Ketoprofen Lysine Salt as Pharmacological Treatment for SARS-CoV-2

Subjects: Infectious Diseases

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COVID-19 is an infective disease resulting in widespread respiratory and non-respiratory symptoms prompted by SARS-CoV-2 infection. Interaction between SARS-CoV-2 and host cell receptors prompts activation of pro-inflammatory pathways which are involved in epithelial and endothelial damage mechanisms even after viral clearance. Since inflammation has been recognized as a critical step in COVID-19, anti-inflammatory therapies, including both steroids and non-steroids as well as cytokine inhibitors, have been proposed. Early treatment of COVID-19 has the potential to affect the clinical course of the disease regardless of underlying comorbid conditions. Non-steroidal anti-inflammatory drugs (NSAIDs), which are widely used for symptomatic relief of upper airway infections, became the mainstay of early phase treatment of COVID-19.

NSAIDs COVID-19 SARS-CoV-2 inflammation ketoprofen

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the novel coronavirus disease 2019 (COVID-19), has been rapidly transmitted around the world during the last three years, causing a global public health emergency [1]. Coronaviruses are pathogens that largely affect the respiratory system but the expression of host SARS-CoV-2 receptor, angiotensin-converting enzyme 2 (ACE2), is not lung-specific, and its presence in a variety of tissues, including the brain, the intestine, the blood vessels, and the kidney, could subject these organs to direct infection by SARS-CoV-2 making COVID-19 a systemic disease [2]. Most patients commonly present with fever, myalgia, shortness of breath, malaise, and dry cough, although patients may present with asymptomatic, mild, moderate, or severe disease. High systemic levels of cytokines, referred to as "cytokine storm", have frequently been found in severe COVID-19 disease. Therefore, targeting inflammation is one of the key strategies in the management of COVID-19 disease. In this scenario, recent data suggest that NSAIDs may represent a safe strategy in the treatment of SARS-CoV-2 infection [3].

2. Pharmacological Agents with Selective Activity against SARS-CoV-2

2.1. Antivirals Targeting SARS-CoV-2

The group of antiviral drugs comprises several molecules directly targeting the pathogen to hinder its growth. According to their different mechanisms of action, antiviral drugs may be categorized into three main subgroups. (1) Inhibitors of S protein; (2) inhibitors of viral proteases; (3) inhibitors of viral RNA dependent RNA polymerase; (4) host-oriented.

2.1.1. Entry Inhibitors

As stated above, S protein is responsible for virus entry. The S protein is a transmembrane protein with N-exo and C-endo terminals. The N terminal S1 subunit contains receptor binding domain (RBD), known to interact with the peptidase domain of ACE2 and to be the main target of neutralizing antibodies, while the C terminal S2 subunit induces membrane fusion. Monoclonal antibodies (mAbs) are laboratory-produced molecules which derive from natural B cells of subjects who have experienced or been injected with the antigen of interest. As a result, mAbs are able to mimic a normal immune response against a predetermined antigen [4]. During SARS-CoV-2 pandemic, various mABs have been progressively approved worldwide, whilst other are currently under investigation [5]. Target population for treatment with Abs is represented by high-risk patients with symptomatic mild to moderate infection, not requiring supplemental oxygen due to COVID-19. High risk features, among others, include older age, chronic kidney disease, obesity, cardiovascular and metabolic disease, and chronic lung diseases.

Bamlanivimab-Etesevimab

In the BLAZE-1 trial (*NCT04427501*), the cocktail of bamlanivimab and etesevimab, has been reported to significantly reduce hospitalizations and death rate in high-risk patients affected by COVID-19. At the end of 29 days observational period, in the bamlanivimab-etesevimab group, a total of 11 of 518 patients (2.1%) experienced COVID-19 related hospitalization or death from any cause, as compared with 36 of 517 patients (7.0%) in the placebo group (absolute risk difference, −4.8 percentage points; 95% confidence interval [CI], −7.4 to −2.3; relative risk difference, 70%; $p < 0.001$).

Casirivimab and Imdevimab

REGN-COV2 (casirivimab and imdevimab; *NCT04452318*) represents a mixture of the human Abs, casirivimab, and imdevimab. Although identified by different methods, they both target the S protein RBD. Subcutaneous casirivimab and imdevimab, 1200 mg, succeeded in preventing progression to symptomatic disease compared to placebo; odds ratio, 0.54 [95% CI, 0.30–0.97]; $p = 0.04$; absolute risk difference, −13.3% [95% CI, −26.3% to −0.3%]).

Sotrovimab

Sotrovimab, a pan-sarbecovirus monoclonal antibody was shown to significantly reduce the risk of disease progression, leading to hospitalization (for >24 h) for any cause or death, as demonstrated in a phase 3, multicenter, randomized, doubleblind, placebo-controlled trial. A total of 3 of 291 patients in the sotrovimab group (1%) experienced hospitalization for >24 h for any cause or death, in comparison to 21 of 292 patients in the placebo group (7%) (relative risk reduction 85%; 97.24% confidence interval [CI], 44 to 96; $p = 0.002$) [6].

Tixagevimab-Cilgavimab

Tixagevimab-cilgavimab is a neutralizing monoclonal antibody combination whose capability to improve outcomes for patients hospitalized with COVID-19 has lately been investigated. Although tixagevimab–cilgavimab did not improve the primary outcome of time to sustained recovery versus placebo, (89% for tixagevimab–cilgavimab and 86% for placebo group at day 90 [(recovery rate ratio [RRR] 1.08 [95% CI 0.97–1.20]; p = 0.21), it must be noted that mortality was lower in the tixagevimab–cilgavimab group (61 [9%]) versus placebo group (86 [12%]; hazard ratio [HR] 0.70 [95% CI 0.50–0.97]; p = 0.032) [7].

Other Anti-SARS-CoV-2 Monoclonal Antibodies

SARS-CoV-2 may mutate over time making certain treatments less useful and allowing the pandemic to spread. In this respect, variants of concern (VOCs) are continuously monitored due to their great impact on decreasing efficacy of treatment with mAbs. As omicron VOC has quickly spread becoming the dominant variant in US, bebtelovimab has been considered the only monoclonal antibody-based treatment approved by the Food and Drug Administration (FDA) at present [8].

2.1.2. Inhibitors of Viral Proteases

SARS-CoV-2 is constituted by four conserved structural proteins—spike (S), envelope (E), membrane (M), and nucleocapsid (N)—and six accessory proteins. Among them, there are two recognized cysteine proteases—Mpro (3CLpro) and PLpro—which are essential for viral replication. Given the absence of human homolog as well as its important role in the viral gene expression, Mpro has been utilized as a potential molecular target.

Lopinavir/Ritonavir

Lopinavir is an anti-retroviral protease inhibitor employed in combination with ritonavir, in the treatment of HIV infection. Although lopinavir/ritonavir administration was not associated with a significant difference in the time to clinical improvement, in a post-hoc analysis, 28-day mortality was lower in treated population compared to control, albeit not significantly (19.2% vs. 25%) [9]. At present, lopinavir/ritonavir is not recommended for COVID-19 treatment and it can only be considered for patients included in clinical trials [8][10].

Nirmatrelvir/Ritonavir

Nirmatrelvir, a novel orally active inhibitor of 3CL protease inhibitor, in combination with ritonavir, has been investigated in a phase III trial in a cohort of 2246 symptomatic, unvaccinated, non-hospitalized adults at high risk for progression. Scholars reported that the incidence of COVID-19-related hospitalization or death by day 28 was 0.77% (3 of 389 patients) in the nirmatrelvir group compared to 7.01% (27 of 385 patients) in the placebo group, with 7 deaths, and a 89.1% relative risk reduction. Results were confirmed in the final analysis involving the 1379 patients with a difference in terms of hospitalization of −5.81 percentage points (95% CI, −7.78 to −3.84; p < 0.001; relative risk reduction, 88.9%) [11].

2.1.3. Inhibitors of Viral RNA Dependent RNA Polymerase (RdRp)

Remdesivir

Originally developed for the treatment of Ebola and Marburg virus infections, remdesivir (GS-5734) was considered early on as a potential candidate for COVID-19 treatment due to its capacity to cause premature termination of SARS-CoV-2 viral RNA transcription. By acting as nucleotide analog, it is incorporated by the RdRp, and RNA synthesis is consequently inhibited. In the Adaptive COVID-19 Treatment Trial (ACTT-1), in a cohort of 1062 randomized patients, subjects who received remdesivir had a median recovery time of 10 days compared to 15 days of the control group (rate ratio for recovery, 1.29; 95% CI, 1.12 to 1.49; $p < 0.001$, by a log-rank test). With regard to mortality, remdesivir has shown superiority compared to placebo both at day 15 and day 29 (6.7% and 11.4% with remdesivir vs. 11.9 and 15.2% in control, respectively; hazard ratio, 0.73; 95% CI, 0.52 to 1.03).

Molnupiravir

Molnupiravir, the biological prodrug of NHC (β-D-N(4)-hydroxycytidine), represents another ribonucleoside analogue with activity against SARS-CoV-2 and other RNA viruses. Started within 5 days of the onset of signs or symptoms, molnupiravir has showed superiority in decreasing the risk of hospitalization for any cause or death through to day 29 compared to controls in a cohort of 1433 nonhospitalized adults with mild-to-moderate COVID-19 with at least one risk factor for severe COVID-19 (28 of 385 participants [7.3%]) than with placebo (53 of 377 [14.1%]) (difference, −6.8 percentage points; 95% confidence interval [CI], −11.3 to −2.4; $p = 0.001$) [12]. On December 2021, the Food and Drug Administration (FDA) approved monlupiravir for the treatment of adults with mild or moderate COVID-19, within five days of symptom onset, with no alternative antiviral therapies available.

2.1.4. Host-Oriented Therapies for SARS-CoV-2 Infection

Novel drugs targeting host immune factors named host-oriented therapies are currently under development. Virus-host cell interaction prompts the innate immune system response which may be ineffective in determining a complete viral clearance [13][14]. Therefore, the possibility to restore the altered immune responses with these host-oriented therapies offers a great opportunity against viral infections [15][16][17]. SNG001 is an inhaled drug containing INF-β, an antiviral protein produced during viral spread and it is under evaluation in clinical trial (NCT04385095). SARS-CoV-2 might weaken the immune system response also through the inhibition of IFN-β expression [18][19]. In this phase 2 trial, COVID-19 patients receiving inhaled SNG001 had greater improvement in clinical symptoms and recovered more rapidly than patients who received placebo [19]. Another host-oriented strategy in evaluation for COVID-19 is the possibility to use IL-7 to support the host's immune system. IL-7 promotes lymphocytic count increase counteracting the lymphocytopenia, a pathologic hallmark of severe COVID-19. In a recent study with a small number of patients with COVID-19, it was shown that IL-7 can be safely administered and it was associated with an increase in lymphocytes count, appearing to counteract a pathologic hallmark of COVID-19 [20]. These results were under evaluation in another trial (NCT04379076), actually terminated for poor accrual. The administration of IL-7 seems to improve clinical outcome as already demonstrated in septic patients [21][22].

3. Anti-Inflammatory Drugs in COVID-19

3.1. Corticosteroids Use in COVID-19 Patients

Corticosteroids (CCS) are steroid hormones implicated in several physiological processes such as the control of inflammatory response, protein catabolism, gluconeogenesis, antiallergy proprieties, and potent immunomodulator effects [23]. In clinical practice, there are two major classes of corticosteroids that are commonly used, glucocorticoids (e.g., dexamethasone, prednisolone and methylprednisolone) named for their gluconeogenic proprieties, and mineralcorticoids (e.g., fludrocortisone) named for their role in salt-water balance [24]. The potent anti-inflammatory effect of these drugs is due to the inhibition of NF-κB pathway, reducing IL-6 and TNF-α expression. Corticosteroids also act in cellular immunity inhibiting $CD8^+$ T cells, TH1 cells, and NK cells [25][26].

3.2. Non-Steroidal Anti-Inflammatory Drugs in the Early Stage of the Therapeutic Scenario of COVID-19

Non-steroidal anti-inflammatory drugs (NSAIDs) are very widely used to alleviate fever, pain, and inflammation (common symptoms of COVID-19 patients) through effectively blocking production of prostaglandins (PGs) via inhibition of cyclooxygenase enzymes, namely COX-1 and COX-2, that catalyze the two-step conversion of arachidonic acid into thromboxane, prostaglandins, and prostacyclins. Prostaglandins are key inflammatory mediators. The use of NSAIDs during the COVID-19 pandemic, especially in the first wave, was controversial and NSAIDs were largely avoided in this phase of COVID-19 pandemic to favor the analgesic antipyretic paracetamol with no anti-inflammatory effect. Later, on the 18th of March 2020 European Medicines Agency (EMA) clarified and concluded that there is no clinical reason to withdraw the use of NSAIDs during the SARS-CoV-2 pandemic [27]. Moreover, some evidence suggested that early use of non-steroidal anti-inflammatory drugs in COVID-19 might interfere with the disease progression in patients with mild-to-moderate COVID-19 [28][29].

NSAIDs are defined nonselective when they inhibit both COX-1 and COX-2, and COX-2 selective. Their main indications are to alleviate fever, inflammation, and pain, including in patients with chronic inflammatory disorders such as rheumatoid arthritis and osteoarthritis. To reduce gastrointestinal side effects mediated essentially by inhibition of COX-1, highly selective COX-2 inhibitors (-coxib) were developed, although a number of recent studies have highlighted more serious potential cardiovascular side effects. The cardiovascular risk is not limited to the use of COX-2 inhibitors but is also correlated with the use of non-selective NSAIDs.

3.3. Ketoprofen Lysine Salt in the Therapeutic Scenario of SARS-CoV-2 Infection

3.3.1. Ketoprofen Lysine Salt Mechanism of Action

An optimal NSAID should give relief and prevent complications and worsening of the disease. Ketoprofen is a NSAID belonging to the family of propionic derivates, with analgesic, anti-inflammatory, antipyretic, and antiplatelet properties [30][31].

Salification of ketoprofen with the lysine amino acid allows for higher solubility that facilitates a more rapid and complete absorption of the drug with a high peak plasma concentration reached after 15 min vs. 60 min [32][33][34][35]. Ketoprofen lysine salt (KLS) is a non-selective NSAID but also demonstrates high activity on COX-2 and inhibits the lipoxygenase pathway of the arachidonic acid cascade leading to a decrease in the synthesis of leukotrienes [36]. Ketoprofen, in common with other NSAIDs, has both peripheral and central sites of action [37] through the inhibition of both nitric oxide (NO) and COX synthase in the brain [38] and is rapidly and readily distributed into the central nervous system passing the blood brain barrier within 15 min, thanks to its high level of liposolubility (**Figure 1**) [33].

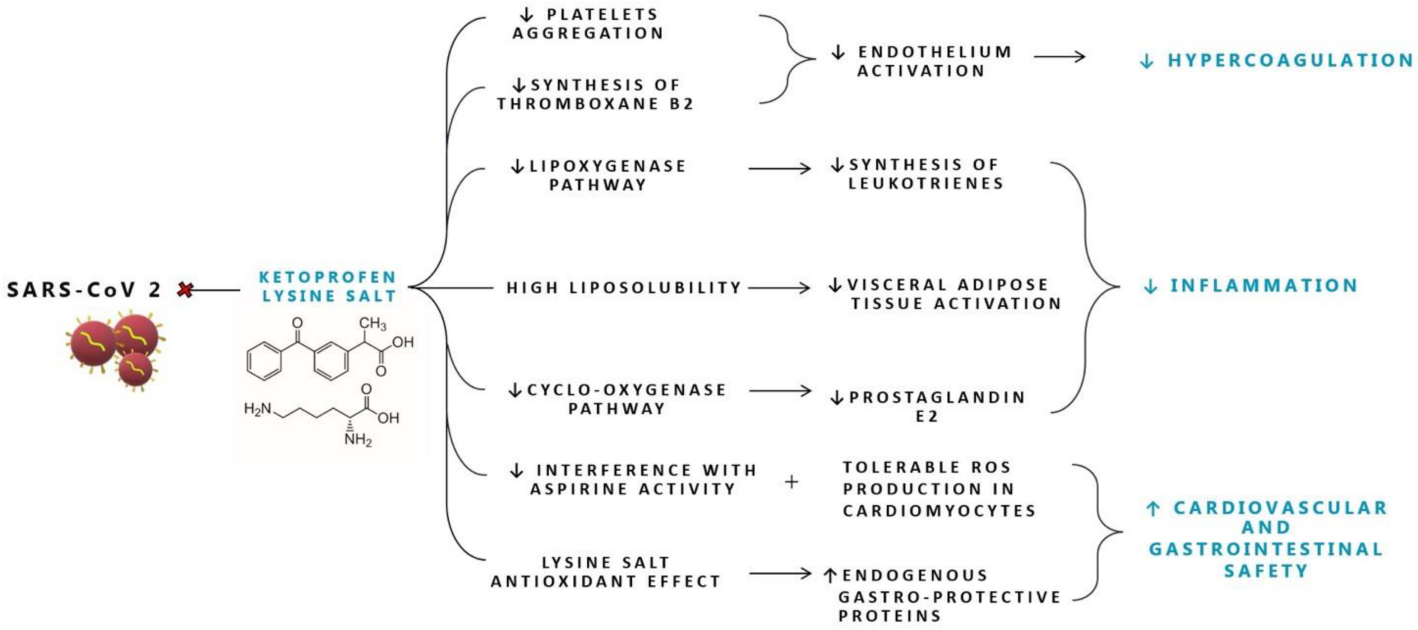

Figure 1. Proposed mechanisms of action of Ketoprofen lysine salt in SARS-CoV-2 infection. ROS: reactive oxygen species.

3.3.2. Ketoprofen Lysine Salt Cardiovascular Safety

In the last two years, real life studies and clinical experience have clarified that SARS-CoV-2 can impair cardiovascular system infecting heart and vascular tissues via ACE2 (angiotensin-converting enzyme 2), highlighting that cardiovascular diseases highly influence the susceptibility to and the outcomes of SARS-CoV-2 infection.

The systemic inflammation related to COVID-19 could accelerate the worsening of subclinical disorders or cause de novo cardiovascular diseases [39][40] such as myocardial injury or acute coronary syndrome largely linked to advanced systemic inflammation. Attention should be paid to the potential drug–disease interactions, preexisting cardiovascular diseases and drug cardiovascular safety profile in COVID-19 patients [41].

4. Conclusions

Targeting pro-inflammatory pathways in early phases of COVID-19 is one of the key strategies in avoiding progression of the disease; NSAIDs, because of their interaction with different pro-inflammatory mediators, may play pleiotropic effects in COVID-19. The evolution of therapeutic strategies for the early stages of SARS-CoV-2 infection should be oriented in developing combination of complementary drugs able to interact with this complex network between virus, host cell, and innate immune cells and large prospective randomized clinical trials are needed to better investigate the efficacy and safety of these drugs also exploring the different pharmacokinetic properties existing among the drugs.

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