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Immunomodulation as a potent COVID-19 pharmacotherapy: past, present and future

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Abstract

In the first year of its appearance, the 2019 coronavirus disease (COVID-19) has affected more than 120 million individuals and killed 2 million people worldwide. The pandemic has also triggered numerous global initiatives to tackle the newly emerging disease, including the development of SARS-CoV-2 vaccines and the attempt to discover potential pharmacological therapies. Nonetheless, despite the success of SARS-CoV-2 vaccines development, the COVID-19 therapy remains challenging. Several repurposed drugs that were documented to be useful in small clinical trials have been shown to be ineffective in larger studies. Additionally, the pathophysiology of SARS-CoV-2 infection displayed the predominance of cytokine storm in inducing multiorgan damage. Therefore, the potential benefits of both immune modulation and suppression in COVID-19 have been extensively discussed. Here, we reviewed the roles of immunomodulation as potential COVID-19 pharmacological modalities based on the existing data and proposed several new immunologic targets to be tested in the foreseeable future.

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Keywords: COVID-19; immunomodulation; immunology; immune system; pharmacotherapy; coronavirus; drug repurposing.

Introduction

The 2019 coronavirus disease (COVID-19) is caused by severe acute respiratory syndrome-associated coronavirus type-2 (SARS-CoV-2) infection. In the first year of its appearance, COVID-19 has affected more than 120 million individuals and killed 2 million people worldwide. In some countries, the numbers are still soaring, while in some of the others, the cases are resurging, entering the second and third waves. Such increase could be attributed to several determinants, including the emergence of novel SARS-CoV-2 variants (e.g., N501Y, E484K, B117), psychological exhaustions (pandemic fatigue) altering the adherence to health protocols, viral reinfection, vaccination delay and the non-existence of potent pharmacological treatments for COVID-19. In most of the contracted patients, COVID-19 is asymptomatic or only causes mild to moderate non-life-threatening symptoms. However, in high-risk individuals, it can cause serious conditions, leading to severe acute respiratory failure, multiorgan dysfunction and death. Therefore, having safe and effective pharmacological agents for COVID-19 is essential to prevent mortality and COVID-19-associated complications (e.g., long COVID).

The pandemic has triggered numerous global initiatives to tackle the newly emerging disease, including the development of SARS-CoV-2 vaccines and the attempt to discover potential pharmacological therapies. Nonetheless, despite the success of SARS-CoV-2 vaccines development, the COVID-19 therapy remains challenging. Several repurposed drugs that were documented to be useful in small clinical trials were ineffective in larger studies. For example, the antimalarial drug chloroquine and antimicrobial azithromycin were effective in reducing COVID-19-associated mortality in 2541 multi-centre patients (Arshad et al., 2020). However, in a meta-analysis, the chloroquine and azithromycin-treated group displayed no significant difference in mortality compared to standard care (Ghazy et al., 2020). Moreover, those drugs were associated with greater adverse effects, including the occurrence of malignant arrhythmias (Sutanto & Heijman, 2020). Similarly, the use of human immunodeficiency virus (HIV) protease inhibitors ritonavir/lopinavir was no longer recommended following studies reporting no benefit compared to standard care (Cao et al., 2020; Group, 2020). Meanwhile, inconclusive findings were documented for antiparasitic ivermectin (Lopez-Medina et al., 2021; Rajter, Sherman, Fatteh, Vogel, Sacks & Rajter, 2021) and antiviral favipiravir (Cai et al., 2020;

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Solaymani-Dodaran et al., 2021). To date, only antiviral remdesivir was shown to facilitate significant clinical improvements and has been authorised for COVID-19 by major drug safety regulators (Beigel et al., 2020; Garibaldi et al., 2021).

Likewise, the pathophysiology and key determinants of the disease have not been fully elucidated. Several evidences pointed toward the strong involvement of proinflammatory mediators, with clear evidences of cytokine storm, which is essential to induce multiorgan dysfunction, worsening the prognosis of COVID-19 (Tang, Liu, Zhang, Xu, Ji & Wen, 2020). Therefore, immunosuppression could potentially be beneficial in the COVID-19 management. However, previous systematic review reported that immunocompromised patients with COVID-19 had higher comorbidities, rates of intensive care and hospital mortality (Belsky, Tullius, Lamb, Sayegh, Stanek & Auletta, 2021), indicating the potential risk of immunosuppression in COVID-19. Thus, in this narrative review, we explore the documented effects of immunosuppressive medications (e.g., corticosteroids, interleukin (IL)-1 inhibitors, IL-6 inhibitors and kinase inhibitors) and immunomodulators (e.g., interferon alpha (IFNα), interferon beta (IFNβ), non-SARS-CoV-2 specific immunoglobulin and convalescent plasma) in COVID-19, and propose some potential immunologic targets to test in the foreseeable future (**Figure 1**).

Immunosuppression in COVID-19

Hyperactivation of immune system is a hallmark of COVID-19 severity. Ample evidences have reported higher number of leukocytes, increased levels of procalcitonin, C-reactive protein (CRP), and other proinflammatory cytokines (e.g., IL-1 and IL-6) / chemokines (e.g., CXCL10 and CCL2) in COVID-19 patients requiring intensive care. Such hyperactive inflammatory response initiates cytokine storm and may contribute to the uncontrolled apoptosis, vascular leakage, thromboembolism, multiorgan damage and death (Tang, Liu, Zhang, Xu, Ji & Wen, 2020). Therefore, immunosuppression has been proposed as a potential therapeutic strategy in COVID-19.

Corticosteroids have a potent anti-inflammatory effect and are currently used to treat dysregulated inflammatory response in autoimmune diseases. In COVID-19, inhaled corticosteroid ciclesonide inhibited SARS-CoV-2 RNA replication by targeting viral replication-transcription complex (Matsuyama et al., 2020). Despite the failure of corticosteroids to show significant benefits and their association with delayed viral clearance in previous coronavirus (SARS-CoV-1 and MERS-CoV) diseases, studies investigating the effects of corticosteroids in COVID-19 showed several promising results (Chatterjee, Wu, Bhardwaj & Siuba, 2020). For example, methylprednisolone lowered COVID-19-associated mortality in patients with acute respiratory distress syndrome and reduced the duration of supplemental oxygen in COVID-19 patients (Chatterjee, Wu, Bhardwaj & Siuba, 2020). More recently, Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, a randomised controlled, open-label trial involving 2104 patients with oral or intravenous dexamethasone reported that dexamethasone lowered the 28-day mortality among patients receiving invasive mechanical ventilation and among those receiving oxygen without invasive mechanical ventilation, but not among those who were receiving no respiratory support at randomisation (Group et al., 2021). In adult patients with non-severe COVID-19, corticosteroids therapy was associated with worse clinical outcomes (Li et al., 2020) and a higher risk of progression of severity and prolonged hospital stay (Chatterjee, Wu, Bhardwaj & Siuba, 2020). Additionally, a recent retrospective study reported that delayed SARS-CoV-2 clearance in moderate/severe COVID-19 was not associated with an early use of corticosteroids (Spagnuolo et al., 2020), highlighting the potential benefits of corticosteroids in the treatment of moderate/severe COVID-19 patients.

Interleukin inhibitors are commonly prescribed in autoimmune diseases and other hyperinflammatory states. Several interleukins are responsible for COVID-19-mediated cytokine storm (e.g., IL-1β, IL-6 and IL-18) and their inhibition could be beneficial. A cohort of 117 patients with respiratory insufficiency and hyperinflammation receiving either IL-1 or IL-6 inhibitors reported that IL-1 inhibition (with anakinra) significantly reduced mortality in COVID-19 patients with respiratory insufficiency and hyperinflammation. Meanwhile, IL-6 inhibition (with tocilizumab or sarilumab) was only effective in a subgroup of patients with high CRP

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or low lactate dehydrogenase (Cavalli et al., 2021). Additionally, IL-6 inhibitors also improved survivals in critically-ill COVID-19 patients receiving intensive organ support (Investigators et al., 2021). Moreover, in a meta-analysis of 71 (heterogenous) studies, tocilizumab was consistently associated with a lower relative risk of mortality in prospective studies, but effects were inconclusive for other outcomes (Khan et al., 2021), underlining the prospective benefits of interleukin inhibition in COVID-19.

Kinase inhibitors inhibit numerous kinases (e.g., ABL, NAK, CDK, PI3K/AKT/mTOR, ERK/MAPK and JAK) that are important for viral infections and predicted to be involved in mediating infection by SARS-CoV-2 (Weisberg et al., 2020). They play important roles in viral entry, intracellular membrane trafficking, viral replication and viral life cycle, and possess an immunomodulatory effect that could be useful against COVID-19-mediated hyperactive immune response. However, a recent*in-vitro* study showed that imatinib, an ABL inhibitor, did not inhibit SARS-CoV-2 entry/infection and replication (Zhao, Mendenhall & Deininger, 2020). Meanwhile, baricitinib, a JAK inhibitor, prevented phosphorylation of key proteins involved in the signal transduction that leads to immune activation and inflammation (e.g., the cellular response to IL-6) (Zhang et al., 2020). In a double-blind, randomised, placebo-controlled trial of 1033 patients, baricitinib/remdesivir was superior to remdesivir alone in reducing recovery time and accelerating clinical improvement, and associated with fewer serious adverse events in COVID-19 patients receiving high-flow oxygen or non-invasive ventilation (Kalil et al., 2021).

Immune system modulation in COVID-19

In addition to immunosuppression, several immunomodulators are proposed in COVID-19 management and expected to restore the immunologic homeostasis in COVID-19 patients.

Interferons are cytokines-made and released by host cells in response to viral pathogens. SARS-CoV-2 could release a series of molecular anti-IFN defences to escape innate immunity early during the infection, altering intrinsic IFN's effect in limiting viral replication and spread (Calabrese, Lenfant & Calabrese, 2020). In a retrospective cohort of 77 adults with moderate COVID-19, treatments using nebulised IFNα-2b yielded a shorter time to viral clearance from the upper respiratory tract and a reduction in systemic inflammation (Zhou et al., 2020). In a randomised controlled trial of 42 patients receiving subcutaneous IFNβ-1a on top of hydroxychloroquine/lopinavir/ritonavir or atazanavir/ritonavir therapies, IFNβ-1a significantly increased discharge rate at day-14 and reduced 28-day mortality (Davoudi-Monfared et al., 2020). Nonetheless, despite these promising results, more data investigating the effects of IFN are required due to an increasing evidence that patients with severe COVID-19 have a robust type-I IFN response, in contrasts with the delayed, possibly suppressed, IFN response in the early phase of SARS-CoV-2 infection (Lee & Shin, 2020).

Non-SARS-CoV-2 specific intravenous immunoglobulin (IVIg) is a product derived from the pooled plasma of donors that provides passive immunity against a broad range of pathogens and commonly used for treatment of primary and secondary immunodeficiencies, autoimmune/inflammatory conditions, neuro-immunologic disorders, and infection-related sequelae (Nguyen, Habiballah, Platt, Geha, Chou & McDonald, 2020). In autoimmune diseases, IVIg modulates the activation and effector functions of B and T lymphocytes, neutralises pathogenic autoantibodies, interferes with antigen presentation and therefore, has a strong anti-inflammatory effect (Bayry et al., 2003). In COVID-19, although the exact mechanism of action is unclear, it is hypothesised that IVIg exerts its beneficial effect through the modulation of inflammation, including the presence of anti-idiotypic antibodies and IgG dimers blocking the FcγR activation on innate immune effector cells (Nguyen, Habiballah, Platt, Geha, Chou & McDonald, 2020), complement scavenging, and reciprocal regulation of effector Th1, Th17 and regulatory T-cells. Moreover, IVIg also decreased plasma IL-6 and CRP levels (Galeotti, Kaveri & Bayry, 2020). A double-blind randomised placebo-controlled trial involving 59 patients with severe COVID-19 who did not respond to initial treatments reported an improvement of clinical outcome and a reduction in mortality following the administration of IVIg (Gharebaghi, Nejadrahim, Mousavi, Sadat-Ebrahimi & Hajizadeh, 2020). Similarly, several retrospective studies also reported the benefits of early IVIg in reducing the 28-day and 60-day mortality, hospital stay, inflammatory

response, and improving multiorgan physiology and clinical outcome of severe COVID-19 patients (Galeotti, Kaveri & Bayry, 2020), which effects are more prominent with those having no comorbidities or treated at earlier stage (Cao et al., 2021).

Hyperimmune globulin and convalescent plasma are derived from individuals with high antibody titres to specific pathogens and can provide passive immunity (i.e., neutralising antibodies) against particular infectious agents. It was effective in treating SARS-CoV-1 and MERS-CoV infections by increasing the discharge rate and lowering mortality (Nguyen, Habiballah, Platt, Geha, Chou & McDonald, 2020). In a retrospective, propensity score-matched case-control study in 39 patients with severe or life-threatening COVID-19, convalescent plasma reduced the oxygen requirements at day-14 after transfusion and improved survivals (Liu et al., 2020). Interestingly, such observation was not documented in randomised control trials (RCTs). For instance, a meta-analysis of 10 RCTs reported that the treatment with convalescent plasma compared with placebo or standard of care was not significantly associated with a decrease in all-cause mortality or with any benefit for other clinical outcomes (Janiaud et al., 2021). Since the majority of the RCTs also involved moderate to severe COVID-19 patients, this finding discrepancy might not be due to the difference on the disease severity.

Phase identification is the key to a prompt immune modulation

The majority of previous clinical trials indicated that both immunosuppression and immunomodulation were effective in severe COVID-19 conditions requiring respiratory support and ventilation, while in non-severe disease phase, immunologic treatments might elicit worse outcome (e.g., corticosteroid) or no significant improvements of clinical outcome or mortality. This fits well with the identified disease pathophysiology (**Figure 2**) implying the hyperinflammatory state with cytokine release syndrome in severe COVID-19. In such conditions, inhibition of proinflammatory cytokines with immunosuppressive agents could reduce the damaging consequences of rogue inflammation and immunomodulation might restore the host immune regulation. On the other hand, in the early phase, immunologic treatments tend to disrupt the activation of immune response against viruses and therefore, could be detrimental.

Future immunologic targets for COVID-19

In the future, several novel immunologic targets such as tumour necrosis factor (TNF)-α inhibitors, RLR and mTOR inhibitors, NLRP3 inflammasome inhibitors, TLR modulators, IL-18 inhibitors and possibly mesenchymal stem cell secretome may be tested due to their reported significance in COVID-19 pathogenesis.

To summarise, both immunosuppression and immunomodulation could serve as potent COVID-19 therapies. However, the benefits could only be attained when they are administered in the appropriate disease stage / severity (**Figure 2**) and have to consider the patients characteristics and comorbidities to minimise adverse effects and complications.

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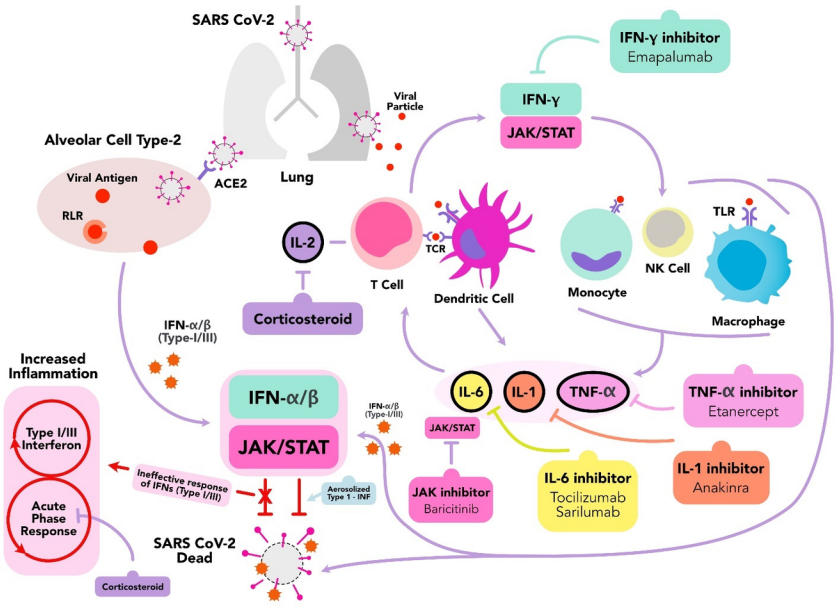

Figure 1. The hyperactive immune response in SARS-CoV-2 infection and druggable immunologic targets in COVID-19. The SARS-CoV-2 enters the infected person via the respiratory tract and attaches to the ACE2 receptors in type-2 alveolar cells of the lungs. It subsequently activates the retinoic acid inducible gene-(RIG) I-like receptors (RLRs), which play an essential role in the activation of antiviral immune responses. Together with the intrinsic response to the viral particles, they induce hyperactive inflammatory response, marked by the activation of proinflammatory cytokines-releasing cells. Several immunologic targets were identified to have an important role in the COVID-mediated cytokine release syndrome / cytokine storm, therefore some pharmacological agents are repurposed to reduce the COVID-induced hyperinflammation and possibly also prevent the viral entry and replications. (ACE2 = angiotensin converting enzyme type-2; CoV = coronavirus; IFN = interferon; IL = interleukin; JAK = janus kinase; SARS = severe acute respiratory syndrome; NK = natural killer; STAT = signal transducer and activator of transcription; TCR = T-cell receptor; TLR = toll-like receptor; TNF = tumour necrosis factor)

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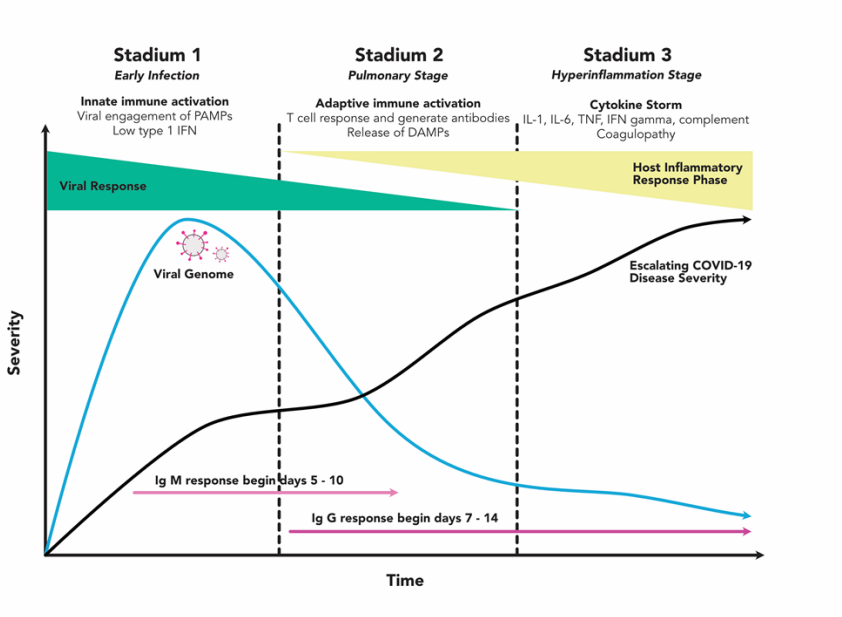

Figure 2. The phases of COVID-19. The COVID-19 can be divided into 3 stadiums: the early infection, the pulmonary and the hyperinflammation stages. In the early infection, the viral load starts to increase and at some points, it begins to activate the host immune response. While the disease progresses into a more severe state, the proinflammatory cytokines build up and start to form antibody against the virus. When the disease is not promptly treated, COVID-19 may fall into the hyperinflammation stage, multiorgan failure and death.