Received: 9 April 2020 | Accepted: 16 April 2020

DOI: 10.1111/dth.13437

DERMATOLOGIC THERAPY WILEY

LETTER

Doxycycline, a widely used antibiotic in dermatology with a possible anti-inflammatory action against IL-6 in COVID-19 outbreak

Dear Editor,

The recent SARS-CoV-2 pandemic, for which there is still no approved vaccine, required research into effective treatments to limit, contain, and improve the outcome of affected patients.[1,2]

Symptoms of coronavirus disease 19 (COVID-19) range from mild to severe and may include fever, dry cough, a sore throat, and shortness of breath.[3] Interstitial pneumonia is among the most commonly reported and serious ongoing and life-threatening complications of infection triggered by the so-called cytokine storm.[4] Interleukin-6 (IL-6) is the protagonist of cytokines that are activated as a result of a dysregulated host immune response at alveolar level, which may contribute to the development of a pulmonary parenchymal inflammation with consequent lung interstitiopathy causing a reduction in respiratory function.[5]

The efficacy and safety of a number of IL-6 receptor antibodies are currently under investigation, with no definitive results available at the moment.

An open-label nonrandomized clinical trial suggested that chloroquine and its less toxic metabolite, hydroxychloroquine, may be effective against COVID-19.[6] Gautret et al supported the synergistic effect of the combination of hydroxychloroquine (200 mg × 3/day for 10 days) and the macrolide antibiotic azithromycin (500 mg on the first day then 250 mg/day for 5 more days) that is known to have a broad spectrum of action against most causes of pneumonia, as well as a potential anti-inflammatory effect.[6] Since then, many authors described the abovementioned combination as therapeutic or prophylactic in the SARS-CoV-2 pandemic.

In view of this, doxycycline (a semisynthetic derivative of tetracycline) would seem to be a valid alternative to azithromycin. In fact, in addition to its well-defined antibiotic effects (bacteriostatic action by inhibition of bacterial protein synthesis), in vitro studies have shown doxycycline to exert anti-inflammatory effects at low (20-40 mg/day) and high (100 or 200 mg/day) doses with inhibitory action on metalloproteases and modulating effects of pro-inflammatory cytokines IL-6, IL-8, and tumor necrosis factor-alpha.[7] The anti-inflammatory properties of doxycycline and other components of tetracycline has been demonstrated for several inflammatory airway diseases, including, acute respiratory distress syndrome.[8] Thereby, low doxycycline doses have been shown to be more effective than high doses to prevent induction of pro-inflammatory cytokines (such as IL-6) in inflammatory diseases.[7]

Doxycycline is rapidly and almost completely absorbed after oral administration. It is a safe and inexpensive drug with a minimal toxicity.[7] The most common side effects are gastrointestinal (stomach pain, nausea, vomiting, diarrhea, and gastritis) and dermatological (rash, sensitivity to the sun).[7] Doxycycline is contraindicated during pregnancy due to its potential adverse teratogenic effects and in children under 8 years of age because of the risk of yellow discoloration of the teeth and dental enamel hypoplasia. Abnormal weight gain and gut microbiota alterations have been reported as side effects during long-term treatment with doxycycline and hydroxychloroquine for diseases such as Q fever endocarditis.[9]

Although there is not yet a general consensus and many clinical trials to date are ongoing or due to start in the countries most affected by COVID-19, we want to stress and encourage research studies and trials on the association between hydroxychloroquine and doxycycline. This combination could prove useful and safer in terms of side effects than the hydroxychloroquine and azithromycin, especially in a home administration context. This is because azithromycin/hydroxychloroquine may influence the QT tract elongation and requires, therefore, electrocardiographic monitoring. In conclusion, low doxycycline doses in association with hydroxychloroquine might be a promising prophylactic and therapeutic strategy for the early phase of COVID-19. Clinical trials are needed to assess their efficacy and safety in suspected or confirmed COVID-19 patients.

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