Rapid Reviews COVID-19 •

Review 1: "Early use of nitazoxanide in mild Covid-19 disease: randomized, placebo-controlled trial"

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RR:C19 Evidence Scale rating by reviewer:

- **Potentially informative.** The main claims made are not strongly justified by the methods and data, but may yield some insight. The results and conclusions of the study may resemble those from the hypothetical ideal study, but there is substantial room for doubt. Decision-makers should consider this evidence only with a thorough understanding of its weaknesses, alongside other evidence and theory. Decision-makers should not consider this actionable, unless the weaknesses are clearly understood and there is other theory and evidence to further support it.

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Review:

This randomized double-blinded trial has been published as a pre-print on the server mdRxiv.

Overall, there are four important questions that need to be answered before the results can be interpreted reliably. If nitazoxanide does demonstrate effects on viral load and symptom resolution, then nitazoxanide is a cheap, generic drug that can be used widely. However, we need to be sure of the drug's analysis before making firm conclusions.

1. In this trial, 475 patients were randomized to either nitazoxanide or a matching placebo. After randomisation, 83 of the patients were excluded from the analysis either because they discontinued treatment (n=41), adverse events (n=7), or hospitalisation (n=10). There were another 27 patients later excluded because of missing data or other reasons. The report focuses on the 392 patients with data available, in a Per-Protocol style of analysis. Normally in an Intent to Treat analysis, all randomized patients would be included with assumptions about the missing data. One approach is to classify all patients with missing data as failures. The number of patients excluded from the analysis reported in the manuscript appears to be similar between the two treatment arms. However, it is not clear if the number of patients who were hospitalized or experienced adverse events was evenly matched.
2. The timing for the primary analysis is very early, compared with equivalent trials of other antivirals evaluated for COVID-19. In this Brazilian trial, responses are assessed after 5 days of treatment. In other trial protocols, responses tend to be

evaluated after 10-14 days. A Day 5 endpoint may be too early to assess the resolution of symptoms.

3. The viral load at baseline appears to be higher in the placebo arm (median 7.49 for placebo versus 7.06 log₁₀ copies/mL in the nitazoxanide arm). This is a difference of 0.43 log₁₀. There is no statistical test to show that this is significant. It is not clear whether differences in baseline viral load are adjusted for when comparing treatment arms on Day 5. At the Day 5 visit, the difference in viral load between the arms was 0.5 log₁₀, which is quite similar to the difference already apparent at baseline. So, were more patients becoming viral load negative on Day 5 in the nitazoxanide arm because the baseline viral load was already lower in this treatment arm? Are there any later evaluations of viral load?
4. More patients in the nitazoxanide arm reported resolution of clinical symptoms at the one-week follow-up visit (Day 12). The percentages with complete resolution of symptoms were 78% for nitazoxanide versus 57% for placebo. This Day 12 time point is more similar to other studies of antiviral treatment where resolution of symptoms shows differences by treatment arm. However, in the paper, there are no further details of the remaining symptoms seen in the two groups. If this assessment included questions on other symptoms, these need to be included in the report.