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Oral Antiviral Treatment for COVID-19 in Patients With Systemic Autoimmune Rheumatic Diseases

Nafsika Gerolymatou[1], Athanasios-Dimitrios Bakasis[2], Paraskevi V. Voulgari[1], and Panayiotis G. Vlachoyiannopoulos[2]

ABSTRACT. ***Objective.*** To describe data on the safety and efficacy of molnupiravir (MP) and nirmatrelvir/ritonavir (NM/R) in patients with systemic autoimmune rheumatic diseases (SARDs).

Methods. Among patients with SARD being followed in 2 tertiary outpatient rheumatology clinics, we retrospectively identified those infected with SARS-CoV-2 between February and August 2022 who received MP or NM/R. Patients' medical files were reviewed for demographics and disease-related characteristics, as well as coronavirus disease (COVID-19) characteristics, including vaccination status, antiviral treatment, side effects, and COVID-19 outcomes.

Results. Seventy-four patients with SARD (52 females) were identified who had been infected with SARS-CoV-2 and received MP (n = 26, 35.1%) or NM/R (n = 48, 64.9%). Most patients were vaccinated against SARS-CoV-2 (n = 62, 83.8%). Among frequently used regimens were glucocorticoids (n = 43, 58.1%), mycophenolate mofetil (n = 26, 35.1%), tumor necrosis factor inhibitors (n = 14, 18.9%), methotrexate (n = 13, 17.6%), and rituximab (n = 12, 16.2%). Common adverse events were reported only by 4 patients receiving NM/R (metallic taste, gastrointestinal upset, hypertension), not leading to drug discontinuation. During follow-up, all but 2 patients (n = 72, 97.3%) recovered at home without COVID-19–related complications. Nonetheless, we describe 2 presumptive cases of COVID-19 rebound who progressed to severe COVID-19.

Conclusion. These data show a favorable outcome and acceptable safety profile of the 2 oral antiviral therapies MP and NM/R among a high-risk SARD population. However, cases of COVID-19 rebound are being increasingly identified. These findings call for continuous surveillance to capture the real-world efficacy and safety profiles in our subpopulations of interest.

Key Indexing Terms: antiviral agents, autoimmunity, COVID-19, SARS-CoV-2

The extraordinary response of the scientific community to the coronavirus disease 2019 (COVID-19) pandemic has led to advances in the pathophysiology of the SARS-CoV-2 infection, as well as in the development of diagnostic tools and treatments for COVID-19. However, the major variable that aided to curb the pandemic, and significantly decreased the morbidity and mortality of infected individuals, was the development of the novel SARS-CoV-2 vaccines. Nevertheless, particular subgroups of patients including those with systemic autoimmune rheumatic diseases (SARDs) under intensive immunosuppressive/immunomodulatory therapies remain sometimes vulnerable and at high risk for severe COVID-19 outcomes.[1]

[1]N. Gerolymatou, MD, PhD, P.V. Voulgari, MD, PhD, Department of Rheumatology, School of Health Sciences, Faculty of Medicine, University of Ioannina, Ioannina; [2]A.D. Bakasis, MD, P.G. Vlachoyiannopoulos, MD, PhD, Department of Pathophysiology, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece.

The authors declare no conflicts of interest relevant to this article.

Address correspondence to Dr. P.V. Voulgari, Department of Rheumatology, School of Health Sciences, Faculty of Medicine, University of Ioannina, Stavros Niarchos Av., Ioannina, 45445, Greece. Email: pvoulgar@uoi.gr.

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At this crucial time of the global pandemic, with the rapid spread of new variants, the emergent authorization of the first 2 oral antiviral therapies—molnupiravir (MP) and nirmatrelvir/ritonavir (NM/R)—introduced a new therapeutic tool in the battle against this pandemic.[2] However, phase II/III placebo-controlled randomized trials supporting the authorization of these 2 antivirals were conducted: (1) before the emergence of the Omicron variants that are now almost 100% dominant, (2) in unvaccinated patients with COVID-19, and (3) excluding those with SARD.[2] Additionally, MP showed marginal (3%) absolute risk reduction in hospitalization or death when compared to the placebo, meaning that 35 patients needed to be treated to prevent one from being hospitalized or dying; on the other hand, NM/R displayed clinically significant drug-drug interactions and cases of COVID-19 rebound are being increasingly identified.[3] Considering all these, postauthorization real-world data on the efficacy and safety of these drugs have become of importance.

Awaiting results of nationwide and registry studies, we sought to describe our experience on the safety and efficacy of MP and NM/R in patients with SARD.

METHODS

Among patients with SARD being followed in 2 tertiary outpatient rheumatology clinics, we retrospectively identified those infected with

SARS-CoV-2 between February and August 2022 who received MP or NM/R as high-risk individuals for severe COVID-19. Patients' medical files were reviewed for the following: (1) demographic characteristics (age and sex) and comorbidities (arterial hypertension, cardiovascular disease, diabetes, dyslipidemia, and chronic lung disease including lung involvement related to the underlying SARD); (2) SARD-related characteristics at the time of COVID-19 occurrence (disease type and disease activity based on physician global assessment [remission or minimal/low vs moderate or severe/high disease activity] and immunosuppressive/immunomodulatory treatment regimens); (3) COVID-19 vaccination-related details (vaccine type and number and dates of doses administered); (4) oral antiviral treatment and side effects; and (5) COVID-19 characteristics (date of infection confirmed by PCR or viral antigen testing on the nasopharyngeal swab material, and COVID-19 severity and outcomes), all of which were previously reported.[1] Comorbidities were defined as those medical conditions existing before or occurring during the clinical course of the index SARD, that were reported in the national electronic database for social security services in Greece (IDIKA) based on the International Classification of Disease, 10th revision,[4] and/or appropriate medications were prescribed by a specialist; those known to be associated with increased risks of hospitalization and death in the wake of the COVID-19 pandemic were also included.[5] All patients had been followed up by their treating physicians 1 month after the administration of antivirals for pharmacovigilance purposes and for mandatory recording of outcome and side effects in the IDIKA database. Due to the noninterventional, retrospective, and anonymized nature of the study, ethics approval and patient consent were not required.

RESULTS

We retrospectively identified 74 patients with SARD who had been infected with SARS-CoV-2 and received MP (n = 26/74, 35.1%) or NM/R (n = 48/74, 64.9%), according to national guidelines[4]. Most patients were vaccinated against SARS-CoV-2 (n = 62/74, 83.8%) either with 2 doses (n = 11/62, 17.7%), 3 doses (n = 43/62, 69.4%), or 4 doses (n = 8/62, 12.9%) of mRNA-based vaccines (Table). Most frequently treatment regimens used were glucocorticoids (n = 43/74, 58.1%), csDMARDs (n = 41/74, 55.4%), bDMARDs (n = 38/74, 51.4%) and other immunosuppressants (n = 32/74, 43.2%). All treatment regimens were modified/withheld according to the American College of Rheumatology recommendation.[6] Half of the patients (n = 39/74, 52.7%) had at least 1 comorbidity, more commonly pulmonary disease (n = 19/74, 25.7%). In 6 cases, co-medications had to be temporarily discontinued (atorvastatin, simvastatin, rivaroxaban) due to potential interactions with NM/R (4 patients did not withhold it although recommended by the treating physician). Overall, no dosage adjustments were required, and no other treatment was provided (including inhalers, antibiotics, or low-molecular-weight heparin). Adverse events were reported only by 4 patients receiving NM/R (metallic taste [n = 2], gastrointestinal upset [n = 1], and self-limiting episode of high blood pressure [n = 1]) that did not lead to drug discontinuation. During follow-up, all but 2 patients (n = 72/74, 97.3%) recovered at home without COVID-19–related complications. Regarding the 2 patients who progressed to severe COVID-19, the first case was a 55-year-old obese female patient with rheumatoid arthritis, in low disease activity, treated with prednisolone 5 mg/day, leflunomide 20 mg/day and rituximab, and vaccinated with a third vaccine dose 130 days prior the infection. Ten days after NM/R treatment completion, the patient was hospitalized due to a relapse of fever and cough. The second case was a 75-year-old female patient with a history of longstanding systemic sclerosis, with lung involvement and arterial hypertension, receiving prednisolone 5 mg/day and mycophenolate mofetil 2 g/day. The patient got infected 86 days after the second vaccine dose and was given MP. Nevertheless, 3 days after completion of the treatment, the patient was hospitalized because of fever relapse and progression of dyspnea. Both patients developed severe respiratory distress that required high-flow nasal cannula ventilation. They both received remdesivir, steroids, antibiotic therapy, and tocilizumab (2 doses and 1 dose, respectively). At follow-up, case 2 symptomatology resolved uneventfully, whereas case 1 remained SARS-CoV-2 positive for ≥ 3 months at sequential testing despite no relevant symptomatology.

DISCUSSION

Our data show a favorable outcome and acceptable safety profile in a primarily fully vaccinated high-risk SARD population amid the Omicron wave. Unfortunately, a control study group could not be identified, since only a few of our patients at high risk refused to receive oral antiviral treatment (n < 10). Nevertheless, our impression is that COVID-19 outcomes in patients receiving oral antivirals seem to be better than those previously reported among other high-risk patients with SARD with breakthrough infection and particularly among those not fully vaccinated individuals infected with pre-Omicron variants.[1,7] Findings are similar in another case series published by Fragoulis et al, where no high-risk patient with SARD taking MP or NM/R progressed to severe COVID-19 requiring hospitalization and, more importantly, no deaths were reported.[8] However, these anticipated differences between up-to-date vaccinated patients with and without oral antiviral treatment for breakthrough infections may have been recently mitigated given that the majority of patients with SARD and additional vaccine doses seem to recover uneventfully even without oral antiviral prophylaxis during the current Omicron wave, as Saxena et al demonstrated in a cohort of patients with systemic lupus erythematosus.[9] Adding to this, a study by Wong et al evaluating the effectiveness of MP and NM/R in a large territory-wide cohort from the general population in China during the Omicron surge, found that early initiation of oral antivirals—especially NM/R—among noninstitutionalized COVID-19 patients, was associated with reduced risks of mortality and in-hospital outcomes.[10] However, neither drug was associated with as high a level of protection among the vaccinated Chinese individuals infected with Omicron, as that seen in their clinical trials among unvaccinated counterparts with the Delta variant. On the contrary, Yip et al showed that the use of NM/R, but not MP, was associated with a reduced risk of hospitalization in real-world patients with COVID-19, whereas no association was found for either of these drugs with a composite of intensive care unit admission, invasive mechanical ventilation use, and/or death.[11]

Recent case reports document that some patients treated with NM/R experienced rebound COVID-19 infections with

Table. Characteristics of the patients included in the study.

	N = 74
Demographics	
Female sex, n (%)	52 (70.3)
Age, yrs, mean (SD)	50.8 (14.6)
Vaccination status (0/1/2/3/4), doses, n (%)	12 (16.2) / 0 (0) / 11 (14.9) / 43 (58.1) / 8 (10.8)
Time duration from last administered dose (2-/3-/4-dose series) and breakthrough infection, days, mean (SD)	191.3 (138.2) / 155.3 (68.1) / 144.6 (71.8)
SARD diagnosis, n (%)	
RA	17 (23)
SpA	10 (13.5)
Connective tissue disease (SLE, SS, SSc)	32 (43.2)
Systemic vasculitis	6 (8.1)
Other (IIM, AOSD, MCTD, IgG4-RD)	9 (12.2)
Disease activity, n (%)	
Remission/low/moderate/high	8 (10.8) / 48 (64.9) / 17 (23) / 1 (1.4)
Treatment	
Glucocorticoids, n (%)	43 (58.1)
Dose of prednisolone, mean (SD)	5.9 (3.3)
csDMARDs, n (%)	41 (55.4)
Methotrexate	13 (17.6)
Hydroxychloroquine	20 (27)
Leflunomide	7 (9.5)
Cyclosporine	1 (1.4)
bDMARDs, n (%)	38 (51.4)
TNFi	14 (18.9)
Rituximab	12 (16.2)
Abatacept	3 (4.1)
IL-6 inhibitor	2 (2.7)
IL-12/23 inhibitor	1 (1.4)
IL-17 inhibitor	2 (2.7)
Belimumab	4 (5.4)
Other immunosuppressants, n (%)	32 (43.2)
Mycophenolate mofetil	26 (35.1)
Azathioprine	4 (5.4)
Cyclophosphamide	2 (2.7)
Comorbidities, n (%)	39 (52.7)
BMI ≥ 30	5 (6.8)
Diabetes mellitus	7 (9.5)
Chronic kidney disease	2 (2.7)
Chronic liver disease	1 (1.4)
Cardiovascular disease	9 (12.2)
Arterial hypertension	14 (18.9)
Pulmonary disease	19 (25.7)

AOSD: adult-onset Still disease; bDMARD: biologic disease-modifying antirheumatic drug; csDMARD: conventional synthetic disease-modifying antirheumatic drug; IgG4-RD: IgG4-related disease; IIM: idiopathic inflammatory myopathy; IL: interleukin; MCTD: mixed connective tissue disease; RA: rheumatoid arthritis; SARD: systemic autoimmune rheumatic disease; SLE: systemic lupus erythematosus; SpA: spondyloarthritis; SS: Sjögren syndrome; SSc: systemic sclerosis; TNFi: tumor necrosis factor inhibitor.

symptomatology 2 to 8 days after completing a 5-day drug course.[3] The US Centers for Disease Control and Prevention advisory updated the public on the potential for COVID-19 rebound after NM/R treatments, highlighting that they occurred in both the treatment and the placebo group and thus might be part of the natural history of SARS-CoV-2.[12] Although a definite COVID-19 rebound cannot be supported due to lack of SARS-CoV-2 testing in our case series, the overall clinical picture in cases 1 and 2 was highly indicative. Fragoulis et al reported that COVID-19 relapsed in 2/31 participants within 1 month after NM/R initiation and negative antigen tests in between, raising the concern whether treatment with immunosuppressive/immunomodulatory drugs could be somehow related.[8] A recent preprint study examining the rates and relative risks of a composite COVID-19 rebound outcome (infections, symptoms, and hospitalizations) after oral antiviral treatment among

92 million patients from a multicenter nationwide database in the United States found that COVID-19 rebound occurred both after NM/R and MP.[13] Of note, "disorders involving the immune mechanisms" and immunosuppressants usage were more frequently found in those experiencing rebound than in those who did not.[13]

Our study has certain limitations. First, this is a retrospective observational study without a known denominator, where patients with SARD who were infected with SARS-CoV-2 were recorded based on self-referral at the time of COVID-19 or upon interviewing at a follow-up physical; therefore, COVID-19 cases and even rebounds might have been missed. Second, a control study group could not be identified, since fewer than 10 patients at high risk refused to receive oral antiviral treatment, as we previously mentioned. Third, although patients were systematically asked for side effects, recall bias cannot be excluded and some side effects could had been confused with COVID-19 manifestations.

In conclusion, SARS-CoV-2 and the pandemic remain one step ahead of us, and our drug choices have nuances related to the patient population and current conditions. As such, without restricting the use of these potentially highly effective antivirals in high-risk patients at this crucial time in the pandemic, recent findings call for continuous surveillance and multicenter, harmonized, and well-defined postapproval data to capture the real-world efficacy and safety profiles in our subpopulations of interest.

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