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Editorial

Molnupiravir and Nirmatelvir/Ritonavir in the Treatment of Patients With Systemic Autoimmune Rheumatic Disease With SARS-CoV-2



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SARS-CoV-2 has certainly been at the forefront of medical discussion and research for the past 3 years. While many are adjusting back to "normal," thanks to the rapid advancements in prevention and treatment, high-risk groups, such as adults with systemic autoimmune rheumatic diseases (SARDs), still require careful monitoring and care. In the abundance of literature surrounding SARS-CoV-2, there remains a paucity of data specific to treatment of SARS-CoV-2 in patients with SARD.

Patients with SARD are known to have worse outcomes from SARS-CoV-2, including higher rates of hospitalization and, in some cases, higher mortality. Those with more comorbidities, older age, and more severe SARD manifestations are at the highest risk for poor outcomes.[1-6] Although vaccination remains the best defense against the virus, patients with SARD may have a blunted response to the vaccine.[7-11] Breakthrough infections in patients with SARD have been described.[12] Booster doses are significantly helpful in this group, have been shown to reduce breakthrough infections,[13] and continue to show benefit with new SARS-CoV-2 subvariants.[14] Monoclonal antibodies have been helpful for those with infection who do not have detectable antibodies[15]; however, they have not shown to be effective in newer subvariants. Antiviral medications, including molnupiravir and nirmatelvir/ritonavir, do seem to retain effectiveness against these variants.[16] Considering this, it is important to understand appropriate use of these antiviral medications in patients with SARD.

Molnupiravir and nirmatelvir/ritonavir are antiviral treatments for mild to moderate SARS-CoV-2 to prevent progression to severe disease in high-risk individuals. Patients with SARD frequently fall into this high-risk group because many are on immunosuppressive agents. Since initial approval, there have been a few studies that have examined antiviral use as it pertains to this population. Fragoulis et al described a case series of primarily vaccinated patients with SARD treated with oral antivirals, with none of the 31 patients requiring hospitalization and with no major safety concerns.[17] Najjar-Debbiny et al demonstrated nirmatelvir/ritonavir has similar efficacy in vaccinated and unvaccinated individuals, and, although not directly examining patients with SARD, nirmatelvir/ritonavir was favored for patients on immunosuppression in a subgroup analysis.[18] Potential concerns have been raised, however, regarding coronavirus disease 2019 (COVID-19) rebound in patients receiving antivirals, as well as concerns over drug-drug interactions. COVID-19 rebound occurs when the patient experiences recurrent COVID-19 infection and symptoms after completing a full course of antiviral therapy with symptom resolution. Wang et al have examined this in a preprint report that looked at patients taking molnupiravir or nirmatelvir/ritonavir.[19] They found rebound rates ranging from 3.53% to 8.59%, with no statistically significant difference in rebound between the 2 agents, but with higher rebound rates in immunosuppressed patients. The need for hospitalization due to COVID-19 rebound was low in this study, at under 1.5%.[19]

In this issue of *The Journal of Rheumatology*, Gerolymatou et al retrospectively reviewed 74 patients with SARD who had received either molnupiravir or nirmatelvir/ritonavir for COVID-19 between February and August 2022, corresponding to the Omicron wave.[20] Most patients were vaccinated with 3 doses of mRNA-based vaccines. Ninety-seven percent of patients recovered at home without complications, whereas 2 patients progressed to severe COVID-19, requiring hospitalization and high-flow nasal cannula supplemental oxygen. Both patients recovered and were subsequently discharged. The Discussion mentions these may have been COVID-19 rebound cases; how-

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ever, it is not clear they had symptom improvement and subsequent recurrence prior to admission, as is seen in rebound cases, and rather likely had progression of their primary COVID-19 infection to severe disease. Overall, tolerability of antivirals in this patient group was very good, with only 4 patients reporting side effects and no patients discontinuing the drug. Although the side effect profile is desirable, drug-drug interactions are still a concern, especially with nirmatelvir/ritonavir, which can interact with CYP3A-dependent drugs, including tacrolimus, cyclosporine, and sirolimus.[21]

Gerolymatou et al[20] mention that patients vaccinated and boosted with the Omicron variant may recover without event regardless of antiviral use due to vaccination status alone, as suggested by prior studies.[13,22] Molnupiravir in particular may not reduce hospitalization rates in vaccinated patients as demonstrated by the PANORAMIC trial[23] and by Yip et al.[24] Nirmatelvir/ritonavir, however, does seem to confer benefit for vaccinated individuals.[18,24] In line with this, Qian et al's preprint study looking at 704 patients with SARD with COVID-19 from January 2022 through May 2022 showed nirmatelvir/ritonavir was beneficial in this patient population in reducing hospitalization or death from severe COVID-19. Importantly, most patients were vaccinated in this study.[25]

Overall, oral antiviral therapy for SARS-CoV-2, particularly nirmatelvir/ritonavir, is a good treatment option for patients with SARD. These medications have been shown to be safe and effective in reducing progression to severe COVID-19 but may have risk of COVID-19 rebound and have known drug-drug interactions. They also appear to remain effective despite Omicron subvariant emergence. Providers should be familiar with these treatment options for their patients with SARD who develop SARS-CoV-2 and should also continue to encourage patients with SARD to become fully vaccinated and boosted against COVID-19.

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