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COX2 inhibition in the treatment of COVID-19: Review of literature to propose repositioning of celecoxib for randomized controlled studies

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Coronavirus-triggered pulmonary and systemic disease, i.e. systemic inflammatory response to virally triggered lung injury, named COVID-19, and ongoing discussions on refining immunomodulation in COVID-19 without COX2 inhibition prompted us to search the related literature to show a potential target (COX2) and a weapon (celecoxib). The concept of selectively targeting COX2 and closely related cascades might be worth trying in the treatment of COVID-19 given the substantial amount of data showing that COX2, p38 MAPK, IL-1β, IL-6 and TGF-β play pivotal roles in coronavirus-related cell death, cytokine storm and pulmonary interstitial fibrosis. Considering the lack of definitive treatment and importance of immunomodulation in COVID-19, COX2 inhibition might be a valuable adjunct to still-evolving treatment strategies. Celecoxib has properties that should be evaluated in randomized controlled studies and is also available for off-label use.

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\textbf{Introduction}

Coronavirus disease 2019 (COVID-19) rapidly became a pandemic and at the time this review was written there were increasing numbers of deaths and new cases. Lack of time to recruit evidence-based treatments led physicians worldwide to implement empiric drug combinations. In several weeks, a number of agents proposed with variable or arguable efficacy became empirical treatments and clinical studies are ongoing in attempts to find the best alternatives until a definitive treatment is found (i.e. vaccine- and/or drug-based). Until definitive treatments are determined, readily available medications might have a role in preventing progression of the disease from Stage 1 to 2 and might decrease the hospitalization rate.

From the beginning of the outbreak, ongoing searches and discussions have included immunomodulation strategies to limit immune-system-related tissue damage, which is now very well accepted as a leading factor in mortality. Nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, Interleukin-6 (IL-6) antagonists, and Janus kinase (JAK) inhibitors are the main actors discussed and used in the treatment of COVID-19. Despite worldwide extensive efforts and ever-increasing numbers of publications, there has been no direct mention of cyclooxygenase-2 (COX2) inhibition and this prompted us to search the related literature to show the availability of a possible target and a weapon to be tested in clinical trials.

\textbf{Pathophysiology of COVID-19}

Severe acute respiratory syndrome (SARS)-associated coronavirus has been demonstrated to induce COX2 in mammalian cells via both its S and N proteins of its nucleocapsid (Liu et al., 2006; Yan et al., 2006). This represents a pivot point to induce subsequent intracellular and then intercellular cascades. It has been shown that coronavirus-induced endoplasmic reticulum (ER) stress leads to unfolded protein response including Mitogen-activated protein kinase (MAPK) activation, autophagy and apoptosis of eukaryotic cells infected with this virus (Fung et al., 2014). It was also shown that coronavirus-induced autophagy is mediated by activation of ER stress sensors, and prolonged ER stress leads to unfolded protein response to restore ER stability which involves MAPK activation (Fung and Liu, 2019). Induction of COX2 and p38MAPK

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plays a role in virally induced pulmonary alveolar, interstitial and then systemic inflammation. Whether virally induced or not, a state of cytokine storm also damages the pulmonary capillary network through activation of the p38MAPK pathway with eventual pulmonary arterial hypertension (Tielemans et al., 2019). Interferon (IFN) -γ-related cytokine storm has been shown after SARS coronavirus infection with lymphopenia and neutrophilia, together with increased levels of IFN-γ (Huang et al., 2005). At pathological levels, IFN-γ is known to induce pulmonary injury via the COX2 and p38MAPK pathways (Choo-Wing et al., 2013).

Hydroxychloroquine is no surprise for possible use in treating COVID-19 since it has been shown that chloroquine inhibits p38MAPK and inhibits coronavirus replication (Kono et al., 2008). Hydroxychloroquine also has been shown to inhibit TNF-α induced endothelial inflammation via inhibition of p38 expression (Li et al., 2018). Inhibiting p38MAPK is also important to prevent IL-1b-mediated acute lung injury. Zheng et al. (2016) showed that inhibition of p38 downregulates expression of IL-1b receptors in pulmonary alveoli and prevents acute lung injury due to ischemia-reperfusion injury. Another hallmark of coronavirus-induced pulmonary disease is interstitial fibrosis in which epithelial–mesenchymal transition plays a role – again p38 MAPK is pivotal in this complex phenomenon (Jolly et al., 2018; Yan et al., 2016). Debates commenced, however, on the use of hydroxychloroquine soon after initial experiences with the medication, questioning the evidence provided for its use (Ferner and Aronson, 2020). Recent literature concerning previous studies of hydroxychloroquine demonstrated that no significant benefit has so far been observed in the use of hydroxychloroquine against COVID-19 (Pathak et al., 2020).

**Selective COX2 inhibition**

COX2 is a critical evolutionary enzyme in many physiologic and pathologic processes. It has a central role in viral infections and regulates expression levels of many serum proteins (Liu et al., 2011). This enzyme has a great effect on proinflammatory cytokines, and its inhibition or deficiency alone does not blunt immune response against viral disease. Pharmacologic inhibition of COX2 by celecoxib decreases TNF-α, G-CSF and IL-6 levels without significant increase in viral titers in bronchoalveolar lavage fluid in mice with Influenza A infection (Carey et al., 2010). Hyperinduction of COX2 has been shown in patients who have died of H5N1 infection, along with increased levels of TNF-α and other major proinflammatory cytokines (Lee et al., 2008). Many of these critical effects might be targeted by the clinically available COX2 inhibitor, celecoxib. These pathophysiologic steps might be especially important in disease progression from Stage 1 to 2, at which many patients can be treated on an outpatient basis. In addition to inhibiting COX2, celecoxib inhibits p38MAPK, although it is not a pure or potent p38MAPK inhibitor (da Silva et al., 2005). However, it is important that inhibition of COX2 might result in delayed specific immunoglobulin production by blunting Lipoxin B4 mediated memory B cell activation (Kim et al., 2018). Notwithstanding, the benefits of alleviating a rapid and immense cytokine storm seem to outweigh the delay in production of specific antibodies (Carey et al., 2005).

Among the proven and putative effects of COX2 inhibition, a number have not been clarified. For instance, celecoxib has been shown to ameliorate hepatic cirrhosis through inhibition of epithelial–mesenchymal transition of hepatocytes (Wen et al., 2014) but other studies have shown that it does not (Harris et al., 2018). Since epithelial–mesenchymal transition is a pivotal evolutionary phenomenon in numerous physiologic and disease states of lung – e.g. lung development, COPD, lung cancer and pulmonary fibrosis (Jolly et al., 2018; Rout-Pitt et al., 2018) – possible antifibrotic effects of COX2 inhibition might benefit COVID-19 patients. Celecoxib has been shown to inhibit TGF-β-induced epithelial–mesenchymal transition in numerous studies. It has also been shown to inhibit FoxO1-mediated phosphorylation and eventual collagen production in human cardiac fibroblasts (Tseng et al., 2019). Additionally, celecoxib reduced peritoneal fibrosis in an animal model (Fabbbrini et al., 2009). Since interstitial pulmonary fibrosis is one of the hallmarks of COVID-19, the effects of celecoxib in fibrotic processes might be worth clinically trialing, preferably with a randomized controlled trial (RCT) or at least off-label under current conditions.

**COVID-19 and COX2 inhibition**

In a pandemic with ongoing and unforeseen effects, there are many obstacles to forming treatment strategies. Absence of definitive drugs and/or vaccines against a highly contagious viral disease creates clinical, scientific and ethical problems. Proposal of many different agents and treatments with variable and arguable efficacy without RCTs is the center of these abovementioned problems. As time passes there are increasing numbers of patients and deaths, together with stretched healthcare systems in many parts of the world. There are examples of old friends like hydroxychloroquine and newer ones like monoclonal antibodies against certain cytokines of the exaggerated inflammatory response triggered by COVID-19.

Despite ongoing studies and scientific discussions showing immunomodulation is one of the main issues in treatment of COVID-19, inhibition of COX2 has seemingly been missed. All clinical trials have evaluated the use of NSAIDs, steroids and newer immunomodulatory agents such as tocilizumab and sarilumab. Similar discussions took place throughout a previous pandemic, the H5N1 avian flu, in which it was argued that adjunctive use of COX inhibitors with antiviral therapy may have a beneficial role in alleviating the robust immune response causing the severe respiratory disease; however, these were never tried or studied using RCTs (Simmons and Farrar, 2008; Zheng et al., 2008). During the early periods of the current pandemic, the use of NSAIDs was strongly objected to by some authors and even governments, arguing that the disease may be aggravated by use of these medications and advocating the use of paracetamol, another NSAID without anti-inflammatory activity (Little, 2020; Willsher, 2020). Paracetamol has been promoted by some studies because of a safer side-effect profile and because other NSAIDs have been demonstrated as a cause of delayed diagnosis and increased rate of complications in respiratory tract infections (de Girolamo et al., 2020; Little, 2020; Sestili and Stocchi, 2020). This creates a paradox between treatment modalities and pathophysiology of COVID-19, since the over-the-counter medications used to ameliorate the symptoms that can be used in the early stages 1 and 2 of the disease (e.g. paracetamol) have no beneficial role in halting the progression of the condition because they have no anti-inflammatory action, which is crucial for keeping the inflammatory state under control. Although it may cause symptomatic relief for patients, in the case of COVID-19 paracetamol has no influence on disease progression, and without anti-inflammatory action this risks masking the symptoms. The number of studies opposing this approach is growing, including a recent cohort suggesting their concomitant use may be potentially harmless (FitzGerald, 2020; Lund et al., 2020). We believe the use of ibuprofen in the case of COVID-19 has been objected to for logical and scientific reasons. Although further research is required, ibuprofen is associated with an upregulation of ACE2 enzyme, which may increase susceptibility to the virus. In addition, as we summarized above, inhibition of COX1 may not be a good idea since it blunts antiviral immunity and
also shows no selective alleviation of cytokine storm. In addition, therapeutic potential of celecoxib was demonstrated in studies employing searching of molecular libraries (Gimeno et al., 2020; Ke et al., 2020).

Celecoxib, as mentioned above, is a candidate for treatment of COVID-19. It is widely available, relatively cheap and has a well-recorded safety profile in adults and children with a long history of clinical use for variable disease states, e.g., osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, colorectal cancer and lung cancer. Likewise, another NSAID, ibuprofen, has been studied for its cardiovascular side-effects in comparative studies. Although some studies indicate that celecoxib increases the incidence of major cardiovascular events – i.e. myocardial infarction, worsening of heart failure and thrombotic cerebral strokes – there are others showing no significant difference compared to non-selective COX inhibitors that are more widely used. Two of the main parameters seemingly important in these studies are the duration of use and the dose of this agent (Masclle et al., 2018). In all these long-term studies, patient groups used celecoxib for many (approximately 20–30) months and suggested that cardiovascular toxicity is time dependent. However, celecoxib has been found to be noninferior to ibuprofen and naproxen, which are used on larger scales (Nissen et al., 2016). For treating COVID, this might not be a major drawback since the expected duration of treatment will not exceed a few days to weeks. However, patients with significant cardiovascular comorbidities (e.g. obesity, uncontrolled diabetes, coronary artery disease or ischemic stroke) might not be ideal candidates for using this agent. To determine such issues will require RCTs (Catella-Lawson and Crofford, 2001).

Conclusions

Considering its high contagiousness, lack of definitive treatment and variable course of disease reflecting biological behavior of immune systems of patients with COVID-19, COX2 inhibition might be a valuable adjunct to still-evolving treatment strategies. Celecoxib has properties that should be evaluated in RCTs, as well as being available for off-label use. We believe that selective COX2 inhibition might have great implications in treating viral diseases because short duration of treatment will not be an issue in terms of major cardiovascular side-effects.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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This paper was a perspective and ethical approval was not required.

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