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Research Article

Selective COX-2 Inhibitors --- A Valuable Tool for COVID-19 Management

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Abstract

Cyclooxygenase 2 (COX-2) is highly induced during coronavirus (COVID-19) infection. We believe selective COX-2 inhibition shall be a valuable tool to reduce virus toxicity in related patients. Dexamethasone, one of potent selective COX-2 inhibitors, has been used successfully in the standard care for patients with COVID-19. Given that low-dose dexamethasone inhibits thrombosis, reduces the death rate by one-third in patients with severe COVID, and is in the same dose range for effective COX-2 inhibition, we believe that vascular COX-2 is coupled to thrombosis and it is critical to selectively inhibit COX-2 to avoid tissue damage and death in patients. We should take efforts to replace dexamethasone with non-steroidal selective COX-2 inhibitors such as celecoxib (Celebrex) and etoricoxib (Arcoxia) to avoid steroidal side effects. For detailed *in vivo* COX-2 analysis in the vasculature and other organs, we should leverage tools such as conditional knockout animal models to avoid cardiovascular congestion caused by renal COX-2 disruption. Detailed preclinic and clinic studies will help to develop selective COX-2 inhibition therapies for consistent applications across the population.

Keywords

COVID, COX-2, Celebrex, Celecoxib, Dexamethasone, Thrombosis, Conditional Knockout

1. Introduction

The coronavirus (COVID-19) pandemic has plagued the world for years [1]. The virus mutates rapidly, indicating that structure-based approaches such as vaccines, antibodies, and anti-viral medicines may lose effectiveness over time [2]. A suitable tool, independent of viral structure, is needed to afford prolonged efficacy for pandemic management. In addition, oral therapeutic agents are preferred, given advantages such as non-invasiveness and convenience of drug administration [3].

We propose to use selective cyclooxygenase-2 (COX-2) inhibitors to manage the COVID pandemic. Although some pilot studies have shown the value of this drug class in treating patients with COVID, additional preclinical and clinical studies are needed to establish its role in the standard care for patients with COVID-19. Detailed molecular studies will help to clarify related mechanisms in tissue and time specific manners in order to optimize the therapeutic strategies. We would like to gain more interest from the medical community to move forward on related research and implementations.

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2. Discussion and Analysis

For COVID-19 infections, one common finding has been the strong induction of COX-2 gene expression in patients [4, 5]. Furthermore, patients with COVID-19 frequently experience pain [6]. COX-2 expression is well correlated with pain in many organs [7]. Based on these observations, COX-2 should be significantly involved in pathophysiology of COVID-19 infection [8]. Especially thrombosis has been frequently documented in COVID-19 infection and contributes significantly to mortality and morbidity [9]. Under *ex vivo* settings, coupling of vascular COX-2 and prothrombotic prostaglandins, such as thromboxane, has been discovered [10, 11], and COX-2 inhibition using celecoxib caused potent vasodilation [12]. The coupling of vascular COX-2 and thrombosis has been further confirmed *in vivo* using dexamethasone, as discussed below. If thrombosis in patients with COVID-19 is related to COX-2 induction, selective COX-2 inhibition should afford critical protection to patients from virus-induced vascular injury. Given that selective COX-2 inhibitors are not based on viral structures [13], they should afford prolonged effectiveness even if the virus mutates rapidly.

Dexamethasone, one of highly potent selective inhibitors of COX-2 [14], has been used to reduce mortality in patients with severe COVID-19 [15]. "Selectively inhibiting COX-2 [16] to reduce mortality" has been validated and utilized to provide standard care for patients with COVID-19 via dexamethasone.

Prostaglandins, the products of cyclooxygenase, can effectively modulate blood flow and thrombosis [17]. Notable, different prostaglandins antagonize each other in terms of thrombosis [18]. For example, thromboxane A_2 (TXA_2) promotes thrombosis, whereas prostacyclin (PGI_2) can prevent thrombosis. In patients with COVID-19, COX-2 expression is highly induced by the virus, and patients are prone to vascular thrombotic attacks. If vascular COX-2 is coupled to anti-thrombotic prostaglandins such as PGI_2, selective COX-2 inhibition by dexamethasone should precipitate thrombosis and increase mortality rate, which is totally opposite to our observations in dexamethasone-treated patients with COVID-19. The success of dexamethasone (with 100% selectivity for COX-2 inhibition and no COX-1 inhibition at all [14]) in COVID therapy strongly suggests that vascular COX-2 is coupled to prothrombotic prostaglandins *in vivo* and selective COX-2 inhibition can stabilize vascular homeostasis in patients with COVID-19.

Indeed, low-dose dexamethasone treatment inhibits arterial thrombosis [19]. It correlates well with the fact that dexamethasone inhibits COX-2 at very low concentrations (IC_{50} = 0.0073 μM) [14]. In terms of COX-2 selectivity and thrombosis, this is a solid evidence that selective COX-2 inhibition prevents thrombosis *in vivo* (dexamethasone has no effects on COX-1 inhibition at all. [14]). In other words, vascular COX-2 is coupled to thrombosis, and following the intense induction of COX-2 by severe acute respiratory syndrome coronavirus 2(COVID-19) [4], the prothrombotic products of COX-2 will attack the vasculature to precipitate thrombosis, resulting in local organ damage and even patient death. Selective COX-2 inhibition should protect the vasculature in related patients. For example, in one study, the selective COX-2 inhibitor-treated group showed a 90% reduction in hospitalization rate [20].

Systemic anticoagulation has been found to significantly improve survival in mechanically ventilated patients with COVID-19 [21]. Accordingly, low-dose dexamethasone has been shown to reduce death by one-third in ventilated patients with COVID-19 [22].

Given the exclusive COX-2 selectivity of dexamethasone [14], selective nonsteroidal COX-2 inhibitors such as celecoxib, rather than non-selective COX-1/COX-2 inhibitors [23, 24] should be considered for replacing dexamethasone to avoid widespread corticosteroid side effects [19, 25].

For example, a pilot study has shown that treatment with celecoxib and famotidine blocked 100% of COVID-19 deaths [26]. In addition, adjuvant treatment with celecoxib has been shown to facilitate the recovery of all types of patients with COVID-19 and further reduce the mortality rate among the elderly and those with comorbidities [27, 28].

Since celecoxib mainly acts by inhibiting COX-2, blockade of COX-2 activity by other agents such as dexamethasone would conceal the benefits of celecoxib. Accordingly, the use of dexamethasone in the treatment group should be excluded in future studies assessing selective COX-2 inhibition treatments for COVID-19 patients [26]. One possible main mechanism for celecoxib-mediated benefits in COVID-19 involves the blockade of vascular thrombosis; however, if thrombosis in the control group is managed by using drugs such as heparin, treatment with celecoxib may appear less beneficial when comparing clinical outcomes from the control group receiving heparin. Clinical trials should be precisely designed to avoid overlapping factors for related biological processes (COX-2 and thrombosis inhibition) to demonstrate the benefits of selective COX-2 inhibition when compared with the control group [29].

Dexamethasone exhibits exclusive selectivity toward COX-2 [14]. However, celecoxib demonstrates only 10-20-fold selectivity toward COX-2 inhibition when compared with COX-1 inhibition [30-32]. Accordingly, instead of celecoxib, a more selective non-steroidal COX-2 inhibitor may afford more benefits in patients with COVID-19.

Notably, the suspicion of celecoxib-induced cardiovascular complications has been dismissed based on findings of the PRECISION study: celecoxib was found to be non-inferior to ibuprofen or naproxen, considering cardiovascular safety [33]. However, long-term COX-2 inhibition may cause cardiovascular congestion owing to salt and water retention [34]. Hence, diuretics may be beneficial to alleviate related symptoms.

It is well-known that the cardiovascular system is regulated by vasculature, the kidneys, the nerve system, and other factors. *In vivo* vascular COX-2 research has been complicated,

especially by cardiovascular congestion caused by COX-2 inhibition/deletion in the kidneys. Mitigating the cardiovascular congestion should unveil many benefits of vascular COX-2 inhibition *in vivo*.

For example, COX-2 inhibitors can decrease blood pressure significantly in patients with furosemide-like salt loss. The authors found that all patients exhibited increased blood pressure during the drug withdrawal period. This finding indicates that the actual blood pressure is considerably lower in the same patients under rofecoxib treatment than after drug discontinuation [35]. Based on the principle that blood pressure is regulated by cardiac output and peripheral vascular resistance [36], the data suggest that rofecoxib causes potent vasodilation, at least in arterioles. The result aligns well with the *ex vivo* finding, suggesting that vascular COX-2 couples with vasoconstriction/thrombosis [12].

If a consensus regarding vascular COX-2 coupling with thrombosis cannot be reached, the use of transgenic animal models, such as conditional knockout [37], will be considered to demonstrate tissue and time-specific effects of COX-2 *in vivo*. Exon 8 of COX-2 should be targeted for murine models, as it has been previously demonstrated to disrupt COX-2 function *in vivo* [38]. With conditional knockout techniques, we should preserve COX-2 functions in kidneys to avoid renal failure, while deleting the gene specifically in organs of interest, such as vasculature. By doing so, we can avoid the interference of cardiovascular congestion on vascular COX-2 analysis. The conditional knockout model will not only help us to understand and confirm the roles of COX-2 in vascular homeostasis (vascular COX-2 knockout) but also help to clarify the roles of COX-2 in immune regulation (immune system COX-2 knockout) and other biological processes under COVID-induced assaults at different stages of virus infection [6].

A detailed study of the *in vivo* mechanism will help us to identify how COX-2 inhibition is involved in the disease process, thereby allowing the recognition of other drugs that mediate different pathways and afford synergistic combination effects for disease management [39]. For example, if we confirm that vascular COX-2 inhibition prevents thrombosis, the need for another anticoagulant reagent should be significantly diminished. Conversely, if we identify a specific anticoagulant that acts on a different pathway for thrombosis formation, combining it with selective COX-2 inhibitors would achieve substantial synergistic effects on thrombosis prevention, if needed. Moreover, detailed pharmacologic studies will establish the optimal timing and dosing of related medications.

Clarifying how vascular COX-2 is coupled to thrombosis *in vivo* would be of considerable scientific interest too. It is intriguing to explore how COX-2 inhibition may modulate platelets, tissue factors, vascular endothelium, vascular smooth muscle and other things for vascular homeostasis [40].

3. Summary

Detailed preclinical and clinical studies are needed to analyze related mechanisms and formulate selective COX-2 inhibition COVID therapies for consistent application across the population. Comparing steroidal COX-2 inhibitors (e.g., dexamethasone) versus non-steroidal selective COX-2 inhibitors and oral COX-2 inhibitors versus intravenous agents (e.g., heparin) for thrombosis management, selective COX-2 inhibitors appear to be an attractive option.

If COVID-related mortality can be reduced to the same level or lower than that observed with the flu, the severity of this pandemic will be dramatically reduced [41], markedly reducing its social burden.

Abbreviations

COX-2	Cyclooxygenase-2
COVID	Coronavirus Disease

Conflicts of Interest

The authors declare no conflicts of interest.

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