Among 123 patients with Crohn disease treated with vedolizumab [0.5 or 2.0 mg/kg] or placebo in two infusions 4 weeks apart, response rates were marginally higher with vedolizumab [49% and 53% vs 41%], but adverse event rates were similar; no mention of ALT elevations or hepatotoxicity).

Baumgart DC. Veto on vedolizumab (MLN0002) for Crohn's disease. Inflamm Bowel Dis 2010; 16: 537-8. PubMed PMID: 19685452.

(Summary of results of the phase 2 trial of vedolizumab [Feagan 2008] and commentary raising issues of marginal efficacy and concerns over safety).

Parikh A, Leach T, Wyant T, Scholz C, Sankoh S, Mould DR, Ponich T, et al. Vedolizumab for the treatment of active ulcerative colitis: a randomized controlled phase 2 dose-ranging study. Inflamm Bowel Dis 2012; 18: 1470-9. PubMed PMID: 22147460.

(Among 47 patients with ulcerative colitis treated with vedolizumab in 3 different doses [2, 6 or 10 mg/kg] or placebo in four infusions at weeks 0, 2, 4 and 12, there were "no clinically significant changes in laboratory parameters", but one patient had an abnormal ALT level at week 2 [137 U/L] that resolved by week 4 and did not increase thereafter with further therapy).

Parikh A, Fox I, Leach T, Xu J, Scholz C, Patella M, Feagan BG. Long-term clinical experience with vedolizumab in patients with inflammatory bowel disease. Inflamm Bowel Dis 2013; 19: 1691-9. PubMed PMID: 23591599.

(Among 72 patients with ulcerative colitis or Crohn disease treated with vedolizumab in maintenance doses of 2, 6 or 10 mg/kg every 8 weeks for up to 3 years, serious adverse events included infections, but neither ALT abnormalities nor instances of hepatotoxicity were reported).

Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, Lukas M, et al.; GEMINI 2 Study Group. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med 2013; 369: 711-21. PubMed PMID: 23964933.

(Among 1115 patients with Crohn disease in controlled trials, clinical remissions were more frequent with intravenous vedolizumab than placebo at week 6 [14.5% vs 7%] and week 52 [36-39% vs 22%], but rates of infections including serious infections were also increased; no mention of ALT elevations or hepatotoxicity).

Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, Van Assche G, et al.; GEMINI 1 Study Group. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2013; 369: 699-710. PubMed PMID: 23964932.

(Among 895 patients with ulcerative colitis in two placebo controlled trials, response rates were more frequent with intravenous vedolizumab than placebo at week 6 [47% vs 26%] and week 42 [42-45% vs 16%], and side effects rates were similar with "no significant differences in... liver-function test results").

Cominelli F. Inhibition of leukocyte trafficking in inflammatory bowel disease. N Engl J Med 2013; 369: 775-6. PubMed PMID: 23964940.

(Editorial in response to Sandborn and Feagan 2013).

Danese S, Fiorino G, Peyrin-Biroulet L, Lucenteforte E, Virgili G, Moja L, Bonovas S. Biological agents for moderately to severely active ulcerative colitis: a systematic review and network meta-analysis. Ann Intern Med 2014; 160: 704-11. PubMed PMID: 24842416.

(Systematic review of biologic agents for ulcerative colitis gives overall rates of adverse events, but not specifics and does not mention ALT elevations, hepatotoxicity or reactivation of hepatitis B).

Sands BE, Feagan BG, Rutgeerts P, Colombel JF, Sandborn WJ, Sy R, D'Haens G, et al. Effects of Vedolizumab induction therapy for patients With Crohn's disease in whom tumor necrosis factor antagonist treatment had failed. Gastroenterology 2014 May 21. [Epub ahead of print] PubMed PMID: 24859203.

(Among 416 patients with Crohn disease who had failed to respond adequately to anti-TNF agents, response rates were no higher with vedolizumab compared to placebo therapy [15% vs 12%] and rates of adverse events, including infections, were similar; no mention of ALT elevations or hepatotoxicity).

Vedolizumab (Entyvio) for inflammatory bowel disease. Med Lett Drugs Ther 2014; 56: 86-7. PubMed PMID: 25211302.

(Concise review of the mechanism of action, efficacy, safety and cost of vedolizumab therapy in ulcerative colitis and Crohn disease shortly after its approval for this indication in the United States; adverse events include hypersensitivity reactions, anaphylaxis, increased risk of infection, and increased "transaminases and bilirubin levels have been reported").