Nirmatrelvir-Ritonavir and Symptoms in Adults With Postacute Sequelae of SARS-CoV-2 Infection: The STOP-PASC Randomized Clinical Trial

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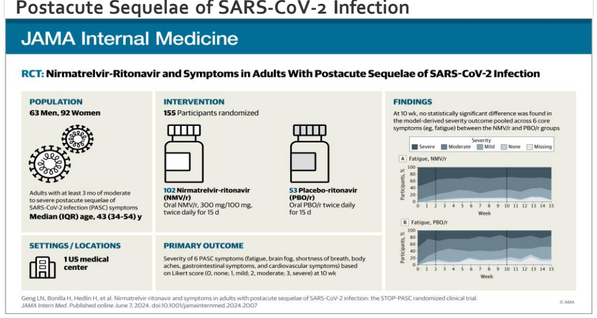
BACKGROUND

- Postacute sequelae of SARS-CoV-2 (PASC), also known as long COVID, affects millions of people for long periods of time and can include many symptoms
- Antiviral agents against SARS-CoV-2 are a possible area for investigation since SARS-CoV-2 virus or viral particle persistence is one of several proposed mechanisms for PASC
- Nirmatrelvir, with low-dose ritonavir was approved by the US FDA for the treatment of mild to moderate COVID-19
- The objectives of the Selective Trial of Paxlovid for PASC (STOP-PASC) were to assess the effect of a 15-day course of NMV/r vs PBO/r in improving PASC symptoms and other patient-reported outcomes

METHODS

- STOP-PASC was a double-blind randomized clinical trial to investigate nirmatrelvir-ritonavir (NMV/r) compared with placebo-ritonavir (PBO/r) in adult participants with PASC (Figure 1)
- 784 prescreened: 168 consented and screened
- The primary end point was core symptoms severity during the past week, pooled at 10 weeks post-randomization in participants treated with NMV/r vs PBO/r
- The primary analysis followed the intent-to-treat (ITT) principle

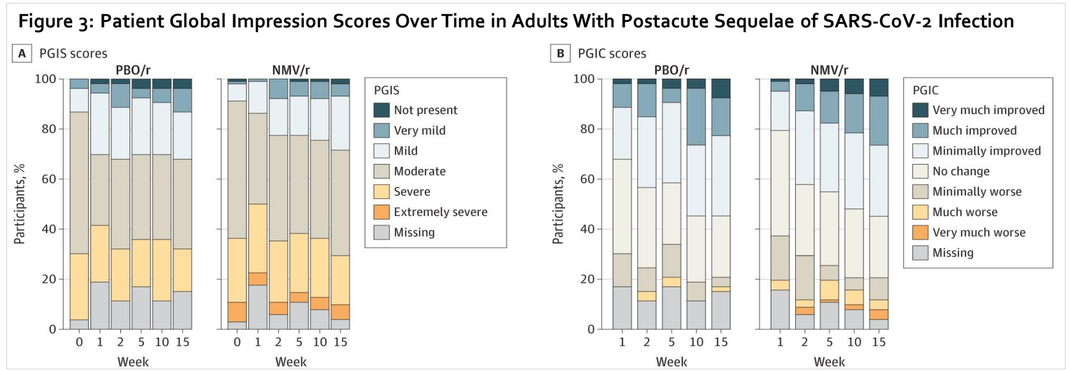
Figure 1: Nirmatrelvir-Ritonavir and Symptoms in Adults With Postacute Sequelae of SARS-CoV-2 Infection



RESULTS

- Considering the 6 core symptoms together (fatigue, brain fog, body aches, cardiovascular symptoms, shortness of breath, gastrointestinal symptoms), there was no statistically significant difference in the pooled symptom severity between NMV/r and PBO/r groups at 10 weeks
- A 15-day course of NMV/r was found to have a safety profile similar to the 5-day acute treatment course and was generally tolerated; however, when compared to placebo-ritonavir, it did not improve select PASC symptoms or other health outcomes
- Both the intervention and control groups exhibited improvements in PASC symptoms over time (Figures 2 and 3), though notably many participants still had symptoms at 15 weeks

Figure 3: Patient Global Impression Scores Over Time in Adults With Postacute Sequelae of SARS-CoV-2 Infection



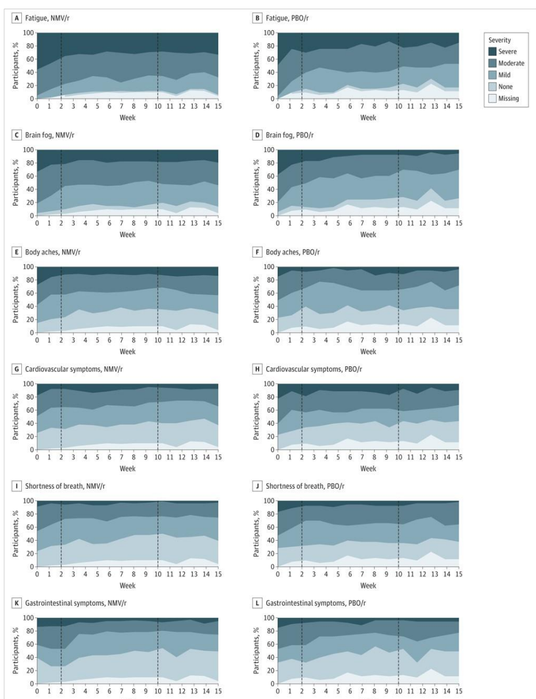


Figure 2: Distribution of Core Symptom Severity Scores Over Time in Adults With Postacute Sequelae of SARS-CoV-2 Infection

Table 2: Select Secondary Outcomes and Adverse Events in Nirmatrelvir-Ritonavir Use for Postacute Sequelae of SARS-CoV-2 Infection

Table 2. Select Secondary Outcomes and Adverse Events in Nirmatrelvir-Ritonavir Use for Postacute Sequelae of SARS-CoV-2 Infection

Outcome or event	NMV/r	PBO/r		
Participants in group	102	53		
Moderate to severe symptoms, change from baseline at 10 wk, % of participants				
Fatigue	−23.5	−43.4		
Brain fog	−28.4	−47.2		
Body aches	−22.5	−20.8		
Cardiovascular	−23.5	−20.8		
Shortness of breath	−20.6	−24.5		
Gastrointestinal	−19.6	−11.3		
	Mean (SD)		**β (95% CI)[a]**	***P* value**
PROMIS, change from baseline to 10 wk				
Physical function	2.73 (6.62)	1.32 (5.75)	0.57 (−1.96 to 3.10)	.66
Fatigue	−3.92 (7.88)	−4.05 (5.90)	0.38 (−2.40 to 3.15)	.79
Dyspnea	−1.96 (7.90)	−2.38 (6.13)	0.60 (−2.55 to 3.75)	.70
Cognitive function	4.84 (8.18)	5.05 (7.56)	0.03 (−3.21 to 3.28)	.98
PGIC score at 10 wk	3.38 (1.31)	3.13 (1.03)	0.10 (−0.48 to 0.67)	.74
PGIS score at 10 wk	4 (1.03)	3.79 (1.06)	0.19 (−0.25 to 0.62)	.40
Summative score at 10 wk	7.62 (3.75)	7.69 (4.09)	−0.24 (−1.46 to 0.97)	.69
			HR (95% CI)	***P* value**
Time to relief of most bothersome symptom[b]			0.74 (0.40 to 1.38)	.33
	No. (%)		**OR (95% CI)**	***P* value**
Experiencing relief at 10 wk[b]	33 (32.4)	22 (41.5)	0.55 (0.27 to 1.09)	.09
Experiencing alleviation at 10 wk[c]	7 (6.86)	5 (9.43)	0.72 (0.21 to 2.44)	.60
	Median (IQR)		**OR (95% CI)[d]**	***P* value**
Proportion of weeks 1-15 with mild or no symptoms				
Fatigue	0.15 (0 to 0.39)	0.15 (0 to 0.77)	0.55 (0.33 to 0.92)	.02
Brain fog	0.31 (0 to 0.75)	0.56 (0.15 to 0.85)	0.50 (0.31 to 0.82)	.01
Body aches	0.54 (0.10 to 0.92)	0.64 (0.29 to 0.83)	1.32 (0.74 to 2.33)	.34
Cardiovascular symptoms	0.67 (0.19 to 0.92)	0.46 (0 to 0.92)	1.37 (0.76 to 2.48)	.29
Shortness of breath	0.769 (0.25 to 1)	0.62 (0.09 to 0.89)	1.32 (0.73 to 2.38)	.35
Gastrointestinal symptoms	0.63 (0.31 to 0.92)	0.52 (0.28 to 0.90)	1.40 (0.79 to 2.47)	.25
	No. (%)			
Participants with AEs	101 (99)	49 (92)		
No. of AEs	771	313		
Total SAE[e]	3 (2.9)	1 (1.9)		
Participants with grade 3 or 4 AEs[f]	5 (4.9)	3 (5.7)		
Fatalities	0	0		

Abbreviations: AE, adverse event; HR, hazard ratio; NA, not applicable; NMV/r, nirmatrelvir-ritonavir; OR, odds ratio; PBO/r, placebo-ritonavir; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; PROMIS, Patient-Reported Outcomes Measurement Information System; SAE, serious adverse event.

[a] Estimated coefficients (βs) for PGIC or PGIS can be interpreted as differences in PGIC and PGIS score values between groups, eg, an estimate of 0.3 means that, on average, those on NMV/r reported PGIC/PGIS 0.3 points higher than those on PBO/r. However, coefficients for PROMIS measures should be interpreted as differences (in NMV/r vs PBO/r) in change scores (baseline vs wk 10). A higher score value corresponds to reduced severity for PROMIS-physical and cognitive function; greater severity for PROMIS-fatigue and dyspnea; worsening status for PGIC; and greater severity for PGIS. Therefore, improvement from baseline to week 10 corresponds to positive change scores for PROMIS-physical and cognitive function, and negative change scores for PROMIS-fatigue and dyspnea.

[b] Relief was defined as a reduction of severity from moderate to none or severe to mild or none for at least 1 core symptom; time to relief was measured in weeks.

[c] Alleviation was defined as improvement of all core symptoms from none or mild at baseline to none or moderate to severe to none or mild.

[d] An OR of 1.5 corresponds to a 50% increase in the odds of experiencing mild or no symptoms for those taking NMV/r compared to those taking PBO/r.

[e] One participant each had blood-loss anemia, forearm fracture, and melanoma in the NMV/r group (all assessed as unrelated to intervention), and 1 participant had hepatitis in the PBO/r group (assessed as possibly related).

[f] Graded per Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1.

CONCLUSIONS

- This trial demonstrated the overall safety of a 15-day course of NMV/r in patients with PASC, but did not find a significant benefit of this therapy for a subset of PASC symptoms among mostly vaccinated cohort with prolonged PASC symptoms
- With the urgent need to find therapies for PASC, studies like STOP-PASC have pushed forward to assess efficacy and safety
- Antivirals may need to be administered earlier in the illness, before downstream and possibly less reversible adverse effects occur
- Longer treatment durations, dose variations, optimal timing, and different phenotypes of PASC should be investigated in future studies
- Multiple pathways may contribute to PASC pathogenesis, thus more combination therapies (eg, antivirals with immunomodulators) should be explored
- Evaluations of molecular and digital biomarkers from the STOP-PASC trial are forthcoming. Findings from this and other trials of NMV/r will collectively determine whether this antiviral can treat PASC

REFERENCES

Geng LN, Bonilla H, Hedlin H, et al. Nirmatrelvir-Ritonavir and Symptoms in Adults With Postacute Sequelae of SARS-CoV-2 Infection: The STOP-PASC Randomized Clinical Trial. JAMA Intern Med. 2024;184(9):1024–1034. doi:10.1001/jamainternmed.2024.2007

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