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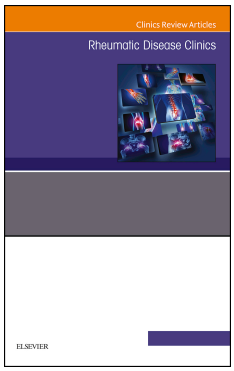

Managing immunosuppression in vasculitis patients in times of COVID-19

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Key Points:

- Patients with vasculitis are among those at greatest risk for COVID-19 and severe outcomes, though outcomes have improved following the introduction of effective vaccinations and anti-viral treatments.
- Certain patients with vasculitis who are treated with B cell depletion and cyclophosphamide, are at especially high risk for blunted responses to vaccination and breakthrough infection, including severe disease.
- Access to early diagnosis and treatment of COVID-19 are critical for improving outcomes for patients with vasculitis during the ongoing COVID-19 pandemic. Additionally, the availability of pre-exposure prophylaxis represents a critical advance for patients who use B cell depletion and other strong immunosuppressants.

Keywords: vasculitis, COVID-19, immunosuppression, risk mitigation

Abstract

The coronavirus disease 2019 (COVID-19) pandemic has led to the emergence of multiple challenges in the care of patients with systemic rheumatic diseases. Patients with vasculitis represent a group of particular concern due to existing risk factors which include a higher burden of comorbidities and specific immunosuppressive therapies used for treatment. Vaccination and the use of other risk mitigation strategies are crucial for the care of these patients. This review provides an overview of existing evidence to contribute to the understanding and specific requirements of the treatment and management of patients with vasculitis in the time of COVID-19.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has represented a major challenge to healthcare

systems worldwide. Since the beginning of the pandemic, patients living with rheumatic diseases have been appropriately considered high risk due to their immunocompromised status associated with the use of anti-rheumatic drugs, a higher burden of comorbidities as well as the hyper-inflammatory and -coagulable states associated with rheumatic disease and COVID-19.[1] Among those with rheumatic disease, patients with vasculitis have been of particular concern given their burden of comorbidities (e.g., lung disease, renal disease), typical demographics (e.g., older age), and frequent use of highly immunosuppressive treatments (i.e., high dose glucocorticoids, B-cell depleting therapies), all of which predispose to severe COVID-19.

Since the beginning of the pandemic, large collaborative efforts including clinical trial platforms and large registries have led to significant improvement in the outcomes of COVID-19 with the establishment of management protocols, repurposing of existing drugs, and discovery of new therapeutics. [2,3] The rapid development of highly effective vaccines against SARS-CoV-2 also reduced the risk of COVID-19 and severe disease (e.g., hospitalization, death) in the general population. Similar benefits have also been observed in individuals with rheumatic diseases.[4] However, the blunted response to SARS-CoV-2 vaccines in patients receiving anti-rheumatic drugs has left certain patients (e.g., patients on B-cell depleting therapies) at high risk for severe disease, even with the recommended booster regimen.[5] Therefore, the ongoing spread and evolution of new SARS-CoV-2 variants continues to impact treatment decisions, including the role of mitigating strategies (e.g., pre-exposure prophylaxis), the risks and benefits of different anti-rheumatic drugs, and recommendations regarding shielding practices (e.g., social distancing, masking) for patients with vasculitis.

The aim of this review is to summarize the existing evidence on risks and outcomes of COVID-19 infection in patients with systemic vasculitis, highlighting some of the current challenges involved in the management of these conditions during the ongoing pandemic. We will also

review the efficacy of COVID-19 vaccination and other mitigation strategies and discuss their implementation in the management of patients with vasculitis.

Outcomes of COVID-19 in patients with vasculitis

Although with some variability, large population-based and healthcare system studies, as well as meta-analyses incorporating these studies, have observed an increased risk of both COVID-19 infection and severe COVID-19 (e.g., hospitalization, intensive care admission, death) in patients with systemic rheumatic diseases when compared to the general population.[6,7] Importantly though, general risk factors for severe COVID-19 among patients with rheumatic disease are similar to those in general population (e.g., age, comorbidities). In a large population-based study investigating the risk of COVID-19 hospitalization risk in patients with specific systemic rheumatic diseases, patients with vasculitis were found to have the highest risk for hospitalization compared to controls (odds ratio [OR] 2.07, 95% confidence interval [CI] 1.06, 4.06).[8] This increased risk was mostly driven by comorbidities and demographics given the observed attenuation in these associations after adjustment for these factors.

Though susceptible to selection bias, some registry-based studies have examined COVID-19 outcomes in patients with vasculitis.[9,10] In the COVID-19 Global Rheumatology Alliance (GRA) registry analysis of 1020 patients with vasculitis and polymyalgia rheumatica, increased risk of poor outcomes (i.e., hospitalization, mechanical ventilation, or death) was associated with older age, male sex, higher burden of comorbidities, prednisone-equivalent doses over 10mg/day, and moderate or high-severe disease activity at baseline.[10] Reassuringly, rates of poor outcomes improved during the study period following June 15, 2020.

Among patients with vasculitis, similar risk factors (e.g., age, male sex, and comorbidities) as in the general population seem to identify those at particularly high risk of poor outcomes of COVID-19. However, the risk of severe outcomes and associated risk factors may vary between

different forms of vasculitis. (Table 1) For instance, those with ANCA-associated vasculitis (AAV), may be at higher risk for worse outcomes compared with patients given higher reported point estimates for severe disease and mortality.[10] Among patients with ANCA-associated vasculitis, risk factors for more severe disease include older age, chronic kidney disease, moderate or high-severe disease activity at baseline, and treatment with higher glucocorticoid doses, cyclophosphamide, and/or rituximab. The increased risk for poor outcomes with rituximab and other B-cell depleting therapies has been reported in multiple conditions and poses an important risk to patients with AAV given the pivotal role of rituximab both in remission induction and maintenance of remission. [7,11,12] Higher rates of severe outcomes have also been observed in patients with giant cell arteritis (GCA).[10] The demographics (e.g., older age) and frequent use of high dose glucocorticoids likely contribute to the higher rates of poor outcomes in this patient population.[13]

Unlike GCA and AAV, registry and cohort studies studying outcomes of COVID-19 infection in patients with Behcet's syndrome have overall shown a lower rate of complications with COVID-19 infection and somewhat lower mortality.[10,14,15] As seen with other systemic rheumatic diseases including case reports of other forms of vasculitis, one study did report flares of their disease during COVID-19 infection in up to 43% of patients, however, there was no signal for increased thrombotic events.[14,16-18] Outside of few case reports, little is known about outcomes of COVID-19 infection in patients with other forms of vasculitis. In the COVID-19 GRA analysis, the majority of patients with other forms of vasculitis did not require hospitalization, though 21 (14.2%) were reported to have died from COVID-19.[10] Interpreting absolute mortality rates from registry-based studies is challenging because the denominator (e.g., all with infection) is unknown.

Reassuringly, outcomes of COVID-19 infection have continued to improve in those with rheumatic disease, including vasculitis, during the pandemic and the risk of severe infection in

patients with COVID-19 is largely observed in those who remain unvaccinated.[4] However, breakthrough infections (e.g., COVID-19 infection after SARS-CoV-2 vaccination) have been found to occur at higher rates in immunocompromised patients, especially those using anti-rheumatic drugs such as B-cell depleting therapies and anti-metabolites, which are known to blunt the immune response and leave many with no detectable antibody response.[19,20] Although large population-based studies have shown similar severity in breakthrough infections between patients with systemic rheumatic disease when compared to general population, severe infection and death do occur and remain a significant concern in vasculitis patients on these treatments.[19,21,22]

Impact of COVID-19 pandemic on patients with vasculitis

The COVID-19 pandemic significantly affected patients with vasculitis who endorsed specific concerns and changed behaviors regarding accessing healthcare and use of vasculitis treatments. A survey of the Vasculitis Patients Powered Research Network (VPPRN), an online cohort of vasculitis patients, done during the earlier months of the pandemic (April-May 2020) reported a high level of concern in patients, which was associated with use of immunosuppression, older age, female sex, and comorbid pulmonary disease.[23] Interruption of medication, without consultation with a clinician, was seen in 10.5% of patients and up to 29% of patients on rituximab avoided their infusions. Both demographic and regional differences were noted with regards to the uptake of telemedicine visits among patients with vasculitis. A survey of GCA and polymyalgia rheumatica patients from UK and the Netherlands also reported a high frequency of anxiety, isolation, depression, and concerns regarding use of immunosuppressive treatments.[24]

A subsequent study of a larger internet-based cohort of patients with rheumatic diseases, which included VPPRN patients, explored anti-rheumatic drug interruptions in patients from March 2020 to May 2021.[25] An association between with self-reported anxiety and medication

interruptions was reported, and although rate of anti-rheumatic drug interruption decreased throughout the study period, an increase was observed during follow-up in periods characterized by COVID-19 surges. Interruptions in treatments were associated with an increased risk of flares. These findings highlight the ongoing impact of the pandemic on patients with vasculitis and other rheumatic disease, even as outcomes improve. Patient education regarding disease management and COVID-19 mitigation strategies as well as interventions focused on securing early access to care and treatments should remain a priority for clinicians and healthcare systems.

COVID-19 Vaccination in patients with vasculitis

The rapid development of effective COVID-19 vaccines has been one of the pivotal events of the pandemic. Widespread use of different forms of COVID-19 vaccines has been employed including mRNA vaccines (e.g., BNT162b2 [Pfizer-BioNtech], mRNA-1273 [Moderna]), viral-vector vaccines (e.g., ChAdOx1 [Astra-Zeneca], Ad26.COV2.S [Johnson & Johnson]), inactivated virus vaccines (e.g. Sinovac and Sinopharm), and protein-subunit vaccines (e.g., NVX-CoV2373 [Novavax]). Unfortunately, patients with systemic rheumatic diseases were generally excluded from the initial trials, even though this population was among those most in need of effective vaccines given their risk for severe disease. While our understanding of the effectiveness of vaccination in patients with vasculitis and other rheumatic diseases treated with immunosuppression has improved since they were introduced to the general population, there remain concerns and knowledge gaps regarding the impact of immunosuppression on the immune response (e.g., cellular, antibody, antibody function).[5]

In contrast to immunocompetent hosts in whom seroconversion following SARS-CoV-2 vaccination is nearly universally observed, studies have reported lower rates of seroconversion, lower antibody titers, and reduced neutralization in many users of anti-rheumatic drugs.[26-29] Seropositivity rates between 85-94% after initial series have been reported in patients with

systemic rheumatic diseases.[29-32] Few studies have reported specific findings in patients with vasculitis. Seropositivity rates of 82.6% (38/46) and 55% (87/159) after initial regimen (1 dose of Ad26.COV2.S or two doses of mRNA vaccine, or two doses of BNT162b2 or ChAdOx1, respectively) have been reported in two separate studies of AAV patients, and rituximab was associated with lack of response in both studies.[33,34] In a study of patients with GCA, seroconversion after initial regimen with BNT162b2 was reported in 93.8% of patients; all patients with impaired serological response were on methotrexate.[35]

Lack of seroconversion has been strongly associated with the use of specific medications such as B-cell depleting therapies as well as antimetabolites such as cyclophosphamide, mycophenolate mofetil, azathioprine, and methotrexate (Table 2).[29,36-38] Other anti-rheumatic drugs including Janus Kinase (JAK) inhibitors and tumor necrosis-α (TNF-α) inhibitors may also impact antibody responses.[29,39] With regards to glucocorticoids, their effect on seroconversion is still unclear since they are typically combined with other anti-rheumatic drugs. However, some studies have shown decreases in seroconversion associated with glucocorticoids, including one large cohort study that showed lower antibody titers, compared to immunocompetent controls, in patients receiving low doses of prednisone (< 7.5 mg/d).[29]

Seroconversion is thought to correlate with neutralizing antibody titers and cellular response. However, one large US study found lower neutralization titers against the delta variant in patients receiving TNF-α monotherapy, despite adequate seroconversion.[29] With regards to cellular response, studies in patients on B-cell depleting agents have shown spike-specific CD4 T-cell response in patients even in the absence of seroconversion. However, it seems that these spike-specific CD4 T cells might have an impaired function, which might explain the observations of increased breakthrough infections, including severe COVID-19, in vaccinated patients on B-cell depleted therapies.[40,41] One single-center study of patients with GCA showed a lack of neutralization activity in 16% and decreased cellular response in 30% of patients,

despite robust seroconversion.[42] The clinical significance of these findings requires further investigation to facilitate better approaches to stratifying risk and advising mitigation strategies.[43]

Enhancing vaccine response

SARS-CoV-2 vaccine boosters, both third and fourth boosters, have been shown to improve antibody response in patients with systemic rheumatic diseases.[44,45] Decreased risk of infection in systemic rheumatic disease patients with a third booster dose has been observed in one large population study.[46] Improvement in seroconversion has also been reported in patients with AAV after a third booster dose, including B-cell depleted patients at the time of the initial series.[47,48] However, this might not be the case for all patients on B-cell depleting therapies since lack of response, including formation of neutralizing antibodies, has been reported even after COVID-19 vaccine booster. In part, some of these differences may have to do with the timing of vaccination relative to B cell depletion therapy. Even more so, one recent study in systemic rheumatic diseases showed that SARS-CoV-2 Omicron (B.1.1.529) is able to evade antibody response in patients with mRNA vaccine booster-induced antibody neutralization. Therefore, although COVID-19 vaccine boosters can certainly enhance response, certain patients with systemic rheumatic diseases remain at high risk for COVID-19.

Given the known effect of some anti-rheumatic drugs on COVID-19 vaccine response, temporarily holding anti-rheumatic drugs (e.g., as in the case of daily medications) or delaying retreatment (e.g., as in the case of rituximab and other medications administered by infusion or subcutaneous injection) has been recommended. While this was empirically recommended based on previous experience with other vaccinations, two recent studies, one including patients using methotrexate and the other including mycophenolate mofetil users, found that temporarily holding medication was associated with an improved antibody response after vaccination.[49,50] Flares were reported in the mycophenolate mofetil study, highlighting the importance of individualized assessment to guide these strategies. With regards to rituximab,

studies have shown that longer periods from last rituximab dosing as well as B-cell reconstitution are strong predictors of seroconversion after COVID-19 vaccination.[37,38,51] In light of this evidence, the American College of Rheumatology has continued to recommend strategies to optimize vaccine response in patients on anti-rheumatic drugs.[52]

Flares and COVID-19 vaccination

A large physician-reported registry of 5121 patients with systemic rheumatic disease reported flares in 4.4% of patients, with only 1.5% of cases requiring changes in medications.[53] In the COVID-19 GRA Vaccine survey which included 2860 participants, flares that required medication changes were reported by 4.6% of patients.[54] A subsequent survey, which included 5619 participants, reported a similar rate of flares requiring medication changes (4.9%).[55] Risk of flares was higher in patients with specific rheumatic diseases such as systemic lupus erythematosus and polymyalgia rheumatica, when compared to rheumatoid arthritis, and in patients with a history of a previous serious reaction to other vaccines, as well as female sex. Overall, the risk of severe flare after COVID-19 vaccination seems to be relatively low. Although emerging case reports have reported either flares of pre-existing vasculitis or even new cases of vasculitis[56,57], the benefits of vaccination in patients with vasculitis and other systemic rheumatic diseases clearly exceeds the risks and vaccination should be encouraged in all patients.

Ongoing challenges in the management of patients with vasculitis

Rituximab

The greatest challenge to the use of rituximab during the COVID-19 pandemic has been the increasing recognition of its impact on the immune response to infection[7,10,11,58,59] as well as on the immunogenicity of COVID-19 vaccines.[22,29,37,60] Because of the associated higher risks for severe COVID-19 and reduced vaccine efficacy, a number of patients and clinicians have had to weigh these risks against the important benefits of rituximab for patients with vasculitis. Indeed,

prior to the pandemic, a number of clinical trials had established the superior efficacy of routine retreatment with B cell depletion for reducing the risk of relapse in AAV.[61-63] The COVID-19 pandemic and the risks associated with B cell depletion during this time have forced many to reconsider the prioritization of continuous B cell depletion for maintaining remission in AAV. Decisions regarding the use of rituximab to treat vasculitis during the COVID-19 pandemic requires shared decision making by the patient and clinician. Factors to consider when making these choices include the patient's history of AAV (e.g., treatment history, organ involvement, and damage), prior COVID-19 immunity (e.g., vaccination prior to rituximab, prior infection), the use of pre-exposure prophylaxis (see below), and the patient's values.

Cyclophosphamide

Like rituximab, cyclophosphamide leads to B cell depletion and has an impact on T cell function as well. This combination leaves patients vulnerable to both severe infection as well as a blunted immune response to vaccination. Given the less frequent use of cyclophosphamide in contemporary practice, there is scant data on COVID-19 outcomes in patients receiving cyclophosphamide.[10,64] In contrast to B cell depleting therapies, however, the use of cyclophosphamide is often limited to short durations to minimize toxicities and the half-life of oral or intravenous formulations is much shorter. To minimize COVID-19 risk, the dose and duration of cyclophosphamide should be minimized as much as possible and, when used, risk mitigating strategies discussed below should be implemented. It may be ideal to delay vaccination until cyclophosphamide is discontinued.

Prolonged Viral Shedding and Within Host Viral Evolution

A growing number of reports describe prolonged viral shedding and within-host viral evolution among patients with COVID-19 who had prior exposure to rituximab and cytotoxic therapies.[65-70] Given the frequent use of rituximab, cyclophosphamide, and other potent immunosuppression

for vasculitis, it is important to consider this population at risk for prolonged viral shedding and within-host viral evolution because of the associated implications for individual patient management and public health. Patients treated with rituximab, cyclophosphamide, or other strong immunosuppressants may be recommended to extend their quarantine during an acute infection and consider themselves contagious beyond the recommended 5-10 day window. Prolonged viral shedding in patients with vasculitis may predispose them to within-host viral evolution during which mutations may develop against monoclonal antibodies or antivirals, as has been previously described.[65] Additional studies are needed to understand the frequency of these events as well as ways to prevent them.

These observations highlight the substantial impact of the impaired immune response in vasculitis patients treated with rituximab and other immunosuppressants. Without an appropriate immune response, viral control may be difficult to attain and this likely contributes to the more frequent severe acute outcomes observed in these patients, such as hospitalization, mechanical ventilation, and death, as described above. Indeed, previous studies have found that some patients with COVID-19 who had prior exposure to rituximab mounted no detectable antibody response to SARS-CoV-2 which is known to be important for controlling viral replication.[59] This highlights the important role that monoclonal antibodies against SARS-CoV-2 may have for patients with vasculitis who are strongly immunosuppressed and unlikely to mount an antibody response. Monoclonal antibodies are approved for outpatient use but use may be considered for high risk inpatients unlikely to mount their own antibody response. Of note, bebtelovimab is the only monoclonal antibody for treatment of COVID-19 that has efficacy against the Omicron variant.

Equity

The COVID-19 pandemic has illuminated many of the ongoing racial and ethnic disparities in health and access to healthcare that exist in the United States and around the world. Racial and

ethnic minorities in the United States, including patients who identify as Black or African American or Hispanic, have been found to have a higher risk for COVID-19 as well as severe outcomes.[71] This has also been observed in patients with rheumatic diseases, including patients with vasculitis.[72] Clinicians should be aware of these disparities and identify opportunities to help their patients with vasculitis get better access to testing, pre-exposure prophylaxis, antiviral treatments, and risk mitigating strategies (e.g., masking, social distancing).

Post-Acute Sequelae of COVID-19 or Long COVID

Post-acute sequelae of COVID-19 (PASC) or "Long COVID" is now a well-recognized complication of COVID-19, defined as symptoms of COVID-19 that persist or develop at least 28 days after the onset of acute infection.[73-77] Common symptoms of PASC include fatigue, myalgia and arthralgia, loss of sense of smell or taste, dyspnea, headaches, and brain fog. Other manifestations of PASC include complications such as new-onset diabetes, chronic kidney disease, and other manifestations of end-organ damage. The etiology of PASC is poorly understood but hypotheses include alterations in inflammatory cytokine profiles [78], cellular immune responses [79], reactivation of chronic viral infections [80], and autoantibody formation.[81,82] Given the heterogeneity of PASC, it is plausible that distinct etiologies may be associated with different hosts recovering from acute illness. Given the association of vasculitis and its treatments with poor acute COVID-19 outcomes, it is possible that this population is more vulnerable to PASC but there is scarce data on this topic. Previous studies have suggested that while anyone recovering from COVID-19, even asymptomatic patients, can develop PASC, those with more severe acute infections tend to be at higher risk. Patients and clinicians should be aware that persistent or new symptoms developing in vasculitis patients after acute infection resolution may reflect PASC and will need to be distinguished from those attributable to the underlying vasculitis. There are no known effective treatments for PASC as of summer 2022.

Mitigation strategies

As discussed, many of the immunosuppressives used to treat vasculitis blunt the immune response to COVID-19 vaccination, leaving this population quite vulnerable to COVID-19, including severe disease. Masking, social distancing, and other measures were widely adopted early in the pandemic to reduce the risk of COVID-19. However, it is increasingly impractical for many to continue these measures indefinitely. These strategies may have negative effects on mental health,[83] including in patients with rheumatic disease,[84] and can make it difficult for patients to carry on their necessary activities of daily living, like working, attending medical appointments, or caring for themselves and their families. Moreover, many governments have dropped requirements for masking, vaccination, or social distancing which further increase the risk for patients with vasculitis when they are in public. Alternative approaches are therefore needed to keep patients with vasculitis safe during the ongoing pandemic (Figure 1).

Pre-Exposure Prophylaxis

The pharmacologic options for pre-exposure prophylaxis (PrEP) against COVID-19 remain limited. As of summer 2022, tixagevimab/cilgavimab is the only US Food and Drug Administration-authorized treatment to prevent COVID-19 in patients who are immunosuppressed. This treatment is a combination of two Fc-modified human monoclonal antibodies that have preserved efficacy against SARS-CoV-2 variants, including Omicron and its sub-variants. The Fc-modifications are meant to extend the half-life, in contrast to other monoclonal antibodies that have been used during the pandemic to treat acute infection and have a shorter half-life. Tixagevimab/cilgavimab is administered as two intramuscular vaccines every 6 months. It was originally studied as PrEP in a randomized clinical trial that enrolled unvaccinated patients who were at increased risk of an inadequate response to vaccination, including immunosuppressed patients (PROVENT trial)[85]; however, only 3.3% of patients enrolled in this trial received immunosuppressive treatment prior to enrollment. Other patients were included in the trial because of other factors that contribute to the risk of poor vaccine

response (e.g., obesity, cardiovascular disease). In PROVENT, the use of tixagevimab/cilgavimab vs placebo was associated with a 82.8% (95% CI 65.8%-91.4%) reduction in the relative risk of COVID-19 over 6 months.[85]

The published data from PROVENT reported outcomes through August 29, 2021, a period characterized by the dominance of pre-Omicron SARS-CoV-2 variants. To further assess the effectiveness of tixagevimab/cilgavimab against the Omicron variant and among immunocompromised patients, an observational retrospective cohort study from Israel compared the risk of COVID-19 among patients who received tixagevimab/cilgavimab vs those who did not.[86] All patients included in the study had been invited to receive tixagevimab/cilgavimab as part of a nationwide campaign for patients at high risk but not all participated. Among those invited to participate in the program (n=5,124), 825 received tixagevimab/cilgavimab and 43.9% of them qualified for tixagevimab/cilgavimab because they had received anti-CD20 treatment in the previous 6 months. Of note, a large portion of patients in this study were receiving anti-CD20 treatment as part of therapy for lymphoma; it is unclear how many had vasculitis or other immune-mediated inflammatory diseases being treated with anti-CD20 monoclonals. In contrast to PROVENT, the majority of patients in this observational study had previously received at least one COVID-19 vaccine. In a multivariable adjusted analysis, those who received tixagevimab/cilgavimab had a 49% lower odds of COVID-19 infection compared with not receiving tixagevimab/cilgavimab (OR 0.51, 95% CI 0.30-0.84). Additionally, there was a strong benefit associated with tixagevimab/cilgavimab vs not receiving tixagevimab/cilgavimab when assessing severe COVID-19 (OR 0.08, 95% CI 0.01-0.54). While there are important limitations to this study related to its design and the way it handled potential confounding, the findings do support the effectiveness and importance of tixagevimab/cilgavimab for reducing the risk of COVID-19, including severe disease.

Collectively, the available data suggests that there is likely to be an important and ongoing role for monoclonal antibodies like tixagevimab/cilgavimab for preventing COVID-19 and severe outcomes in patients with vasculitis who are often severely immunosuppressed. Indeed, the current recommendations suggest that tixagevimab/cilgavimab be considered in many patients who would be considered moderately-to-severely immunocompromised, not only those who have received B cell depleting therapies in the United States.[87] Many centers have started programs whereby patients are able to receive tixagevimab/cilgavimab at the same time that they are receiving anti-CD20 therapies or at the time of another clinical encounter. Tixagevimab/cilgavimab is well-tolerated but there is a risk of an injection site reaction and/or hypersensitivity reaction.[88] Additionally, based on some observations during its development program, there is an associated warning regarding a potentially higher risk of cardiovascular events associated with tixagevimab/cilgavimab. In our practice, we have considered the potential benefits of tixagevimab/cilgavimab to outweigh these potential risks, except in patients with high risk of cardiovascular disease. Use of tixagevimab/cilgavimab requires a careful review of the risks and benefits with patients.

Post-Exposure Prophylaxis

Post-exposure prophylaxis (PEP) has also been used to prevent COVID-19 in immunosuppressed patients exposed to COVID-19. Similar to PrEP, options available for PEP have been limited to monoclonal antibodies.[89,90] The experience using monoclonal antibodies as PEP, however, has illuminated the challenges associated with this approach in the face of SARS-CoV-2 evolution towards variants with resistance to treatments, including monoclonal antibodies. As of the summer 2022, there are no longer monoclonal antibody treatments authorized for use as post-exposure prophylaxis because current SARS-CoV-2 variants in circulation have resistance to previously authorized treatments.[87,89,90] Previously,

bamlanivimab/etesevimab and casirivimab/imdevimab had been authorized for use as PEP in patients at high risk for severe COVID-19.

Access to Testing and Treatment

It is critical that patients with vasculitis be counseled to reach out to their providers if they are exposed to COVID-19 or test positive for COVID-19. We counsel our patients to keep a supply of rapid antigen tests at home, if they have access to these tests, and to contact us immediately if they test positive. Indeed, the early initiation of antiviral therapy with remdesevir[91], ritonavir-boosted nirmatrelvir[92,93], or molnupiravir[94], is critical for reducing the risk of severe disease in patients with vasculitis who are often on treatments or have comorbidities associated with a higher risk of severe disease.[87] Additionally, a monoclonal antibody with evidence of neutralizing ability against Omicron - bebtelovimab - is an option for those who may not be able to receive an antiviral. However, the evidence supporting the efficacy of bebtelovimab is limited.

According to the most recent US National Institutes of Health guidance (as of August 8, 2022) [87], ritonavir-boosted nirmatrelvir or remdesevir are preferred over molnupiravir or bebtelovimab because of the stronger efficacy data supporting their use. Of note, it is important to review the drug-drug interactions associated with ritonavir-boosted nirmatrelvir. For patients with vasculitis, it is important to know that there are potential interactions of ritonavir-boosted nirmatrelvir with glucocorticoids, colchicine, avacopan, and cyclophosphamide. In these instances, ritonavir-boosted nirmatrelvir may increase exposure to the metabolites of glucocorticoids and cyclophosphamide, leading to higher risk of toxicities.

One must also consider the dose reduction needed for patients with an estimated glomerular filtration rate (eGFR) of 30-60ml/min; it is contraindicated in patients with an eGFR < 30ml/min, due to renal excretion of nirmatrelvir[95], which has relevance for many patients living with vasculitis. Similarly, the safety of remdesivir for patients with an eGFR < 30ml/min is

controversial and large safety studies are lacking. Both the drug itself and its carrier (sulfobutylether-β-cyclodextrin) may contribute to kidney injury.[5] Therefore, the use of remdesivir in patients with an eGFR < 30ml/min or who are receiving dialysis should be done so in collaboration with infectious disease and nephrology experts.

Conclusions

The COVID-19 pandemic has substantially impacted the lives of patients living with vasculitis and has imposed a number of challenges for the management of vasculitis. Many patients with vasculitis remain at higher risk for COVID-19 and severe outcomes, despite advances such as vaccines, anti-virals, and other management strategies. In part, this increased risk is because many of the medications that are highly effective for vasculitis, such as rituximab, also interfere with the immune response to vaccination and infection. The use of pre- and post-exposure treatment, as well as access to early diagnosis and treatment for those infected are essential for reducing the risk of severe COVID-19 in patients with vasculitis. Patients and clinicians can use the expanding data on outcomes of COVID-19 in patients with vasculitis in the context of evolving COVID-19 and vasculitis management strategies to make decisions together regarding their vasculitis care in this uncertain time. Moving forward, clinical trials of therapeutics that enroll patients with vasculitis and others who use immunosuppression are needed to inform management strategies.

Clinics Care Points

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Figure 1. Ongoing challenges and mitigation strategies in the management of vasculitis patients during the COVID-19 pandemic. Created with BioRender.com.

COVID-19: coronavirus disease 2019, mAb: monoclonal antibody, RTX: rituximab

Table 1. Risk factors for severe COVID-19 infection in patients with vasculitis

Risk factors	
Non-Modifiable	Older age Race/ethnicity Male sex Comorbidities (chronic kidney disease in AAV) Obesity (GCA)
Modifiable	High disease activity Use of rituximab or cyclophosphamide High dose glucocorticoids

AAV: ANCA-associated vasculitis, GCA: giant cell arteritis

Table 2. Anti-rheumatic drugs used for treatment of vasculitis and their association with antibody response to SARS-CoV-2 vaccination

Significantly reduce antibody response	**Probably reduce antibody response**	**May not affect antibody response**
Rituximab	TNF-α inhibitors	IL-6 inhibitors
Cyclophosphamide	Janus kinase inhibitors	Apremilast
Methotrexate	Abatacept	Colchicine
Azathioprine		
Mycophenolate		
Leflunomide		

Glucocorticoids		

TNF: tumor necrosis factor, IL: interleukin