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Letter to the Editor

Coronavirus disease 2019 (COVID-19) treatment versus mycobacterial infections: Better safe than sorry?

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To the Editor—More than 1 year after the onset of the coronavirus disease 2019 (COVID-19) pandemic, severe acute respiratory coronavirus virus 2 (SARS-CoV-2) has infected ~113 million people and has caused ~2.5 million deaths, according to the World Health Organization (WHO). Vaccination campaigns have been implemented in several countries worldwide as a prevention strategy for preventing new cases, preventing overcrowding of health facilities and decreasing COVID-19–associated deaths. Nevertheless, the total number of vaccines produced is still not sufficient to address the world population, especially developing countries, and many people continue to be infected daily, requiring hospitalization and health care.[1]

Currently, there is no effective treatment for COVID-19. However, some drugs and immunomodulators agents have been suggested to prevent the aggravation of clinical conditions: azithromycin, hydroxychloroquine, remdesivir, lopinavir, ritonavir, dexamethasone, tocilizumab, and others.[2] Previous studies have also alluded to the importance of differential diagnosis to facilitate adequate treatment because other infectious lung diseases, such as tuberculosis (TB) and nontuberculous mycobacteria (NTM) pulmonary diseases, may present similar symptoms and result in increased disease severity if they are not correctly identified early.[3] Furthermore, TB–COVID-19 and NTM–COVID-19 coinfections have also been described.[3,4] Some medications used in COVID-19 therapy can cause drug–drug interactions with first-line anti-TB drugs, such as antivirals and corticosteroids with rifampicin,[5,6] or they can increase the risk of latent TB reactivation and NTM pulmonary diseases, such as antirheumatic and immunomodulatory agents.[7,8] In addition, azithromycin, which has been adopted in the medication management of COVID-19 patients based on its anti-inflammatory and antiviral properties, may result in the development of macrolide-resistant mycobacterial strains (Table 1).[9]

Therefore, when COVID-19 is suspected, differential diagnoses should be performed to prevent risk factors for mycobacterial disease due to inadequate patient treatment. On the other hand, patients with concomitant mycobacterial and COVID-19 etiology require simultaneous treatment, but coadministration of rifampicin with antiviral drugs (eg, remdesivir, lopinavir and ritonavir) should be avoided due to the gastrointestinal and liver toxicity risk in addition to the reduction of antivirals drugs to subtherapeutic concentrations.[6] In a related study, high cortisol levels have been proposed as a possible prognostic marker for COVID-19 associated with adverse outcomes. However, concomitant use of rifampicin with dexamethasone can result in increased dexamethasone metabolism and altered cortisol levels.[5,10] Under these circumstances, an antimycobacterial protocol should be maintained to reduce the selection of resistant mycobacterial strains, and drug therapy for COVID-19 should be limited to severe cases.[3]

During the COVID-19 pandemic, TB surveillance programs have also been affected by social isolation and limited patient access to health services, resulting in delayed diagnosis and treatment failure. Moreover, COVID-19 and TB share socioeconomic determinants and comorbidities, so TB–COVID-19 coinfection should be considered, especially in endemic regions, because it can result in potentiated pathogenesis of both diseases and consequent worsening of the patient's condition. Some measures that may be used in pandemic management to improve TB monitoring include assessing patient and family exposure history and implementing digital health-assistive technologies.[3]

Due to the absence of specific treatment of COVID-19, only ongoing drug trials have been used to improve the outcomes of hospitalized patients. Nevertheless, drug therapy protocols for COVID-19 can increase susceptibility to mycobacterial infections.[3,4] Thus, further studies analyzing the therapeutic agents used for COVID-19 and their influence on mycobacterial viability and virulence are needed. Their findings will contribute to clinical decision making regarding the best treatment strategy while preventing the development of mycobacterial infections or serious complications in TB–COVID-19 and NTM–COVID-19 coinfections, especially in elderly patients with comorbidities and in TB-endemic countries, such as Brazil and India, which are among the 3 countries with the highest burden of COVID-19 worldwide.[1,3]

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Table 1. Therapeutic Suggested Approaches for COVID-19 and Possible Risk Factors for Mycobacterial Diseases

Therapeutic Agent	Pharmacological Class	Proposed Mechanism of Action in COVID-19	Risk Factors for Mycobacterial Disease	Reference
Azithromycin	Antibiotic	Immunomodulatory properties and *in vitro* antiviral activity	Potential emergence of macrolide-resistant NTM	9
Hydroxychloroquine	Antirheumatic	Anti-inflammatory action and preventing viral entry into the cell	Increased risk of NTM disease	7
Remdesivir	Antiviral	Inhibition of RdRp, preventing viral RNA synthesis	Drug–drug interaction with rifampicin	6
Lopinavir	Antiviral	Protease inhibitory activity, preventing viral replication	Drug–drug interaction with rifampicin	6
Ritonavir	Antiviral	Protease inhibitory activity, preventing viral replication	Drug–drug interaction with rifampicin	6
Dexamethasone	Corticosteroid	Anti-inflammatory and immunosuppressive properties, preventing cytokine storm and damage to lung tissue	Drug–drug interaction with rifampicin	5
Anakinra	Immunomodulator	Blocking IL-1 signaling, preventing cytokine storm and damage to lung tissue	Reactivation of latent TB	8
Canakinumab	Immunomodulator	Blocking IL-1 signaling, preventing cytokine storm and damage to lung tissue	Reactivation of latent TB	8
Tocilizumab	Immunomodulator	Blocking IL-6 signaling, preventing cytokine storm and damage to lung tissue	Increased risk of NTM disease and reactivation of latent TB	8
Ruxolitinib	Immunomodulator	JAK1 and JAK2 inhibition, preventing cytokine storm and damage to lung tissue	Increased risk of NTM disease and reactivation of latent TB	8

Note. NTM, non-tuberculous mycobacteria; TB, tuberculosis; RdRp, RNA-dependent RNA polymerase; IL, interleukin; JAK, Janus kinases.

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Conflicts of interest. All authors report no conflicts of interest relevant to this article.

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