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Repositioning of pentoxifylline as an immunomodulator and regulator of the renin-angiotensin system in the treatment of COVID-19

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ABSTRACT

Pentoxifylline (PTX) is a phosphodiesterase inhibitor that increases cyclic adenosine monophosphate levels, which in turn activate protein kinase, leading to a reduction in the synthesis of proinflammatory cytokines to ultimately influence the renin-angiotensin system (RAS) in vitro by inhibiting angiotensin 1 receptor (AT1R) expression. The rheological, anti-inflammatory, and renin-angiotensin axis properties of PTX highlight this drug as a therapeutic treatment alternative for patients with COVID-19 by helping reduce the production of the inflammatory cytokines without deleterious effects on the immune system to delay viral clearance. Moreover, PTX can restore the balance of the immune response, reduce damage to the endothelium and alveolar epithelial cells, improve circulation, and prevent microvascular thrombosis. There is further evidence that PTX can improve ventilatory parameters. Therefore, we propose repositioning PTX in the treatment of COVID-19. The main advantage of repositioning PTX is that it is an affordable drug that is already available worldwide with an established safety profile, further offering the possibility of immediately analysing the result of its use and associated success rates. Another advantage is that PTX selectively reduces the concentration of TNF-α mRNA in cells, which, in the case of an acute infectious state such as COVID-19, would seem to offer a more strategic approach.

Background

The immune dysregulation observed in COVID-19 clinically translates into a secondary hemophagocytic syndrome or lymphohistiocytosis, acute respiratory distress syndrome (ARDS), and multiple organ failure. However, multiple studies have indicated that immunosuppression with corticosteroids impairs the immune response to various respiratory viruses as it affects the induction of antiviral interferon (IFN) type I. Therefore, the decision to immunosuppress a hospitalized patient with COVID-19 due to the possible benefits of reducing inflammation must be carefully weighed against the potential deleterious effect of delaying virus clearance or promoting bacterial superinfection. In addition to the adverse effects of immunosuppression therapy that further complicates the management of a hospitalized patient, the use of systemic steroids may worsen lung injury, which is particularly relevant in the case of treating patients with COVID-19.

Similar risks of perpetuating viral infection and bacterial or fungal superinfection must be considered when administering a drug that influences IFN-mediated signalling, including JAK inhibitors and interleukin (IL)-6 blockers, because the IL-6R-JAK-STAT3 signalling pathway is an essential component of the type I IFN pathway. Moreover, IL-6 can play an essential role in initiating the response against virus infections by promoting viral clearance by neutrophils; this was demonstrated in a study where deficiency of IL-6 or IL-6R in mice favoured the persistence of influenza infection leading to death in the experimental group.

Therefore, in the face of this global emergency that is witnessing rapid degeneration in patients’ clinical conditions toward more serious situations that can be overwhelming to primary physicians (despite the best standards of care), the opportunity to redirect medications offers an ethical and legal solution as medications outside of their usual indications can be prescribed as long as there is sufficient justification to do so.

Hypothesis

We here propose the repositioning of pentoxifylline (PTX) in the treatment of COVID-19. PTX is a phosphodiesterase (PDE) inhibitor that increases cyclic adenosine monophosphate (cAMP) levels, which in turn activate protein kinase (PKA), leading to a reduction in the synthesis of the proinflammatory cytokines IL-1, IL-6, and tumour necrosis factor-alpha (TNF-α). PTX has also been shown to influence the renin-angiotensin system (RAS) in vitro by inhibiting angiotensin 1 receptor (AT1R) expression. The effects of PTX on restoration of glutathione...
levels, maintenance of mitochondrial viability, inhibition of TNF-α production, and preservation of microvascular blood flow, along with reports of improvement in endothelial function and coagulation have encouraged its use in the treatment of neonatal sepsis, leading to a reduction in hospital stay and mortality. Moreover, in the context of COVID-19, PTX has shown evidence of improvement in experimental ARDS models.

Moreover, since it is a short-lived drug, the effect of PTX can be rapidly suppressed if severe adverse reactions arise due to excessive suppression of TNF-α. Furthermore, the rheological properties of PTX could be useful when faced with the atypical presentation of ARDS associated with COVID-19, characterized by marked hypoxemia with preservation of the ventilatory mechanics. This suggests that the loss of regulation of pulmonary perfusion and hypoxic vasoconstriction (vasoplegia) can be associated with microvascular obstructive inflammatory thrombus syndrome of the lungs (i.e., MicroCLOTS).

Overall, the rheological, anti-inflammatory, and renin-angiotensin axis properties of PTX highlight this drug as a therapeutic treatment alternative for patients with COVID-19, which can help reduce the production of the inflammatory cytokines TNF-α, IL-6, IFN-γ, and IL-17 and increase the anti-inflammatory cytokine IL-10.

PTX also favours restoring the balance of the immune response, reducing damage to the endothelium and alveolar epithelial cells, improving circulation, and avoiding microvascular thrombosis. Moreover, PTX decreases the neutrophil/lymphocyte ratio and restores the ratio of Treg/Th17 lymphocyte subpopulations. PTX decreases C-reactive protein (CRP), ferritin, lactic dehydrogenase, and D-dimer, with consequent improvement in the ventilatory parameters PaO2/FiO2 and SatO2.

In view of this evidence, it seems reasonable to reposition a drug with a proven safety profile and that is widely available as an alternative treatment of COVID-19 to reduce inflammation without the trade-off of conventional immunosuppression. Moreover, such repositioning avoids ethical or legal barriers allowing for immediate application in an acute setting.

**Evaluation of the hypothesis**

**SARS-CoV-2 and the RAS**

The SARS-CoV-2 spike protein (Spike S) binds only to human angiotensin-converting enzyme type 2 (ACE2) as a cell entry receptor [1]. This interaction partially explains why the lung is the organ most vulnerable to infection with SARS-CoV-2. Zhao et al. [2] demonstrated that 83% of the cells in the healthy lung tissue expressing ACE2 are type II alveolar epithelial cells (AECII cells), suggesting that these cells can serve as a reservoir for viral infection. Moreover, genetic analysis revealed that ACE2-expressing AECII cells have high levels of regulatory genes related to multiple viral processes, including the viral life cycle, assembly, and genome replication, further supporting that ACE2 expressed in AECII cells facilitates the replication of coronavirus in the lungs [2]. Similarly, other extrapulmonary tissues, including the heart, kidney, endothelium, and intestine, express ACE2 [3–7]. This broad distribution of ACE2 tissue expression could partially explain the multi-organ dysfunction seen in patients with severe SARS-CoV infection [8–10].

Compounding these effects, the coupling of S protein to its cell-binding site of ACE2 leads to the downregulation of ACE2, resulting in excess production of angiotensin (Ang) by angiotensin-converting enzyme (ACE). The reduction in ACE2 concentrations in turn decreases the production of the heptapeptide vasodilator or Ang1–7, which contributes to lung injury, since the stimulation of angiotensin type 1 receptors (AT1Rs) by Ang II increases the permeability of the pulmonary vasculature [11,12].

The RAS plays an essential role in maintaining blood pressure homeostasis, as well as in fluid and electrolyte balance [13–15], whereas ACE2 functions as a negative regulator of the RAS [3,16,17]. Specifically, ACE cleaves the Ang I decapetide into the Ang II octapeptide [13,14], ACE2 cleaves a single Ang I residue to generate Ang1–9 [16,17] and a single Ang II residue to produce Ang 1–7 [17], thereby negatively regulating RAS by inactivating Ang II [16].

Imai et al. [11] demonstrated that Ang II receptor subtypes are responsible for ACE/ACE2-regulated acute lung injury (ALI) based on experiments of a mouse model with genetic loss of AT1a receptor (Rat1a) expression, which showed markedly improved lung function and reduced oedema formation. Conversely, inactivation of the AT2 receptor (Rat2) was shown to aggravate ALI [15]. Moreover, they attempted to prevent ALI in the ACE2-knockout mice using RAT1- and RAT2-specific antagonists. Pharmacological inhibition of RAT1 attenuated the severity of acid-induced lung injury, whereas RAT2 inhibition had no apparent effect on the phenotypes of ALI in ACE2 knockout mice [11,15]. Collectively, these data show that Ang II–RAT1a interactions play a role in the development and severity of ALI [15]. ACE contributes to an increase in vascular permeability and a decrease in the survival of pneumocytes [18]. At the same time, Ang II is considered to function as a growth factor that regulates cell proliferation/apoptosis and fibrosis, as well as a mediator that attracts inflammatory cells to sites of tissue injury [19].

All of the evidence accumulated to date has led to the widely accepted belief that Ang II is the primary factor responsible for the exacerbation of lung tissue lesions through the activation of RAT1 (20–22). Similarly, Ang II exerts its fibrotic effects by inducing the production of transforming growth factor-beta 1 (TGF-β1), thereby triggering fibroblast proliferation and differentiation in collagen-secreting cells [23].

Accordingly, it would be reasonable to consider that dysregulation of the RAS could partially explain the observations made by a group of doctors in Italy that patients with COVID-19 pneumonia who meet the Berlin criteria of ARDS present an atypical form of ARDS. The main characteristic of these patients was a dissociation between their relatively well-preserved lung mechanics and the severity of hypoxemia. These doctors suggested that this disconnect may be explained by the loss of regulation of pulmonary perfusion and hypoxic vasoconstriction (i.e., vasoplegia) [24].

The obstructive inflammatory thrombus syndrome of the lungs that occurs in patients with COVID-19 could offer another explanation for this atypical presentation of ARDS involving inflammation of the endothelial vascular lesions, which may involve dysregulation of the RAS (i.e., MicroCLOTS) [25]. That is, the high concentration of ACE2 in the endothelial cells of the arteries, veins, and arterial smooth muscle cells favours viral replication along with secondary cell damage, consequently releasing alarms that are generated during cell death, thereby triggering the host’s innate immune response through various mechanisms, including activation of complement via lectin and alveolar macrophages through TNF-α and other mediators [25].

Complement activation would not only cause direct endothelial damage but also participate in leukocyte recruitment through C3a and C5a formation, leading to massive local production of the cytokines IL-1, IL-6, IL-8, and IFN-γ. Along with this massive host immune response, lymphocytes, resident macrophages, monocytes, and neutrophils perform their inflammatory functions, causing increased endothelial and alveolar epithelial cell damage and microvascular thrombosis, as reflected in elevations of lactic dehydrogenase and Dimer D [25]. This endothelial damage could be progressive and potentially involve the microvascular beds of the kidney, brain, and other organs [1].

An attractive alternative to deal with the COVID-19 pandemic, which may even be able to handle the emergence of new strains due to acquired mutations of SARS-CoV-2, is to search for agents that could block the activity of the AT1Rs [26] while simultaneously reducing the vascular injury mediated by Ang II characterized by inflammation and oxidative stress. Since nuclear factor-kappa B (NF-kB) is stimulated after the coupling of RAT1 and Ang II, it would be beneficial to activate
the expression of various cytokines such as TNF-α, IL-6, IL-8, MCP-1, and VCAM-1 by generating oxidative stress, altering endothelial nitric oxide, and inducing the activity of NADPH oxidase that increases the production of superoxide and peroxynitrite [27–30].

Therefore, increasing ACE2 expression through ATIR blockade [26] may affect viral replication and the release of useful viral materials. This would confer protection against the ALI generated by SARS-CoV-2 due to the counterbalance of the excess production of Ang II and its potentially harmful effects [18,26]. However, a limitation in the use of available ATIR blockers is the risk or potential of deleterious hemodynamic effects of arterial hypotension [26]. Although there is currently a lack of detailed information on hypotension rates among hospitalized patients with SARS-CoV-2 during this pandemic [26], Yu and colleagues [31] reported that half of the patients with SARS-CoV infection developed hypotension during their hospitalization.

In this regard, PTX, as the drug we are considering repositioning for COVID-19 treatment, has shown ATR blocking effects in experimental studies, along with clinical evidence in humans showing no secondary effect on blood pressure [32–34].

**Inflammation and the immune response in COVID-19**

All available reports and anecdotal information indicate that the pathological process contributing to severe cases of COVID-19 is largely related to dysregulation of the immune system owing to a storm of cytokine production, characterized by increased expression levels of inflammatory cytokines and chemokines with a concomitant decrease in naive CD4 + T cells, CD8 + T cells, and regulatory T cells (Tregs) [36,37]. These findings may be related to previous descriptions of an association of higher levels of serum inflammatory cytokines with extensive lung damage in patients with other coronavirus infections in addition to SARS-CoV-2, including SARS-CoV and MERS-CoV [36]. This is due to induction of the production of large amounts of chemokines and cytokines (IL-1β, IL-1RA, IL-7, IL-8, IL-10, basic FGF2, GCSF, GMCSF, IFN-γ, IP10/MCP1, MIP1α, MIP1β, PDGFB, TNF-α, and VEGF). Similarly, patients admitted to the intensive care unit showed high levels of proinflammatory cytokines, including IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP1α, and TNF-α.

In another study [44], the viral load of SARS-CoV-2 in serum (RNAemia) was positive only in critically ill patients with more severe lymphopenia and a higher number of neutrophils, and the degree of RNAemia was positively correlated with both IL-6 levels and the mortality rate. Notably, the authors acknowledged that they did not measure other cytokines due to the lack of available reagents; however, this association of RNAemia with disease severity suggests a correlation with other inflammatory markers [44]. This possibility is particularly relevant given our suggestion of not limiting immunomodulatory strategies in the treatment of COVID-19 to the current trend of focusing on the IL-6R JAK-STAT3 pathway, whose cost-benefit analysis would also be questionable.

Xu et al. [39] documented the characteristics of a patient in China who died of severe SARS-CoV-2 infection, indicating substantial reduction in CD4 + and CD8 + T-cell counts. They also found that these cells were overactive, showing high proportions of HLA−DR (CD4 3–47%) and CD38 (CD8 39.4%) double-positive fractions and a high concentration of pro-inflammatory CD4 + CCR6 + Th17 cells [39]. Furthermore, this patient had high concentrations of cytotoxic granules, which is another marker of hyperactive CD8 + T cells, 31.6% of which were perforin-positive, 64.2% were granulysin-positive, and 30.5% were both perforin- and granulysin-positive. This dysregulation of the immune system clinically manifests as respiratory failure with extensive lung damage, which is histopathologically related to the massive infiltration of neutrophils and macrophages, diffuse alveolar damage with the formation of hyaline membranes, and diffuse thickening of the alveolar wall [39,42]. In addition to the pathological findings of patients who died from SARS-CoV-2 infection, splenic atrophy and necrosis of the lymph nodes have been observed, further suggesting the progression to shock and multiple organ failure due to tissue damage to the heart, liver, and kidneys [35,39].

Dysregulation of the immune response in COVID-19 involves an immunosuppression stage with a subsequent inflammatory state characterized by a substantial reduction in peripheral lymphocyte counts that is correlated with disease severity [45]. As CD4 + and CD8 + T cells are the most affected subpopulations in this process, the immune
response to the virus is consequently compromised, thereby increasing the risk of bacterial superinfection [46,47]. Although the detailed mechanism underlying the pathogenesis of lymphopenia is not fully understood, one of the pathways involved in lymphopenia induced by respiratory viral infections is cell death triggered by activation of the Fas–Fas-ligand interaction, as well as induction of the apoptosis axis from TNF-α ligands [47–49].

Overall, these compounding effects of SARS-CoV-2 infection on the immune response and inflammation lead to the conclusion that it is necessary to search for appropriate immunomodulatory strategies to dampen inflammatory responses without simultaneously suppressing the immune response to avoid any deleterious effects. In this regard, in 2003, Bermejo et al. [50] suggested the use of PTX for the treatment of SARS-CoV infection due to its anti-inflammatory effect by reducing TNF-α and IFN-γ. This proposal was further based on the ability of PTX to regulate activation of the transcription factors NF-κB and NFAT and to inhibit various viruses such as herpes simplex virus, human immunodeficiency virus, tick-borne encephalitis virus, and rotavirus in cell cultures. With this background, in 2006, Barnard et al. [51] tested the effects of PTX on the replication of SARS-CoV in vitro and in a mouse model of experimental infection. Although they found no effective inhibition of SARS-CoV replication in vitro, PTX showed a weak effect in inhibiting the replication of the virus in the lungs of mice, albeit without statistical significance.

Justification of the hypothesis: role of PTX in inflammation, the RAS, and oxidative stress demonstrating potential for Covid-19 treatment

PTX is a drug with multifactorial action, including PDE inhibition [52] and increasing cAMP levels, which in turn activate PKA [53], leading to a reduction in the synthesis of the inflammatory cytokines IL-1, IL-6, and TNF-α [52–54]. These inhibitory effects on PDEs result in an overall reduction of inflammation [54,55]. Similarly, PTX modulates IFN-γ [56–58] and other molecules such as intracellular adhesion molecule type 1 (ICAM-1), vascular cellular adhesion molecule type 1 (VCAM-1), and CRP [59,60].

Based on these foundations, several models of kidney disease and clinical studies have shown that PTX is capable of attenuating proteinuria through modulating inflammatory cytokines [61–69]. In addition, clinical trials with diabetic nephropathy patients demonstrated that PTX enhanced the antiproteinuric effect of angiotensin receptor blockade [70,71]. The effect of PTX on the RAS appears to be primarily related to its inhibition of AT1R expression. This speculation was supported by studies using a rat model of heart failure induced by coronary artery ligation, in which PTX infusion to the paraventricular hypothalamic nucleus attenuated the increase in AT1R expression [32] and PTX treatment could prevent the overexpression of AT1R mRNA [33]. In addition, Azhar and El-Bassossy [72] showed that PTX significantly decreased AT1R expression in the aortic tissue in a rat model of metabolic syndrome, and counteracted the induced hypertension by reducing the degree of inflammation, based on significantly lower levels of TNF-α and higher levels of the anti-inflammatory cytokine adiponectin.

Further, PTX shows promise as a useful therapeutic tool for COVID-19 because the RAS is one of the most critical systems activated during oxidative stress. Upon binding of Ang II with AT1Rs, the secondary messengers inositol triphosphate and diacylglycerol are produced, resulting in the production of reactive oxygen and vasoconstriction [73].

A meta-analysis showed that PTX had an anti-inflammatory effect in adults with a variety of disorders, including coronary artery disease, type 2 diabetes mellitus, idiopathic or ischemic cardiomyopathy, and chronic kidney disease. The statistically significant differences were corroborated by a reduction in plasma concentrations of TNF-α and CRP and no deleterious effects on blood pressure [34].

From a practical perspective to reposition PTX for COVID-19, Li et al. [74] proposed using PTX as a treatment strategy for ARDS in 2016 based on its ability to specifically interfere with cAMP signalling [24]. Considering that an increase in both Tregs and Th lymphocytes producing interleukin IL-17 (Th17 cells) along with an imbalance of the Treg/Th17 ratio are among the main immune alterations observed in ARDS [75–80], targeting cAMP signalling is a reasonable strategy to induce immune tolerance. In particular, cAMP signalling plays a critical role in the proliferation and function of Tregs and effector T cells; that is, cAMP suppresses the adaptive differentiation of Tregs mediated by TGF-β1 to reduce the Treg content [81,82]. Using a mouse model of cecal ligation and puncture-induced ARDS, Li et al. [74] demonstrated that PTX pre-treatment attenuated lung injury and reduced the mortality rate. The authors further observed an increase in the cAMP levels of the spleens of the PTX-prefreated mice, whereas the number of Tregs and Th17 cells decreased. More interestingly, overexpression of STAT3, which is required for Th17 differentiation, restored the Treg/Th17 ratio, accompanied by a decrease in IL-2, IL-6, IL-10, and IL-17 levels, and significant inhibition of the expression of Foxp3 and RORγt [74]. Considering that these transcription factors are essential regulators of the differentiation and function of Tregs/Th17 cells [82,83], Li and colleagues concluded that PTX-induced increases in CAMP might have partially restored the Treg/Th17 balance by modulating Foxp3 and RORγt transcription through the STAT3 pathway. Therefore, regulating the Treg/Th17 balance and the subsequent immune response through cAMP signalling was proposed as a feasible treatment strategy for ARDS [74].

Moreover, PTX was shown to inhibit TNF-α production by alveolar macrophages [84,85]. Because pulmonary sarcoidosis is a chronic inflammatory disease, interactions between an antigen-presenting cell and an unknown antigen are perceived by naïve CD4+ lymphocytes (Th0 cells) and alveolar macrophages, leading to the activation and proliferation of both cell types and the consequent release of IL-2, TNF-α, and IFN-γ [86]. In support of these effects, adding PTX to a systemic steroid regimen allowed for a steroid dose reduction [87]. Park et al. [88] confirmed this steroid-sparing effect of PTX in a randomized controlled clinical trial in patients with pulmonary sarcoidosis, in which PTX improved the pulmonary diffusion of carbon monoxide and arterial blood oxygen pressure during exercise, especially in patients who were naive to steroid treatment.

In addition to these anti-inflammatory properties, PTX has also been reported to suppress tissue fibrosis by blocking TGF-β1 and preventing the deposition of type I collagen [89,90]. Several in vitro studies have shown that PTX inhibits fibroblast proliferation and extracellular matrix production [91–93], and a clinical study demonstrated that administration of PTX to obese patients decreased the plasma levels of plasminogen activator inhibitor-1 (PAI-1) [94]. These findings motivated Lee and colleagues [95] to test the effect of PTX administration in an experimental model of radiation-induced pulmonary fibrosis in rats, and found a decrease in the expression levels of both fibronectin and PAI-1. This was considered to be particularly relevant in light of evidence that PAI-1 expression is elevated in fibrotic pathological conditions. Indeed, PAI-1 contributes to a reduction in fibrinolysis rates and a subsequent decrease in the degradation of components of the extracellular matrix, including fibronectin, leading to tissue fibrosis [96]. Since there are no clinical guidelines for the management of pulmonary fibrosis, PTX is currently recommended for the prevention and treatment of this condition [97]. Moreover, PTX was shown to prevent the development of pneumonitis in patients with breast and lung cancers [98,99].

Taken together, the evidence highlighted herein strongly points to the benefits of redirecting PTX as an ethical and legal attempt in the treatment of COVID-19, which can help support patients in critical care and overwhelmed hospital resources in the face of this pandemic.
Declaration of conflicts of interest

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers’ bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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