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Vedolizumab

Updated: August 20, 2020.

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. Since its approval and more widespread use, there have been a few isolated reports of liver injury occurring during vedolizumab therapy but usually in the presence of other competing causes.

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, 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 promptly 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.

Likelihood score: D (possible rare cause of clinically apparent liver injury).

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: 20 August 2020

Abbreviations: IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis.

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").

MacNaughton WK, Sharkey KA. Pharmacotherapy of inflammatory bowel disease. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 944-54.

(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 failed. Gastroenterology. 2014;147:618–627.e3. 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;56:86–8. 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 US; adverse events include hypersensitivity reactions, anaphylaxis, increased risk of infection, and increased "transaminases and bilirubin levels have been reported").

Stine JG, Wang J, Behm BW. Chronic cholestatic liver injury attributable to vedolizumab. J Clin Transl Hepatol. 2016;4:277–80. PubMed PMID: 27777897.

(23 year old man with ulcerative colitis developed jaundice after a 3rd dose of vedolizumab [bilirubin 13.3 mg/dL, ALT 27, AST 52, Alk P 370 U/L], liver enzymes being minimally increased from the elevated levels present before treatment and jaundice persisting for 4-5 months after stopping the monoclonal antibody).

Lim TY, Pavlidis P, Gulati S, Pirani T, Samaan M, Chung-Faye G, Dubois P, et al. Vedolizumab in inflammatory bowel disease associated with autoimmune liver disease pre- and post-liver transplantation: a case series. Inflamm Bowel Dis. 2016;22:E39–40. PubMed PMID: 27556837.

(Case series of 10 patients with PSC and IBD who were treated with vedolizumab for 1-13 months with remissions in the IBD in 4 and no hepatobiliary complications).

Christensen B, Micic D, Gibson PR, Yarur A, Bellaguarda E, Corsello P, Gaetano JN, et al. Vedolizumab in patients with concurrent primary sclerosing cholangitis and inflammatory bowel disease does not improve liver biochemistry but is safe and effective for the bowel disease. Aliment Pharmacol Ther. 2018;47:753–62. PubMed PMID: 29377235.

(Analysis of 34 adults with IBD and PSC who were treated with vedolizumab for an average of 9 months, there were no significant changes in Alk P, ALT or bilirubin and one patient with normal liver enzymes at baseline developed an Alk P of 351 U/L and ALT of 264 U/L, which returned to normal 3 months after stopping vedolizumab).

Pavlidis P, Graham J, Gulati S, Dubois P, Heneghan M, Joshi D, Hayee B. Letter: vedolizumab for autoimmune liver disease associated inflammatory bowel disease. Aliment Pharmacol Ther. 2018;47:1422–3. PubMed PMID: 29676010.

(In response to Christensen [2018], the authors mention that among 17 patients with IBD and PSC who were treated with vedolizumab there was no improvement in liver biochemistry results and 2 patients developed colorectal cancer).

Christensen B, Gibson PR, Rubin DT. Letter: vedolizumab for autoimmune liver disease associated inflammatory bowel disease-Authors' reply. Aliment Pharmacol Ther. 2018;47:1423–4. PubMed PMID: 29676007.

(In response to letter from Pavlidis [2018], the authors mention that they have had no instance of colorectal cancer but have had 3 serious hepatic adverse events among the 34 patients with IBD and PSC who received vedolizumab).

Lenti MV, Levison S, Eliadou E, Willert R, Kemp K, Carter A, Stansfield C, et al. A real-world, long-term experience on effectiveness and safety of vedolizumab in adult patients with inflammatory bowel disease: The Cross Pennine study. Dig Liver Dis. 2018;50:1299–304. PubMed PMID: 30077465.

(Among 203 patients with IBD treated in UK medical centers between 2014 and 2018, 128 had a sustained clinical response at 2 weeks, while adverse events included elevated liver tests in 2 patients; no details provided).

Kapila N, Flocco G, Shen B, Modaresi Esfeh J. The use of vedolizumab in patients with concomitant cirrhosis and Crohn's disease. Cureus. 2018;10:e3080. PubMed PMID: 30305988.

(Three patients with Crohn disease and cirrhosis [autoimmune hepatitis, hepatitis C and cryptogenic] were treated with vedolizumab and all three had a clinical response and none had worsening of the liver disease or decompensation after 5, 32 and 36 months of the monoclonal antibody).

Kopylov U, Avni-Biron I, Ron Y, Koslowsky B, Waterman M, Daher S, Ungar B, et al. Effectiveness and safety of vedolizumab for maintenance treatment in inflammatory bowel disease-The Israeli real world experience. Dig Liver Dis. 2019;51:68–74. PubMed PMID: 30172649.

(Among 193 patients with IBD from 9 centers in Israel who were treated with vedolizumab, the 52 week response rate was approximately 50% and only 18 patients had adverse events; no mention of ALT elevations or hepatotoxicity).

Kopylov U, Verstockt B, Biedermann L, Sebastian S, Pugliese D, Sonnenberg E, Steinhagen P, et al. Effectiveness and safety of vedolizumab in anti-TNF-naïve patients with inflammatory bowel disease-a multicenter retrospective European study. Inflamm Bowel Dis. 2018;24:2442–51. PubMed PMID: 29788318.

(Among 184 patients with IBD treated with vedolizumab at 23 European enters, the remission rate ranged from 64-68% and only 20 patients [11%] had adverse events including one with cholestasis and one undergoing liver transplantation).

Spadaccini M, Aghemo A, Caprioli F, Lleo A, Invernizzi F, Danese S, Donato MF. Safety of vedolizumab in liver transplant recipients: A systematic review. United European Gastroenterol J. 2019;7:875–80. PubMed PMID: 31428411.

(Systematic review of safety of vedolizumab in liver transplant recipients identified 31 patients among whom 23% developed an infection and 1 patient had an episode of acute rejection, but no patient died and 77% had a clinical response in IBD activity).

Caron B, Peyrin-Biroulet L, Pariente B, Bouhnik Y, Seksik P, Bouguen G, Caillo L, et al. Vedolizumab therapy is ineffective for primary sclerosing cholangitis in patients with inflammatory bowel disease: a GETAID multicentre cohort study. J Crohns Colitis. 2019;13:1239–47. PubMed PMID: 31056693.

(Among 75 patients with IBD and PSC treated with vedolizumab at 22 medical centers for at least 30 weeks, there was no significant change in serum enzyme levels during extended treatment averaging 19 months, 7 patients developed colorectal cancer and 2 cholangiocarcinoma).

Lynch KD, Chapman RW, Keshav S, Montano-Loza AJ, Mason AL, Kremer AE, Vetter M, et al. International Primary Sclerosing Cholangitis Study Group (IPSCSG), Levy C. Effects of vedolizumab in patients with primary sclerosing cholangitis and inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2020;18:179–187.e6. PubMed PMID: 31100458.

(Among 102 patients with IBD and PSC treated with vedolizumab and followed for an average of 412 days, serum Alk P, ALT and bilirubin levels increased slightly [by 10% to 20%] and liver related adverse events occurred in 22 patients, including new onset ascites [n=6], cholangitis [n=9] and liver transplantation [n=8], but no patient died or developed cholangiocarcinoma).