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Azithromycin for mild-to-moderate COVID-19

Authors' reply

We thank Jigar Patel and colleagues for their comments. The mean duration of symptoms at enrolment was 5.77 days (SD 3.49) in the azithromycin group and 6.27 days (3.55) in the standard care group. 19 (13%) of 147 participants in the azithromycin group and 21 (14%) of 148 participants in the standard care group had symptoms for more than 10 days at randomisation.

Most COVID-19-related deaths occur due to sudden, late respiratory decompensation, peaking at day 14 after symptom onset.¹ Azithromycin was postulated to have both antiviral and anti-inflammatory properties, and it was presumed that the latter might have potential efficacy against late respiratory decompensation.

Eligible participants were deemed appropriate for initial ambulatory management. By this definition, which was applied uniformly at all centres, we excluded people with severe disease (ie, those requiring supplemental oxygen) at enrolment. Thoracic imaging was not a prerequisite for enrolment, but was done in most (265 [89%] of 297) people at baseline as part of routine clinical assessment.

The electronic case report form ensured that enrolment and randomisation occurred sequentially within a few minutes, and all patients were on clinical pathways requiring rapid

assessment and discharge from hospital to ambulatory care.

To avoid failure to detect a clinically significant effect due to underdosing, we selected the highest dose of azithromycin already licensed in the UK for any indication; namely, 500 mg daily for 14 days recommended for Lyme disease. This dose is known to be well tolerated and of sufficient duration to cover the period during which the anti-inflammatory effects could be most beneficial.

The protocol² excluded any antibiotics considered to have potentially relevant antiviral or anti-inflammatory properties at enrolment and during follow-up. Other antibiotics including β -lactams might have been taken for various indications, including treatment of suspected bacterial pneumonia, but they would not be expected to be confounders for the outcome of interest in COVID-19.

Our strict definition of full compliance was administration of the first dose within 4 h of randomisation and ingestion of at least 80% of doses. A completed 500 mg dose required ingestion of two tablets, therefore, 80% compliance required ingestion of 24 tablets (22/28 tablets is only 78.6% of doses, which does not reach the protocol definition of at least 80% compliance). The 76 (52%) of 147 participants who achieved full compliance is an underestimation, as it excludes 20 (14%) participants in whom compliance rates were unknown. Even

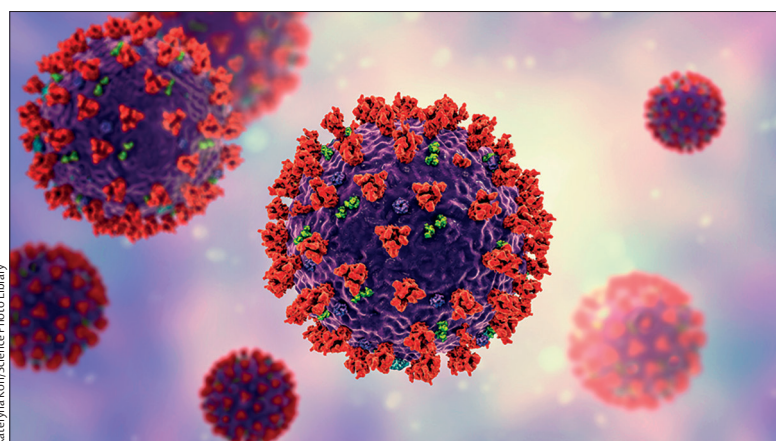
the 51 (35%) participants with known suboptimal compliance took a median of six tablets (IQR 2–17), equivalent to 500 mg azithromycin daily for 3 days, which is the entire dosing schedule used in the PRINCIPLE trial. Azithromycin has a long half-life of approximately 72 h, with lower concentrations detectable for 30 days³ and marked accumulation in granulocytes.² The three compliers for whom we do not have the number of tablets taken each reported taking azithromycin for at least 13 days and did not report having remaining tablets or adherence issues. Therefore, most participants were exposed to clinically significant concentrations of drug for several days.

We cited the study protocol because it explains the rationale for the study design with references to alternative concurrent UK studies. These studies targeted different phases of the disease and were all of shorter duration than our study; therefore, individually, they were unable to address both early antiviral and late anti-inflammatory activities. It is widely accepted that antivirals are most effective if given early in the disease course. In COVID-19, the viral load is high in the first 5 days of infection but decreases rapidly thereafter, with viable virus generally undetectable by day 8.⁴ Mathematical modelling and clinical studies showing benefit of remdesivir only if given in the first 9 days of symptoms⁵ all support the priority for early initiation of antivirals.

The findings of this pragmatic, real-world trial are directly applicable to patients presenting to secondary care with clinically diagnosed COVID-19. In such ambulatory care settings in many health-care systems globally, results of PCR tests are frequently unavailable to guide immediate management decisions. Nonetheless, we already reported that there were no detectable differences in outcomes between the intention-to-treat (ITT) population and the ITT positive population (ie, all randomly assigned patients with a positive baseline COVID-19 test based on baseline swabs). We are therefore



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confident our results have validity to exclude a clinically significant benefit of azithromycin in the population described, particularly when assessed in light of concordant findings from other randomised controlled trials, including COALITION I, COALITION II, PRINCIPLE, and RECOVERY.

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