Rebound Phenomenon after Nirmatrelvir/Ritonavir Treatment of Coronavirus Disease-2019 in High-Risk Persons

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ABSTRACT

In a cohort of 483 high-risk patients treated with nirmatrelvir/ritonavir for coronavirus disease-2019, two patients (0.4%) required hospitalization by day 30. Four patients (0.8%) experienced rebound of symptoms, which were generally mild, at median of 9 days after treatment, and all resolved without additional COVID-19-directed therapy.

INTRODUCTION

Nirmatrelvir, the main protease inhibitor of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), co-formulated with ritonavir as its pharmacokinetic booster, is authorized for treatment of mild to moderate coronavirus disease-2019 (COVID-19) in high-risk individuals [1]. This emergency use authorization (EUA) is supported by the EPIC-HR randomized controlled trial that demonstrated an 89% relative risk reduction of hospitalization and death among unvaccinated patients who received treatment [2]. With widespread use since January 2022, recurrence of symptoms in some patients after completion of nirmatrelvir-ritonavir (NM/R) treatment have been increasingly reported [3]. We aimed to gain insight into this rebound phenomenon by assessing the incidence, clinical course, and outcomes of patients treated with NM/R in our program.

METHODS

After Institutional Review Board (IRB# 22-004922) approval, we performed a retrospective review of patients at Mayo Clinic in Rochester who received NM/R for mild-to-moderate SARS-CoV-2 infection. At our center, outpatient therapies were coordinated by the Monoclonal Antibody Treatment Program and the Midwest COVID-19 Care Team, a centralized multidisciplinary team that assesses patients for eligibility for treatment according to the FDA EUA criteria [4]. Each patient is assigned a Monoclonal Antibody Screening Score (MASS) and COVID Antibody Screening Tool Score (CAST) that categorizes a person's risk for severe disease progression, to facilitate appropriate allocation of NM/R therapy [5]. If eligible, patients were given the option for oral NM/R, intravenous remdesivir, or intravenous monoclonal antibody (sotrovimab, bebtelovimab). The final decision on drug treatment is based on shared decision making between patients and providers. Notably, immunocompromised patients and their providers have preferred anti-spike neutralizing monoclonal antibodies due to the potential for drug-drug interactions and the overall positive outcomes from prior reports [6].

High-risk individuals were also offered telemedicine follow-up using the COVID-19 remote patient monitoring program. Using this program, we reviewed the clinical symptoms of patients at time of SARS-CoV-2 diagnosis until completion of NM/R therapy, at which point patients who met criteria for release of isolation graduated from the program. Electronic Health Records were reviewed to identify "rebound" of clinical symptoms following completion of 5-day course of NM/R therapy.

Rebound was defined as recurrence of COVID-19 symptoms following successful completion of 5 days of NM/R therapy and was assessed for up to 30 days after treatment. To meet criteria, patients needed to have demonstrated 1) test-confirmed diagnosis of symptomatic SARS-CoV-2 infection prior to initiation of NM/R, 2) improvement in most or all symptoms during therapy with NM/R, and 3) absence of an alternate explanation for recurrent symptoms. Patients who failed to complete the 5-day course of NM/R, lacked significant improvement in symptoms (deemed treatment failure), or had persistent symptoms signifying long COVID were excluded from analysis of the rebound phenomenon. Institutional diagnostic stewardship task force guidelines prevent repeat testing within 90 days following diagnosis of SARS-CoV-2 unless clearly indicated. Hence microbiologic data including viral load to demonstrate pattern of viral replication in the context of rebound was not available for all patients. Basic descriptive statistics of the patients meeting our inclusion criteria were performed using R version 4.1.2. [7].

RESULTS

The study population of 483 patients had a median age of 63 years (interquartile range [IQR] 51-74) and 56% were female. The median Monoclonal Antibody Screening Score was 3 (IQR, 1-5), suggesting a high-risk for severe disease progression. The majority (n=448 (93%)) were fully vaccinated. Time from positive SARS-CoV-2 test to being prescribed NM/R was 1 day (IQR, 1-2) (Table 1). Within 30 days of diagnosis, 2 (0.4%) patients were hospitalized for reasons unrelated to rebound, and both required intensive care unit (ICU) level of care. No patients died (Table 1).

Four patients (0.8%) experienced rebound of symptoms at a median of 9 days (IQR, 7-14.5) after NM/R treatment. All four patients were fully vaccinated. Two patients presented to their primary care

provider. No patient needed hospitalization. All improved without requiring further COVID-19 directed therapies. No alternative diagnoses were found. Their clinical course and outcome are detailed below.

Patient 1:

75-year-old male with coronary artery disease, chronic obstructive pulmonary disease, diabetes mellitus started NM/R 3 days after testing positive for SARS-CoV-2 by nasopharyngeal PCR. He was fully vaccinated (3-doses of mRNA vaccine; last dose administered 156 days prior). His symptoms of cough, rhinorrhea, headache, and fever resolved by day 5 post NM/R. However, nineteen days after NM/R, he had increased cough with wheezing and dyspnea. CT chest demonstrated mild ground-glass and reticular opacities consistent with COVID-19 pneumonia. He received symptom-directed therapy.

Patient 2:

40-year-old female with obesity, chronic kidney disease, and hypertension started on NM/R 3 days after testing positive for SARS-CoV-2 by home nasal antigen test. She was fully vaccinated (3 doses of mRNA vaccine; last dose administered 119 days prior). Her symptoms of fever, non-productive cough, palpitations, and diarrhea resolved at completion of NM/R regimen. Six days later, she had worsening pharyngitis, fatigue, malaise managed with symptom-directed therapy.

Patient 3:

69-year-old male with hypertension and obesity started NM/R 1 day after testing positive for SARS-CoV-2 by nasopharyngeal PCR. He was fully vaccinated (3 doses of mRNA vaccine; last dose administered 185 days prior). His symptoms of fever, cough, rhinorrhea, myalgia, and dyspnea had improved following completion of NM/R therapy. Ten days later, he had worsening rhinorrhea and cough, which was managed with symptom-directed therapy.

Patient 4:

70-year-old male with history of prostate cancer, hypertension, dyslipidemia, obesity started NM/R 1-day after testing positive for SARS-CoV-2 by home nasal antigen test. He was fully vaccinated (3 doses of mRNA vaccine; last dose administered 171 days prior). His symptoms of productive cough, fever, rhinorrhea, headache, and pharyngitis had resolved at completion of NM/R regimen. Eight days later, he had recurrence of rhinorrhea and sinus congestion which was managed with symptom-directed therapy.

DISCUSSION

Anecdotal reports of rebound phenomenon after completion of NM/R is being increasingly reported [3]. Our retrospective review of 483 patients with mild SARS-CoV-2 infection treated with NM/R found a low rate of rebound phenomenon. Only 0.8% of patients experienced recurrence of symptoms following completion of therapy. Overall, high-risk patients who received early NM/R treatment had favorable outcomes with 0.4% requiring hospitalization and ICU admission, and no deaths at 30 days after diagnosis.

One explanation for this rebound phenomenon is the resumption of SARS-CoV-2 viral replication following completion of therapy, triggering a secondary immune-mediated response that manifests as recurrence of clinical symptoms. The manufacturer had reported to the FDA of several such cases of rebound in SARS-CoV-2 RNA levels in <2% of patients at day 10 or 14 following NM/R completion [1]. It is unclear if this represents resumption of viral replication in persons with incompletely controlled infection due to inadequate length of therapy (5-days) or a natural biphasic pattern of viral replication [8]. Data about potential presence of viral rebound in patients from EPIC-HR who received placebo therapy would be helpful in delineating this question. Furthermore, prospective studies evaluating viral RNA replication during and following completion of NM/R in those with and without relapse symptoms are needed. Because institutional guidance did not allow for repeat testing, we were not able to determine viral replication kinetics in this retrospective review.

Extending the duration of NM/R treatment to prevent this rebound phenomenon has been suggested. However, our data suggests that this may not be necessary. The rate of rebound is low (0.8%) and extending treatment to all patients to prevent rebound in the small number of patients would be a

suboptimal strategy. Identifying risk factors may help distinguish patients who are more likely to experience rebound phenomenon. We are unable to define risk factors in this study due to small number of cases, but it is notable that the four patients with rebound had multiple underlying medical comorbidities and had received SARS-CoV-2 vaccine more than 90 days prior to NM/R therapy. Studies have shown that persons with multiple comorbidities are more likely to have unfavorable course despite COVID-19 directed therapies. Nonetheless, the four patients with rebound had favorable outcomes even without additional COVID-19-directed treatment.

A limitation of our review was the retrospective nature of the chart review and the challenges of subjective evaluation of symptom rebound. To mitigate the risk of ascertainment bias, all patients receiving NM/R had close clinical follow-up and opportunity to self-report progression of symptoms through a centralized COVID-19 remote monitoring program until completion of therapy and graduation from the program. We also employed 2-independent physician adjudication to identify suspected cases of rebound. The results of this study should be interpreted in the context of our patient cohort, who have high vaccination rates but with an under-representation of immunocompromised individuals. As noted above, in our program, immunocompromised patients and their providers preferred anti-spike neutralizing monoclonal antibody therapy or intravenous remdesivir, instead of NM/R, for the treatment of COVID-19.

CONCLUSION

Rebound after NM/R treatment is uncommon in our population of high-risk, but mostly non-immunocompromised patient population. Among the patients who developed rebound of symptoms after NM/R treatment, the clinical presentation was mild and did not require COVID-19 directed therapies. In our cohort, the outcomes of patient with rebound phenomenon were very good overall.

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Table 1: Baseline demographics of patients with mild-to-moderate SARS-CoV-2 infection treated with NM/R

Characteristic	Patients treated with NM/R (n=483)
Ethnicity	
Hispanic/Latino	5 (1%)
Not Hispanic/Latino	461 (95%)
Other/Did not disclose	17 (4%)
Sex	
Male	211 (44%)
Female	272 (56%)
Age (years)	63 (IQR 51-74)
BMI	28 (IQR 26-31)
Monoclonal Antibody Screening Score (MASS)	3 (IQR 1-5)
Fully Vaccinated	448 (93%)
Days from positive test to prescription	1 (IQR 1-2)
Outcomes	
Hospital Admission within 30 days	2 (0.4%)
ICU Admission within 30 days	2 (0.4%)
Death within 30 days	0 (0%)