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GEORGE & FAY YEE Centre for Healthcare Innovation

Nirmatrelvir/Ritonavir for Non-Hospitalised Adults with Mild/Moderately Severe COVID-19

A Systematic Evidence Review of Randomised Controlled Trials and Real-World Studies with Meta-Analysis and Trial Sequential Analysis

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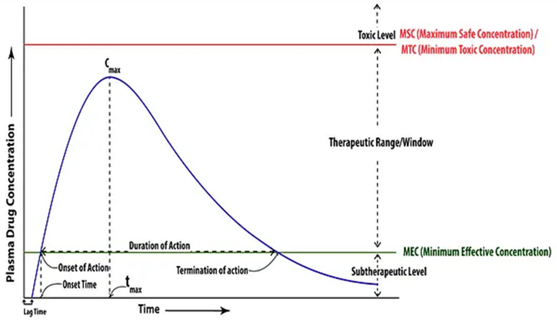
The authors declare that they have no perceived conflicts of interest

Background

The controversies that still surround influenza antiviral drugs despite several years of research should serve as a warning that more needs to be done to properly investigate antiviral drugs for coronavirus disease 2019 (COVID-19). Nirmatrelvir, a protease inhibitor with demonstrated activity against a viral protease, the MPRO, has been shown to have antiviral potentials against all coronaviruses that are known to infect humans. On the other hand, ritonavir has a strong inhibitory ability against cytochrome P450 (CYP) 3A4 and pharmacokinetic boosting ability, and therefore, when co-administered with nirmatrelvir, increases nirmatrelvir concentration in the blood plasma to the target therapeutic range for optimum activity against the coronaviruses **(figure 1)**. The efficacy/effectiveness and safety of nirmatrelvir/ritonavir regimen for treatment of COVID-19 remain unclear, with many unanswered important clinical questions.

Figure 1: *Plasma level time curve*

(obtained from: https://pharmaeducation.net/plasma-level-time-curve/)



Methods

In view of accumulating evidence and for more insights to better inform clinical practice and research, we systematically identified randomised controlled trials (RCTs) and real-world studies [RWS] (observational studies) of efficacy/effectiveness and/or safety of the approved nirmatrelvir/ritonavir regimen (oral administration of 300mg of nirmatrelvir with 100mg of ritonavir twice daily over 5 days) for laboratory-confirmed mild/moderately severe COVID-19 (PROSPERO registration: CRD42020216817). Appropriate data (adjusted estimates for RWS) were pooled using an inverse variance, random-effects model. Statistical heterogeneity was calculated using the I^2 statistic. Results are relative risk with associated 95% confidence intervals. We assessed risk of bias and study quality and graded the evidence from RCTs. Further, we conducted trial sequential analysis (TSA) of the evidence from RCTs to provide information on adequacy of the overall sample size of pooled estimates for each outcome to inform evidence-based clinical practice and to guide future evidence reviews on the topic.

Results

We included 4 RCTs (4,070 persons) and 16 RWS (1,925,047 persons) on adults (≥18-year-olds). One RCT was of low risk of bias whereas three RCTs were of unclear risk of bias. The RWS were of good quality. Nirmatrelvir/ritonavir significantly reduced COVID-19 hospitalisation compared with placebo/no treatment (0.17 [0.10 – 0.31], I^2 77.2%, 2 RCTs, 3,542 persons, moderate certainty evidence) **[figure 2]**, but there was **no significant difference** for:

- reduction in worsening severity (0.82 [0.66 – 1.01], I^2 47.5%, 3 RCTs, 1,824 persons, moderate certainty evidence) **[fig 3a]**,
- viral clearance (1.19 [0.93 – 1.51], I^2 82%, 2 RCTs, 528 persons, low certainty evidence) **[fig 3b]**,
- adverse events (1.41 [0.92 – 2.14], I^2 70.6%, 4 RCTs, 4,070 persons, low certainty evidence) **[fig 3c]**,
- serious adverse events (0.82 [0.41 – 1.62], I^2 0%, 3 RCTs, 3,806 persons, moderate certainty evidence) **[fig 3d]**,
- and all-cause mortality (0.27 [0.04 – 1.70], I^2 49.9%, 3 RCTs, 3,806 persons, moderate certainty) **[fig 3e]**.

However, unlike for hospitalisation outcome, TSA suggested that the current total sample sizes for these outcomes are not enough for conclusions to be drawn.

RWS also demonstrated significantly reduced COVID-19 hospitalisation (0.48 [0.37 – 0.60], I^2 95.0%, 11 RWS, 1,421,398 persons: **figure 4**) and all-cause mortality (0.24 [0.14 – 0.34], I^2 65%, 7 RWS, 286,131 persons: **figure 5**) for nirmatrelvir/ritonavir compared with no treatment. Exploration of the observed high levels of heterogeneity in some of the pooled analyses was not possible due to a paucity of contributing studies (for RCTs) and poorly-defined study characteristics (for RWS).

Figure 2: *TSA for hospitalisation*

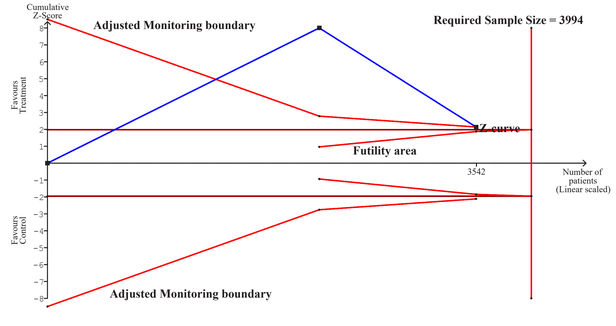


Figure 3a: *TSA for worsening severity*

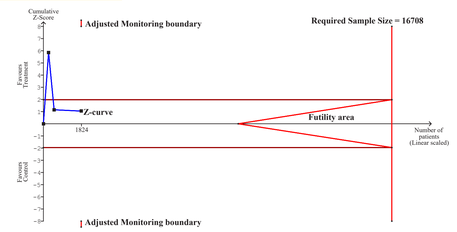


Figure 3b: *TSA for viral clearance*

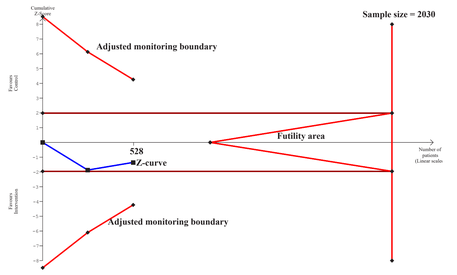


Figure 3c: *TSA for adverse events*

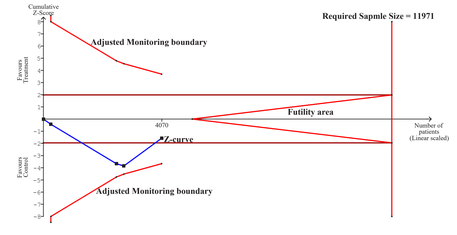


Figure 3d: *TSA for serious adverse events*

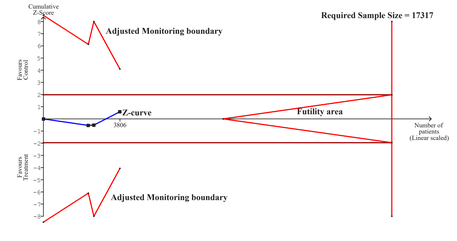


Figure 3e: *TSA for all-cause mortality*

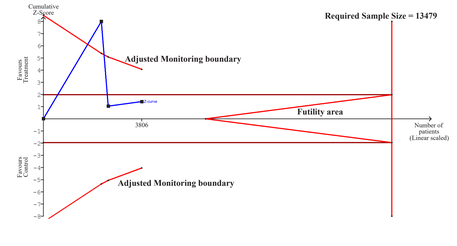


Figure 4: *Forest plot for hospitalisation* (RWS)

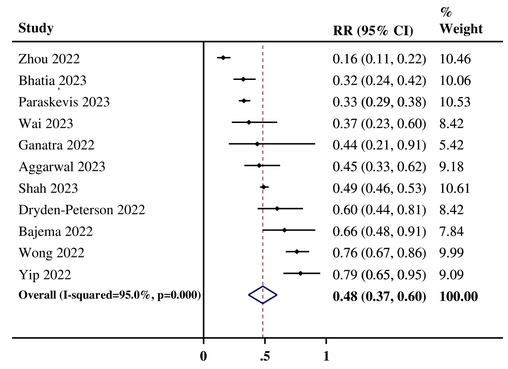
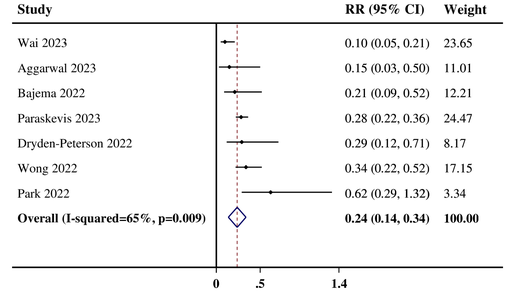


Figure 5: *Forest plot for all-cause mortality* (RWS)



Conclusions

The approved nirmatrelvir/ritonavir regimen seems promising for preventing hospitalisation, and potentially, for reducing all-cause mortality in adults with mild/moderately severe COVID-19. However, more high quality RCTs are needed for a stronger evidence base. For now, the regimen should be treated as an experimental and not a definitive antiviral drug treatment regimen for COVID-19.

References for the included studies

1. Balykova et al. Pharmacy & Pharmacology. 2022;10(4):371-386.
2. Hammond et al. N Engl J Med. 2022;386(15):1397-1408.
3. Liu et al. Lancet Reg Health West Pac. 2023; 33:100694.
4. Aggarwal et al. Lancet Infect Dis. 2023;23(6):696-705.
5. Al-Obaidi et al. Am J Med. 2023;136(6):577-584.
6. Bajema et al. medRxiv. 2022. doi: 10.1101/2022.12.05.22283134.
7. Bhatia et al. medRxiv. 2023. doi: 10.1101/2023.05.03.23289084.
8. Dryden-Peterson et al. Ann Intern Med. 2023;176(1):77-84.
9. Ganatra et al. Clin Infect Dis. 2022;76(4):563-572.
10. Lewnard et al. Lancet Infect Dis. 2023;23(7):806-815.
11. Najjar-Debbiny et al. Clin Infect Dis. 2023;76(3): e342-e349.
12. Paraskevis et al. medRxiv. 2023. doi.org/10.1101/2023.02.09.23285737.
13. Park et al. Osong Public Health Res Perspect. 2022;13(6):443-447.
14. Schwartz et al. CMAJ. 2023;195(6): e220-e226.
15. Shah et al. Am J Transplant. 2023;23(1):150-155.
16. Wai et al. Lancet Reg Health West Pac. 2023; 30:100602.
17. Wong et al. Lancet. 2022;400(10359):1213-1222.
18. Yip et al. Clin Infect Dis. 2022.
19. Zhou et al. medRxiv. 2022. doi.org/10.1101/2022.09.13.22279908.
20. Pfizer. ClinicalTrial.gov. https://clinicaltrials.gov/study/NCT05011513?tab=results#more-information.

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