

REVIEW

The late adverse events of rituximab therapy – rare but there!

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Abstract

Rituximab, an anti CD20 monoclonal antibody, has now become a cornerstone in the treatment of many CD20 positive hematological malignancies and a variety of autoimmune disorders. In contrast to the acute allergic and cytokine associated reactions, late adverse events of rituximab are indeed uncommon but at the same time probably under-reported. In this review, we detail late adverse events reported since its use in hemato-oncological neoplasias and other disorders. These adverse events include the development of late-onset neutropenia, defects of immune reconstitution with associated immune compromise, infections, progressive multifocal leukoencephalopathy, reactivation of hepatitis, intestinal perforation and interstitial pneumonitis. Possible mechanisms involved in rituximab-associated complications and the pathogenesis of these adverse effects are reviewed and discussed. Evidence based graded recommendations for the management of these adverse effects are proposed.

Keywords: Antibody-based immunotherapy, immunotherapy, lymphoma and Hodgkin lymphoma

Introduction

Rituximab is a chimeric human/mouse monoclonal antibody that binds to the CD20 antigen present on the surface of normal and neoplastic B lymphocytes. In recent years, it has emerged as effective therapy for B-cell neoplasms. Rituximab kills B-cells via a number of different mechanisms including complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), induction of apoptosis and sensitization to chemotherapy [1].

During the last decade, rituximab has been approved for the treatment of newly diagnosed, relapsed and refractory indolent and aggressive CD20-positive non-Hodgkin lymphoma (NHL) and has also been extensively studied as maintenance treatment for follicular lymphoma and other indolent B-cell neoplasms [2,3]. It is also being used for several autoimmune disorders such as rheumatoid

arthritis and systemic lupus erythematosus (SLE) and as part of the conditioning regimen in hematopoietic stem cell transplantation (HSCT). The most common documented adverse events are acute infusion reactions, whereas overt cytokine release syndrome and hematological adverse events are less commonly encountered [4]. The latter events usually occur during the first few hours or days after the administration of rituximab. However, with the increase in the number of patients treated with rituximab, long term and rarer adverse events, occurring several weeks or months after the administration of rituximab, are being reported more frequently. In this literature review, we summarize these adverse events.

In this review, late effects were defined as events occurring after a period of several days from the administration of rituximab and not related to acute allergic reactions or acute cytokine release syndrome. PubMed search for late adverse effects of rituximab

was performed according to potentially affected systems/organs. All grades of adverse events were reviewed according to the National Cancer Institute common terminology criteria (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf).

The quality of design and strength of evidence was used to grade authors' recommendations [5].

Hematological adverse effects

According to the pivotal study of rituximab immunotherapy for indolent NHL, hematological adverse effects were rarely encountered and usually mild and reversible [6]. Grade 3/4 neutropenia, thrombocytopenia and anemia were reported in only 4.2%, 1.7% and 1.1% of patients, respectively [6]. Nonetheless, during the last 5 years, late onset cytopenias, particularly late onset neutropenia (LON), have emerged as complications of rituximab therapy which are of major concern.

In a retrospective analysis of 130 patients with a follow-up of at least 12 months (range 12–132 months), the incidence of all grades of LON was 8% in the rituximab group when compared with 0% in the control group and based on a statistical model, the true rate of LON was estimated to be 35.5% [7]. In this respect, another study from Japan reported an incidence of grade 3–4 LON as high as 25% among patients treated with rituximab-containing regimens [8]. The time range from the administration of immunochemotherapy to the onset of LON was 46–384 days [8,9] and although LON episodes were usually well tolerated and self limited, G-CSF administration was reported to accelerate their resolution [8,10]. In a systematic review of non-cytotoxic drug-associated agranulocytosis, the median number of infusions before LON onset was four and the duration of neutropenia was 11 days [11]. In this regard, there seems to be a correlation between the intensity of the treatments given other than rituximab, and the development of LON. For example, LON occurs less frequently in patients with autoimmune diseases, where rituximab is given with less aggressive immunosuppressive therapy, compared with that given for hematological malignancies, although the number of rituximab courses administered is usually smaller in these disorders. In a retrospective analysis of 23 patients with various autoimmune diseases, only one patient developed LON [12] in contrast to the higher incidence of various grades of LON (15–70%) reported in patients treated with high dose therapy followed by autologous stem cells transplantation [8,10,13,14]. High dose methotrexate-containing regimens have also been associated with a higher incidence of LON

[8]. The number of rituximab doses given also correlated with the development of LON, with more than four doses being significantly associated with LON development [9].

Patients with LON have typical findings in the bone marrow including hypocellularity and maturation arrest at the promyelocyte stage [15,16]. A few studies have reported that the onset of LON generally coincides with or precedes B lymphocyte cell recovery after initial suppression of lymphopoiesis, induced by rituximab [6,7]. Furthermore, there is also evidence for an inverse correlation between the time period for B cell recovery and the occurrence of LON [7]. Several hypotheses have been suggested to explain this association. Voog *et al.* showed that several months after rituximab treatment, the repopulating B cells produce anti-neutrophil autoantibodies, which decrease the number of neutrophils [17]. However, this phenomenon was not reported in other studies [7,14,15]. Another study suggested that the B cell recovery after rituximab results in decreased granulopoiesis during the recovery period. This finding is supported by the reciprocal dynamics between bone marrow lymphocyte and neutrophil populations which is consistent with a cellular competition within a developmental niche defined by a common location and shared growth resources for both co-existing cell populations [18]. Suppression of one population, i.e. B cells, by rituximab, may during its recovery, indirectly cause deprivation of growth factors which are also necessary for the other population. This hypothesis gains support from several possible mechanisms associated with cytokine production, for example, stromal derived factor-1 (SDF-1) which is known to regulate neutrophil egress from the bone marrow. In fact, it has been shown that B cell recovery after the administration of combined immunochemotherapy including rituximab is associated with a decreased production of SDF-1 and a delay in neutrophil egress from the bone marrow [7]. Another cytokine influenced by rituximab administration is B cell activating factor (BAFF) which plays a role in human B-cell survival, expansion and development. BAFF levels are undetectable prior to rituximab administration, increase after treatment and peak at a time interval which coincides with the occurrence of LON [19]. Nonetheless, it is still unclear whether BAFF plays a role in the development of LON or whether it only serves as a surrogate marker for the risk of developing LON.

Yet another study suggests that after rituximab therapy there is proliferation of T-large granular lymphocytes which express and secrete large amounts of Fas and Fas ligand, which may perhaps cause apoptosis of mature neutrophils [20].

On the basis of aforementioned phenomena, our recommendation for patients developing LON post rituximab is basically close monitoring for the occurrence of infections. In patients, who develop infections, especially those individuals with additional risk factors such as hypogammaglobulinemia or those patients receiving other immunosuppressive treatments, G-CSF administration should be considered.

There is only sparse data regarding the late onset anemia and thrombocytopenia after rituximab therapy. Cattaneo *et al.* reported a cohort of 77 patients who developed late onset thrombocytopenia and anemia in 10% and 5% of patients, respectively [9]. Thrombocytopenia developed after a median of four (range 3–15) weeks lasting for a median of 10 (range 2–22) weeks while anemia developed after a median of five (range 5–11) weeks, also lasting for a median of 10 (range 7–22) weeks [9]. The mechanism of these late cytopenias is probably different from that associated with early rituximab – associated acute cytopenia which is most likely mediated through a complement and cytokines' cascade, as previously described by us and others [21]. Only well designed prospective studies taking into account patients' risk factors, treatment modalities and bone marrow pathophysiology might shed light on this phenomenon and help in predicting it and identifying the specific risk factors.

Immunological adverse effects

Reconstitution of B lymphocytes usually takes several months after the administration of rituximab and the B cell pool returns to its pre-treatment values after about 1 year [6,7,22,23]. A decrease in the number of B cells has been documented in offsprings of women treated with rituximab during pregnancy [24,25]. Although reconstitution of B cells occurred several months later, no infectious complications have been reported.

Although there is evidence for a reduction in serum immunoglobulin levels after rituximab treatment, it is unclear whether this process is clinically significant. The median levels of IgG, IgM and IgA were found to be lowest at 12, 6 and 9 months, respectively [23]. A similar pattern of transient hypogammaglobulinemia was also reported in association with adjuvant rituximab treatment after autologous stem cell transplantation (ASCT), with normalization of immunoglobulin levels after 24 months [26]; however in a recent study in which rituximab was added to chemotherapy for the mobilization of stem cells, there were no significant changes recorded in the reconstitution pattern, nor in the serum immunoglobulin levels in the group of patients treated with rituximab [27]. One retrospective study published as abstract

found that the occurrence of hypogammaglobulinemia was significant only in patients who received more than six doses of rituximab [28]. Nevertheless, these results should be interpreted with much caution.

Paradoxically, a substantial number of patients with lymphoplasmacytic lymphoma have been reported to suffer from IgM flare-up after rituximab administration [29]. This phenomenon usually starts during the first month after rituximab administration and may last for 4 months. Although controversial, some reports claim that this flare-up is associated with an increased risk for hyperviscosity [30–32].

As expected, rituximab administration does not significantly affect the number of T cells in individuals receiving this agent. The overall importance of the aforementioned phenomena will be discussed further in the infectious complications section of this review.

Several late immunologic phenomena have been described to occur several weeks after the administration of rituximab in association with B cell depletion. These include an acute rheumatoid arthritis-like flare-up, leukocytoclastic vasculitis and psoriatic skin manifestations [33–35]. Similar to other antibodies used in clinical practice, serum sickness has also been described 1–13 days after the administration of rituximab [36–42].

Infectious adverse effects

General considerations

Hemato-oncological patients may suffer from either primary infections because of primary exposure to a certain pathogen or secondary infections resulting from reactivation of latent pathogens due to immune suppression caused by the disease or the therapy given. Pooled data from 356 patients receiving rituximab as monotherapy showed an overall incidence rate of 30% for all grades of infections [43]. Bacterial infections occurred in 19% of the patients, viral in 10% and fungal in 1%. According to a systematic review published in 2005 the mortality rate among all reported cases was 2% [44].

A recently published systematic review evaluating infectious complications of monoclonal antibodies administered in cancer patients failed to demonstrate a significant increase in the incidence of infections with the addition of rituximab to chemotherapy. This review was based on data from five randomized controlled trials that reported on different grades of infectious episodes [45]. Similarly, no change in infections rate was found in patients who received conditioning regimens including rituximab prior to allogeneic stem cell transplantation or in those

receiving it as a maintenance treatment after autologous stem cell transplant [46,47]. On the other hand, two recently published meta-analyses of randomized controlled studies on rituximab maintenance showed that prolonged rituximab treatment was associated with a significantly increased rate of grade 3/4 infections [3,48]. The main risk factor for infections was treatment with purine analogs prior to rituximab administration [48]. This highlights the importance of close monitoring of patients who receive combinations of drugs affecting both B and T cells function.

Viral infections

A recently published systematic review summarizing all the reported data on viral infections associated with rituximab identified 64 cases [49]. However, since rituximab was given as monotherapy in only two patients it is difficult to draw conclusions regarding its role as a sole agent in the development of these infections. Of the 64 patients reported, 26 had hepatitis B and C reactivation and there were also only a few instances of cytomegalovirus and varicella zoster virus reactivation. Other viral agents associated with rituximab-induced infections include: parvovirus B19, respiratory syncytial virus and West-Nile virus [49–51]. It is also noteworthy that a few cases of enterovirus encephalitis have also been reported [52,53]. The median time period from the start of rituximab treatment to the diagnosis of the viral infection was 5 months [49]. Gammaglobulins have been administered in several cases with some response [50,52].

Phase II and III trials in patients with HIV suffering from B cell NHL and treated with rituximab have shown that this treatment was associated with a higher risk of infectious-related death in patients with low CD4 counts ($<50/\mu\text{L}$), mainly due to opportunistic infections [54,55]. Rituximab has also been associated with exacerbation of Kaposi's sarcoma (KS) lesions in 75% of patients with HIV with a previous history of KS, probably due to B cell depletion [56,57].

Bacterial infections

Rituximab has not been associated with a higher occurrence of bacterial infections [58]. However, recent reports have identified several potential risk factors for the occurrence of bacterial infections including decreased pretreatment serum IgM levels, a shorter time interval between courses of rituximab and the use of higher doses of rituximab [59,60].

We did not identify any association between rituximab administration and mycobacterial

infection except for a single case report describing the development of pulmonary tuberculosis in a patient who received combined immunochemotherapy containing rituximab and who had undergone subsequent autologous stem cell transplantation [61].

Fungal infections

Although yeast and mold infections occur rarely in patients with lymphoma, a retrospective study published in 2007 showed that elderly patients with diffuse large B cell lymphoma (DLBCL) treated with R-CHOP (cyclophosphamide, adriamycin, vincristine and prednisone with rituximab) might have a higher risk for fungal infections, mainly *Candida* spp. [58,62].

While the pivotal trials did not report an higher prevalence of *Pneumocystis jirovecii* (carinii) pneumonia (PCP) in association with rituximab, recent clinical observations suggest that there is an association between rituximab based regimens and PCP infections [58,63]. Whether these relate to the rituximab therapy alone or to the combination with other drugs remains to be proven.

Table I summarizes the literature on PCP infections in patients with hematological malignancies treated with rituximab and chemotherapy. Fifteen HIV-negative patients with DLBCL have been reported [64–68] and all of them were treated with CHOP based chemotherapy regimens, 88% receiving

Table I. *Pneumocystis jirovecii* (carinii) pneumonia in HIV-negative patients with hematological malignancies treated with rituximab.

References	Age	Disease	Chemotherapy regimen	Course interval (d)	Onset after course (mos.)
[64]	34	DLBCL	CHOP	21	6
[65]	NR	DLBCL	CHOP	14	NR
	NR	DLBCL	CHOP	14	NR
[66]	39	DLBCL	CHOP	14	8
	61	DLBCL	CHOP	14	2
	21	DLBCL	CHOP	14	8
[67]	30	DLBCL	CHOEP	14	4
	61	DLBCL	CHOEP	14	6
	47	DLBCL	CHOEP	14	6
	47	DLBCL	CHOEP	14	6
	49	DLBCL	CHOEP	14	5
	58	DLBCL	CHOEP	14	5
[68]	NR	DLBCL	CHOP	14	NR
	NR	DLBCL	CHOP	14	NR
	NR	DLBCL	CHOP	14	NR

NR, not reported; DLBCL, diffuse large B cell lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristin, prednisone; CHOEP, cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone; mos., months; d, days.

a dose dense treatment, based on courses administered every 14 days. Onset of symptoms occurred after a mean of six (range two to eight) courses and most of the patients responded to antibiotic therapy.

Several risk factors such as low serum IgG levels and low CD4 counts appeared to increase the susceptibility for PCP [66,68]. Although it is clear that significantly more PCP infections occurred in patients treated with dose dense regimens like CHOP-14, it is unclear whether this was related to rituximab alone or to the more intensive steroid and/or chemotherapy doses administered, since it is well established that patients treated with high dose steroids are more susceptible to PCP infection. On the other hand rituximab may indeed have also contributed, as B cells play a central role in the activation of CD4 T cells and their expansion as shown in response to murine *Pneumocystis carinii* [69].

Parasitic infections

Rituximab has rarely been associated with protozoal infection but an exception to this rule is the tick-borne illness babesiosis. A significant association was demonstrated between babesiosis and rituximab administration. Among a series of 14 immune compromised patients diagnosed with babesiosis, eight had been previously treated with rituximab [70]. This relatively rare infection may at times be fatal in patients with B cell dysfunction [71].

Progressive multifocal leukoencephalopathy

This rare demyelinating infection of the central nervous system (CNS) caused by the JC papovavirus (JCV) usually results in death or an irreversible neurologic insult [72]. Primary infection occurs in childhood in 75% of the cases, and the virus remains in a latent form in the kidneys and in mononuclear and B lymphocytes for life where it is activated during periods of immunosuppression [72,73]. These cells probably play a role in the transport of the virus to the central nervous system where it infects the oligodendrocytes and astrocytes [74]. Although it is not clear how the JCV penetrates the oligodendrocytes, it is assumed that the 5HT_{2a} serotonin cell receptor is involved in this process [75].

Progressive multifocal leukoencephalopathy (PML) usually presents with subacute neurologic deficits including altered mental status and various motor dysfunctions. The gold standard for diagnosis is brain biopsy. Alternatively, the diagnosis can be established by a PCR assay detecting JCV DNA in the cerebrospinal fluid [76].

There is no proven effective treatment for JCV. It is rational to try first to eliminate the immunosup-

pressive treatment. Several treatments such as cytarabine and the anti-viral drug cidofovir have shown some effect on the course of the disease by stabilising the neurologic condition [77–81].

In 2005, García-Suárez *et al.* reviewed the relevant literature reporting on the influence of rituximab and other novel therapies on the occurrence of PML in HIV-negative lymphoproliferative disorders (LPD) [82]. They analyzed 46 documented cases with confirmed LPD-associated PML published during the period 1958–2004. Only four patients had received rituximab, all of them post HSCT.

On the basis of two patients who had developed PML, the FDA released in December 2006 an alert regarding the use of rituximab in patients with SLE (<http://www.fda.gov/CDER/Drug/InfoSheets/HCP/rituximab.pdf>). This led to a critical review which was recently published, summarizing FDA and manufacturer data, personal communication and the relevant literature. This surveillance reported on 57 PML cases associated with rituximab administration, the majority of whom had LPD [78]. A median of six (range, 1–28) doses of rituximab preceded PML diagnosis and the median time from last rituximab treatment to PML diagnosis was 5.5 months. The most common presenting sign was confusion and disorientation. Median time to death after PML diagnosis was 2 months with a case-fatality rate of 90%.

The mechanism responsible for reactivation of JCV by rituximab remains unclear given the fact that rituximab mainly impairs humoral and not cellular immunity. Goldberg *et al.* suggested that in patients undergoing ASCT with the addition of rituximab, a delay in T cell reconstitution might be expected [83]. Others have suggested that rituximab associated B cell depletion might affect T cell activation and eventually also cause cell-mediated immunity dysfunction [84]. It is also possible that other coinciding factors like low serum IgG levels and low CD4 counts may in addition contribute to JCV reactivation [85]. Treating physicians using rituximab should be aware of this severe complication and maintain a high index of suspicion especially in patients developing neurological symptoms post rituximab treatment. Long term surveillance is required to quantify the true incidence of this complication which might turn to be the most serious late adverse event of rituximab.

Hepatic and gastrointestinal adverse effects

General considerations

Viral hepatitis reactivation and liver damage have been associated with a variety of chemotherapy

regimens. Although rituximab administration has been associated mainly with hepatitis B virus (HBV) reactivation, recently, hepatitis C virus (HCV) and other rare viral hepatitis reactivations have been reported as well [86].

Hepatitis B virus reactivation

Presentation and progression of chronic hepatitis B infection is mainly affected by viral replication and host immunity. Following acute infection, the majority of patients has spontaneous resolution and will have persistent immunity characterized by hepatitis B surface antibody (HBsAb). Those patients unable to resolve after an acute infection usually become chronic carriers and remain clinically silent for prolonged periods of time and are identified by the presence of HBs antigen (Ag) and hepatitis B core (HBc)Ab positivity. Occasionally, patients lose HBsAg and will remain with isolated HBc Ab, reflecting occult infection [87].

Reactivation of hepatitis B has been increasingly reported since the introduction of rituximab [88]. The majority of reports on HBV reactivation secondary to rituximab administration have been described in chronic carriers of HBV because this group of patients can be easily identified by serology. Conversely, reactivation of HBV in patients with resolved hepatitis B has also been reported rarely [89–95].

Targhetta *et al.*, who analyzed retrospectively 1087 patients with NHL, found that 5% were overt HBV chronic carriers and 36% had occult HBV infection [96]. Overt acute hepatitis B disease developed in 2.7% of the patients treated with combined immunochemotherapy containing rituximab. Yeo *et al.* [97] who monitored prospectively 46 patients with DLBCL with occult HBV infection who had been treated with either CHOP or R-CHOP regimens (the same regimen containing also rituximab) found that none of the patients treated with CHOP alone had HBV reactivation, whereas 25% of those treated with R-CHOP developed HBV reactivation, including one patient who died of hepatic failure. On the other hand, other retrospective studies reported that most patients with a previous HBV infection tolerated the combination of rituximab and chemotherapy very well [98,99].

Rituximab depletes mainly B cells which act both as antigen presenting cells during the immune attack against positive-HBsAg-hepatocytes, and as mediators for cytotoxic T cell response to HBcAg [100,101]. Accordingly, depletion of these cells may play a role in aiding HBV to escape recognition by the immune system thereby contributing to persistence of the virus [100]. The question why

only a minority of patients carrying HBV is affected by rituximab administration remains an open issue but a recent publication by Miyagawa *et al.* [102] may indeed shed some light on the issue of the pathogenesis of HBV reactivation following rituximab therapy. These authors showed that after the administration of rituximab, there is reactivation of a slowly-replicative mutated HBV, as opposed to the common wild type HBV. This slow-replicating virus probably benefits more from the reduction in antigen presentation, occurring after rituximab administration than the wild type virus.

Antiviral prophylaxis has been recommended for two groups of patients with prior HBV exposure, based on pretreatment viral serology [87,103]. The first group includes chronic carriers with positive HBsAg who have normal liver function tests. The efficacy of prophylaxis for this group has already been established and prophylaxis should be initiated 7 days prior to rituximab administration and continued for more than 1 year after the end of the treatment, Figure 1. Serial monitoring of liver function tests and serum HBV DNA copy numbers every 3 months is recommended [87]. For the second group which includes patients with occult HBV infection, the role of prophylaxis is less certain, yet is still recommended [87,103]. Indeed, in a phase II trial by He *et al.* none of HBV carriers treated with prophylactic lamivudine prior to and during the administration of rituximab developed HBV associated hepatitis [104]. Prospective randomized trials are warranted to assess the need for prophylaxis as opposed to only close monitoring in these patients. Physicians dealing with these patients should take into consideration possible clinically relevant drug interactions, between lamivudine and other nucleoside analogues used for

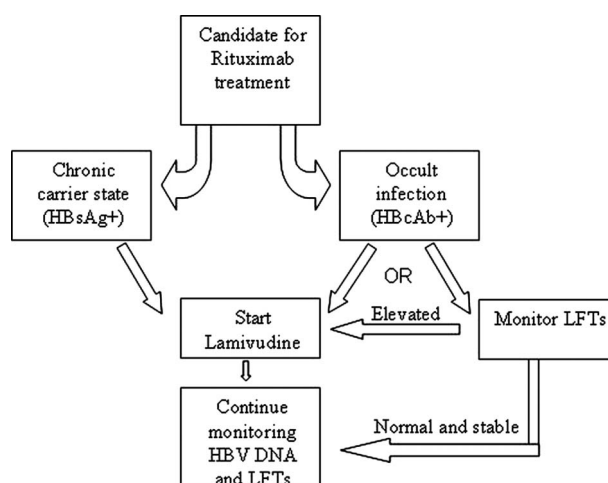


Figure 1. A suggested scheme for the monitoring and treatment of chronic hepatitis B carrier patients who require therapy with rituximab. LFTs, liver function tests.

the treatment of lymphoma, like fludarabine or cladribine if co-administered, since both require activation by phosphorylation [105].

Hepatitis C virus reactivation

The true incidence of HCV reactivation in association with rituximab administration is debated. Furthermore, it is not clear whether there is a direct correlation between the rise in viral load secondary to rituximab administration and clinical or laboratory evidence for liver disease. Rituximab has rarely been associated with HCV reactivation and only three reports documented HCV reactivation with the development of hepatitis after treatment with rituximab based regimens [106–108]. Ennishi *et al.* who monitored HCV RNA levels and liver function tests in five patients treated with rituximab found that one patient developed severe liver dysfunction accompanied by a slight increase in HCV RNA levels [109]. In another report, all four patients with positive HCV Ab prior to rituximab administration developed a transient increase in viral load post rituximab treatment without significant hepatitis [110]. Conversely, in another study, no association was found between the administration of rituximab and HCV reactivation [111]. Sansonno and colleagues who reported on 20 patients with HCV and mixed cryoglobulinemia treated with rituximab, showed that there was a sustained effect on virogenesis in responding patients reflecting a two-fold increase in the viral load 12 months after treatment, but without any overt clinical or laboratory evidence for hepatitis [112]. On the other hand Dizar *et al.* have recently reported that in high risk patients with chronic active hepatitis and a high baseline HCV viral load and HBV co-infection, the mortality rate was as high as 45% after combined immunochemotherapy regimens including steroids as well and rituximab [113].

Data regarding the pathogenesis of rituximab-induced HCV reactivation is sparse. One possible explanation for this relationship could relate to the fact that B lymphocytes of infected patients carry HCV particles and shed them during B cell destruction [114]. Another explanation relates to the fact that rituximab may induce a drop in the titer of anti-HCV IgG antibodies which may lead to viral evasion from the immune system, thereby favoring accelerated viral replication [115].

It is noteworthy that most of the patients who have been reported with reactivation of HCV had DLBCL and received rituximab for only a short period of time. There are at present no data relating to HCV reactivation in patients receiving maintenance treatment with rituximab. This might be an important issue since it is possible that prolonged intermittent

exposure to rituximab may induce a continuing increased HCV-RNA load which may carry with it an higher risk for HCV associated complications.

Other gastrointestinal complications

Treatment of lymphoma involving the gastrointestinal tract may carry a high risk for complications associated with bowel perforation. While sporadic case reports indicated a possible association between rituximab and bowel perforation, a retrospective study did not find any relationship [116–118].

Post marketing information indicates 47 cases of bowel obstruction and 37 cases of gastrointestinal perforation. The majority of cases occurred in patients with lymphoma. It is hard to draw a definite conclusion regarding the role of rituximab in these cases, as the affected patients had multiple risk factors including lymphomatous involvement of the gastrointestinal tract, other gastrointestinal disorders and the risk of concomitant treatments with chemo/radiotherapy and corticosteroids. Nonetheless, a pooled analysis of clinical trials in patients with NHL has indicated a higher incidence of gastrointestinal perforation in the rituximab plus chemotherapy arm as compared to the chemotherapy only arm (0.38% vs. 0.15%). The mean time to the onset of symptoms was 6 days from the start of therapy (range 1–77 days). Large cohort studies are required to assess the incidence of this complication in patients with and without gastrointestinal involvement.

Pulmonary adverse effects

Severe but usually reversible adverse pulmonary effects occur during the first infusion of rituximab in 10% of patients and are mostly bronchospasm [43]. Occasionally, severe manifestations including pulmonary infiltrates and even acute respiratory distress syndrome may occur early after the administration of rituximab.

In contrast to these early pulmonary adverse effects, delayed pulmonary damage has also been reported. Two main pathogenetic mechanisms may be responsible for delayed rituximab-induced pulmonary insult. The first mechanism involves the increased susceptibility of the host to pulmonary infections related to the immunosuppression induced by the antibody itself and this has already been discussed in the infectious complications section. The second mechanism relates to an inflammatory reaction resulting in diffuse parenchymal lung disease. Most patients reported to have diffuse parenchymal lung disease, presented with interstitial

lung disease although other manifestations such as bronchiolitis obliterans with organizing pneumonia, diffuse alveolar hemorrhage, pulmonary cysts and

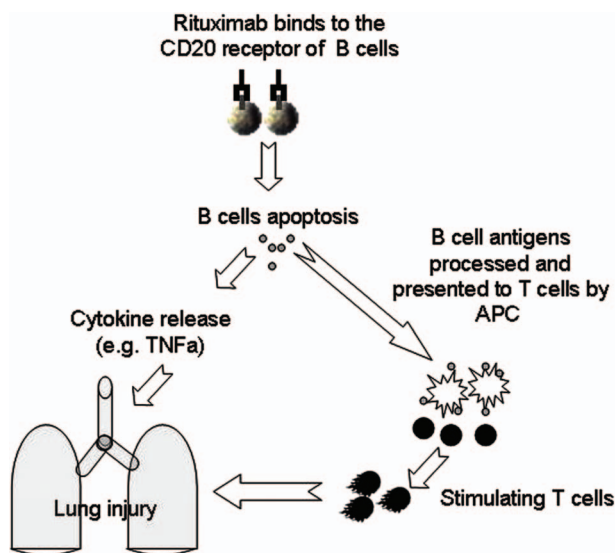


Figure 2. A proposed model of the mechanism for the lung injury associated with rituximab therapy. Binding of rituximab to CD20 positive B cells induces apoptosis of these cells. Apoptotic products are presented to T cells causing T cell stimulation and subsequent damage to pulmonary cells presenting similar antigens. Alternatively, apoptotic B cells may facilitate cytokine production and specific lung injury. APC, antigen presenting cells. To view in colour online please go to: www.informaworld.com/glal

pulmonary hypertension have also been reported [119–122].

The incidence of diffuse parenchymal lung disease is unknown, but is probably low since only a few dozens of cases have been reported with this complication [123]. The manufacturers have reported on an incidence of less than 0.03% [124]. However it is indeed possible that there are many more which have not been reported after the initial reports have been published.

Of particular interest are the observations of Liu *et al.* who recently reported an incidence of 8% of all grades of interstitial pneumonitis among 107 patients receiving rituximab containing regimens seen on computer tomography scans [125]. Although this high incidence is exceptional it may possibly be linked to an increased genetic susceptibility to drug-induced interstitial lung disease in Japanese patients. Nevertheless, its significance lies in the relatively uniform evaluation and follow-up of the cases they documented. The most common presenting symptom in this reported series was fever (90% of patients) with only 33% of the cases complaining of dyspnea, which is in clear contrast to a previously published review reporting dyspnea as the presenting symptom in 81% of the patients [126]. The median number of rituximab cycles received prior to onset of symptoms in this series was two, which was similar to another post-marketing report published in 2008

Table II. Authors' recommendations for some of the late adverse events (based on the grading of the quality of design and strength of evidence) [5].

Adverse event	Relevant studies	Level of evidence	Grade of recommendation	Authors' recommendations
Late onset neutropenia	[8,10]	3	D	Close monitoring for infections Consider G-CSF to accelerate neutrophils recovery
Delayed immune reconstitution of B cells		4	D	No intervention
Infections				
Bacterial infections		4	D	Treat symptomatic patients as per standard practice
Viral infections				
Fungal infections				
PCP infections	[67]	2–	D	Prophylaxis treatment for patients treated with dose dense regimen
PML	[77–81]	3	D	Close monitoring for development of neurological signs Discontinue immunosuppressive medications
HBV carriers				
Chronic carriers (HBsAg+)	[87,104]	2+	C	Prophylaxis with lamivudine
Occult carriers (isolated HBc Ab+)	[87,103,104]	4	D	Close monitoring of LFTs or prophylaxis with lamivudine
HCV carriers/past infection		4	D	Close monitoring of LFTs
Bowel obstruction/perforation		4	D	Close monitoring of patients with significant GI involvement
Interstitial pneumonitis	[125]	3	D	Rule out infectious etiology Consider early treatment with high dose steroids

G-CSF, granulocyte-colony stimulating factor; PCP, *pneumocystis jiroveci* (carinii) pneumonia; PML, progressive multifocal leukoencephalopathy; LFTs, liver function tests; HBV, hepatitis B virus; HCV, hepatitis C virus; GI, gastrointestinal tract.

[127]. All patients were treated with a 3 days-course of steroids with gradual tapering-off and the majority of patients were treated simultaneously with an empirical course of antibiotics. Most of the reported patients (90%) responded to corticosteroid therapy with full recovery while one patient died of pulmonary infection. Two of the four patients rechallenged with rituximab had recurrence of interstitial pneumonitis [125], but because bronchoalveolar lavage was not performed, an infectious etiology and other related complications could not be ruled out.

The pathogenesis of rituximab-induced interstitial lung disease has not yet been fully elucidated. One hypothesis suggests that rituximab by attacking CD20 positive cells, induces B cell apoptosis. This in turn causes maturation of antigen presenting cells, like dendritic cells, which engulf the apoptotic cells and cross-present them, thereby inducing cytotoxic T cell activation which is eventually responsible for vascular and alveolar damage [128,129] (Figure 2). This ongoing process, occurring sometime after the transfusion of rituximab, might explain the lag period between the administration of rituximab and the onset of symptoms. These events are in contrast to the acute bronchospasm, occurring during or shortly after rituximab transfusion. Another possible pathogenetic mechanism involves cytokine release, mainly TNF α , occurring in the wake of the B cell apoptosis caused by rituximab, which might also induce pulmonary injury [126]. These cytokines have been reported to play a central role in rituximab associated acute adverse events [21] as well as in a bronchiolitis obliterans type of lesion in an animal model [130]. However, the latter theory does not explain the time lag between rituximab administration and the onset of symptoms.

In conclusion, although rarely encountered, late pulmonary manifestations are of clinical significance and should be vigorously investigated so as to first exclude a possible infectious etiology. After ruling out an infection, steroid therapy should be initiated early on, in order to improve pulmonary outcome.

Conclusions

Rituximab is now considered an essential part of the treatment for CD20 positive lymphoproliferative malignancies and autoimmune diseases and the number of indications for therapy with this antibody is increasing steadily with time. Despite the fact that it is not considered a harmful agent the 'dark side' of this medication is slowly being revealed in recent years with the reports of rare, and mostly late onset drug related side effects.

Delayed immune reconstitution and reactivation of chronic HBV should be seriously considered prior to initiating treatment. Other rare complications such as PML, LON and DPLD should be taken into account and managed if relevant symptoms occur. Table II summarizes our recommendations based on the grading of the quality of design and strength of evidence as well as the grading of the results of this treatment. With the steadily increasing use of rituximab as maintenance therapy, these manifestations may well become even more prevalent in the near future. Physicians caring for lymphoma patients must take these late effects into consideration when choosing appropriate treatment for B cell lymphomas.

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