REVIEW ARTICLE

Renal Disease and Transplantation Forum
2022, vol. 15, no. 3, 129–132

ISSN 2720–2771
e-ISSN: 2720-4189
DOI: 10.5603/RDTF.2022.0014

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Specific issues related to the use of monoclonal antibodies — rituximab and eculizumab – in patients after kidney transplantation

ABSTRACT

There are specific indications to use modern monoclonal antibodies in selected patients after kidney transplantation, such as desensitization, treatment of humoral rejection, management of post-transplant recurrence of nephrotic syndrome, therapy of lymphoproliferative disease (PTLD) for rituximab, and a prophylaxis/treatment of recurrence of the atypical hemolytic uremic syndrome (aHUS) for eculizumab. The use of rituximab, a depleting antibody against B_{CD20} cells is related to hypogammaglobulinemia and late-onset neutropenia, which increases the risk of secondary viral, bacterial, and fungal infections. *Pneumocystis jiroveci*-related pneumonia is the most severe complication. Eculizumab, as a blocker of the complement system, predominantly increases the risk of meningococcal infections; however, some associations with other types of infections, like cryptococcal and JC-virus-related infections have also been reported. The use of both monoclonals includes specific mandatory prophylaxis, with trimethoprim/sulfamethoxazole (TMP-SMX) in rituximab and anti-meningococcal vaccination/penicillin administration in eculizumab-treated patients. There are specific issues associated with the use of both monoclonals in terms of COVID-19-related infections, as administration of rituximab is related to the prolonged failure of response to relevant vaccinations (including the third, booster dose), whereas blocking of the complement system may ameliorate the COVID-19-infection-related cytokine storm.

Renal Disease and Transplantation Forum 2022, vol. 15, no. 3, 129–132

Key words: monoclonal antibodies, rituximab/ /eculizumab, related infections, transplantation

INTRODUCTION

Biologic drugs are used in organ transplantation for variable purposes and with variable timing, before or after transplantation, and if after transplantation: early or late. Rituximab, a monoclonal depleting antibody against B_{CD20} cells is used for desensitization in patients presenting a high concentration of donor-specific antibodies (DSA), in treatment of humoral rejection, management of post-transplant recurrence of nephrotic syndrome, and therapy of the lymphoproliferative disease (PTLD) and B-cell non-Hodgkin lymphomas [1–3]. Eculizumab, a monoclonal antibody, blocking the complement system, is used mainly in prophylaxis and/or treatment of post-transplant recurrence of atypical hemolytic uremic syndrome (aHUS); however, it may also be also used in treatment of humoral rejection [4]. Therefore, riruximab is mainly used in the therapy of specific pathologies, while the (prophylactic) use of eculizumab is more often pre-scheduled in earlier identified patients at risk.

MECHANISMS OF ACTION

The binding of rituximab to CD20 receptors on B-cells leads to depletion of the target cells in three ways: complement-dependent cytotoxicity (CDC), apoptosis, and antibody-dependent cell-mediated cytotoxicity (ADCC). The range of target cells includes pre-B cells, immature, mature, and activated B-cells [5]. Duration of effect on the immune system is dose-dependent as protocols of 1–4 weekly

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Table 1. Incidence of infectious adverse events of rituximab therapy in a rheumatologic setting (adapted from [9], with modification)

Adverse effect	Manifestation	Incidence
Infection (overall) Severe infections JC virus reactivation with neurologic consequences	Upper respiratory infections, bronchitis, urinary tract infections Pneumonia Progressive multifocal leukoencephalopathy	40% 5–11% 0.4/100 000
Hypogammaglobulinemia	Low IgM concentration Low IgG concentration	23–32% 5–18%
Cytopenia	Late-onset neutropenia	5%

intravenous (*i.v.*) doses are used (depending on indication) and may be extended up to 6–12 months after drug administration [6]. Eculizumab is a humanized monoclonal antibody that targets complement protein C5, inhibiting cleavage into C5a and C5b, and therefore preventing formation of the membrane attack complex [4]. A dose is administered (*i.v.*) every two weeks. The new formula, ravulizumab, is a long-acting, second-generation complement component 5 inhibitor, which may be administered *i.v.* every 8 weeks [7]. Despite the formula, the blockade of complement is used for at least 6 months (in some cases for years) to prevent the recurrence of aHUS after kidney transplantation [4, 8].

DUE TO HYPOGAMMAGLOBULINEMIA

The incidence of infectious rituximab-related adverse events correlates with the duration of drug-induced B-cell depletion, therefore, it increases with the number of doses and with repeated courses of therapy [9,10]. The data from rheumatologic studies show, that the respiratory tract is the main localization of post-treatment infections. Another common adverse event is hypogammaglobulinemia in both subclasses (IgG and IgM). Late-onset neutropenia is the third significant relevant phenomenon. The data are presented in Table 1 [9].

There are several confounding factors, which add some impact on the incidence and severity of rituximab-related infections. Concomitant immunosuppression is one of the most important (particularly in a transplantation setting), as the use of mycophenolate mofetil increases the risk of neutropenia. Hypogammaglobulinemia is regarded as a significant risk factor for opportunistic infections, particularly within the first 6 months after transplantation (the period of predominance of viral infections), therefore there are suggestions to use a preemptive supplementation of the IVIG in organ recipients presenting moderate/severe hypogammaglobulinemia [11]. The threshold of hypogammaglobulinemia is an important risk factor, as in patients with a sustained severe deficit (IgG < 400 mg/dL), regardless of the type of transplanted organ, the risk of one-year all-cause mortality is 21.91 times higher [12]. The deficit of IgG clinically translates to a higher incidence of CMV-related, fungal, and respiratory infections. Supplementation of IgG, achieved by administration of IVIG, may be an important factor potentially decreasing the adverse impact of rituximab on the incidence of post-transplant infections. In the study evaluating patients undergoing desensitization, a similar incidence of infections between patients treated and non-treated with rituximab could be (at least partially) associated with the use of IVIG [13].

SPECIFIC DRUG — RELATED INFECTIONS

The most clinically threatening infection, associated with the use of rituximab, is *Pneumocystis jiroveci* pneumonia. B-cell depletion is related to the 3 times higher risk of this infection despite specific prophylaxis [14]. There are variable recommendations on the duration of trimethoprim/sulfamethoxazole (TMP-SMX) (as first-line) prophylaxis [15]. Six months of administration is regarded as a minimum in kidney recipients; however, there are suggestions to prolong this protocol up to 1 year due to infections occurring after scheduled termination of prophylaxis (at 6 months) in rituximab-treated patients [14]. For lung and small bowel transplant recipients and any transplant recipient with a history of *Pneumocystis jiroveci* pneumonia or chronic CMV infections — lifelong prophylaxis is recommended [14]. In specific situations, second-line prophylaxis of *Pneumocystis jiroveci* pneumonia includes the use of dapsone, atovaquone, pentamidine, and clindamycin/pyrimethamine [14]. Pneumonia of this etiology may still be fatal despite specific and intensive therapy [16]. Late-onset

neutropenia is another clinical problem, related to rituximab therapy and it may occur up to 6–12 months after the treatment. Rescue therapy with bone marrow stimulating agents (G-CSF, granulocyte colony-stimulating factor) is necessary [17]. Eculizumab may interfere with defending properties of the primary immune system by blocking the complement. This is particularly important in terms of meningococcal infections [18]. Effective vaccination against meningococci is a crucial safety measure. Nevertheless, there are reports on vaccination failure in immunocompromised patients after kidney transplantation [19, 20]. Therefore, the KDIGO recommendations underline the need for additional antibiotic prophylaxis, aimed at meningococci, which should be given not only to non-vaccinated patients in whom the eculizumab treatment was introduced as rescue therapy but also to vaccinated patients on immunosuppression. It was also recommended that antibiotic prophylaxis should be maintained beyond duration of eculizumab therapy (if relevant) up to 3 months after (eculizumab) discontinuation [21]. Blocking of the complement system in transplanted patients may be associated with other, rare infectious complications, such as the *polyoma JC virus* reactivation and development of a progressive multifocal leukoencephalopathy (PML) as a consequence [22]. Other rare complications in immunocompromised patients treated with eculizumab were disseminated cryptococcosis and *Neisseria species*-related infections localized in the respiratory and urinary tracts [23, 24].

MONOCLONALS AND THE COVID-19 PANDEMIC

In the era of the COVID-19 pandemic, the association between this infection and the use of monoclonals became a topic of interest. Some data show a favorable impact of complement blocking by eculizumab on the cytokine storm and more rapid resolution of acute inflammation, coagulopathy, and organ dysfunction in infected patients [25], including kidney transplant recipients [26]. A case of successful rescue therapy with eculizumab in a patient with COVID-19-triggered thrombotic microangiopathy with cardiac failure has been reported [27]. Adverse unfavorable associations have been described between rituximab and COVID-19-related infections; however, it should be stressed that these data come mainly from the autoimmune diseases-related patient community where cumulative doses (and repeated courses of the treatment) may be (at least partially) responsible for a higher exposure to rituximab. The drug was identified as a significant factor in negative outcomes in COVID-19-infected patients, with a higher negative impact, as compared to any other immunosuppressants [28]. Another important issue was the impaired immunogenicity of COVID-19 vaccines in patients treated with rituximab. The concomitant negative effect of steroids and mycophenolate mofetil (used in combined therapy) should be stressed in this context [29]. This negative effect of rituximab may also be present in patients receiving a third dose of the COVID-19 vaccine [30]. Therefore, a more aggressive diagnostic and therapeutic algorithm for COVID-19-related disease was suggested in B-cell-depleted patients after rituximab treatment [31].

SUMMARY

Biologic drugs used in transplantation, such as rituximab and eculizumab, reduce the activity of humoral and primary immune systems in a specific way related to the drug mechanism, which is favorable in terms of targeting the detailed receptor pathways of immune systems relevant to the disease, however, may substantially decrease immune capability. Rituximab induces hypogammaglobulinemia and neutropenia and impairs immunogenicity to COVID-19 vaccines. The most threatening infection associated with the use of rituximab is *Pneumocystis jiroveci*-related pneumonia. Eculizumab increases the risk of meningococcal infections despite relevant vaccinations; however, it may help treat SARS-CoV-2-infected patients. The use of both monoclonals must be accompanied by specific prophylaxis.

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