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Nirmatrelvir Treatment Duration and Frequency of COVID-19 Rebound

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Abstract

Background: Nirmatrelvir has been shown to reduce morbidity and mortality associated with COVID-19. However, it is underutilized due to concerns regarding COVID-19 symptom rebound following nirmatrelvir's standard 5-days to 10-days course. This study aims to identify and evaluate a nirmatrelvir dosage regimen that lowers symptom rebound.

Methods: Based on nirmatrelvir pharmacokinetics, we propose a novel 8-days regimen, 2 doses twice-daily followed by 6 doses once-daily to reduce rebound frequency. We then carried out a retrospective case series study of clinical outcomes among our patients to investigate their frequency of COVID-19 symptom rebound following nirmatrelvir usage.

Results: Among the 58 prescribed case patients, 49 filled and initiated the prescription. Of those 49 patients, 4 took the medication for fewer than 5 days, 24 for 5 days and 21 for 7 days or 8 days. Among 5-day treatment cases (n=24), 8(33.3%) experienced clinical rebound, while among the 7-day or 8-day treatment cases (n=21), 2(9.5%) experienced rebound.

Conclusion: These findings suggest that a longer nirmatrelvir/ritonavir course might reduce rebound symptoms compared to the standard 5-days regimen.

Keywords: Paxlovid; COVID-19; Rebound; Nirmatrelvir

Introduction

Current COVID-19 treatment is a 5-days course of twice-daily nirmatrelvir/ritonavir [1]. Despite its effectiveness, nirmatrelvir/ritonavir remains underutilized due to concerns of symptom recurrence following treatment [2]. While US authorities concluded no association between nirmatrelvir/ritonavir treatment and a rebound in COVID-19 symptoms, many may avoid treatment due to concerns regarding overall symptom prolongation [2,3].

To reduce the frequency of symptom recurrence, we prescribed a novel extended regimen based on the pharmacokinetics of nirmatrelvir/ritonavir: Twice-daily dosing the first 2 days, followed by daily dosing for the next 6 days, totaling 8 days of treatment. This dosing regimen provides a 2-days loading dose and the longest duration of additional dosing days available with a standard 10-dose nirmatrelvir/ritonavir pack.

A Monte Carlo simulation was conducted simulating nirmatrelvir/ritonavir administration at a 300 mg/100 mg twice-daily dosing for 2 days, followed by 300 mg/100 mg daily dosing for 6 days using a pharmacokinetic model of 5,149 measurements in 1,237 participants with COVID-19 [4]. The model predicted the median nirmatrelvir concentrations with a 90% prediction interval (5^{th} percentile-95^{th} percentile). We compared these values to the nirmatrelvir concentration required to inhibit 90% of *in vitro* replication (IC_{90}) of SARS-CoV-2 virus (0.292 mcg/mL) [5]. The median trough on the 8-day nirmatrelvir/ritonavir regimen was 0.58 mcg/mL, with 79% of troughs above the IC_{90} value (Figure 1). These pharmacokinetic data suggest that the 8-days regimen may inhibit SARS-CoV-2 viral growth throughout treatment.

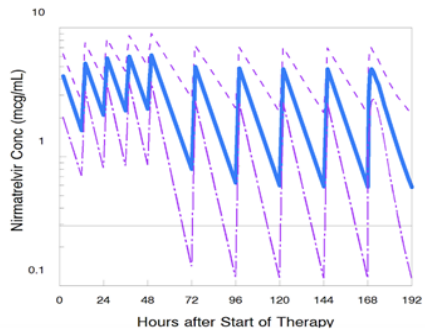

Figure 1: Monte Carlo simulation with a 90% prediction interval where nirmatrelvir/ritonavir was administered at 300 mg/100 mg twice-daily for 2 days, followed by 300 mg/100 mg once-daily for an additional 6 days. Note: (- - -): 95th% COVID (+); (—): Median BIDx2D-QDx5 COVID (+); (—): IC90 (0.292 mcg/mL)

To understand the clinical validity of this model, we examined differences between the 5-days regimen and our longer-duration regimen among our patients.

We asked patients who were prescribed and completed nirmatrelvir/ritonavir in our telehealth practice to report any worsening clinical symptoms following a period of clinical improvement after completion of treatment.

Of 49 patients, 4 took the medication for fewer than 5 days, 24 for 5 days and 21 for 7 days or 8 days. Among the 5-days treatment cases 8(33.3%) of 24 reported clinical rebound, while among the 7-day or 8-day treatment cases only 2(9.5%) of 21 reported rebound (Figure 2). None experienced severe disease, hospitalization or death.

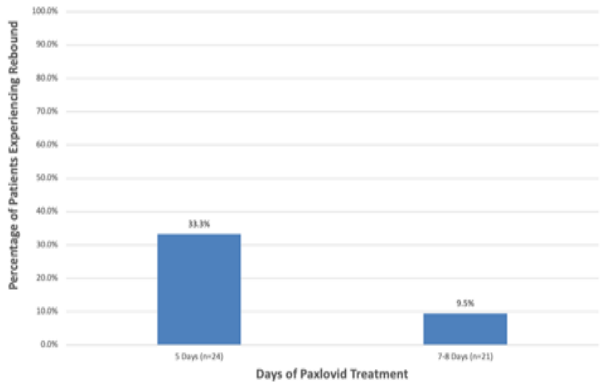

Figure 2: COVID-19 rebound frequencies following nirmatrelvir/ritonavir treatment of varying durations.

Conclusion

Our theoretical model and clinical reports suggest that a longer nirmatrelvir/ritonavir course might reduce clinical rebound frequency compared to the 5-days course. Additional studies are needed to determine the optimal treatment duration that maximizes the clinical benefits of while lowering frequency of rebound.

Acknowledgment

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Author Contributions

Jeffrey D. Klausner conceptualized and designed the report. Nathan Sudeep collected and analyzed clinical data. Noah Kojima analyzed pharmacokinetic data. Nathan Sudeep wrote the first draft of the manuscript with input from Jeffrey D. Klausner and Noah Kojima. All authors reviewed and approved the final version of the manuscript.

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