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SHORT PAPER

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Treatment of COVID-19 with pentoxifylline: Could it be a potential adjuvant therapy?

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Abstract

The world is facing a viral pandemic of a new coronavirus called COVID-19. Pentoxifylline is a methyl-xanthine derivative and it inhibits the phosphodiesterase IV (PDE IV). This drug is known for its unique features as an immunomodulatory and anti-inflammatory agent, also it could have antiviral affects. This is a scoping review, in which all related articles on COVID-19 and the probable benefits of Pentoxifylline against COVID-19 pathogenesis, in Medline, Scopus, Web of Sciences, and Google Scholar up to 20 March 2020 with proper keywords including: pentoxifylline, Pentoxil, COVID-19, coronavirus, treatment, anti-inflammatory, immunomodulatory, antifibrosis, oxygenation, circulation, bronchodilator, ARDS, and organ failure. We found many confirmatory data on proper efficacy of pentoxifylline on controlling COVID-19 and its consequences. The antiviral, anti-inflammatory, anti-oxidative, immune-modulatory, bronchodilator and respiratory supportive effects and protective roles in organ failures of PTX, along with its main functions means better circulation-oxygenation properties, low price and safety, make it a promising drug to be considered for COVID-19 treatment, especially as an adjuvant therapy in combination with other drugs.

KEYWORDS

antifibrosis, anti-inflammatory, anti-oxidant, apoptosis-regulatory, ARDS (acute respiratory distress syndrome), bronchodilator, circulation, coronavirus, COVID-19, immunomodulatory, oxygenation, pentoxifylline, Pentoxil, perfusion, review, SARS (severe acute respiratory syndrome), treatment

1 | INTRODUCTION

The world is facing a viral pandemic of COVID-19 as a new coronavirus.[1] The clinical presentation of COVID-19 could vary from asymptomatic or flu-like symptoms to systemic involvements presenting as sepsis, septic shocks and multiple organ dysfunction syndrome or to serious even fatal conditions, including respiratory failure and acute respiratory distress syndrome (ARDS), which require mechanical ventilation and admission to ICUs.[1,2] No definitive virus-specific treatments have been yet proposed for COVID-19. The main treatments are supportive or for controlling the disease consequences. Prevention is therefore the best method of tackling the transmission.[3]

With potential antiviral effects on severe acute respiratory syndrome (SARS) and as a methyl-xanthine derived inhibitor of phosphodiesterase-4, pentoxifylline basically functions as a hemorrheologic agent for a better circulation and oxygenation and exerts unique effects on immune modulation, inflammation and oxidative stress.[4] As the main regulator of cAMP metabolism, posphodiesterase-4 plays a key role in proinflammatory and immune cells. Pentoxifylline plays its anti-inflammatory role by reducing the

production of proinflammatory cytokines such as TNF-a, IL-1, and IL-6. Given its unique impacts on immune modulation, homeostasis and fibrinolysis and its supportive effects on oxidative stress and organ failure, pentoxifylline can constitute a multipurpose and generally safe adjuvant therapy for COVID-19 patients.[5-8]

2 | METHODS

This scoping review thoroughly investigated the pathogenesis of COVID-19 and searched Medline, Scopus, Google Scholar, and Web of Sciences for the articles suggesting the role of pentoxifylline in many pathogenic pathways and consequences during infection with COVID-19.

The keywords used comprised pentoxifylline, Trental, Pentoxil, pentoxifylline SR, COVID-19, coronavirus, COV-19, treatment, therapy, antioxidant, anti TNF-a, anti-interleukin, anti-inflammatory, immunomodulatory, antifibrosis, oxygenation, bronchodilator, ARDS, and end-organ damage. All the relevant articles published from 1985 to 2020 were reviewed.

This review focused on the anti-oxidative, apoptosis-regulatory, anti-inflammatory, antifibrotic, antiviral, and oxygenation-circulation modulating activities of the medicine. Its preventive, protective, and therapeutic functions were also highlighted in ARDS, respiratory dysfunction and critical end organ damage.

3 | RESULTS

Certain beneficial properties of pentoxifylline can affect the pathogenesis of COVID-19 and its associated outcomes.

3.1 | Antiviral activities

The antiviral properties of pentoxifylline associated with its immunoregulatory effects have been frequently reported in literature. These activities are especially important for treating SARS, which resembles COVID-19 and confirms the hypothesis of this review.[4,9]

3.2 | Immunomodulatory and anti-inflammatory characteristics

Pentoxifylline increases the chemotoxicity and deformability of leukocytes, decreases their adhesion to the endothelium and activity of natural killer cells and contributes to the degranulation of neutrophils, release of super-oxides, production of monocyte-derived TNF, IL-1 induced leukocyte responses, IL-6, TNF-α and interferon-mediated responses and inhibits the activation of T and B lymphocytes. All these effects predict the potential benefits of this medication in the deregulation of apoptosis and cytokine storms, which exist in COVID-19.[5-7]

3.3 | Fibrinolytic and antifibrotic effects

Evidence shows fibrotic pathogenic events during systemic involvements in COVID-19, especially in the lung. The potential positive effects of pentoxifylline can be explained by its contribution to increasing collagenase in fibroblasts and decreasing the production of collagen, fibronectin and glycosaminoglycan, all of which can be modulated by its anti-TNF-α activities.[8,10]

3.4 | Bronchodilatory effects

The anti-inflammatory and bronchodilatory properties of pentoxifylline have been approved such that it is six times more potent than theophylline in terms of anti-inflammatory properties.[4]

3.5 | Vascular and hemorheological effects

As one of the first known medications for their key role in hemorheology, pentoxifylline increases erythrocyte deformability and decreases blood viscosity through increasing the levels of erythrocyte adenosine triphosphate and other cyclic nucleotides. Pentoxifylline inhibits thromboxane, increases prostacyclin synthesis, plasminogen activators, plasmin and antithrombin III and decreases platelet aggregation and adhesion, fibrinogen, alpha 2-antiplasmin, alpha-1 antitrypsin, alpha-2 macroglobulin, and the risk of thrombophilia. The increase in leukocyte deformability caused by pentoxifylline highlights the potential contribution of polymorphonuclear leukocytes to whole blood viscosity. As an almost completely rheological medication, pentoxifylline therefore increases blood flow to the affected microcirculation and enhances tissue oxygenation in patients with chronic peripheral arterial disease.[6,11]

3.6 | Protective effects in organ injuries

As the final fatal picture of COVID-19, organ failure, especially respiratory failure, requires in-depth investigation. Pentoxifylline constitutes a beneficial medication for ARDS and respiratory failure.[12,13] Research suggests the efficacy of pentoxifylline in improving end organ damage involving the heart,[14] the kidney,[15] the liver[16] and the brain.[17] Pentoxifylline helps more effectively control sepsis and lower its mortality in adults and neonates.[18,19]

4 | DISCUSSION

Despite the current unavailability of a gold standard for COVID-19 treatment, overwhelming evidence suggests the promising effects of immune modulators such as pentoxifylline on SARS-related coronavirus. As single or adjuvant therapies, pentoxifylline may is recommended for treating diseases associated with coronaviruses given

its mechanism of action that manifests itself as better circulation and oxygenation and its anti-inflammatory, anti-oxidative, apoptosis-regulatory, antiviral, immunomodulatory, and bronchodilatory properties, its accessibility as well as acceptable safety profile and cost effectiveness. Hypercoagulable states and microcirculatory dysfunction have been reported in COVID-19 patients even in skin biopsies on which pentoxifylline could adequately affect, as the main pharmacologic function of this medication.[4,20] Pentoxifylline is functionally classified as an immune modulator or immune booster rather than an immunosuppressive. This medicine can therefore be of great value in treating viral disorders. Pentoxifylline was also found effective in olfactory loss as a COVID-19 symptom.[21] Likewise, some recent studies have discussed pentoxifylline and COVID-19, but in a narrower aspect, which supports our hypothesis.[22,23]

5 | CONCLUSION

Pentoxifylline can be used as a multipurpose medication in a wide range of medical conditions. Many reports have shown the potential antiviral properties of pentoxifylline and its applicability to many circumstances encountered during the course of COVID-19, especially its positive role in controlling inflammation and the associated complications such as pulmonary fibrosis, ARDS, organ failure, primary cutaneous manifestations associated with COVID-19 and sepsis. Pentoxifylline can be therefore used as an adjuvant therapy for COVID-19 based on individual characteristics of patients, clinical considerations and contraindications.

Especially as an adjuvant therapy in combination with other medications, pentoxifylline can be considered a promising alternative for treating COVID-19 and preventing its complications given its main roles (better circulation-oxygenation) and the additional antiviral, anti-inflammatory, anti-oxidative, immunomodulatory roles and bronchodilatory effects, respiratory support, protective role in organ failure, accessibility, cost effectiveness and low toxicity. The anti-inflammatory properties of pentoxifylline and many other medications proposed for COVID-19 such as anti-TNF-α agents and tocilizumab as an anti-IL-6 agent help confirm the present study hypothesis. Immune modulators, especially non-immunosuppressive ones, can play a major role in treating viral disorders such as COVID-19 with less concern about the aggravation of viral infection itself.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest in this study.

AUTHOR CONTRIBUTIONS

The authors contribute equally to all stages of this study. The team has reviewed the manuscript and the data, and all contributors were in full agreement.

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