Nonsteroidal anti-inflammatory drugs and glucocorticoids in COVID-19

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ABSTRACT

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is characterized by a wide spectrum of symptom severity, which is manifested at different phases of infection and demands different levels of care. Viral load, host innate-immune response to SARS-CoV-2, and comorbidities have a direct impact on the clinical outcomes of COVID-19 patients and determine the diverse disease trajectories. The initial SARS-CoV-2 penetrance and replication in the host causes death of infected cells, determining the viral response. SARS-CoV-2 replication in the host triggers the activation of host antiviral immune mechanisms, determining the inflammatory response. While a healthy immune response is essential to eliminate infected cells and prevent spread of the virus, a dysfunctional immune response can result in a cytokine storm and hyperinflammation, contributing to disease progression.

Current therapies for COVID-19 target the virus and/or the host immune system and may be complicated in their efficacy by comorbidities. Here we review the evidence for use of two classes of anti-inflammatory drugs, glucocorticoids and nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment of COVID-19. We consider the clinical evidence regarding the timing and efficacy of their use, their potential limitations, current recommendations and the prospect of future studies by these and related therapies.

1. Introduction

Coronavirus disease 19 (COVID-19), caused by severe acute respiratory syndrome–coronavirus (SARS-CoV)-2, broke out in Wuhan (China) as atypical interstitial pneumonia in late 2019 (Wu et al., 2020b). SARS-CoV-2 infection has now spread to over 220 countries, leading to a global pandemic (Zheng, 2020). As of July 2021, more than 188 million individuals worldwide have tested positive for SARS-CoV-2 and over 4 million people have died due to COVID-19 (https://www.who.int/emergencies/diseases/novel-coronavirus-2019).

COVID-19: pathogenesis. SARS-CoV-2 is an enveloped β-coronavirus, containing one positive-strand RNA (Lu et al., 2020). Its

genome comprises 29.9 kilobases, contains 14 open reading frames encoding 27 proteins and shares 88%, 79.5% and 50% identity with two bat-derived SARS-like coronaviruses, SARS-CoV and Middle East respiratory syndrome-related (MERS)-CoV, respectively (Lu et al., 2020). However, dissimilarity in their surface proteins and viral load kinetics determines the differential rates of transmission of the various coronaviruses (Cevik et al., 2020). SARS-CoV-2 binds, via spike-glycoproteins (S protein) expressed on its envelope, host receptors like angiotensin-converting enzyme 2 (ACE2) and neuropilin for its attachment and entry into the target cells (Cantuti--Castelvetri et al., 2020; Daly et al., 2020; Hoffmann et al., 2020). After the S protein is cleaved by the host transmembrane protease serine 2 (TMPRSS2) and endocytic cathepsin L, the host-viral membrane fusion occurs and determines the release of the viral RNA genome into the host cell cytoplasm (Hoffmann et al., 2020; Wrapp et al., 2020).

SARS-CoV-2 is a cytopathic virus and upon penetrance and replication causes lysis of infected cells, release of cytokines (TNF$-\alpha$, IL-6, IL-8), free radicals, and activation of several non-specific responses including (C-reactive protein (CRP), D-dimer, ferritin, lactate dehydrogenase and fibrinogen), determining the early viral response. In addition, SARS-CoV-2 replication in the host cell triggers activation of host antiviral immune mechanisms, including recruitment and activation of specific leukocyte subsets, induction of interferon (INF)γ, and additional release of cytokines, chemokines and other inflammatory mediators, determining the inflammatory response (Cevik et al., 2020). A healthy immune response is essential to eliminate the infected cells and prevent the spread of the virus, while an aberrant host immune response further contributes to the pathogenesis of COVID-19 by causing hyper-inflammation and a cytokine storm (Moore and June 2020; Song et al., 2020). Timing and biological context determines whether a given immune response is beneficial or detrimental. However, the distinction between these two phases of infection varies between people, reflecting differences in viral load, cellular defense and immune competence, and the presence of comorbidities and they cannot be easily distinguished clinically. This complicates the decision to intervene with immunomodulatory therapies and yet timing of intervention is likely to be an important determinant of therapeutic response.

COVID-19: Clinical response. SARS-CoV-2 infection can evoke a broad spectrum of clinical response ranging from asymptomatic infection and mild upper respiratory symptoms (fever, sore throat, cough) to severe complications including acute respiratory distress syndrome (ARDS), acute renal failure, heart attack, stroke, and death, with persistent morbidity in some survivors (Ortiz-Prado et al., 2020; Young et al., 2020; Zhang et al., 2020a). Early symptoms of SARS-CoV-2 infection may include myalgias/arthralgias, chest pain, headache, tiredness/exhaustion, loss of taste or smell, rash on skin or discoloration of the toes, and gastrointestinal issues (Zhang et al., 2020a). However, these responses are not specific to SARS-CoV-2. Older age, male sex, and preexisting comorbidities have been associated with worse outcomes (Docherty et al., 2020; Grasselli et al., 2020; Richardson et al., 2020). The large span of symptom severity, which may be manifest within an individual at different stages of the disease, demand different levels of care. A diversity of immune phenotypes has been described in COVID-19 but their precise mechanistic relationship to clinical outcomes remains to be elucidated. Predicting the clinical progression and outcome of SARS-CoV-2 infection (Wadman et al., 2020), which reflects heterogeneity in the host-immune response (Blanco-Melo et al., 2020; Giamarellos-Bourboulis et al., 2020; Kuri-Cervantes et al., 2020; Lucas et al., 2020; Mathew et al., 2020), represents one of the greatest challenges in managing patients with COVID-19.

COVID-19: Therapy. Current therapies for COVID-19 target the virus and/or the host immune system and may be complicated in their efficacy by comorbidities. Remdesivir is the only antiviral drug approved or authorized for emergency use from several international drug agencies, but not by the World Health Organization (WHO), to treat hospitalized COVID-19 patients (https://www.covid19treatmentguidelines.nih.gov/antiviral-therapy/remdesivir/; https://www.ema.europa.eu/en/news/ema-provides-recommendations-compassionate-use-remdesivir-covid-19; https://www.tga.gov.au/media-release/australias-first-covid-treatment-approved; https://www.who.int/news-room/feature-stories/detail/who-recommends-against-the-use-of-remdesivir-in-covid-19-patients). While the potential clinical efficacy of molecules emerging from high throughput screens is explored (Pham et al., 2021), the use of dexamethasone in patients with severe disease has been established with the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial (Horby et al., 2021). More controversial is the use of glucocorticoids in patients who are not on supplemental oxygen in the Intensive Care Unit and the use of nonsteroidal anti-inflammatory drugs (NSAID)s to quell the immune response at any stage of the disease.

In this review we discuss the clinical evidence regarding the timing and efficacy of using glucocorticoids and NSAIDs in COVID-19 patients, their potential limitations, current recommendations and the prospect of future studies by these and related therapies.

1.1. Glucocorticoids in COVID-19

Dexamethasone, prednisone and methylprednisolone are synthetic compounds which mimic the biological effects of the endogenous glucocorticoids, namely cortisone or hydrocortisone, by binding to the glucocorticoid receptor. The various glucocorticoids differ in their potency and selectivity for corticosteroid receptors, in half-life, duration of action, and frequency of administration. Glucocorticoids have pleiotropic physiological effects, including regulation of cell-growth, metabolism, reproduction, development, inflammation, appetite and the immune system. They are extensively used to treat autoimmune disease, asthma, inflammatory and allergic disorders (Brunton et al., 2018). Given their powerful anti-inflammatory and immunomodulatory effects, glucocorticoids have been used in SARS-CoV-2 infection to counter aberrant host immune responses and prevent the immune-mediated damage observed in some COVID-19 patients (Huang et al., 2021). The anti-inflammatory action of glucocorticoids is mostly due to inhibition of the NF-κB pathway, which can be activated by SARS-CoV-2 (Hadjadj et al., 2020; Kircheis et al., 2020). Glucocorticoids, by inducing I kappa B synthesis, prevent translocation of activated NF-kB into the nucleus and the consequent upregulation of pro-inflammatory genes with release of cytokines, chemokines, and prostanoids (Auphan et al., 1995; Brunton et al., 2018; Scheinman et al., 1995). The plasma levels of some of these cytokines have been associated with COVID-19 severity (Hadjadj et al., 2020; Moore and June 2020). In addition, glucocorticoids can inhibit fibrosis of healing tissue (Weber, 1992). This could be particularly beneficial in COVID-19

patients, considering the high rate of fibrosis in late stages of disease (George et al., 2020). Moreover, glucocorticoids can potentially activate ACE-2 or modulate its expression in contrast to its downregulation caused by SARS-CoV-2 (Xiang et al., 2020).

Many clinical trials have been conducted with glucocorticoids in COVID-19 patients and they have yielded contrasting results, with beneficial effects depending on disease severity (Angus et al., 2020; Dequin et al., 2020; Fadel et al., 2020; Horby et al., 2021; Hu et al., 2020; Jeronimo et al., 2021; Tomazini et al., 2020; Villar et al., 2020; Wu et al., 2020a). Interestingly, a similar conclusion was drawn from clinical studies on the use of the glucocorticoids in septic shock (Finfer, 2008; Lamontagne et al., 2018) and in ARDS not related to COVID-19 (Reddy et al., 2020; Segel, 2007).

The RECOVERY trial provides the most reliable data on the use glucocorticoids in severe COVID-19 patients. In this large randomized clinical trial, >6,400 patients in this arm of the study, the use of dexamethasone for up to ten days was associated with reduction of 28-day mortality of hospitalized COVID-19 patients on mechanical ventilation by about 30% and on oxygen supplementation by 20% compared to standard care. However, dexamethasone did not provide a beneficial effect in hospitalized COVID-19 patients who were not receiving respiratory support (Horby et al., 2021). Although this trial presents some methodological flaws, did not measure the activation of the immune system and did not assess side effects, it clearly defined a precise target population which could benefit by the treatment with glucocorticoids. Consistently, a prospective meta-analysis of seven clinical trials with different glucocorticoids in critically ill COVID-19 patients revealed a lower 28-day all-cause mortality in patients systemically treated with glucocorticoids compared with placebo or usual care (Sterne et al., 2020). Subsequent studies further tried to identify subsets of severe COVID-19 patients which are more likely to respond to therapy with glucocorticoids. For example, an observational study reported an association between glucocorticoid use and reduced risk of mortality or mechanical ventilation only in hospitalized COVID-19 patients with high levels of CRP ($\geq$20 mg/dL) (Keller et al., 2020). Another study reported that therapy with glucocorticoids was associated with lower 60-day all-cause mortality only in severe COVID-19 patients with a ratio of neutrophils to lymphocytes (NLR) > 6.11 at admission (Cai et al., 2021).

Other clinical studies with glucocorticoids in COVID-19 patients were inconclusive and presented several limitations, including being underpowered, lacking clear indices of clinical progress, or inadequate investigation into potential side effects (Angus et al., 2020; Dequin et al., 2020; Jeronimo et al., 2021; Villar et al., 2020). So far, therapy with glucocorticoids is the only therapeutic intervention able to reduce mortality in severe COVID-19 patients.

A few retrospective studies also reported benefits from glucocorticoids in hospitalized COVID-19 patients with pneumonia since SARS-CoV-2 infection triggers a massive influx and activation of leukocytes in lung parenchyma (Fernández-Cruz et al., 2020; Liu et al., 2020a; Wang et al., 2020; Wu et al., 2020a). These studies included both patients requiring oxygen therapy or mechanical ventilation and patients with normal blood oxygen level. In a study conducted in hospitalized COVID-19 patients, including only patients which did not require oxygen therapy or mechanical ventilations, the short-course and low-dose applications of corticosteroids, co-administered with immunoglobulin, reached neutral results in term of some clinical outcomes (progression to severe illness and time from illness onset to viral clearance) and increased the length of the hospital stay compared to COVID-19 patients not treated with corticosteroids with relatively milder disease (Hu et al., 2020). The studies on the effect of glucocorticoids in hospitalized COVID-19 patients with pneumonia are not conclusive, since they enrolled COVID-19 patients with heterogeneous disease severity and they had different clinical end-points, so therefore additional investigations are needed.

Very little evidence is available regarding the effectiveness of the therapy with glucocorticoids in COVID-19 patients with mild disease in the outpatient setting. A recent open-label, parallel-group, phase 2, randomised controlled trial reported that the early administration of budesonide, an inhaled glucocorticoid, in non-hospitalized COVID-19 patients with mild symptoms was associated with reduced likelihood of needing urgent medical care and accelerated time of recovery compared to usual care (Ramakrishnan et al., 2021). Budesonide is now approved for off-label use to treat COVID-19 patients on a case-by-case basis in United Kingdom (www.cas. mhra.gov.uk). Additional clinical trials are investigating the effect of early glucocorticoid administration in COVID-19 patients in the outpatient setting. These results have not been published yet (2020-001622-64; NCT04377711). A recently implemented home treatment algorithm indicates that the early use of glucocorticoids in non-hospitalized COVID-19 patients with increased inflammatory indexes (CRP, neutrophil count) may reduce the risk of hospitalization (Suter et al., 2021). Further research is warranted to clarify the benefits over risk associated with the use of glucocorticoids in outpatients in the early phase of COVID-19 infection.

Since the need for an adequate immune response to control viral infection and the immunosuppressive effects of glucocorticoids, the use of this class of drugs prior to or during the early viral response to SARS-CoV-2 could worsen the outcome of the infection, and, in particular in immunocompromised patients, increase the risk of secondary infections and other complications. Moreover, impairment of immune function may enable viral spread, harm the host via a direct cytotoxic viral effect and prolong viral shedding. Indeed, ongoing chronic therapy with glucocorticoids at medium-high doses could potentially increase the risk of infections (Favalli et al., 2020; Youssef et al., 2016). Chronic use of glucocorticoids has been associated with increased odds of hospitalization or mortality in COVID-19 patients with RA, inflammatory bowel disease or with chronic obstructive pulmonary disease and asthma (Brenner et al., 2020; Gianfrancesco et al., 2020; Schultze et al., 2020). Although there are contrasting data regarding the effect of glucocorticoids on viral clearance in COVID-19 patients (Huang et al., 2020; Ji et al., 2020; Liu et al., 2020a, 2020b; Tang et al., 2021), therapy with glucocorticoids should be restricted to severe COVID-19 patients with proven excessive activation of the immune system.

Based on the data currently available, the use of systemic glucocorticoids is now recommended by international agency and societal guidelines for treatment of COVID-19 patients with severe or critical illness who are mechanically ventilated or who require supplemental oxygen (https://www.covid19treatmentguidelines.nih.gov/immunomodulators/corticosteroids/; https://www.ema. europa.eu/en/news/ema-endorses-use-dexamethasone-covid-19-patients-oxygen-mechanical-ventilation; https://www.who.int/ publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1; https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/).

Additionally, more than 80 clinical trials are ongoing to investigate further the use of glucocorticoids in different groups of COVID-19 patients (Raju et al., 2021).

1.2. Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are amongst the most commonly used over-the-counter drugs in world. They are taken to treat a wide range of inflammatory conditions [e.g. osteoarthritis (OA), RA, gout, etc.], to reduce pain and to decrease fever. The principal therapeutic effect of NSAIDs is based on the inhibition of the cyclooxygenase activity of the prostaglandin-endoperoxide synthase (PTGS)1 and 2 and the consequent suppression of the formation of arachidonic acid (AA) metabolites known as prostanoids (Brunton et al., 2018).

Prostanoids, including prostaglandins (PGs) (PGD$_2$, PGE$_2$, PGF$_{2\alpha}$), prostacyclin (PGI$_2$) and thromboxane (TxA$_2$), after they are formed locally, bind to their receptors, in autocrine or paracrine fashion, and evoke a very wide range of biological actions. They are implicated in homeostasis and normal function (e.g. gastrointestinal protection, platelet function, renal function, vascular tone) and in pathophysiological processes (e.g.: thrombosis; inflammation, infection, cancer) (Ricciotti and FitzGerald, 2011). During viral infection, prostanoids play complex roles in regulating the virus-host interactions and modulating the host immune and inflammatory responses necessary for clearing the virus particles and establishing immunological memory. Prostanoids can both promote and restrain the host immunological responses to viral infection (Dennis and Norris, 2015; Ricciotti and FitzGerald, 2011; Sander et al., 2017).

All NSAIDs used in the clinic, with the exception of aspirin, are reversible PTGS inhibitors. They are a chemically heterogeneous group of compounds and they are characterized by varying degrees of selectivity for PTGS1 and PTGS2 inhibition. Celecoxib, etoricoxib and diclofenac are NSAIDs selective for PTGS2 inhibition, while ibuprofen and indomethacin are nonselective PTGS inhibitors. At low doses (<150 mg daily), aspirin functions as an antiplatelet drug since it causes irreversible inhibition of PTGS1 expressed in platelets, the only PTGS isozyme present in these anucleate cells, and consequent inhibition of TxA$_2$, a potent platelet agonist. Low-dose aspirin is effective for the secondary prevention of cardiovascular disease (Ricciotti and FitzGerald, 2021). At higher doses, aspirin causes irreversible inhibition of both PTGS1 and PTGS2 and functions as an anti-inflammatory drug. Acetaminophen is a nonselective PTGS inhibitor which suppresses prostanoid formation, to a lesser extent than other NSAIDs at the most common daily dose of 1000 mg. It does this by inhibiting the peroxidase activity of the bifunctional PTGS isozymes. Therefore, acetaminophen has only a weak anti-inflammatory activity, but it is an effective antipyretic due to its capacity to pass the blood-brain barrier.

NSAIDs, although they are effective in modulating pain, inflammation and fever, can cause serious side-effects. They can damage the gastrointestinal mucosa, raise blood pressure, impair kidney function and cause adverse cardiovascular events, including myocardial infarction, stroke and heart failure, particularly after long term use, in the elderly and in subjects with other comorbidities (Bjarnason et al., 2018; Grosser et al., 2017).

1.3. Prostanoids in COVID-19

Prostanoids, like other AA metabolites, can influence SARS-CoV-2 entry, replication and clearance (Theken and FitzGerald, 2021). Also, SARS-CoV-2 can trigger the release of prostanoids from the infected host cells.

Several elements of the prostanoid pathway or compounds that target them have been reported potentially to interact with SARS-CoV-2. A network analysis and molecular mapping for SARS-CoV-2 reported PTGS2 as an important gene in the network regulating pathways involved in the coronavirus infection (More et al., 2021). Microsomal prostaglandin E synthase-2 (PTGES2) expressed in the host-cell may functionally interact with non-structural protein 7 (NSP-7) of SARS-CoV-1, SARS-CoV-2, and MERS-CoV (Gordon et al., 2020a, 2020b). In silico screening suggests that an antagonist of PGE$_2$ receptor 4 (EPR4), grapiprant, interferes with the interaction between SARS-CoV-2 and cell surface binding of an immunoglobin protein by locking the substrate binding domain in a closed conformation (Zhang et al., 2021). In addition, a docking-based virtual screening of antiplatelet FDA-approved drugs revealed that iloprost and epoprostenol, two stable prostacyclin analogs, have promising binding interactions with S-protein (Abosheasha and El-Gowily, 2021). However, the impact of these interactions on viral entry or replication has yet to be elucidated.

As seen with other coronaviruses, SARS-CoV-2 infection increases prostanoid production by upregulating the expression of some of the genes involved in their biosynthesis. Expression of PTGS1, PTGS2 and cytosolic prostaglandin E synthase (PTGES3) are upregulated in peripheral blood mononuclear cell (PBMC)s isolated from COVID-19 patients compared to healthy controls (Yan et al., 2021). Similarly, SARS-CoV-2 infection upregulates PTGS2 expression *in vitro* in human cells (Calu-3 cells, ACE2-overexpressing A549 cells and primary human bronchial epithelial cells) and *in vivo* in K18-hACE2 mice (Chen et al., 2021). Prostaglandin D synthase and D prostanoid receptor 2 (DPR2 or CRTH2) have been reported to be highly expressed in kidney tubules from COVID-19 autopsies and co-expressed with SARS-CoV-2 nucleocapsid and S-protein antigens (Diao et al., 2021). In contrast, lipopolysaccharide (LPS)- stimulated CD14$^+$ monocytes isolated from patients with severe COVID-19 present a lower expression of PTGS2 compared to healthy controls, indicating an impairment of innate immune response caused by SARS-CoV2 infection (Mann et al., 2020). Along these lines, SARS-CoV-2 has also been reported to dampen Th2-polarized immune responses by lowering CRTH2 expression in eosinophils and basophils cells isolated from COVID-19 patients compared to healthy controls (Vitte et al., 2020).

The biosynthesis of several prostanoids has been reported to be perturbed in response to SARS-CoV-2 infection in small studies in humans. Urinary PGE$_2$ levels are reportedly ~10 fold higher in hospitalized COVID-19 patients compared to healthy controls (Hong et al., 2020). Similarly, COVID-19 patients showed higher serum PGE$_2$ levels than healthy controls, but serum PGE$_2$ levels do not correlate with disease severity (Kazancioglu et al., 2021). PGF$_{2\alpha}$ levels are reportedly also elevated in serum from COVID-19 patients compared to healthy controls (Yalçın Kehribar et al., 2020). Elevated levels of prostaglandins and thromboxane have been measured in

the bronchoalveolar lavages of intubated COVID-19 patients compared to healthy controls (Archambault et al., 2021). Higher levels of TxB$_2$ are released by ADP stimulated platelets from COVID-19 patients compared to healthy controls, suggesting the contribution of this prostanoid to the pro-thrombotic phenotype observed in patients infected with SARS-CoV-2 (Manne et al., 2020). Consistently, plasma from COVID-19 patients is able to cause *in vitro* aggregation of platelets from healthy controls and this phenomenon is prevented by the treatment with antiplatelet drugs, including aspirin (Canzano et al., 2021). Indeed, aspirin has been reported to reduce *ex vivo* platelet hyperactivity of patients with severe COVID-19 (Manne et al., 2020). However, aspirin is not able to prevent platelet-induced tissue factor expression by monocytes from COVID-19 patients (Hottz et al., 2020). Plasma levels of TxB$_2$ have been reported to be independently associated with the composite of thrombosis or death, thrombosis and all-cause of death in COVID-19 patients (Barrett et al., 2020). The PGI$_2$ metabolite, 6-keto-prostaglandin F$_{1\alpha}$, a marker of endothelial dysfunction, was found to be significantly elevated in the plasma of patients infected with SARS-CoV-2 compared to healthy controls (Canzano et al., 2021).

These initial observations regarding prostanoid levels in biological samples from COVID-19 patients should be interpreted with substantial caution since they derive from small retrospective studies in which prostanoid biosynthesis was often measured by antibody-based assays of questionable specificity and their levels were not corrected for known factors that influence their levels like age, sex and use of NSAIDs, glucocorticoids or biological drugs. Moreover, since prostanoids have a short half-life and do not circulate, their plasma levels may be reflective of artifacts due to venipuncture and *ex vivo* platelet activation (Grosser et al., 2018).

Considering these limitations, these data, although suggestive of a role of prostanoids in COVID-19, are merely preliminary. More definitive, well controlled data may yield patterns of formation that reflect the intensity of disease and forecast its course, but also provide the opportunity to intervene with potentially preventative therapies before the disease progresses to a severe stage. Therapies that modulate prostanoid biosynthesis or action may particularly be beneficial during the initial phase of SARS-CoV-2 infection.

1.4. NSAIDs in COVID-19

At the beginning of the pandemic, it was debated whether people taking NSAIDs, in particular ibuprofen, would have higher susceptibility to SARS-CoV-2 infection or a worse outcome if they contracted COVID-19 (FitzGerald, 2020). These initial concerns arose from limited data on ibuprofen and other NSAIDs which, by upregulating the expression of ACE2 (Qiao et al., 2015) and masking initial signs of viral infection like inflammation and fever, could have increased the risk of acquiring SARS-CoV-2 or aggravated disease severity. Based on anecdotal reports, the French Health Authorities and the National Health Service in the United Kingdom initially recommended to use another NSAID, acetaminophen, instead of ibuprofen, in COVID-19 patients (Day, 2020; Sodhi and Etminan, 2020). Afterwards, the World Health Organization (WHO), the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), and Australia's Therapeutic Goods Administration did not advocate against the use of ibuprofen in COVID-19 patients due to lack of scientific evidence (https://www.cbc.ca/news/health/ibuprofen-covid-19-novel-coronavirus-1.5501496; https://www.ema.europa.eu/en/news/ema-gives-advice-use-non-steroidal-antiinflammatories-covid-19; https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19 https://www.tga.gov.au/alert/no-evidence-support-claims-ibuprofen-worsens-covid-19-symptoms).

Current data, based on mostly small population-based cohorts, observational and retrospective studies, have quite consistently reported a lack of association between ongoing NSAID therapy and increased susceptibility to SARS-CoV-2 infection ((Mancia et al., 2020); https://www.england.nhs.uk/coronavirus/publication/acute-use-of-non-steroidalantiinflammatory-drugs/; https://www.who.int/publications/i/item/the-use-of-non-steroidal-anti-inflammatory-drugs-(nsaids)-in-patients-with-covid-19), higher mortality (Abu Esba et al., 2021; Lund et al., 2020; Rinott et al., 2020; Wong et al., 2021) or worsening of clinical outcomes (Abu Esba et al., 2021; Choi et al., 2020; Kragholm et al., 2020; Lund et al., 2020; Rinott et al., 2020) in COVID-19 patients in the general population. Similar trends were also observed in populations most likely to be exposed to chronic NSAID therapy like patients with preexisting RA or OA. The ongoing use of NSAID in RA patients did not increase the odds of hospitalization for COVID-19 (Gianfrancesco et al., 2020) or COVID-19 related death (Wong et al., 2021) compared to nonusers. Ongoing NSAID therapy in OA patients was not associated with an increased risk of infection due to SARS-CoV-2 or all-cause mortality compared to co-codamol (paracetamol and codeine) or co-dydramol (paracetamol and dihydrocodeine) (Chandan et al., 2021).

Fewer retrospective studies were conducted in hospitalized COVID-19 patients, but they also failed to report an association between the routine use of NSAIDs prior to hospital admission and increased hospitalization or mortality rate (Bruce et al., 2020; Imam et al., 2020). Consistently, a recent large prospective, multicentre cohort study based on the ISARIC Clinical Characterisation Protocol UK dataset (>78,000 patients) failed to identify an association between pre-existing NSAID use (within two weeks before hospitalization) with higher in-hospital mortality or worse outcome (critical care admission, need for invasive ventilation, need for oxygen, and acute kidney injury) in hospitalized COVID-19 patients. In a subgroup analysis, ibuprofen use was not associated with an increased risk of mortality compared to other NSAIDs or no NSAIDs (Drake et al., 2021). Similarly, an Israeli retrospective cohort study reported that the use of ibuprofen before SARS-CoV-2 infection was not associated to increased mortality or the need for respiratory support (oxygen administration and mechanical ventilation) compared to non-NSAID users or acetaminophen users (Rinott et al., 2020).

In contrast, a retrospective study based on South Korea's nationwide healthcare database reported that prior NSAID use (prescribed 7 days before hospitalization) was linked to higher odds of worse clinical outcomes (in-hospital death, intensive care unit admission, mechanical ventilation use, and sepsis) in hospitalized COVID-19 patients compared to non-users (Jeong et al., 2020). Unexpectedly, NSAID use was not associated with a higher risk of cardiovascular complications (myocardial infarction, stroke, heart failure) and acute renal failure, which are known NSAID-related complications (Bhala et al., 2013).

A few studies attempted to explore the potential interactions between NSAID use, age and sex on COVID-19 outcomes, however they were insufficiently powered (Chandan et al., 2021; Lund et al., 2020). Since PG biosynthesis and NSAID efficacy have been

reported to show sex and age differences (Pace et al., 2017a, 2017b), future studies should address the safety and efficacy of NSAID use in these different settings.

The aforementioned retrospective studies present a number of limitations including: small sample size, non-randomized allocation of treatment, confounding by indication bias, variable dosage and duration of NSAID therapy and lack of information on drug adherence, over the counter use of NSAIDs, disease severity, viral replication, side-effects and socioeconomic status. However, at the moment, in the absence of randomized controlled data, the consistency of results between most of these retrospective studies provides reassurance about the safety of ongoing NSAID therapy in COVID-19 patients.

NSAIDs are also used as immune adjuvants for managing some of the COVID-19 symptoms and perhaps controlling SARS-CoV-2 infection. Present evidence on the efficacy of NSAIDs in adult COVID-19 patients comprises a few small, non-randomized, open label interventional studies. In a small prospective study, the use of celecoxib, qd or bid for 7-14 days in hospidalized COVID-19 patients, reduced urinary PGE_2 levels, prevented clinical deterioration and improved chest CT grading compared to standard therapy (Hong et al., 2020). However, the discontinuation of therapy with celecoxib allowed urinary PGE_2 to rise and was associated with relapse of pneumonia in a few patients (Hong et al., 2020). By contrast, in a retrospective "real-world" clinical data analysis, the use of indomethacin, a nonselective COX inhibitor and of an PGES2 inhibitor, but not of celecoxib, reduced the need for hospitalization in COVID-19 patients treated in an outpatient setting (Gordon et al., 2020a). In a retrospective study, short-term treatment with etoricoxib (median duration 3 days) in hospitalized COVID-19 patients with pneumonia was not associated with disease progression (supplemental oxygen use, intensive care unit admission, mechanical ventilation and mortality) compared to the control group (Ong et al., 2020). Moreover, etoricoxib reduced plasma IL-6 levels in a small subset of COVID-19 patients. The use of etoricoxib was not found to be associated with gastrointestinal or cardiovascular side effects but the treatment period was brief.

Interventional clinical studies are ongoing to investigate the efficacy of several NSAIDs, alone or in combination with other drugs, for the prevention of complications and improvement of clinical outcomes in COVID-19 patients (NCT 04334629; NCT04382768; NCT 04344457, NCT 04488081).

Some NSAIDs, in addition to their anti-inflammatory and analgesic proprieties, have been reported, often at high doses, to have antiviral activity *in vitro* which has been speculated to contribute to their efficacy in the treatment of COVID-19. Celecoxib, at concentrations not clinically achievable (50 microM), inhibits the main protease of SARS-CoV-2, M-pro, *in vitro* (Gimeno et al., 2020), but the effect on viral entry or replication was not assessed. Naproxen prevented SARS-CoV-2 nucleoprotein oligomerization by binding its N-terminal domain and inhibited viral replication in VERO E6 cells and reconstituted human pulmonary epithelium (Terrier et al., 2021). In silico analyses of publicly available transcriptomic databases of rat kidney tissues treated with multiple NSAIDs *in vivo* found modulated expression of receptors for SARS-CoV-2. Diclofenac, meloxicam, piroxicam, naproxen and nimesulide significantly reduced the expression of *Ace2*; naproxen, diclofenac and rofecoxib increased the expression of *Tmprss2*; meloxicam and acetaminophen reduced the expression of *Tmprss2* (Saheb Sharif-Askari et al., 2020). Ibuprofen was reported to upregulate *Ace2* in rat lungs and human alveolar type-II pneumocyte cells, but this effect was counteracted by spike protein internalization (Valenzuela et al., 2021). In contrast, indomethacin or meloxicam did not change *Ace2* expression, SARS-CoV-2 entry or replication *in vitro* in Calu-3 and Huh 7.5 cells. Similarly, meloxicam did not have an impact on SARS-CoV-2-induced weight loss or lung viral burden *in vivo* in mice (Chen et al., 2021). ACE2 and TMPRSS2 expression in nasal epithelial cells was not significantly modified by daily aspirin therapy in asthmatic patients compared to healthy controls not taking an NSAID (Buchheit et al., 2021).

The potential antiviral activity of some NSAIDs needs to be investigated by controlled studies *in vivo*, in appropriate model systems, using therapeutically relevant concentrations of the drugs.

1.5. Low-dose aspirin in COVID-19

As for ibuprofen, there were concerns whether ongoing therapy with low-dose aspirin for cardioprevention could worsen the clinical outcome of COVID-19. At the moment, the results of two retrospective studies on the effect of low-dose aspirin treatment before SARS-CoV-2 infection support the safety of this drug regimen during the COVID-19 pandemic.

A small retrospective study reported that the prior use of low-dose aspirin for cardioprevention was not associated with a higher risk of in-hospital mortality in COVID-19 patients with coronary artery disease admitted in the Tongji hospital in Wuhan (Yuan et al., 2021). Retrospective analysis of data from the American Veterans Health Administration national electronic health record database reported that prescription of aspirin prior to diagnosis (the dose was not specified) was associated with reduced 14-day and 30-day mortality rates in Veterans tested positive for SARS-CoV-2 (Osborne et al., 2021).

Although it is still debated whether human platelets express receptors for SARS-CoV-2 (Manne et al., 2020; Zaid et al., 2020; Zhang et al., 2020b), COVID-19 may be complicated by coagulopathy, an increase in D-dimer concentrations due to endothelial dysfunction and microvascular thrombosis (Cui et al., 2020; Helms et al., 2020; Spiezia et al., 2020; Zaid et al., 2020). Therefore, the use of low-dose aspirin as an anti-platelet drug could be beneficial in COVID-19 patients at higher risk for atherothrombotic events. However, the increased risk of bleeding, even with low-dose aspirin, should be taken in account. For instance, low-dose aspirin is not recommended for the primary prevention of cardiovascular diseases in the general population due to an unfavorable benefit-to-risk ratio (Ricciotti and FitzGerald, 2021). The results of small retrospective studies on the use of aspirin as antithrombotic agent in the adult COVID-19 population with different disease severity are encouraging but not conclusive.

A propensity-matched analysis of real-world clinical data from the Cleveland Clinic found that overall mortality in symptomatic COVID-19 inpatients and outpatients was not affected by new or ongoing treatment with low-dose aspirin or NSAIDs. Surprising, aspirin therapy was associated with an increased risk of combined thrombotic endpoints, including myocardial infarction, cerebrovascular accident and venous thromboembolism, probably reflecting confounding by indication (Sahai et al., 2021). A propensity

matched study conducted in several hospitals in the United States reported that short term use of low-dose aspirin, started within 24 h of admission or 7 days before admission, was associated with a reduced risk of mechanical ventilation, ICU admission and in hospital mortality in patients with ARDS related to COVID-19 compared to non-aspirin users. There was no effect of aspirin on major bleeding or overt thrombosis (Chow et al., 2021). Another propensity score-matched analysis conducted in the Unites States reported that the use of in-hospital low-dose aspirin was associated with a lower cumulative incidence of in-hospital death compared to no antiplatelet therapy (Meizlish et al., 2021). Consistent with the American studies, a small propensity score-matched case-control study conducted in China reported that the use of low-dose aspirin for at least 5 days reduced 30-day and 60-day mortality in hospitalized adult COVID-19 patients compared to non-aspirin group, but it did not impact the viral duration time (Liu et al., 2021). An Iranian study reported that the use of low-dose aspirin in hospitalized COVID-19 patients was associated with reduced mortality risk compared to nonusers (Haji Aghajani et al., 2021).

In contrast, in the recent large RECOVERY trial, with nearly 15,000 hospitalized COVID-19 patients enrolled in the aspirin arm, the allocation to daily low-dose aspirin was not associated with decreased odds of 28-day mortality, risk of progressing to invasive mechanical ventilation or death compared to standard care. As expected, the allocation to low-dose aspirin was associated with a reduction of thrombotic events and with an increase of major bleeding (https://www.medrxiv.org/content/10.1101/2021.06.08.21258132v1). The timing of aspirin initiation, the baseline cardiovascular risk, and the disease severity of the patients may have contributed to the neutral effect of low-dose aspirin on the survival of hospitalized COVID-19 patients reported in this arm of the RECOVERY trial. This result is also consistent with the lack of a clinical benefit reported with anticoagulants in severe COVID-19 patients ((Sadeghipour et al., 2021); https://www.medrxiv.org/content/10.1101/2021.03.10.21252749v1).

Based on the current evidence, the use of low-dose aspirin is not recommended for the primary prevention of arterial thrombosis events in hospitalized COVID-19 patients. However, scientific societies and regulatory health authorities recommend continuing ongoing antiplatelet therapy with low-dose aspirin for the secondary prevention of cardiovascular disease in eligible patients.

Several interventional and observational clinical trials are still ongoing to investigate the effect of aspirin, alone or in combination with other treatments, in the context of SARS-CoV-2 infection in different patient groups (NCT04365309; NCT04363840; NCT04768179; NCT04410328, NCT04808895; NCT04498273; NCT04324463, NCT04381936; NCT04466670, NCT04333407; NCT04483960; NCT02735707; NCT04703608).

1.6. Future directions

In addition to NSAIDs, other drugs or compounds targeting the formation or function of prostanoids are under consideration as adjuvant therapeutics in COVID-19 patients. Prostacyclin receptor analogs, epoprostenol and iloprost, are approved for the treatment of pulmonary hypertension and have been used in COVID-19 patients for their anti-aggregating and vasodilatory properties (DeGrado et al., 2020; Li et al., 2020; Moezinia et al., 2020; Sonti et al., 2021). Asapiprant (BGE-175), a potent DPR1 antagonist under clinical development for the treatment of allergic rhinitis and asthma, is currently being evaluated in hospitalized COVID-19 patients who are not in respiratory failure (NCT04705597). Other compounds like sonlicromanol, an PTGES inhibitor (Hoxha, 2020) and ramatroban, a DPr2 and TPr antagonist (Gupta and Chander Chiang, 2020; Gupta et al., 2020) could be beneficial in COVID-19 patients for their anti-inflammatory and immuno-modulatory proprieties.

The use of NSAIDs could shift the metabolism of AA toward the lipoxygenase (LOX) pathway, resulting in an increased formation in potent chemotactic and immunomodulatory molecules called leukotrienes. Therefore, dual PTGS/5-LOX inhibitors could be potentially beneficial in COVID-19 patients. The interconnectivity between the different AA metabolic pathways and the potential substrate rediversion in response to drug treatments should be assessed in future studies using broad spectrum of eicosanoid assays (Mazaleuskaya et al., 2016).

2. Conclusion

Ultimately, based on current knowledge, therapy with glucocorticoids should be initiated only in severely ill patients with proven signs of excessive immune system activation. Future clinical studies should investigate more rigorously the safety and the efficacy of glucocorticoids, alone or in combinations with antiviral drugs, in COVID-19 patients with less severe disease. These might be augmented by incorporation of biomarkers of severity and response that could identify patients likely to benefit. Further investigations should also determine the type of glucocorticoid drug, the optimal dose and the duration of the treatment. Additional studies are also needed to investigate the effect of ongoing therapy with glucocorticoids on the prevalence and outcome of SARS-CoV-2 infection.

Ongoing NSAID therapy or low-dose aspirin for other indications does not increase the susceptibility to SARS-CoV-2 infection or confer an additional risk of morbidity or mortality to COVID-19. Therefore, patients taking NSAIDs or low-dose aspirin for a comorbid condition should not stop using them if they are being exposed to COVID-19.

There is little evidence of a beneficial effect of NSAID therapy in mitigating the inflammatory response in COVID-19 patients. Given the pro-inflammatory role played by prostanoids during SARS-CoV2 infection, their inhibition through the use of NSAIDs might be beneficial during the initial phase of the viral infection before ARDS develops. However, caution should be observed in patients at risk of NSAID complications, such as those with poor kidney function, cardiovascular risk factors or who are elderly.

There is not a clear clinical benefit from low-dose aspirin use for primary prevention of thrombotic events in hospitalized COVID-19 patients, therefore the use of aspirin in this setting is not recommended.

The efficacy and safety of therapy with NSAIDs or low-dose aspirin in COVID-19 remain to be established by international large-scale prospective cohort studies and appropriately designed clinical trials in patient groups with diverse disease severity. Further

studies are also needed to determine the timing of NSAID or aspirin initiation, dosing, duration of treatment, and to identify subgroups of COVID-19 patients that could benefit most from these treatments.

Finally, considering the similarity between the different coronaviruses (Lu et al., 2020), our current understanding on the use and glucocorticoids and NSAIDs in COVID-19 may inform the future use of these medications in other coronavirus infections.

Declaration of competing interest

The authors declare no competing financial interests.

CRediT authorship contribution statement

Emanuela Ricciotti: Conceptualization, Writing – review & editing, Writing – original draft. **Krzysztof Laudanski:** Writing – review & editing, Writing – original draft. **Garret A. FitzGerald:** Conceptualization, Writing – review & editing.

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