



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Letter to Editors

Pentoxifylline and complicated COVID-19: A pathophysiologically based treatment proposal

To the Editor,

Accumulating evidence suggests that a subgroup of patients with COVID-19 might suffer from severe complications, such as acute respiratory distress syndrome (ARDS), coagulopathy with thromboses and acute cardiac injury, increasing the risk of mortality. A proposed common pathogenetic mechanism for these complications is a SARS-CoV-2-induced proinflammatory state (cytokine storm syndrome-CSS) [1]. Immunomodulatory medications such as inhibitors of interleukin (IL)-6 (tocilizumab) or IL-1 (anakinra) have been proposed as potential treatments for the CSS.

Pentoxifylline (PTX), a non-specific inhibitor of phosphodiesterases and well-established hemorheological factor, exhibits pluripotent properties which could be of value in the context of COVID-19-associated complications. First, PTX inhibits the synthesis of diverse pro-inflammatory cytokines (tumour necrosis factor- α , IL-1, IL-6) and prevents the activation, cell proliferation, adhesion, polarisation and hemotaxis of T cells and neutrophils [2]. Second, PTX antagonizes the inhibitory effect of TNF- α on surfactant synthesis by human type II pneumocytes, which is a pivotal mechanism of ARDS pathogenesis [3]. Third, PTX inhibits platelet aggregation and promotes the fibrinolytic activity, which might decrease the risk of thromboses [4]. Fourth, it exerts cardioprotective actions mediated by its beneficial hemorheological, anti-platelet and anti-inflammatory properties [5]. Its antiviral activity against SARS-CoV-2 has not been tested, but PTX exerts potent in vitro activity against HIV, herpes simplex virus, rotavirus and tick-borne encephalitis virus [6].

To our opinion, this profile of actions of PTX is identically harmonized with several levels of the pathophysiology of COVID-19-associated complications, justifying its trial for the prevention or treatment of severe COVID-19.

Funding sources

The article has no funding source.

Prior presentation

No data from this manuscript were presented in a scientific meeting before.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

- [1] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020;395(10229):1033–4.
- [2] Kretz S, Ledderose C, Luchting B, Weis F, Thiel M. Immunomodulatory properties of pentoxifylline are mediated via adenosine-dependent pathways. *Shock* 2010;34(1):10–6.
- [3] Balibrea-Cantero JL, Arias-Diaz J, Garcia C, Torres-Melero J, Simon C, Rodriguez JM, et al. Effect of pentoxifylline on the inhibition of surfactant synthesis induced by TNF-alpha in human type II pneumocytes. *Am J Respir Crit Care Med* 1994;149(3 Pt 1):699–706.
- [4] Schroer RH. Antithrombotic potential of pentoxifylline A hemorheologically active drug. *Angiology* 1985;36(6):387–98.
- [5] Namdar H, Zohori R, Aslanabadi N, Entezari-Maleki T. Effect of pentoxifylline in ameliorating myocardial injury in patients with myocardial infarction undergoing thrombolytic therapy: a pilot randomized clinical trial. *J Clin Pharmacol* 2017;57(10):1338–44.
- [6] Bermejo Martin JF, Jimenez JL, Munoz-Fernandez A. Pentoxifylline and severe acute respiratory syndrome (SARS): a drug to be considered. *Med Sci Monit* 2003;9(6):SR29–34.

Stelios F. Assimakopoulos*, Fotios Seintis, Markos Marangos
 Department of Internal Medicine, Division of Infectious Diseases, University
 of Patras Medical School, Patras, Greece
 E-mail address: sassim@upatras.gr (S.F. Assimakopoulos).

* Corresponding author at: Department of Internal Medicine and Division of Infectious Diseases, University of Patras Medical School, Patras 26504, Greece.