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REVIEW

Therapeutic role of immunomodulators during the COVID-19 pandemic – a narrative review

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ABSTRACT

The emergency state caused by COVID-19 saw the use of immunomodulators despite the absence of robust research. To date, the results of relatively few randomized controlled trials have been published, and methodological approaches are riddled with bias and heterogeneity. Anti-SARS-CoV-2 antibodies, convalescent plasma and the JAK inhibitor baricitinib have gained Emergency Use Authorizations and tentative recommendations for their use in clinical practice alone or in combination with other therapies. Anti-SARS-CoV-2 antibodies are predominating the management of non-hospitalized patients, while the inpatient setting is seeing the use of convalescent plasma, baricitinib, tofacitinib, tocilizumab, sarilumab, and corticosteroids, as applicable. Available clinical data also suggest the potential clinical benefit of the early administration of blood-derived products (e.g. convalescent plasma, non-SARS-CoV-2-specific immunoglobins) and the blockade of factors implicated in the hyperinflammatory state of severe COVID-19 (Interleukin 1 and 6; Janus Kinase). Immune therapies seem to have a protective effect and using immunomodulators alone or in combination with viral replication inhibitors and other treatment modalities might prevent progression into severe COVID-19 disease, cytokine storm and death. Future trials should address existing gaps and reshape the landscape of COVID-19 management.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the single-stranded ribonucleic acid virus behind the coronavirus disease 2019 (COVID-19) pandemic. By October 2021, close to 220 million cases of COVID-19 have been reported, with more than 4.5 million lives claimed by the disease. Similar to other pathogenic coronavirus infections (e.g. severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS)), SARS-CoV-2 can infect respiratory airways and rapidly progress into acute respiratory distress syndrome (ARDS), acute respiratory failure, and other serious complications [1]. In most cases, SARS-CoV-2 infection manifests as asymptomatic or very mild, with higher mortality observed in the more severe forms of the disease [2,3].

Considering the high transmissibility, morbidity, and mortality of COVID-19, understanding disease pathology, identifying prognostic markers, and establishing optimal treatment approaches has become vital. COVID-19 is first and foremost a viral disease. Following the initial viral replication phase, the virus elicits a pro-inflammatory response characterized by cytokine and chemokine release. In its more severe forms, SARS-CoV-2 infection causes uncontrolled systemic inflammatory response, or a 'cytokine storm,' with long-term implications on lung tissues and other organs [4,5]. With the absence of vaccines, the immunopathological changes caused by COVID-19 have thus become a subject of great interest in hopes of guiding clinical management of the disease beyond simple inhibition of viral replication [6]. In this context, this narrative review aims to capture the most recent

information and complement available data on the role of immunomodulators as potential drugs for the management of COVID-19.

2. Cytokine storm in COVID-19

A cytokine storm is known as an excessive immune response to an external stimulus that can be fatal. Its pathogenesis is complex but a cytokine storm is usually triggered by viral infections, autoimmune disorders and immunotherapies [7,8]. Cytokine storms present a diagnostic and a therapeutic challenge due to significant overlap in their pathophysiological and clinical presentation with other inflammatory and infectious syndromes. As immune cells get abnormally activated, excessive pro-inflammatory cytokine release targeting pathogen elimination progresses rapidly into a cytokine storm that does not spare host tissue [8]. The resulting cytokine release syndrome leads to tissue toxicity, which can be observed on a wide variety of organs, in addition to high fever, diffuse intravascular coagulation, shock, multiple-organ failure, and mortality [8,9].

Similar to SARS and MERS [7,8], severe COVID-19 infection may result in a pro-inflammatory cytokine storm and acute respiratory distress/failure. The hyperinflammatory state of patients with severe SARS-CoV-2 infection can be traced back to pathogenic T-cells and mononuclear cells triggering the release of pro-inflammatory cytokines [10]. More specifically, the induction of the cytokine Interleukin 1 (IL-1) in both macrophages and mast cells by SARS-CoV-2 leads to an increase in the release of pro-inflammatory complexes (composed of IL-6 and TNF) following the maturation of IL-1β. These complexes are associated with lung inflammation, fever, and fibrosis [11,12]. To that end, the prevention of the descent into a hyperinflammatory state through both traditional (IL-1 inhibitors) and novel (inhibitory cytokines IL-37 and IL-37) approaches were suggested as a promising approach against COVID-19 [11,12], later to be supported by clinical studies. In fact, evidence clearly shows that severe COVID-19 patients are particularly prone to present with elevated inflammatory markers and reduced lymphocyte counts [1,13]. Patients admitted to the intensive care unit (ICU) are significantly more likely to have elevated levels of pro-inflammatory mediators (e.g. IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), interferon-gamma (IFN-γ) and tumor necrosis factor-α (TNF-α)) when compared to non-ICU patients. Elevated levels of IL-6 are actually associated with worse prognosis and clinical outcomes in COVID-19 [14].

In this perspective, immunomodulation and targeting key drivers of COVID-19-induced cytokine storm thus became a promising therapeutic approach. That being said, emerging evidence on the unintended effects of immunomodulators, such as vaccine-induced neutralizing antibodies as well as the long-term effect of the virus' own spike protein (long-COVID syndrome) highlight the importance of a multifaceted approach against the COVID-19 pandemic [15]. The arsenal against COVID-19's deadly cytokine storm should therefore be supplemented both with the modulation of disease outcomes, such as the oxidative stress produced by COVID-19, as well as prophylaxis (vaccination and the reduction of viral shedding) [15,16]. Both of these approaches are outside of the scope of this review, which will focus on the use of immunomodulators for the management of COVID-19.

3. Immunomodulators for cytokine storm in COVID-19 confirmed case

It is now established that innate immunity dysregulation and cytokine storm are associated with a severe form of SARS-CoV-2 infection. As the dysregulation in the balance between T helper cells 1 and 2 (Th1 and Th2) lymphocytes increases, cytokines, such as IL-4, IL-13, IL-6 and IL-5 rise in both sera and lung tissue of COVID-19 patients, leading to a state of hyper immunity, cytokine storm, and death. However, the hyperinflammatory stage is the final one of three progressive stages in the SARS-CoV-2 [17]. Preventing progression into cytokine storms through the use of immunomodulators can be potentially lifesaving, particularly in severe COVID-19 cases. To that end, a "window of opportunity" early in the course of infection where active treatment will be most effective should not be missed [17]. Early signs of systemic involvement should be recognized and quickly addressed in a concerted effort to limit progression into a hyperinflammatory stage. While many randomized controlled trials (RCTs) remain underway, observational, retrospective, anecdotal data, and clinical cases guide current treatment strategies and limited evidence-based treatment for COVID-19 currently exists [18]. Several immunomodulators can be repurposed for COVID-19 treatment and show to be promising at different disease stages according to preliminary clinical data, as summarized in Table 1.

3.1. Convalescent plasma

Convalescent plasma was initially one of the most common biological interventions under clinical trial [19,20] and one of the few therapies to have gained an Emergency Use Authorization (EUA) by the Food and Drug Administration (FDA) for COVID-19. In addition to cytokine profile modification and the increase of anti-SARS-CoV-2 neutralizing antibodies [21,22], convalescent plasma was shown to lead to a significant reduction in immune system exhaustion and the activation of memory B and T cells 28 days after the infusion [22] as well as a reduction in circulating IL-6 and IFN-γ [23]. Neutralizing antibodies in the plasma can be detected through SARS-CoV-2 spike protein receptor binding domain (RBD) antibody titers [24] and anti-spike ectodomain titers [25]. However, the sustainability of the anti-RBD response was initially unclear. Neutralizing antibody titers were shown to significantly decrease in the months following the onset of COVID-19 symptoms [26,27], with the decline potentially starting after an initial spike at day 7 [28]. Generally, the clinical benefit of convalescent plasma remains debated. Convalescent plasma seems to be well tolerated and might improve clinical outcomes (e.g. inflammation, pulmonary function) and prognosis in severe COVID-19 cases [29,30]. One non-randomized trial from Iran confirmed a significant decrease in length of hospitalization, an improvement in

Table 1. Summary of guidance and evidence on the use of immunomodulators in the management of COVID-19.

Intervention	FDA EUA	NIH recommendation	Potentially optimal use/efficacy	Potential benefit
Convalescent plasma	Yes, high-titer plasma only	• No recommendation for or against in non-hospitalized patients, with or without impaired humoral immunity • Recommendation against use in hospitalized patients without impaired humoral immunity.	• Early disease. • High-titer • Hospitalized patients with impaired humoral immunity.	• Increase in anti-SARS-CoV-2 neutralizing antibodies. • Reduction in immune system exhaustion. • Activation of memory B and T cells. • Reduction in pro-inflammatory cytokines and mediators (e.g. IL-6 and IFN-γ). • Improvement in clinical outcomes (e.g. inflammation, pulmonary function, length of hospitalization, need for intubation, progression to severe disease). • Decrease in mortality risk.
IVIGs				
SARS-CoV-2-specific IVIG	No.	No recommendation for or against.	N/A	N/A
Non-SARS-CoV-2-specific IVIG	No.	Recommendation against, except: • In a clinical trial. • When indicated for COVID-19 complications.	• Early disease. • Severe disease. • Hospitalized patients. • Indicated COVID-19 complications	• Increase in clinical improvement (e.g. reduced hospital length of stay, reduced need for mechanical ventilation, improvement in hypoxia). • Decrease in mortality.
Anti-SARS-CoV-2 monoclonal antibodies				
Bamlanivimab/ etesivimab	Yes.	Recommended in non-hospitalized patients with mild to moderate COVID-19 who are at high risk of clinical progression in regions where the combined frequency of potentially resistant SARS-CoV-2 variants is low	• Non-hospitalized. • Adults and pediatric (>12 years and >40Kgs). • Mild-to-moderate disease. • Confirmed SARS-CoV-2 infection. • High risk of progression to severe COVID-19 and/or hospitalization. • Infection with susceptible variant of interest.	• Reduction of viral load. • Decreased hospitalizations. • Decreased mortality.
Casirivimab/imdevimab	Yes.	Recommended for non-hospitalized patients with mild to moderate COVID-19 who are at high risk of clinical progression.	• Non-hospitalized • Adults and pediatric (>12 years and >40Kgs). • Mild-to-moderate disease. • Confirmed SARS-CoV-2 infection. • High risk of progression to severe COVID-19 and/or hospitalization.	• Reduction of viral load. • Decreased hospitalizations. • Decreased mortality.
Sotrovimab	Yes.	Recommended for non-hospitalized patients with mild to moderate COVID-19 who are at high risk of clinical progression.	• Non-hospitalized • Adults and pediatric (>12 years and >40Kgs). • Mild-to-moderate disease. • Confirmed SARS-CoV-2 infection. • High risk of progression to severe COVID-19 and/or hospitalization.	• Reduction of progression in patients with mild-to-moderate disease. • Safe and tolerable.
IFNs				
IFN-α	No.	• Recommendation against in non-hospitalized patients. • Recommendation against in hospitalized patients outside of a clinical trial.	• Early disease. • Hospitalized patients.	• Increase in viral clearance. • Decrease in inflammatory markers. • Decrease in length of hospitalization. • Improvement in clinical outcomes. • Decrease in mortality.

Table 1. (Continued).

Intervention	FDA EUA	NIH recommendation	Potentially optimal use/efficacy	Potential benefit
IFN β (1a and 1b)	No.	Recommendation against	• Early disease. • Mild-to-moderate disease. • Hospitalized and non-hospitalized patients.	• Faster clinical improvement • Increase in virological clearance rates. • Reduction in hospitalizations. • Decrease in mortality.
IL Inhibitors				
IL-1 inhibitors: Anakinra	No.	No recommendation for or against.	• Severe to critical disease. • Hospitalized patients.	• Decrease in severe respiratory failure and the need for mechanical ventilation and oxygen supplementation. • Management of the cytokine storm syndrome and alleviation of hyperinflammation. • Decrease in mortality. • Decrease in hospital stay
Canakinumab	No.	Recommendation against, except in a clinical trial.	• N/A	• N/A
IL-6 inhibitors				
Sarilumab	No.	Can be used instead of tocilizumab if it is not available in the same recommended categories.	• Early disease. • Severe disease. • Hospitalized. • Need for oxygen supplementation. • Need for oxygen through high-flow. device or non-invasive ventilation. • Need for mechanical ventilation or extracorporeal membrane oxygenation.	• Increase in clinical improvement. • Improvement in prognosis. • Reduced mortality. • Reduced time to ICU discharge. • Increased number of organ support-free days.
Tocilizumab	No.	• Recommendation for the addition of tocilizumab to dexamethasone and/or remdesivir, only specific cases when rapid respiratory decompensation and systemic inflammation due to COVID-19 is seen: • Hospitalized patients with requirement for oxygen supplementation: • Hospitalized patients with requirement of oxygen through a high-flow device or non-invasive ventilation • Recommendation for the combination of IV tocilizumab with dexamethasone for: • Hospitalized patients requiring mechanical ventilation or extracorporeal membrane oxygenation who are within 24 hours of hospital admission.	• Early disease • Severe disease • Hospitalized. • Need for oxygen supplementation. • Need for oxygen through high-flow. device or non-invasive ventilation. • Need for mechanical ventilation or extracorporeal membrane oxygenation.	• Resolution of inflammation. • Decrease in invasive ventilation risk. • Decrease in mortality. • Reduced time to ICU discharge. • Increased number of organ support-free days.
Siltuximab	No.	Recommendation against, except: • In a clinical trial.	N/A	N/A
TNF inhibitors	No.	N/A	N/A	• Decrease in invasive ventilation risk. • Decrease in hospitalization risk. • Decrease in mortality.

Table 1. (Continued).

Intervention	FDA EUA	NIH recommendation	Potentially optimal use/efficacy	Potential benefit
Kinase Inhibitors				
JAK inhibitors: Baricitinib	Yes. in combination with remdesivir in hospitalized patients ≥2 years of age requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation.	Baricitinib is recommended only in combination with dexamethasone, with or without remdesivir, in hospitalized patients who require oxygen supplementation through a high flow device or non-invasive therapy.	• Hospitalized patients. • Requiring non-invasive oxygen support.	• Increase in clinical improvement. • Improvement of pulmonary function. • Decrease in hospital admission. • Decrease in mortality.
Tofacitinib	No.	Recommendation to use instead of baricitinib in case: • Baricitinib is not available. • Baricitinib cannot be used.	• Hospitalized. • Requiring non-invasive oxygen support.	• Decrease in mortality • Decrease in respiratory failure.
BTK inhibitors	No.	Recommendation against, except: • In a clinical trial.	N/A	• Improvement in oxygenation. • Improvement in inflammation.
Corticosteroids				

Dexamethasone (or equivalent prednisone, methylprednisolone, or hydrocortisone)	No.	• Recommendation against in mild-to-moderate non-hospitalized
		• Recommendation for dexamethasone:
		  • Orally for patients with increasing oxygen needs that were discharged due to scarce resources. Recommended only for the duration of oxygen supplementation, not to exceed 10 days.
		  • Alone or in combination with other drugs (remdesivir and/or baricitinib or IV tocilizumab) in hospitalized patients requiring supplemental oxygen or oxygen delivery through a high-flow device or non-invasive ventilation.
		  • Alone for hospitalized patients requiring invasive mechanical ventilation or extracorporeal membrane oxygenation or in combination with IV tocilizumab in patients within 24 hours of admission.
			• Hospitalized and requiring oxygen support (oxygen supplementation, oxygen through high-flow device or non-invasive ventilation, mechanical ventilation or extracorporeal membrane oxygenation).
			• Non-hospitalized due to scarce resources but unstable and requiring oxygen supplementation
				• Decreased time on ventilators.
				• Decreased mortality.

Colchicine	No.	Recommendation against for: • Non-hospitalized patients. • Hospitalized patients	• Moderate-to-severe disease. • Hospitalized patients. • Non-hospitalized patients.	• Decrease in need for oxygen supplementation and invasive ventilation. • Decrease in inflammation. • Prevention of disease progression. • Increase in clinical improvement. • Decrease in mortality. • Decrease in duration of hospitalization.

BTK: Bruton's kinase; COVID-19: coronavirus disease 2019; EUA: Emergency Use Authorization; FDA: Food and Drug Administration; ICU: Intensive Care Unit; IL: Interleukin; INF: Interferon; IV: Intravenous; IVIG: Intravenous Immunoglobulin; JAK: Janus kinase; NIH: National Institutes of Health; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; TNF: Tumor Necrosis Factor

discharge rates and a decrease in the need for intubation in patients receiving convalescent plasma compared to those who did not [31]. The largest case-controlled study to date demonstrated decreased risk of 7-day and 14-day mortality, but not 28-day mortality, in hospitalized COVID-19 patients receiving convalescent plasma [32]. Early evidence thus seemed to suggest that the potential of convalescent plasma to reduce mortality could be limited to early in the disease

course [33,34]. Moreover, early administration of high-titer convalescent plasma (within 72 hours of symptom onset) in older adults can reduce the progression of COVID-19 to severe respiratory disease [35]. Consistently, the EUA for convalescent plasma limited its use to high-titer plasma administered early in the disease course of hospitalized COVID-19 patients [36]. However, the clinical benefit of convalescent plasma does not persist when available data is taken collectively, with meta-analyses finding no conclusive evidence supporting the use of convalescent plasma in COVID-19, regardless of disease severity [37–39]. A recent meta-analysis of data from approximately 16500 patients showed no significant improvement in all-cause mortality with the use of convalescent plasma [38], while another also shows lack of efficacy in other clinical outcomes (length of stay, clinical improvement, clinical deterioration, mechanical ventilation) compared to placebo [39]. The lack of detectable clinically relevant therapeutic effect is evident in completed clinical trials in different settings such as early vs deferred use of convalescent plasma [40], moderate COVID-19 [41], severe or life-threatening COVID-19 [24,42], and hospitalized patients with or without oxygen supplementation [43,44]. An in-depth exploratory analysis reveals that the efficacy of convalescent plasma was highest when patients were receiving high-titer plasma and recent treatment modalities, particularly remdesivir and corticosteroids, were not in use [45]. Moreover, convalescent plasma is not beneficial in non-hospitalized COVID-19 patients. Disease progression was actually not prevented by the early administration of convalescent plasma to high-risk outpatients [46]. As such, the U.S. National Institutes of Health (NIH) guidelines do not recommend in favor or against the use of convalescent plasma for non-hospitalized COVID-19 patients regardless of humoral immunity impairment (or lack thereof). The initial EUA was also updated to limit the previous authorization to the use of high-titer plasma, and only for the treatment of hospitalized patients who have impaired humoral immunity. This was based on an updated retrospective analysis demonstrating lower risk of death with high-titer plasma compared to plasma with lower levels of antibodies, particularly in hospitalized patients that were not receiving mechanical ventilation [47].

3.2. Immunoglobulin (IG)

In a similar approach to convalescent plasma, immunoglobulins (IGs) can also be used to treat diseases with inflammatory involvement. Theoretically, intravenous IG (IVIG) may have a role in the management of COVID-19, particularly in those with bacterial superinfection and in conditions where the differential diagnosis between autoimmune disease and infections is indistinguishable [48]. However, it is important to accurately select target patients due to limited availability and cost-effectiveness. With no robust clinical evidence and sometimes controversial effects [49], the NIH guidelines currently recommend against non-SARS-CoV-2-specific IVIG outside of a clinical trial or the occurrence of complications where this treatment modality is indicated. As for SARS-CoV-2-specific IG, the guidelines did not offer a statement supporting or recommending against their use. Purifying SARS-CoV-2-specific IG and administering it to infected patients is not currently described by clinical data, but RCTs on the use of anti-COVID-19 IG are expected in the future [50]. On the other hand, non-SARS-CoV-2 specific IVIG has been the focus of several case reports, retrospective studies and randomized clinical trials. IVIG has been used as adjuvant treatment in one case [51], with a retrospective review of 58 cases also revealing the potential of adjuvant IVIG to reduce mechanical ventilation, length of stay in the hospital and the ICU, as well as 28-day mortality in patients with severe COVID-19 pneumonia [52]. IVIG seems to be well tolerated and particularly promising in deteriorating or critical cases of severe COVID-19 when administered in high doses early in disease stages [53–55]. As for non-severe patients, IVIG administration seems to be yield comparable duration of fever, virus clearance time, length of hospital stay, use of antibiotics, progression to severe disease or death [56]. IVIG could also be combined with moderate-dose corticosteroids to treat COVID-19 patients deteriorating with low-dose therapy [57]. Evidence from RCTs remains limited, but one controlled double-blind RCT consistently demonstrated that IVIG administration leads to clinical improvement and reduced mortality in severe COVID-19 infection unresponsive to initial treatment [58]. Another available RCT consists of an open-label pilot study showing a significant improvement in hypoxia, progression to mechanical ventilation and hospital length of stay after the addition of IVIG to standard of care [59]. Most recent evidence showed that the reduction of 28-day mortality in patients with severe COVID-19 was most prominent when treatment is administered at an earlier stage in the disease course [60]. However, there does not seem to be any advantage to the combination of IVIG in combination with hydroxychloroquine and lopinavir/ritonavir in treatment of severe COVID-19 cases [61].

3.3. Anti-SARS-CoV-2 monoclonal antibodies

The natural response to COVID-19 is variable, which is evident in the great variation of antibody titers in patients infected with the virus. It was therefore logical that anti-SARS-COV-2 monoclonal antibodies were developed against the viruses' spike protein, later receiving EUAs from the FDA based on safety and efficacy data of early clinical trials. By early April 2021, two monoclonal antibodies had received EUAs either as monotherapy (bamlanivimab) or in combination with another antibody (e.g. bamlanivimab/etesivimab and casirivimab/imdevimab). Bamlanivimab was first authorized for use as single dose (700 mg) monotherapy in patients with mild-to-moderate COVID-19 in patients ≥12 years old who weigh ≥40 kg and are at high risk of progressing to severe disease and/or hospitalization. It later received an EUA for use in combination with etesivimab (2800 mg each) on the 9th of February 2021, considering emerging clinical data demonstration of the significant reduction of viral load at day 11 with the use of combination therapy, but not monotherapy bamlanivimab [62]. Data from the phase 3 BLAZE-1 trial showed less mortality and hospitalizations in high-risk ambulatory patients receiving bamlanivimab/etesivimab compared to placebo [63]. Moreover, patients receiving bamlanivimab/etesivimab had a greater decline in viral load [63]. The latest bamlanivimab trials adopted a lower dose of

bamlanivimab/etesivimab (700 mg/1400 mg) considering its comparable efficacy to the higher dose and reported a significant reduction in death or hospitalization due to COVID-19 in patients receiving the intervention [64,65]. While the combination of bamlanivimab and remdesivir does not seem to offer clinical benefit [66], monotherapy bamlanivimab might be beneficial for the prevention of COVID-19 infection [67]. Despite its clear efficacy, the use of the combination of bamlanivimab/etesivimab proved to be strain-dependent. The 25th of June 2021 saw the discontinuation of bamlanivimab/etesivimab distribution in American states and territories due to reduced susceptibility of circulating SARS-CoV-2 variants of concern at that time (Gamma and Beta variants) [68]. This drug combination was later reinstated on the 2nd of September 2021 to combat the prevalent Delta variant, against which it is effective. As it now stands, bamlanivimab/etesivimab may be considered for the treatment of mild-to-moderate COVID-19 at high-risk of clinical progression, contingent upon the combined frequency of potentially resistant SARS-CoV-2 variants being low in the region.

Currently, two other monoclonal antibodies are recommended for the treatment of early mild-to-moderate non-hospitalized COVID-19 disease at high risk of progression, namely casirivimab/imdevimab and sotrovimab. Casirivimab was granted an EUA by the FDA in November 2020 to be used together with imdevimab by IV infusion in the same patient population approved for bamlanivimab/etesivimab. Early evidence showed that this combination can significantly reduce viral load by day 7 after baseline compared to placebo, in addition to reducing hospitalization for COVID-19 within 28 days after treatment [69]. Casirivimab/imdevimab might be more effective when administered in patients prior to the initiation of the natural immune response, or in patients with high viral load at baseline [70]. The EUA of casirivimab/imdevimab was later updated to recommend a lower drug dose (600 mg vs 1200 mg) and allow subcutaneous administration in case IV were not feasible [71], based on emerging evidence from phase 3 clinical trials. Compared to placebo, casirivimab/imdevimab reduced the risk of COVID-19 related hospitalization in outpatients, in addition to decreasing mortality of any cause. Additionally, symptom resolution and decrease of viral load was faster in outpatients receiving casirivimab/imdevimab [72]. In hospitalized patients, casirivimab/imdevimab seems to decrease 28-day mortality, albeit dependently of baseline antibody status [73]. In fact, the proportional decrease in mortality was evident in patients who were seronegative at baseline, while those who were seropositive had comparable mortality rates with usual care. Real-world data on the use of casirivimab/imdevimab combination in outpatient setting are emerging, reflecting a positive experience with the treatment [74]. Encouraging results were also reported among solid organ transplantation patients [75]. Regardless, the optimal use of casirivimab/imdevimab remains sensitive to scalable antibody testing, appropriate patient selection and timely administration [76].

On the 26th of May 2021, another investigational drug, sotrovimab, was also granted authorization for emergency use in an outpatient setting [77]. An interim analysis of the COMET-ICE, sotrovimab proved effective in the reduction of COVID-19 progression in patients with mild-to-moderate disease while remaining safe and tolerable [78].

Clinical trials are ongoing and result publication is awaited. However, it remains to be seen how available monoclonal antibody regimens would fare against each other in direct head-to-head comparison. Moreover, it would be interesting to determine the clinical efficacy of monoclonal antibodies in hospitalized patients with severe COVID-19 seeing as none of the currently recommended anti-SARS-CoV-2 antibodies are indicated in the inpatient setting.

3.4. Interferons (IFN)

IFNs have been suggested as a therapeutic or prophylactic measure in COVID-19 based on *in vitro* evidence revealing primed antiviral response following type I IFN pre-activation [79]. The results of several RCTs have been published, shedding valuable insights into the clinical value of IFN administration. Regardless, the clinical benefit of IFNs remains to be demonstrated and their use is generally not recommended outside the context of a clinical trial in light of their toxicity risks. The combination of lopinavir/ritonavir with a novel IFN, Novaferon, was reported to significant increased viral clearance rates in COVID-19 patients compared to lopinavir/ritonavir alone [80]. Another novel interferon, a novel genetically engineered recombinant super-compound interferon, was shown to lead to faster clinical improvement when administered in combination baseline antiviral agents compared to traditional IFN-α [81]. Peginterferon lambda data is currently contradictory. In the outpatient setting, one trial showed no benefit in terms of viral shedding or symptom improvement after a single 180 mg subcutaneous dose within 72 hours of diagnosis [82], while the same intervention proved effective in prevention clinical deterioration and shortening the duration of viral shedding when used within 7 days of symptom onset or first positive swab [83].

Other data describe the effect of IFN β-1a, IFN β-1b, and IFN-α2b on COVID-19 prognosis and suggests the potential of type 1 IFNs in reducing mortality and increasing hospital discharge [84].

IFN B-1A

Inhaled nebulized interferon β-1a SNG001 seems to be well tolerated, leading to clinical improvement and faster recovery in hospitalized COVID-19 patients [85]. Results from the phase 3 SPRINTER trial of SNG001 in hospitalized COVID-19 patients are currently awaited. On the other hand, subcutaneous IFN β-1a administration was also investigated. Injections were added 3 times per week to an RCT protocol of hydroxychloroquine plus lopinavir-ritonavir or atazanavir-ritonavir, inducing significantly reduced mortality and improved discharge rates, albeit without affect time to clinical response [86]. In a non-controlled trial, results also supported the use of IFN-β-1a in

combination with hydroxychloroquine and lopinavir/ritonavir in the management of COVID-19 based on virological clearance rates, fever resolution, hospitalization time and safety profile [87]. Retrospective data also reveal a potential survival advantage by the addition of using IFN-β1-a to lopinavir and ritonavir in combination with standard of care [88]. In a recent RCT, high dose subcutaneous IFN-β1-a added to lopinavir and ritonavir yielded similar rates of mortality and time to clinical improvement compared to low dose subcutaneous IFN-β1-a [89]. Interestingly, another phase 3 RCT, the COVIFERON II trial, failed to demonstrate an improvement in virologic clearance or clinical status at day 15 with a combination regimen of lopinavir/ritonavir-IFN-β-1a [90]. To note that in the COVIFERON trial, the addition of IFN-β1-a was shown to lead to a significant reduction in time to clinical improvement compared to control (oral lopinavir/ritonavir with one dose of hydroxychloroquine), while IFN-β1-b yielded no improvement [91]. However, larger studies were suggested to be necessary to confirm these findings. That being said, available clinical evidence remains insufficient to recommend the systemic use of IFN-β in hospitalized patients.

IFN B-1B

Nebulized IFN-β-1b inhalation therapy was also suggested to safely target the lungs and avoid systemic complications from COVID-19 treatment [92]. However, this was not validated in an RCT, where moderate-to-severe COVID-19 patients receiving inhaled IFN-β-1b therapy in addition to favipiravir had comparable clinical outcomes compared to those receiving hydroxychloroquine [93]. In parallel, subcutaneous IFN β-1b administration along with lopinavir/ritonavir or atazanavir/ritonavir plus hydroxychloroquine for 7–10 days significantly decreased time to clinical improvement, ICU admission rate and all cause 28-day mortality compared to patients not receiving IFN β-1b [94]. Another triplet therapy investigated in an RCT constituted of the addition of subcutaneous IFN β-1b to lopinavir-ritonavir, and ribavirin was shown to be effective and safe in the management of mild-to-moderate COVID-19 symptoms and viral shedding [95]. However, evidence suggests that IFN-β-1a is superior in its clinical benefit to IFN-β-1b [91].

IFN-A2B

Nebulized IFN-α2b alone or in combination with arbidol was suggested as a potential measure for the decrease of inflammatory markers in the blood of COVID-19 patients and accelerate viral clearance in an uncontrolled exploratory study [96]. However, the role of IFN-α2b in the suppression of viral shedding seems to wane when confounding variables are accounted for [97]. Time of administration seems to have important implications, with early administration suggested to confer both a survival advantage, as well as favorable clinical response [98]. As for subcutaneous administration of IFN-α2b, observational data of its use in

combination with lopinavir/ritonavir were shown to decrease the duration of detectable virus in the upper respiratory tract, in addition to reducing the average time patients spent in the hospital [99]. PegIFN-α2b added to standard of care was shown to limit the duration of supplemental oxygen, ensure early viral clearance and improve clinical status among subjects with moderate COVID-19 [100]. Recombinant human IFN-α nasal drops were also suggested to aid in preventing COVID-19 in medical staff [101]. Moreover, recombinant IFN added to baseline antiviral agents were found to be more effective in speeding clinical improvement compared to traditional IFN-α [102].

3.5. Interleukin (IL) inhibitors

IL-6 inhibitors

IL-6 is thought to be a key driver of the dysregulated inflammation process and cytokine storm observed in COVID-19 seeing as it is associated with COVID-19 severity regardless of patient age and sex [103]. IL-6 inhibitors could theoretically improve clinical outcomes in patients with cytokine storm and the use of monoclonal antibodies directed against IL-6 (e.g. siltuximab) or its receptor (e.g. sarilumab and tocilizumab) was thus suggested. However, the use of anti-IL-6 monoclonal antibodies, such as siltuximab, is currently not recommended by the NIH outside of the context of a clinical trial. While few trials are set to investigate siltuximab, published evidence seems to support the clinical use of the IL-6 receptor antagonist tocilizumab. Suppression of biomarkers of infection [104], such as C-reactive protein (CRP), mark the effectiveness of IL-6 R antagonism through tocilizumab in severe COVID-19 [105]. The use of tocilizumab either as a subcutaneous injection or IV infusion seems to be more effective in the early stages of respiratory failure [106], but more importantly seems to offer clinical benefit in severe stages of infection [107]. In fact, tocilizumab can be used to reduce mortality and invasive ventilation risk in patients with COVID-19-associated cytokine storm syndrome whose rapid respiratory deterioration was not resolving after high-dose intravenous methylprednisolone for five consecutive days [108]. Similarly, the addition of IV tocilizumab to the standard of care of patients hospitalized with moderate-to-severe COVID-19 pneumonia was shown to reduce mortality, mechanical ventilation and non-mechanical ventilation risk at day 14 [109]. Observational data showed that high IL-6 levels predict the need for mechanical ventilation and could indicate early tocilizumab use seeing as this intervention can improve oxygenation and decrease mortality in such patients [110]. Tocilizumab alone or in combination with favipiravir can help resolve pulmonary inflammation and prevent clinical deterioration [111] such as progression to mechanical ventilation or death [112]. Improvement in survival with little to no toxicity upon use of tocilizumab in severe COVID-19 was reported both compared to control [113] and other therapies [114]. Low-dose tocilizumab might also be effective in the treatment of hospitalized patients with COVID-19 [115]. That being said, some studies failed to demonstrate improvement in survival [112], or clinical

parameters with the addition of tocilizumab to the management hospitalized COVID-19 patients [116]. Single IV infusion of tocilizumab was also suggested to lead to higher mortality without any clinical advantage to its addition to standard of care in terms of clinical improvement after 15 days [117]. Moreover, tocilizumab did not seem to prevent disease progression to a greater extent than standard of care in hospitalized adult patients with COVID-19 pneumonia [118]. Robust non-biased data from large-scale randomized clinical trials remain needed in order to guide the use of this drug in clinical practice. Overall, available evidence from the RECOVERY and REMAP-CAP trials support the use of IV tocilizumab only in combination with dexamethasone for severely ill COVID-19 patients with hypoxia and a significant inflammatory response [119,120]. The NIH recommendation for tocilizumab also extends to the combination of dexamethasone and remdesivir in hospitalized patients requiring oxygen supplementation, as well as those needing oxygen through a high-flow device or non-invasive ventilation granted the patient is showing signs of systemic inflammation and rapidly increasing oxygen needs. This recommendation remains despite recent evidence from an RCT (the REMDACTA trial) showing a lack of improvement with the use of tocilizumab in combination with remdesivir, compared to placebo, particularly in the time to hospital discharge [121].

Another IL-6 receptor inhibitor, sarilumab, has also been investigated in several uncontrolled trials or case series, which suggest the promise of intravenous sarilumab for clinical improvement (e.g. CRP levels, oxygenation, and discharge) and better prognosis of severe COVID-19-related pneumonia [122,123]. There are also data supporting the early and aggressive use of sarilumab with standard of care to treat COVID-19 clinical and inflammatory parameters [124]. However, one study demonstrated the comparability of sarilumab and standard of care in terms of clinical improvement and mortality in severe COVID-19 [125], and a recent RCT showed no efficacy with the use of sarilumab in hospitalized patients requiring oxygen supplementation [126]. Randomized controlled trials are still needed and are planned for sarilumab [127,128] and its effect remains uncertain [129]. As of yet, preliminary results from the REMAP-CAP suggest comparable efficacy between sarilumab and tocilizumab, with improvement on the level of different clinical outcomes (i.e. mortality, time to ICU discharge, and the number of organ support-free days) [120]. In another RCT, results showed numerical improvement in clinical status and mortality rates with the use of sarilumab in COVID-19, albeit no statistical significance could be reached [130]. While sarilumab might be promising in the management of severe COVID-19, the limited number of trial participants on sarilumab challenges the robustness of these findings, and by extension, prevents the formulation of a recommendation on its use. Sarilumab thus remains recommended only as a replacement for tocilizumab in case the latter is not available.

IL-1 inhibitors

NIH guidelines highlighted that no conclusive evidence is available on the use of IL-1 inhibitors in COVID-19 treatment.

The CAN-COVID clinical trial found no supportive data for the use of canakinumab in hypoxic COVID-19 patients not requiring ventilatory support. Canakinumab sis not lead to improvement in survival rates without need for mechanical ventilation when compared to placebo [131]. The IL-1 inhibitor anakinra was more widely studied in COVID-19, as reported in case reports, retrospective cohort studies or open-label interventional studies, and some RCTs. An open label single group trial of soluble urokinase-type plasminogen activator receptor-guided anakinra showed the ability of this drug to decrease severe respiratory failure and restore the balance between pro- and anti-inflammatory mediators [132]. However, anakinra was not associated with clinically significant improvement in patients with mild-to-moderate COVID-19 pneumonia compared to standard of care alone, as shown in the open-label CORIMUNO-ANA-1 RCT [133]. Lack of clinical efficacy with anakinra was also reported in critically ill COVID-19 patients in the REMAP-CAP trial [134]. On the other hand, the SAVE-MORE trial in COVID-19 patients at high risk of progressing into respiratory failure demonstrated the ability of anakinra to ensure better clinical status, lower mortality, and shorter hospital stay compared to placebo [135].

Anakinra might provide a treatment option and improved prognosis for patients not-responding to previous corticosteroids alone or in combination with tocilizumab [136]. Evidence points toward anakinra not being inferior to tocilizumab, and being a potential alternative for patients in which tocilizumab cannot be used [137,138]. In severe COVID-19, reports suggest the role of anakinra in the safe management of the cytokine storm syndrome [139,140], albeit with potential risks, such as sepsis [141]. Data seem to consistently show the ability of anakinra to alleviate hyperinflammation in critical COVID-19 cases, with reported effects on CD4 count [136], fever, ferritin plasma levels, as well as other clinical parameters [142,143] and inflammatory markers [144,145]. This was observed even in patients with evidence of superadded bacterial infection [146]. Anakinra addition to standard of care could also improve survival and decrease the need for mechanical ventilation and oxygen supplementation in severe COVID-19 cases [143,144,147]. The rapid resolution of systemic inflammation and improvement of respiratory parameters observed with anakinra [148] warrants further investigation in the context of an RCT. Anakinra has also been successfully combined with corticosteroids [149] such as glucocorticoids [150–152], resulting in resolution of hyperinflammation [150] and improvement of mortality risk [149,151,152].

3.6. TNF inhibitors

Anti-TNF antibodies have been on the market for more than 20 years and are used as the mainstay treatment for many inflammatory diseases. Although, cytokine dysregulation and inflammation are documented in COVID-19, there is little evidence from randomized clinical trials reporting TNF blockade in COVID-19. Observational data from rheumatological disease registries suggested that anti-TNF alone or in combination with other immunomodulatory therapies might be associated with improvements in a composite of death or hospital admission due to COVID-19 [153], and fewer hospital admissions

[154]. Other data from patients receiving immunomodulatory drugs showed that TNF blockade reduced the requirement for ventilator support or death compared to non-TNF biologics [155]. However, these data are from patients with inflammatory diseases and does not necessarily reflect the impact of first-time administration of anti-TNF on COVID-19 infection. Comparable risk of hospitalization for COVID-19 was also reported between patients who received anti-TNF-α agents in the year prior to the pandemic and the general population [156]. While continued anti-TNF therapy seems to have protective effect in COVID-19 without leading to disease exacerbations, the use of an anti-TNF agent (infliximab) has been reported in the acute setting to lead to improvement clinical (symptoms, chest imaging) and inflammatory (decrease in cytokines) parameters in populations with [157] or without [158] inflammatory diseases. In a small RCT, adalimumab in combination with remdesivir and dexamethasone was studied in severe COVID-19 cases and was not reported to lead to a significant improvement in mortality rates or other outcomes (mechanical ventilation, length of hospital and ICU stay) [159]. While anti-TNF blockade is a valid treatment approach, few studies are currently investigating its clinical applicability in COVID-19 (e.g. ISRCTN40580903, ISRCTN33260034, NCT04593940, and NCT04425538).

3.7. Kinase inhibitors

The use of Bruton's kinase (BTK) for COVID-19 treatment remains as of yet not recommended in daily clinical practice and is thus restricted to off-label use and clinical trials. While clinical data on BTK and JAK inhibition in COVID-19 and its effect on the hyperinflammatory state and disease progression remain relatively limited, the immunomodulatory effect of these drugs is well established in immune-diseases. The blood monocytes of severe COVID-19 patients show significant elevations in BTK activity and IL-6 production compared to healthy controls. The off-label use of the BTK inhibitor acalabrutinib was thus attempted and led to improvement in oxygenation and normalization of inflammation markers [160].

Furthermore, the continuation of BTK or JAK inhibition in case of COVID-19 infection in patients already receiving this therapy was debatable. Published clinical cases provide evidence in support of BTK inhibition continuation seeing as it could protect from lung lesions and improve respiratory function while remaining relatively safe and tolerable in patients already receiving it [161–163]. Mild to no toxicity and uneventful COVID-19 disease course reported in patients already receiving JAK inhibitors [164]. Analysis of SECURE-IBD registry data showed that the use of JAK inhibitor tofacitinib did not seem to modify clinical outcomes and complications of COVID-19 in IBD patients compared to other medications [165], further supporting the case for treatment continuation [166].

The JAK inhibitor ruxolitinib, seemed to be a promising therapeutic option for COVID-19 that can normalize genes induced by SARS-CoV-2 related to interferons and severity markers, such as IL-6 and complement system components [167]. Through this, ruxolitinib could serve to attenuate the hyperinflammatory state characteristic of COVID-19 and reduce the need for respiratory support [168]. Evidence from a RCT showed that the addition of ruxolitinib to standard of care ensured a numerical increase in clinical improvement time, as well as significant chest imaging improvement [169]. In fact, one case series revealed that the majority of critically ill COVID-19 patients completely recovered respiratory function after 14 days of treatment with ruxolitinib [170]. The improvement in pulmonary, inflammatory, and clinical parameters in response to ruxolitinib is promising [171], and preliminary insights suggest that patients already receiving ruxolitinib should be continued on treatment to avoid higher mortality risk [172]. Ruxolitinib have also been combined with steroids to target the inflammatory process and lung lesions induced by COVID-19 [173,174], and has been successfully used in stem cell transplantation recipients infected with COVID-19 [175,176].

Available evidence suggest that targeting the immune dysregulation caused by COVID-19 might best be achieved with a three-step combination therapy involving remdesivir along with dexamethasone in combination with the JAK inhibitor baricitinib [177]. Retrospectively, patients receiving baricitinib alone compared to those receiving tocilizumab alone or in combination with baricitinib were admitted less often to the ICU and had numerically lower mortality rates [178]. In a RCT, baricitinib plus remdesivir in hospitalized adults with COVID-19 led to significantly faster clinical improvement compared to remdesivir alone, with fewer side effects. This effect was more pronounced in patients receiving respiratory support [179]. The supplementation of corticosteroids with baricitinib also seems to improve pulmonary function [180]. Baricitinib could act through the prevention of disease progression into a severe state by targeting inflammatory mediators such as IL-6, IL-1β, and TNF-α [181]. Clinical and respiratory improvement has been reported with the use of baricitinib in moderate COVID-19 [182] and a case of severe respiratory failure unresponsive to a combination therapy of antiretroviral, hydroxychloroquine, and IL-6 antagonist [183]. Baricitinib received an EUA in combination with remdesivir in hospitalized adults and children aged ≥2 years with COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation in November 2020 [184]. Based on this evidence, in addition to the more recent data on mortality reduction with the use of baricitinib with standard of care [185] the NIH only recommends the use of baricitinib in combination with dexamethasone (or another corticosteroid), with or without remdesivir, for patients that were recently hospitalized and require oxygen supplementation or oxygen through a high-flow device or non-invasive ventilation (and not invasive ventilation) to address rapidly increasing oxygen needs and systemic inflammation.

Baricitinib and tofacitinib remain the only JAK kinase inhibitors recommended in the NIH guidelines. Clinical data on the use of tofacitinib are still lacking. That being said, the NIH guidelines suggest that tofacitinib can be used to replace baricitinib should the latter not be available or not feasible to use. This is supported by its proven efficacy in reducing 28-day mortality as well as the risk of respiratory failure in hospitalized patients with COVID-19 pneumonia [186]. More conclusive evidence from RCTs remains needed to support the

hypothesized effects and draw robust conclusions and recommendations on baricitinib's role in the management of COVID-19.

3.8. Corticosteroids

The role of adjunctive corticosteroid therapy in the management of COVID-19 infected patients remains currently controversial. Experts agreed that systemic corticosteroid is indicated for viral pneumonia when exacerbation of obstructive lung disease or septic shock coexists. On one hand, corticosteroids might delay recovery from lung injury in patients with COVID-19 infection when cases are not severe [187] and might also prolong viral shedding in short-term early use [188]. Preliminary reports also indicate that high-dose dexamethasone might offer no clinical benefit in COVID-19 patients with mild-to-moderate acute respiratory distress syndrome [189]. Lessons learned from previous viral pandemics of coronaviruses (SARS and MERS) indicate that corticosteroids might not necessarily correlate with improved survival, but rather delayed viral clearance and worse clinical outcomes [190,191]. This was also evident in a meta-analysis of 10 observational studies with 6,548 patients with influenza pneumonia, where corticosteroids were associated with an increased mortality and risk of secondary infections [192].

On the other hand, dexamethasone, or an alternative corticosteroid, such as prednisone, methylprednisolone, or hydrocortisone was recommended in the NIH guidelines for use alone or in combination with other drugs (i.e. remdesivir, baricitinib (or tofacitinib), IV tocilizumab (or IV sarilumab) for COVID-19 patients that are hospitalized and require oxygen supplementation, non-invasive or invasive ventilation. The use of dexamethasone or other systemic corticosteroids is not supported in non-hospitalized patients that are stable and do not require oxygen supplementation. This is due to the lack of evidence in this population, as corticosteroids were discontinued in discharged patients during the RECOVERY trial, and no benefit was observed in hospitalized patients not requiring oxygen supplementation.

It is clear that current recommendations was largely based on the results of the RECOVERY trial, which demonstrated the efficacy of dexamethasone compared standard of care in reducing the mortality of hospitalized COVID-19 patients, but only when oxygen supplementation was required [193]. The improvement in patient survival ensured by systemic corticosteroid use was revealed in a meta-analysis of available RCTs (including the RECOVERY trial) comparing corticosteroids to standard of care or placebo [194]. However, the RECOVERY trial cohort seems to largely account for the decreased mortality in patients receiving corticosteroids, whose survival advantage is not observed when other RCTs are taken into consideration alone [195]. Patients with moderate or severe ARDS receiving IV Dexamethasone in combination with standard of care spend significantly less time on ventilators compared to those receiving standard of care alone [196]. Another RCT had positive implications for hydrocortisone use in terms of reduction of organ support needs [197]. As for the choice of

corticosteroid, methylprednisolone seems to offer better clinical outcomes in hospitalized hypoxic COVID-19 patients compared to dexamethasone [198].

In this perspective, ongoing and planned RCTs should provide further insights into the role of corticosteroids in treating COVID-19. Furthermore, the potential risks and variability in corticosteroid study results warrants caution when used in patients with COVID-19, unless a concomitant compelling indication co-exists (obstructive lung disease and septic shock).

3.9. Colchicine

Colchicine is an FDA-approved medication for use in autoinflammatory disorders to prevent and treat flares with underlying IL-1 or IL-6 activation [199]. Recent literature supports the ability of colchicine to inhibit inflammatory cytokines implicated in the NLRP3 inflammasome [200], which is known to be induced by the novel coronavirus' viroporin-E [201]. Limited data are available on the use or effectiveness of colchicine in the management of COVID-19. Early evidence suggests the potential of colchicine to induce clinical improvement [202], reduce the risk of mechanical ventilation [203] and significantly reduce mortality [202–207]. Colchicine has been reported in the management of 6 of 7 pediatric cases of severe COVID-19, all of whom exhibited complete recovery [208]. Generally, patients receiving colchicine seem to have lower discharge rates compared to standard of care [202,205]. Other clinical indicators in favor of colchicine include less intubation rates [205], decreased need for supplemental oxygen [209] and a more significant decrease in inflammatory markers for D-dimer, ferritin [205], and CRP [209]. On the contrary, the GRECCO-19 trial showed no significant different in cardiac (cardiac troponin) or inflammatory (CRP) biomarkers with the use of colchicine [210]. Evidence in COVID-19 thus suggests that in addition to increasing the time till clinical deterioration [210], colchicine could help weather the cytokine storm [202] and potentially prevent progression into a hyperinflammatory state when administered early in the course of the disease [211,212] while providing prophylaxis for venous thromboembolism [213] and other cardiovascular events characteristic of COVID-19 [214,215]. Moreover, a RCT supported the safety and tolerability of colchicine in moderate-to-severe COVID-19 patients, and its capacity to reduce the length of both, supplemental oxygen therapy and hospitalization [216]. The use of colchicine could prove particularly useful in an outpatient setting for defervescence and prevention of hospitalization [217] considering its oral administration and low cost. Evidence from larger trials do not support the benefit of colchicine both in hospitalized and non-hospitalized patients and this therapeutic approach is therefore not currently recommended in COVID-19 by the NIH. The COLCORONA trial indicated a potential benefit to the use of colchicine in non-hospitalized polymerase chain reaction-confirmed COVID-19 patients. While it was observed that colchicine could potentially reduce hospitalizations or death, the study did not reach its primary endpoint [218]. The most recent evidence from the

PRINCIPLE trial also reports a lack of efficacy in improving the time to recovery from COVID-19 in high-risk populations from the community [219]. That being said, colchicine did not ensure a significant reduction of 28-day mortality in hospitalized COVID-19 patients from the RECOVERY trial. A similar lack of efficacy was observed on the level of duration of hospital stay, and risk of progressing to invasive mechanical ventilation or death [220].

That being said, these data are generally limited to case-control studies and observational or retrospective studies, with the exception of few clinical trials. Moreover, the optimal timing, dose, and duration of colchicine in COVID-19 patients remain unknown. Large-scale controlled clinical trials are currently recruiting (e.g. NCT04416334) and are critical for the elucidation of the clinically potential and optimal use of colchicine in COVID-19.

4. Conclusions

The treatment landscape of COVID-19 is rapidly evolving. Large-scale RCTs are still critically needed to provide structure to the multi-pronged management of COVID-19 and establish the setting in which each immunomodulator is most effective. A standardized and comprehensive approach to clinical investigation of immunomodulators is needed, considering the inadequacies or inconsistencies in the design, reporting, and interventions of available clinical trials. Evidence remains inconclusive, often biased and thus of low quality. However, therapies such as convalescent plasma, JAK inhibitor baricitinib and tofacitinib, corticosteroids, IL-6 receptor inhibitors tocilizumab and sarilumab as well as anti-SARS-CoV-2 monoclonal antibodies (bamlanivimab/etesivimab, sotrovimab, and casirivimab/imdevimab) have garnered EUAs and/or recommendations for clinical use and might thus prove vital in improving prognosis and alleviating the burden of COVID-19. The role of other immunomodulators, while promising, remains to be established.

Authors' contributions

All authors were involved in setting the review's concept and objective and selection criteria. All authors participated in data extraction, synthesis, and interpretation. All authors provided input and agreed on the final version of the manuscript.

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