

## Cardiac safety and potential efficacy: two reasons for considering minocycline in place of azithromycin in COVID-19 management

Currently, there is no effective therapy for COVID-19, and several approaches are under investigation. Nevertheless, some drugs are used off-label despite the absence of clear data on their effectiveness. Among these, hydroxychloroquine suppresses SARS-CoV-2 replication *in vitro*,<sup>1</sup> and clinical trials are ongoing to evaluate its use as an anti-COVID-19 agent. To date, the FDA and EMA allow its use only in hospitalized patients with severe COVID-19 or in those at high risk, in cases where other trials are not feasible. According to a small non-randomized study, hydroxychloroquine's efficacy might be enhanced by azithromycin, as the combination of these two drugs appeared to accelerate viral clearance.<sup>2</sup> However, these findings were not substantiated by another study performed in severe COVID-19 cases.<sup>3</sup>

In addition to the lack of consistent or conclusive efficacy data of these drugs, whether they are used individually or in combination, concern is increasing about potential safety issues. Both hydroxychloroquine and azithromycin may lead to QT prolongation-related life-threatening arrhythmias through the blockage of the rapid delayed rectifier potassium current (IKr). Their combination seems to be more harmful than their single use. Importantly, the risk of azithromycin-mediated QT prolongation is higher in males and in elderly groups,<sup>4</sup> that represent a large proportion of the COVID-19 population. Data from a recent Chinese report showed that 16.7% of hospitalized COVID-19 patients and 44.4% of those in intensive care units had arrhythmias.<sup>5</sup> The two main mechanisms involved could be hypoxia and electrolyte abnormalities, common features in the acute phase of severe illness. These factors may further enhance the risk of arrhythmic toxicity associated with hydroxychloroquine or azithromycin.

Therefore, strategies to mitigate this potential risk have been proposed. The American College of Cardiology suggested QT monitoring in

order to discontinue azithromycin (if used) and/or reduce the hydroxychloroquine dose in the case of QT prolongation.

While drugs currently used against COVID-19 may seem crucial to treat the infection (in the absence of better options), it is imperative to mitigate toxicity to guarantee the maximum possible safety.

According to 2019 international guidelines by the American Thoracic Society and Infectious Diseases Society of America, in pneumonia patients with QT prolongation, macrolides should be replaced by tetracyclines. While providing a broad-spectrum antibiotic activity, compared with other antibiotics tetracyclines also display additional properties that can be advantageous in COVID-19.

In particular, the tetracycline derivative minocycline exerts anti-inflammatory effects by suppressing proinflammatory cytokines, including interleukin-6 (IL-6), which plays a key role in COVID-19, and may inhibit poly(ADP-ribose) polymerase-1 (PARP-1) which seems to be implicated in SARS-CoV-2 replication.<sup>6,7</sup> Moreover, minocycline displays a synergistic effect when added to hydroxychloroquine.<sup>8</sup> Compared with azithromycin, minocycline does not prolong the QT interval, and experimental evidence suggests that it may even be beneficial in conditions associated with increased risk of QT prolongation or arrhythmia. In an experimental model of epilepsy, intrathecal administration of minocycline, by antagonizing the action of microglia, reduced autonomic nervous system activity and seizure-induced QT prolongation.<sup>9</sup> In other murine models, treatment with minocycline attenuated ischaemia-induced arrhythmias by blocking the mitochondrial K-ATP channel and inhibiting the PI3K/Akt signalling pathway mediated by L-type calcium channels both involved in myocardial ischaemia-induced arrhythmias.<sup>10</sup> Although not proven in humans yet, it is reasonable to believe that minocycline may prevent (or at least mitigate) the increased risk of QT prolongation, and potentially fatal arrhythmias, due to hydroxychloroquine/azithromycin combination therapy, while having the same efficacy as azithromycin but a lower arrhythmogenic effect.

For these reasons, until clinical trials prove the efficacy of azithromycin alone or in combination with hydroxychloroquine, we


suggest that, whenever antibiotic prophylaxis is needed, azithromycin should be replaced by minocycline.

**Conflict of interest:** none declared.

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