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Hypogammaglobulinemia, late-onset neutropenia, and infections following rituximab

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Abstract

Rituximab is a chimeric anti-CD20 monoclonal antibody that targets CD20-expressing B-lymphocytes, has a well-defined efficacy and safety profile, and is broadly used to treat a wide array of diseases. In this review, we cover the mechanism of action of rituximab and focus on hypogammaglobulinemia and late-onset neutropenia—two immune effects secondary to rituximab—as well as subsequent infection. We review risk factors and highlight key considerations for immunological monitoring and clinical management of rituximab-induced secondary immune deficiencies. In patients treated with rituximab, monitoring for hypogammaglobulinemia and infections may help to identify the subset of patients at high risk for developing poor B-cell reconstitution, subsequent infections, and adverse complications. These patients may benefit from early interventions such as vaccination, antibacterial prophylaxis, and immunoglobulin replacement therapy. Systematic evaluation of immunoglobulin levels and peripheral B-cell counts by flow cytometry, both at baseline and periodically after therapy, are recommended for monitoring. Additionally, in those patients with prolonged hypogammaglobulinemia and increased infections following rituximab use, immunologic evaluation for inborn errors of immunity may be warranted in order to further risk stratify, increase monitoring, and assist in therapeutic decision making. As the immunologic effects of rituximab are further elucidated, personalized approaches to minimize the risk of adverse reactions while maximizing benefit will allow for improved care of patients with decreased morbidity and mortality.

Keywords

Rituximab; rituxan; anti-CD20; hypogammaglobulinemia; late-onset neutropenia; infection; secondary immune deficiency; humoral immune deficiency

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Introduction

Rituximab is a chimeric anti-CD20 monoclonal antibody that targets B-lymphocytes expressing the CD20 surface antigen [1,2]. Initially approved by the United States Food and Drug Administration in 1997, rituximab is used for a number of autoimmune conditions and B-cell malignancies, including rheumatoid arthritis, granulomatosis with polyangiitis, non-Hodgkin lymphoma, and chronic lymphocytic leukemia [3]. Rituximab is increasingly used off-label for treatment of kidney, autoimmune rheumatologic, and neurological diseases [4–7]. Rituximab therapy yields full B-cell depletion within 72 hours, a state of low or undetectable B-cell levels for 2–6 months, and a return to pretreatment B-cell levels within 12 months of rituximab treatment alone [8–10].

Although plasma cell and existing antibody levels are not altered, rituximab-induced B-cell depletion can affect humoral immune responses [8]. As a result, secondary immune deficiency —an acquired decrease in immune cell count or function due to extrinsic, non-genetic factors such as a medication [11]—can occur. Notably, in a subset of patients, rituximab has been associated with hypogammaglobulinemia and late-onset neutropenia, and these secondary immune deficiencies have subsequently been linked to increased risk of infection (Figure 1) [12–18]. Several risk factors have been identified that predispose patients to the development of hypogammaglobulinemia, late-onset-neutropenia, and infection following rituximab therapy. In these patients, monitoring serum immunoglobulins and peripheral B-cell flow cytometry can help to risk stratify and mitigate morbidity and mortality.

In this review, we begin with a summary of the mechanism of action of rituximab. Hypogammaglobulinemia and late-onset neutropenia, which are two notable secondary immune effects due to rituximab, and their risk factors are reviewed. We then cover infections following rituximab and risk factors thereof, which comprise a major consequence of rituximab-induced immune deficiency. Immunological monitoring and clinical management of rituximab secondary immune deficiencies are highlighted. Other considerations, such as unmasking of inborn errors of immunity, are briefly explored. We conclude with an eye towards future research.

Mechanism of Action of Rituximab

Rituximab is a chimeric monoclonal antibody (mAb) that targets the CD20 surface molecule, which is a B-cell marker expressed by the vast majority of pre-B-cells, mature B-lymphocytes in the periphery and bone marrow, and memory B-cells, but not by hematopoietic stem cells, pro-B-cells, or terminally-differentiated plasma cells [1,2]. Rituximab consists of the variable region of murine anti-human CD20 fused to the Fc portion of human IgG1 kappa immunoglobulin [19]. Structurally, rituximab binds to an epitope on the large extracellular loop of CD20, inducing the redistribution of CD20 into lipid raft microdomains [1,20–22]. CD20 notably does not become internalized or shed from the cell membrane following mAb binding [23], and the close proximity of CD20's extracellular epitopes to the cell membrane improves mAb effector function efficacy [24]. Together, these features enable the sustained immunologic effect of rituximab [23].

Rituximab is thought to operate through several effector mechanisms. First, rituximab can cause direct signaling of apoptosis through caspase-dependent and caspase-independent pathways [19,25–31]. Second, the antibody's Fc portion can initiate complement-dependent cytotoxicity (CDC) and B-cell lysis via the assembly of a membrane attack complex through the classical complement pathway [32–34]. Third, rituximab can cause antibody-dependent cellular cytotoxicity (ADCC) when its Fc region binds to the FcγRIIIa of natural killer (NK) cells, leading to the formation of a non-selective pore on the target B-cell membrane and target cell apoptosis through the actions of NK-released perforin and granzyme B, respectively [35–37]. Fourth, antibody-dependent cellular phagocytosis (ADCP) can occur when macrophages recognize rituximab-coated target cells through various Fcγ receptors on the macrophage cell surface, leading to phagocytosis of the target cell [37]. Synergistic and antagonistic interactions may exist between these different effector mechanisms [35,38–40].

Hypogammaglobulinemia After Rituximab

Hypogammaglobulinemia following rituximab has been reported in a subset of patients [41,42]. Specifically, low IgG following rituximab has been reported in 3.5–40% of adult patients [13,43–45] and up to 27–50% of pediatric patients [46–50]. Hypogammaglobulinemia after rituximab appears to vary based on the underlying indication for rituximab, with lower rates of hypogammaglobulinemia after rituximab in patients treated for autoimmune conditions and higher for patients with underlying malignancy [51]. Additionally, both the prevalence [49,52] and severity [12] of hypogammaglobulinemia may increase with rituximab use. For example, in a cohort of 4,479 patients treated with rituximab, 19.3% of patients with normal IgG levels prior to rituximab developed hypogammaglobulinemia, 23.1% of patients with mild hypogammaglobulinemia pre-rituximab progressed to moderate or severe hypogammaglobulinemia, and 21.5% of those with moderate hypogammaglobulinemia pre-rituximab progressed to severe post-rituximab [12]. While less often described in the literature, decreases in IgM and IgA have also been reported [49].

Risk Factors for Hypogammaglobulinemia After Rituximab

Numerous potential demographic, clinical, and pharmacologic risk factors have been associated with the development of hypogammaglobulinemia following rituximab (Table 1).

Low immunoglobulin levels at baseline

In multiple adult and pediatric patient populations, lower serum IgG levels prior to the start of rituximab therapy have been found to be strongly predictive of hypogammaglobulinemia [12,49,51–57]. Several studies have also found lower IgM levels at baseline or IgM deficiency to be predictive of low post-rituximab immunoglobulin levels [48,57–59]. Additionally, in a smaller set of studies and particularly in the pediatric subset, lower IgA levels or IgA deficiency has been documented as a risk factor [48,49].

Longer rituximab treatment

The number of rituximab treatment cycles (i.e., longer-term rituximab treatment) has been shown to be a risk factor for hypogammaglobulinemia in numerous patient populations,

including in many studies of rheumatoid arthritis patients [45,60–63]. A clinical trial of more than 2,500 rheumatoid arthritis patients followed for over 5,000 person-years demonstrated that multiple rituximab infusions are one of the most important predictors of hypo-IgM: with each subsequent 6-month treatment cycle, the proportion of patients with low IgM increased, with an increase of ~10% of patients following the initial cycle and up to 40% of patients after five cycles [64,65]. In lymphoma patients, rituximab given in more than 8 doses was associated with prolonged hypogammaglobulinemia longer than 6 months [66]. Similarly, in a small cohort of 15 neuromyelitis optica patients, longer rituximab treatment was associated with hypogammaglobulinemia [67]. In a pediatric population of roughly 400 patients with varying indications for rituximab use, a retrospective study found that the higher the number of doses of rituximab, the stronger the association with hypogammaglobulinemia [68]. Taking the evidence together, a recent review has found that the use of more than one dose of rituximab and maintenance regimens of the antibody represent risk factors for hypogammaglobulinemia [51].

Glucocorticoids

Use of glucocorticoids has been associated with hypogammaglobulinemia, in particular moderate-to-high prednisone exposure at rituximab onset [69] and prednisolone use at 12 months following rituximab [53] in patients with autoimmune rheumatic diseases. Of note, hypogammaglobulinemia incidence was reported to be more pronounced in a subgroup of ANCA-associated vasculitis patients (45%) as compared to rheumatoid arthritis patients (22%) and connective tissue disorder patients (9.1%) [69]. Further indirect evidence supporting glucocorticoid use as a risk factor for hypogammaglobulinemia can be found in studies of multiple sclerosis patients treated with rituximab, where IgG levels post-treatment remain stable when concomitant systemic glucocorticoids not used [64,70,71]. In a pediatric cohort of rituximab-treated patients, glucocorticoid therapy in the month prior to rituximab use was a significant predictor of both new-onset hypogammaglobulinemia and infectious complications [50]. In rare cases, dexamethasone has been implicated as a risk factor for hypogammaglobulinemia in immune thrombocytopenia patients treated with rituximab [72].

Other immunosuppressants

Use of immunosuppressive medications such as mycophenolate mofetil, when used in conjunction with rituximab, is associated with hypogammaglobulinemia [51,58,73]. When the immunological mechanisms of these drugs are considered together, a two-pronged pathway emerges explaining how coadministration may lead to decreased levels of immunoglobulin and yield persistent hypogammaglobulinemia: naive, mature, and memory B-cells are depleted due to rituximab, while T cell and B-cell proliferation are inhibited due to the mycophenolate mofetil [74]. Data on the risk of hypogammaglobulinemia with other immunosuppressants such as cyclophosphamide have been mixed, perhaps due to heterogeneity in patient populations assessed. Some studies have linked concomitant cyclophosphamide use [75,76], cumulative cyclophosphamide dose in patients with granulomatosis with polyangiitis [55], and prior cyclophosphamide exposure [53] with increased risk of IgG depletion post-rituximab. However, an association between cyclophosphamide and hypogammaglobulinemia was not replicated in studies of patients with autoimmune disorders such as lupus [52,77].

Chemotherapeutics

In patients with B-cell malignancies such as non-Hodgkin lymphoma, certain chemotherapeutic drugs have been identified as risk factors for low immunoglobulin levels post-rituximab in some studies, but the evidence is mixed. For instance, purine analogues [43,51,78] and fludarabine [66,78–80] have been identified as predictors of hypogammaglobulinemia in some studies. However, other studies have demonstrated no significant difference in hypogammaglobulinemia rates when rituximab and fludarabine are co-administered versus fludarabine regimens alone [78].

Disease-specific medical history

Disease- and context-specific medical history has been shown to be an important predictor of hypogammaglobulinemia. For example, in children with autoimmune cytopenias, the diagnosis of autoimmune hemolytic anemia or Evans syndrome is a risk factor for the development of hypogammaglobulinemia [48]. In lymphoma patients with complicated nephrotic syndrome, a past history of steroid-resistant nephrotic syndrome is a risk factor [56]. In pediatric patients with autoimmune diseases, the presence of autoimmune central nervous system disease is a risk factor for hypogammaglobulinemia [46]. In patients with granulomatous polyangiitis, kidney involvement has been shown to be a risk factor [55]. In lymphoma patients, there have been reported cases of hypogammaglobulinemia post-rituximab when patients were subjected to further cellular immunosuppression, such as organ transplantations [81–83], stem cell transplantations [84–86], and HIV infection [87]. In particular, allogeneic stem cell transplants were complicated with low immunoglobulins more often than autologous transplantation [88].

Age

Age has been implicated as a risk factor for post-rituximab hypogammaglobulinemia, associated with the extremes of age. In adult patients, older age was found to be predictive of low IgG levels in numerous studies [12,54,55,63]. However, in pediatric patients with autoimmune cytopenias, younger age at rituximab use was associated with low immunoglobulin post-therapy [48]. In children with steroid-dependent nephrotic syndrome, a lower median age was associated with hypogammaglobulinemia in cohorts from Japan, France, and Italy [47,73,89].

Biological sex

The association between biological sex and hypogammaglobulinemia has been generally inconclusive. Some studies suggest that female sex is associated with decreased immunoglobulin levels [53], while other studies suggest that male sex is associated [55].

Late-Onset Neutropenia After Rituximab

Late-onset neutropenia has been an increasingly common following rituximab and is defined as low absolute neutrophil counts $<1.5 \times 10^9$/L occurring 4 or more weeks after the last dose of rituximab, in the absence of pre-existing neutropenia, and without any other identifiable cause [90]. Late-onset neutropenia has been reported to occur a median of 38 to 175 days following rituximab use [18,91,92]. The prevalence of late-onset neutropenia ranges

depending on underlying disease from 1.3 to 27% [17,93–96]. In the majority of cases, this late-onset neutropenia is benign and resolves spontaneously, while in a subset of patients with neutropenia, subsequent infection develops. However, some studies argue that late-onset neutropenia does not contribute to infection risk as much as hypogammaglobulinemia [65,97,98].

Risk Factors for Late-Onset Neutropenia After Rituximab

Several risk factors for late-onset neutropenia have been identified, though there sometimes exists heterogeneity in the patient populations analyzed [99]. Nevertheless, possible risk factors for late-onset neutropenia can be grouped into the following thematic categories: cancer stage and chemotherapeutics, receptor polymorphisms, immunological, and demographic (Table 2).

Cancer stage and chemotherapeutics

More advanced stages of cancer have been associated with late-onset neutropenia in B-cell lymphoma patient populations in several studies [100–102]. For instance, in one particular retrospective cohort study, an advanced stage of cancer was associated with a 356% increase (HR CI: 1.02–12.7) in the risk of developing late-onset neutropenia [102]. Similarly, higher Ann Arbor staging was associated with a 607% higher odds (OR CI: 1.47–25.13) of late-onset neutropenia in diffuse large B-cell lymphoma patients undergoing combination chemotherapy [100]. Previous exposure to chemotherapeutics such as purine analogs is also a significant risk factor for late-onset neutropenia in several studies [18,96,101,103–105].

Receptor polymorphisms

Polymorphisms in the FCGR3A gene encoding the IgG Fcγ IIIa receptor—particularly the 158V/F and 158V/V variants—may correlate with increased risk of late-onset neutropenia post-rituximab [17,93,106]. In one study of autologous stem cell transplant patients, each additional V allele tripled a patient's risk of neutropenia [106]. Results in B-cell lymphoma patients echoed these results, with one particular study highlighting that having the 158V/V or 158V/F polymorphism led to a 47% higher odds (OR CI: 1.21–1.78) of late-onset neutropenia as compared to 158F/F [107,108].

Immunological

Prior autologous peripheral blood stem cell transplantation was identified as a risk factor in several studies [103–105,109]. Previous treatment with immunosuppressants such as methotrexate has been identified as a neutropenic risk factor in a set of studies [101,102,110]. In contrast to hypogammaglobulinemia, there are fewer reports that support an association between longer rituximab treatment and late-onset neutropenia, and the evidence is mixed. While one study has reported that greater than four rituximab doses is a risk factor for late-onset neutropenia [110], other studies have found that more doses are not a significant risk factor [102]. As it pertains to immunologic pathology, bone marrow involvement of diffuse large B-cell lymphoma was a risk factor for late-onset neutropenia in a single cohort of 181 patients [100].

Demographic

Several studies have shown that older age, defined as >60 years or >65 years, is a risk factor of late-onset neutropenia [98,100,102,111,112]. However, two larger retrospective studies of combination chemotherapy with rituximab did not implicate old age as a factor of late-onset neutropenia [113,114]. Female gender has also been implicated as a risk factor of late-onset neutropenia in a few studies [98,100]. Age and gender both were not identified as risk factors in another study [110].

Infections After Rituximab

A number of viral, bacterial, fungal, and protozoal infections have been observed in patients treated with rituximab. Growing evidence suggests that rituximab predisposes to infections and can cause immunosuppression via hypogammaglobulinemia, late-onset neutropenia, and delayed onset cytopenia, particularly with maintenance therapy [115,116]. Cohort studies have reported an increase in severe infections after rituximab use [12]. Prevalence of post-rituximab severe infections has been estimated to be 15.4% in a large meta-analysis of ANCA-associated vasculitis patients (CI: 8.9%–23.3%) [117], and 23.7% in pediatric patients [49], with sinopulmonary infections as some of the most commonly reported particularly in patients with hypogammaglobulinemia [118,119]. A pooled analysis of global clinical trial data reported that the overall serious infection rate was 3.94/100 patient-years in a population of 3,194 rheumatoid arthritis patients [65].

The association between infection and rituximab therapy appears to be dependent on the underlying disease process and cohort studied. For instance, recent systematic reviews and meta-analyses in patients with lymphoma have found that rituximab maintenance therapy was associated with significantly increased rates of infection and infection-related adverse events [115,120,121]. However, in randomized control trials conducted with rituximab in rheumatoid arthritis patients, some studies have reported higher infection incidence [115,122,123] while others have not [124]. Little data is available regarding infection in organ transplant recipients on rituximab, while evidence supports increased infection risk in renal transplant patients [115].

It remains challenging to determine if these infections are directly caused by rituximab-mediated processes such as low immunoglobulin levels or low neutrophil count, or whether they are facilitated by immune dysregulation inherent to the underlying disease pathologic process or concomitant immunomodulation therapy. Therefore, patients should be monitored for signs and symptoms of infection throughout the course of their rituximab regimens.

Acute viral infections

Several viral infections have been described in association with rituximab [125]. These include enteroviral meningoencephalitis [126–129], parvovirus B19 [130–133], cytomegalovirus [86,134,135], and West Nile virus [136,137]. In context, enteroviral meningoencephalitis is a known complication in other B-cell immunodeficiencies, parvovirus B19 often co-presents with progressive bicytopenia or pure red cell aplasia in reported rituximab cases, and cytomegalovirus is highly uncommon except in cases of allogeneic transplant or concomitant HIV [125]. Rare cases of viral infection with varicella zoster virus [138–140], herpes

simplex virus [139], echovirus [134], BK virus [141,142], and influenza A virus [134,143] have been reported [115].

In one particular study that documented both bacterial and viral infections post-rituximab, the most common type of infection that manifested was upper respiratory infection and bacterial sinopulmonary infection, followed by pneumonia and cellulitis [43]. A few cases of urinary tract infection, ocular infection, and respiratory syncytial virus were also observed in singular occurrences [43].

COVID-19

Large cohort studies and meta-analyses have demonstrated that rituximab therapy is associated with severe SARS-CoV-2 (COVID-19) outcomes [7,144–147]. Several case reports echo these results, finding that COVID-19 outcomes are more likely to be fatal in addition to having longer, more relapsing, and more atypically-symptomatic clinical courses post-rituximab therapy [148,149]. A study of multiple sclerosis and neuromyelitis optica spectrum disorder patients indicated that rituximab therapy was associated with a higher incidence of COVID-19 infection, a higher case fatality rate, and a higher frequency of serious illness [150].

Chronic viral infections

There is established evidence for increased viral infections with chronic pathology following rituximab [125]. In particular, rituximab has been linked with reactivation of latent hepatitis B virus, with sequelae including acute hepatitis and fulminant liver failure, following chemotherapy in numerous cases of hematologic malignancies [125,151–155]. Screening for latent hepatitis B infection is recommended prior to initiating rituximab [156]. Additionally, screening for hepatitis B core antibody prior to initiation of immunoglobulin replacement therapy (IgRT) is recommended as hepatitis B core antibody can be transferred passively through IgRT [157]. In patients on IgRT who require treatment with rituximab, presence of a positive hepatitis B core antibody may lead to concern for chronic latent hepatitis B that requires treatment with antivirals given the risk of reactivation of hepatitis B, which can potentially be fatal. Rituximab has also been associated with progressive multifocal leukoencephalopathy, caused by the JC polyomavirus, mainly in cases of hematologic malignancies but also in rheumatoid arthritis, immune cytopenia, and systemic lupus erythematosus [86,125,142,158].

Bacterial infections

Rituximab has been associated with acute infection from a variety of bacterial microbes. Multiple reports have documented infection with *Haemophilus influenzae* [13,116,159]. Several cases have reported infection with *Campylobacter fetus* [160–162] and *C. jejuni* [163,164]. Rare cases of *Staphylococcus aureus*, *Streptococcus pneumoniae*, shigella, and listeria have been reported [115,123,154]. Severe infections with *Mycobacterium kansasii, M. avium*, and *M. wolinskyi* have been reported [165,166]. The treatment setting may also contribute to infection risk. For instance, in patients with systemic autoimmune diseases, hospital-acquired infection may be an important cause of bacterial infections [167].

Fungal and protozoal infections

Fungal and protozoal infections have been reported rarely following rituximab. The risk for fungal and protozoal infections after rituximab is likely multifactorial due to factors including concomitant medications such as steroids or the underlying disease process. An additional potential mechanism that has been proposed is that given the effect of rituximab on B- cells, there may be a deleterious impact on the induction, maintenance, and activation of cell-mediated immunity due to impaired B- and T- cell cooperation [115,168,169]. Fungal infections such as *Pneumocystis jirovecii* pneumonia have been described in several patients, though this has often been in combination with other immunosuppressive medications in the setting of hematological malignancies, autoimmune diseases, and organ transplantation [125,134,170–177]. Other rare cases include aspergillosis [178,179] and osteomyelitis due to *Cryptococcus neoformans* var. *grubii* [180,181].

Infections with protozoan parasites have also been reported post-rituximab. A case-control study demonstrated that rituximab was associated with persistent babesiosis caused by *Babesia microti* [182]. A report documented a case of cerebral toxoplasmosis caused by *Toxoplasma gondii,* with circulation of parasite DNA in the cerebrospinal fluid, presence of bradyzoites in the brain tissue, and existence of a strong temporal relationship between rituximab treatment and neurologic symptom onset [183]. *Acanthamoeba* encephalitis was reported in a patient with lupus nephritis at one month post-rituximab [184].

Risk Factors for Infections After Rituximab

Many of the risk factors for post-rituximab hypogammaglobulinemia are similar to the risk factors for infection. Risk factors for infection can be conceptually grouped into the following categories: immunological, pharmacological, clinical comorbidities, and demographic (Table 3).

Immunological

Low IgG levels at the initiation of the rituximab course [51,119,185] and increased number of rituximab courses [51,186,187] have been implicated as risk factors for infection in many studies. Similarly, pre-existing hypogammaglobulinemia has been linked with post-rituximab infection risk, suggesting that routine screening of patients to identify those individuals at higher infection risk or with baseline immune dysfunction may be beneficial [12]. Low IgG or IgM levels post-rituximab therapy, in addition to the presence of low IgG levels for more than 6 months, have also been implicated as potential risk factors for infection in adult and pediatric patients [49,51,119,186].

Other immunological variables such as low count of CD4+ T helper lymphocytes at rituximab initiation, low baseline count of CD19+ B-lymphocytes, G-CSF administration following neutropenia, and low lymphocyte counts at nadir represent risk factors for infection [51,168,185,188]. Notably, G-CSF administration may be a marker of the severity of neutropenia rather than an independent risk factor.

Pharmacological

Concomitant use of glucocorticoids and other immunosuppressants have been identified as risk factors of infection [168,185,189,190]. Chemotherapy drugs have also been attributed as risk factors in some studies, though the results have been mixed. In one retrospective cohort study of autoimmune disease patients, it was found that previous cyclophosphamide treatment was a notable predictor of infection [190]. However, in randomized control trials of lymphoma patients and in meta-analyses, the addition of rituximab to cyclophosphamide and fludarabine, as well as combination therapies such as FCM (fludarabine, cyclophosphamide, and mitoxantrone) and CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), did not result in an increased incidence of infections [125,191–195].

Clinical comorbidities

In several patient populations, risk factors for infection include clinical comorbidities such as cardiac insufficiency, chronic lung disease, diabetes, cancer, and extra-articular involvement in rheumatoid arthritis [51,119,168,189,190]. Certain risk factors, however, appear to be more specific to particular patient populations. A low creatinine clearance rate was found to be a risk factor for infection in patients with systemic autoimmune diseases in a single-center case control study [185]. In patients with hematologic malignancies, HIV serostatus and type of malignancy were independently associated with infection in a two-year London cohort. A recent review suggests that smoking history and those who required a therapy switch are associated with infection risk in patients with underlying rheumatologic diseases [187]. Lack of pneumococcal vaccination was found to be predictive of infection in a cohort of patients with autoimmune diseases [190].

Demographic

Older age has been identified as a risk factor for infection in numerous studies [51,196]. In a single-center retrospective cohort of patients with autoimmune diseases, a higher Charlson comorbidity index and male gender was associated with higher infection risk [190].

Immunologic Monitoring and Clinical Management

Immunological monitoring can be used for surveillance and early identification in order to predict adverse outcomes such as hypogammaglobulinemia or infection both during and after the course of a patient’s rituximab therapy. Known immunological characteristics of B-cell depletion and B-cell reconstitution in rituximab patients can help guide immunological monitoring strategies. For example, the estimated duration of B-cell depletion ranges between 6 and 9 months in patients on rituximab therapy alone, and between 18 and 24 months in patients on chemotherapy in addition to rituximab [10]. However, some studies have reported delayed recovery of B-cells, with a median of 23 months post-rituximab [41]. The recovery of the CD27+ memory B-cell pool is slower than the recovery of non-memory B-cells, with CD27+ memory B-cells remaining significantly lower than that of controls (4.4% vs 31%) even after 1 year post-rituximab [197].

Serum immunoglobulin surveillance and peripheral B-cell flow cytometry

Measuring serum immunoglobulin levels and peripheral B-cell flow cytometry can aid in identifying pre-existing immune dysfunction as well as the development of immune dysfunction following rituximab. Pre-rituximab evaluation can identify baseline hypogammaglobulinemia, enabling preliminary risk stratification of patients from the start of rituximab initiation, and periodic monitoring following rituximab can aid with identification of secondary hypogammaglobulinemia or immune dysfunction that develops [12]. In addition, peripheral B-cell flow cytometry can help identify pre-existing B-cell deficiencies as well as detect B-cell recovery, improving longitudinal monitoring of complications [12].

Neutropenia

Since opportunistic infections due to rituximab can be due to associated late-onset neutropenia, a complete blood count can be of clinical utility in monitoring neutrophil levels. However, neutropenia often develops asymptomatically and patients only present to the hospital when the infection is in advanced stages, so there are no widely accepted guidelines regarding timing and monitoring for neutropenia [198–200].

Clinical management

There are several key features in management of hypogammaglobulinemia and infection risk following rituximab, such as vaccination, consideration of antibacterial prophylaxis, and initiation of immunoglobulin replacement (IgRT) in specific cases. Maintaining routine age-appropriate vaccination is critical in infection prevention in patients receiving rituximab. Decreased vaccine responses following rituximab use have been described for polysaccharide, protein, and conjugated vaccines. Given this, vaccinations are recommended 5–12 months following the last course of rituximab and 4 weeks before the next if possible [201–205]. Avoidance of live vaccines in patients on rituximab therapy is recommended as rituximab is considered high-level immunosuppression [204,206]. Additionally, patients with persistent hypogammaglobulinemia and/or recurrent infections may be considered for antibacterial prophylaxis, and/or immunoglobulin replacement therapy to reduce the risk of infections [12].

At our center, our approach is to extrapolate from the primary immune deficiency literature guidelines regarding evaluation of the function of antibodies using assessment of specific vaccine responses to determine if IgRT is warranted (Figure 2). This includes repeating the IgG level to assess for persistent hypogammaglobulinemia, as well as checking IgA and IgM. We then proceed with assessment of the *Streptococcus pneumonia* and tetanus IgG levels, with vaccination challenge if these are not adequately protective [207,208]. We consider an adequately protective response to the pneumococcal polysaccharide vaccine to be at least 70% or more serotypes to be ≥1.3 mcg/mL in adults and 50% or more serotypes to be to be ≥1.3 mcg/mL in children ages 2–5 years [207,209,210]. We consider an adequate protective level for tetanus vaccine to be 0.15 IU/mL [207,211]. These specific antibody levels are repeated 4–6 weeks after vaccination to assess for immunologic response. Of note, vaccination challenge can be difficult to interpret in those patients without adequate B-cell recovery, so should be delayed to at least 5 months after the last course of rituximab if possible.

If antibody levels are persistently low, we recommend shared decision making with the patient regarding initiation of IgRT (e.g., subcutaneous immunoglobulin or intravenous immunoglobulin) at a dose of 400–600 mg/kg/month as per the primary immune deficiency guidelines [208,212]. For IgG levels <150 mg/dL, we initiate IgRT without additional functional evaluation [208]. There is disease specific data for solid organ transplants and hematologic malignancies for consideration of IgRT for IgG levels <400 mg/dL [208]. In those patients with severe, recurrent, or atypical infections, we may also consider initiation of IgRT after risk/benefit discussion with the patient. We additionally evaluate lymphocyte subset and B-cell phenotyping if B-cells are present. Baseline and serial monitoring of B-cell counts can be useful in identifying patients with failure of B-cell reconstitution as well as prognostication regarding recurrence or relapse of disease [79,213,214]. Additionally, B-cell phenotyping can evaluate B-cell differentiation and recovery of switched memory B-cells [197], which may signal risk of relapse. We recheck immune monitoring labs periodically, including immunoglobulin levels and B-cell flow cytometry every 6 to 12 months to assess for immunologic impact and evidence of immune recovery (Figure 2).

Other Considerations in Rituximab Secondary Immune Deficiencies Unmasking of inborn errors of immunity

Rituximab has been associated with the unmasking of inborn errors of immunity and underlying immune deficiencies, particularly in pediatric patients [48,49]. Determining whether the immune defect is a primary immune deficiency or secondary to rituximab can be challenging since patients with inborn errors of immunity may first present with autoimmune cytopenias, malignancy, or granulomatous disease [215–218] and be treated with rituximab. This can confound the diagnosis and make it difficult to ascertain if hypogammaglobulinemia and B-cell dysfunction is a primary defect (i.e., due to genetics) that is being unmasked by the use of rituximab or secondary (i.e., due to medication effect [rituximab] alone). This problem is amplified since the majority of patients do not undergo immunologic screening prior to starting rituximab [12].

However, evaluating pretreatment immunoglobulin levels and B-cell counts may help to identify patients with underlying immune deficiency or immune dysregulation. For example, one of the diagnostic criteria for common variable immunodeficiency (CVID) is low levels of IgG in combination with low IgA and/or IgM [219]. There can be a significant delay in diagnosis of CVID and these patients may first present with, and be treated with rituximab for, autoimmune cytopenias [216]. Evaluating pre-treatment immunoglobulin levels may thus be helpful in uncovering underlying inborn errors of immunity and aid in the early diagnosis of a humoral immunodeficiency. This, in turn, may help to reduce morbidity and mortality due to increased monitoring and consideration of immunoglobulin replacement. In those cases where an underlying inborn error of immunity is suspected, genetic testing may be helpful. Additionally, periodic monitoring post-rituximab can help to identify immune recovery.

Conclusion

Rituximab is a monoclonal antibody that targets CD20-expressing B-cells and used for a wide array of indications. While generally well-tolerated with excellent efficacy, prolonged hypogammaglobulinemia and late-onset neutropenia can occur following rituximab and can be clinically significant with an increased risk for infections. Given this, systematic serum surveillance of immunoglobulin levels and B-cell counts by flow cytometry, both at baseline and periodically after therapy, may be helpful tools for identifying those patients at high risk who may benefit from intervention with vaccination, antibacterial prophylaxis, or immunoglobulin replacement therapy. In those patients with prolonged hypogammaglobulinemia and increased infections following rituximab use, additional immunologic evaluation for underlying inborn errors of immunity may be warranted in order to further risk stratify, increase monitoring, and assist in therapeutic decision making. Additionally, in patients with infection following rituximab, a complete blood count can be of clinical utility in monitoring neutrophil levels. Notably, there have been an increasing number of B-cell targeted therapies developed including other CD20 targeting agents such as ofatumumab, ocrelizumab, and obinutuzumab, which are human/humanized anti-CD20 therapies, designed to minimize immunogenicity while enhancing binding affinity or increasing cytotoxicity [220–223]. Given the expansion of B-cell targeted therapies, such as mAbs against CD19 [224,225], CD22 [226], and B-cell activating factor (BAFF) [227], BTK inhibitors [228], and chimeric antigen receptor (CAR) T-cell therapy targeting CD19 [229,230] and B-cell maturation antigen (BCMA) [231], the data gleaned from the rituximab experience will be of significant utility in identifying potential immunologic impacts and risks for infection, morbidity, and mortality.

Future research to identify predictive clinical and laboratory biomarkers of persistent hypogammaglobulinemia and infectious risk will be of great utility. As the mechanisms of rituximab on the immune system are further elucidated, tailored approaches to minimize risk of adverse reactions while maximizing benefit will be critical for providing personalized care for patients to improve outcomes.

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Abbreviations/Acronyms:

mAb	monoclonal antibody
IgG	immunoglobulin G
IgM	immunoglobulin M
IgA	immunoglobulin A
Fc	fragment crystallizable region of antibody

FcγRIIIa	Fc gamma receptor IIIa
NK	natural killer cell
CDC	complement-dependent cytotoxicity
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
G-CSF	granulocyte colony stimulating factor
BAFF	B-cell activating factor
BCMA	B-cell maturation antigen
IgRT	immunoglobulin replacement therapy
IVIG	intravenous immunoglobulin
scIg	subcutaneous immunoglobulin
OR	odds ratio
HR	hazard ratio
CI	95% confidence interval

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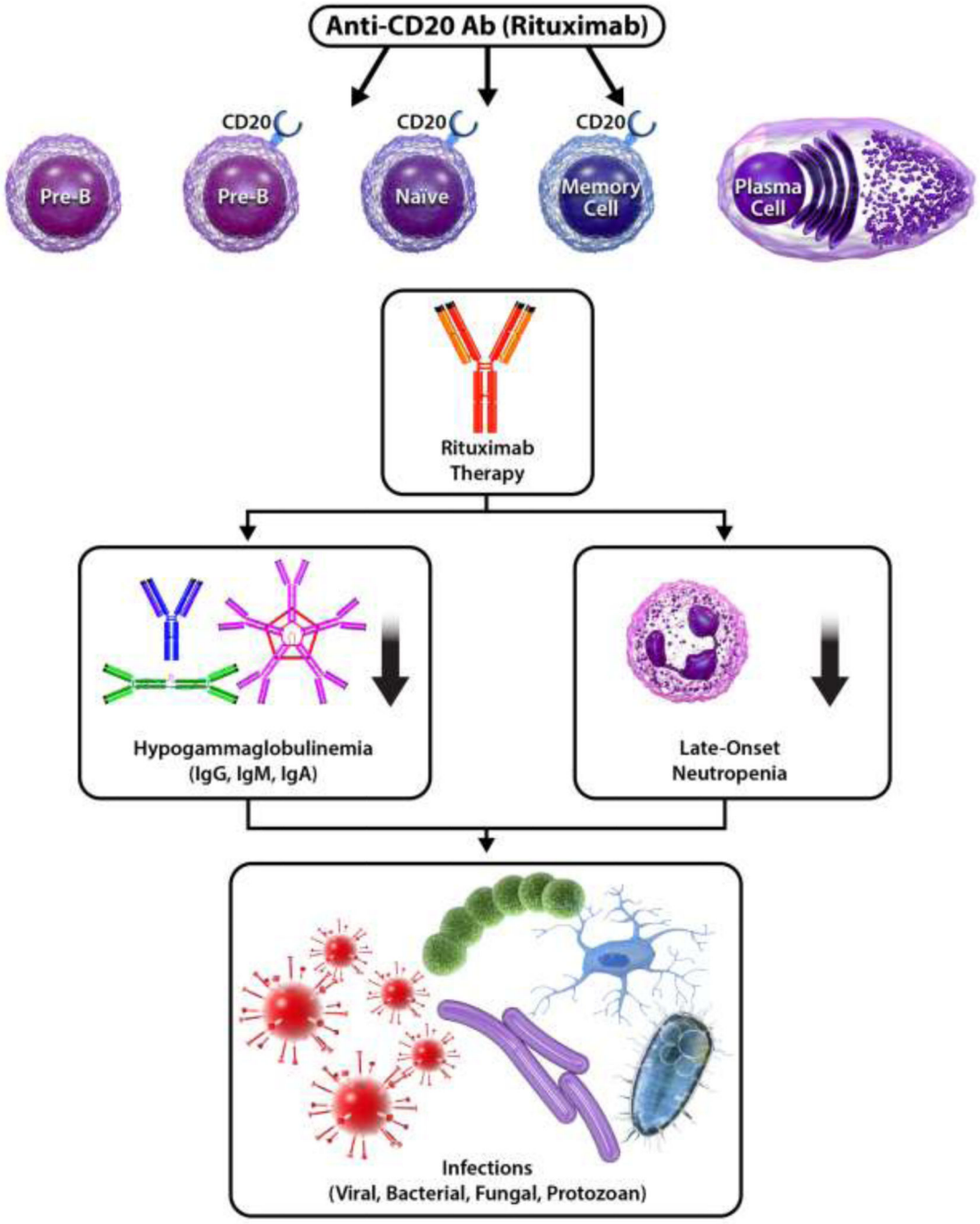

Figure 1.

Secondary immune deficiencies following rituximab, such as hypogammaglobulinemia and late-onset neutropenia, subsequently lead to increased infection risk.

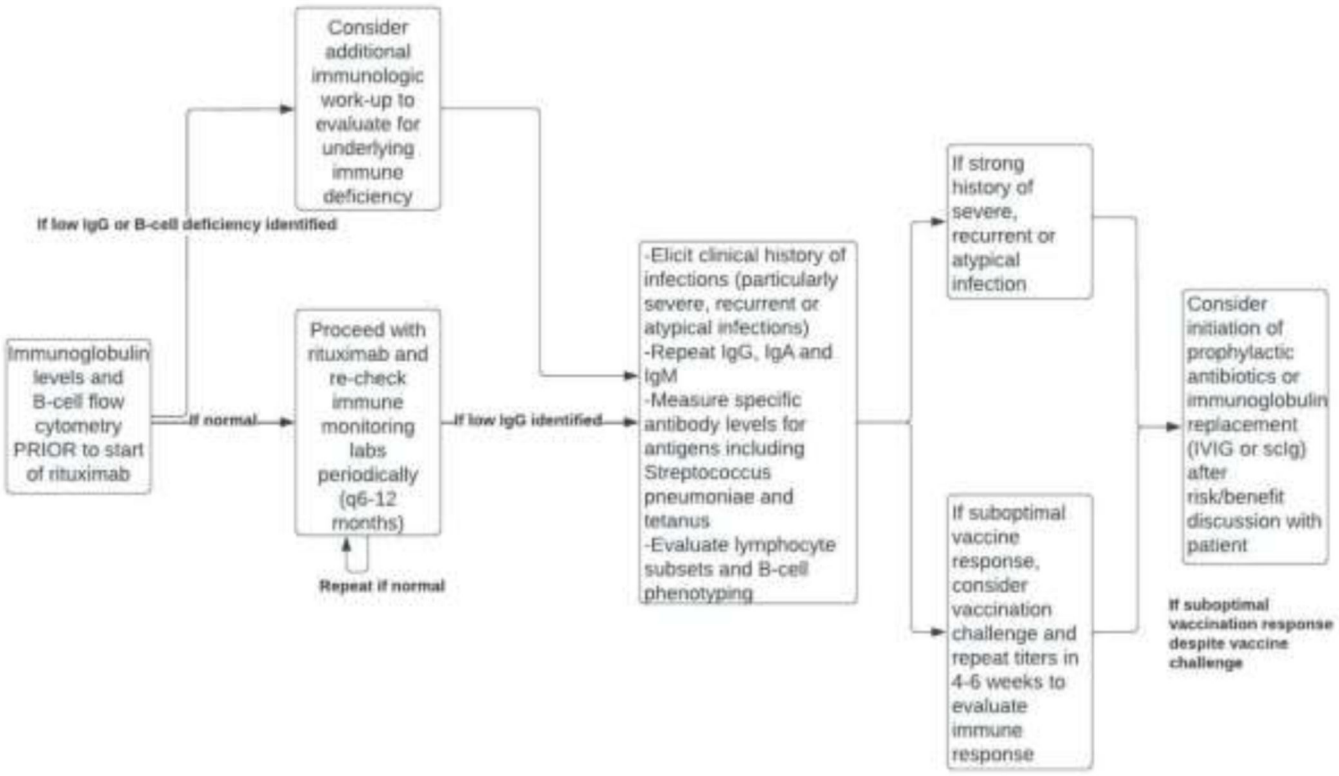

Figure 2.
Considerations for evaluation and management with rituximab.

Table 1.

Potential risk factors for hypogammaglobulinemia after rituximab supported by multiple studies

Risk Factor	References
Low baseline serum IgG	Besada et al. 2014; Roberts et al. 2015; Christou et al. 2017; Barmettler et al. 2018; Boleto et al. 2018; Evangelatos et al. 2021; Labrosse et al. 2021; Tieu et al. 2021; Inoki et al. 2022
Low baseline serum IgM	Reddy et al. 2017; Ottaviano et al. 2020; Evangelatos et al. 2021; Evangelatos et al. 2022
Low baseline serum IgA	Ottaviano et al. 2020; Labrosse et al. 2021
Number of rituximab treatment cycles (i.e., longer-term rituximab treatment)	Keystone et al. 2007; Van Vollenhoven et al. 2010; De La Torre et al. 2012; Einarsson et al. 2017; Fierro et al. 2019; Van Vollenhoven et al. 2013; Kridin & Ahmed 2020; Filanovsky et al. 2016; Marcinnò et al. 2018; Newman et al. 2022; Christou et al. 2017
Glucocorticoids	Tieu et al. 2021; Wade and Kyttaris 2021; Guilpain et al. 2021; Ong et al. 2022
Mycophenolate mofetil	Christou et al. 2017; Reddy et al. 2017; Fujinaga & Tomii 2020
Cyclophosphamide	Venhoff et al. 2012; Kado et al. 2016; Besada et al. 2014; Tieu et al. 2021
Purine analogues	Christou et al. 2017; De Angelis et al. 2015; Casulo et al. 2013
Fludarabine	Cabanillas et al. 2006; De Angelis et al. 2015; Filanovsky et al. 2016; Sacco & Abraham 2018
Younger age in children	Ottaviano et al. 2020; Marzuillo et al. 2019; Fujinaga & Tomii 2020; Parmentier et al. 2020
Older age in adults	Van Vollenhoven et al. 2010; Besada et al. 2014; Barmettler et al. 2018; Boleto et al. 2018

Table 2.

Potential risk factors for late-onset neutropenia after rituximab supported by multiple studies

Risk Factor	References
Advanced stage of cancer	Choi et al. 2014; Nitta et al. 2007; Arai et al. 2015
Exposure to chemotherapeutics (e.g., purine analogs)	Wolach et al. 2010; Nitta et al. 2007; Hirayama et al. 2009; Lemieux et al. 2004; Cattaneo et al. 2006; Cairoli et al. 2004
IgG FcγIIIa receptor polymorphism (158V/V or 158V/F)	Weng et al. 2010; Tesfa and Palmblad 2011; Wolach et al. 2012; Li et al. 2010; Keane et al. 2012
Autologous peripheral blood stem cell transplantation	Lemieux et al. 2004; Hirayama et al. 2009; Cairoli et al. 2004; Flinn et al. 2000
Immunosuppressants (e.g., methotrexate)	Nitta et al. 2007; Arai et al. 2015; Castillo et al. 2019
Older age	Moore 2016; Freifeld et al. 2011; Salmon et al. 2015; Choi et al. 2014; Arai et al. 2015

Table 3.

Potential risk factors for infection after rituximab supported by multiple studies

Risk Factor	References
Low baseline serum IgG	Gottenberg et al. 2010; Heusele et al. 2014; Christou et al. 2017
Number of rituximab treatment cycles	Kanbayashi et al. 2009; Christou et al. 2017; Varley & Winthrop 2021
Low serum IgG or IgM post-therapy	Kanbayashi et al. 2009; Gottenberg et al. 2010; Christou et al. 2017; Labrosse et al. 2021
Glucocorticoids and prednisone	Heusele et al. 2014; Guilpain et al. 2021; Stabler et al. 2021; Xavier et al. 2022
Clinical comorbidities (cardiac insufficiency, chronic lung disease, diabetes, cancer, and extra-articular involvement in rheumatoid arthritis)	Gottenberg et al. 2010; Christou et al. 2017; Guilpain et al. 2021; Stabler et al. 2021; Xavier et al. 2022
Older age	Christou et al. 2017; Kronbichler et al. 2018