Clinical Infectious Diseases
CORRESPONDENCE
IDSA Infectious Diseases Society of America
hivma hiv medicine association
OXFORD

Safety and Tolerability of Paxlovid (Nirmatrelvir/Ritonavir) in High-risk Patients

To the Editor—We read with great interest the analysis by Saliba and colleagues on the real-world experience with nirmatrelvir/ritonavir (Paxlovid) in reducing severe coronavirus disease 2019 (COVID-19) and mortality in high-risk patients [1]. This is the largest retrospective cohort study to date that demonstrated Paxlovid treatment and vaccination status were associated with significant decrease in the rate of severe COVID-19 or mortality with adjusted hazard ratio (HR) 0.54 (95% confidence interval, 0.39–0.75) and 0.2 (95% confidence interval, 0.17–0.22), respectively. Timely real-world data are important to evaluate the effectiveness of Paxlovid in populations outside of the clinical trial, but the authors were unable to assess medication tolerability and safety.

As of 14 May 2022, Assistant Secretary for Preparedness and Response estimated 668 954 Paxlovid courses were given in the United States [2]. In the randomized clinical trial, EPIC-HR (Evaluation of Protease Inhibition for Covid-19 in High-Risk Patient), Paxlovid appeared to be well tolerated but real-world data are lacking [3]. At the University of Washington Medicine, we developed a standardized process to prioritize high-risk patients meeting National Institutes of Health Tier 1 and 2 criteria and assessed patient tolerability and safety through telephonic postprescription outreach when supplies were initially limited. Patients who were prescribed Paxlovid were interviewed over the phone using a standardized questionnaire to assess adverse effects and adherence within 1 week of starting therapy.

Between January 5 and 21, 2022, 50 patients were prescribed Paxlovid (Table 1). The median age was 48 years, with 64% of females and 20% of Latino/Hispanic ethnicity. The majority (82%) had immunocompromising conditions with a median of 5 comorbid conditions and 8.5 concomitant medications. Sixteen (32%) patients required chronic medication adjustment while taking Paxlovid. All patients were contacted within 1 week of starting Paxlovid, 19 (38%) and 21 (42%) patients were interviewed during therapy and after completion of therapy, respectively, whereas 9 (18%) patients were lost to follow-up and 1 (2%) patient did not start Paxlovid. Among the 40 respondents, 34 (85%) had experienced at least 1 adverse effect. Twelve (30%) patients reported ≥ 3 adverse effects and all were ≥ 5 concomitant chronic medications. The most frequently reported adverse effect was dysgeusia (57.5%).

Table 1. Baseline Characteristics of Patients Who Were Prescribed Paxlovid and Reported Adverse Effects Associated With Paxlovid

		EPIC-HR (2)	
	UW Medicine	Paxlovid	Placebo
Demographics (N = 50)			
Median age in years (range)	48.5 (24–92)	45 (18–86)	46.5 (18–88)
Females	32 (64%)	49.5%	48.3%
Ethnicity (% Hispanic/Latino)	10 (20%)	45%	45%
Median number of concomitant medications (IQR)	8.5 (5–12)		
Median number of comorbidities (IQR)	5 (3–7)		
Immunocompromised	41 (82%)	<1%	<1%
Chronic medication adjustment	16 (32%)		
Events that emerged during treatment (N = 40)			
Reported at least 1 adverse effect	34 (85%)	22.6%	23.9%
Reported 3 or more adverse effects	12 (30%)		
Serious adverse events[a]	4 (10%)	1.6%	6.6%
Discontinued therapy because of adverse effects	7 (17.5%)	2.1%	4.2%
Reported adverse effects (N = 40)			
Dysgeusia	23 (57.5%)	5.6%	0.3%
Diarrhea	15 (37.5%)	3.1%	1.6%
Headache	13 (32.5%)	1.4%	1.3%
Abdominal pain	6 (15%)		
Myalgia	6 (15%)	1%	<1%
Nausea	5 (12.5%)	1.4%	1.7%
Vomiting	4 (10%)	1.1%	0.8%

Abbreviation: IQR, interquartile range.

[a]Serious adverse events and adverse events leading to discontinuation of Paxlovid or placebo were coded according to the Medical Dictionary for Regulatory Activities (MedDRA), version 24.0, in the EPIC-HR trial.

Most patients reported the onset of 1 to 2 hours after taking Paxlovid and usually subsided within 24 hours after discontinuation of therapy.

We reported a high incidence of adverse effects with 85% of patients reporting at least 1 side effect while taking Paxlovid leading to 17.5% of patients discontinuing therapy prematurely compared with 2% observed in the EPIC-HR trial. Most notably, dysgeusia was reported in 57.5% of patients compared to 5.6% in clinical trial [3]. We used this information to better prepare our patients for anticipated side effects and provided mitigation strategies based on our evaluation. To the best of our knowledge, this is the first report to date evaluating the tolerability and safety of Paxlovid through telephonic postprescription outreach in the real-world setting. This underscores the importance of close monitoring and postmarketing surveillance with medications that are still under investigation.

Note

Potential conflicts of interest. R. J. reports consulting fees paid to the author as a clinical consultant for online content from Wolters-Kluwer textbook company. S. D. reports unpaid participation on Data Safety Monitoring Board or Advisory Board for HPV Vaccine to Interrupt Progression of Vulvar and Anal Neoplasia (VIVA) Trial: A randomized, double-blind, placebo-controlled trial. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Bryan Pesko,[1,2] Alexandra Deng,[2] Jeannie D. Chan,[2,3,4] Santiago Neme,[4] Shireesha Dhanireddy,[4] and Rupali Jain[1,2,4,]

[1]Department of Pharmacy, University of Washington Medicine, University of Washington Medical Center – Montlake, Seattle, Washington, USA; [2]University of Washington School of Pharmacy, Seattle, Washington, USA; [3]Department of Pharmacy, University of Washington Medicine, Harborview Medical Center, Seattle, Washington, USA; and [4]Department of Medicine, Division of Allergy and Infectious Diseases, University of Washington School of Medicine, Seattle, Washington, USA

References

1. Najjar-Debbiny R, Gronich N, Weber G, et al. Effectiveness of Paxlovid in reducing severe COVID-19 and mortality in high risk patients. Clin Infect Dis **2022**:ciac443. doi:10.1093/cid/ciac443.
2. ASPR. Fact Sheet: update on COVID-19 therapeutics distribution. Available at: https://aspr.hhs.gov/COVID-19/Therapeutics/updates/Documents/ASPR-Fact-Sheet_Therapeutics-Utilization.pdf. Accessed 24 June 2022.
3. Hammond J, Leister-Tebbe H, Gardner A, et al. EPIC-HR Investigators. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. N Engl J Med **2022**; 386:1397–408.

Correspondence: R. Jain, University of Washington Medical Center, 1959 NE Pacific Street, Box 356015, Seattle, WA 98195 (rupali@uw.edu).

Clinical Infectious Diseases®

https://doi.org/10.1093/cid/ciac588