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Rituximab

Updated: June 18, 2018.

OVERVIEW

Introduction

Rituximab is a chimeric mouse/human monoclonal antibody to CD20 a cell surface antigen found on pre-B and mature B lymphocytes and which is approved for use in non-Hodgkin lymphoma and chronic lymphocytic leukemia as well as in several autoimmune conditions, including rheumatoid arthritis and Wegener granulomatous. Rituximab has been linked to many cases of severe and even fatal liver injury as a result of reactivation of inactive or previously resolved hepatitis B.

Background

Rituximab (ri tux' i mab) is a human mouse chimeric monoclonal immunoglobulin G1 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 B cell neoplasms such as non-Hodgkin lymphoma and 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 rituximab 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 decrease in IgG and IgM levels, but in only 10% to 15% of patients do immunoglobulin levels fall below the normal range. Rituximab was approved for use in non-Hodgkin lymphoma and chronic lymphocyte leukemia in the United States in 1997, and indications were subsequently expanded to severe autoimmune conditions including refractory rheumatoid arthritis and Wegener granulomatosis (granulomatosis with polyangiitis). Rituximab is used off-label and is under active investigation in several other malignant conditions and autoimmune diseases. Rituximab is available in liquid solution in single use vials of 100 and 500 mg (10 mg/mL) under the brand name Rituxan. The dose and regimen varies by indication. Common side effects include infusion reactions, chills, fever, skin rash, fatigue, leukopenia and infections. Less common, but potentially severe side effects include cutaneous reactions (Stevens Johnson syndrome), infections, reactivation of tuberculosis, progressive multifocal leukoencephalopathy, cardiac arrhythmias, renal toxicity and bowel obstruction. Because of the potential severity of infusion reactions, premedication with antihistamines and acetaminophen is recommended and rituximab should be administered under close medical observation.

Hepatotoxicity

Mild-to-moderate serum aminotransferase elevations are not uncommon (10% to 15%) during rituximab therapy, but are usually self-limited and resolve even with continuing cyclic therapy, and are no more common than with comparator chemotherapy arms without rituximab. In trials of rituximab in rheumatoid arthritis, serum ALT elevations were uncommon. Serum ALT elevations above 5 times the upper limit of normal (ULN)

occur in 0.5% to 1.5% of patients, but clinically apparent liver injury during these episodes is rare. Few isolated case reports of clinically apparent, acute liver injury with symptoms or jaundice attributed to rituximab have been published. These have generally been marked by a rapid and abrupt onset of severe liver injury within days of starting rituximab. The association with administration of the monoclonal antibody is uncertain. The injury resembled acute hepatic necrosis as might occur with a direct toxin or with ischemia.

Rituximab is, however, a major cause of reactivation of hepatitis B which typically causes acute hepatocellular injury that can be severe and lead to acute liver failure and death or need for emergency liver transplantation. More than 100 cases of clinically apparent reactivation of hepatitis B attributed to rituximab have been reported in the literature, many of which have been severe or fatal. Reactivation can occur in patients who are HBsAg carriers and undergo chemotherapy with rituximab, but also 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 rituximab therapy. The usual sequence of events is appearance of rising levels of HBV DNA in serum shortly after rituximab is started, followed by 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 rituximab can result in recurrence of injury, although corticosteroid or 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 rapid institution of treatment with oral antiviral agents.

Finally, rituximab can reactivate other viral infections, and severe instances of acute hepatitis due to adenovirus, parvovirus and other opportunistic viral infections after rituximab therapy have been described.

Likelihood score: A (well known cause of reactivation of hepatitis B and rare cause of immune mediated, clinically apparent liver injury).

Mechanism of Injury

The mechanism of liver injury in reactivation of hepatitis B appears to be a brisk immunological response to rising levels of viral antigens on hepatocytes. Injury often arises after rituximab therapy has stopped or between courses of treatment.

Outcome and Management

Guidelines for management of patients who are to receive rituximab 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 monthly 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 many months after stopping chemotherapy (including fatal instances) have been described. For these reasons, monitoring during withdrawal of antiviral therapy is 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 rituximab generally have poor responses to vaccination and this approach has not been critically evaluated in prospective controlled studies.

Drug Class: Antineoplastic Agents, Monoclonal Antibodies; Antirheumatic Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Rituximab – Rituxan®

DRUG CLASS

Antineoplastic Agents

Antirheumatic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Rituximab	174722-31-7	Monoclonal Antibody	Not Available

ANNOTATED BIBLIOGRAPHY

References updated: 18 June 2018

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").

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).

Ng HJ, Lim LC. Fulminant hepatitis B virus reactivation with concomitant listeriosis after fludarabine and rituximab therapy: case report. Ann Hematol 2001; 80: 549-52. PubMed PMID: 11669307.

(53 year old woman with acute leukemia and HBsAg developed reactivation of HBV 3 months after completing 4 monthly courses of rituximab [bilirubin 10.8 mg/dL, ALT 1479 U/L, HBV DNA present], dying 12 days later with progressive hepatic failure and sepsis).

Dervite I, Hober D, Morel P. Acute hepatitis B in a patient with antibodies to hepatitis B surface antigen who was receiving rituximab. N Engl J Med 2001; 344: 68-9. PubMed PMID: 11187122.

(69 year old man with lymphoma who had anti-HBc without HBsAg in serum developed jaundice 6 months after 4 weekly infusions of rituximab [HBsAg, IgM anti-HBc and HBV DNA positive, no liver tests provided], recovering thereafter, but remaining HBsAg positive).

Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, Morel P, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002; 346: 235-42. PubMed PMID: 11807147.

(Among 399 patients with diffuse large cell lymphoma treated with 8 cycles of either CHOP or CHOP-rituximab, remission rates and survival were greater, but "clinically relevant toxicity was not significantly greater" with rituximab; grade 3 or 4 liver toxicity occurring in 1.5% [rituximab] vs 2.5% and no deaths occurred from liver failure).

Kami M, Hamaki T, Murashige N, Kishi Y, Kusumi E, Yuji K, Miyakoshi S, et al. Safety of rituximab in lymphoma patients with hepatitis B or hepatitis C virus infection. Hematol J 2003; 4: 159-62. PubMed PMID: 12750737.

(Among 5 patients with HBsAg and non-Hodgkin lymphoma treated with rituximab and given lamivudine prophylaxis, none developed reactivation of HBV; among 3 patients with HCV infection and lymphoma receiving rituximab, none developed a flare of disease during or after treatment).

Westhoff TH, Jochimsen F, Schmittel A, Stoffler-Meilicke M, Schafer JH, Zidek W, Gerlich WH, et al. Fatal hepatitis B virus reactivation by an escape mutant following rituximab therapy. Blood 2003; 102: 1930. PubMed PMID: 12930732.

(71 year old man with lymphoma and anti-HBc and anti-HBs without HBsAg developed jaundice 3 months after starting rituximab therapy [HBsAg and HBV DNA positive], dying of hepatic failure 19 days after presentation).

Tsutsumi Y, Kawamura T, Saitoh S, Yamada M, Obara S, Miura T, Kanamori H, et al. Hepatitis B virus reactivation in a case of non-Hodgkin's lymphoma treated with chemotherapy and rituximab: necessity of prophylaxis for hepatitis B virus reactivation in rituximab therapy. Leuk Lymphoma 2004; 45: 627-9. PubMed PMID: 15160930.

(68 year old woman with non-Hodgkin lymphoma and HBsAg developed reactivation of HBV and hepatic failure 3-4 weeks after a fourth course of rituximab, cyclophosphamide, doxorubicin and vincristine [bilirubin not given, ALT ~1800 U/L], resolving with lamivudine therapy).

Edwards JC, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, Stevens RM, et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med 2004; 350: 2572-81. PubMed PMID: 15201414.

(Among 161 patients with rheumatoid arthritis treated with rituximab with methotrexate or cyclophosphamide versus methotrexate alone, side effects included infusion reactions and infections, no mention of ALT levels or clinically apparent liver injury).

Sarrecchia C, Cappelli A, Aiello P. HBV reactivation with fatal fulminating hepatitis during rituximab treatment in a subject negative for HBsAg and positive for HBsAb and HBcAb. J Infect Chemother 2005; 11: 189-91. PubMed PMID: 16133710.

(53 year old man with CLL and anti-HBc and anti-HBs without HBsAg developed reactivation of HBV after 3 monthly infusions of rituximab [bilirubin 17.1 mg/dL, ALT 2120 U/L, HBV DNA positive], with progressive liver failure and death within 27 days).

Law JK, Ho JK, Hoskins PJ, Erb SR, Steinbrecher UP, Yoshida EM. Fatal reactivation of hepatitis B post-chemotherapy for lymphoma in a hepatitis B surface antigen-negative, hepatitis B core antibody-positive patient: potential implications for future prophylaxis recommendations. Leuk Lymphoma 2005; 46: 1085-9. PubMed PMID: 16019563.

(67 year old Korean man with B cell lymphoma and anti-HBc without HBsAg developed reactivation of HBV 3 weeks after completing a course of CHOP-rituximab, progressing to hepatic failure [HBsAg positive, bilirubin not given, ALT 2204 U/L, INR 2.8 rising to 7.5] and dying within 10 days of admission despite lamivudine therapy).

Niscola P, Del Principe MI, Maurillo L, Venditti A, Buccisano F, Piccioni D, Amadori S, Del Poeta G. Fulminant B hepatitis in a surface antigen-negative patient with B-cell chronic lymphocytic leukaemia after rituximab therapy. Leukemia 2005; 19: 1840-1. PubMed PMID: 16094417.

(51 year old man with CLL and anti-HBc without HBsAg developed reactivation of hepatitis B after 6 monthly courses of rituximab, becoming HBV DNA positive, but without a period of HBsAg detectability and progressive liver failure and death).

Qazilbash MH, Qu Z, Hosing C, Couriel D, Donato M, Giralt S, Champlin R. Rituximab-induced acute liver failure after an allogeneic transplantation for chronic myeloid leukemia. Am J Hematol 2005; 80: 43-5. PubMed PMID: 16138357.

(21 year old woman with chronic myelogenous leukemia underwent bone marrow transplantation and was then treated with rituximab for autoimmune hemolytic anemia and developed jaundice 3 days later [bilirubin 20.5 rising to 62 mg/dL, ALT >2000 U/L, with progressive liver failure and death within 3 days; timing makes it unlikely to have been due to rituximab).

Ozgönenel B, Moonka D, Savaşan S. Fulminant hepatitis B following rituximab therapy in a patient with Evans syndrome and large B-cell lymphoma. Am J Hematol 2006; 81: 302. PubMed PMID: 16550511.

(21 year old man with non-Hodgkin lymphoma with unknown HBV status developed reactivation of HBV within a few weeks of completing 3 courses of CHOP-rituximab [HBsAg positive, IgM anti-HBc negative, HBV DNA >200 million copies/mL, no liver test results given], and died within 15 days of admission despite lamivudine therapy).

Iyer A, Mathur R, Deepak BV, Sinard J. Fatal adenoviral hepatitis after rituximab therapy. Arch Pathol Lab Med 2006; 130: 1557-60. PubMed PMID: 17090202.

(60 year old man with Waldenstrom macroglobulinemia developed cough and fever after a third course of rituximab and pneumonitis, progressing to multiorgan failure and death with marked elevations in liver enzymes shortly before [ALT 8408 U/L, bilirubin not given], autopsy showing adenoviral pneumonia and hepatitis).

Sera T, Hiasa Y, Michitaka K, Konishi I, Matsuura K, Tokumoto Y, Matsuura B, et al. Anti-HBs-positive liver failure due to hepatitis B virus reactivation induced by rituximab. Intern Med 2006; 45: 721-4. PubMed PMID: 16819252.

(59 year old man with lymphoma and anti-HBc without HBsAg developed reactivation of HBV shortly after a third course of rituximab [bilirubin 26.4 mg/dL, ALT 359 U/L, GTP 199 U/L, HBsAg positive, HBV DNA ~9 million copies/mL], with progressive liver failure and death 3-4 months later).

Klepfish A, Rachmilevitch E, Schattner A. Parvovirus B19 reactivation presenting as neutropenia after rituximab treatment. Eur J Intern Med 2006; 17: 505-7. PubMed PMID: 17098597.

(58 year old woman with primary biliary cirrhosis and thrombocytopenic purpura developed neutropenia 4 months after 4 weekly infusions of rituximab and was found to have parvovirus B19 IgM and IgG antibody; no mention of liver test results).

Yamagata M, Murohisa T, Tsuchida K, Okamoto Y, Tsunoda S, Nakamura M, Kusano K, et al. Fulminant B hepatitis in a surface antigen and hepatitis B DNA-negative patient with diffuse large B-cell lymphoma after CHOP chemotherapy plus rituximab. Leuk Lymphoma. 2007; 48: 431-3. PubMed PMID: 17325912.

(54 year old man with diffuse large cell lymphoma and anti-HBc without HBsAg in serum developed rising titers of HBV DNA one month after finishing a 7 month course of monthly CHOP-rituximab, followed 3 months later by acute hepatitis, progressive liver failure and death).

Ono K, Iyama S, Matsunaga T, Sato T, Sato Y, Okuda T, Takada K, et al. [Reactivation of hepatitis B virus due to rituximab plus CHOP after preemptive lamivudine administration in a patient with diffuse large B-cell lymphoma]. Gan To Kagaku Ryoho 2007; 34: 1509-12. Japanese. PubMed PMID: 17876158.

(59 year old woman with B-cell lymphoma developed reactivation of HBV 2 months after stopping lamivudine which had been given during and for 3 months after CHOP-rituximab therapy, resolving with restarting lamivudine and adding interferon beta).

Yang SH, Kuo SH. Reactivation of hepatitis B virus during rituximab treatment of a patient with follicular lymphoma. Ann Hematol 2008; 87: 325-7. PubMed PMID: 17932671.

(41 year old woman with lymphoma and HBsAg had reactivation of HBV after 4 months of chlorambucil [bilirubin 1.2 mg/dL, ALT 1698 U/L, HBV DNA 40 million copies/mL], which responded to lamivudine therapy, but recurred when she was treated with rituximab without lamivudine [bilirubin 1.7 mg/dL, ALT 819 U/L, HBV DNA 228 million copies/mL], resolving again after restarting lamivudine).

Dillon R, Hirschfield GM, Allison ME, Rege KP. Fatal reactivation of hepatitis B after chemotherapy for lymphoma. BMJ 2008; 337: a423. PubMed PMID: 18595895.

(21 year old woman with B cell lymphoma and unknown HBV status developed HBV reactivation 2 weeks after a 4th cycle of CHOP-rituximab [liver tests not given, HBsAg positive, IgM anti-HBc negative, HBV DNA 450 million IU/mL], with progressive liver failure and death).

Garcia-Rodriguez MJ, Canales MA, Hernandez-Maraver D, Hernandez-Navarro F. Late reactivation of resolved hepatitis B virus infection: an increasing complication post rituximab-based regimens treatment? Am J Hematol 2008; 83: 673-5. PubMed PMID: 18528824.

(53 and 68 year old women with lymphoma and resolved hepatitis B treated with CHOP-rituximab developed reactivation 9 months and 1 year after completing therapy, one dying of acute liver failure and one recovering on lamivudine followed by entecavir therapy).

Targhetta C, Cabras MG, Mamusa AM, Mascia G, Angelucci E. Hepatitis B virus-related liver disease in isolated anti-hepatitis B-core positive lymphoma patients receiving chemo- or chemo-immune therapy. Haematologica 2008; 93: 951-2. PubMed PMID: 18515881.

(Among 395 patients with non-Hodgkin lymphoma and anti-HBc without HBsAg in serum who were treated with chemotherapy between 1989 and 2006, 4 developed clinically apparent reactivation of hepatitis B including 0.8% treated with chemotherapy only and 2.7% given rituximab; while all 4 recovered clinically, all remained HBsAg positive in follow up).

Wasmuth JC, Fischer HP, Sauerbruch T, Dumoulin FL. Fatal acute liver failure due to reactivation of hepatitis B following treatment with fludarabine, cyclophosphamide and rituximab for low grade non-Hodgkin's lymphoma. Eur J Med Res 2008; 13: 483-6. PubMed PMID: 19008178.

(Abstract: Patient developed reactivation of hepatitis B after 6th cycle of rituximab with fludarabine and cyclophosphamide).

Sanchez MJ, Buti M, Homs M, Palacios A, Rodriguez-Frias F, Esteban R. Successful use of entecavir for a severe case of reactivation of hepatitis B virus following polychemotherapy containing rituximab. J Hepatol 2009; 51: 1091-6. PubMed PMID: 19836097.

(62 year old man with CLL and anti-HBc without HBsAg in serum developed reactivation of HBV 4 weeks after a 4th cycle of rituximab based chemotherapy [bilirubin rising to 10.3 mg/dL, ALT 3481 U/L, INR 1.8, HBV DNA ~80 million IU/mL] treated with entecavir and recovered, but remained HBsAg positive).

Takahashi T, Koike T, Hashimoto S, Miura T, Nakamura J, Yamada S, Miura T, et al. A case of lamivudine-sensitive de novo acute hepatitis B induced by rituximab with the CHOP regimen for diffuse large B cell lymphoma. Hepatol Int 2009; 3: 316-22. PubMed PMID: 19669383.

(57 year old HBsAg-negative woman with B cell lymphoma developed HBsAg and hepatitis after 12 courses of CHOP-rituximab [bilirubin 0.5 mg/dL, ALT 1113 U/L, Alk P 423 U/L, HBV DNA ~50 million copies/mL], recovering on lamivudine therapy, but remaining HBsAg positive).

Fukushima N, Mizuta T, Tanaka M, Yokoo M, Ide M, Hisatomi T, Kuwahara N, et al. Retrospective and prospective studies of hepatitis B virus reactivation in malignant lymphoma with occult HBV carrier. Ann Oncol 2009; 20: 2013-7. PubMed PMID: 19561036.

(Among 24 patients with anti-HBc without HBsAg in serum who were monitored during treatment with chemotherapy, 2 developed rising HBV DNA levels [one after HCT and one after rituximab therapy] and were promptly treated with entecavir, both with rapid resolution).

Stange MA, Tutarel O, Pischke S, Schneider A, Strassburg CP, Becker T, Barg-Hock H, et al. Fulminant hepatic failure due to chemotherapy-induced hepatitis B reactivation: role of rituximab. Z Gastroenterol 2010; 48: 258-63. PubMed PMID: 20127601.

(62 and 53 year old men with lymphoma developed reactivation of HBV after 4 and 6 courses of rituximab based chemotherapy, one undergoing liver transplant and one dying after attempts at hepatocyte transplantation; prestatus unknown, but both were HBsAg positive, IgM anti-HBc negative).

Artz AS, Somerfield MR, Feld JJ, Giusti AF, Kramer BS, Sabichi AL, Zon RT, et al. American Society of Clinical Oncology provisional clinical opinion: chronic hepatitis B virus infection screening in patients receiving cytotoxic chemotherapy for treatment of malignant diseases. J Clin Oncol 2010; 28: 3199-202. PubMed PMID: 20516452.

(Statement from the American Society of Clinical Oncology that there is inadequate medical evidence to recommend routine screening for HBV markers in patients scheduled for cancer chemotherapy, but that "ASCO assumes no responsibility for any injury or damage to persons or property arising out of use" of ASCO clinical opinions).

Li X, Lin Q, Dong M, Wen JY, Wei L, Ma XK, Chen ZH, et al. Prognostic analysis of acute exacerbations of hepatitis-B after chemotherapy in combination with rituximab in 19 patients with lymphoma. Leuk Lymphoma 2010; 51: 1678-85. PubMed PMID: 20807095.

(Among 19 Chinese patients with reactivation of HBV after rituximab therapy, 9 died; factors predicting poor outcome included INR, total bilirubin and shorter time between last rituximab course and onset).

Del Prete CJ, Cohen NS. A case of rituximab-induced hepatitis. Cancer Biother Radiopharm 2010; 25: 747-8. PubMed PMID: 21204770.

(38 year old man with ITP developed fever and jaundice after third dose of rituximab [bilirubin 12 mg/dL, ALT 256 U/L, Alk P 313 U/L, HBV markers negative], with rapid resolution on stopping rituximab).

Zhang B, Wang J, Xu W, Wang L, Ni W. Fatal reactivation of occult hepatitis B virus infection after rituximab and chemotherapy in lymphoma: necessity of antiviral prophylaxis. Onkologie 2010; 33: 537-9. PubMed PMID: 20926902.

(50 year old man with B cell lymphoma developed jaundice 10 days after the 4th course of CHOP-rituximab [bilirubin ~8.0 rising to 45 mg/dL, ALT ~2500 U/L, HBsAg and HBV DNA present], dying of liver failure despite entecavir treatment and liver transplantation).

Villadolid J, Laplant KD, Markham MJ, Nelson DR, George TJ Jr. Hepatitis B reactivation and rituximab in the oncology practice. Oncologist 2010; 15: 1113-21. PubMed PMID: 20930099.

(Review of the frequency, cause and management of reactivation of hepatitis B).

Chung SM, Sohn JH, Kim TY, Yoo KD, Ahn YW, Bae JH, Jeon YC, et al. [Fulminant hepatic failure with hepatitis B virus reactivation after rituximab treatment in a patient with resolved hepatitis B]. Korean J Gastroenterol 2010; 55: 266-9. Korean. PubMed PMID: 20389182.

(Four anti-HBc-positive, HBsAg-negative Korean patients with lymphoma treated with rituximab based chemotherapy developed reactivation of hepatitis B with reappearance of HBsAg and high levels of HBV DNA, one of whom died of acute liver failure).

Muñoz Bertrán E, Pérez Ceballos E, Gómez Espín R, Ortega González I. [Hepatitis B reactivation in an HbsAg-negative/anti-HBc-positive patient with B-cell non-Hodgkin lymphoma receiving chemotherapy with rituximab]. Gastroenterol Hepatol 2010; 33: 377-81. Spanish. PubMed PMID: 20363054.

(81 year old man with non-Hodgkin lymphoma and anti-HBc without HBsAg in serum developed reactivation of hepatitis B five months after starting rituximab based chemotherapy [bilirubin 2.2 mg/dL, ALT 551 U/L, Alk P 1,146 U/L, HBsAg and HBV DNA positive], with progressive liver failure and death).

Méndez-Navarro J, Corey KE, Zheng H, Barlow LL, Jang JY, Lin W, Zhao H, et al. Hepatitis B screening, prophylaxis and re-activation in the era of rituximab-based chemotherapy. Liver Int 2011; 31: 330-9. PubMed PMID: 20738779.

(Among 1429 patients who received rituximab for non-Hodgkin lymphoma, screening for HBV status was done in 524 [37%], 20 of whom had HBsAg and 10 had HBV reactivation; among patients who were not screened, 5 developed clinically apparent reactivation and one died of acute liver failure).

Zachou K, Dalekos GN. Hepatitis B re-activation with rituximab therapy: treat the patient not the disease. Liver Int 2011; 31: 277-9. PubMed PMID: 21281426.

(Editorial in response to Mendez-Navarro [2011] on need to screen for HBV markers in patients who are to receive rituximab both as cancer chemotherapy and for autoimmune conditions).

Oketani M, Ido A, Tsubouchi H. Changing etiologies and outcomes of acute liver failure: A perspective from Japan. J Gastroenterol Hepatol 2011; 26 Suppl 1: 65-71. PubMed PMID: 21199516.

(Analysis of from multicenter study in Japan lists reactivation of HBV as an increasing cause of acute liver failure).

Watanabe M, Shibuya A, Tsunoda Y, Danbara M, Ishii R, Ohsaka M, Takada J, et al. Re-appearance of hepatitis B virus following therapy with rituximab for lymphoma is not rare in Japanese patients with past hepatitis B virus infection. Liver Int 2011; 31: 340-7. PubMed PMID: 21134110.

(In a retrospective analysis of 45 patients with lymphoma and anti-HBc without HBsAg in serum who underwent chemotherapy, 5 of 24 [21%] who received rituximab, but none of 21 who did not, developed HBV DNA during or following chemotherapy).

Nooka A, Shenoy PJ, Sinha R, Lonial S, Flowers CR. Hepatitis C reactivation in patients who have diffuse large B-cell lymphoma treated with rituximab: a case report and review of literature. Clin Lymphoma Myeloma Leuk 2011; 11: 379-84. PubMed PMID: 21729690.

(52 year old man with lymphoma and chronic hepatitis C had slight elevations in HCV RNA levels without change in serum enzymes or liver injury during or after CHOP-rituximab therapy).

Mastroianni CM, Lichtner M, Citton R, Del Borgo C, Rago A, Martini H, Cimino G et al. Current trends in management of hepatitis B virus reactivation in the biologic therapy era. World J Gastroenterol 2011; 17: 3881-7. PubMed PMID: 22025876.

(Review of the cause and risk factors for reactivation of HBV, the role of rituximab and preventive strategies).

Cheung WI, Lin SY, Leung VK, Fung KS, Lam YK, Lo FH, Chau TN. Prospective evaluation of seropositive occult hepatitis B viral infection in lymphoma patients receiving chemotherapy. Hong Kong Med J 2011; 17: 376-80. PubMed PMID: 21979474.

(Among 47 Chinese patients with lymphoma given chemotherapy during a 1 year period, 10 [21%] had anti-HBc without HBsAg in serum of whom one developed reactivation of HBV 32 weeks after starting rituximab based therapy [bilirubin normal, ALT 1430 U/L, HBV DNA 2 million IU/mL, HBeAg positive but HBsAg negative], resolving rapidly with entecavir therapy).

Coppola N, Tonziello G, Pisaturo M, Messina V, Guastafierro S, Fiore M, Iodice V, et al. Reactivation of overt and occult hepatitis B infection in various immunosuppressive settings. J Med Virol 2011; 83: 1909-16. PubMed PMID: 21915865.

(Among 23 Italian patients with symptomatic reactivation of HBV, the 13 who had anti-HBc without HBsAg before therapy had lower peak HBV DNA levels and were more likely to have malignant disease and receive rituximab than the 10 who were HBsAg positive before therapy).

Lock G, Helmich F, Bertram M. [Impending liver failure after chemoimmunotherapy-induced reactivation of hepatitis B - successful treatment with entecavir]. Dtsch Med Wochenschr 2012; 137: 1248-50. German. PubMed PMID: 22644491.

(83 year old woman with leukemia developed reactivation of HBV 2 weeks after a 6th cycle of rituximab and bendamustine [bilirubin 27.8 mg/dL, ALT 1353, INR 1.68, HBsAg, HBeAg and HBV DNA present], resolving with entecavir therapy and HBsAg became negative 8 months later).

Sagnelli E, Pisaturo M, Sagnelli C, Coppola N. Rituximab-based treatment, HCV replication, and hepatic flares. Clin Dev Immunol 2012; 2012: 945950. PubMed PMID: 22919406.

(Review of literature on effects of rituximab therapy on HCV replication identified 5 studies in 59 patients found that rises in HCV RNA levels during therapy are common [~95%] and flares of disease can occur [~40%] that rarely may be severe).

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).

Mahale P, Kontoyiannis DP, Chemaly RF, Jiang Y, Hwang JP, Davila M, Torres HA. Acute exacerbation and reactivation of chronic hepatitis C virus infection in cancer patients. J Hepatol 2012; 57: 1177-85. PubMed PMID: 22871500.

(Retrospective analysis of 308 patients with chronic hepatitis C who received cancer chemotherapy found acute exacerbations of disease [greater than 3 fold increase in ALT] in 33 [11%], higher risk was associated with rituximab therapy and hematologic malignancy; none of 32 patients with anti-HCV without HCV RNA developed evidence of reactivation).

Keystone EC, Cohen SB, Emery P, Kremer JM, Dougados M, Loveless JE, Chung C, et al. Multiple courses of rituximab produce sustained clinical and radiographic efficacy and safety in patients with rheumatoid arthritis and an inadequate response to 1 or more tumor necrosis factor inhibitors: 5-year data from the REFLEX study. J Rheumatol 2012; 39: 2238-46. PubMed PMID: 23027887.

(Among 480 patients with rheumatoid arthritis treated in an open label study of rituximab for up to 5 years, adverse events were most frequent during the first year and stable thereafter; there were no cases of reactivation of HBV and no mention of ALT elevations or hepatotoxicity).

Pyrpasopoulou A, Douma S, Vassiliadis T, Chatzimichailidou S, Triantafyllou A, Aslanidis S. Reactivation of chronic hepatitis B virus infection following rituximab administration for rheumatoid arthritis. Rheumatol Int 2011; 31: 403-4. PubMed PMID: 19830433.

(56 year old woman with rheumatoid arthritis and HBsAg but low levels of HBV DNA in serum developed fever and raised serum enzymes one month after starting rituximab infusions [bilirubin normal, ALT 150 U/L, HBV DNA 100 million IU/mL], resolving with tenofovir therapy).

Andres M, Courtney P. No hepatitis B reactivation in a patient with refractory antisynthetase syndrome successfully treated with rituximab. Joint Bone Spine 2011; 78: 653-4. PubMed PMID: 21807545.

(46 year old HBsAg-positive man with antisynthetase syndrome was successfully treated with rituximab and given prophylaxis with lamivudine and did not develop reactivation of the underlying hepatitis B).

Ferreira R, Carvalheiro J, Torres J, Fernandes A, Giestas S, Mendes S, Agostinho C, et al. Fatal hepatitis B reactivation treated with entecavir in an isolated anti-HBs positive lymphoma patient: a case report and literature review. Saudi J Gastroenterol 2012; 18: 277-81. PubMed PMID: 22824772.

(78 year old woman with non-Hodgkin lymphoma and anti-HBc and anti-HBs without HBsAg in serum developed severe reactivation of HBV 40 days after finishing 4th course of chemotherapy [bilirubin 21.6 mg/dL, ALT 2935 U/L, HBsAg and IgM anti-HBc positive, HBV DNA 2400 IU/mL, INR 1.66], dying of liver failure 27 days after presentation despite entecavir therapy).

Fylaktou A, Daoudaki M, Dimou V, Sianou E, Papaventsis D, Mavrovouniotis I, Fouzas I, et al. Hepatitis B reactivation in a renal transplant patient due to a surface antigen mutant strain: a case report. Transplant Proc 2012; 44: 2773-5. PubMed PMID: 23146520.

(52 year old man with HBsAg in serum underwent renal transplantation and developed reactivation of HBV 4 months later after one dose of rituximab and while on cyclosporine, mycophenolate, and prednisone [ALT 92 U/L, HBV DNA 2 million IU/mL, HBsAg, HBeAg], no mention of recovery).

Pei SN, Ma MC, Wang MC, Kuo CY, Rau KM, Su CY, Chen CH. Analysis of hepatitis B surface antibody titers in B cell lymphoma patients after rituximab therapy. Ann Hematol 2012; 91: 1007-12. PubMed PMID: 22273839.

(Among 29 patients with B cell lymphomas who had anti-HBs without HBsAg in serum, anti-HBs and total IgG levels decreased with rituximab and 8 patients became anti-HBs negative, all of whom had low levels before therapy; 1 patient developed HBV reactivation and died of acute liver failure).

Ceccarelli L, Salpini R, Sarmati L, Svicher V, Bertoli A, Sordillo P, et al. Late hepatitis B virus reactivation after lamivudine prophylaxis interruption in an anti-HBs-positive and anti-HBc-negative patient treated with rituximab-containing therapy. J Infect 2012; 65: 180-3. PubMed PMID: 22138369.

(72 year old woman with B cell lymphoma and anti-HBs without anti-HBc or HBsAg in serum developed reactivation of HBV 18 months after finishing rituximab based chemotherapy and 12 months after stopping lamivudine [bilirubin 7.2 mg/dL, ALT 1904 U/L, HBV DNA 231,000 IU/mL], with no mention of recovery or follow up).

Ghrénassia E, Mékinian A, Rouaghe S, Ganne N, Fain O. Reactivation of resolved hepatitis B during rituximab therapy for rheumatoid arthritis. Joint Bone Spine 2012; 79: 100-1. PubMed PMID: 21944979.

(78 year old man with rheumatoid arthritis and resolved hepatitis B developed reactivation of HBV 3 months after 4th 6-month course of rituximab [bilirubin not given, ALT 421 U/L, Alk P 87 U/L, HBsAg, HBeAg and HBV DNA present], resolving on entecavir therapy).

Papamichalis P, Alexiou A, Boulbou M, Dalekos GN, Rigopoulou EI. Reactivation of resolved hepatitis B virus infection after immunosuppression: is it time to adopt pre-emptive therapy? Clin Res Hepatol Gastroenterol 2012; 36: 84-93. PubMed PMID: 21920838.

(68 year old man and 75 year old woman with lymphoma had anti-HBc without HBsAg before chemotherapy and were found to have serum ALT elevations, HBsAg and HBV DNA in serum after rituximab therapy).

Francisci D, Falcinelli F, Schiaroli E, Capponi M, Belfiori B, Cecchini E, Baldelli F. Reactivation of hepatitis B virus replication due to cytotoxic therapy: a five-year prospective study. Tumori 2012; 98: 220-4. PubMed PMID: 22677988.

(Among 478 Italian patients with hematological malignancies undergoing cancer chemotherapy, 75 had anti-HBc without HBsAg in serum of whom 5 [7%] developed reactivation of HBV with reappearance of HBsAg in serum, all responding to antiviral therapy and none died).

Latus J, Klein R, Koetter I, Schwab M, Fritz P, Kimmel M, Alscher MD, et al. Cholestatic liver disease after rituximab and adalimumab and the possible role of cross-reacting antibodies to Fab 2 fragments. PLoS One 2013; 8: e78856. PubMed PMID: 24244376.

(Analysis of serum samples from unclear number of patients with liver injury on adalimumab or rituximab identified cross reacting antibodies to Fab 2 fragments).

Sperl J, Frankova S, Kieslichova E, Oliverius M, Janousek L, Honsova E, Trunecka P, et al. Urgent liver transplantation for chemotherapy-induced HBV reactivation: a suitable option in patients recently treated for malignant lymphoma. Transplant Proc 2013; 45: 2834-7. PubMed PMID: 24034061.

(Three cases, 2 men and 1 woman, ages 42-49 years, with lymphoma developed reactivation of HBV after 8-13 cycles of rituximab therapy [bilirubin 21-35 mg/dL, ALT 2340-3000 U/L, HBsAg and high levels of HBV DNA in serum], all undergoing urgent liver transplantation with long term survival, tumor free and HBsAg negative on HBIG and oral antiviral therapy).

Yang JD, Girotra M, Vaid A, Duarte-Rojo A. Hepatitis B reactivation in patient with non-Hodgkin's lymphoma receiving rituximab-based chemotherapy: need for education and attention. J Ark Med Soc 2013; 110: 110-2. PubMed PMID: 24367885.

(Abstract: 58 year old man with lymphoma and chronic hepatitis B developed severe reactivation while receiving rituximab).

Tsutsumi Y, Yamamoto Y, Shimono J, Ohhigashi H, Teshima T. Hepatitis B virus reactivation with rituximab-containing regimen. World J Hepatol 2013; 5: 612-20. PubMed PMID: 24303089.

(Review of reactivation of hepatitis B with rituximab-containing chemotherapy).

van Vollenhoven RF, Emery P, Bingham CO 3rd, Keystone EC, Fleischmann RM, Furst DE, Tyson N, et al. Long-term safety of rituximab in rheumatoid arthritis: 9.5-year follow-up of the global clinical trial programme with a focus on adverse events of interest in RA patients. Ann Rheum Dis 2013; 72: 1496-502. PubMed PMID: 23136242.

(Among 3194 patients with rheumatoid arthritis followed in a global clinical trial program for up to 9.5 years, rates of serious adverse events and infections were stable over time and similar to comparator arms; there were no cases of HBV reactivation and no mention of hepatotoxicity).

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 and 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: 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).

Kusumoto S, Tanaka Y, Mizokami M, Ueda R. Strategy for preventing hepatitis B reactivation in patients with resolved HBV infection following rituximab-containing chemotherapy. Hepatology 2014; 60: 765-6. PubMed PMID: 24347499.

(Letter in response to Hsu [2013] stressing shortcomings of prospective monitoring for HBV DNA).

Gigi E, Georgiou T, Mougiou D, Boura P, Raptopoulou-Gigi M. Hepatitis B reactivation in a patient with rheumatoid arthritis with antibodies to hepatitis B surface antigen treated with rituximab. Hippokratia 2013; 17: 91-3. PubMed PMID: 23935355.

(64 year old woman with resolved hepatitis B and rheumatoid arthritis developed reactivation of HBV 2 years after starting rituximab and methotrexate [bilirubin not given, ALT 605 U/L, GGT 154 U/L, HBsAg and HBeAg positive despite presence of anti-HBs], with rapid loss of HBsAg and resolution of enzyme elevations within 6 months of stopping chemotherapy and starting entecavir).

Matsui T, Kang JH, Nojima M, Tomonari A, Aoki H, Yamazaki H, Yane K, et al. Reactivation of hepatitis B virus in patients with undetectable HBsAg undergoing chemotherapy for malignant lymphoma or multiple myeloma. J Med Virol 2013; 85: 1900-6. PubMed PMID: 23926082.

(Among 109 Japanese patients who were HBsAg negative and underwent chemotherapy for malignancy and were followed with monthly testing for HBV DNA, 4 of 59 [7%] with anti-HBc, but no other patient developed HBV reactivation, all 4 received rituximab and corticosteroids, during chemotherapy in 3 and afterwards in 1, none developed HBsAg or ALT elevations and all recovered, 2 with entecavir therapy).

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).

Zachou K, Sarantopoulos A, Gatselis NK, Vassiliadis T, Gabeta S, Stefos A, Saitis A, et al. Hepatitis B virus reactivation in hepatitis B virus surface antigen negative patients receiving immunosuppression: A hidden threat. World J Hepatol 2013; 5: 387-92. PubMed PMID: 23898372.

(Retrospective analysis of 14 Greek HBsAg-negative patients who developed HBV reactivation after immunosuppression identified 10 with anti-HBc alone and 4 with both anti-HBc and anti-HBs before therapy, 11 received rituximab, all developed HBV DNA and ALT elevations 6 to 48 months after starting chemotherapy, 2 developed chronic hepatitis B, 3 developed acute liver failure and 2 died).

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).

Kusumoto S, Tanaka Y, Mizokami M, Ueda R. Is antiviral prophylaxis necessary to prevent hepatitis B virus (HBV) reactivation in patients with HBV-resolved infection receiving rituximab-containing chemotherapy? J Clin Oncol 2013; 31: 4480. PubMed PMID: 24220561.

(Letter in response to Huang [2013] suggesting that monthly monitoring and early intervention with antiviral therapy may be a more cost effective means of dealing with HBV reactivation).

Oh MJ, Lee HJ. A study of hepatitis B virus reactivation associated with rituximab therapy in real-world clinical practice: a single-center experience. Clin Mol Hepatol 2013; 19: 51-9. PubMed PMID: 23593610.

(Retrospective analysis of 79 patients treated with rituximab found HBV reactivation in 4 of 12 patients with HBsAg [3 despite prophylaxis with lamivudine], and 2 of 67 [3%] with anti-HBc without HBsAg, both of whom died of acute liver failure).

Dong HJ, Ni LN, Sheng GF, Song HL, Xu JZ, Ling Y. Risk of hepatitis B virus (HBV) reactivation in non-Hodgkin lymphoma patients receiving rituximab-chemotherapy: a meta-analysis. J Clin Virol 2013; 57: 209-14. PubMed PMID: 23562041.

(Metaanalysis of 9 studies of reactivation of HBV in patients with non-Hodgkin lymphoma after chemotherapy found increased relative risk with rituximab [1.6 in HBsAg-positive and 5.5 in HBsAg-negative, anti-HBc-positive patients] compared to standard chemotherapy without rituximab).

Droz N, Gilardin L, Cacoub P, Berenbaum F, Wendling D, Godeau B, Piette AM, et al. Kinetic profiles and management of hepatitis B virus reactivation in patients with immune-mediated inflammatory diseases. Arthritis Care Res (Hoboken) 2013; 65: 1504-14. PubMed PMID: 23436730.

(Analysis of 35 cases of HBV reactivation in French patients with immune mediated diseases [23 with HBsAg; 12 with anti-HBc without HBsAg], arising 2 weeks to 7 years after starting therapy [86% on corticosteroids, 20% anti-TNF, 31% methotrexate, 11% rituximab], of whom 89% were symptomatic, but none developed acute liver failure or died from liver disease).

Feeney SA, McCaughey C, Watt AP, Agnaf MR, McDougall N, Wend UC, Gerlich WH et al. Reactivation of occult hepatitis B virus infection following cytotoxic lymphoma therapy in an anti-HBc negative patient. J Med Virol 2013; 85: 597-601. PubMed PMID: 23359331.

(71 year old man with lymphoma and no detectable HBsAg or anti-HBc developed reactivation of HBV with HBsAg and rising levels of HBV DNA 6 months after finishing a series of courses of rituximab, ultimately responding to tenofovir therapy, but never developing anti-HBc; molecular sequencing revealing an unusual genotype [D4] perhaps acquired in New Guinea).

Kavcic M, Fisher BT, Seif AE, Li Y, Huang YS, Walker D, Aplenc R. Leveraging administrative data to monitor rituximab use in 2875 patients at 42 freestanding children's hospitals across the United States. J Pediatr 2013; 162: 1252-8, 1258.e1. PubMed PMID: 23269206.

(In a retrospective analysis of 2875 children treated with rituximab for varying conditions in 42 US childrens hospitals, 6% developed sepsis, but only one had a discharge diagnosis of hepatitis B).

Wang YH, Fan L, Wang L, Zhang R, Xu J, Fang C, Li JY, et al. Efficacy of prophylactic lamivudine to prevent hepatitis B virus reactivation in B-cell lymphoma treated with rituximab-containing chemotherapy. Support Care Cancer 2013; 21: 1265-71. PubMed PMID: 23151650.

(In a retrospective analysis of 69 patients with lymphoma given prophylaxis with lamivudine during rituximab based chemotherapy, 1 of 38 with HBsAg, but none of 31 with anti-HBc without HBsAg, developed HBV reactivation; the one case being associated with lamivudine resistant HBV mutation and was anicteric, mild [peak ALT 278 U/L] and resolved with adefovir therapy).

Mitroulis I, Hatzara C, Kandili A, Hadziyannis E, Vassilopoulos D. Long-term safety of rituximab in patients with rheumatic diseases and chronic or resolved hepatitis B virus infection. Ann Rheum Dis 2013; 72: 308-10. PubMed PMID: 22930597.

(Among 41 patients with rheumatic diseases who were treated with rituximab, 2 were HBsAg positive and received antiviral prophylaxis and 19 had anti-HBc without HBsAg and were monitored on no prophylaxis; no patient developed HBV reactivation and anti-HBs titers were stable).

Tonziello G, Pisaturo M, Sica A, Ferrara MG, Sagnelli C, Pasquale G, Sagnelli E, et al. Transient reactivation of occult hepatitis B virus infection despite lamivudine prophylaxis in a patient treated for non-Hodgkin lymphoma. Infection 2013; 41: 225-9. PubMed PMID: 22855434.

(80 year old woman with non-Hodgkin lymphoma and anti-HBc without HBsAg developed asymptomatic reactivation of HBV 18 months after stopping CHOP-rituximab and 6 months after stopping lamivudine

[bilirubin and ALT normal, HBsAg positive and HBV DNA 8000 IU/mL], resolving without therapy within one month).

Liu CY, Chandrasekar PH, Masood A, Schiffer CA. Adherence to hepatitis B screening and prophylactic lamivudine for prevention of rituximab-associated hepatitis B reactivation. J Oncol Pharm Pract 2013; 19: 18-23. PubMed PMID: 22635416.

(Among 280 patients who received rituximab during an 18 month period at a single US medical center, screening for HBV markers was done on 84% of cancer and 58% of non-cancer patients; only one person was found to have HBsAg and he developed severe reactivation arising 6 months after rituximab chemotherapy despite lamivudine therapy [bilirubin 28.2 mg/dL, ALT 777 U/L, HBV DNA 2180 IU/mL], recovering after switching to tenofovir therapy).

Chew E, Thursky K, Seymour JF. Very late onset hepatitis-B virus reactivation following rituximab despite lamivudine prophylaxis: the need for continued vigilance. Leuk Lymphoma 2014; 55: 938-9. PubMed PMID: 23772645.

(64 year old man with HBsAg [without HBV DNA and with normal enzymes] and Waldenstrom macroglobulinemia received prophylaxis with lamivudine during and for 12 months after a 2 year course of chlorambucil and rituximab, but developed reactivation of hepatitis B 6 months later [ALT 2260 U/L, HBV DNA 28,812 IU/mL], resolving rapidly with tenofovir therapy).

Tamori A, Hino M, Kawamura E, Fujii H, Uchida-Kobayashi S, Morikawa H, Nakamae H, et al. A prospective long-term study of hepatitis B virus reactivation in patients with hematologic malignancy. J Gastroenterol Hepatol 2014; 29: 1715-21. PubMed PMID: 24730465.

(Among patients with anti-HBc without HBsAg not receiving prophylaxis, reactivation of HBV occurred in 26% of 19 patients undergoing HCT [onset at 9-36 months] and 10% of 30 patients given rituximab based chemotherapy [onset after 2-10 months], all of whom had anti-HBs titers below 200 mIU/mL before therapy and all of whom were successfully treated with entecavir).

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 published by the FDA in September 2013, based upon 109 spontaneous reports of fatal HBV reactivation, 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).

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: 694-701. 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).

Ronan BA, Agrwal N, Carey EJ, De Petris G, Kusne S, Seville MT, Blair JE, et al. Fulminant hepatitis due to human adenovirus. Infection 2014; 42: 105-11. PubMed PMID: 23979854.

(70 year old woman with CLL treated with fludarabine and rituximab developed fever and lymphopenia 3 months after stopping treatment [peak bilirubin 5.4 mg/dL, ALT 1699 U/L, Alk P 282 U/L], dying of multiorgan failure on day 13, liver biopsy showing adenoviral positive viral inclusions).

Yang F, Zhu HL, He C, Li JJ, Xiang B, Cui X, Huang J, et al. Effect of antiviral prophylaxis strategy for chemotherapy-associated hepatitis B reactivation in non-Hodgkin's lymphoma patients with hepatitis B virus infection: A retrospective cohort study. Indian J Hematol Blood Transfus 2014; 30: 97-104. PubMed PMID: 24839363.

(Retrospective analysis of rates of reactivation of HBV among Chinese patients with non-Hodgkin lymphoma treated with chemotherapy found lower rates with antiviral prophylaxis).

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. 24944464. 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).

Buensalido JA, Chandrasekar PH. Prophylaxis against hepatitis B reactivation among patients with lymphoma receiving rituximab. Expert Rev Anti Infect Ther 2014; 12: 151-4. PubMed PMID: 24341369.

(Review of guidelines regarding screening for HBV and management of patients with lymphoma receiving rituximab; recommends screening for HBsAg, anti-HBc and anti-HBs, providing prophylaxis with antivirals for patients with HBsAg, and close monitoring of those with anti-HBc without HBsAg applying antiviral therapy if HBV reactivation occurs).

Huang H, Li X, Zhu J, Ye S, Zhang H, Wang W, Wu X, et al. Entecavir vs lamivudine for prevention of hepatitis B virus reactivation among patients with untreated diffuse large B-cell lymphoma receiving R-CHOP chemotherapy: a randomized clinical trial. JAMA 2014; 312: 2521-30. PubMed PMID: 25514302.

(Among 121 HBsAg-positive patients with B cell lymphoma treated with rituximab-CHOP given prophylaxis with either entecavir or lamivudine, reactivation of HBV occurred in 4 of 61 [7%] given entecavir, none of whom developed hepatitis and 18 of 60 [30%] given lamivudine, 8 of whom developed HBV related hepatitis, one of which was fatal [arising after lamivudine was stopped]).

Jo T, Horio K. Severe liver damage and nonallergic bronchitis with eosinophilia in a patient with follicular lymphoma treated with bendamustine plus rituximab. Case Rep Oncol 2014; 7: 497-502. PubMed PMID: 25232317.

(66 year old woman with lymphoma developed hepatitis and unexplained cough and bronchitis after a single cycle of bendamustine and rituximab [peak bilirubin 6.2 mg/dL, ALT 577 U/L, Alk P 947 U/L, eosinophils 36%], resolving within 2 months with corticosteroid therapy; the role of rituximab vs bendamustine being unclear).

Tsuji H, Yoshifuji H, Fujii T, Matsuo T, Nakashima R, Imura Y, Yukawa N, et al. Visceral disseminated varicella zoster virusinfection after rituximab treatment for granulomatosis with polyangiitis. Mod Rheumatol 2017: 27: 155-61. PubMed PMID: 25159158.

(30 year old Japanese woman with granulomatosis with polyangiitis developed rash, fever and abdominal pain 2 months after starting prednisolone and rituximab [bilirubin not given, ALT 484 U/L, INR 1.63, platelets 25,000/uL], dying of disseminated coagulopathy, autopsy showing disseminated VSV infection).

Salah-Eldin MA, Ebrahim MA, El-Sadda W. Clinical outcome of HCV-positive patients with diffuse large B-cell lymphoma treated with rituximab-based chemotherapy. Ann Hematol 2014; 93: 1903-11. PubMed PMID: 24951125.

(Among 280 patients with chronic hepatitis C and diffuse large B-cell lymphoma, evidence of liver injury [ALT elevations] arose in 68% those receiving rituximab and 54% receiving chemotherapy without rituximab; ALT elevations >5 times ULN occurring in 27% vs 14%]).

Viganò M, Mangia G, Lampertico P. Management of patients with overt or resolved hepatitis B virus infection undergoing rituximab therapy. Expert Opin Biol Ther 2014; 14: 1019-31. PubMed PMID: 24909454.

(Review and expert recommendations on the use of antiviral agents as prophylaxis against reactivation during therapy with rituximab).

Kusumoto S, Tanaka Y, Suzuki R, Watanabe T, Nakata M, Takasaki H, Fukushima N, et al. Monitoring of hepatitis B virus (HBV) DNA and risk of HBV reactivation in B-cell lymphoma: a prospective observational study. Clin Infect Dis 2015; 61: 719-29. PubMed PMID: 25935551.

(Among 223 patients with B cell lymphoma who had anti-HBc and/or anti-HBs without HBsAg in serum, monthly monitoring for HBV DNA during rituximab based chemotherapy, 21 developed rising levels of HBV DNA [8.3% at 1.5 years], generally within 2-6 months, but 2 after 1 year; all had anti-HBc at baseline and all responded to entecavir therapy with rapid loss of HBV DNA and none developed hepatitis).

Hua Q, Zhu Y, Liu H. Severe and fatal adverse events risk associated with rituximab addition to B-cell non-Hodgkin's lymphoma (B-NHL) chemotherapy: a meta-analysis. J Chemother 2015; 27: 365-70. PubMed PMID: 25872413.

(Systematic review of controlled trials of rituximab therapy of B cell non-Hodgkin lymphoma for rates of severe adverse events found higher rates of fatal infections, but no significant differences in rates of other severe adverse events, including liver failure).

Bauer H, Luxembourger C, Gottenberg JE, Fournier S, Abravanel F, Cantagrel A, Chatelus E, et al.; Club Rhumatismes et Inflammation, a section of the French Society of Rheumatology. Outcome of hepatitis E virus infection in patients with inflammatory arthritides treated with immunosuppressants: a French retrospective multicenter study. Medicine (Baltimore) 2015; 94: e675. PubMed PMID: 25860212.

(Survey of French physicians treating patients with rheumatic diseases identified 23 patients who developed acute hepatitis E while being treated with immunosuppressive regimens [10 on anti-TNF, 4 rituximab, 2 abatacept, 2 tocilizumab and 16 receiving methotrexate, 4 leflunomide and 1 cyclosporine]; all recovered and cleared HEV RNA, some after reduction in immunosuppression and 5 with ribavirin 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).

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, 49 were attributed to antineoplastic agents [5.5%], but none were attributed to rituximab or to HBV reactivation).

Hsu PI, Lai KH, Cheng JS, Kao SS, Li YR, Sun WC, Chen WC, et al. Prevention of acute exacerbation of chronic hepatitis B infection in cancer patients receiving chemotherapy in a hepatitis B virus endemic area. Hepatology 2015; 62: 387-96. PubMed PMID: 26041578.

(Introduction of a computerized entry based alert system improved the frequency of screening of patients for hepatitis B before receiving cancer chemotherapy).

Cho Y, Yu SJ, Cho EJ, Lee JH, Kim TM, Heo DS, Kim YJ, et al. High titers of anti-HBs prevent rituximab-related viral reactivation in resolved hepatitis B patient with non-Hodgkin's lymphoma. J Med Virol 2016; 88: 1010-7. PubMed PMID: 26531242.

(Among 108 patients with lymphoma treated with rituximab based chemotherapy who had anti-HBc without HBsAg, reactivation of HBV occurred in none of 51 with high titers of anti-HBs [above 100 IU/mL] compared to 8 of 57 [14%] with low titers, and in none of 39 who received prophylaxis with antiviral agents active against HBV; only 1 of 8 cases was fatal).

Varisco V, Viganò M, Batticciotto A, Lampertico P, Marchesoni A, Gibertini P, Pellerito R, et al. Low risk of hepatitis B virus reactivation in HBsAg-negative/anti-HBc-positive carriers receiving rituximab for rheumatoid arthritis: a retrospective multicenter Italian study. J Rheumatol 2016; 43: 869-74. PubMed PMID: 26879359.

(Among 33 patients with rheumatoid arthritis and anti-HBc without HBsAg in serum who received rituximab, 6 had decreases in anti-HBs titers, but only 1 developed low levels of HBV DNA [and was treated with lamviduine], and none developed HBsAg or hepatitis).

Yilmaz B. Fulminant hepatitis B as a result of reactivation in hematologic patient after rituximab therapy. J Med Virol 2016; 88: 1289-90. PubMed PMID: 27249067.

(64 year old man with lymphoma with anti-HBc and anti-HBs [titer 88 IU/mL] without HBsAg in serum developed fatal reactivation of HBV 10 months after starting and 2 months after stopping riituximab based chemotherapy).

Seto WK, Wong DK, Chan TS, Hwang YY, Fung J, Liu KS, Gill H, et al. Association of hepatitis B core-related antigen with hepatitis B virus reactivation in occult viral carriers undergoing high-risk immunosuppressive therapy. Am J Gastroenterol 2016; 111: 1788-95. PubMed PMID: 27644733.

(Among 124 patients with anti-HBc without HBsAg in serum who received rituximab or underwent hematopoietic cell transplantation, 31 developed reactivation of HBV at a rate of 40% by 2 years, rates being higher in those who tested positive for HBcrAg at baseline [72%] than those who were negative [31%]).

Hayashi K, Ishigami M, Ishizu Y, Kuzuya T, Honda T, Tachi Y, Ishikawa T, et al. Clinical characteristics and molecular analysis of hepatitis B virus reactivation in hepatitis B surface antigen-negative patients during or after immunosuppressive or cytotoxic chemotherapy. J Gastroenterol 2016; 51: 1081-9. PubMed PMID: 26943169.

(Clinical description of 30 HBsAg-negative patients who developed reactivation of HBV after cancer or immunosuppressive therapy).

Castelli R, Ferraris L, Pantaleo G, Lambertenghi Deliliers G, Cicardi M. High rate of hepatitis B viral breakthrough in elderly non-Hodgkin lymphomas patients treated with rituximab based chemotherapy. Dig Liver Dis 2016; 48: 1394-7. PubMed PMID: 27590841.

(Among 85 elderly patients with non-Hodgkin lymphoma with anti-HBc without HBsAg in serum, 9 [10%] developed reactivation of HBV despite receiving lamivudine prophylaxis, but all responded to treatment with entecavir).

Torres HA, Hosry J, Mahale P, Economides MP, Jiang Y, Lok AS. Hepatitis C virus reactivation in patients receiving cancer treatment: A prospective observational study. Hepatology 2018; 67: 36-47. PubMed PMID: 28653760.

(Among 100 patients with chronic hepatitis C and cancer, 23 had a greater than 1 log10 rise in HCV RNA during cancer chemotherapy, 10 of whom had a concurrent flare of hepatitis and 6 of whom required at least transient delay of chemotherapy; rises in HCV RNA were associated with hematologic malignancy, use of rituximab and exposure to high dose corticosteroids).

Bajema KL, Simonson PD, Greninger AL, Çoruh B, Pottinger PS, Bhattacharya R, Liou IW, et al. Acute liver failure due to Echovirus 9 associated with persistent B-cell depletion from rituximab. Open Forum Infect Dis 2017; 4: ofx174. PubMed PMID: 28948184.

(19 year old man with nephrotic syndrome treated with corticosteroids and rituximab for 3 years developed relapsing meningoencephalitis followed by acute liver failure, ultimately attributed to Echovirus 9 infection in the setting of B cell depletion and severe hypogammaglobulinemia).

Buti M, Manzano ML, Morillas RM, García-Retortillo M, Martín L, Prieto M, Gutiérrez ML, et al. Randomized prospective study evaluating tenofovir disoproxil fumarate prophylaxis against hepatitis B virus reactivation in anti-HBc-positive patients with rituximab-based regimens to treat hematologic malignancies: The Preblin study. PLoS One 2017; 12: e0184550. PubMed PMID: 28898281.

(Among 61 patients with lymphoma treated with rituximab who had anti-HBc without HBsAg in serum, reactivation occurred in none of 33 patients treated with tenofovir vs 3 of 28 [11%] who were closely monitored, 2 of whom were rapidly treated with tenofovir, the third having a mild anicteric hepatitis).

Wood PR, Caplan L. Drug-induced gastrointestinal and hepatic disease associated with biologics and nonbiologic disease-modifying antirheumatic drugs. Rheum Dis Clin North Am 2018; 44: 29-43. PubMed PMID: 29149926.

(Review of gastrointestinal and hepatic side effects of antirheumatic drugs mentions the risk of reactivation of hepatitis B with rituximab therapy in susceptible patients).

Khan ZH, Ilyas K, Ghazanfar H, Khan HH, Hussain Q, Hammad S, Munir A, et al. Fatal fulminant hepatitis from rituximab-induced hepatitis B reactivation in a patient with follicular lymphoma: A case report and a brief review of literature. Cureus 2018; 10: e2257. PubMed PMID: 29725560.

(79 year old man with lymphoma developed fatal reactivation of HBV two months after completing chemotherapy with rituximab, cyclophosphamide, vincristine and prednisone [bilirubin 29.3 mg/dL, ALT 2122 U/L, INR 5.9, HBsAg and HBeAg positive, HBV DNA 4.53 milion IU/mL]).

Kelling M, Sokol L, Dalia S. Hepatitis B reactivation in the treatment of non-Hodgkin lymphoma. Cancer Control 2018; 25: 1073274818767879. PubMed PMID: 29606020.

(Review of reactivation of hepatitis B in patients with non-Hodgkin lymphoma recommends screening patients for HBsAg and anti-HBc and giving prophylaxis with entecavir or tenofovir in patients at high risk for reactivation).

Yeo D, Hossain I, Lim ST, Farid M, Tao M, Quek R, Tang T, et al. Management of hepatitis B reactivation in lymphoma patients on rituximab with past hepatitis B exposure: An observational study. J Oncol Pharm Pract 2018 Jan 1. [Epub ahead of print] PubMed PMID: 29554828.

(Among 75 patients with anti-HBc without HBsAg who received rituximab based therapy for lymphoma, 3 patients developed reactivation and there was wide variation in the use of antiviral prophylaxis and the degree of monitoring during therapy and in follow up).