Pentoxifylline: A Drug with Antiviral and Anti-Inflammatory Effects to Be Considered in the Treatment of Coronavirus Disease 2019

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Abstract

In December 2019, a new coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged from China, causing pneumonia outbreaks first in the Wuhan region and has now spread worldwide. There are no specific drugs for the disease caused by this virus, coronavirus disease 2019 (COVID-19). Considering that new synthesized drugs cannot be applied immediately to patients, conventional drug in new use is a feasible solution. Chloroquine, remdesivir, favipiravir, lopinavir, ribavirin, and ritonavir have shown efficacy to inhibit coronavirus in vitro. Pentoxifylline, a drug with anti-inflammatory, immunomodulatory, and bronchodilatory effects, has previously been shown to inhibit several viral infections. Immunological studies have shown that most patients with severe COVID-19 exhibit substantially elevated serum levels of pro-inflammatory cytokines. Pentoxifylline is a phosphodiesterase inhibitor that increases the levels of cyclic adenosine monophosphate, which in turn activates protein kinase, leading to a reduction in the synthesis of pro-inflammatory cytokines and immune cell migration. Here, we propose pentoxifylline, a drug with low cost and toxicity, as a possible treatment for COVID-19 based on its interesting properties.   © 2020 The Author(s).
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Introduction

In the past 2 decades, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) were transmitted from animals to humans, causing severe respiratory diseases SARS and MERS in endemic areas. In December 2019, another coronavirus was discovered in patients with infectious respiratory disease in Wuhan, China, and was found to have the ability for human-to-human transmission. The disease, now termed coronavirus disease 2019 (COVID-19), has spread rapidly all over the world, resulting in a pandemic [1]. In the absence of any known efficient therapy and because of the situation of a public health emergency, efforts of laboratories and medical teams have been focused on repurposing FDA-approved drugs to treat the most severe cases of infection [2]. Immunological studies have shown that most patients with severe COVID-19 exhibit substantially elevat-

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ed serum levels of pro-inflammatory cytokines including interleukin (IL)-6, IL-1β, IL-2, IL-8, IL-17, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, IP10, MCP1, MIP1α (also known as CCL3), and tumor necrosis factor (TNF), characterized as a cytokine storm [3]. Therefore, combined use of anti-inflammatory and antiviral drugs may be more effective than using either modality alone [2]. Here, we propose pentoxifylline, a drug commonly used in vascular indications, as a possible treatment for COVID-19 on the basis of its interesting properties.

Discussion

Pentoxifylline is a methylxanthine derivative and has been used for treating human vascular diseases. In addition to being a cardiovascular drug, pentoxifylline has also been shown high antiviral activity against herpes simplex virus, vaccinia virus, rotavirus, and tick-borne encephalitis virus, suggesting that this drug has broad-spectrum virus inhibitory properties [4]. Furthermore, pentoxifylline also showed inhibition of HIV expression in acutely and chronically infected cells in vitro and in human peripheral blood mononuclear cells [5]. Pentoxifylline is a methylxanthine derivative that inhibits phosphodiesterase 4 (PDE-4), presenting interesting immunomodulatory and antiviral properties. PDE-4 is an abundant and major regulator of cAMP metabolism in almost every pro-inflammatory and immune cells. Specific inhibitors of this isoenzyme are being developed for use in the treatment of a wide range of disease states with an inflammatory component, including dermatological, neurological, and respiratory conditions [6].

The anti-inflammatory effects of pentoxifylline are due to the reduction in the production of the pro-inflammatory cytokines such as TNF-α and interferon (IFN)-γ. Pentoxifylline also downregulates the activation of NF-κB and NFAT transcription factors (involved in the replication of several viruses) [7]. cAMP elevation mediated by PDE-4 inhibition leads to a bronchodilatory effect [8]. There is evidence to suggest that pentoxifylline may influence other inflammatory cytokines such as IL-1 and IL-6 [9]. In particular, the inhibition of the isozyme PDE-4 is likely to be important. PDE-4 is highly expressed in inflammatory cells including neutrophils, macrophages, T cells, and endothelial cells. Inhibition of PDE-4 in immune cells and the subsequent elevation of cAMP results in an anti-inflammatory effect in the respiratory system [6]. A study by Ardizzoia et al. [10] confirmed the capacity of pentoxifylline to inhibit TNF-α secretion in patients with acute respiratory distress syndrome. Moreover, pentoxifylline therapy improved the symptoms related to this syndrome without particular toxic effects. *Pneumocystis carinii* β-glucan-induced TNF-α release from alveolar macrophages in an animal model was inhibited by both dexamethasone and pentoxifylline, 2 pharmacological agents with potential activity in controlling *P. carinii*-induced lung inflammation [11]. Pentoxifylline has been studied in animals and human adults and newborns to ameliorate inflammatory conditions such as sepsis, bronchopulmonary dysplasia, meconium aspiration, and hypoxic ischemic encephalopathy [12–14]. Pentoxifylline was reported to inhibit the secretion of superoxide anion and TNF-α by alveolar macrophages from patients with sarcoidosis in vitro in a dose-dependent manner via a prostaglandin synthesis-dependent mechanism that was independent of the glucocorticoid receptor [15]. SARS-CoV-2 binds to alveolar epithelial cells and then activates the innate and adaptive immune systems, resulting in the release of a large number of cytokines, including IL-6 [16]. In addition, due to the role of these pro-inflammatory factors, vascular permeability increases, allowing the influx of fluid and blood cells into the alveoli, resulting in dyspnea and even respiratory failure [17]. As previously reported, pro-inflammatory cytokines released by stimulated macrophages in the alveoli could have a prominent role in pathogenesis of COVID-19. TNF-α and IFN-γ have also been suggested to cause hemophagocytosis observed in lung biopsies of SARS patients [18] and pentoxifylline downregulates TNF-α and IFN-γ [19]. TNF-α is considered a key inflammatory mediator and is known to modulate the synthesis of other cytokines. Consequently, it is a recognized pathogenic factor in a variety of illnesses such as bronchial asthma, pulmonary fibrosis, and acute respiratory syndromes [20]. Pentoxifylline is known to reduce inflammation in lung interstitium and also has a bronchodilatory effect [21].

Based on these observations, it is logical to consider the use of pentoxifylline for treating respiratory syndromes. It should be used at an early stage when the inflammation is active and the diffuse alveolar damage is not yet established. Pentoxifylline would feature possible antiviral activity along with cytokine-modulating activity, downregulating pro-inflammatory cytokines but leaving functional the rest of the immune response. Furthermore, pentoxifylline is an inexpensive drug. It presents very low toxicity and minimal side effects such dizziness, headache, nausea, and stomach discomfort [22]. Thus, all the characteristics of pentoxifylline make it a promising and effi-

cient therapeutic drug to treat patients suffering from CO-VID-19. However, clinical trials and approvals are required before incorporating pentoxifylline as a routine treatment of COVID-19. Taken together, the evidence highlighted here strongly points to the potential benefits of pentoxifylline for the treatment of COVID-19, which can help support patients in critical care and overwhelmed hospital resources in the face of this pandemic. In line with this, other researchers have proposed pentoxifylline as a beneficial drug for the treatment of COVID-19 [23–25].

Conclusion

The use of agents that can interfere with viral replication and concomitantly suppress viral infection by modulating the immune system is a strategy that can be used to prevent viral infections. Based on previous studies on the effects of pentoxifylline on several viral infections and due to its anti-inflammatory properties, we encourage further investigation of the antiviral and anti-inflammatory effects of this drug on SARS-CoV-2 and suggest pentoxifylline as another potential alternative for the treatment of COVID-19.

Statement of Ethics

Not required.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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