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

Morteza Ghasemnejad-Berenji^a Sarvin Pashapour^b Sonia Sadeghpour^c

^aDepartment of Pharmacology and Toxicology, Faculty of Pharmacy, Urmia University of Medical Science, Urmia, Iran; ^bDepartment of Pediatrics, Faculty of Medicine, Motahari Hospital, Urmia University of Medical Science, Urmia, Iran; ^cDepartment of Obstetrics and Gynecology, School of Medicine, Urmia University of Medical Science, Urmia, Iran

Keywords

Severe acute respiratory syndrome coronavirus-2 · Coronavirus disease 2019 · Pentoxifylline

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)
Published by S. Karger AG, Basel

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 elevated

ed serum levels of pro-inflammatory cytokines including interleukin (IL)-6, IL-1 β , IL-2, IL-8, IL-17, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, IP10, MCP1, MIP1 α (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- κ B 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 capac-

ity 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 as 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 COVID-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.

References

- Hirano T, Murakami M. COVID-19: a new virus, but a familiar receptor and cytokine release syndrome. *Immunity*. 2020 May 19;52(5):731–3.
- Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). *Drug Discov Ther*. 2020;14(1):58–60.
- Cao X. COVID-19: immunopathology and its implications for therapy. *Nat Rev Immunol*. 2020;20(5):269–70.
- Amvros'eva T, Votikov V, Andreeva O, Vladiko G, Nikolaeva S, Orlova S, et al. New properties of trental as an inhibitor of viral activity with a wide range of activity. *Vopr Virusol*. 1993;38:230–3.
- Navarro J, Punzón MC, Pizarro A, Fernández-Cruz E, Fresno M, Muñoz-Fernández MA. Pentoxifylline inhibits acute HIV-1 replication in human T cells by a mechanism not involving inhibition of tumour necrosis factor synthesis or nuclear factor-kappa B activation. *AIDS*. 1996;10(5):469–75.
- Li H, Zuo J, Tang W. Phosphodiesterase-4 inhibitors for the treatment of inflammatory diseases. *Front Pharmacol*. 2018;9:1048.
- Navarro J, Punzón C, Jiménez JL, Fernández-Cruz E, Pizarro A, Fresno M, et al. Inhibition of phosphodiesterase type IV suppresses human immunodeficiency virus type 1 replication and cytokine production in primary T cells: involvement of NF-κB and NFAT. *J Virol*. 1998;72:4712–20.
- Haas F, Bevelacqua F, Levin N, Salazar-Schicchi J, Reggiani JL, Axen K, et al. Pentoxifylline improves pulmonary gas exchange. *Chest*. 1990;97(3):621–7.
- Schandené L, Vandenbussche P, Crusiaux A, Alègre ML, Abramowicz D, Dupont E, et al. Differential effects of pentoxifylline on the production of tumour necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6) by monocytes and T cells. *Immunology*. 1992;76(1):30.
- Ardizzoia A, Lissoni P, Tancini G, Paolorossi F, Crispino S, Villa S, et al. Respiratory distress syndrome in patients with advanced cancer treated with pentoxifylline: a randomized study. *Support Care Cancer*. 1993;1(6):331–3.
- Vassallo R, Standing JE, Limper AH. Isolated pneumocystis carinii cell wall glucan provokes lower respiratory tract inflammatory responses. *J Immunol*. 2000;164(7):3755–63.
- Harris E, Schulzke SM, Patole SK. Pentoxifylline in preterm neonates: a systematic review. *Paediatr Drugs*. 2010;12(5):301–11.
- Schulzke SM, Kaempfen S, Patole SK. Pentoxifylline for the prevention of bronchopulmonary dysplasia in preterm infants. *Cochrane Database Syst Rev*. 2014(11):CD010018.
- Schüller SS, Kempf K, Unterasinger L, Strunk T, Berger A. Intravenous pentoxifylline is well tolerated in critically ill preterm infants with sepsis or necrotizing enterocolitis. *Eur J Pediatr*. 2020 Aug;179(8):1325–30.
- Körber M, Kamp S, Kothe H, Braun J, Dalhoff K. [Pentoxifylline inhibits secretion of O2- and TNF-alpha by alveolar macrophages in patients with sarcoidosis]. *Immun Infekt*. 1995;23(3):107–10.
- Zhang C, Wu Z, Li J-W, Zhao H, Wang G-Q. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality. *Int J Antimicrob Agents*. 2020;55(5):105954.
- Guan W-j, Ni Z-y, Hu Y, Liang W-h, Ou C-q, He J-x, et al. Clinical characteristics of 2019 novel coronavirus infection in China. *MedRxiv*; 2020.
- Russell B, Moss C, George G, Santaolalla A, Cope A, Papa S, et al. Associations between immune-suppressive and stimulating drugs and novel COVID-19—a systematic review of current evidence. *Ecanermedalscience*. 2020 Mar 27;14:1022.
- Tsujino A, Nakamura T, Nishiura Y, Shirabe S, Furuya T, Goto H, et al. Pentoxifylline down-regulates adhesion molecule expression and inflammatory cytokine production in cultured peripheral blood mononuclear cells from patients with HTLV-I-associated myelopathy. *J Neuroimmunol*. 1997;73(1–2):191–6.
- Bhatia M, Mochhala S. Role of inflammatory mediators in the pathophysiology of acute respiratory distress syndrome. *J Pathol*. 2004;202(2):145–56.
- Michetti C, Coimbra R, Hoyt DB, Loomis W, Junger W, Wolf P. Pentoxifylline reduces acute lung injury in chronic endotoxemia. *J Surg Res*. 2003;115(1):92–9.
- Martin JFB, Jiménez JL, MuEóz-Fernández A. Pentoxifylline and severe acute respiratory syndrome (SARS): a drug to be considered. *Med Sci Monit*. 2003;9:SR29–34.
- Dhameliya H, Thakkar V, Trivedi G, Mesara S, Subramanian R. Pentoxifylline: an immunomodulatory drug for the treatment of COVID-19. *J Pure Appl Microbiol*. 2020;14:861–7.
- Maldonado V, Alderete JC. Repositioning of pentoxifylline as an immunomodulator and regulator of the renin-angiotensin system in the treatment of COVID-19. *Med Hypotheses*. 2020 Jun 9;144:109988.
- Seirafianpour F, Mozafarpour S, Fattahi N, Sadeghzadeh-Bazargan A, Hanifiha M, Goodarzi A. Treatment of COVID-19 with pentoxifylline: Could it be a potential adjuvant therapy? *Dermatol Ther*. 2020 Jul;33(4):e13733.