European Review for Medical and Pharmacological Sciences 2020; 24: 7494-7496

Potential usefulness of pentoxifylline, a non-specific phosphodiesterase inhibitor with anti-inflammatory, anti-thrombotic, antioxidant, and anti-fibrogenic properties, in the treatment of SARS-CoV-2

H. GONZÁLEZ-PACHECO[1], L.M. AMEZCUA-GUERRA[2], J. SANDOVAL[2], A. ARIAS-MENDOZA[1]

[1]Coronary Care Unit, National Institute of Cardiology in Mexico City, Mexico City, Mexico
[2]Department of Immunology, National Institute of Cardiology in Mexico City, Mexico City, Mexico

Abstract. – Although most patients with coronavirus disease 2019 (COVID-19) have a good prognosis, in some cases, the disease progresses rapidly, and the mortality rate is high. Some evidence suggests that infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) produces a 'cytokine storm', which is related to acute respiratory distress syndrome or multi-organ dysfunction leading to physiological deterioration and death. It is important to highlight the state of hypercoagulability that can be triggered, involving microvascular thrombosis and vascular occlusive events, which are relevant to such poor outcomes. At present, no specific antiviral drug or vaccine is available for SARS-CoV-2 infection, and current research is aimed at preventing and mitigating damage to the target organs, mainly the lungs. In seeking therapies for patients with COVID-19, immunomodulators, cytokine antagonists and early anti-coagulation therapies have been tested in attempts to reduce the mortality rate. Pentoxifylline, a non-specific phosphodiesterase inhibitor widely used to improve the rheological properties of blood, has beneficial anti-inflammatory properties and can significantly reduce the serum levels of pro-inflammatory cytokines such as interleukin (IL)-6, IL-1, tumour necrosis factor-alpha, C-reactive protein and other immunoregulators. It has also been found to exert anti-thrombotic, antioxidant and anti-fibrogenic actions. These properties could help to prevent or mitigate the inflammatory response and hypercoagulability that develop with SARS-CoV-2 infection, decreasing multi-organ dysfunction manifesting primarily as acute lung injury.

Key Words:
Pentoxifylline, COVID-19, SARS-CoV-2, Cytokine storm.

Introduction

The outbreak of infections with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) began in Wuhan, the capital of Hubei Province, China, but rapidly spread to many other countries[1]. Critically ill patients have the following common features: (1) sudden deterioration in the disease around 1-2 weeks after onset; (2) very low levels of lymphocytes, especially natural killer cells, in peripheral blood; (3) extremely high levels of inflammatory parameters, including C-reactive protein (CRP) and pro-inflammatory cytokines such as interleukin (IL)-6 and -8, and tumour necrosis factor-alpha (TNF-a), collectively called a 'cytokine storm'; (4) most infiltrating immune cells in lung lesions comprise monocytes and macrophages, but minimal infiltration of lymphocytes is seen; and (5) vasculitis, hypercoagulability and multiple organ damage[2]. A cytokine storm is considered to be one of the major causes of acute respiratory distress syndrome and multi-organ failure. Therefore, the treatment of a cytokine storm has become an important part of rescuing critically ill patients[3]. At present, no specific antiviral drugs or vaccines are available for SARS-CoV-2 infection, so the therapeutic strategies are only supportive and preventive, aiming to reduce transmission. Thus, the identification of well-characterised and approved drugs could be especially useful in such pandemics[4,5].

Therapeutic Utility of Pentoxifylline

Pentoxifylline, a non-specific phosphodiesterase inhibitor, has been used extensively for the

Corresponding Author: Héctor González-Pacheco, MD; e-mail: hectorglezp@hotmail.com

treatment of vascular peripheral and cerebrovascular diseases, as it improves the rheological properties of blood by decreasing its viscosity, primarily through a reduction in plasma fibrinogen. Pentoxifylline also increases the deformability of erythrocytes, decreases platelet aggregation and increases the filterability of blood by suppressing neutrophil activation, resulting in therapeutic benefits via improved microcirculation and tissue oxygenation[6,7]. Pentoxifylline has also been widely reported to have both antioxidant and anti-inflammatory properties. The antioxidant effects of pentoxifylline arise from a decrease in the activation of neutrophils—which generate reactive oxygen species (ROS)—thereby protecting against unwanted tissue damage[8]. Pentoxifylline also has important anti-inflammatory properties and a wide range of documented immunomodulatory effects. Pentoxifylline has been shown to suppress the production of IL-1b, IL-6, IL-8, TNF-a and CRP both *in vitro* and *in vivo*[9-11]. Pentoxifylline has also been shown to increase the levels of anti-inflammatory IL-10[12] and inhibit T cell and natural killer cell cytotoxicity[13,14]. Additionally, pentoxifylline completely inhibits the surface expression of intercellular adhesion molecule-1 and the production of IL-8 and monocyte chemoattractant protein-1 by cytokine-activated human pulmonary epithelial cells[15,16]. Acute respiratory distress syndrome is the most severe form of acute lung injury seen in patients with COVID-19, and the mortality rate for those requiring mechanical ventilation is very high[17]. The severe deterioration of some patients, as well as acute lung damage, has been closely related to very high levels of various proinflammatory cytokines (IL-6, IL-8, IL-1β and TNF-a), granulocyte and macrophage colony-stimulating factor, ROS and chemokines such as CC chemokine ligand (CCL)-2, -5, and -3 and interferon gamma (IFNg)-induced protein 10. Dysregulation of the cytokine/chemokine response triggers an inflammatory cytokine storm accompanied by immunopathological changes in the lungs[3]. An outstanding finding in patients with severe COVID-19 infection is coagulopathy; thus, approximately two-thirds of patients who died from COVID-19 developed disseminated intravascular coagulation (DIC) during their hospital stay[18]. The levels of D-dimer, fibrin/fibrinogen degradation products and fibrinogen in all cases of COVID-19 were substantially elevated, with manifestations of the hypercoagulable phase of DIC with microvascular thrombosis and vascular occlusive events[19]. Therefore, early anti-coagulant therapy might help block thrombogenesis and reduce the formation of microthrombi. In clinical studies, pentoxifylline treatment has been found to protect against sepsis-induced microcirculatory derangement and decrease the incidence of DIC and multiple organ dysfunction syndrome[20,21]. Pentoxifylline also has anti-fibrogenic properties and can be beneficial in treating fibrosis[22]. Therefore, it is used in therapy for radiation-induced lung injury in both the acute phase of pneumonitis and the prevention of pulmonary fibrosis by radiation, conditions related to elevated plasma levels of IL-1a and IL-6[23,24].

Conclusions

We suggest that the pentoxifylline could be a valuable adjuvant treatment in patients with COVID-19. Its anti-inflammatory, anti-thrombotic, rheological, antioxidant and anti-fibrogenic properties might help to prevent or mitigate the inflammatory response and occlusive thrombotic events, thereby decreasing multi-organ dysfunction and acute lung injury. We hope that this work can provide a basis for future studies on the safe and effective use of pentoxifylline in patients with such infections.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Bogoch II, Watts A, Thomas-Bachli A, Huber C, Kraemer MUG, Khan K. Potential for global spread of a novel coronavirus from China. J Travel Med 2020; 27: taaa011.
2) Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, Wang J, Qin Y, Zhang X, Yan X, Zeng X, Zhang S. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID 19): the perspectives of clinical immunologists from China. Clin Immunol 2020; 214: 108393.
3) Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19 [published online ahead of print, 2020 Apr 10]. J Infect 2020; S0163-4453(20)30165-1.
4) Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res 2020; 178: 104787.

5) Georgiev T. Coronavirus disease 2019 (COVID-19) and anti-rheumatic drugs. Rheumatol Int 2020; 40: 825-826.

6) Salhiyyah K, Forster R, Senanayake E, Abdel-Hadi M, Booth A, Michaels JA. Pentoxifylline for intermittent claudication. Cochrane Database Syst Rev 2015; 9: CD005262.

7) Ott E, Lechner H, Fazekas F. Hemorheological effects of pentoxifylline on disturbed flow behavior of blood in patients with cerebrovascular insufficiency. Eur Neurol 1983; 22: 105-107.

8) Crouch SP, Fletcher J. Effect of ingested pentoxifylline on neutrophil superoxide anion production. Infect Immun 1992; 60: 4504-4509.

9) Neuner P, Klosner G, Schauer E, Pourmojib M, Macheiner W, Grünwald C, Knobler R, Schwarz A, Luger TA, Schwarz T. Pentoxifylline in vivo down-regulates the release of IL-1 beta, IL-6, IL-8 and tumour necrosis factor-alpha by human peripheral blood mononuclear cells. Immunology 1994; 83: 262-267.

10) González-Espinoza L, Rojas-Campos E, Medina-Pérez M, Peña Quintero P, Gómez-Navarro B, Cueto-Manzano AM. Pentoxifylline decreases serum levels of tumor necrosis factor alpha, interleukin 6 and C-reactive protein in hemodialysis patients: results of a randomized double-blind, controlled clinical trial. Nephrol Dial Transplant 2012; 27: 2023-2028.

11) Shaw SM, Shah MK, Williams SG, Fildes JE. Immunological mechanisms of pentoxifylline in chronic heart failure. Eur J Heart Fail 2009; 11: 113-118.

12) Fernandes JL, de Oliveira RT, Mamoni RL, Coelho OR, Nicolau JC, Blotta MH, Serrano CV Jr. Pentoxifylline reduces pro-inflammatory and increases anti-inflammatory activity in patients with coronary artery disease--a randomized placebo-controlled study. Atherosclerosis 2008; 196: 434-442.

13) Heinkelein M, Schneider-Schaulies J, Walker BD, Jassoy C. Inhibition of cytotoxicity and cytokine release of CD8þ HIV-specific cytotoxic T lymphocytes by pentoxifylline. J Acquir Immune Defic Syndr Hum Retrovirol 1995; 10: 417-424.

14) Reed WR, DeGowin RL. Suppressive effects of pentoxifylline on natural killer cell activity. J Lab Clin Med 1992; 119: 763-771.

15) Neuner P, Klosner G, Pourmojib M, Knobler R, Schwarz T. Pentoxifylline in vivo and in vitro down-regulates the expression of the intercellular adhesion molecule-1 in monocytes. Immunology 1997; 90: 435-439.

16) Krakauer T. Pentoxifylline inhibits ICAM-1 expression and chemokine production induced by proinflammatory cytokines in human pulmonary epithelial cells. Immunopharmacology 2000; 46: 253-261.

17) Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; the Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA 2020; e206775.

18) Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost 2020; 18: 844-847.

19) Li T, Lu H, Zhang W. Clinical observation and management of COVID 19 patients. Emerg Microbes Infect 2020; 9: 687-690.

20) Y Mándi, G Farkas, I Ocsovszky. Effects of pentoxifyllin and pentaglobin on TNF and IL-6 production in septic patients. Acta Microbiol Immunol Hung 1995; 42: 301-308.

21) Adel M, Awad HA, Abdel-Naim AB, Al-Azizi MM. Effects of pentoxifylline on coagulation profile and disseminated intravascular coagulation incidence in Egyptian septic neonates. J Clin Pharm Ther 2010; 35: 257-265.

22) Windmeier C, Gressner AM. Pharmacological aspects of pentoxifylline with emphasis on its inhibitory actions on hepatic fibrogenesis. Gen Pharmacol 1997; 29: 181-196.

23) Hanania AN, Mainwaring W, Ghebre YT, Hanania NA, Ludwig M. Radiation-induced lung injury: assessment and management. Chest 2019; 156: 150-162.

24) Giridhar P, Mallick S, Rath GK, Julka PK. Radiation induced lung injury: prediction, assessment and management. Asian Pac J Cancer Prev 2015; 16: 2613-2617.