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Evolving Role of Antivirals in COVID-19 Prophylaxis and Treatment

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Introduction

Paxlovid™ (nirmatrelvir 300 mg-ritonavir 100 mg) oral tablets were granted emergency use authorization (EUA) for treatment of coronavirus disease 2019 (COVID-19) by the Food and Drug Administration (FDA) in 2021.[1] In 2023 this medication received FDA-approval for treatment of mild-to-moderate COVID-19 in adults at high risk for progression to severe COVID-19, including hospitalization and death.[2] The approval was based upon results from the EPIC-HR randomized controlled trial (RCT), which showed nirmatrelvir-ritonavir reduced hospitalization or death among non-hospitalized, unvaccinated, high-risk adults by 89% compared to placebo.[3]

Data from 2 trials were recently published (April 2026) which showed that nirmatrelvir-ritonavir does not reduce the incidence of hospitalization or death among vaccinated, high-risk patients with COVID-19 compared to usual care.[4] However, the combination antiviral treatment did accelerate recovery for adults with confirmed infection.[4] This newsletter will summarize the data from those 2 trials.

In addition, the FDA recently approved a new oral antiviral, Xocova® (ensitrelvir), for post-exposure prophylaxis of COVID-19 in adults and children aged 12 years and older following contact with an individual who has COVID-19.[5] The pivotal trial that led to the FDA approval will be reviewed in this newsletter.

Design of the PANORAMIC and CanTreatCOVID Trials

The PANORAMIC trial was conducted in the United Kingdom (n=3,516) and the CanTreatCOVID trial was conducted in Canada (n=716).[4] The CanTreatCOVID trial was stopped early owing to slow recruitment and because the supply of nirmatrelvir–ritonavir was discontinued.[6] Both trials were open-label RCTs that enrolled higher-risk adults either 50 years of age and older or adults 18 years of age and older with coexisting conditions (i.e., diabetes, asthma) who tested positive for COVID-19 and had been ill for 5 days or less.[4] Participants were randomly assigned 1:1 to receive usual care plus nirmatrelvir-ritonavir twice a day for 5 days or to receive usual care alone.[4] Participants began to receive medication within 3 to 4 days after symptom onset.[4] The primary outcome was hospitalization or death from any cause within 28 days of trial enrollment.[4] A secondary outcome was early sustained recovery, which was defined as participant reported recovery by day 14 after randomization that was sustained to day 28.[4]

Demographics

In the PANORAMIC and CanTreatCOVID trials, most of the participants were female (68% and 65%, respectively), White (94% and 78%, respectively) and had been vaccinated with 2 or more doses of the COVID vaccine (98-99%).[4] The mean age of participants in both trials was 55 years (range:18 to 96 years).[4] Most participants had symptoms for over 2 days and many had coexisting conditions (range: 45%-67%).[4] Demographics were balanced between the usual care and usual care plus antiviral treatment groups. Attrition was low in both trials (less than 10%).[4]

Results

In the PANORAMIC trial, 0.8% of the nirmatrelvir–ritonavir group and 0.7% of the usual-care group were hospitalized or died (adjusted odds ratio (OR), 1.18; 95% Bayesian credible interval, 0.55 to 2.62; probability of superiority, 0.334).[4] In the CanTreatCOVID trial, 0.6% in the nirmatrelvir–ritonavir group and 1.2% in the usual-care group were hospitalized or died (adjusted OR, 0.48; 95% Bayesian credible interval, 0.08 to 2.23; probability of superiority, 0.830).[4] In both trials, the incidence of early sustained recovery was higher in the nirmatrelvir–ritonavir group than in the usual-care group.[4] Results for the primary and secondary outcomes in both trials are presented in **Table 1**.

Table 1. Results from PANORAMIC and CanTreatCOVID Trials[4]

Outcome	Nirmatrelvir -Ritonavir x 5 days	Usual Care	Adjusted Odds Ratio (95% Credible Interval)*
PANORAMIC Trial			
Hospitalization or Death	14/1698 (0.8%)	11/1673 (0.7%)	1.18 (0.55-2.62)
Early Sustained Recovery	510/1546 (33%)	330/1492 (22.1%)	1.74 (1.48 to 2.04)
CanTreatCOVID Trial			
Hospitalization or Death	2/343 (0.6%)	4/324 (1.2%)	0.48 (0.08 to 2.23)
Early Sustained Recovery	191/277 (69%)	130/245 (53.1%)	1.99 (1.40 to 2.87)

*Adjusted odds ratios were obtained from a Bayesian logistic-regression model adjusted for age, vaccination status, and coexisting conditions at baseline, with a 95% Bayesian credible interval. An odds ratio of less than 1 favors nirmatrelvir–ritonavir.[4]

Participants in the PANORAMIC trial had a median recovery time of 14 days with the antiviral versus 21 days with usual care.[4] In the CanTreatCOVID trial, antiviral-treated patients had a median recovery time of 6 days compared to 9 days with participants who received usual care.[4] A sub-study of the PANORAMIC trial showed the viral load at day 5 had been reduced to below the lower limit of detection in 78 of 267 participants (29.2%) in the nirmatrelvir-ritonavir group compared with 36 of 218 participants (16.5%) in the usual-care group.[4]

Safety

Most of the participants (96.2%) in the nirmatrelvir–ritonavir group in the PANORAMIC trial had adverse events, and 9 of 1612 participants (0.6%) had serious adverse events.[4] In the CanTreatCOVID trial, the percentage of participants with serious adverse events was higher in the usual-care group than in the nirmatrelvir–ritonavir group (12 of 358 participants [3.4%] vs. 4 of 312 participants [1.3%]).[4] In the PANORAMIC trial, 242 participants assigned to receive nirmatrelvir–ritonavir discontinued treatment; in 128 of these participants, the reason for discontinuation was side effects, with dysgeusia, nausea, or both reported as the most common reason (in 99 participants).[4] None of the participants in the CanTreatCOVID trial discontinued treatment because of adverse events.[4]

Post-Exposure Prophylaxis with Ensitrelvir

The oral antiviral, ensitrelvir received FDA approval on June 1, 2026.[5] In the pivotal phase 3, double-blind RCT, people who were at least 12 years of age, were household contacts of a patient with COVID-19 (the index patient) and tested negative for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), were randomized 1:1 to receive either ensitrelvir tablets (375 mg on day 1 and 125 mg daily on days 2 through 5) or placebo.[7] Treatment was initiated within 72 hours after symptom onset in the index patient.[7] The primary end point was COVID-19 (defined by a central laboratory-confirmed positive assay and the presence of 1 or more of 14 prespecified COVID-19 symptoms lasting 48 hours and longer) by day 10 in a household contact.[7]

The modified intention-to-treat (mITT) population included 1030 participants in the ensitrelvir group and 1011 in the placebo group.[7] The mean age of participants was 42 years and 98% tested positive for SARS-CoV-2 antibodies, reflecting prior virus exposure or vaccination.[7] Baseline demographics were balanced between the active comparator and placebo arms.[5] The incidence of Covid-19 was lower in the ensitrelvir group than in the placebo group (2.9% vs. 9.0%; risk ratio, 0.33; 95% confidence interval [CI], 0.22 to 0.49; P<0.001).[7]

The most common adverse events (occurring in ≥1% of all participants) were headache, diarrhea, nasopharyngitis, cough, fatigue, and influenza.[7] The incidence of adverse events during the trial was similar in the two groups (15.1% in the ensitrelvir group and 15.5% in the placebo group), as was the incidence of serious adverse events (0.2% in each group).[7] No COVID-19-related hospitalizations or deaths were reported.[7] In this RCT, a 5-day regimen of ensitrelvir postexposure prophylaxis, as compared with placebo, was effective in preventing COVID-19 among household contacts.[7]

Cost of Anti-Viral Prophylaxis or Treatment without Insurance Coverage

-The anticipated cost of ensitrelvir is expected to be $240.00 for each 125 mg tablet or $1680.00 for a five-day course of prophylactic therapy.[8]

-Per Myers and Stauffer Provider Resources, the cost of nirmatrelvir-ritonavir 300 mg-150 mg is $1500.00 for a five-day treatment course.[9]

Conclusions

The settings of PANORAMIC and CanTreatCOVID are distinct from the original EPIC-HR trial that was the basis for FDA approval of nirmatrelvir-ritonavir. EPIC-HR enrolled unvaccinated patients in late 2021, a time when population immunity was very rare. In that trial, reduction in severe disease and death demonstrated the efficacy of nirmatrelvir-ritonavir.[3] COVID-19 is a less serious condition today than it was in 2021.[10] The PANORAMIC and CanTreatCOVID trials assessed outcomes for predominantly vaccinated adults in the community who were at increased risk for severe outcomes.[4] In these trials, early treatment with nirmatrelvir–ritonavir did not reduce the incidence of hospitalization or death in either trial.[4]

Although no definitive conclusions can be drawn for secondary outcomes, the participant-reported time to recovery appeared to be shorter with open-label nirmatrelvir–ritonavir than with usual care alone.[4] An open-label design does not allow estimation of the contribution of either placebo or nocebo effects to any observed differences in participant-reported outcomes, such as time to recovery.[4]

In an accompanying New England Journal of Medicine editorial, former National Institute of Allergy and Infectious Diseases (NIAID) clinical research director H. Clifford Lane, MD, and former NIAID director Anthony S. Fauci, MD, discussed the findings and the shift in use of nirmatrelvir-ritonavir.[6] “Taken together, these new data indicate that the 89% relative risk reduction seen in the analysis of

hospitalizations or death associated with the use of nirmatrelvir–ritonavir in the EPIC-HR trial does not apply to the current circumstances, in which most adults have varying degrees of preexisting immunity and the circulating variants are different."[6] "However, one should be cautious not to overinterpret the new data and conclude that nirmatrelvir–ritonavir is not of current value."[6] "The enhanced recovery and more-rapid reduction in viral load indicate a degree of clinical efficacy and antiviral activity."[6] "Clinicians may become more selective regarding which patients to refer for treatment, but it still would seem prudent to consider antivirals on a case-by-case basis, particularly in older adults, persons with a compromised immune system, and persons for whom more-rapid recovery is a priority."[6]

Take Away Points for Consideration

- The settings of PANORAMIC and CanTreatCOVID trials are distinct from the original trial that was the basis for FDA approval of nirmatrelvir-ritonavir.
- Recent data assessed outcomes for predominately vaccinated adults at risk for severe COVID-19 outcomes.
- In recent trials, treatment with nirmatrelvir-ritonavir did not reduce the incidence of hospitalization or death compared to usual care.
- Providers may become more selective regarding which patients should be treated and consider antivirals on a case-by-case basis, particularly in older adults, persons with a compromised immune system, and persons for whom more-rapid recovery is a priority.
- A 5-day course of ensitrelvir tablets administered to household contacts of patients with COVID-19 was effective in preventing COVID-19 in the household contacts. This is the only FDA-approved agent for post-exposure prophylaxis to COVID-19.

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