# Tetracycline Treatment for COVID-19

## COVID-19 için Tetrasiklin Tedavisi

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**ABSTRACT**

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak that originated in late 2019 has become a serious global threat to human health. Presently, there are no drugs approved to combat the disease (COVID-19). Therefore, it is important to find effective drugs against COVID-19 and to conduct clinical trials of these drugs. Drug repurposing is a well-known strategy used to redeploy licensed drugs for newer indications, thereby providing the fastest possible transition from bench to bedside for meeting therapeutic needs. The anti-SARS-CoV-2 effects of tetracyclines (TCs), (e.g., doxycycline and minocycline), have recently attracted considerable attention. We believe that treatment with TC alone or in combination with other drugs is promising and may open the door for an international strategy to fight this emerging viral infection.

**Keywords***:* Severe acute respiratory syndrome coronavirus 2, COVID-19, tetracycline

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**ÖZET**

2019'un sonlarında ortaya çıkan şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2) salgını, insan sağlığı için ciddi bir küresel tehdit haline geldi. Şu anda, hastalıkla (COVID-19) savaşmak için onaylanmış herhangi bir ilaç bulunmamaktadır. Bu nedenle COVID-19'a karşı etkili ilaçların bulunması ve bu ilaçların klinik denemelerinin yapılması önemlidir. İlaç yeniden kullanım amacı, lisanslı ilaçları daha yeni endikasyonlar için yeniden dağıtmak için kullanılan iyi bilinen bir stratejidir ve böylece terapötik ihtiyaçların karşılanması için tezgahtan başucuna mümkün olan en hızlı geçişi sağlar. Tetrasiklinlerin (TC'ler) (örneğin, doksisiklin ve minosiklin) anti-SARS-CoV-2 etkileri son zamanlarda büyük ilgi görmüştür. Tek başına veya diğer ilaçlarla kombinasyon halinde TC ile tedavinin umut verici olduğuna ve ortaya çıkan bu viral enfeksiyonla mücadele için uluslararası bir stratejinin kapısını açabileceğine inanıyoruz.

**Anahtar Sözcükler:** Şiddetli akut solunum sendromu koronavirüs 2, COVID-19, tetrasiklin

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak that originated in late 2019 has become a serious global threat to human health. Presently, there are no drugs approved to combat the disease (COVID-19). Therefore, it is important to find effective drugs against COVID-19 and to conduct clinical trials of these drugs. Drug repurposing is a well-known strategy used to redeploy licensed drugs for newer indications, thereby providing the fastest possible transition from bench to bedside for meeting therapeutic needs. The anti-SARS-CoV-2 effects of tetracyclines (TCs), (e.g., doxycycline (DOX) and minocycline), have recently attracted considerable attention.

TCs are well-known antibiotics in clinical use. They are highly lipophilic and chelate zinc compounds on matrix metalloproteinases (MMPs). Several SARS-CoV-2 functions are associated with the host MMP complex, including replication. Therefore, the zinc-chelating properties of TCs may aid in inhibiting COVID-19 in humans, thus limiting the ability of SARS-CoV-2 to replicate within the host (1, 2). Moreover, TCs are reported to inhibit the binding of the SARS-CoV-2 spike protein to angiotensin-converting enzyme 2 (3). Indeed, DOX inhibits cell entry and SARS-CoV-2 replication *in vitro* (4). Besides the anti-SARS-CoV-2 effects, TCs possess anti-inflammatory and immunomodulatory effects to reduce the production of tumor necrosis factor-α, interleukin (IL)-6, and IL-8 in a dose-dependent manner (5).

Regarding TC treatment for mild and moderate COVID-19, Yates et al. reported successful treatment of four high-risk patients with COVID-19 accompanied by comorbid pulmonary disease with DOX at doses of 100–200 mg/day over a period of 5–14 days (6). In addition, Gironi et al. reported that dermatologic patients with moderate COVID-19 were successfully treated with DOX at doses of 100–200 mg/day over a period of 10–30 days and with minocycline at doses of 50–200 mg/day over a period of 10–30 days (7).

COVID-19 is characterized by early exponential viral replication, cytokine-associated organ damage and dysfunction, including acute respiratory distress syndrome (ARDS), severe life-threatening comorbidity, and endothelial injury with proximal platelet aggregation with thrombosis (8). Moreover, elevated levels of blood IL-6, IL-8, IL-10, and tumor necrosis factor-α were noted in COVID-19-induced ARDS (9).

Regarding ARDS treatment, treatment with TC was associated with 75% reduced likelihood for mechanical ventilation during hospital stay. Furthermore, treatment with TC corresponded to significant reductions in the length of mechanical ventilation use and intensive care unit stay in patients with ARDS (10). Although this study was performed in patients without COVID-19, these results suggest that TC may show efficacy in COVID-19-induced ARDS via the reduction of cytokine.

In COVID-19, neuropsychiatric manifestations such as fatigue, febrile seizures, psychiatric symptoms, and delirium are observed. The neuroinflammatory response to viral antigens and proinflammatory mediators/immune cells is speculated to relate to these manifestations. Microglia cells mediate the overproduction of inflammatory cytokines, free radicals, and damage signals, leading to neurotoxic consequences. TCs possess neuroprotective and anti-inflammatory effects. In addition, TCs can inhibit microglial reactivity and neuroinflammation by inhibiting nuclear factor kappa B signaling, cyclooxygenase 2, and MMPs. Thus, treatment with TC may be able to control neuropsychiatric manifestations associated with SARS-CoV-2 (11).

Taken together, treatment with TC may show efficacy in COVID-19 in mild to severe stages and may be beneficial throughout the course of COVID-19.

Presently, several licensed drugs other than TCs, such as hydroxychloroquine, macrolide antibiotics (e.g., azithromycin and clarithromycin), ivermectin, corticosteroids, and tocilizumab, have been used because of their potential efficacy in inhibiting COVID-19. Treatment with TC combined with the aforementioned drugs may be more effective than treatment with TC alone because of the synergistic effect of the different mechanisms of action of these drugs. Regarding combined therapy, successful treatments with DOX, azithromycin, ivermectin, and corticosteroids (12) as well as with DOX and ivermectin for mild and moderate COVID-19 (13) have been reported. In general, macrolide antibiotics treatment has been associated with reduced mortality in ARDS (14); therefore, treatment with DOX and macrolide antibiotics may be a currently available solution to stop the death due to COVID-19-induced ARDS.

In any case, we believe that treatment with TC alone or in combination with other drugs is promising and may open the door for an international strategy to fight this emerging viral infection.

**Conflict of interest**
No conflict of interest was declared by the authors.

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