



# Multi-drug Treatment for COVID-19-induced Acute Respiratory Distress Syndrome

## COVID-19 Kaynaklı Akut Solunum Sıkıntısı Sendromu için Çoklu İlaç Tedavisi

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### ABSTRACT

Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), broke out in late 2019 to become a serious global threat to human health. In the absence of specific treatments for COVID-19, treatment options are being examined. Recently, the anti-SARS-CoV-2 activities of tetracyclines, macrolide antibiotics, and ivermectin (IVM), have attracted considerable attention for their potential as a single or multi-drug treatment regimen. Moreover, tetracyclines, macrolide antibiotics, and IVM possess anti-inflammatory and immunomodulatory effects to reduce the production of cytokines. COVID-19 is characterized by early exponential viral replication, cytokine storm-associated organ damage, including acute respiratory distress syndrome (ARDS) and thrombosis. Considering anti-inflammatory and immunomodulatory effects of the aforementioned drugs and corticosteroids, early treatment with doxycycline, azithromycin, IVM, and corticosteroids is thought to be the most promising option for combating COVID-19-induced ARDS.

**Key words:** COVID-19, doxycycline, azithromycin, ivermectin, corticosteroid

### ÖZ

Şiddetli akut solunum yolu sendromu-koronavirüs-2'nin (SARS-CoV-2) neden olduğu Koronavirüs hastalığı-2019 (COVID-19), 2019'un sonlarında patlak vererek insan sağlığı için ciddi bir küresel tehdit haline gelmiştir. COVID-19 için spesifik tedavilerin yokluğunda tedavi seçenekleri inceleniyor. Son zamanlarda, tetrasiklinlerin, makrolid antibiyotiklerin ve ivermektinin (IVM) anti-SARS-CoV-2 aktiviteleri, tek veya çoklu ilaç tedavi rejimi olarak potansiyelleri nedeniyle büyük ilgi görmüştür. Dahası, tetrasiklinler, makrolid antibiyotikler ve IVM sitokin üretimini azaltmak için anti-inflamatuar ve immünomodülatör etkilere sahiptir. COVID-19, erken üstel viral replikasyon, akut solunum sıkıntısı sendromu (ARDS) ve tromboz dahil sitokin fırtınası ile ilişkili organ hasarı ile karakterizedir. Bahsi geçen ilaçların ve kortikosteroidlerin antiinflatuar ve immünomodülatör etkileri göz önüne alındığında, doksisisiklin, azitromisin, IVM ve kortikosteroidlerle erken tedavinin, COVID-19 kaynaklı ARDS ile mücadelede en umut verici seçenek olduğu düşünülmektedir.

**Anahtar kelimeler:** COVID-19, doksisisiklin, azitromisin, ivermektin, kortikosteroid

### INTRODUCTION

Coronavirus disease-2019 (COVID-19), caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), broke out in late 2019 to become a serious global threat to human health. In the absence of specific treatments for COVID-19, treatment options are being examined. Recently, the anti-SARS-CoV-2 activities of tetracyclines [e.g., doxycycline (DOX)], macrolide antibiotics [e.g., azithromycin (AZM), and clarithromycin

(CAM)], and macrolide antiparasitic [e.g., ivermectin (IVM)], have attracted considerable attention for their potential as a single or multi-drug treatment regimen.

Apart from anti-SARS-CoV-2 activities, DOX, AZM, and IVM possess anti-inflammatory and immunomodulatory effects to reduce the production of interleukin-6 (IL-6), IL-8, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ); IL-1, IL-6, IL-8, and TNF- $\alpha$ ; and IL-1, IL-6, and TNF- $\alpha$ , respectively.<sup>1-3</sup>

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In single-drug treatment studies in COVID-19, DOX,<sup>4</sup> CAM,<sup>5</sup> and IVM<sup>6</sup> have proven effective against COVID-19.

In multi-drug treatment studies, Alam et al.<sup>7</sup> found that a combination of IVM and DOX was effective for viral clearance in patients with mild and moderate COVID-19. Prasad<sup>8</sup> reported on a patient where COVID-19 accompanied by pulmonary lesion was successfully treated with the early administration of IVM (6 mg twice daily for 3 days), AZM (500 mg daily for 5 days), DOX (100 mg twice daily for 5 days), and prednisolone (50 mg daily for 5 days) followed by dexamethasone (6 mg daily).

The primary purpose of the aforementioned drug treatments is to improve mild and moderate COVID-19 cases and prevent them from further deteriorating into the severe, life-threatening stage. Severe COVID-19 involves cytokine storm-associated organ damage, including acute respiratory distress syndrome (ARDS). Elevated blood levels of IL-6, IL-8, IL-10, and TNF- $\alpha$  were noted in COVID-19-induced ARDS,<sup>9</sup> which was effectively treated with cytokine storm suppression, either using IL-6 inhibitor tocilizumab (TCZ)<sup>10</sup> or a combination of TCZ and IVM.<sup>11</sup>

Corticosteroids known to reduce the production of IL-6, IL-8, IL-10, and TNF- $\alpha$ ,<sup>12</sup> were also found to reduce mortality in the patients with COVID-19-induced-ARDS and non-COVID-19-induced ARDS.<sup>13</sup>

Tetracycline treatment within a year before ARDS diagnosis was associated with 75% reduced likelihood for mechanical ventilation during a hospital stay.<sup>14</sup> Furthermore, tetracycline treatment corresponded to significant reductions in the length of mechanical ventilation use and intensive care unit stay in patients with ARDS.<sup>14</sup> Although this study was conducted in patients with non-COVID-19, these results suggest that tetracycline is effective for COVID-19-induced ARDS. Additionally, treatment with macrolide antibiotics has also been associated with reduced mortality in ARDS.<sup>15</sup>

Multi-drug treatment is thought to be more effective than single-drug treatment because of the synergistic effect of the different mechanisms of action of the component drugs.<sup>16</sup>

Taken together, from a medical economic standpoint, early treatment with IVM, DOX, AZM, and corticosteroids may be the most promising option for combating COVID-19-induced ARDS.

However, clinical trials need to be conducted to better assess the optimal doses and durations for these medications as well as the efficacy and tolerability of this treatment before it can be implemented on a wider scale.

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