Rituximab-related Severe Toxicity

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Introduction

Rituximab is an immunoglobulin G (IgG)κ monoclonal chimeric human/murine antibody targeting CD20 antigen [1]. CD20 is a surface antigen specific to mature B lymphocytes, from pre-B cells to memory B cells [2]. Rituximab induces early (24–48 h) and prolonged (2–6 month) B cell depletion via different mechanisms: antibody-dependent cellular cytotoxicity, direct cross-linking of CD20, complement dependent cytotoxicity, and opsonization-induced phagocytosis ([3]; Fig. 1).

Rituximab is increasingly used in various types of patients with hematology, internal medicine, rheumatology or orphan diseases (Table 1). Rituximab was conceptually designed for the treatment of non-Hodgkin lymphomas of B cell lineage and remains a major drug in this indication [4]. Indeed rituximab, in association with polychemotherapy, provides benefit for the treatment induction of various non-Hodgkin lymphomas, such as diffuse large B cell lymphoma [5, 6], chronic lymphocytic leukemia (CLL) [7], or for maintenance therapy of non-Hodgkin lymphomas, such as follicular lymphoma [8]. Moreover, rituximab is now recognized to be effective and is widely used in many autoimmune diseases such as rheumatoid arthritis [9] or anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis [10, 11].

Critical care physicians may be using rituximab in severe forms of autoimmune diseases requiring emergency treatment along with the management of acute respiratory failure, acute kidney injury (AKI) and neurologic or cardiac involvement. In a recent series of 381 patients with systemic autoimmune disease (connective tissue
Fig. 1  

**a** Mechanisms of action related to direct rituximab-induced signaling. **b** Mechanisms of action related to rituximab-induced CMC and ADCC with potential that these two mechanisms can be antagonistic. **CMC**: complement dependent cytotoxicity; **ADCC**: antibody-dependent cellular cytotoxicity. From [83] with permission

disease or multisystemic vasculitis) requiring admission to the intensive care unit (ICU), 3.9% received rituximab in the ICU [12]. In the ICU setting, anti-CD20 antibodies are also administered in patients with aggressive lymphomas receiv-
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Table 1  Clinical conditions for which rituximab has been approved

| Approved therapeutic indications for rituximab (EMA, FDA) | HEMATOLOGY | IMMUNOLOGY |
|----------------------------------------------------------|------------|------------|
| Follicular lymphoma                                      | Rheumatoid arthritis |
| Diffuse large B-cell lymphoma                            | Granulomatosis with polyangiitis |
| Chronic lymphocytic leukemia                              | Microscopic polyangiitis |

Other potential indications for rituximab (off-label)

| Burkitt lymphoma                                          | Cardiac and renal transplantation |
| MALT lymphoma                                             | Autoimmune hemolytic anemia |
| Central nervous system lymphoma                           | Immune thrombocytopenia |
| Hodgkin lymphoma                                          | Thrombotic thrombocytopenic purpura |
| Post-transplant lymphoproliferative disorder              | Lupus nephritis |
| Graft versus host disease                                | Membranous nephropathy |

FDA: US Food and Drug Administration; EMA: European Medicines Agency

...ing chemotherapy in the ICU or patients with unresponsive thrombotic microangiopathies.

In pivotal studies and large clinical trials [5, 8], few events have complicated rituximab infusion. Nonetheless, after a decade of use and numerous patients treated, it appears that rituximab may induce a rare but wide panel of potentially serious and even lethal toxicities. This chapter, a systematic review, focuses on these severe adverse events, classified as acute or severe late onset toxicity (Table 2).

To perform the review, we searched the MEDLINE database for all articles concerning rituximab-induced toxicity. We first crossed “rituximab” with “toxicity” as Medical Subject Headings. Then we crossed “Rituximab” with the medical subject heading of any toxicity we found (e.g., “Progressive multifocal leukoencephalopathy”). Any type of manuscript, from 1999 to 2017 was taken into account: case reports, retrospective or prospective series, randomized controlled trials and meta-analyses. Redundant cases were excluded. Only articles written in English or French languages were selected.

Table 2  Major acute and late onset toxicities of rituximab

| ACUTE ONSET TOXICITY | SEVERE LATE ONSET TOXICITY |
|----------------------|---------------------------|
| Infusion related reaction | Pneumocystis pneumonia |
| Tumor lysis syndrome | Viral reactivation (HBV, JC, VZV) |
| Digestive perforation | Bacterial infection |
| Thrombocytopenia | Late onset neutropenia |
| Serum sickness | Hypogammaglobulinemia |
| Lung toxicity (ARDS) | Organizing pneumonia |

ARDS: acute respiratory distress syndrome; VZV: Varicella zoster virus; HBV: hepatitis B virus
**Acute Onset Toxicity**

**Infusion Reactions**

Infusion reaction, also called cytokine release syndrome, is well described in the current literature and has led to the formulation of recommendations for rituximab administration in hematology-oncology patients. It has been reported in 4% [13, 14], 14.6% [15] and 23% [16] of patients depending on the particular study and has especially been encountered during the first infusion of the drug. Usual mild infusion reactions include rash, hot flushes, dyspnea and pruritus [13]. Less common mild reactions may consist of dry throat feeling, palpitations, headaches, restless leg syndrome, chills, hypertension and fever. Severe cytokine release syndrome is infrequent (0.5%) [16] but can be lethal, with anaphylactoid reactions such as bronchospasm, angioedema, shock and hypoxemia [17]. Cardiogenic shock, myocardial infarction and ventricular fibrillation have been reported by the US Food and Drug Administration (FDA). Fatal reactions may occur in 0.04–0.07% of patients [3].

Risk factors identified for a rituximab infusion reaction include: first infusion, large tumor burden or high levels of circulating B lymphocytes [15, 18, 19]. This toxicity has been ascribed to the release of tumor necrosis factor (TNF), interleukin (IL)-6 or other cytokines by B lymphocytes, following the binding of rituximab to CD20 [19]. To prevent these reactions, the FDA recommends slow infusion rates, especially for the first administration of rituximab (initial rate of 50 mg/h with an increase of 50 mg/h every 30 min, to a maximum of 400 mg/h unless signs of infusion reaction occur). Subsequent infusions can be accelerated to 100 mg/h increasing to 400 mg/h by steps of 100 mg/h every 30 min. Recent protocols with 90-minute infusion rates do not seem to increase the incidence of infusion reactions in previously treated patients [13, 15, 19, 20]. Moreover, premedication with antihistamine, steroids and acetaminophen prior to rituximab infusion is often sufficient to prevent infusion reactions [13].

The treatment of infusion reactions consists of infusion interruption and symptomatic treatment. The best-documented case of severe respiratory failure following a first rituximab administration in a case of Asian-variant intravascular lymphoma is shown in Fig. 2.
Fig. 2 A very well-documented case of severe pulmonary complications after initial treatment with rituximab for Asian-variant intravascular lymphoma. The chest X-ray before (a) and after (b) rituximab administration. The post-rituximab chest films showed newly developed infiltrations and consolidation. High-resolution computed tomography of the chest (panel c) showed ground-glass opacity and consolidation associated with reticulation in both lungs as well as moderate bilateral pleural effusions. The diagnostic impression was interstitial pneumonitis. Histopathological examination (panel d) showed pulmonary hemorrhage with an intra-alveolar proteinaceous exudate containing erythrocytes and necrotic neutrophils suggestive of acute capillaritis. From [84] with permission.
Tumor Lysis Syndrome

Tumor lysis syndrome is a life-threatening complication of highly aggressive malignancies, described mainly in lymphomas with high tumoral burden and hyperleukocytic leukemias. It is characterized by a massive release of the content of tumoral cells (mainly potassium, phosphate and nucleic acids) into the blood circulation, spontaneously or following cancer chemotherapy, immunotherapy or targeted therapy. Tumor lysis syndrome may be complicated by AKI, which impacts negatively on the prognosis of patients with cancer [21]. Although tumor lysis syndrome is a well-described complication of chemotherapy for aggressive lymphoma, it has not been frequently reported in patients treated with rituximab. Only a few cases have been reported in the literature. In these cases, it is noteworthy that the tumor lysis syndrome occurred in the context of high burden lymphoproliferative disorders (bulky lymphadenopathies or high white blood cell [WBC] count) [22]. Mortality rate was high since 4/8 patients died from the tumor lysis syndrome [23, 24]. However, the lack of case reports of tumor lysis syndrome following rituximab infusion...
may be linked to a publication bias because only severe or uncommon tumor lysis syndrome cases may have been published.

**Digestive Perforation**

Digestive tract perforation is a rare but serious complication of rituximab infusion. It was reported in 37 cases/730,000 exposures in a 2006 vigilance report, resulting in 4 deaths [25]. Digestive tract perforation occurred exclusively in the setting of lymphoma, mostly post-transplant lymphoproliferative disorders involving the gut. Although this complication may occur with other chemotherapies, treatment with rituximab increases the risk of digestive perforation from 0.15 to 0.38% [26]. In a series of 46 patients with post-transplant lymphoproliferative disorders receiving rituximab monotherapy, one patient experienced gut perforation [27]. The median time from rituximab infusion to perforation is 6 days (range 1–77) [26]. The small bowel and colon may be involved equally [25, 28–30].

**Serum Sickness**

Serum sickness is linked to a hypersensitivity reaction (Gell and Coombs classification type III), with immune complex deposits. Indeed, an antigen and its antibody form an immune complex which deposits in vessel walls and tissues and induces complement cascade activation and inflammation. Serum sickness may be a rare complication of rituximab infusion. Clinical signs usually occur between day-7 to day-14 following rituximab infusion, and consist of fever, polyarthritis, purpura, palmar erythema, urticarial rash and AKI. Complement activation is observed as C3, C4 and CH50 rates decrease in the serum [31].

Only 32 cases of rituximab-induced serum sickness have been reported in the literature. This complication occurred mostly in the setting of autoimmune diseases, such as Sjögren syndrome [32] and immune thrombocytopenic purpura [33]. It is less described in the context of non-Hodgkin lymphomas. These different incidences may be explained by the fact that polychemotherapies are often used in non-Hodgkin lymphomas and may reduce the inflammatory reaction; or by the fact that identified risk factors for serum sickness [32], namely polyclonal hypergamma-globulinemia and rheumatoid factor are more frequently reported in autoimmune diseases, especially Sjögren syndrome.

HACAs (human anti-chimeric antibodies) may be observed and could explain part of the physiopathology. HACA and rituximab form immune complex deposits and activate the complement cascade. HACAs were studied in seven cases of serum sickness under rituximab, and were present in five cases [32]. Steroids are often effective to treat this complication [34].

A similar complication may occur when rituximab is used to treat cryoglobulinemic vasculitis. Sène et al. [35] described four cases of severe “flare” and two of serum sickness among 22 patients treated with rituximab for hepatitis C virus
(HCV)-associated mixed cryoglobulinemic vasculitis. The pathophysiology of disease flare is similar to serum sickness as rituximab and cryoglobulin precipitate in vessel walls, inducing vasculitis. This interaction is due to the rheumatoid factor activity of mixed cryoglobulins. Cryoglobulinemia flares with rituximab occurred 1–2 days after rituximab infusion, and were successfully treated by methylprednisolone pulses and plasma exchanges.

**Thrombocytopenia**

Rituximab-induced acute thrombocytopenia is rare and reported in only 17 case reports in the literature [36, 37]. Identified risk factors included mantle cell lymphoma (70%), splenomegaly and/or bone marrow infiltration by lymphoma. Thrombocytopenia occurred 1–3 days after rituximab infusion and resolved quickly over 7–10 days. It was profound, with a median platelet count of 10,000/mm³ but benign since no severe hemorrhage was reported. Nonetheless, most patients received platelet transfusion. Thrombocytopenia relapsed in 42% of patients in whom rituximab was reintroduced.

**Delayed Onset Toxicity**

**Lung Toxicity**

Rituximab has been involved in several cases of diffuse interstitial pneumonia. Two literature reviews of 45 [38] and 126 [39] cases are available. The overall mortality rate is around 15%. Lung toxicity occurred mostly in the setting of non-Hodgkin lymphoma (93% cases) with an estimated frequency of 0.01–0.03% cases. Three types of diffuse interstitial pneumonia have been described according to their delay of onset:

1. **Hyperacute pneumonia** (11%), occurring a few hours after rituximab infusion, in the context of infusion reaction. This pneumonia usually evolves to acute respiratory distress syndrome (ARDS) requiring mechanical ventilation. Here, the cytokine release is most likely to be responsible for ARDS as described above and in Fig. 2.

2. **Acute/subacute pneumonia** (82%), occurring within two weeks following rituximab infusion, after a median of four treatments. Patients describe fever and dyspnea and 27% need mechanical ventilation. Chest computed tomography (CT) usually shows multifocal alveolar densities, associated with ground glass attenuation. Bronchoalveolar lavage (BAL) fluid shows mostly CD4 lymphocyte alveolitis. Organizing pneumonia is the prominent histological pattern at lung biopsy and steroids are effective in most cases. Relapses occur in 80% of cases after rituximab reintroduction.
3. Deferred and chronic pneumonia (7%), occurring in the eight weeks following the final rituximab infusion. Patients have multiple asymptomatic pulmonary macronodules and BAL fluid shows lymphocytic alveolitis. Lung biopsy shows organizing pneumonia and steroids are effective.

**Pneumocystis Pneumonia**

*Pneumocystis jirovecii* pneumonia is a dreaded opportunistic infection commonly described in patients with lymphoma, since they exert T cell defects from the lymphoproliferative disease, polychemotherapy and steroid administration. Although *P. jirovecii* pneumonia has been largely attributed to CD4+ lymphocyte immunosuppression, as usually seen in human immunodeficiency virus (HIV) infection, B cells and antibodies seem to be involved in the host defense against this fungal infection [40]. Until recently, it was not clear whether rituximab actually increased the risk for *P. jirovecii* pneumonia or not, because patients on anti-CD20 therapy frequently also receive chemotherapy and steroids (increasing *per se* the risk of *P. jirovecii* pneumonia) and/or co-trimoxazole prophylaxis (decreasing the risk of *P. jirovecii*) [26]. Nonetheless, a recent meta-analysis showed a higher risk of *P. jirovecii* under rituximab therapy in patients treated by polychemotherapy and steroids for lymphoma. The incidence was 28/942 (3%) with rituximab versus 5/977 (0.5%) without rituximab. The relative risk of *P. jirovecii* pneumonia with rituximab is estimated to be 3.65 (IC95% = 0.09–0.94). No case has been described under prophylaxis with co-trimoxazole [41]. In a case series of 30 patients who developed *P. jirovecii* pneumonia under rituximab, 10% had no lymphoma but auto-immune diseases (immune thrombocytopenia, rheumatoid arthritis or granulomatosis with polyangeitis). Moreover, 10% occurred under rituximab alone [40]. *P. jirovecii* pneumonia occurred with a median delay of 77 days after the final rituximab infusion. For the 10 patients with available data, low CD4+ lymphocyte levels were found. The manifestations were serious, as 88.5% of patients had criteria for ARDS and 30% died.

**JC Virus Reactivation: Progressive Multifocal Leukoencephalopathy**

Progressive multifocal leukoencephalopathy (PML) is a sub-acute/chronic infection of the brain, linked to JC virus (JCV) reactivation, seen in immunocompromised subjects. This opportunistic infection is usually observed in advanced stages of HIV infection, but has also been described in lymphoid neoplasms, and following immunosuppressive drugs, such as rituximab [42]. JCV is a ubiquitous double-stranded DNA virus [43]. Its seroprevalence is estimated at around 80–90% and asymptomatic primary infection occurs in childhood in 75% of the cases. The virus then remains latent in the kidney and mononuclear immune cells [26]. PML is a demyelinating disease of the central nervous system (CNS), occurring when JCV reactivation occurs in the context of lymphoid depletion. The spectrum of clinical manifestations associated with PML includes confusion, motor weakness, ataxia,
aphasia, visual symptoms [44]. These manifestations usually progress over weeks to months.

Brain magnetic resonance imaging (MRI) usually shows multifocal areas of subcortical and periventricular white matter demyelination. These lesions typically predominate in the parieto-occipital territory. They are hypointense in T1-weighted sequences, not enhanced after gadolinium injection, and hyperintense in T2-weighted sequences. JCV detection by polymerase chain reaction (PCR) in the cerebrospinal fluid (CSF) has an estimated sensitivity of 92% and a specificity of 92% in patients with acquired immunodeficiency disease (AIDS) [45]. In a series of 57 cases of rituximab-associated PML in non-AIDS patients, JCV was found in the CSF of only 54% of the cases [44]. If there is a high suspicion of PML with a negative PCR, brain biopsy must be performed [42]. No treatment has been shown to be effective except for immune restoration whenever possible. Mortality is high, around 90% over a median of 2 months.

Among 57 patients with PML receiving rituximab therapy [44], 52 had lymphoid malignancy, 2 had systemic lupus erythematosus, 1 had rheumatoid arthritis, and 2 had autoimmune cytopenia. A median of six rituximab doses (1–28) were administered before PML diagnosis (after a median delay of 5.5 months (0.3–66 months) following the last rituximab administration). As PML has largely been described in patients with non-Hodgkin lymphoma, the accountability of rituximab in this context is unclear. Indeed, PML has been associated with non-Hodgkin lymphoma (0.07% cases [44]), resulting from both the disease and the treatment-induced immunosuppression. In a 2005 report of 46 cases of PML occurring after non-Hodgkin lymphoma polychemotherapy, only four patients had received rituximab [46]. Among 307 HIV infected patients treated with rituximab for lymphoproliferative disorders, the incidence of PML was 1.4 cases/1,000 patient-years, which was not higher than what is usually described in AIDS patients (0.5–1.3/1,000 patient years) [43]. Nonetheless, in a monocenter retrospective study, no case of PML was described among 459 patients not exposed to rituximab but five cases were described among 517 exposed patients, making a rate difference of 2.2 (0.1–4.3)/1,000 person-years between the two groups [47].

In patients with connective tissue diseases, PML incidence is much lower. It is estimated to affect 0.4/100,000 patients with rheumatoid arthritis, and 4/100,000 patients with systemic lupus erythematosus [42]. Rituximab is the only disease-modifying drug that is clearly associated with an increased risk of developing PML in patients with rheumatoid arthritis. A 10-fold increased risk is estimated under rituximab therapy for patients with rheumatoid arthritis [42]. For patients with other connective tissue diseases, the risk modification is unknown since the use of rituximab is less common.

**Hepatitis B Reactivation**

Hepatitis B (HBV) reactivation may occur in patients with occult HBV infection (HbS Ag+, HbC ab+, HBV DNA–) treated with anti-cancer polychemotherapy, es-
Table 3 Prevalence of reactivation in hepatitis-B virus (HBV) seroconverted patients receiving rituximab

| First author (date, reference) | Prevalence % |
|-------------------------------|--------------|
| Kim (2013) [81]               | 2.4%         |
| Lu (2015) [58]                | 2.7%         |
| Matsui (2013) [82]            | 6.8%         |
| Hsu (2012) [55]               | 11.3%        |
| Huang (2013) [59]             | 17.9%        |
| Yeo (2009) [56]               | 23.8%        |

Especially when rituximab is added to the regimen. The prevalence of reactivation in these patients is estimated at between 16 and 80% [48]. In a recent meta-analysis, rituximab was a significant risk factor for HBV reactivation in HBsAg+ patients treated with polychemotherapy (RR 2.14; 95% CI 1.42–3.22) [49]. Thus, it is recommended that preventive antiviral treatment (lamivudine, entecavir or tenofovir) be given to exposed patients [50–52]. Moreover, rituximab promotes HBV reactivation in patients with ‘resolved’ (seroconverted) HBV infection (HBsAg–, HbCab+, HBV DNA–). Table 3 reports HBV reactivation rates in patients treated with rituximab. The relative risk of HBV reactivation in seroconverted HBV patients under rituximab therapy was estimated to be 5.52 (95%CI: 2.05–14.85) in a recent meta-analysis [49].

In patients with autoimmune diseases, rituximab-induced HBV reactivation in seroconverted patients has been reported as a rare event [53, 54]. The median time from the start of chemotherapy to HBV reactivation is 21 weeks (range, 3–57) [55]. The clinical severity of these reactivations varies from asymptomatic cases to severe hepatitis (2.7%) [55], hepatic failure or death (0.05%) [56]. Moreover, HBV reactivation could be associated with higher mortality rates in non-Hodgkin lymphoma patients, because of the need to discontinue chemotherapy in this context [57]. Identified risk factors for HBV reactivation in HBV seroconverted patients are: undetectable baseline HbSab [56, 58], male sex [56] and elevated International Prognostic Index (IPI) score ≥ 3 [58].

For the prevention of HBV reactivation in HBV-seroconverted patients, two strategies are described in the literature. The first is monthly monitoring of blood HBV DNA, with antiviral treatment only when HBV PCR becomes positive. The second is preventive treatment. Although there seem to be more cases of viral load elevation with the first strategy, both approaches are equally effective to prevent mortality, hepatitis and delayed chemotherapy administration [55, 57–59]. As lamivudine is not effective to reduce mortality in case of HBV reactivation [57], curative treatment with entecavir or tenofovir is recommended.

**Varicella-Zoster Virus Reactivation**

In several randomized controlled trials (RCTs), varicella-zoster virus (VZV) reactivation was more frequent in groups receiving rituximab [3]. Overall, the incidence of herpes zoster infection increased from 1% (control group) to 4.5% (rituximab
group) in elderly patients treated with polychemotherapy for non-Hodgkin lymphoma [5]. In patients with rheumatoid arthritis, rituximab was associated with an incidence of VZV infection of 1.87/100 patient-years. This risk was not higher in the rituximab group than in a group of patients receiving other biotherapies [60] or placebo [16].

Among 64 reported cases of serious viral infections under rituximab, 9.4% were reported to be linked to VZV [61]. For these six patients, there was only cutaneous involvement, but several dermatomes could be involved. There are only three case reports of disseminated VZV infections under rituximab associated with other chemo/immunotherapies, with no clear evidence of rituximab accountability [62]. Despite its severity, with a mortality rate estimated to be 29%, it is most often observed in very immunocompromised patients and the role of rituximab in disseminated VZV infection is controversial [62].

**Bacterial Infections**

Rituximab does not seem to increase the risk of bacterial infections overall. In the context of polychemotherapy for non-Hodgkin lymphoma, rituximab did not increase the risk of bacterial infections in RCTs or subsequent meta-analyses [3, 63]. In patients with rheumatoid arthritis, the adjunction of rituximab was not associated with a risk of bacterial infection compared to standard treatment alone as published in available RCTs and meta-analyses [16, 64]. Bacterial pneumonias were the most common severe infections (2%). In highly sensitized renal transplant recipients, rituximab did not increase the risk of bacterial infections, compared to other immunosuppressive regimens in a retrospective study [65, 66]. However, when rituximab is used as maintenance monotherapy in indolent non-Hodgkin lymphoma, the risk of severe bacterial infections increases, with one report noting that 19% developed bacterial infections and 1–4% grade III–IV infections [3]. Meta-analyses report a relative risk between 1.67 and 2.85 for the risk of bacterial infections and of 3.55 for grade III–IV infections [8, 67].

**Late-Onset Neutropenia**

Late-onset neutropenia under rituximab treatment is defined as a leukocyte count < 1,000/mm³, occurring 3–4 weeks after the last injection of the drug and a spontaneous return to a normal neutrophil count thereafter. Overall, late-onset neutropenia is estimated to occur in 14% of patients receiving rituximab therapy [68] and the risk of infection is estimated at 17% in patients with late-onset neutropenia [68]. The incidence of this complication varies according to the indication for rituximab. Neutrophil counts < 500/mm³ were described in 5–13% of patients treated for non-Hodgkin lymphoma, in 42% of patients receiving hematopoietic stem cell transplantation, and in 3% of those treated for autoimmune diseases [68]. Late-onset
neutropenia occurred in 42% of kidney transplant recipients receiving rituximab, compared to 28% of patients not receiving rituximab [69].

Late-onset neutropenia has been reported between 46 and 384 days after the first injection of rituximab [26]. Neutrophils return to normal after between 1 to 17 weeks [67, 70, 71]. Late-onset neutropenia resolution can also be obtained using granulocyte colony-stimulating factor (G-CSF) administration [72].

The mechanism of late-onset neutropenia is linked to inhibition of granulopoiesis with a maturation blockade in the bone marrow [70]. The hypothesis that late-onset neutropenia could be due to a defect of granulopoiesis linked to a competition with intra-medullary B lymphopoiesis has been voiced. This hypothesis was sustained by more intense B-cell activating factor (BAFF) elevation in patients with late-onset neutropenia [69, 73]. Other authors have hypothesized that late-onset neutropenia could be due to autoantibody production against neutrophils progenitors [74, 75]. Finally, large granular lymphocyte proliferation was observed in several patients with rituximab-induced late-onset neutropenia [26, 68]. This could explain late-onset neutropenia as large granular lymphocyte oligoclonal proliferation is known to induce neutropenia [76].

**Hypogammaglobulinemia**

Although rituximab does not target plasmocytes that do not present the CD20 antigen, a decrease in serum immunoglobulin levels has been reported under this treatment [26]. In a series of patients treated with rituximab for indolent non-Hodgkin lymphoma, there was a decrease in IgM levels to 73% of baseline in patients receiving long-term treatment, but not in IgG or IgA levels. These patients did not present more infectious events [77].

In 22.4% of patients with rheumatoid arthritis under rituximab therapy, there was a significant decrease in IgM levels, 3.5% in IgG levels and 1.1% in IgA levels. These patients also had no increased infection rate during follow-up [16]. In a series of 30 children treated with rituximab for immune thrombocytopenia, a slight decrease in IgG, A, and M levels was reported over the year following rituximab therapy, without any case of infection [78]. In a multicenter retrospective study, 3/189 (1.6%) patients receiving rituximab for immune thrombocytopenic purpura developed hypogammaglobulinemia < 5 g/l. They presented chronic sinusitis, recurrent bronchitis, and one case had enteroviral meningoencephalitis. The authors analyzed published data on rituximab use in immune thrombocytopenic purpura and noted that 21/192 (10%) patients had an asymptomatic decrease in gammaglobulins. Moreover, there are only four other cases in the literature of symptomatic hypogammaglobulinemia under rituximab for immune thrombocytopenic purpura. Among them, another case developed enteroviral meningoencephalitis [79].
Conclusion

In summary, rituximab is an effective and widely used treatment for non-Hodgkin lymphoma, autoimmune, inflammatory and orphan diseases, with a good tolerance and safety profile, but rare toxic events. The drug is administered as curative treatment, alone or in combination with chemotherapy, as well as in preventive and maintenance therapy. Therefore, the exposed population is large and increasing, making these toxic events likely to present in our ICUs. Critical care specialists must be aware of the drug’s different potentially serious adverse effects, which may occur immediately, or short- or long-term after rituximab infusion, depending on the mechanism of toxicity. The toxicity of more recently released anti-CD20 antibodies is less known. Nonetheless, ofatumumab (used in CLL) or obinutuzumab (used in both CLL and follicular lymphoma) seem to share toxicities with rituximab (e.g., infusion reaction, late cytopenia, progressive multifocal leucoencephalopathy or HBV reactivation [82]), prompting careful surveillance of patients receiving new anti-CD20 antibodies.

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