Pentoxifylline and Covid-19: A Systematic Review

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Citation

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Abstract

At more than 10 months after the first case of COVID-19 was documented, the understanding of the pathogenesis of this viral illness is growing on a daily basis. A massive pro-inflammatory response on infected individuals involving several cytokines seems to play a key role on disease. As a result, therapeutic efforts have focused on anti-inflammatory strategies to ameliorate the disease, in sight of a lack of a truly effective anti-viral agent. Pentoxifylline (PTX) has been proposed by multiple authors as a potential therapeutic ally, targeting a variety of mechanisms as it has been shown to have antiviral, anti-inflammatory and hemodynamic effects. Importantly, anti-inflammatory effects center on down-regulation of cytokines such as interleukins and tumor necrosis factor. In pre-pandemic studies, PTX has demonstrated to change the clinical course of inflammatory diseases such as acute respiratory distress syndrome, which is a hallmark of severe COVID-19. Researchers agree it is pertinent to experimentally evaluate the effect this drug has on COVID-19 patients. The objective of this review is to summarize all the proposed mechanisms by which PTX may aid in the treatment of COVID-19, as well as prevent its deadly complications. Our interpretation of the literature is that the benefits PTX may bring to a patient with COVID-19 outweigh the risks this drug might pose on them. As a result, there is consensus regarding the evaluation of PTX in further experimental studies to better characterize its effects on COVID-19 patients.

INTRODUCTION

In late 2019, the Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China, presumably as a zoonotic infection originating from bats.(1) This virus, which causes the coronavirus disease 19 (COVID-19), rapidly expanded worldwide, as travel restrictions failed to optimally control the spread. As of January 21st, the first case of COVID-19 was identified in the United States. Recent experience with viral respiratory epidemics with similar characteristics was limited to SARS and MERS outbreaks, as well as the 2009 H1N1 pandemic. However, it has a slightly higher rate of transmission than these viruses, and shares almost 80% of its genome with SARS-CoV.(1,2) As major pharmaceutical companies and research efforts race to find an effective therapeutic agent, many anti-viral medications were quickly tested and discarded from the list of potential medications with the exception of remdesivir, which has demonstrated a reduction in symptom duration, but is still reserved for severe cases. (3). It has been well described that a subset of patients may develop coagulopathy, as a result of the cytokine storm mediated amid an aggressive inflammatory response to the SARS-CoV-2, ultimately leading to complications like acute respiratory distress syndrome (ARDS).(4) As a result, investigators have proposed alternative drugs with multiple mechanisms of action in light of finding a lower rate of complications from this disease, and potentially lower the mortality. Pentoxifylline (PTX) is a methylxanthine derivative, currently used for peripheral vascular disease, with anti-inflammatory and immunomodulatory properties(5–7). Moreover, the main pharmacodynamic properties of this drug are aimed at improving circulation by increasing erythrocyte deformability.(8) Additionally, a safe side effect profile, and a low cost make PTX a strong candidate to be considered as an aid in the treatment for high risk COVID-19 patients. This drug was initially proposed as an alternative treatment for the SARS outbreak in 2003. Subsequently, there has been some attention to this drug as the COVID-19 pandemic began to spread. Accordingly, no published study has analyzed the clinical impact of utilizing this drug as a potential therapeutic agent. The purpose of this study is to systematically gather all the latest evidence on pentoxifylline as a potential treatment for COVID-19 and analyze the feasibility of further trials as well as trends in treatment strategies.

METHODS

Currently, no systematic review of the literature looking at the use of pentoxifylline as a potential treatment for COVID-19 has been published. The PROSPERO database was revised, and no study of this characteristics was found. We sought to identify all scientific literature analyzing the potential benefits of pentoxifylline against COVID-19. We queried Pubmed and Google scholar search engines utilizing the following commands: (Pentoxifylline AND COVID), (Pentoxifylline AND Coronavirus), and (Pentoxifylline AND SARS). For obvious reasons, only publications from 2020 were considered. There was no language limitation. Only published manuscripts were eligible. Information regarding potential mechanisms of action of Pentoxifylline against COVID-19 and its complications was extracted. This systematic review is structured using the PRISMA guidelines.

RESULTS

A total of 11 studies were found using the described methodology. One study which was a clinical trial proposal preprint was excluded. We identified a total of 8 research items eligible for our review which are summarized in table 1. No experimental study was found.

Table 1

Summary of articles proposing pentoxifylline as a potential treatment strategy for COVID-19 patients. PDE-4: Phosphodiesterase-4, TNF-: Tumor Necrosis Factor alpha, TNF-: Tumor Necrosis Factor beta, DIP: Dipyridamole, IL-1: Interleukin-1, IL-1b: Interleukin-1 beta, IL-6: Interleukin-6, IL-8: Interleukin-8, IL-10: Interleukin-10, NF-: Nuclear Factor kappa beta, ICAM-1: Intercellular adhesion molecule 1, VCAM-1: Vascular cell adhesion molecule 1, NFAT: Nuclear factor of activated T-cells, MCP-1: Monocyte Chemoattractant Protein-1, PAI-1: Plasminogen activator inhibitor-1, TGF- 1: Transforming growth factor beta 1, IFN-y: Interferon gamma, CRP: C-reactive protein, AT1R: Angiotensin II type 1 receptor, A2AR: Adenosine A2A receptor, STAT3: Signal transducer and activator of transcription 3

Title	Author	Relevant proposed mechanism:	Conclusion:	Favors the use of PTX?
COVID-19: Older drugs for a novel disease—Chloroquine, hydroxychloroquine, and possible Pentoxifylline (9)	Pugazhenthan Thangaraju	PDE-4 inhibition. Down regulation of NF kappa B and NFAT transcription factors.	The anti-inflammatory and immunomodulatory actions of pentoxifylline could play an important role in the treatment of the respiratory distress due to the COVID 19.	Yes
COVID-19: Pentoxifylline as a potential adjuvant treatment (10)	Amir Feily	PDE-4 inhibition. Suppression of TNF- α and modulation of inflammatory cytokines.	Pentoxifylline, with its potent anti-inflammatory effects and therapeutic effect on pulmonary fibrosis, can be a potential adjuvant treatment against COVID-19.	Yes
Harnessing adenosine A2A receptors as a strategy for suppressing the lung inflammation and thrombotic complications of COVID-19: Potential of pentoxifylline and dipyridamole (2)	DiNicolantonio	Potentiation of the responsiveness of A2AR receptor (A2AR) to adenosine.	PTX and DIP potentiate the signaling activity of extracellular adenosine and increase extracellular levels of adenosine respectively. The use of PTX with DIP can be used in advanced COVID-19, making them a possibility to improve outcomes in these patients.	Yes
Pentoxifylline is a potential cytokine modulator therapeutic in COVID-19 patients (11)	Hendry	PDE-4 inhibition. Down-regulation of TNF- α, IL1b, IL6, FN gamma, ICAM1, and VCAM1. Down-regulation A2AR.	Pentoxifylline has anti-inflammatory properties, including down regulation of TNF- α, IL-1b, IL-6 and other cytokines. This can reduce lung damage in patients with COVID-19.	Yes
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 (12)	Gonzalez-Pacheco	Suppression of TNF- α, IL-1b, IL-6, IL-8, and CRP production. Increase in levels of IL-10. Inhibition of T cell and natural killer cell cytotoxicity. Inhibition of surface expression of intracellular adhesion molecule 1 and the production of IL-8 and monocyte chemoattractant protein-1. Suppression of neutrophil activation. Reduction of plasma fibrinogen.	PTX has 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. This suggests it could be a valuable adjuvant treatment in patients with COVID-19.	Yes
Repositioning of pentoxifylline as an immunomodulator and regulator of the renin-angiotensin system in the treatment of COVID-19. (13)	Maldonado	PDE inhibition. Modulation of IFN- γ, ICAM-1, VCAM, CRP and AT1R. Inhibition of TNF- α production by alveolar macrophages. Blockage of TGF-b1 and prevention of type-1 collagen deposition. Decrease in expression levels of fibronectin and PAI-1	Various mechanisms of PTX are potential targets to treat COVID-19. It's anti-inflammatory properties, along with its mechanism to regulate fibrosis and modulate the renin-angiotensin-aldosterone syndrome make this drug a reasonable and ethical candidate for attempting a new treatment strategy.	Yes
Treatment of COVID-19 with pentoxifylline: Could it be a potential adjuvant therapy? (14)	Seirafianpour	PDE-4 inhibition. Decreases leukocyte adhesion to the endothelium. Inhibition of activity of T and B lymphocytes. Increase in collagenase in fibroblasts. Decrease in production of collagen, fibronectin and glycosaminoglycan. Increase in prostacyclin synthesis, plasminogen activators, plasmin and antithrombin. Decrease in fibrinogen, platelet aggregation, α2-antiplasmin, α1 antitrypsin, and α2 macroglobulin and thromboxane.	PTX is efficient in improving end organ damage involving the heart, kidney, liver, and brain. PTX helps control sepsis and lower its mortality in adults. PTX is functionally classified as an immune modulator or immune booster rather than an immunosuppressive, which is very helpful in the case of COVID-19 infection.	Yes
Pentoxifylline: An Immunomodulatory Drug for the Treatment of COVID-19 (15)	Dhamsiya	Inhibit the actions of PDE, IL-1, TNF-α, and TNF-β, NF-αβ. Reduces expression of ICAM-1, IL-8 and MCP-1	PTX reduces cytokine production, immune cell migration, and suppress signal transduction pathways, minimizing inflammatory damage in the lung tissues.	Yes

DISCUSSION

COVID-19 illness is a virus-mediated syndrome which may develop a host cytokine storm. This pro-inflammatory response plays a key role in the damage viral infections cause on a host and may correlate with worse outcomes. There is growing evidence suggesting a subset of these patients are at risk of developing devastating complications such as myocarditis, acute respiratory distress syndrome (ARDS), acute kidney injury, and coagulopathy, among others. These complications are associated with a significant rate of morbidity and mortality, especially in patients with

comorbidities, non-white race or in poverty. (16–19)

Attempts to find an effective antiviral drug have been futile. The conventional antiviral drug, remdesivir seems to have a potential benefit, although there is mixed evidence regarding its effectiveness in reducing mortality and length of stay. (3,20) It has been shown that most of the dangerous complications are due to an overt inflammatory response by the host, rather than viral cytotoxicity by itself. A certain degree of inflammation is necessary to eliminate any kind of infection. However, it has been shown that persistent elevations of pro-inflammatory cytokines are associated with worst outcomes in patients with ARDS. (21) SARS-CoV-2 induces excessive and prolonged cytokine responses in some individuals, known as the cytokine storm. It is this exaggerated response, that may trigger multiple organ dysfunction. (4) As a result, immunomodulatory and anti-inflammatory drugs have received attention as potential mitigators of severe COVID-19.

Some specific drugs immune modulator drugs with diverse mechanisms of action have the ability to attenuate the cytokine storm. Particularly, steroids such as dexamethasone, and interleukin antagonists like tocilizumab, and anakinra, among others, have received attention as treatment strategies for the hyperinflammatory response. (22,23) A recent study by the RECOVERY collaborative group, found a mortality reduction of 17% in the treatment arm with daily 6mg of dexamethasone for 10 days in hospitalized COVID-19 patients. (24)

Pentoxifylline has demonstrated anti-inflammatory, anti-thrombotic, immunomodulatory, hemodynamic, and antiviral properties which makes it a valuable candidate for consideration as alternative or complementary treatment for patients with moderate to severe symptoms. Modulation of TNF- , IL1, IL6, ICAM1, VCAM1 and TNF, as well as inactivation of PDE and prevention of platelet aggregation are among the proposed mechanisms that could aid as treatment options for moderate to severe COVID-19 patients.(5,6,8,13,25,26) PTX has proven to be useful in patients with ARDS, from different etiologies and to improve pulmonary function and control pulmonary fibrosis. (27–29), Furthermore, the potential of pentoxifylline as a therapeutic agent is warranted as there is little to no downside in using this drug because of a safe adverse effect profile and a low cost.

Amid an urge for an effective treatment with a positive effect on morbidity and mortality, hundreds of drugs have been proposed as treatment strategies. This review summarizes the best available evidence showing potential benefits of using PTX as a broad-spectrum treatment mainly aimed at preventing and treating the pro-inflammatory complications of COVID-19. Limitations in our study include that no statistical analysis could be made, as no tangible evidence has been published to date.

CONCLUSION

Our interpretation of the available literature is that there is ample evidence suggesting a wide portfolio of mechanisms through which PTX may be beneficial in the treatment of COVID-19. As a result, we believe PTX has a well-suited profile to prevent and treat potential COVID-19-associated complications. Moreover, it's low cost and minimal adverse effects make it a safe drug to consider for pilot clinical trial studies. We encourage researchers to study the clinical benefit of this drug in moderate to severe COVID-19 patients.

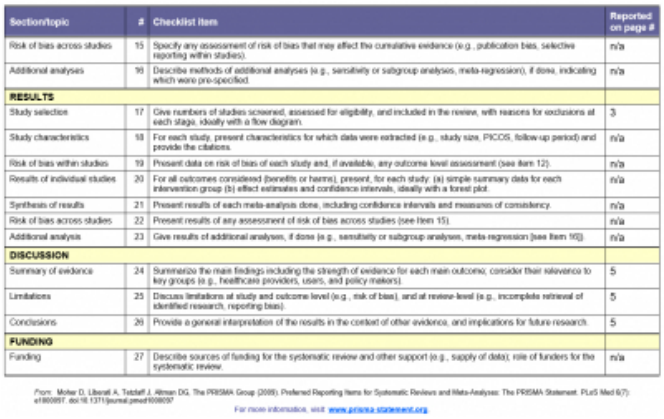
Table 2

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	n/a
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	n/a
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	n/a
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	n/a
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	n/a
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	n/a

Table 2b

PRISMA 2009 Checklist



Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	n/a
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	3
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	n/a
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	n/a
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	n/a
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	n/a
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	n/a
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	n/a
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	5
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	5
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	5
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	n/a

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org

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