U.S. National Library of Medicine
National Center for Biotechnology Information

NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Alemtuzumab. [Updated 2016 Feb 23].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Alemtuzumab

Updated: February 23, 2016.

OVERVIEW

Introduction

Alemtuzumab is a recombinant humanized monoclonal antibody to human CD52 which is used in the therapy of chronic lymphocytic leukemia, and off-label for induction regimens for solid organ transplantation and for resistant or relapsing multiple sclerosis. Alemtuzumab has been linked to occasional serum enzyme elevations during therapy and, while alemtuzumab has not been linked to cases of idiosyncratic, clinically apparent liver injury, it is a potent immunosuppressive agent and can lead to reactivation of chronic hepatitis B and exacerbations of chronic hepatitis C that can be severe and even fatal.

Background

Alemtuzumab (al" em tooz' ue mab) is a recombinant, humanized IgG1 kappa monoclonal antibody which is directed at and binds avidly to the human cell surface marker CD52 which is present on T and B cells, monocytes, macrophages and other bone marrow cells. Alemtuzumab therapy leads to depletion of lymphocytes with suppression of B cells for 6 to 12 months and T cells for 12 to 24 months. Alemtuzumab was approved in the United States in 2004 for use in chronic lymphocytic leukemia. It has also been used extensively off-label as a part of induction therapy for prevention of rejection after solid organ transplantation. It is currently under evaluation in several autoimmune diseases including resistant or relapsing multiple sclerosis. Alemtuzumab is available in single use vials of 30 mg/mL under the brand name Campath. The typical dose and regimen varies with indication. Alemtuzumab has significant adverse side effects, largely due to the profound immunosuppression. Common adverse events include epistaxis, headache, hypertension, rhinitis, dry skin, back pain, excessive bleeding and skin rash. Uncommon, but serious complications include severe infusions reactions, cytopenias (including fatal autoimmune anemia and thrombocytopenia) and opportunistic infections.

Hepatotoxicity

In large clinical trials, alemtuzumab therapy has been associated with a high rate of side effects including serious infusion reactions, infections and bone marrow suppression, but hepatotoxicity and serum ALT elevations were usually not mentioned in published reports. Since its approval in the United States and clinical use, there have been no specific published reports of clinically apparent liver injury attributed to alemtuzumab.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Importantly, however, alemtuzumab is a potent immunosuppressive agent and predisposes to opportunistic bacterial, viral, fungal and viral infections including reactivation of hepatitis B and C. Several instances of reactivation of hepatitis B have been reported in patients with HBsAg in serum who were treated with this

monoclonal antibody. In addition, some patients with anti-HBc without HBsAg in serum have developed HBV reactivation with reappearance of HBsAg (reverse seroconversion) with alemtuzumab therapy. These episodes can be severe and fatal instances have been reported. Finally, exacerbation and possibly reactivation of hepatitis C has been described in patients receiving alemtuzumab therapy.

Mechanism of Injury

Alemtuzumab is a monoclonal antibody and, while metabolized in the liver, is metabolized to small peptides and amino acids that are not likely to be immunogenic or toxic. The immunosuppression caused by alemtuzumab, on the other hand, may cause reactivation of hepatitis B and exacerbations of chronic hepatitis C.

Outcome and Management

Alemtuzumab appears to have little intrinsic hepatotoxicity and idiosyncratic liver injury must be very rare, if it occurs at all. In contrast, alemtuzumab is capable of causing reactivation of hepatitis B and worsening of hepatitis C. For these reasons, it is appropriate to screen patients for hepatitis B and C infection before starting therapy, and providing prophylaxis or treatment of these viral infections before or concurrent with starting monoclonal antibody therapy.

Drug Class: Antineoplastic Agents, Monoclonal Antibodies; Transplant Agents; Multiple Sclerosis Agents

Other Drugs in the Subclass, Transplant Agents, Monoclonal Antibodies: Basiliximab, Daclizumab, Muromonab

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Alemtuzumab – Campath®

DRUG CLASS

Antineoplastic Agents, Monoclonal Antibodies

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Alemtuzumab	**216503-57-0**	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 23 February 2016

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 that "the biological immunosuppressants are largely free from hepatotoxicity, with the exception of the TNF alpha antagonists"; no specific discussion of alemtuzumab).

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).

Rai KR, Freter CE, Mercier RJ, Cooper MR, Mitchell BS, Stadtmauer EA, Santábarbara P, et al. Alemtuzumab in previously treated chronic lymphocytic leukemia patients who also had received fludarabine. J Clin Oncol 2002; 20: 3891-7. PubMed PMID: 12228210.

(Among 24 patients with resistant CLL treated with alemtuzumab, all [100%] developed infusion reactions and ten [41%] severe, opportunistic infections including 4 with pneumocystis jiroveci pneumonia; no mention of ALT elevations, hepatitis or hepatotoxicity).

Marcos A, Eghtesad B, Fung JJ, Fontes P, Patel K, Devera M, Marsh W, et al. Use of alemtuzumab and tacrolimus monotherapy for cadaveric liver transplantation: with particular reference to hepatitis C virus. Transplantation 2004; 78: 966-71. PubMed PMID: 15480160.

(Among 76 adults undergoing liver transplantation who received induction therapy with alemtuzumab, subsequent rates of rejection, graft loss, death and adverse reactions were similar to a cohort of 84 contemporaneous transplant recipients; no mention of hepatotoxicity).

Tzakis AG, Tryphonopoulos P, Kato T, Nishida S, Levi DM, Madariaga JR, Gaynor JJ, et al. Preliminary experience with alemtuzumab (Campath-1H) and low-dose tacrolimus immunosuppression in adult liver transplantation. Transplantation 2004; 77: 1209-14. PubMed PMID: 15114087.

(Among 40 adults undergoing liver transplantation who received induction therapy with alemtuzumab and low dose tacrolimus, subsequent rates of graft loss, death and adverse reactions were similar to a cohort of 50 contemporaneous transplant recipients given conventional immunosuppressive therapy; routine liver test results were similar between the two groups).

Heider U, Fleissner C, Zavrski I, Jakob C, Dietzel T, Eucker J, Ockenga J, et al. Treatment of refractory chronic lymphocytic leukemia with Campath-1H in combination with lamivudine in chronic hepatitis B infection. Eur J Haematol 2004; 72: 64-6. PubMed PMID: 14962266.

(69 year old man with CLL and anti-HBc without HBsAg in serum developed reactivation of hepatitis B after chemotherapy with CHOP, rituximab and fludarabine that responded to lamivudine therapy and did not worsen when he was subsequently treated with alemtuzumab).

Iannitto E, Minardi V, Calvaruso G, Mulè A, Ammatuna E, Di Trapani R, Ferraro D, et al. Hepatitis B virus reactivation and alemtuzumab therapy. Eur J Haematol 2005; 74: 254-8. PubMed PMID: 15693796.

(Two patients with CLL with anti-HBc without HBsAg in serum developed reactivation of hepatitis B with alemtuzumab therapy, one 4 weeks after starting and one 5 months after alemtuzumab treatment and two months after withdrawal of lamivudine prophylaxis; both recovered with antiviral therapy).

Cortelezzi A, Viganò M, Zilioli VR, Fantini NN, Pasquini MC, Deliliers GL, Colombo M, et al. Adefovir added to lamivudine for hepatitis B recurrent infection in refractory B-cell chronic lymphocytic leukemia on prolonged therapy with Campath-1H. J Clin Virol 2006; 35: 467-9. PubMed PMID: 16316778.

(49 year old man with CLL and anti-HBc without HBsAg in serum developed severe reactivation of HBV after treatment with high doses of chlorambucil, responding to lamivudine and adefovir therapy, and without rise in HBV DNA levels during subsequent rescue therapy with alemtuzumab).

Moses SE, Lim ZY, Sudhanva M, Devereux S, Ho AY, Pagliuca A, Zuckerman M, et al. Lamivudine prophylaxis and treatment of hepatitis B Virus-exposed recipients receiving reduced intensity conditioning hematopoietic stem cell transplants with alemtuzumab. J Med Virol 2006; 78: 1560-3. PubMed PMID: 17063522.

(Among 8 alemtuzumab treated bone marrow transplant recipients who had anti-HBc without HBsAg in serum, reactivation occurred in 1 of 2 patients who did not receive prophylaxis, but in none of 6 who did receive prophylactic lamivudine).

Fiegl M, Falkner A, Hopfinger G, Brugger S, Zabernigg A, Bauer F, Haslbauer F, et al.; Austrian Collaborative Study Group on Alemtuzumab in Chronic Lymphocytic Leukemia. Routine clinical use of alemtuzumab in patients with heavily pretreated B-cell chronic lymphocytic leukemia: a nation-wide retrospective study in Austria. Cancer 2006; 107: 2408-16. PubMed PMID: 17054106.

(Retrospective analysis of results of alemtuzumab therapy in 115 patients with CLL reported side effects of severe infections in 51%, severe neutropenia in 26%, and severe hypersensitivity reactions in 8%, but did not mention ALT elevations or hepatotoxicity).

Magliocca JF, Knechtle SJ. The evolving role of alemtuzumab(Campath-1H) for immunosuppressive therapy in organ transplantation. Transpl Int 2006; 19: 705-14. PubMed PMID: 16918530.

(Review of efficacy of alemtuzumab in various forms of organ transplantation; no discussion of ALT elevations or hepatotoxicity).

James DF, Kipps TJ. Alemtuzumab in chronic lymphocytic leukemia. Future Oncol 2007; 3: 29-42. PubMed PMID: 17280499.

(Review of history of development, clinical efficacy and toxicity of alemtuzumab as therapy of CLL, no mention of hepatotoxicity or ALT elevations).

Hillmen P, Skotnicki AB, Robak T, Jaksic B, Dmoszynska A, Wu J, Sirard C, et al. Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia. J Clin Oncol 2007; 25: 5616-23. PubMed PMID: 17984186.

(Among 297 patients with chronic lymphocytic leukemia treated with alemtuzumab or chlorambucil, adverse events included infusion reactions, CMV infections, anemia and neutropenia; no mention of ALT elevations or hepatotoxicity).

Demko S, Summers J, Keegan P, Pazdur R. FDA drug approval summary: Alemtuzumab as single-agent treatment for B-cell chronic lymphocytic leukemia. Oncologist 2008; 13: 167-74. PubMed PMID: 18305062.

(Independent FDA review of studies in support of alemtuzumab as therapy of chronic lymphocytic leukemia listed common side effects including infusion reactions [87%], CMV viremia [56%], neutropenia [14%] and anemia [13%]; no mention of hepatotoxicity or ALT elevations).

Hui CK, Cheung WW, Leung KW, Cheng VC, Tang BS, Li IW, Luk JM et al. Retracted: outcome and immune reconstitution of HBV-specific immunity in patients with reactivation of occult HBV infection after alemtuzumab-containing chemotherapy regimen. Hepatology 2008; 48: 1-10. PubMed PMID: 18452145.

(Among 21 patients with HBV DNA without HBsAg in serum [17 with anti-HBc] treated with alemtuzumab chemotherapy, 6 developed reactivation of hepatitis B with reappearance of HBsAg in all and rise in liver enzymes in 5, despite early intervention with lamivudine therapy; this article was later retracted).

Alemtuzumab (Campath) off-label for relapsing multiple sclerosis. Med Lett Drugs Ther 2009; 51 (1307) 17-8. PubMed PMID: 19265776.

(Discussion of the off-label use of alemtuzumab for relapsing multiple sclerosis mentions that side effects include infusion reactions, autoimmune thyroid disorders and thrombocytopenic purpura, but does not mention ALT elevations or clinically apparent hepatotoxicity).

Dhesi S, Boland B, Colquhoun S. Alemtuzumab and liver transplantation: a review. Curr Opin Organ Transplant 2009; 14: 245-9. PubMed PMID: 19417659.

(Short review of induction therapy using alemtuzumab in preparation of liver transplantation summarizing results from two US studies suggesting lower rates of rejection and ability to use lower doses of maintenance therapy).

Cai J, Terasaki PI. Induction immunosuppression improves long-term graft and patient outcome in organ transplantation: an analysis of United Network for Organ Sharing registry data. Transplantation 2010; 90: 1511-5. PubMed PMID: 21057388.

(Since 2003, most solid organ transplant recipients have received induction therapy and analyses of the UNOS registry for this period, shows highest rates of patient and graft survival with alemtuzumab [89% 5 year patient survival] as compared to antithymocyte globulin [89%], basiliximab [84%], daclizumab [77%], steroids [75%], or no induction [71%]).

Anoop P, Wotherspoon A, Matutes E. Severe liver dysfunction from hepatitis C virus reactivation following alemtuzumab treatment for chronic lymphocytic leukaemia. Br J Haematol 2010; 148: 484-6. PubMed PMID: 19874308.

(39 year old man with CLL had anti-HCV and normal ALT levels without HCV RNA in serum, but developed high levels of HCV RNA and ALT levels 34 days after starting weekly infusions of alemtuzumab and prednisone, not having had reactivation during rituximab or previous fludarabine and prednisone therapy).

Hanaway MJ, Woodle ES, Mulgaonkar S, Peddi VR, Kaufman DB, First MR, Croy R, et al. INTAC Study Group. Alemtuzumab induction in renal transplantation. N Engl J Med 2011; 364: 1909-19. PubMed PMID: 21591943.

(Among 474 patients undergoing renal transplantation and given alemtuzumab or convention induction therapy, acute rejection rates during the first 3 years were lower with alemtuzumab than basiliximab in low risk patients [15% vs 24%], but were similar with alemtuzumab and antithymocyte globulin in high risk patients [30% vs 24%]).

Kim SJ, Moon JH, Kim H, Kim JS, Hwang YY, Intragumtornchai T, Issaragrisil S, et al. Non-bacterial infections in Asian patients treated with alemtuzumab: a retrospective study of the Asian Lymphoma Study Group. Leuk Lymphoma 2011; 53: 1515-24. PubMed PMID: 22273250.

(Retrospective analysis of infectious complications among 182 patients treated with alemtuzumab between 2003-2009 in 6 Asian countries identified 66 cases of CMV, 25 VZV, 31 fungal infections, 4 PjP, HBV reactivation 4 [in previously HBsAg negative patients], and tuberculosis 16).

Putra J, Suriawinata AA. Adenovirus hepatitis presenting as tumoral lesions in an immunocompromised patient. Ann Hepatol 2014; 13: 827-9. PubMed PMID: 25332270.

(59 year old man with T-cell leukemia treated with alemtuzumab developed fever and adenovirus hepatitis, responding to cidovir therapy).

Di Bisceglie AM, Lok AS, Martin P, Terrault N, Perrillo RP, Hoofnagle JH. Recent US Food and Drug Administration warnings on hepatitis B reactivation with immune-suppressing and anticancer drugs: just the tip of the iceberg? Hepatology 2015; 61: 703-11. PubMed PMID: 25412906.

(Review of the pathogenesis, clinical course, treatment and prevention of HBV reactivation in patients receiving immunosuppressive or anticancer therapies, with particular focus on rituximab and ofatumumab).