



The Outcome of COVID-19 in Patients with a History of Taking Rituximab: A Narrative Review

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What's Known

- Rituximab is widely used for the treatment of various diseases, mostly autoimmune diseases and some malignancies.
- Previous studies indicated that rituximab may be associated with the increased risk of infection.

What's New

- Despite the fact that several reports revealed that COVID-19 may not be ominous in rituximab therapy, we suggest rituximab use with caution, since the clinical course of the disease and subsequent morbidity and mortality are yet to be determined.

Abstract

Coronavirus disease 2019 (COVID-19) is a recently emerging disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Notably, the safety of immunosuppressive medications is a major concern during an infectious disease pandemic. Rituximab (RTX), as a monoclonal antibody against CD20 molecule, is widely used for the treatment of various diseases, mostly autoimmune diseases and some malignancies. Previous studies indicated that RTX, as an immunosuppressive medication, may be associated with the increased risk of infections. Moreover, given the wide use of RTX, a necessity of determining the different aspects of RTX use in the COVID-19 era is strongly felt. We reviewed current studies on the clinical courses of patients with SARS-CoV-2 infection. It appears that the use of RTX does not increase morbidity and mortality in most patients. However, underlying diseases and other concomitant medications may play a role in the disease course, while the concerns of vaccine efficacy in patients receiving RTX still need to be addressed. Therefore, more controlled studies are needed for a better conclusion.

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Introduction

Coronavirus disease 2019 (COVID-19) is a recently emerging disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) firstly described in a series of patients with unexplained pneumonia in Wuhan, China.¹ Since then, it has spread all over the world and became a global challenge. In this regard, the patients with COVID-19 represent a various spectrum of the disease's severity, ranging from a totally asymptomatic disease in most cases to a severe fatal disease leading to acute respiratory distress syndrome (ARDS) and a subsequent multi-organ failure in a number of patients, specifically in older patients and those with comorbidities.¹⁻³ At the very beginning of the COVID-19 pandemic, there were increasing concerns on safety and the possible hazards of immunosuppressive medications in diseases, in which immunosuppressive medications are considered as the cornerstones of treatment.

Rituximab (RTX), a monoclonal antibody against CD20 molecules expressed by B cells, was firstly approved by the US Food and Drug Administration in 1997 for non-Hodgkin lymphoma (NHK).⁴ Correspondingly, RTX was shown to play a key role in the

management of several diseases, including B-cell hematologic malignancies,⁵ multiple sclerosis (MS),⁶ neuromyelitis optica spectrum disorder (NMOSD),⁷ myasthenia gravis,⁸ vasculitis,⁹ rheumatoid arthritis,¹⁰ systemic sclerosis (SSc),¹¹ pemphigus disease,¹² idiopathic thrombocytopenia purpura (ITP),¹³ and certain renal diseases.¹⁴ Previous studies indicated that RTX, as an immunosuppressive medication, may be associated with the increased risk of infections.¹⁵⁻¹⁷ Moreover, given the wide use of RTX, a necessity of determining the different aspects of RTX use in the COVID-19 era is strongly felt. In this study, we attempted to review what we know about RTX during the COVID-19 pandemic.

Neurologic Disorders

There are some concerns about the safety of RTX during the COVID-19 pandemic. Accordingly, Montero-Escribano and others investigated the SARS-CoV-2 infection among 60 patients with MS and some related disorders in Madrid, Spain. In the mentioned study, before the pandemic, 54 patients were under treatment with RTX, and the remaining six patients were treated with ocrelizumab, which is another monoclonal anti-CD20 antibody-drug. Seven patients receiving RTX and two patients receiving ocrelizumab were infected by SARS-CoV-2. Moreover, therein, none of the patients suffered from serious complications, and only one patient was hospitalized. However, the diagnosis of COVID-19 was mainly based on clinical findings, rather than a positive SARS-CoV-2 reverse transcription- polymerase chain reaction (RT-PCR) test.¹⁸ Woo and others reported clinical courses of a patient with MS and a patient with NMOSD infected by SARS-CoV-2, and both of them were receiving RTX. The first patient was a 44-year-old woman with relapsing-remitting MS receiving her last dose of RTX three months before her admission with the symptoms of COVID-19, the elevated inflammatory biomarkers, and the radiologic evidence of COVID-19 pneumonia, and a positive test result for SARS-CoV-2 PCR. Despite the absence of B cells and negative anti-SARS-CoV-2 IgG, she was discharged four days following the admission, and her PCR test was negative in a follow-up visit held four weeks later. The second patient was a 68-year-old woman with NMOSD and several comorbidities receiving her last dose of RTX five months prior to her admission. Subsequently, she was admitted to the intensive care unit with severe respiratory failure. Her disease was complicated with bacterial superinfection, and she was intubated, but finally recovered. Although she

developed anti-SARS-CoV-2 IgG during her disease course, she had low B cells.¹⁹ Louapre and others studied 15 patients with NMOSD and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) with SARS-CoV-2 infection. Among the 15 patients, 10 of them were receiving RTX, five patients required hospitalization, and one of them was under mechanical ventilation for three days. All the hospitalized patients were receiving RTX. Fortunately, none of them died from the infection.²⁰ In a study by Sahraian and others, 149 patients with NMOSD were contacted via phone and were asked about the COVID-19 symptoms. Thus, five patients were diagnosed with COVID-19, all receiving RTX; three of them required hospitalization and one subject had a severe infection. Fortunately, all these patients finally recovered.²¹ A case report published by Devogelaere and others described a 33-year-old woman with MS, who received the last dose of RTX five months before the RT-PCR test was confirmed as SARSCoV2 infection. Although her B cells were depleted, she spent an uneventful hospitalization and was discharged after a week.²² Another report by Creed and others described the clinical course of a 59-year-old woman with NMOSD, depleted B cells, with the symptoms of COVID-19, and positive RT-PCR for SARS-CoV-2, who was under chronic treatment with RTX. She was hospitalized for three days with no complications and then, fully recovered.²³ A similar result was also reported by Wurm and others about a 59-year-old female patient with MS under treatment with RTX, who developed fever, low oxygen saturation, and a positive SARS-CoV-2 RT-PCR test. Accordingly, at the time of the presentation, her B cells were completely depleted. She rapidly recovered and 14 days later, two nasopharyngeal swab tests and a cerebrospinal fluid sample were reported negative for SARS-CoV-2; however, she did not produce any antibody against SARS-CoV-2.²⁴ Meca-Lallana and others also described seven patients infected by SARS-CoV-2 treated with anti-CD20 antibody medications. These patients didn't have another underlying disease. One of them was under treatment with RTX and the other six subjects were treated with ocrelizumab. The first patient was a 60-year-old man receiving his last RTX dose seven months before being diagnosed with COVID-19. He was discharged five days after admission. On the other hand, the other six patients receiving ocrelizumab mostly experienced a mild disease course, and all recovered with no sequela. Two of these six patients were diagnosed with COVID-19 without performing any RT-PCR tests

for confirmation. Anti-SARS-CoV-2 antibody formation was confirmed in three patients.²⁵ Safavi and others performed a study utilizing an online questionnaire to determine the factors affecting SARS-CoV-2 in MS patients in Tehran, Iran. They stated that utilizing B-cell depleting agents was associated with the increased contracting of the virus (RR: 3.55, 95%; CI: 1.45, 8.68; P=0.005). Accordingly, among the 712 patients responding to the questionnaire, only two required hospitalization, and none of them needed intensive care.²⁶ Parrotta and others also found no increased risk of hospitalization or fatal outcome in 76 MS patients receiving disease modifying therapy, including anti-CD20 therapies (44.7%) and sphingosine-1-phosphate receptor modulators (13.5%).²⁷

Wanschitz and colleagues reported the case of a 71-year-old woman with myasthenia gravis (MG), who received RTX seven months before being diagnosed and hospitalized with the SARS-CoV-2 infection and the exacerbation of MG. She was managed with non-invasive positive pressure ventilation and the treatment for MG, however, weekly SARS-CoV-2 PCR tests were positive six weeks after discharge.²⁸

Rheumatologic Diseases

In recent years, it was indicated that RTX plays a role as an essential medication in many rheumatologic diseases and its safety has become the main concern for physicians and patients. Guilpain and others, for the first time, described a 52-year-old woman with granulomatosis with polyangiitis (GPA), hypertension, and COVID-19. She received RTX for vasculitis relapse, and a day later, she manifested COVID-19 symptoms, and the disease was confirmed with an RT-PCR test. She was also receiving 15 mg prednisolone (PDN) at the time of the infection. Her condition deteriorated during her hospitalization course, and endotracheal intubation was required, however, she finally recovered, and thereafter the RT-PCR was negative.²⁹ A 27-year-old woman with GPA under treatment with RTX (last dose two months ago) and 30 mg PDN daily with severe COVID-19 presentation and hypoxia, was reported in Sharmeen and others' study. She was tested positive for SARS-CoV-2. No mechanical ventilation was needed and her symptoms finally improved.³⁰ Another case with GPA was a 77-year-old woman under treatment with RTX, 5 mg PDN daily, and 20 mg methotrexate (MTX) weekly, admitted due to the symptoms of SARS-CoV-2 infection, which was later confirmed with RT-PCR. During the hospitalization course, her B cells were depleted; nevertheless, she

recovered totally with no complications.³¹

Unfortunately, the reports of patients with rheumatoid arthritis (RA) are somewhat worrisome. Loarce-Martos and others screened 76 patients receiving RTX in the previous 12 months, and 13 patients were diagnosed with SARS-CoV-2 infection. Among those patients, five had RA, three had systemic vasculitis, two had Sjögren syndrome, and two had systemic lupus erythematosus (SLE). Eight of these patients were hospitalized, and three died from acute respiratory distress syndrome, one of the deceased patients had SLE, the other had systemic vasculitis, and the last patient had RA.³² Schulze-Koops and others reported two patients. The first patient was a 71-year-old man with erosive RA and mild chronic obstructive pulmonary disease, who received RTX two weeks prior to getting the infection and with a weekly usage of 15 mg of MTX. The other case was an 80-year-old woman with erosive RA, hypertension, and osteoporosis, and her last RTX dose was taken six months before getting infected. In addition, she received MTX 10 mg subcutaneously per week and 5 mg PDN daily. Both patients died due to COVID-19.³³

In a work by Avouac and colleagues, SARS-CoV-2 infection was described in three patients with systemic sclerosis (SSc). All patients received RTX for refractory SSc. At the time of infection, the B cells of all three patients were depleted. All of these patients experienced clinical deterioration during their hospitalization and two required intensive care, but none of them underwent tracheal intubation. One of them was discharged, and the remaining subjects were still hospitalized when the report was released.³⁴

Skin Diseases

Daneshpazhooch and others reported a case of mucous membrane pemphigoid (MMP) with COVID-19. The patient was a 41-year-old man, who received RTX three months before getting the infection. He was receiving 40 mg PDN and 2 g mycophenolate mofetil daily. He was admitted for the progression of underlying diseases and received intravenous immunoglobulins, when he started to show the symptoms of SARS-CoV-2 infection. Despite hypoxia at the time of admission, he had an uneventful hospitalization and was discharged seven days later.³⁵

A concerning topic during treatment with RTX is whether the patients are at a higher risk of infection by SARS-CoV-2. In a study by Shahidi-Dadras and others, 167 patients with pemphigus vulgaris (PV) under treatment with RTX were asked about COVID-19 symptoms via telephone, and then, CT scan was performed for

the suspicious cases. Therein, only five patients represented the symptoms of SARS-CoV-2 infection, and these five patients had typical radiologic findings of COVID-19. However, no RT-PCR test was conducted in this study.³⁶

Malignancies

RTX is present in multiple chemotherapy regimens performed against different malignancies. Fürstenau and others studied seven patients with chronic lymphocytic leukemia under chemotherapy with venetoclax-based combinations presenting COVID-19 symptoms. Accordingly, all the combinations included an anti-CD-20 medication, three of which were with RTX. All these three patients required hospitalization, two of them needed oxygen support, one via nasal cannula and the other via high flow nasal cannula. All of these three patients finally recovered.³⁷ In addition, another case report was a 26-year-old man with mediastinal large B-cell lymphoma admitted to receive his third chemotherapy cycle with DAEPOCH-R (dose-adjusted etoposide, vincristine, cyclophosphamide, prednisone, doxorubicin, and rituximab) regimen. The patient became febrile and was diagnosed with neutropenic fever. At the time, his lymphocyte count was calculated as 0.68×10^3 cells/L. Although his neutrophil count returned to normal, the patient was still febrile with opacities in both lungs and was finally diagnosed with COVID-19 through an RT-PCR test. He was then discharged a month later and needed no ventilator during his disease course.³⁸ SARS-CoV-2 infection is not always a mild disease in patients with malignancies suffering from COVID-19. Tepassee and colleagues described two fatal cases of COVID-19. The first patient was a 65-year-old man with cerebral relapse of diffuse large B-cell lymphoma under treatment with R-DeVIC (Rituximab, Dexamethasone, Etoposide, Ifosfamide, and Carboplatin) for numerous months, and the latest cycle was two weeks prior to getting infected. The second patient was a 66-year-old man with mantle lymphoma in remission receiving maintenance treatment with rituximab (the last cycle was prescribed two weeks before the infection) and Ibrutinib daily. B cell counts were totally depleted in both patients. Moreover, both of them were diagnosed with COVID-19 by use of nasopharyngeal RT-PCR tests. They showed severe SARS-CoV-2 viremia detected via RT-PCR tests performed on peripheral blood samples. Both needed tracheal intubation and finally passed away at days 22 and 26, respectively.³⁹

Discussion

Rituximab exerts its therapeutic effect through depleting B cells that are mainly responsible for producing antibodies against different antigens. In order to better understand the possible role of RTX in COVID-19, it is essential to determine the immunological event during the infection by the virus, the clearance of the virus, and later immunity from re-infection. SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2), as the entrance receptor. ACE2 is expressed in many organs, such as lung, kidneys, vessels, intestine, and many other tissues.⁴⁰ Furthermore, SARS-CoV-2 utilizes the infected cells to produce the proteins and RNAs needed for its replication. In this process, both innate and adaptive immune responses act in defense against SARS-CoV-2.⁴¹ CD8+T cells, CD4+T cells, and B cells are the pillars of the adaptive immune response. CD4+T cells activate B cells, which then produce antibodies against SARS-CoV-2. However, CD8+T cells, which kill infected cells, play a critical role in clearing SARS-CoV-2 from the lung, as 80% of the infiltrated cells in pulmonary interstitium are CD8+T cells.³⁸ Several studies reported many patients with COVID-19 developing an antibody against SARS-CoV-2. Still, the role of antibodies in clearing the virus is yet to be discovered, since some mild patients do not produce antibody, or produce it in lower titers.⁴² Interestingly, in a report by Quinti and others, patients with agammaglobulinemia showed COVID-19 symptoms, but they totally recovered.⁴³ Even Novi and colleagues suggested that the B-cell depletion may have a favorable effect on patients' clinical courses.⁴⁴ Several case reports of patients with MS receiving ocrelizumab and with depleted B cells mentioned that they have also experienced mild disease courses;⁴⁵⁻⁴⁷ however, these reports are conflicting. Tepassee and others stated that RTX therapy may be associated with persisted viremia and fatal outcome.³⁹ In most of the studies discussed above, recovery was seen in patients with MS, NMO, MMP, PV, GPA, and SSc, but not RA or malignancies (lymphoma). However, whether underlying diseases, comorbidities, concomitant medications, the time of RTX administration, age, and other factors could change the clinical outcome of patients with COVID-19 is still unclear. Therefore, more studies are needed, since such results are only speculated from case reports.

Previous studies demonstrated that RTX could increase the risk of infections.⁶⁻⁸ These infections could include various types of viruses and complicate the course of the disease.⁴⁸

Meanwhile, it is still unclear whether RTX therapy increases the risk of infection with SARS-CoV-2. Safavi and others revealed that being on B-cell depleting antibodies in comparison with other diseases modifying medications used for MS is associated with a 2.6-fold increase in the risk of being in the COVID-19-suspect group. In another study by Shahidi-Dadras and others, only five out of 167 patients showed COVID-19 symptoms. However, no statistical analysis was performed to compare the infection rate in the normal population.^{26, 36}

Another major issue in treatment with RTX is the ability to produce a protective antibody against SARS-CoV-2 after the vaccination, or infection, since vaccination is an important tool to contain the virus during the pandemic. Several previous studies demonstrated that RTX treatment may interfere with the production of adequate antibodies following vaccination against other pathogens. Hence, vaccination might not be efficient even nine months after RTX treatment,⁴⁹⁻⁵³ and there is no reason to believe that SARS-CoV-2 would be an exception. In some case reports, patients under RTX developed antibodies against SARS-CoV-2;^{19, 25} however, most of these cases had different results and no antibody was detected after infection. Reports from the patients with MS infected by SARS-CoV-2 and under treatment with ocrelizumab displayed no antibody production against SARS-CoV-2 during or after getting the infection, and the result could be similar for patients under the treatment with RTX. However, more research are needed in this regard.⁵³⁻⁵⁶

COVID-19 is a big challenge for physicians.⁵⁷⁻⁶⁰ RTX as an important immunosuppressive medicine for different diseases,⁶¹⁻⁶³ and its potential benefit in the treatment of hyperinflammatory state in patients with COVID-19,⁶⁴ can make this challenge more complicated.

Conclusion

Despite the fact that the initial reports stated that COVID-19 may not be considered as a contraindication for RTX therapy, we suggested RTX use with caution, since most studies included in this review are reports and lack control groups. Any conclusion regarding using RTX in patients with COVID-19 should be made with caution and the clinical course of the disease and subsequent morbidity and mortality are yet to be determined. Furthermore, RTX might interfere with patients' immunity following a possible vaccination and make them susceptible to COVID-19 months after performing an appropriate therapy.

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