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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-. Ofatumumab. [Updated 2015 Jun 18].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Ofatumumab

Updated: June 18, 2015.

OVERVIEW

Introduction

Ofatumumab is a recombinant human monoclonal antibody to CD20 a cell surface antigen found on pre-B and mature B lymphocytes and which is approved for use in resistant chronic lymphocytic leukemia. Ofatumumab therapy has not been associated with serum enzyme elevations during therapy or to cases of idiosyncratic, clinically apparent liver injury. However, ofatumumab has potent immunosuppressive activity and its use has been associated with cases of reactivation of inactive or previously resolved hepatitis B which can be severe and can result in fatality.

Background

Ofatumumab (oh" fa toom' ue mab) is a human monoclonal IgG1 antibody to the cell surface antigen CD20 (also known as human B lymphocyte restricted differentiation antigen: Bp35), which is found on mature B cells as well as 90% of neoplastic B cell such as occur in chronic lymphocytic leukemia. CD20 is not present on pro-B cells, hematopoietic stem cells, normal plasma cells or other normal lymphocytes, circulating cells or tissues. Engagement of ofatumumab with CD20 leads to B cell lysis and depletion of circulating and tissue B cells for an extended period, up to 6 to 8 months. There is an accompanying mild decrease in IgM, but no change in IgG or IgA levels. Ofatumumab was approved for use in previously treated, resistant chronic lymphocyte leukemia United States in 2009. Ofatumumab is available in liquid solution in single use vials of 100 and 1000 mg (20 mg/mL) under the brand name Arzerra. The dose and regimen varies by indication, but it is usually given intravenously in 300 to 2000 mg amounts in 28 day cycles. Common side effects include infusion reactions, chills, fever, nausea, diarrhea, fatigue, dyspnea, cough, bronchitis, pneumonia, skin rash, neutropenia and infections. Less common, but potentially severe side effects include cutaneous reactions (Stevens Johnson syndrome), tumor lysis syndrome, prolonged neutropenia, thrombocytopenia and anemia. Because of the potential severity of infusion reactions, premedication with antihistamines, acetaminophen and corticosteroids is recommended, and ofatumumab should be administered under close medical observation.

Hepatotoxicity

Serum aminotransferase elevations are uncommon during ofatumumab therapy and rarely mentioned in large clinical trials of its use in CLL and autoimmune diseases. Clinically apparent liver injury has not been reported with ofatumumab therapy either in prelicensure clinical trials or subsequent to its more widescale clinical use.

On the other hand, ofatumumab is a potent immunosuppressive agent and has been reported to cause reactivation of hepatitis B. Specific features of the reactivation caused by ofatumumab have not been published, but HBV reactivation is typically associated with acute hepatocellular injury that can be severe and lead to acute

liver failure and death or need for emergency liver transplantation. Rituximab, another monoclonal antibody to CD20 that has been extensively used for several decades, is a well known cause of HBV reactivation, so it is not surprising that ofatumumab would have a similar effect. Reactivation typically occurs in patients who are HBsAg carriers with inactive hepatitis B who undergo chemotherapy for cancer. Reactivation can also occur in persons who have recovered from hepatitis B, who have no detectable HBsAg but have antibody to hepatitis B core antigen (anti-HBc), with or without antibody to HBsAg (anti-HBs) in serum. The onset of liver injury is delayed and may occur months after 3 to 6 courses of immunosuppressive therapy. The usual sequence of events is appearance of rising levels of HBV DNA in serum shortly after chemotherapy is started, followed by a rise in levels of HBsAg and HBeAg. When therapy is stopped and immune reconstitution has begun, serum ALT and AST levels start to rise followed by symptoms and jaundice. Reactivation of hepatitis B tends to be severe and the mortality rate in jaundiced cases exceeds 10%. Liver histology demonstrates an acute hepatitis-like pattern with focal or confluent necrosis and prominent lymphocytic infiltrates of activated T cells, which is compatible with an immune mediated hepatic injury. Restarting chemotherapy can result in recurrence of injury, although concurrent antiviral treatment may block recurrence.

Reactivation of HBV in persons who have resolved hepatitis B (anti-HBc without HBsAg in serum) is usually referred to as "reverse seroconversion", and reactivation in persons with preexisting HBsAg in serum as "typical" HBV reactivation. The two forms of reactivation have somewhat different clinical, biochemical and virology courses. In general, patients with reverse seroconversion have received more rigorous immunosuppression, the latency until onset is longer, peak levels of HBV DNA are lower, and the disease course is more severe in patients than in patients with typical reactivation. The time to appearance of clinically apparent reactivation tends to be 3 to 6 months in patients with typical reactivation, but 12 to 36 months in those with reverse seroconversion. Outcomes may also be different, reverse seroconversion tending to be more severe and more likely to resolve with disappearance of HBsAg than typical reactivation. Exceptions occur in both situations; however, some patients with reverse seroconversion do not revert back to being HBsAg negative, particularly those who have had hematopoietic cell transplantation (HCT). In addition, some patients with classic reactivation of hepatitis B ultimately clear HBsAg as a result of the acute liver injury. Both forms of reactivation appear to be ameliorated by early intervention with oral antiviral therapy, but institution of therapy after appearance of clinical disease and jaundice may not be effective and many instances of fatal reactivation have occurred despite treatment with oral antiviral agents. Many cases of reverse seroconversion have been reported with rituximab therapy; the occurrence with ofatumumab has been implied, but specific cases have not been published.

Mechanism of Injury

The mechanism of liver injury in reactivation of hepatitis B appears to be a brisk immunological response to viral antigens. Injury generally arises after immunosuppressive or cancer chemotherapy has stopped or between courses of treatment.

Outcome and Management

Guidelines for management of patients who are to receive ofatumumab recommend routine screening for hepatitis B before starting treatment. Screening should include tests for HBsAg and anti-HBc (and perhaps also anti-HBs as this may help in management). Prophylaxis with a potent oral, antiviral agent effective against hepatitis B is recommended for all persons who have HBsAg in serum and is suggested for those with anti-HBc without HBsAg. An alternative approach is careful monitoring for HBV DNA during therapy and early institution of antiviral therapy if levels rise. This approach, however, is problematic in that reactivation may occur late during chemotherapy or even after it is completed. The choice of antiviral agents includes lamivudine, telbivudine, adefovir, tenofovir or entecavir. All are given once a day and are extremely well tolerated. Lamivudine is less expensive than the other agents, but is associated with a high rate of antiviral resistance, particularly if given for more than 6 months. Tenofovir and entecavir are the most potent and have high barriers

to antiviral resistance, which is important if long term therapy is planned. However, there are no prospectively acquired controlled studies to support use of one of these agents over another. Finally, the appropriate duration of treatment is unclear. The typical recommendation is to continue antivirals for at least 6 months after stopping cancer chemotherapy, but cases of reactivation following withdrawal of antiviral therapy (including fatal instances) have been described and some degree of monitoring during withdrawal of antiviral therapy is perhaps appropriate. In patients with anti-HBc without HBsAg, boosting titers of anti-HBs before or in-between treatment courses may be helpful in preventing reactivation. However, patients with lymphoma or autoimmune conditions and those who are receiving ofatumumab generally have poor responses to vaccination and this approach has not been critically evaluated in prospective controlled studies.

Drug Class: Antineoplastic Agents, Monoclonal Antibodies

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Ofatumumab – Arzerra®

DRUG CLASS

Antineoplastic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Ofatumumab	**679818-59-8**	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 rituximab and problems of reactivation of hepatitis B, but also states that "the biological immunosuppressants are largely free from hepatotoxicity, with the exception of the TNF alpha antagonists"; no specific discussion of ofatumumab).

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).

Yeo W, Chan PK, Zhong S, Ho WM, Steinberg JL, Tam JS, Hui P, et al. Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: a prospective study of 626 patients with identification of risk factors. J Med Virol 2000; 62: 299-307. PubMed PMID: 11055239.

(Among 71 Chinese patients with HBsAg who underwent cancer chemotherapy [not with rituximab] for various malignancies, 15 developed reactivation of HBV, including 6 with jaundice and 3 with acute liver failure, but none died).

Hagenbeek A, Gadeberg O, Johnson P, Pedersen LM, Walewski J, Hellmann A, Link BK, et al. First clinical use of ofatumumab, a novel fully human anti-CD20 monoclonal antibody in relapsed or refractory follicular lymphoma: results of a phase 1/2 trial. Blood 2008; 111: 5486-95. PubMed PMID: 18390837.

(In a pilot study of ofatumumab in 40 patients with refractory lymphoma, "no significant changes in serum chemistry were observed").

Coiffier B, Lepretre S, Pedersen LM, Gadeberg O, Fredriksen H, van Oers MH, Wooldridge J, et al. Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: a phase 1-2 study. Blood 2008; 111: 1094-100. PubMed PMID: 18003886.

(Pilot study of ofatumumab in escalating doses once weekly for 4 weeks in 33 patients with refractory CLL, the maximum tolerated dose was not reached, one patient developed "cytolytic hepatitis"; a 74 year old man who had elevated tests the day of the first infusion, but also had abnormal values before therapy).

Østergaard M, Baslund B, Rigby W, Rojkovich B, Jorgensen C, Dawes PT, Wiell C, et al. Ofatumumab, a human anti-CD20 monoclonal antibody, for treatment of rheumatoid arthritis with an inadequate response to one or more disease-modifying antirheumatic drugs: results of a randomized, double-blind, placebo-controlled, phase I/II study. Arthritis Rheum 2010; 62: 2227-38. PubMed PMID: 20506254.

(Two studies of ofatumumab in patients with resistant rheumatoid arthritis given two infusions of ofatumumab [at 3 different doses] or placebo 2 weeks apart in 264 patients; B cell depletion occurred in all doses and response rates ranged from 40-49% [vs 11% in controls]; side effects were common, but usually mild to moderate in severity and no significant changes were found in routine laboratory results).

Ofatumumab (Arzerra) for CLL. Med Lett Drugs Ther 20108; 52 (1341): 51-2. PubMed PMID: 20585286.

(Concise review of efficacy, safety and cost of ofatumumab in CLL shortly after its approval in the US; mentions that severe side effects include infusion reactions, cytopenias, opportunistic infections and PMLE; no mention of hepatotoxicity or ALT elevations).

Taylor PC, Quattrocchi E, Mallett S, Kurrasch R, Petersen J, Chang DJ. Ofatumumab, a fully human anti-CD20 monoclonal antibody, in biological-naive, rheumatoid arthritis patients with an inadequate response to methotrexate: a randomised, double-blind, placebo-controlled clinical trial. Ann Rheum Dis 2011; 70: 2119-25. PubMed PMID: 21859685.

(Among 260 patients with rheumatoid arthritis treated with ofatumumab or placebo [two infusions 2 weeks apart], clinical responses at week 24 were more frequent with ofatumumab [50%] than placebo [27%], and common side effects were rash [21%] and urticaria [12%], but there were no liver related serious adverse events and ALT elevations were not reported).

Nightingale G. Ofatumumab: a novel anti-CD20 monoclonal antibody for treatment of refractory chronic lymphocytic leukemia. Ann Pharmacother 2011; 45: 1248-55. PubMed PMID: 21896924.

(Review of the mechanism of action, pharmacology, efficacy and safety of ofatumumab; no mention of hepatotoxicity or ALT elevations).

Schmedt N, Andersohn F, Garbe E. Signals of progressive multifocal leukoencephalopathy for immunosuppressants: a disproportionality analysis of spontaneous reports within the US Adverse Event Reporting System (AERS). Pharmacoepidemiol Drug Saf 2012; 21: 1216-20. PubMed PMID: 22821419.

(Analysis of spontaneous adverse event reporting of progressive PMLE in the US between 2004-2010 identified 635 cases with higher than expected number of cases from several immunosuppressive monoclonal antibodies, including rituximab [n=124], natalizumab [123] and efalizumab [12], but not ofatumumab).

Hwang JP, Vierling JM, Zelenetz AD, Lackey SC, Loomba R. Hepatitis B virus management to prevent reactivation after chemotherapy: a review. Support Care Cancer 2012; 20: 2999-3008. PubMed PMID: 22933131.

(Review of reactivation of HBV from chemotherapy stresses need for routine screening for HBV markers, particularly for patients who are to receive rituximab).

Mitka M. FDA: Increased HBV reactivation risk with ofatumumab or rituximab. JAMA 2013; 310: 1664. PubMed PMID: 24150447.

(News report of the FDA alert to physicians of the high risk of HBV reactivation in patients receiving ofatumumab or rituximab).

Hsu C, Tsou HH, Lin SJ, Wang MC, Yao M, Hwang WL, Kao WY, et al.; on behalf of the Taiwan Cooperative Oncology Group. Chemotherapy-induced hepatitis B reactivation in lymphoma patients with resolved HBV infection: A prospective study. Hepatology 2014; 59 (6): 2092-100. PubMed PMID: 24002804.

(Among 150 patients with non-Hodgkin lymphoma who had anti-HBc without HBsAg in serum and were treated with rituximab containing regimens without prophylaxis and followed with monthly testing for HBV DNA, 27 [18%] developed HBV reactivation 3-57 weeks after starting chemotherapy [6 after stopping], 12 developed HBsAg, 7 HBeAg and 10 ALT elevations despite prompt therapy with entecavir, but none had acute liver failure or died).

Kim SJ, Hsu C, Song YQ, Tay K, Hong XN, Cao J, Kim JS, et al. Hepatitis B virus reactivation in B-cell lymphoma patients treated with rituximab: analysis from the Asia Lymphoma Study Group. Eur J Cancer 2013; 49: 3486-96. PubMed PMID: 23910494.

(Retrospective analysis of rates of HBV reaction in 340 patients with lymphoma receiving rituximab based chemotherapy identified HBV reactivation in 45 of 162 [28%] of HBsAg positive and 10% of HBsAg negative but anti-HBc positive patients, risk factors being lack of antiviral prophylaxis and absence of anti-HBs and failures of prophylaxis being mostly due to lamivudine rather than entecavir).

Huang YH, Hsiao LT, Hong YC, Chiou TJ, Yu YB, Gau JP, Liu CY, et al. Randomized controlled trial of entecavir prophylaxis for rituximab-associated hepatitis B virus reactivation in patients with lymphoma and resolved hepatitis B. J Clin Oncol 2013; 31: 2765-72. PubMed PMID: 23775967.

(Among 80 Chinese patients with lymphoma and anti-HBc without HBsAg in serum, 41 received entecavir and 39 were monitored during rituximab based chemotherapy; reactivation of HBV occurred in 2% on entecavir [1 patient after stopping prophylaxis] versus 18% of controls; while HBsAg reverse seroconversion occurred in 0% on entecavir and 10% of controls; only 1 patient developed hepatitis and none had acute liver failure).

Martin ST, Cardwell SM, Nailor MD, Gabardi S. Hepatitis B reactivation and rituximab: a new boxed warning and considerations for solid organ transplantation. Am J Transplant 2014; 14: 788-96. PubMed PMID: 24592928.

(Commentary on the boxed warning for rituximab and ofatumumab published by the FDA in September 2013, questioning the need for prophylaxis in patients undergoing solid organ transplant who typically receive a single dose of rituximab and in whom there have been few reports of reactivation).

Sorensen PS, Lisby S, Grove R, Derosier F, Shackelford S, Havrdova E, Drulovic J, et al. Safety and efficacy of ofatumumab in relapsing-remitting multiple sclerosis: a phase 2 study. Neurology 2014; 82: 573-81. PubMed PMID: 24453078.

(Among 38 patients with relapsing multiple sclerosis treated with two infusions of 3 doses of ofatumumab or placebo 2 weeks apart and followed for 24 weeks, new brain lesions were less on MR imaging after ofatumumab therapy and "results of clinical laboratory tests... were unremarkable").

Mikulska M, Nicolini L, Signori A, Rivoli G, Del Bono V, Raiola AM, Di Grazia C, et al. Hepatitis B reactivation in HBsAg-negative/HBcAb-positive allogeneic haematopoietic stem cell transplant recipients: risk factors and outcome. Clin Microbiol Infect 2014; 20 (10): O694-701. PubMed PMID: 24575948.

(Among 754 patients undergoing hematopoietic cell transplantation, 14 patients developed HBV reactivation, occurring only among the 137 who had anti-HBc without HBsAg before transplant at a rate of 2% at one year rising to 26% at 7 years; risk factors included lack of HBV immunity in the donor and length of therapy with cyclosporine).

Yazici O, Sendur MA, Aksoy S. Hepatitis C virus reactivation in cancer patients in the era of targeted therapies. World J Gastroenterol 2014; 20: 6716-24. PubMed PMID: 24944464.

(Systematic review of studies of HCV reactivation in patients receiving monoclonal antibody and immunomodulatory therapies for cancer found little evidence that hepatitis C is worsened, but advised caution regardless).

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).