Azithromycin for severe COVID-19

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Hydroxychloroquine with or without azithromycin was identified, outside of randomised controlled trials, as an early candidate for treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. A number of trials evaluating hydroxychloroquine as pre-exposure prophylaxis, as early treatment, and in patients admitted to hospital with COVID-19 were subsequently initiated. To date, randomised trials have found no evidence of a benefit of hydroxychloroquine compared with placebo at any disease stage for COVID-19, and a number of trials were discontinued early because of difficulties with enrolment and emerging evidence that hydroxychloroquine was not effective.[1–3]

Although the preponderance of evidence indicates that there is no benefit of hydroxychloroquine in the treatment of COVID-19, fewer studies have evaluated azithromycin, a broad-spectrum antibiotic that has anti-inflammatory properties. Azithromycin is commonly used for bacterial respiratory infections, and could potentially treat or prevent co-infection with SARS-CoV-2. Azithromycin might also have antiviral activity against some RNA viruses.[4,5] Azithromycin has been shown to be effective in vitro against viruses such as Zika and rhinovirus, in addition to SARS-CoV-2,[4,5] and to have antiviral effects in bronchial epithelial cells.[6] Azithromycin has also been shown to be immunomodulatory,[7] and can reduce exacerbations in chronic airway diseases.[8] Azithromycin is widely available and has an excellent safety profile; thus, if shown to be effective, could be easily scaled up as a first-line treatment for patients with COVID-19.

In *The Lancet*, Remo Furtado and colleagues[9] report the primary results of COALITION II, an open-label randomised trial evaluating azithromycin in addition to standard of care, which included hydroxychloroquine, compared with standard of care alone in patients admitted to hospital with severe COVID-19, including patients receiving oxygen supplementation at more than 4 L/min, or use of high-flow nasal cannula or non-invasive or invasive mechanical ventilation. The trial enrolled 447 adult participants (aged >18 years) at multiple hospitals in Brazil, approximately a third of whom were women. The primary outcome was clinical status at 15 days, assessed using a six-level ordinal scale ranging from not hospitalised to death. Participants were followed up for 29 days in total to assess 29-day mortality. Furtado and colleagues found no benefit of azithromycin on clinical outcomes, including clinical status or mortality, when added to the standard of care regimen (odds ratio 1·36 [95% CI 0·94–1·97]; p=0·11), and no evidence of an increase in adverse events with the addition of azithromycin. There was no evidence of a difference in outcomes by sex, although a prespecified subgroup analysis suggested potentially worse clinical status at 15 days in younger patients receiving azithromycin. A major strength of COALITION II was that it was randomised, which eliminated the confounding by indication inherent in observational analyses. Despite the open-label design, the authors attempted to minimise bias in outcome ascertainment by using a masked outcome adjudicator.

Although masking outcome assessors is an important step towards minimising bias, open-label designs are more prone to bias than fully masked placebo-controlled trials. With the use of a placebo, treating physicians, patients, and others involved in patient care are unaware of the patient's treatment assignment. Differences in patient care between groups could influence outcomes, even with the use of masked outcome assessors. The azithromycin intervention in COALITION II was administered in the context of hydroxychloroquine, which was the standard of care in Brazil at the time the study was done. Given the results of trials assessing hydroxychloroquine in COVID-19, it

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is unlikely that hydroxychloroquine has any effect on disease progression, but its use might bias estimates towards the null compared with treatment with azithromycin alone.

The results of COALITION II corroborate those of COALITION I,[10] which was done by the same study group and evaluated hydroxychloroquine with or without azithromycin in patients admitted to hospital with mild or moderate COVID-19. In COALITION I, there was no significant difference in outcomes in patients receiving hydroxychloroquine with or without azithromycin, and no evidence of an increase in adverse events. The results of these trials suggest that azithromycin might not provide benefit to patients once the disease has progressed and patients require hospitalisation. Because azithromycin is currently the most commonly prescribed outpatient therapy for COVID-19, establishing whether azithromycin is helpful earlier in the disease course is an important research priority. If azithromycin does not have a role in the treatment of COVID-19, avoiding its use would reduce unnecessary antibiotic consumption.

The results of COALITION II are an important contribution to the randomised trials evaluating therapeutics for COVID-19. For patients with COVID-19, the addition of azithromycin to existing standard of care regimens does not appear to improve outcomes. Additional placebo-controlled trials in hospitalised patients, and earlier in the disease course, would strengthen the evidence and provide a comprehensive understanding of the role of azithromycin in COVID-19.

We declare no competing interests.

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