

Anti-CD20 monoclonal antibodies and associated viral hepatitis in hematological diseases

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clonal antibodies potentially lead to severe viral infections, such as hepatitis B virus (HBV), hepatitis C virus (HCV), parvovirus B19, and herpes viruses, in patients who are undergoing immune therapy or immunotherapy. Of these infections, HBV- and HCV-related hepatitis are a great concern in endemic areas because of the high morbidity and mortality rates in untreated patients. As a result, prophylaxis against HBV infection is becoming a standard of care in these areas. Parvovirus B19, a widespread pathogen that causes red blood cell aplasia in immunocompromised hosts, also causes hepatitis in healthy individuals. Recently, its association with hepatitis was recognized in a patient treated with rituximab. In addition, adenovirus, varicella-zoster virus, hepatitis E virus, and rituximab itself have been linked to the occurrence of hepatitis during or after rituximab treatments. The epidemiologies and pathogenesis of these etiologies remain unknown. Because of the increasing use of anti-CD20 monoclonal antibodies for the treatment of hematological malignancies or autoimmune hematological disorders, it is imperative that physicians understand and balance the risks of hepatotropic virus-associated hepatitis against the benefits of using anti-CD20 monoclonal antibodies.

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Key words: CD20; Monoclonal antibody; Hepatitis; Hepatitis B virus; Hepatitis C virus

Abstract

Over the past decade, the administration of anti-CD20 monoclonal antibodies such as rituximab has demonstrated various degrees of effectiveness and has improved patients' outcomes during the treatment of autoimmune hematological disorders and hematological malignancies. However, the depletion of B-cells, the distribution of T-cell populations, and the reconstruction of host immunity resulting from the use of anti-CD20 mono-

Core tip: Anti-CD20 monoclonal antibodies are widely used for the treatment of hematological malignancies and autoimmune disorders. These agents produce prolonged B-cell depletion and significant immune suppression. In this review, we summarized the clinical use of anti-CD20 monoclonal antibodies and the reports of acute or chronic hepatitis associated with the use of these agents. Most of these hepatitis cases had viral etiologies. We discuss the mechanisms of the hepatitis caused by these drugs. These infections not only interrupted the immunotherapy but are also associated with high mortality and morbidity.

This review may prompt physicians to monitor patients' liver function more closely and to provide adequate prophylaxis while using these agents.

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INTRODUCTION

The nonglycosylated transmembrane phosphoprotein CD20 is a differentiation marker of B cells that was characterized over 30 years ago^[1]. CD20 is expressed from early pre-B cells to mature B cells but not in plasma cells^[2]. The majority of B-cell lymphomas variably express the CD20 surface marker^[3]. CD20 can form multimeric complexes^[4,5], interact with B-cell receptors in lipid rafts^[5-7], mediate calcium influx^[4,7], and regulate the cell cycle and apoptosis^[8-11].

Because of the ubiquitous expression of CD20 in normal and malignant B cells, CD20 is an excellent target molecule for the treatment of B cell-related diseases. Rituximab, a genetically engineered chimeric murine/human monoclonal antibody (mAb)-targeting CD20, contains murine light- and heavy-chain variable regions and human constant regions^[12]. Rituximab is used to exert cytotoxic effects on B cells by 3 mechanisms: antibody-dependent cell-mediated cytotoxicity (ADCC), complement-mediated lysis (CDC), and a direct apoptosis-inducing effect on CD20⁺ cells^[12,13].

Based on a pivotal trial, rituximab was first approved by the United States Food and Drug Administration in 1997 for relapsed or refractory follicular and low-grade B-cell non-Hodgkin's lymphoma (NHL)^[14]. New anti-CD20 mAbs have been developed over the last few years, and these mAbs have been classified into 2 groups (type I and type II) according to their different activities in inducing CDC, ADCC, apoptosis, and lipid raft redistribution while binding to CD20^[15,16]. Because anti-CD20 mAbs have optimized antibody structures and sometimes conjugated radioisotopes, they are used and indicated for the treatment of not only hematological malignancies but also autoimmune diseases^[17]. However, following the widespread use of these agents, reports of infections related to B-cell depletion began to appear increasingly. Here, we discuss the clinical applications, the immunocompromising effects, and the association with hepatitis of anti-CD20 mAbs.

APPLICATIONS OF ANTI-CD20 MABS IN HEMATOLOGICAL DISEASES

Malignancies

Rituximab, the first mAb approved for the treatment

of malignancies, was initially indicated for relapsed or refractory indolent B-cell NHL^[14]. In this pivotal trial, the schedule consisted of 4 weekly doses of 375 mg/m². Nearly half of the 166 patients responded, with a projected median time-to-progression of 13 mo. Infusion reactions were the most frequently encountered acute adverse event^[14]. The promising response and excellent tolerance to rituximab in indolent B-cell NHL cases were further demonstrated in clinical trials involving extended use and retreatment^[18,19]. The excellent single-agent activity of rituximab was demonstrated not only in relapsed or refractory cases but also in newly diagnosed indolent B-cell NHL cases. In a phase II trial of single-agent rituximab for patients with low-grade NHL, the initial response rate (RR) after 4 weekly doses of rituximab was 54%, and the RR improved to 64% when rituximab retreatment was administered^[20]. In addition to rituximab monotherapy, several studies have demonstrated that the combination of rituximab and chemotherapeutic agents provided high RRs and long time-to-progression in relapsed, refractory, or newly diagnosed indolent B-cell NHL cases^[21-25]. To prolong disease control after the initial treatment, maintenance therapies after initial chemotherapy alone^[21,26] or rituximab in addition to chemotherapy^[21,27,28] have been tested in relapsed, refractory, or newly diagnosed indolent B-cell NHL cases. All of these studies demonstrated considerable improvement in the response duration or progression-free survival^[21,26-28]. Moreover, the clinical successes of rituximab were partially recapitulated in diffuse large B-cell lymphoma (DLBCL)^[29-35]. The benefits of maintenance therapy were not observed after first-line chemotherapy with or without rituximab or autologous stem-cell transplantation used for treating cases of relapsed DLBCL^[34,35]. The difference may reflect the distinct nature of the indolent and aggressive B-cell NHLs.

Because of the clinical benefits demonstrated in rituximab-based regimens, efforts have been made to improve the efficacy of rituximab through the development of new anti-CD20 mAbs or the conjugation of radioisotopes (Table 1). Overall, the administration of yttrium-90 ibritumomab tiuxetan or iodine-131 tositumomab radioimmunotherapy (RIT) has not consistently yielded improved efficacy and survival in relapsed, refractory, or newly diagnosed B-cell NHL cases^[36-44]. However, the use of RIT, which offers the theoretical benefits of radiotherapy, can be a viable option for patients who have not responded to prior rituximab treatments or as an alternative or a supplemental method to stem-cell transplantation. Second- and third-generation humanized anti-CD20 mAbs were designed with improved binding affinities for CD20 or the FcγRIIIa receptor for enhanced CDC or ADCC. The efficacy of these agents was also investigated with or without chemotherapy in relapsed, refractory, or newly diagnosed B-cell NHL cases^[45-59]. Details regarding these anti-CD20 mAbs are summarized in Table 1.

Autoimmune hematological diseases

The essential mechanism of autoimmune diseases is the

Table 1 Anti-CD20 monoclonal antibodies and associated hepatitis

Antibody	Structure	Clinical applications	Associated hepatitis	Ref.
Rituximab	IgG1, chimeric murine/human mAb	B-cell NHL, RA, SLE, MS, AIHA, TTP, ITP, acquired hemophilia, cryoglobulinemia	HBV, HCV, parvovirus B19, VZV, adenovirus, HEV, drug-related? HBV	[14,18-35,60-65,71, 73,74,78,85,89-93,102-111, 140-147,172,174-179] [36-38,112]
Y-90 ibritumomab tiuxetan	IgG1, mouse mAb, conjugated with tiuxetan to yttrium-90	B-cell NHL	None	[39-44]
I-131 tositumomab	IgG2, mouse mAb, covalently bound to iodine-131	CLL, B-cell NHL, RA, MS, AIHA	HBV or drug-related?	[45-50,68,114-116]
Ofatumumab	IgG1, human mAb	B-cell NHL, ITP	Drug-related?	[51,69]
Veltuzumab	IgG1, humanized mAb	B-cell NHL, RA, SLE, MS	None	[52]
Ocrelizumab	IgG1, humanized mAb	CLL, B-cell NHL	Drug-related?	[53-57]
Obinutuzumab	IgG1, humanized mAb, modified Fc	CLL, B-cell NHL	None	[58]
PRO131921	IgG1, humanized mAb, modified Fc	B-cell NHL	None	[59]
Ocaratuzumab	IgG1, humanized mAb, modified Fc			

mAb: Monoclonal antibody; NHL: Non-Hodgkin lymphoma; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; MS: Multiple sclerosis; AIHA: Autoimmune hemolytic anemia; TTP: Thrombotic thrombocytopenic purpura; ITP: Immune thrombocytopenic purpura; DM: Diabetes mellitus; HBV: Hepatitis B virus; HCV: Hepatitis C virus; VZV: Varicella-zoster virus; HEV: Hepatitis E virus; CLL: Chronic lymphocytic leukemia; None: No associated hepatitis reported in hematological autoimmune disorders or malignancies at the time of review (excluding non-hematological diseases).

loss of self-tolerance, which enables the immune system to evoke autoreactive humoral and cellular responses. Elimination of B cells with rituximab is effective in the treatment of autoimmune hematological diseases such as autoimmune hemolytic anemia (AIHA)^[60], immune thrombocytopenic purpura (ITP)^[61], acquired hemophilia^[62], thrombotic thrombocytopenic purpura (TTP)^[63], and cryoglobulinemia^[64,65]. B cells produce autoantibodies and cytokines, act as antigen-presenting cells, promote naïve CD4⁺ T-cell differentiation, and affect dendritic cell homeostasis^[66]. However, the responses of these autoimmune diseases to the off-label use of rituximab varied widely^[67]. The varied results may be partially attributed to the underlying heterogeneity in the etiologies and pathogenesises of these diseases.

The data about the use of non-rituximab anti-CD20 mAbs for the treatment of autoimmune diseases are extremely limited. RIT may also be a valuable option, but its use for the treatment of autoimmune hematological diseases has not been reported. Ofatumumab, approved by the US Food and Drug Administration for treating chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab, was demonstrated to be effective in CLL complicated with AIHA^[68]. In a phase I trial, veltuzumab demonstrated a RR of 55% in relapsed ITP cases, and long durations of response were observed in some patients^[69]. Second- and third-generation humanized anti-CD20 mAbs are being developed for treating nonhematological autoimmune disorders, such as rheumatoid arthritis, systemic lupus erythematosus (SLE), and multiple sclerosis.

HEPATITIS RELATED TO RITUXIMAB AND OTHER ANTI-CD20 MABS

Immune system changes after anti-CD20 mAb treatments

In general, peripheral blood B cells are depleted rapidly

and effectively after anti-CD20 mAb treatment. The level of peripheral B cells remains extremely low and recovers gradually until 6 to 12 mo after the last dose of rituximab^[61-65,70,71]. The depletion or recovery of B cells is not uniform among the various subsets and locations of B cells and may also depend on the baseline B-cell counts, the nature of the disease, and the dose, duration and type of anti-CD20 mAbs used^[36,40,45,46,49-53,55,56,65,71,72]. The recovery of B cells starts with the immature or transitional B cells (CD38⁺, CD24⁺, CD10⁺, CD27⁺, IgD⁺) followed by naïve B cells (CD38⁺, CD27⁺, IgD⁺); however, memory B cells (CD27⁺, CD38⁺, IgD⁺) may remain considerably depleted for at least 2 years^[73-76]. The pattern of B-cell repopulation is similar between autoimmune disease and B-cell NHL cases^[73-76]. The effects of B-cell depletion on plasma immunoglobulin levels and blunted responses to immunization are individualized and heterogeneous among the different diseases treated with rituximab^[18,19,21,29,60-65,70,77-80]. Typically, the levels of complements do not change substantially^[64,70], but a major increase of C4 levels in the serum was noted after rituximab treatment in type II mixed cryoglobulinemia cases^[65]. The levels, subsets, and functional status of T cells and natural killer (NK) cells after rituximab treatment are more complex because these factors depend on the expression of CD20 on T and NK cells^[74] and the nature of the disease process^[17,18,45,46,61,62,64,74,81-87]. Early and persistent reduction of peripheral CD4⁺/CD40L⁺ T cells was observed after treatment of SLE with rituximab^[84]. The abnormalities of T-cell homeostasis can be reversed after rituximab administration^[81-83,87], accompanied by increased CD4⁺CD25⁺ regulatory T cells^[82,84,85,87], CD8⁺CD25⁺ T cells^[85], or decreased autoreactive CD4⁺ T cells^[81]. In a mouse model, B-cell depletion inhibited CD4⁺ but not CD8⁺ T-cell activation and clonal expansion in response to new exogenous antigens. Therefore, adequate antigen-specific CD4⁺ T-cell responses still

required the presence of B cells^[88]. The limited data on T cell, NK cell, complement, and immunoglobulin levels following treatments with anti-CD20 mAbs other than rituximab were highly similar compared with those with rituximab^[36,51-54,69]. Because of the immunodeficiency induced by anti-CD20 mAbs, hepatitis and other infections have become a growing concern since the approval of rituximab.

Hepatitis B virus

Acute hepatitis and even fulminant hepatic failure are a well-documented threat in patients receiving chemotherapy, particularly in lymphoma cases^[89]. In a prospective study, 44% (34/78) of hepatitis B virus (HBV; hepatitis B surface antigen, HBsAg⁺) carriers developed some form of hepatitis. Of these cases, 44% (15/34) were attributed to HBV reactivation^[89]; 6 of these 15 were patients with lymphoma, and all of them had been treated with adriamycin, cyclophosphamide, vincristine, and prednisolone, also known as the CHOP regimen^[89]. In addition, 4 of these 6 patients with lymphoma were seropositive for hepatitis B e antigen (HBeAg) at baseline and developed HBV reactivation sooner than the HBeAg-negative carriers^[89]. In addition to those observations in lymphoma cases, HBV reactivation has been frequently reported in other hematological malignancies^[90]. Corticosteroids, which are immunosuppressive agents frequently used in hematological malignancies and autoimmune diseases, may increase the risk of liver injury in HBV carriers^[90,91]. Steroid-sparing regimens can be used to reduce the risk of HBV reactivation^[92]. Additionally, adriamycin, a component of the CHOP regimen, can stimulate the replication of HBV^[93]. Because the use of anti-CD20 mAb is common, designing a treatment plan that prevents the risk of HBV reactivation may be more complex than administering chemotherapy for hematological malignancies or immunosuppressants for autoimmune diseases.

The natural history of HBV infection depends on the interaction of the host immunity, hepatocytes, and viral replication. Chronic HBV infections acquired early in life have 3 phases: the immune tolerance phase, the immune active phase, and the low-replication phase^[94-96]. Some inactive HBV carriers (HBeAg seroconversion) can unexpectedly reenter the immune clearance phase and experience HBV reactivation with elevated HBV DNA and/or HBeAg reversion^[97]. The incidence of HBV flares varies among studies and may depend on sex, HBV genotype, age at HBeAg seroconversion, and HBV DNA levels^[96,97]. In adults, NK cells and type I interferon responses induced by HBV infection were observed before HBV-specific CD4⁺ and CD8⁺ T-cell responses^[98]. In chronic HBV infections, HBV-specific CD8⁺ T cells presented HBV antigens regardless of the status of antibody to hepatitis B core antigen (anti-HBc)^[99]. Both anti-HBc⁺ patients and inactive HBV carriers exhibited strong memory CD8⁺ T-cell responses^[99]. However, the levels of FoxP3⁺, CD25⁺, and CD4⁺ regulatory T cells that inhibit HBcAg-specific responses were also higher in chronic HBV infection cases^[100].

HBV replication within the liver and the subsequent spread of virions into the circulation may occur in cancer patients with immunosuppression induced by the diseases or treatments. Hepatitis flares can develop early or late, during immunosuppressive therapy or after its completion. The effects can range from asymptomatic elevation of HBV DNA to fulminant hepatitis. HBV reactivation has been reported not only in patients undergoing chemotherapy or steroid therapy but also in patients undergoing rituximab treatment, regardless of their HBV status^[101-104]. In HBsAg⁺ carriers with B-cell NHL, HBV reactivation occurred in 80% (8/10) of patients without prophylaxis^[105]. Significantly fewer cases of HBV reactivation were consistently observed in HBsAg⁺ carriers with prophylaxis^[101]. In patients with resolved HBV (HBsAg⁻/anti-HBc⁺) and B-cell NHL, the rituximab-CHOP regimen led to more cases of HBV reactivation (reverse seroconversion or elevated HBV DNA) than the CHOP regimen alone did (23.8% *vs* 0%)^[102]. The incidence rates of HBV reactivation and HBV hepatitis flare were reported as 10.4 and 6.4 per person-year in this group of patients, respectively^[106]. The timing of HBV reactivation is closely associated with the lymphopenic state. The reconstruction of host immunity induced by rituximab and the recovery of B- and T-lymphocytes after rituximab may result in damage to HBV-infected hepatocytes by cytotoxic T-lymphocytes^[90,104,106,107]. The impairment of the immune system appears to be more severe in patients treated with rituximab-CHOP than in those treated with rituximab alone^[107].

Rituximab treatments, with or without steroids, were generally well-tolerated by patients with autoimmune hematological disorders such as AIHA^[60,108], ITP^[61,109], acquired hemophilia^[62], TTP^[63], and cryoglobulinemia^[64,65]. No HBV reactivation was reported, most likely because of the exclusion of patients with positive HBV serology, a limited number of cases, or lesser immunosuppression in these autoimmune diseases compared with hematological malignancies. However, HBV reactivation is a major threat in patients with autoimmune disorders who are undergoing immunosuppressive therapy^[110]; therefore, concurrent antiviral treatments are often prescribed to reduce the risk of reactivation^[111].

Patients with chronic or resolved HBV receiving RIT or anti-CD20 mAbs are subject to the same or an even greater risk of HBV reactivation, and although these effects were not fully characterized in most prospective trials^[36-59], scattered cases have been reported^[111,112], both of which were successfully treated with lamivudine^[112,113]. The United States Food and Drug Administration announced that physicians should be alert to potential HBV reactivation caused by ofatumumab^[114]. Liver toxicities had been reported with ofatumumab with or without chemotherapy in hematological malignancies. However, the data on HBV reactivation in these cases were lacking^[45,50,115,116].

HBV is endemic in the Asia-Pacific region with a prevalence of more than 10% in Taiwan, southern China, and certain areas of Southeast Asia^[117]. In clinical prac-

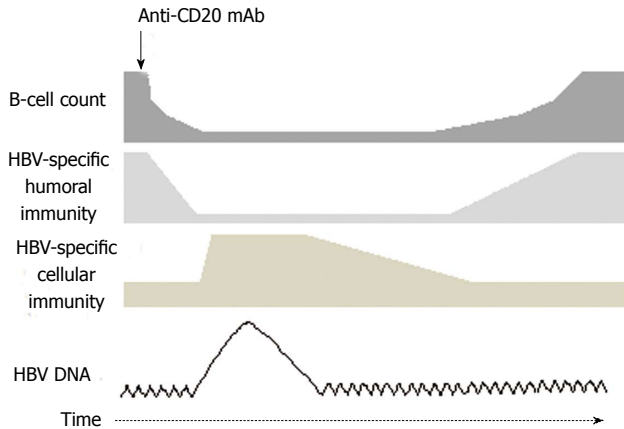


Figure 1 Anti-CD20 monoclonal antibodies and dynamic immunity in hepatitis B virus infection. This illustration summarizes the dynamic changes of hepatitis B virus (HBV) DNA and immune responses during HBV reactivation. Notably, the viral-specific T-cell immunity before and after the administration of anti-CD20 monoclonal antibody (mAb) depends on the carrier status, that is, hepatitis B surface antigen (HBsAg)⁺ carrier or resolved HBV (anti-HBc/HBsAg⁺, anti-HBs⁺ or ⁻) status. HBV prophylaxis should be considered to maintain low level of HBV replication and prevent HBV-specific T-cell-mediated liver damage. The prophylaxis should be maintained for at least 6 mo after anti-CD20 mAb when HBV-specific T-cell immunity recovers.

tice, a greater than 10-fold increase above the baseline in serum HBV DNA levels, an absolute increase of more than 9 log₁₀ copies/mL, a reappearance of HBV DNA in HBsAg, or a new onset of HBV DNA viremia in HBsAg-negative patients can be considered as an indication of HBV reactivation. In addition, an hepatitis flare is considered if the serum alanine transaminase (ALT) level is 3 times greater than the normal upper limit, or if an ALT level of more than 100 IU/L with a concomitantly increased HBV DNA level of more than 10 times the typical level is detected^[89,118]. In high-risk endemic areas, HBV screening must be considered before implementing anti-CD20 mAb treatment^[119-123]. In a cost-effectiveness study, screening for HBsAg in all patients about to receive rituximab-CHOP treatment considerably reduced the rate of HBV reactivation and cost the least^[124]. The recommended tests for screening include HBsAg, anti-HBc, and anti-HBs (according to the CDC)^[122], HBsAg and anti-HBc (AASLD and EASL)^[121,125], and HBsAg with or without anti-HBc (ASCO)^[123]. A more complex algorithm for screening in different at-risk populations was proposed^[126]. Currently, oral agents approved for HBV treatment include lamivudine, adefovir, telbivudine, tenofovir, and entecavir. Based on research findings, the optimal start time and duration of HBV prophylaxis has not yet been determined^[119-123]; however, initiating short-term antiviral therapy before starting anti-CD20 mAb treatment appears to be beneficial and safe. In a randomized trial involving HBsAg⁺ patients with NHL, the prophylactic use of lamivudine reduced considerably the occurrence of HBV reactivation and hepatitis flares^[127]. In a meta-analysis, all-cause mortality, HBV reactivation, HBV-related mortality, and interruption of anti-CD20 mAb therapy were considerably reduced with lamivudine prophylaxis^[128]. One major problem of lamivudine, telbi-

vudine, and adefovir is that drug resistance and hepatitis flares increase with continuous use^[125,129]; therefore, the use of entecavir and tenofovir was suggested for longer duration of prophylaxis^[125]. In addition to HBsAg⁺ patients, HBV prophylaxis must be considered in patients with resolved HBV because the risk of reactivation remains (Figure 1)^[106,130]. In a recent retrospective study of HBV reactivation by the Asia Lymphoma Study Group, the authors showed that patients receiving entecavir prophylaxis had a lesser incidence of HBV reactivation than those with lamivudine. Prospective studies to validate these findings are warranted.

Hepatitis C virus

The epidemiology of hepatitis C virus (HCV) differs from that of HBV, particularly because of the existence of a wide variation of HCV genotypes worldwide^[131]. The most common types in Taiwan, China, Japan, and Korea are genotypes 1b and 2; by contrast, more diversity exists in North America and Europe^[131]. The natural history of HCV infection consists of ramp-up and plateau phases in acute infections and various spontaneous clearances in chronic phases depending on several viral and host factors, including HCV genotypes, host immunity, and the genetic polymorphism of *IFNL3* (*IL-28B*)^[131]. The treatment of chronic HCV consists primarily of interferon- α , ribavirin, and protease inhibitors that are accompanied by major toxicities^[131].

During acute infections, HCV-specific T cells activated by CD8⁺ and CD4⁺ are generated readily against multiple epitopes within 10 wk^[132]. In patients with chronic infections and persistent viremia, HCV-specific CD8⁺ T cells are rarer and responsive to fewer epitopes than in those without viremia, where even HCV-specific CD8⁺ T cell responses are mounted^[132]. In addition, CD8⁺ T cells are exhausted in chronic HCV with increased expression of programmed death-1 and cytotoxic T-lymphocyte-associated antigen-4^[133]. HCV-specific CD8⁺ T cells are suppressed by increased CD25⁺ and CD4⁺ regulatory T cells^[134]. In addition to evading CD8⁺ T-cell responses, HCV also evades CD4⁺ T-cell responses and humoral immunity with escape mutants because of its error-prone RNA polymerase^[135-137].

HCV itself is highly associated with the development of lymphoproliferative disorders, particularly with B-cell NHL with or without mixed cryoglobulinemia^[138,139]. HCV-related fulminant hepatitis occurring after chemotherapy with or without corticosteroids was rare in patients with lymphoma^[140,141]. Liver dysfunction after chemotherapy was less common in HCV than in HBV patients (18.2% *vs* 75.0%) with hematological malignancies^[142]. The incidence of HCV-associated liver dysfunction appeared to be higher in rituximab-containing regimens^[143,144]. In addition, increased HCV RNA levels were common during or after rituximab-based chemotherapy and were followed by hepatitis flares and decreased HCV RNA levels in various intervals^[144-146]. In contrast to persistent B-cell depletion for several months after rituximab treatments, the HCV viral load and the number of

regulatory T cells were elevated initially, then decreased, indicating that B-cell depletion and HCV-specific T-cell responses participate in the mechanism of HCV reactivation in patients treated with rituximab-based regimens^[64,147,148]. Although the elevation of HCV RNA load was not the major problem for lymphoma patients treated with standard courses of immunochemotherapy, the persistent elevation of HCV RNA load and subsequent liver cirrhosis can occur in follicular lymphoma patients treated with rituximab-maintenance therapy^[147]. However, these studies evaluated HCV reactivation during and after rituximab regimens according to different criteria. The HCV RNA levels may increase up to 10 times above the baseline in chronic HCV infections^[149]. In a retrospective study involving cancer patients, the acute exacerbation of chronic HCV was defined as a 3-fold or greater increase in ALT levels without tumor infiltration within the liver, without the use of hepatotoxic drugs or blood transfusion, and no concomitant systemic infections^[150]. In addition, an at least 1 log₁₀ IU/mL increase in HCV RNA levels after treatment with immunosuppressive agents was considered for HCV reactivation^[150]. The same criteria may apply for HCV reactivation in anti-CD20 mAb treatments. A simple algorithm for monitoring ALT and HCV RNA in patients undergoing immunosuppressive therapy was proposed^[151]. Although rituximab was also widely used in autoimmune hematological disorders such as HCV-related cryoglobulinemia, HCV reactivation with hepatitis flares was rare^[65,152,153]. No data were available for RIT and non-rituximab anti-CD20 mAbs.

Traditionally, anti-HCV therapy is not considered in patients receiving immunosuppressive agents because of potential drug-drug interactions, the major side effects of anti-HCV therapy, and the rarity of severe HCV-related hepatitis flares. Currently, there is no consensus regarding the optimal strategy for the treatment and prevention of HCV reactivation in patients undergoing immunosuppressive therapy even though ribavirin with or without interferon- α has been successfully administered to patients with hematological malignancies^[154,155].

Parvovirus B19

Parvovirus B19 infections are common infections that spread through respiratory droplets or blood, and seropositivity rates are increasing in people of all ages^[156]. The disease spectrum can range from asymptomatic disease to hydrops fetalis, fifth disease, arthropathy, aplastic anemia, autoimmune disorders, meningitis, encephalitis, and even fulminant hepatitis^[156,157]. This virus has a tropism for erythroid progenitors in the blood, bone marrow, and fetal liver^[156]. In healthy adults, acute infections result in viremia within 2 wk, immediately followed by virus-specific IgM and IgG responses and clearance of the virus in the serum^[158]. Humoral immunity appears to be critical for controlling this virus, and patients with immunodeficiency disorders can have chronic infections^[159]. Virus-specific CD8⁺ T cell responses toward multiple epitopes also develop soon after acute infec-

tion, and these striking CD8⁺ T-cell responses may have long durations with continuous viremia^[160]. In addition, interferon- γ -secreting, virus-specific CD62L⁺ and CD4⁺ T cells developed within 3 mo of acute infection^[161].

Parvovirus B19 infection is a major problem in immunocompromised hosts^[162-164]. The seropositivity rate was high in cancer patients receiving chemotherapy^[162,165], and half of patients exhibited detectable viral DNA in their serum^[165]. Several studies have demonstrated that acute parvovirus B19 infections are associated with fever, arthralgia, hepatitis, myocarditis, pneumonia, pancytopenia, and even graft dysfunction^[162-164]. Most importantly, immunosuppressive therapies can impair humoral immunity, exposing patients to a high risk of parvovirus B19 infection^[164,166]. Several case studies have reported that parvovirus B19 infection-related symptoms can develop in B-cell NHL or immune thrombocytopenia patients treated with rituximab-containing regimens or after being treated with rituximab-containing regimens^[167-172]. The major parvovirus B19 infection-related symptom was cytopenia in the erythroid lineage, but neutropenia or thrombocytopenia without anemia occurred in some patients. The onset was preceded by fever and skin eruptions in 2 patients^[169,171]. Our group identified the first case with acute hepatitis^[172]. Most patients developed the clinical manifestations at least 2 mo after the initiation of rituximab. The patients in 2 cases recovered without treatment, and the others responded positively to intravenous immunoglobulin (IVIG). However, the hepatitis flare in our patient persisted for 7 mo and was paralleled with cytopenia, which was correlated with the recovery of B cells after rituximab treatment^[172]. The effects of other anti-CD20 mAbs on parvovirus B19 are unknown.

The diagnosis of parvovirus B19 reactivation or infection is based on serology and viral DNA analysis^[156]. However, conducting virus-specific serology may be problematic in immunocompromised hosts^[164,166]. The pathogenesis of parvovirus B19-related hepatitis is largely unknown, and either direct cytopathic or indirect immunity-related mechanisms are possible. In addition, the pathology images obtained during liver biopsies are nonspecific. Although viral DNA or RNA can be detected in hepatocytes, the clinical significance remains to be defined^[173]. The most reasonable diagnostic sequence may be to exclude the other common hepatotropic viruses first, such as HBV or HCV, and then to analyze serum serology and viral DNA if the tests for hepatotropic viruses are negative. Because liver biopsy is invasive, it must be considered last. The most effective treatment and prevention methods for parvovirus B19-related hepatitis remain unknown; however, IVIG can be used for treating severe cases because of the clinical success achieved in using it in other parvovirus B19-related diseases^[156,166-169,171].

Other causes

In addition to HBV, HCV, and parvovirus B19, critical viral infections from cytomegalovirus, varicella-zoster virus (VZV), herpes simplex virus, echovirus, enterovirus,

influenza A virus, or BK/JC virus can occur in lymphoma patients treated with rituximab regimens^[174]. Most of them did not induce hepatitis. However, there are reports of 2 cases of hepatitis associated with adenovirus, one case of hepatic necrosis associated with disseminated VZV, and one of chronic hepatitis E virus infection that developed after rituximab treatment^[175-178]. These pathogens are rarely connected to the use of rituximab, and the underlying mechanisms of these pathogenesis associated with hepatitis are less characterized. However, the actual incidence rates of these uncommon viral infections in lymphoma patients treated with rituximab regimens may be underestimated. One patient with ITP experienced drug-induced acute hepatitis, and the pathogen was not identified; however, the patient recovered soon after rituximab treatment was stopped^[179]. There were also scattered reports of anti-CD20 mAb-related liver function abnormalities in patients with hematological disorders. However, the etiology was most likely related to anti-CD20 mAb^[45,50,51,55,69,115,116].

Future in vivo or in vitro studies

There are numerous reports of animal lymphoma models to test the preclinical activity of anti-CD20 mAbs^[180-182]. However, the safety data in liver toxicities of these animal models are very limited^[180-182]. In addition, no animal or in vitro models of viral hepatitis-induced by anti-CD20 mAbs has been established. It would be very difficult to establish the animal model with viral hepatitis reactivated by anti-CD20 mAbs because most of previous studies used tumor xenografts implanted into mice with severe combined immunodeficiency in their animal model. However, immune-mediated liver damage is important for anti-CD20 mAb-associated viral hepatitis. Most likely, this may work in evaluating the precise mechanism of hepatitis caused by the aforementioned viruses during and after anti-CD20 mAbs alone when using the immunocompetent animal model.

CONCLUSION

This review summarized the clinical use of anti-CD20 mAbs and reports of acute or chronic hepatitis associated with the use of these agents. Most data are from cases where rituximab was used to treat hematological malignancies. The majority of diseases studied were caused by viral infections. These infections must be clinically recognized soon after their occurrence because they not only interrupt immunotherapy but are also associated with high mortality and morbidity. Close monitoring of HBV and HCV infections before and during anti-CD20 mAb treatment is highly recommended in endemic areas. The prophylactic therapy for HBV has become standard of care, but patient selection and the optimal regimen or duration remain to be defined. Physicians must monitor patients being treated with rituximab-based regimens for the risks of hepatotropic viruses, including HBV, HCV,

parvovirus B19, and other viruses. Nevertheless, this review has limitations. Some pathogens that rarely induce hepatitis may not be reported in the literature; therefore, the causal relation, epidemiology, and pathogenesis of these pathogens are not the most accurate. Occasionally, the causal association between hepatitis and rituximab is difficult to confirm because of the concurrent use of multiple immunosuppressants or hepatotoxic drugs. The data on non-rituximab anti-CD20 mAbs are limited, likely because most clinical trials employ strict case selection criteria and exclude patients with hepatitis. Therefore, in vivo or in vitro studies are warranted to establish the actual roles of these viruses in the pathogenesis of hepatitis during and after anti-CD20 mAb treatments.

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