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Natalizumab

Updated: June 18, 2015.

OVERVIEW

Introduction

Natalizumab is a monoclonal antibody to human alpha-4 integrin which has potent immune suppressive activity and is used in the therapy of severe inflammatory bowel disease and relapsing multiple sclerosis. Natalizumab has been linked to rare instances of idiosyncratic acute liver injury and may be a rare cause of reactivation of hepatitis B.

Background

Natalizumab (na" ta liz' ue mab) is a humanized monoclonal antibody to alpha-4 integrin, which binds avidly to the cellular adhesion molecule found on leukocytes which blocks their ability to migrate to inflammatory foci. Inhibition of alpha-4 integrin activity leads to modulation of inflammatory pathways that are activated in autoimmune disorders. Natalizumab was shown to improve vision and motor function in patients with multiple sclerosis and to decrease inflammation, symptoms and relapses in patients with Crohn disease. Natalizumab was approved for use in the United States in 2005 and indications included severe Crohn disease and relapsing multiple sclerosis. However, after its general availability, natalizumab was linked to several instances of progressive multifocal leukoencephalopathy (PML), a severe neurological condition which is believed to be due to reactivation of the JC virus in neural cells. Because of this severe complication (which is often fatal), natalizumab has been restricted in use and is available only by a special program that requires thorough assessment of risks and careful monitoring and reporting. Natalizumab is available in 15 mL vials of 300 mg under the brand name Tysabri. The recommended dose is 300 mg intravenously every 4 weeks. Common side effects include headache, fatigue and infusion reactions. Natalizumab is also capable of causing immune suppression, resulting in an increased susceptibility to severe viral and bacterial infections.

Hepatotoxicity

In large clinical trials, serum aminotransferase elevations occurred in an average of 5% of patients on natalizumab therapy and in a slightly lower, although similar proportion (~3%) of those who received placebo. While there were no individual case reports of liver injury attributed to natalizumab therapy, at least 59 instances of hepatic injury were reported to the Adverse Event Reporting System maintained by the FDA. In a report summarizing six clinically apparent cases of liver injury attributable to natalizumab, all were associated with jaundice. The onset of injury followed the initial infusion of natalizumab in 4 patients, and after 5 and 12 courses of treatment in the other two reported cases. The pattern of liver injury was hepatocellular in 5 cases and cholestatic in one. Several cases were accompanied by autoantibodies and were treated with corticosteroids (Case 1), but autoimmune features were not prominent and immunoallergic features (fever, rash, eosinophilia)

were not reported. The clinical cases were moderate in severity and no patient developed acute liver failure or progressed to chronic liver injury or vanishing bile duct syndrome. Natalizumab can cause immune suppression and has been linked to bacterial and viral infections, but interestingly has not been reported to cause reactivation of tuberculosis or hepatitis B. Nevertheless, because of its mechanism of action, it should be considered as a potential cause of reactivation.

Mechanism of Injury

The mechanism of liver injury caused by natalizumab is probably immunologically mediated, perhaps as a result of its effects on leukocyte function. It is a monoclonal antibody and like other proteins it is taken up by cells by endocytosis and is metabolized into amino acids.

Outcome and Management

The hepatotoxicity of natalizumab is usually moderate in severity and reversible with discontinuation of infusions. Recurrence of injury with a shorter latency and more severe course has been reported. There is no information about cross sensitivity to liver injury with other monoclonal antibodies or immune modulating agents, but at least one reported case had a history of liver injury due to interferon beta therapy of multiple sclerosis. Other immunomodulatory monoclonal antibodies used to treat autoimmune diseases include adalimumab, certolizumab, and infliximab.

Drug Class: Gastrointestinal Agents, Inflammatory Bowel Disease Agents; Monoclonal Antibodies, Multiple Sclerosis Agents

CASE REPORT

Case 1. Acute hepatocellular injury due to natalizumab.

[Modified from: Bezabeh S, Flowers CM, Kortepeter C, Avigan M. Clinically significant liver injury in patients treated with natalizumab. Aliment Pharmacol Ther 2010; 31: 1028-35. PubMed Citation]

A 43 year old man with multiple sclerosis developed fatigue, fever and back pain 8 days after the fifth monthly dose of natalizumab. On hospital admission, he was found to have elevations in serum enzymes but was not jaundiced. Serum ALT was 410 U/L, AST 134 U/L, INR 1.17 and bilirubin 0.4 mg/dL. Over the next several days, his liver tests worsened, serum bilirubin peaking at 3.0 mg/dL. A liver biopsy showed acute lobular and portal hepatitis with mild fibrosis. Recovery was slow and prednisone was given. Natalizumab was not continued. Over the next 6 months liver tests returned to normal, whereupon natalizumab was restarted. After the second monthly infusion, however, he redeveloped fatigue and jaundice and liver tests were again abnormal: ALT 3494 U/L, AST 1259 U/L and bilirubin 13.4 mg/dL. The antinuclear antibody, which was negative during the first episode, was positive in titers >1:320. Natalizumab was again stopped and prednisone was given with subsequent improvement.

Key Points

Medication:	Natalizumab (300 mg infusions monthly for 5 months)
Pattern:	Hepatocellular (R=21.5)
Severity:	3+ (jaundice, hospitalization)
Latency:	11 days after 5th monthly infusion initially; shortly after second monthly infusion on rechallenge 6 months later
Recovery:	6 months initially, unknown upon rechallenge
Other medications:	Spirulina (food supplement), multivitamins, prednisone

Comment

This patient developed clinically apparent acute hepatocellular injury within 2 weeks of receiving his fifth monthly infusion of natalizumab for relapsing multiple sclerosis. The injury was moderate in severity, but slow to resolve. Liver histological features suggested an element of autoimmunity, and he was treated with prednisone but tolerated its withdrawal and had normal liver tests six months later. Upon reexposure, he redeveloped the liver injury with a shorter latency and with a more severe course. At this point, he was found to have high titers of ANA and prednisone was restarted. Although compatible with spontaneous autoimmune hepatitis (which has been reported in patients with multiple sclerosis), the timing of onset and recurrence of similar injury upon reexposure is reasonably convincing evidence that it was due to natalizumab, perhaps an autoimmune hepatitis that was triggered by the immunomodulatory therapy. This example was case 2 from the six case series reported by the FDA, which were based upon review of spontaneous adverse event reports during the first 4 years of general availability of natalizumab. The six cases were selected as the clinically apparent examples among a total of 59 separate reports of liver injury. The authors estimated the frequency of idiosyncratic clinically apparent liver injury from natalizumab to be 17 per 100,000 exposed patients. Events occurring at this low rate are unlikely to be detected in premarketing studies.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Natalizumab – Tysabri®

DRUG CLASS

Gastrointestinal Agents; Multiple Sclerosis Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Natalizumab	189261-10-7	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 18 June 2015

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 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 the report of six cases of severe liver injury attributed to natalizumab report to the FDA Adverse Event Reporting System database).

Wallace JL, Sharkey KA. Pharmacotherpay of inflammatory bowel disesae. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1350-62.

(Textbook of pharmacology and therapeutics).

Gordon FH, Lai CW, Hamilton MI, Allison MC, Srivastava ED, Fouweather MG, Donoghue S, et al. A randomized placebo-controlled trial of a humanized monoclonal antibody to alpha4 integrin in active Crohn's disease. Gastroenterology 2001; 121: 268-74. PubMed PMID: 11487536.

(Randomized controlled trial of natalizumab in 30 patients with mild-to-moderate Crohn's disease found no difference in side effects compared to placebo; no mention of ALT elevations or hepatotoxicity).

Miller DH, Khan OA, Sheremata WA, Blumhardt LD, Rice GP, Libonati MA, Willmer-Hulme AJ, et al.; International Natalizumab Multiple Sclerosis Trial Group. A controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2003; 348: 15-23. PubMed PMID: 12510038.

(Randomized controlled trial of 6 months of natalizumab versus placebo in 213 patients with relapsing multiple sclerosis; adverse events were similar in natalizumab and placebo treated patients, but no mention of liver toxicity or ALT levels).

Keeley KA, Rivey MP, Allington DR. Natalizumab for the treatment of multiple sclerosis and Crohn's disease. Ann Pharmacother 2005; 39: 1833-43. PubMed PMID: 16219898.

(Literature review of safety and efficacy of natalizumab; abnormal liver tests were reported in 5% of natalizumab and 3% of placebo recipients).

Sandborn WJ, Colombel JF, Enns R, Feagan BG, Hanauer SB, Lawrance IC, Panaccione R, et al.; International Efficacy of Natalizumab as Active Crohn's Therapy(ENACT-1) Trial Group; Evaluation of Natalizumab as Continuous Therapy(ENACT-2) Trial Group. Natalizumab induction and maintenance therapy for Crohn's disease. N Engl J Med 2005; 353: 1912-25. PubMed PMID: 16267322.

(Summary of two controlled trials of natalizumab in 905 patients with active Crohn disease; total as well as serious adverse events were similar between the two groups; no mention of liver toxicity or ALT elevations).

Calabrese LH, Zein NN, Vassilopoulos D. Hepatitis B virus(HBV) reactivation with immunosuppressive therapy in rheumatic diseases: assessment and preventive strategies. Ann Rheum Dis 2006; 65: 983-9. PubMed PMID: 16627542.

(Review of the problem of reactivation of hepatitis B in patients with rheumatic diseases treated with immunosuppressive agents, with recommendations on prevention).

Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, Phillips JT, et al.; AFFIRM Investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006; 354: 899-910. PubMed PMID: 16510744.

(Randomized controlled trial of natalizumab vs placebo in 942 patients with relapsing multiple sclerosis; fatigue and allergic reactions were more common in natalizumab treated patients; abnormal liver tests were reported in 5% of natalizumab vs 4% of placebo recipients).

Sands BE, Kozarek R, Spainhour J, Barish CF, Becker S, Goldberg L, Katz S, et al. Safety and tolerability of concurrent natalizumab treatment for patients with Crohn's disease not in remission while receiving infliximab. Inflamm Bowel Dis 2007; 13: 2-11. PubMed PMID: 17206633.

(Randomized controlled trial of natalizumab vs placebo in 79 patients with Crohn disease who were receiving infliximab; adverse events were similar in the two groups and no clinically significant abnormalities were observed in laboratory parameters).

Targan SR, Feagan BG, Fedorak RN, Lashner BA, Panaccione R, Present DH, Spehlmann ME, et al.; International Efficacy of Natalizumab in Crohn's Disease Response and Remission(ENCORE) Trial Group. Natalizumab for the treatment of active Crohn's disease: results of the ENCORE Trial. Gastroenterology 2007; 132: 1672-83. PubMed PMID: 17484865.

(Randomized controlled trial of natalizumab vs placebo in 509 patients with active Crohn disease reported side effects of headache, nausea, fatigue, abdominal pain and dizziness; no mention of liver toxicity or ALT elevations).

Natalizumab (Tysabri) for Crohn's disease. Med Lett Drugs Ther 2008; 50: 34-6. PubMed PMID: 18458669.

(Concise summary of use of natalizumab for Crohn disease mentions that postmarketing hepatic toxicity had occurred).

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).

Khokhar OS, Lewis JH. Hepatotoxicity of agents used in the management of inflammatory bowel disease. Dig Dis 2010; 28: 508-18. PubMed PMID: 20926880.

(Review of the hepatotoxicity of drugs used to treat inflammatory bowel disease focusing upon sulfasalazine, thiopurines, TNF inhibitors, and methotrexate).

Bezabeh S, Flowers CM, Kortepeter C, Avigan M. Clinically significant liver injury in patients treated with natalizumab. Aliment Pharmacol Ther 2010; 31: 1028-35. PubMed PMID: 20163378.

(Summary of 6 clinically apparent hepatic adverse events reported to the FDA over a 4 year period included 1 man and 5 women, ages 26 to 59 years, arising after the first to 11th dose [bilirubin 4.5 to 16.1 mg/dL, ALT 753-3494 U/L, Alk P 46-1043 U/L], all resolving, all were icteric and symptomatic and 5 were hepatocellular; 3 had autoantibodies but immune features were not prominent: Case 1).

André MC, Pacheco D, Antunes J, Silva R, Filipe P, Soares de Almeida LM. Generalized skin drug eruption to natalizumab in a patient with multiple sclerosis. Dermatol Online J 2010; 16: 14. PubMed PMID: 20579469.

(29 year old man with multiple sclerosis developed generalized rash 30 days after starting natalizumab with abnormal liver tests [bilirubin not given, ALT 185 U/L, GGT 320 U/L, eosinophils 2150 cells/L], resolving within 3 weeks).

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

(Review of liver injury due to antirheumatic drugs discusses ALT elevations caused by anti-TNF agents and autoimmune hepatitis due to infliximab; no mention of natalizumab).

Van Assche G, Lewis JD, Lichtenstein GR, Loftus EV, Ouyang Q, Panes J, Siegel CA, et al. The London position statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organisation: safety. Am J Gastroenterol 2011; 106: 1594-602. PubMed PMID: 21844919.

(Systematic review of the literature and position statement on use and safety of anti-TNF agents and natalizumab in Crohn disease; no specific discussion of hepatotoxicity or reactivation of hepatitis B).

Mulero P, Caminero AB, Neri Crespo MJ, Fernández-Herranz R, Téllez Lara N. Latent tuberculosis seems not to reactivate in multiple sclerosis patients on natalizumab. J Neuroimmunol 2012; 243: 103-5. PubMed PMID: 22226471.

(Among 27 patients with multiple sclerosis treated with natalizumab, 6 had a reactive tuberculin test, but none had clinical evidence of reactivation during an average of 19 months of therapy; furthermore, worldwide at least 88,100 patients have been treated with natalizumab, but there have been no reports of tuberculosis associated with treatment in the literature).

Lisotti A, Azzaroli F, Brillanti S, Mazzella G. Severe acute autoimmune hepatitis after natalizumab treatment. Dig Liver Dis 2012; 44: 356-7. PubMed PMID: 22154948.

(31 year old woman developed ALT elevations after a first injection of natalizumab and jaundice after a second [bilirubin 23.1 mg/dL, ALT > 50 times ULN, "mild elevation" in Alk P, INR 2.6, ANA 1:160], with response to corticosteroid therapy and no recurrence on long term azathioprine).

O'Connor P, Goodman A, Kappos L, Lublin F, Polman C, Rudick RA, Hauswirth K, et al. Long-term safety and effectiveness of natalizumab redosing and treatment in the STRATA MS Study. Neurology 2014; 83: 78-86. PubMed PMID: 24898925.

(Among 1094 patients with multiple sclerosis formerly enrolled in clinical trials of natalizumab and continued on therapy [300 mg every 4 weeks] for up to 5 years, 171 [16%] had at least one serious adverse event including 7 listed as "hepatobiliary" [without specific details] and 8 confirmed cases of PML).

Butzkueven H, Kappos L, Pellegrini F, Trojano M, Wiendl H, Patel RN, Zhang A, et al.; TYSABRI Observational Program (TOP) Investigators. Efficacy and safety of natalizumab in multiple sclerosis: interim observational programme results. J Neurol Neurosurg Psychiatry 2014; 85: 1190-7. PubMed PMID: 24532785.

(Among 4821 patients with multiple sclerosis being treated with natalizumab enrolled in a prospective observational program, 3599 continued on treatment, among whom there were 465 serious adverse events including 7 were abnormal liver tests [0.1% yearly], 18 cases of PML [0.4%] and 9 deaths, but none due to liver disease).