Is it prime time to consider a clinical trial of doxycycline for the management of COVID-19?

The spectrum of the SARS-CoV-2 coronavirus disease (COVID-19) ranges from minimally symptomatic to severe pneumonia and acute respiratory distress syndrome. While specific and targeted antiviral therapy is awaited, an early intervention strategy involving drugs with antiviral/anti-inflammatory activity either alone or in combination with antibiotics has been advocated. In this regard, a regimen including hydroxychloroquine and macrolides (mainly azithromycin) has been preferentially used in various clinical settings.1

The rationale proposed in current drug-therapy modalities involves targeting the virus itself as well as life-threatening complications associated with the cytokine release syndrome that accompanies the more severe forms of the disease. Indeed, there are accumulating data that SARS-CoV-2 induces mild or severe ‘cytokine storm’ reactions. Interleukin-6 (IL-6) is a multifunctional cytokine, which has a central role in the cytokine storm and predicts respiratory failure in hospitalised symptomatic patients with COVID-19.2 Monoclonal antibodies such as tocilizumab, targeting membrane and cellular IL-6 receptors, have been described in early uncontrolled publications to be efficacious in this setting. However, many experts support an earlier intervention against the detrimental effects of IL-6.

Doxycycline is a broad-spectrum antibiotic of the tetracycline family that is active against a wide range of microorganisms including respiratory system pathogens. The safety profile of doxycycline is rather favourable and is associated with a low incidence of adverse effects, such as drug hypersensitivity syndrome, hyperpigmentation and dizziness, compared with other agents of the same family. Doxycycline has been successfully used in the course of treatment of various bacterial and viral infections. Interestingly, for the case of COVID-19, it has been reported that doxycycline lowers significantly pro-inflammatory cytokines (including IL-6) and has a favourable effect in the mortality of dengue haemorrhagic fever, associated with reductions in IL-6 and tumour necrosis factor α (TNF-α).3 4

Efficacy and safety concerns are being raised with the use of chloroquine or hydroxychloroquine and azithromycin, especially in combination, in the management of SARS-CoV-2 infection. Co-administration of azithromycin with these agents potentiates the risks of prolongation of the QTc interval especially in patients with pre-existing heart disease, which comprise a vulnerable group of infected patients. The lack of effective treatment options for COVID-19 is becoming more evident with the results of recent clinical trials.5

Based on these observations, doxycycline may represent a safe, efficacious, affordable and widely available antibiotic with anti-inflammatory properties that are clinically relevant in the management of the COVID-19 clinical syndrome. Clinical trials in the direction of early administration of doxycycline in patients with COVID-19 are urgently needed.

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