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Certolizumab

Updated: February 10, 2017.

OVERVIEW

Introduction

Certolizumab is a Fab fragment of a monoclonal antibody to human tumor necrosis factor alpha (TNFα) which has potent antiinflammatory activity and is used in the therapy of severe rheumatoid arthritis and inflammatory bowel disease. Certolizumab has had limited use and has yet to be specifically linked to instances of idiosyncratic acute liver injury or reactivation of hepatitis B, but is likely to cause similar hepatic injury to what has been described for other TNFα antagonists such as infliximab and adalimumab.

Background

Certolizumab (ser" toe liz' ue mab) is a Fab fragment of a humanized recombinant monoclonal antibody to TNFα linked to polyethylene glycol. The monoclonal antibody fragment binds avidly to serum and tissue bound TNFα causing its inactivation and degradation. Inhibition of TNFα activity leads to modulation of the inflammatory and pain pathways activated by this cytokine. The polyethylene glycol alters its pharmacokinetics, prolonging its half-life, and allowing for every 4 week administration. Certolizumab was approved in the United States in 2007 for use in Crohn disease and its indications were subsequently extended to rheumatoid and psoriatic arthritis and ankylosing spondylitis. Certolizumab is considered a disease modifying antirheumatic drug (DMARD) and has been shown to improve symptoms as well as joint and cartilage damage in the inflammatory arthritides. Certolizumab is available as lyophilized powder for reconstitution or in prefilled syringes as 200 mg/1.0 mL under the brand name of Cimzia. The typical dose of certolizumab for Crohn disease is 200 to 400 mg subcutaneously initially and at weeks 2 and 4, followed by 400 mg every 4 weeks. Recommendations vary slightly by indicationCommon side effects include injection site reactions, headache, nausea, abdominal discomfort, diarrhea, skin rash and fever. Severe side effects include bone marrow suppression and hypersensitivity reactions. TNFα antagonists are also capable of causing immune suppression, which can result in reactivation of microbial infections including tuberculosis and hepatitis B.

Hepatotoxicity

Certolizumab has been associated with a low rate of serum aminotransferase elevations during therapy, similar to the rate found with placebo therapy. The ALT elevations have been transient, mild and asymptomatic, and have rarely required dose modification. Certolizumab has been available for a relatively short period of time, and case reports of clinically apparent hepatic injury due to its use have not been published. Nevertheless, it is likely that certolizumab, like infliximab and adalimumab, is capable of inducing clinically apparent liver injury that resembles autoimmune hepatitis, which generally arises after at least 3 months of use and is associated with a

hepatocellular pattern of serum enzyme elevation and autoantibody formation. Autoimmune hepatitis induced by anti-TNFα blocking agents can be severe and self-sustained and require corticosteroid therapy.

Certolizumab, like other TNFα antagonists, can also be expected to cause reactivation of chronic hepatitis B. Reactivation typically occurs in patients who are inactive HBsAg carriers, with normal serum aminotransferase levels and no or only low levels of HBV DNA in serum. The immune suppression caused by the immunomodulatory agent leads to an increase in HBV replication and rise in serum HBV DNA levels. With stopping the immunosuppression (or between cycles of therapy), restoration of immune function leads to an acute immunological response to the heightened viral replication and a flare of hepatitis, that can be severe and can result in hepatic failure and death. Reactivation in patients with anti-HBc without HBsAg (serologic pattern of previous HBV infection) has been reported only rarely in patients treated with anti-TNF antagonists, and is more common after therapy with rituximab and bone marrow transplantation. The anti-TNF inhibitors have little or no effect on hepatitis C virus levels and have been used safely in patients with chronic hepatitis C.

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

Mechanism of Injury

The mechanism of liver injury due to certolizumab and other TNFα antagonists is not known, but is likely caused by immune modulation and induction of autoimmunity.

Outcome and Management

Most published cases of hepatotoxicity due to anti-TNFα agents have been mild and self-limited. Patients who are to start certolizumab therapy should be screened for evidence of hepatitis B, and those with preexisting HBsAg should be offered prophylaxis with an oral antiviral agent such as lamivudine, tenofovir or entecavir. Patients who develop an autoimmune hepatitis-like syndrome during certolizumab therapy may not recover promptly with stopping the TNFα antagonist and may require corticosteroid therapy. In this event, the corticosteroid dose should be kept to a minimum to control the disease and, ultimately, attempts should be made to withdraw immunosuppression (or decrease to levels used before administration of certolizumab). Rechallenge with another monoclonal antibody based TNFα antagonist after hepatotoxicity from certolizumab has not been reported, but there does not appear to be cross reactivity in hepatic injury between either adalimumab or infliximab and etanercept, which is not a monoclonal antibody, but rather an altered form of the TNFα receptor.

References on the hepatotoxicity and safety of the anti-TNF necrosis factor agents are given together at the end of the Overview section on the Tumor Necrosis Factor Antagonists.

Drug Class: Antirheumatic Agents; Gastrointestinal Agents, Inflammatory Bowel Disease Agents

Other Drugs in the Subclass, Tumor Necrosis Factor Antagonists: Adalimumab, Etanercept, Golimumab, Infliximab

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Certolizumab – Cimzia®

DRUG CLASS

Antirheumatic Agents; Gastrointestinal Agents

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COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Certolizumab Pegol	428863-50-7	Monoclonal antibody	Not available

ANNOTATED BIBLIOGRAPHY

References updated: 10 February 2017

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; no mention of tumor necrosis factor antagonists such as infliximab or certolizumab).

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; "the biological immuno-suppressants are largely free from hepatototxicity, with the exception of the TNF alpha antagonists").

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).

Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, Smolen J, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999; 354: 1932-9. PubMed PMID: 10622295.

(Controlled trial of infliximab vs placebo for 30 weeks in 428 patients with rheumatoid arthritis receiving methotrexate, found no difference in rates of ALT elevations between the two groups [37% vs 29%] and no cases of clinically apparent liver injury).

Menghini VV, Arora AS. Infliximab-associated reversible cholestatic liver disease. Mayo Clin Proc 2001; 76: 84-6. PubMed PMID: 11155419.

(44 year old woman with Crohn disease developed fatigue 19 days after single infusion of infliximab with subsequent jaundice [bilirubin 7.4 rising to 19.2 mg/dL, ALT 149 U/L, Alk P 55 U/L, ANA weakly positive], liver biopsy showing bland cholestasis and abnormalities resolving within 2 months of stopping: Case 1).

Nathan DM, Angus PW, Gibson PR. Hepatitis B and C virus infections and anti-tumor necrosis factor-. therapy: guidelines for clinical approach. J Gastro Hepatol 2006; 31: 1366-71. PubMed PMID: 16911678.

(Review and proposed guidelines for use of anti-TNF therapy in patients with underlying chronic viral hepatitis; recommended screening for HBV and HCV, careful monitoring during therapy and prophylaxis or early intervention with lamivudine in HBsAg-positive patients).

Vassilopoulos D, Calabrese LH. Risks of immunosuppressive therapies including biologic agents in patients with rheumatic diseases and co-existing chronic viral infections. Curr Opin Rheumatol 2007; 19: 619-25. PubMed PMID: 17917544.

(Review of use of anti-TNF agents in patients with chronic hepatitis B, C and HIV infection).

Sandborn WJ, Feagan BG, Stoinov S, Honiball PJ, Rutgeerts P, Mason D, Bloomfield R, et al.; PRECISE 1 Study Investigators. Certolizumab pegol for the treatment of Crohn's disease. N Engl J Med 2007; 357: 228-38. PubMed PMID: 17634458.

(Controlled trial of certolizumab for 26 weeks in 662 adults with Crohn disease; "No clinically significant changes in laboratory values occurred in either study group"; no mention of hepatotoxicity or ALT elevations).

Domm S, Cinatl J, Mrowietz U. The impact of treatment with tumour necrosis factor-alpha antagonists on the course of chronic viral infections: a review of the literature. Br J Dermatol 2008; 159: 1217-28. PubMed PMID: 18945310.

(Review of literature on efficacy and safety of TNF antagonists in patients with chronic hepatitis B and C, recommends screening and monitoring).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease in the US collected from 2004 to 2008, 3 were attributed to etanercept, but none to infliximab, adalimumab or certolizumab).

Li S, Kaur PP, Chan V, Berney S. Use of tumor necrosis factor-alpha(TNF-alpha) antagonists infliximab, etanercept, and adalimumab in patients with concurrent rheumatoid arthritis and hepatitis B or hepatitis C: a retrospective record review of 11 patients. Clin Rheumatol 2009; 28: 787-91. PubMed PMID: 19291350.

(Retrospective analysis of 11 patients with rheumatoid arthritis and either hepatitis B [n=3] or C [n=8] during 3 to 60 months anti-TNF therapy, 3 had transient minimal ALT elevations [peak levels 51, 73 and 51 U/L], without symptoms or jaundice).

Shao LM, Chen MY, Cai JT. Meta-analysis: the efficacy and safety of certolizumab pegol in Crohn's disease. Aliment Pharmacol Ther 2009; 29: 605-14. PubMed PMID: 19183161.

(Metaanalysis of safety in 3 controlled trials of certolizumab in 1313 patients with Crohn disease; no increase in serious adverse events except for infections, but no specific data on rates of ALT elevation or liver injury provided).

Smolen J, Landewé RB, Mease P, Brzezicki J, Mason D, Luijtens K, van Vollenhoven RF, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. Ann Rheum Dis 2009; 68: 797-804. PubMed PMID: 9015207.

(Controlled trial of methotrexate with or without certolizumab in 619 patients with rheumatoid arthritis; ALT elevations occurred in 5% of patients on methotrexate alone vs 2% on the combination; 5 cases of tuberculosis on certolizumab, but no mention of clinically apparent liver injury).

Shale MJ, Seow CH, Coffin CS, Kaplan GG, Panaccione R, Ghosh S. Review article: chronic viral infection in the anti-tumour necrosis factor therapy era in inflammatory bowel disease. Aliment Pharmacol Ther 2010; 31: 20-34. PubMed PMID: 19681818.

(Extensive review of literature on effects of anti-TNF therapies on underlying chronic hepatitis B and C; among 28 HBV-infected patients, reactivation was common in those not on antiviral therapy, more frequent with monoclonal antibodies than etanercept; among 110 HCV-infected patients, little evidence of worsening of disease and in some instances a decrease in HCV RNA levels).

Smith LS, Nelson M, Dolder CR. Certolizumab pegol: a TNF-{alpha} antagonist for the treatment of moderate-to-severe Crohn's disease. Ann Pharmacother 2010; 44: 333-42. PubMed PMID: 20118143.

(Review of structure, mechanism of action, pharmacology, safety and efficacy of certolizumab focusing upon Crohn disease; no mention of liver injury or ALT elevations).

Lichtenstein GR, Thomsen O~O, Schreiber S, Lawrance IC, Hanauer SB, Bloomfield R, Sandborn WJ; Precise 3 Study Investigators. Continuous therapy with certolizumab pegol maintains remission of patients with Crohn's disease for up to 18 months. Clin Gastroenterol Hepatol 2010; 8: 600-9. PubMed PMID: 20117244.

(Among 241 patients with Crohn disease continued on certolizumab for up to 80 weeks, 2 patients developed tuberculosis, 1 a lupus-like syndrome, 16 [11%] ANA and 4 [2%] anti-dsDNA reactivity; no mention of liver injury or ALT elevations).

Sokolove J, Strand V, Greenberg JD, Curtis JR, Kavanaugh A, Kremer JM, Anofrei A, et al.; CORRONA Investigators. Risk of elevated liver enzymes associated with TNF inhibitor utilisation in patients with rheumatoid arthritis. Ann Rheum Dis 2010; 69: 1612-7. PubMed PMID: 20448284.

(Retrospective analysis of ALT and AST elevations among 6861 patients with rheumatoid arthritis enrolled in a North American database receiving TNF inhibitors followed for an average of 1.5 years with ~1.7 determinations yearly; any elevation of ALT or AST occurred in 5.4% of visits, >2 times ULN in 0.6%, >5 times ULN in 0.1%; rates slightly higher for those on infliximab or when combined with methotrexate and leflunomide).

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 sulfaxalazine, thiopurines, TNF inhibitors, and methotrexate).

Carroll MB, Forgione MA. Use of tumor necrosis factor alpha inhibitors in hepatitis B surface antigen-positive patients: a literature review and potential mechanisms of action. Clin Rheumatol 2010; 29: 1021-9. PubMed PMID: 20556450.

(Review of literature on anti-TNF therapy in patients with hepatitis B identified 35 cases, 7 cases of reactivation occurred, including 7 of 17 on infliximab but none of 12 on etanercept or 6 on adalimumab; 18 received lamivudine, but only 7 as prophylaxis).

Pérez-Alvarez R, Díaz-Lagares C, García-Hernández F, Lopez-Roses L, Brito-Zerón P, Pérez-de-Lis M, Retamozo S, et al.; BIOGEAS Study Group. Hepatitis B virus (HBV) reactivation in patients receiving tumor necrosis factor (TNF)-targeted therapy: analysis of 257 cases. Medicine (Baltimore) 2011; 90: 359-71. PubMed PMID: 22033451.

(Systematic review of literature identified 257 patients with preexisting HBV markers who received anti-TNF therapy, reactivation occurred in 39% of 89 patients with HBsAg [5 had acute liver failure, 4 died], but only 5% of 168 with anti-HBc without HBsAg [1 died]; lamivudine prophylaxis decreased, but did not eliminate reactivation [62% vs 23% in HBsAg carriers).

Brunasso AM, Puntoni M, Gulia A, Massone C. Safety of anti-tumour necrosis factor agents in patients with chronic hepatitis C infection: a systematic review. Rheumatology (Oxford) 2011; 50: 1700-11. PubMed PMID: 21690185.

(Systematic review of literature identified 153 patients with chronic hepatitis C treated with anti-TNF agents, mostly etanercept, with only 1 with definite worsening of disease on treatment).

Vassilopoulos D, Calabrese LH. Management of rheumatic disease with comorbid HBV or HCV infection. Nat Rev Rheumatol 2012; 8: 348-57. PubMed PMID: 22565315.

(Clinical review of chronic hepatitis B and C and the implications in patients with rheumatic disorders with interpretation of virologic markers and recommendations for screening and prophylaxis against HBV during immunosuppressive therapy)

Aaltonen KJ, Virkki LM, Malmivaara A, Konttinen YT, Nordström DC, Blom M. Systematic review and meta-analysis of the efficacy and safety of existing TNF blocking agents in treatment of rheumatoid arthritis. PLoS One 2012; 7: e30275. PubMed PMID: 22272322.

(Systematic review of 26 controlled trials of anti-TNF agents for rheumatoid arthritis found similar rates of efficacy with different agents, but slightly lower rates of adverse events with etanercept, as measured by rates of discontinuation for adverse events [risk ratio=0.71]).

Ghabril M, Bonkovsky HL, Kum C, Davern T, Hayashi PH, Kleiner DE, Serrano J, et al.; US Drug-Induced Liver Injury Network. Liver injury from tumor necrosis factor-α antagonists: analysis of thirty-four cases. Clin Gastroenterol Hepato 2013; 11: 558-64. PubMed PMID: 23333219.

(Description of 6 cases of acute liver injury due to anti-TNF agents from the US included 5 women [83%], ages 28 to 54 years, onset after 2-52 weeks of treatment with infliximab [n=3], etanercept [n=2] or adalumimab [n=1], ANA present in 3, [peak bilirubin 1.5-34.2 mg/dL, ALT 384-1687 U/L, Alk P 83-1311 U/L], 5 treated with corticosteroids, but all ultimately recovered).

Motaparthi K, Stanisic V, Van Voorhees AS, Lebwohl MG, Hsu S. From the Medical Board of the National Psoriasis Foundation: Recommendations for screening for hepatitis B infection prior to initiating anti-tumor necrosis factor-alfa inhibitors or other immunosuppressive agents in patients with psoriasis. J Am Acad Dermatol 2013 Nov 9. [Epub ahead of print] PubMed PMID: 24220724.

(Recommendations for screening and monitoring for hepatitis B in patients with psoriasis treated with anti-TNF agents).

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America. An analysis of published reports. Ann Hepatol 2014; 13: 231-9. PubMed PMID: 24552865.

(Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, the most common implicated agents being nimesulide [n=53: 30%], cyproterone [n=18], nitrofurantoin [n=17], antituberculosis drugs [n=13] and flutamide [n=12: 7%]; but none were attributed to a TNF antagonist).

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, 6 cases were attributed to TNF antagonists: 1 to adalimumab, 2 etanercept and 3 infliximab, but none to certolizumab or golimumab).

Petríková J, Jarčuška P, Svajdler M, Pella D, Macejová Z. Autoimmune hepatitis triggered by adalimumab and allergic reactions after various anti-TNFα therapy agents in a patient with rheumatoid arthritis. Isr Med Assoc J 2015; 17: 256-8. PubMed PMID: 26040057.

(33 year old woman with rheumatoid arthritis developed fatigue after 3 doses of adalimumab [bilirubin not given, ALT 888 U/L, Alk P 348 U/L, ANA positive], biopsy showing interface hepatitis, resolving with prednisolone; later having allergic reactions to etanercept and certolizumab, but responding to anakinra).