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Letter to Editors

# Doxycycline or minocycline may be a viable treatment option against SARS-CoV-2

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As of June 21, coronavirus SARS-CoV-2 has infected almost 9 milions of people and the number of laboratory-confirmed COrona-VIrus Disease 2019 (COVID-19) deaths are 461,715, worldwide [1]. The virus causes acute respiratory distress syndrome (SARS) and, eventually, death from multiple organ failure, in a non-neglectable portion of patients [2]. As such, COVID-19 is an international public health emergency. Although some recent reports suggested the efficacy of diverse agents, there is currently no standard therapy for COVID-19.

Several preclinical studies showed that doxycycline (DOX) and minocycline (MIN), semi-synthetic tetracyclines frequently used in clinical practice against a variety of infective agents and well tolerated, are also effective against some RNA viruses [3,4]. It is commonly recognized that tetracyclines act selectively inhibiting microbial protein synthesis by binding to the 16S rRNA [5]. Recent evidence suggested that the precise site of interaction between DOX/MIN and 16S rRNA as well as other cellular RNA molecules could be double-stranded RNAs (dsRNAs) [6]. The dsRNA-binding mechanism could explain the tetracyclines broad antimicrobial and antiviral properties [6]. Indeed, rRNAs form numerous double-stranded structures that are essential to protein synthesis. Furthermore, dsRNAs have been observed as intermediates of the viral replication of positive-stranded viruses, including SARS coronaviruses [7,8]. SARS-CoV-2 is a positive-stranded RNA virus and, interestingly, DOX/MIN antiviral efficacy was hitherto reported mostly against positive-sense RNA viruses [3,4]. Besides, replication of RNA viruses occurs in the host cell cytoplasm, where Mg + concentration is most favorable to DOX/MIN binding [5]. As such, DOX/MIN may be effective also against SARS-CoV-2 infection. In this regard, accumulating evidence shows that SARS is associated with an aberrant induction of inflammatory cytokines/chemokines, mostly activated by dsRNA intermediates of viral replication [9,10]. In particular, the robust viral replication and delayed IFN-γ signaling accompanying the initial steps of SARS seem to be consequence of the coronavirus ability to initially evade the host dsRNA-sensors [10,11]. Therefore, it is plausible that early administration of dsRNA-binding DOX/MIN may reduce the risk of SARS. This hypothesis is strengthened by the fact that both DOX and MIN are known to have relevant anti-inflammatory properties [12]. In detail, the tetracyclines inhibit pro-inflammatory cytokines and matrix metalloproteinases that play a key role in coronavirus acute infection and are involved in chemokine activation and in tissue destruction, such as perivascular basement membrane and parenchymal extracellular matrix, thereby facilitating inflammatory cells infiltration [12,13]. Of note, also this immunomodulatory effect seems to be dsRNA-mediated [5]. Hence, DOX/MIN may inhibit both the viral replication and the host exuberant inflammatory response. Taken together, all evidence suggests that DOX/MIN may be active against SARS-CoV-2 and clinical trials investigating these drugs are urgently warranted.

## Conflict of Interest

All authors report no conflict of interest.

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