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SYSTEMATIC REVIEWS

Immunomodulatory therapy for the management of critically ill patients with COVID-19: A narrative review

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Abstract

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the ongoing coronavirus disease 2019 (COVID-19) pandemic. Understanding the physiological and immunological processes underlying the clinical manifestations of COVID-19 is vital for the identification and rational design of effective therapies.

AIM

To describe the interaction of SARS-CoV-2 with the immune system and the subsequent contribution of hyperinflammation and abnormal immune responses to disease progression together with a complete narrative review of the different immunoadjuvant treatments used so far in COVID-19 and their indication in

severe and life-threatening subsets.

METHODS
A comprehensive literature search was developed. Authors reviewed the selected manuscripts following the PRISMA recommendations for systematic review and meta-analysis documents and selected the most appropriate. Finally, a recommendation of the use of each treatment was established based on the level of evidence of the articles and documents reviewed. This recommendation was made based on the consensus of all the authors.

RESULTS
A brief rationale on the SARS-CoV-2 pathogenesis, immune response, and inflammation was developed. The usefulness of 10 different families of treatments related to inflammation and immunopathogenesis of COVID-19 was reviewed and discussed. Finally, based on the level of scientific evidence, a recommendation was established for each of them.

CONCLUSION
Although several promising therapies exist, only the use of corticosteroids and tocilizumab (or sarilumab in absence of this) have demonstrated evidence enough to recommend its use in critically ill patients with COVID-19. Endotypes including both, clinical and biological characteristics can constitute specific targets for better select certain therapies based on an individualized approach to treatment.

Key Words: COVID-19; Critically ill patients; Treatment; Immunomodulary drugs; Phenotype; Immunosupression

Core Tip: Two years after the onset of the pandemic the search for the most appropriate treatment of coronavirus disease 2019 (COVID-19) continues. Few treatments have been evaluated in the context of critically ill patients with COVID-19 considering it in most clinical trials as a negative "end point" of the disease rather than a study subject. This fact makes it extremely difficult to establish degrees of recommendation regarding the different therapeutic options currently available. This review aims to summarize the immunopathogenesis and the current evidence regarding the different immunomodulatory strategies tested in critically ill patients with COVID-19. In addition, the presence of different immunophenotypes that in the future will serve as a basis for individualized treatments is demonstrated.

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INTRODUCTION

In late 2019, a virus, currently named coronavirus disease 2019 (COVID-19), caused an outbreak of 27 acute respiratory distress syndrome cases related to a seafood market in Wuhan, China. From that moment, the virus has spread rapidly worldwide until, on March 11th, the World Health Organization (WHO) classified it as a pandemic[1]. As of July 24th, 2021, more than 190 million people have been infected, and it has caused more than 4 million deaths[2].

Although most people with COVID-19 have only mild or uncomplicated symptoms, 10%-15% requires hospitalization and oxygen therapy[3,4]. From the beginning, a large number of patients presented severe respiratory failure, needing mechanical ventilation (MV) and intensive care unit (ICU) admission, exceeding the capacity of many of them and turning COVID-19 into a challenge for health systems all over the world[5-9]. Furthermore, we observed a relationship between ICU caseload and mortality[10,11].

The lack of an available, effective treatment has led to a spate of treatment recommendations[12-15], which are not always backed by sufficient scientific evidence[16,17]. We paid particular attention to a presumed specific cytokine storm secondary to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection[18-20], with a special effort to modulate the inflammatory response of these patients. One year after the onset of the disease, many questions remain unanswered, and we continue to search

for the most appropriate treatment. This review aims to summarize the current evidence regarding the different immunomodulatory strategies tested in critically ill patients with COVID-19.

MATERIALS AND METHODS

A comprehensive literature search was developed by using the keywords: "immunotherapy", "immunosuppressives", "haemophagocytic syndrome", "inflammation", "antimalarials", "hydroxychloroquine", "chloroquine", "anakinra", "canakinumab", "tocilizumab", "sarilumab", "corticosteroids", "dexamethasone", "methylprednisolone", "immunoglobulins or convalescent" "JAK inhibitors", "cyclosporine", "colchicine", "statins", "interleukin 7", "thymosin", "PD1 and PD1-L blockers". We restricted the search to: "SARS-CoV-2", "COVID-19", "severe COVID-19" and "treatment" to identify articles published in English from MEDLINE, PubMed, and The Cochrane Library (until January 2021). The meta-analysis, clinical trials, case-control or cohort studies, brief reports, reviews, and systematic reviews were included. *Reference Citation Analysis*, an artificial intelligence technology-based open citation analysis database was employed. Current international guidelines on the management of COVID-19 were also retrieved and included (Centers for Disease Control and Prevention, European Centre for Disease Prevention and Control, Infectious Diseases Society of America, WHO, National Health Service, Spanish Society of Intensive Care Medicine). Articles in preprint format were also evaluated if they were considered relevants and well designed. The authors reviewed the selected manuscripts and selected the most appropriate. Finally, we established a recommendation of the use of each treatment based on the level of evidence of the articles and documents reviewed. This recommendation was made based on the consensus of all the authors. We carried out the rest of the work methodology following the PRISMA recommendations for systematic review and meta-analysis documents (http://prisma-statement.org/PRISMAStatement/Checklist).

RESULTS

Viral infection and the inflammatory response

SARS-CoV-2 infects cells that express surface receptors for angiotensin-converting enzyme 2 (ACE-2) like airway epithelial cells, type II pneumocytes, vascular endothelial cells, and macrophages in the lung, and transmembrane protease, serine 2[21-23]. Active replication and release of the virus cause the host cell to undergo pyroptosis and release of damage-associated molecular patterns, including nucleic acids, adenosine triphosphate (ATP), and atypical squamous cell oligomers. These molecules are recognized by neighboring epithelial cells, endothelial cells, and alveolar macrophages, triggering the liberation of proinflammatory cytokines and chemokines [including interleukin (IL)-2γ, IL-6, IL-8, granulate-macrophage colony-stimulating factor, macrophage inflammatory protein 1α (MIP1α), MIP1β, and monocyte chemoattractant protein 1]. These mediators attract macrophages, monocytes, and T lymphocytes to the site of infection, promoting increased inflammation and establishing a pro-inflammatory feedback loop[24]. This inflammatory response is much more exaggerated in the subgroup of patients who require ICU admission and those with fatal outcomes and affects different organs and systems, including the endothelium[25-28].

Dysregulated immune response and COVID-19 immunophenotypes

In severe COVID-19, many patients express a dysregulated immune response characterized by a defective adaptive response and an exacerbated innate immune response. This situation leads to poor control of the virus, and overproduction of proinflammatory cytokines that initially damage lung infrastructure[29-31]. A cytokine storm similar to that in hemophagocytic syndrome has been described in a subgroup of COVID-19 patients with elevated levels of proinflammatory cytokines, particularly soluble receptor for IL-2γ, IL-6, and tumor necrosis factor-α (TNF-α)[32]. The resulting hypercytokinemia extends to other tissues and can cause considerable organic damage[28]. This finding would justify the use of immunosuppressive therapies such as corticosteroids or cytokine-targeted therapy.

Inflammation is not always the dominant phenomenon in COVID-19[33-35]. Different authors have revealed that in many severe cases of COVID-19 the presence of immune downregulation with profound immunosuppression as primary phenomenon precedes hyperinflammation. These immunological alterations are varied and can be classified into different subsets or phenotypes[30,36,37]. One of these immunophenotypes would be characterized by the presence in most patients with severe COVID-19 of coexisting alterations in numbers, subset composition, cycling, activation, and gene expression of T cells. Numerous studies show a relationship between profound lymphopenia with a worse prognosis and higher mortality in COVID-19[38-40]. This lymphopenia affects the different subsets of T cells, and the cause is not well established. We postulate several causes: T cell exhaustion, migration and sequestration of T cells to affected tissues (especially the lungs), a deficit of lymphopoiesis induced by the

presence of hypercytokinemia, or an increase in apoptosis mediated by a virus-induced overexpression of type 1 programmed death receptors (PD-1) and its ligand (PD-L1).

Another immunophenotype is characterized by decreased antigen presentation capacity, demonstrated by a deficit in human leukocyte antigen-DR expression in mononuclear-phagocytic system cells, particularly in intermediate monocytes. We observed this phenotype in more than 50% of severe and critical forms of COVID-19, and it is inversely related to the inflammatory activity mediated by cytokines such as IL-6[37,41]. In this regard, hypercitokinemia (both: Pro and anti-inflammatory cytokines) is another typical phenotype in severe forms of COVID-19. IL-6, IL-8, IL-1β, and IL-10 levels were higher in COVID-19, and the increases were severity-related. Induced protein 10 (IP-10) CXCL10, a chemokine rapidly and transiently induced following vaccination and other virus infections, almost invariably increased in COVID-19 and was severity-related[42]. Thus, many patients with COVID-19 were described by a severity-related triad of IP-10, IL-6, and IL-10[20,32,36,43]. Finally, emerging data indicate that complement and neutrophils contribute to an inadequate immune response that fuels hyperinflammation and thrombotic microangiopathy, increasing COVID-19 mortality. High plasma levels of neutrophil extracellular traps, tissue factor activity, and sC5b-9 were detected in critical patients[44,45]. All these conditions constitute immune signatures associated with a worse prognosis of COVID-19 that, on the other hand, could also suppose therapeutic targets.

Antimalarials: Hydroxychloroquine and chloroquine

Hydroxychloroquine (HCQ) is an antimalarial 4-aminoquinoline that showed *in vitro* activity against various RNA viruses, including SARS-CoV-2[46]. Some authors believe that HCQ acts against SARS-CoV-2 through multiple mechanisms[47]: Inhibition of viral entry; inhibition of viral release in the host cell; reduction of viral infectivity and immune modulation.

The absence of efficacious treatment tools at the beginning of the pandemic led to the wide use of chloroquine and HCQ. Thus, in several controlled studies carried out in Chinese hospitals, chloroquine treatment was able, compared to controls, to prevent the development of pneumonia, improve the radiological lung image, accelerate the elimination of the virus and shorten the duration of the disease [48-50]. Similarly, a French study with a small sample size found that treatment with HCQ accelerated conversion to a state of seronegativity for the virus[51]. However, these studies had significant methodological limitations that made their results questionable.

Nowadays, the body of evidence on HCQ e showed no benefit in terms of mortality reduction, invasive MV requirements, or time to clinical improvement. Until now, 31 randomized controlled trials (RCTs), including 16536 patients, have compared HCQ or chloroquine against standard of care or other treatments. The Recovery trial was the biggest, with over 11800 patients randomized to different treatment arms. 1561 patients were randomized to receive HCQ and 3155 to receive usual care after an interim analysis determined a lack of efficacy. Death within 28 d occurred in 421 patients (27.0%) in the HCQ group and in 790 (25.0%) in the usual-care group [rate ratio (RR) = 1.09; 95% confidence interval (CI): 0.97-1.23; P = 0.15]. The results suggested that patients in the HCQ group were less likely to be discharged from the hospital alive within 28 d than those in the usual-care group (59.6% *vs* 62.9%; RR = 0.90; 95%CI: 0.83-0.98). Moreover, among the patients who were not undergoing MV at baseline, those in the HCQ group had a higher frequency of invasive MV or death (30.7% *vs* 26.9%; RR = 1.14; 95%CI: 1.03-1.27)[52]. More recently, in the Solidarity trial, 947 patients were assigned to receive HCQ. Death occurred in 104 of 947 patients receiving HCQ and in 84 of 906 receiving its control (RR = 1.19; 95%CI: 0.89-1.59; P = 0.23)[53].

The main RCTs that have compared the effect of HCQ or chloroquine on mortality have been included in two metanalyses. The one made by the WHO combined the Recovery and Solidarity trials with other six smaller studies involving hospitalized patients with suspected or confirmed COVID-19. The results of this metanalysis showed that HCQ or chloroquine probably increase mortality, RR = 1.08 (95%CI: 0.99-1.19); does not reduce invasive MV requirement; RR = 1.05 (95%CI: 0.9-1.22) and may not improve time to symptom resolution, RR = 1.05 (95%CI: 0.94-1.18)[54]. These results are consistent with other published metanalysis that included 28 published or unpublished RCTs, with 10319 patients, obtaining a combined odds ratio (OR) on all-cause mortality for HCQ of 1.11 (95%CI: 1.02-1.20; I^2 = 0%; 26 trials; 10012 patients) and a combined OR for chloroquine of 1.77 (95%CI: 0.15-21.13, I^2 = 0%; 4 trials; 307 patients)[55]. In contrast, in a recent retrospective observational study conducted by Schlesinger *et al* [56] in 3451 unselected patients hospitalized in 33 clinical centers in Italy, HCQ use was associated with a 30% lower risk of in-hospital death COVID-19 hospitalized patients. In conclusion, awaiting new randomized clinical trials focused on critically ill patients, the treatment with HCQ is associated with increased risk of mortality in COVID-19 patients, and there was no benefit of chloroquine. For these reasons, its use is discouraged in patients with severe COVID-19 infection.

Colchicine

Colchicine has been in the spotlight as a treatment for SARS-CoV-2 infected patients given its anti-inflammatory and antiviral properties, which lead to the hypothesis that it might be beneficial with the systemic inflammation observed in the most severe cases. Many are the mechanism of action involved in colchicine's properties, but they are underpinned mainly by inhibiting neutrophil chemotaxis by interfering with microtubule formation, modulation of proinflammatory cytokines, and attenuation of

Table 1 Summary of studies addressing interleukin-1 blockers on coronavirus disease 2019

Ref.	Patients	Intervention	Comparison	Outcome
CORIMUNO-19 Collaborative group[74], RCT	Hospitalized patient with mild-to-moderate pneumonia, non-ICU admitted	Anakinra (200 mg twice a day on days 1-3, 100 mg twice on day 4, 100 mg once on day 5) (n = 59)	Standard care (n = 55)	No difference in NIV/MV/death at day 4. Stopped early following the recommendation of the data and safety monitoring board
Cavalli *et al*[75], observational	Pneumonia with moderate-to-severe ARDS and hyperinflammation (non-MV, non-ICU admitted)	Anakinra (high dose: 5 mg/kg twice a day intravenously, n = 29; or low dose: 100 mg twice a day subcutaneously, n = 7)	Standard care (retrospective cohort) (n = 16)	Survival. High-dose anakinra: 72%, SC: 56%, P = 0.009
Huet *et al*[76], observational	Bilateral pneumonia (non-ICU admitted)	Anakinra (100 mg twice daily for 72 h, followed by 100 mg daily for 7 d) (n = 52)	Standard care (historical group) (n = 44)	Death/MV. Anakinra: HR = 0.22 (95%CI: 0.11-0.41), P < 0.0001. Death. Anakinra: HR = 0.30 (95%CI: 0.12-0.71), P = 0.0063. MV: Anakinra: HR = 0.22 (95%CI: 0.09-0.56), P = 0.0015
Kooistra *et al*[77], observational	ICU admitted pneumonia (MV: 100%)	Anakinra (300 mg iv, followed by 100 mg iv/6 h) (n = 21)	Standard care (n = 39)	No differences in duration of MV, ICU length of stay, or mortality

RCT: Randomized clinical trial; ICU: Intensive care unit, NIV: Non-invasive ventilation; MV: Mechanical ventilation; ARDS: Acute respiratory distress syndrome; HR: Hazard ratio; SC: Standard of care; CI: Confidence interval.

NOD-like receptor family pyrin domain containing 3 inflammasome formation, among others[56].

Several studies have explored the potential risk-benefit ratio of colchicine in ambulatory and inpatient based on its properties. A meta-analysis reported a survival benefit (OR = 0.62; 95%CI: 0.48-0.81) of patients with Colchicine treatment with a tendency towards a decreased need of MV [0.75 (95%CI: 0.45-1.25)][57]. However, most studies focus on the out-hospital or mild cases of COVID-19 patients. Not much has been reported about colchicine in the most severe cases. In this sense, Scarsi *et al* [58] observed that colchicine was independently associated with survival [hazards ratio (HR) = 0.151; 95%CI: 0.062-0.368] despite it was given to patients with worse PaO_2/FiO_2. Similarly, Brunetti *et al*[59] also observed a significant decreased mortality in patients with severe COVID-19 among those who received colchicine (OR = 0.20; 95%CI: 0.05-0.80; P = 0.023).

To date, only one prospective, open-label, randomized trial has explored the potential benefits of colchicine among severe COVID-19 patients. In this trial, patients who received colchicine did show an improved time to clinical deterioration compared to those without colchicine[60]. However, recently, the RECOVERY trial closed the recruitment of colchicine for hospitalized COVID-19 patients after a review did not observe any clinical benefit[61].

In conclusion, given the disparity, we cannot recommend colchicine despite initial data being promising until further evidence. Among more than 30 clinical randomized trials ongoing analyzing the effect of Colchicine in COVID-19, only 3 focus specifically on severe cases or patients admitted to the ICU: In particular ECLA PHRI COLCOVID Trial (NCT04328480), COMBATCOVID trial (NCT04363437), and COLHEART-19 (NCT04762771). These trials will explore the requirement for MV, severe complications, or death among moderate-to-severe hospitalized COVID-19 patients.

Calcineurin inhibitors: Cyclosporine A and tacrolimus

Cyclosporine A and tacrolimus (also called FK-506) are immunosuppressive drugs known to prevent rejection after organ transplantation and for autoimmune diseases. These drugs bind to different cellular cyclophilins and FK506-binding proteins, respectively. This binding inhibits calcineurin (calcium-calmodulin-activated serine/threonine-specific phosphatase) blocking the translocation of the nuclear factor of the activated T cells from the cytosol to the nucleus, preventing the transcription of several genes that encode key cytokines involved in different immunological mechanisms[62-64].

Cyclosporin A binds cyclophilin A, which is essential for the replication of, among other viruses, SARS-CoV-2[65]. Therefore, the binding of cyclosporin A with the corresponding cyclophilin can block the replication of SARS-CoV-2[66]. Tacrolimus binds to FK506-binding proteins and inhibits calcineurin, in addition to suppressing the early phase of T-cell activation and the expression of numerous cytokines (IL-2, IL-4, TNF-α, INF-γ), which are necessary for the activation of the T cell in the immune response, perhaps preventing the cytokine storm seen in severe COVID-19 pneumonia[67].

In vitro evidence of inhibition of cyclosporine-mediated replication of various coronaviruses (including SARS) has been found. The cyclosporin analog, alisporivir, has been reported to inhibit SARS-CoV-2 *in vitro* but has never been tested in a clinical setting[68]. Given the antiviral and anti-inflammatory properties of calcineurin inhibitors, they could have the potential to prevent the uncontrolled inflammatory response and replication of SARS-CoV-2, in addition to acute lung injury. However, there is not enough evidence to recommend its use in severe COVID-19. Currently, several clinical trials are studying the possible benefit of the administration of cyclosporine (NCT04492891,

NCT04540926, and NCT04341038) or tacrolimus (NCT04341038) in the treatment of hospitalized patients with pneumonia due to COVID-19. Unfortunately, to date, there are no studies with these drugs focused on critically ill patients.

IL-1 blocker: Anakinra, canakinumab

Anakinra is a recombinant human IL-1 receptor antagonist that blocks the activity of the proinflammatory cytokines IL-1α and IL-1β, and it is approved to treat patients with rheumatoid arthritis, Still's disease, and some rare auto-inflammatory syndrome. Reanalysis of data from a phase III randomized controlled trial showed anakinra is related to a significant improvement in survival in the subset of septic patients with features of macrophage activation syndrome (MAS)[69,70].

MAS is a subgroup of secondary hemophagocytic lymphohistiocytosis mainly appearing in rheumatologic disorders. It is an acute syndrome with a hyperinflammatory immune state characterized by the activation and expansion of macrophages and T-lymphocytes. This persistent activation leads to a cytokine storm with high IL-1, IL-6, IL-18, soluble IL-2 receptor (CD 25), IFN-γ, and TNF-α, and is thought to be responsible for the multiorgan failure and the high mortality of this syndrome[71,72].

A subgroup of severe COVID-19 patients shows hyperinflammatory symptoms similar to MAS, with the release of IL-1, IL-6, IL 18, and IFN-γ, and the evidence shows a direct correlation between the severity of systemic inflammation, progression to respiratory failure, and fatal outcome[73,74]. For this reason, it has been proposed to treat this patient subgroup with anakinra. At the date, only the RCT CORIMUNO-ANA-1 investigating the role of anakinra in COVID-19 patients has been published[75]. In this trial, patients were randomized to intravenous anakinra or usual care in mild-to-moderate COVID-19 pneumonia (not requiring ICU admission) with serum C-reactive protein (CRP) levels higher than 25 mg/L. They could not demonstrate that the use of anakinra effectively reduced the need for non-invasive ventilation (NIV), MV, or mortality. The study was stopped due to futility. Another trial within the CORINOMUNO platform (CORINOMUNO-ANA-2) aimed to assess the effect of anakinra in patients with more severe COVID-19 patients (ICU admitted) has now been completed, and it is being analyzed.

Few observational studies analyze the treatment with anakinra in COVID-19 patients, and they have methodological limitations (Table 1). Cavalli *et al*[75] have analyzed high-dose (5 mg/kg twice daily) of intravenous anakinra compared to standard care: Higher survival rate and progressive improvements in PaO_2/FiO_2 ratio have been observed, without significant differences in days free of MV. Huet *et al*[76] have studied subcutaneous anakinra *vs* standard treatment, and they observed that anakinra significantly reduced the need for MV or mortality. The control group was a historical cohort with high mortality (about 50%).

Kooistra *et al*[77] have analyzed mechanically ventilated COVID-19 patients treated with intravenous anakinra *vs* standard care in critically ill patients. Anakinra has been linked to a significant reduction in clinical signs of hyperinflammation, without significant differences in clinical outcomes. Dimopoulos *et al*[78] have studied rescue treatment with intravenous anakinra in seven MV-ICU patients and one non-ICU patient, all of them with a hemophagocytosis score positive. They concluded that anakinra could improve respiratory function and reduce mortality compared with the historical series of patients with MAS in sepsis. Canakinumab is a monoclonal antibody against IL-1β approved to treat familial Mediterranean fever and other chronic autoinflammatory syndromes[79].

In the setting of COVID-19 pneumonia, a small retrospective study has analyzed 10 patients with respiratory failure (not requiring MV) and hyperinflammation treated with canakinumab. A rapid improvement of the inflammatory response and oxygenation was observed[80]. An ongoing clinical phase 3, randomized, double-blind trial studies the efficacy and safety of canakinumab on Cytokine Release Syndrome in patients with COVID-19 pneumonia (NCT04362813). In conclusion, there is not enough data supporting the efficacy or safety of anakinra or canakinumab in treating critically ill patients with COVID-19, and therefore, we can't establish a recommendation on their use or the optimal timing to start the treatment.

IL-6 blockers: Tocilizumab and sarilumab

COVID-19 patients who develop severe respiratory failure use to show a hyperinflammatory response, either MAS (driven by IL-1β) or, primarily, immune dysregulation (driven by IL-6). IL-6 is an inflammatory cytokine that exerts its effects inducing acute phase reactants (as CRP, fibrinogen, and hepcidin) in the liver and promotes antibody production and CD4 T helper and CD8 cytotoxic T cell differentiation[81,82]. A direct relationship between IL-6 levels and viral load, duration of SARS-CoV-2 viral positivity, the severity of COVID-19, and the need for MV has been observed[83-88].

Tocilizumab (TCZ) and sarilumab are two monoclonal antibodies that work by blocking the IL-6 soluble and membrane receptor. TCZ is approved to treat inflammatory diseases such as rheumatoid arthritis, juvenile idiopathic arthritis, giant cell arteritis, and cytokine release syndrome associated with chimeric antigen receptor T-cell therapy and sarilumab is approved for the treatment of rheumatoid arthritis[89]. Its use has been proposed to reduce the inflammatory response in COVID-19 patients. The first available data obtained from case series showed clinical, analytical, and radiological improvement after TCZ administration, even in patients needing MV[90-94].

Table 2 Summary of studies addressing interleukin-6 blockers on coronavirus disease 2019 (randomized clinical trials and observational studies including critically ill patients)

Ref.	Patients	Intervention	Comparison	Outcomes	Overinfection rate
Salama *et al*[110], RCT	377	TCZ (8 mg/kg, 1-2 doses)	Placebo	MV/ECMO/mortality 28 d; 19.3% TCZ *vs* 12% placebo, $P = 0.004$	TCZ 10% *vs* placebo 12.6%
Rosas *et al*[113], RCT	438	TCZ (8 mg/kg, 1-2 doses)	Placebo	Mortality: NS. Hospital LOS: TCZ: 20, placebo: 28 d ($P = 0.037$). ICU admission: TCZ: 23.6%, SC: 40.6% ($P = 0.01$). ICU, LOS: TCZ: 9.8, SC: 15.5 d ($P = 0.045$)	TCZ 21% *vs* placebo 25.9%
Stone *et al*[90], RCT	242	TCZ (8 mg/kg, max 800 mg, 1 dose)	Placebo	MV or death. TCZ: 10.6%, SC: 12.5% (NS). Clinical worsening. TCZ: 19.3%, SC: 17.4% (NS)	TCZ 8.15% *vs* placebo 17.1%
Salvarani *et al* [111], RCT	123	TCZ (8 mg/kg, max 800 mg, 1-2 doses)	Standard of care	NS	TCZ 1.7% *vs* TE 6.3%
Mariette *et al* [112], RCT	131	TCZ (8 mg/kg, max 800 mg, 1-2 doses)	Standard of care	NIV/MV/death at day 4. TCZ: 19%, SC: 28% (NS). Survival without HFNO/NIV/MV at day 14. TCZ: 24%, SC: 36% (probability: 95%). 28 d mortality. TCZ: 10.9%, SC: 11.9% (NS)	TCZ 3.2% *vs* TE 16.4%
RECOVERY Collaborative Group[115], RCT	4166	TCZ (different regimes)	Standard of care	28 d mortality: TCZ: RR = 0.86 (95%CI: 0.77-0.96, $P = 0.006$)	Not available
REMAP-CAP Investigators *et al* [116], RCT	826	TCZ (8 mg/kg, max 800 mg, 1-2 doses) ($n = 366$). Sarilumab (400 mg) ($n = 48$)	Standard of care	Days free of respiratory/hemodynamic support at day 21. TCZ: 10 d, sarilumab: 11 d, SC: 0 d. Hospital mortality. TCZ: 28%, sarilumab: 22.2% SC: 35.8% (probability TCZ better: 99.6%, probability sarilumab better: 99.5%)	TCZ 0.2% *vs* TE 0%
Veiga *et al*[114], RCT	129	TCZ (8 mg/kg, max 800 mg)	Standard of care	Stopped early due to higher mortality in TCZ patients	PB 15% *vs* SC 16%
Tleyjeh *et al*[121], MA	9850	TCZ (variable regimen)	Standard of care	Mortality: TCZ: OR = 0.58 (0.51-0.66)	TCZ: RR = 0.63 (0.38-1.06)
Gupta *et al*[106], OS	3491	TCZ (regimen not specified)	Standard of care	Hospital mortality. TCZ: HR = 0.71 (95%CI: 0.56-0.92)	TCZ 32.3% *vs* SC 31.1%
Somers *et al*[108], OS	154	TCZ (8 mg/kg, max 800 mg)	Standard of care	Mortality. TCZ: HR = 0.54 (95%CI: 0.35-0.84)	TCZ 54% *vs* SC 26%. Pneumonia 45% *vs* 20%. Bacteremia 14% *vs* 9%
Fisher *et al*[109], OS	115	TCZ (400 mg)	Standard of care	30 d mortality. TCZ: OR = 1.04 (95%CI: 0.27-3.75)	TCZ 28.9% *vs* SC 25.7%
Biran *et al*[102], OS	764	TCZ (400 mg, 1-2 doses)	Standard of care	Hospital mortality. TCZ: HR = 0.64 (95%CI: 0.47-0.87, $P = 0.004$)	TCZ 17% *vs* SC 13%
Guaraldi *et al* [101], OS	544	TCZ (8 mg/kg, max 800 mg, 2 doses) ($n = 179$)	Standard of care	Death/MV. TCZ: HR = 0.61 (95%CI: 0.4-0.92), $P = 0.020$	TCZ 13% *vs* SC 4%
Rossotti *et al* [105], OS	222	TCZ (8 mg/kg, max 800 mg, 1-2 doses) ($n = 74$)	Standard of care	Survival rate TCZ: HR = 2.004 (95%CI: 1.050-3.817), $P = 0.035$. Survival rate in critically ill patient. HR = 30.055 (95%CI: 1.420-636.284), $P = 0.029$	TCZ 24.4%; SC: NA
Rojas-Marte *et al* [107], OS	193	TCZ (regimen not specified)	Standard of care	Mortality TCZ: 52%, SC: 62%, $P = 0.09$. Mortality in non-ventilated patients: TCZ: 6.1%, SC: 26.5%, $P = 0.024$	Bacteremia: TCZ 12.5% *vs* SC 23.7%. Fungemia: TCZ 4.2% *vs* SC 3.1%

TCZ: Tocilizumab; RCT: Randomized clinical trial; MA: Metha-analysis; OS: Observational study; MV: Mechanical ventilation; ICU: Intensive care unit; NIV: Non-invasive ventilation; LOS: Long of stay; HNFO: High nasal flow oxygen therapy; ECMO: Extracorporeal extracorporeal membrane oxygenation; SC: Standard of care; NS: Non-significative; RR: Relative risk; OR: Odds ratio; CI: Confidence interval; HR: Hazard ratio; NA: Not applicable.

The results obtained from comparative observational studies (cohorts or case-controls) were also promising[95-98]. Although some studies failed to show relevant differences between TCZ-treated and untreated patients[99,100], most of them showed a beneficial effect of the administration of TCZ: Oxygenation improvement, more days free of MV, less need for ICU admission or MV, and higher survival[101-105].

There are scarce studies that analyze the effect of TCZ in critically ill patients with COVID-19. In one of them, Biran *et al*[102] in 630 propensity score-matched ICU patients (> 90% of them receiving MV) found a lower in-hospital mortality risk (HR = 0.64; 95%CI: 0.47-0.87; $P = 0.004$) in patients treated with TCZ (400 mg). Rossotti *et al*[105] described similar results showing a lower risk of mortality in the

general analysis and patients receiving MV, but not in less severe cases; Gupta *et al*[106] found an in-hospital reduction in mortality in those critically ill patients who received TCZ in the first 2 d of ICU admission. On the other hand, Rojas-Marte *et al*[107] analyzed 193 patients (62.7% with MV) and found that TCZ was related to lower mortality in non-ventilated patients (6.1% *vs* 26.5%, $P = 0.024$), but not in MV patients.

In addition, we have contradictory data from two studies focused on patients on MV. One of them shows a reduction in mortality risk (HR = 0.55; 95%CI: 0.33-0.90)[108], and the other failed to detect significant differences between those treated with TCZ and untreated patients[109,110]. More recently, we began to know the results of RCT investigating the effects of TCZ in COVID patients[85,111-113]. Among these, once again, there is no unanimity regarding the results. Salama *et al*[110] and Mariette *et al*[112], in hospitalized patients with SARS-CoV-2 pneumonia (not needing respiratory support), demonstrated a reduction in the risk of death or need of MV in patients treated with one or two doses of TCZ (8 mg/kg, maximum 800 mg). However, Stone *et al*[90] and Salvarani *et al*[111] failed to demonstrate a beneficial effect in patients treated with TCZ in similar patients (respiratory failure needing conventional oxygen therapy).

In a mixed population, including 38% of patients on MV, the COVACTA trial shows no evidence of improvement in the clinical situation on day 28 (primary outcome) but it shows a shorter hospital stay, less ICU admission, and less clinical failure rate in patients randomized to treatment with TCZ (8 mg/kg, max 800 mg, one or two doses)[113]. TOCIBRAS trial was prematurely interrupted because an excess of deaths at 15 d after randomization was detected in the TCZ group; this study included severe and critically ill COVID patients (23% receiving HFNO/NIV and 16% receiving MV)[114].

Recently, results of the RECOVERY platform trial were released[115]. In patients with clinical evidence of progressive COVID-19 (CRP ≥ 75 mg/L and need for supplemental oxygen to achieve oxygen saturation > 92%), treatment with TCZ improved survival and decreased the need for MV. The reduction in mortality with TCZ was higher in patients who also receive corticosteroids. REMAP-CAP trial addressed the impact of TCZ focused on critically ill patients. In this RCT, patients were randomized to be treated with TCZ ($n = 366$), sarilumab ($n = 48$), or usual care ($n = 412$). The authors reported that patients treated with IL-6 blockers (TCZ 8 mg/kg, max 800 mg, one or two doses; or sarilumab, 400 mg), within 24 h after the start of organ support, had more days free of hemodynamic or respiratory support and lower in-hospital mortality. Furthermore, it appears that the treatment effect is more significant when TCZ was combined with corticosteroids[116]. A summary of studies addressing IL-6 blockers on COVID-19 is available in Table 2.

One of the main concerns when using TCZ is the risk of superinfections. However, a higher incidence of superinfections in patients treated with TCZ has not been confirmed in critically ill COVID-19 patients (see Table 2). In the same way as TCZ, sarilumab administration has been related to series, clinical, analytical, and radiological improvement but the available data are scarce[117-120]. It has not shown benefit in comparative observational studies[121], but it has been shown in the aforementioned REMAP-CAP trial[116]. In most positive studies, TCZ is associated with corticosteroids (see Table 3), thus given the positive results described and the absence of significant side effects of this combination, it should be considered early in COVID-19 patients admitted to the ICU.

Janus kinase pathway inhibition: Ruloxitinib, bariticinib

Most viruses, SARS-CoV-2 included, enter cells through receptor-mediated endocytosis after binding its spike protein to the human ACE-2 receptor[122]. This endocytosis is mediated by clatrine and other mechanisms. AP2-associated protein kinase 1 (AAK1) and cycling G-associated kinase (GAK) regulates this process[123]. Disabling AAK1 might stop the virus's entry into cells and the intracellular assembly of virus particles[124]. Janus kinase (JAK) inhibitors are biological agents that mainly inhibit type I/II cytokine receptors[125]. There are several JAK inhibitors such as fedratinib, tofacitinib, sunitinib, or erlotinib. Still, they have many secondary effects, which turns their use in COVID-19 patients controversial, but ruxolitinib and baricitinib may play a role in this setting. However, Food and Drug Administration recently raised a warning regarding treatment with JAK-inhibitors that we have to bear in mind before starting treatment: Increased thromboembolism risk or increased frequency of herpes zoster virus reactivation; pan-JAK inhibitors may repress some cytokines required for antiviral defense (IFN-α/β) or immune restoration (IL-2, IL-7)[126-128].

Baricitinib is an oral anti-JAK inhibitor, acting against JAK1 and JAK2, with less potency for JAK3, with an exceptionally high affinity for AAK1. It inhibits the JAK signal transducer and activator of the transcription (STAT) pathway[129]. Moreover, it can also inhibit the cyclin GAK, another regulator of endocytosis, so it has been suggested as a potential drug against SARS-CoV-2 due to its double effect: Decreasing both the immune response (inhibiting the proinflammatory signal of several cytokines, such as IL-6, IL-12, IL-23, and IFN-α) and interrupting the virus entry and assembly in the cells[130]. It is currently approved for rheumatoid arthritis[131]. Its advantages include once-a-day oral administration (either 2 mg or 4 mg), acceptable safety profile (can be used in combination with other treatments because of low plasma protein binding and minimum cytochrome P450 interactions), and the double mechanism of action[132]. There is certain reluctance about baricitinib due to the simultaneous inhibition of AAK1 and JAK, which can reduce IFN-α levels, leading to a worse immune response, as mentioned above[133]. A pilot study from Italy showed significantly improved clinical and laboratory

Table 3 Coronavirus disease 2019 patients treated with tocilizumab and corticosteroids

Ref.	Tocilizumab group	Control
Salama *et al*[110], RCT	80.3%	87.5%
Rosas *et al*[113], RCT	36.1%	54.9%
Stone *et al*[90], RCT	11%	6%
Salvarani *et al*[111], RCT	10%	7.6%
Mariette *et al*[112], RCT	33%	61%
RECOVERY Collaborative Group[115], RCT	82%	82%
REMAP-CAP Investigators *et al*[116], RCT	> 80%	
Veiga *et al*[114], RCT	69%	73%
Gupta *et al*[189], observational	18.7%	12.6%
Somers *et al*[108], observational	29%	20%
Fisher *et al*[109], observational	73.3%	78.6%
Biran *et al*[102], observational	46%	42%
Guaraldi *et al*[101], observational	30%	17%
Rossotti *et al*[105], observational	Not reported	
Rojas-Marte *et al*[107], observational	43%	33%

RCT: Randomized clinical trial.

parameters in 12 patients with mild to moderate COVID-19 pneumonia. None of them required admission to the ICU nor MV[134].

An RCT evaluated baricitinib plus remdesivir in hospitalized COVID-19 patients. The treatment group needed fewer days to recovery (7 *vs* 8 d, $P = 0.03$) and 30% higher odds of improvement in clinical status at day 15. Precisely, patients on NIV or HFNO needed significantly less time to recovery (10 *vs* 18 d) and had fewer serious adverse events (16% *vs* 21%, $P = 0.03$)[135]. In conclusion, baricitinib combines anti-inflammatory characteristics and antiviral activity, making it a strong candidate for future evaluation in RCT.

Ruxolitinib is another oral JAK-kinase inhibitor currently indicated for intermediate or high-risk myelofibrosis, polycythemia vera, hemophagocytic lymphohistiocytosis, or steroid-refractory graft-*versus*-host disease. Ruxolitinib reduces the high level of cytokine release associated with these diseases [136,137]. It blocks JAK kinase activity and impedes STAT activation, decreasing levels of inflammatory cytokines (such as IL-1β, IL-2, IL-5, IL-6, IL-7, IL-13, IL-15, and IFN-γ)[138]. Pharmacokinetically, ruxolitinib has rapid oral absorption and a half-life of approximately 3 h and reaches peak plasma concentrations[139].

A non-randomized clinical study conducted in 93 severe COVID-19 patients not requiring MV at baseline showed a significant improvement in survival rate (89.1% *vs* 57.1%, $P = 0.0034$), a reduction of the inflammatory response (absence of fever and a decrease of at least 30% in CRP levels; 87% *vs* 23%, $P = 0.0001$) and no significant adverse event in patients treated with half the approved dose of ruxolitinib for hematologic diseases plus corticosteroids[140]. Similar results were communicated by La Rosée *et al* [140], in his retrospective study performed in 14 patients receiving ruxolitinib (10 receiving NIV, 1 HFNO, and 1 MV); they used a COVID inflammation score to evaluate the systemic inflammation, watching a reduction by 42% and 58% achieved on day 5 and 7 of treatment.

Only one Chinese RCT studied the efficacy of ruxolitinib. No death (14.3% *vs* 0%, $P = 0.232$) or deterioration [need for NIV/MV: (29% *vs* 10%, $P = 0.663$)/(14.3% *vs* 0%, $P = 0.232$)] occurred in ruxolitinib group, but no statistically difference was found. Both groups received a similar proportion of corticosteroids and antivirals[141]. To summarize, ruxolitinib may play a role in those patients with hypoxemic COVID-19 pneumonia but not yet needing MV, attenuating the immune response and therefore may prevent the progression of lung damage, bearing in mind that an early administration could favor viral replication. There is no data in critically ill patients regarding JAK inhibitors to establish a strong recommendation but, maybe, baricitinib could be used in patients on NIV or HFNO who are also receiving remdesivir, in order to shorten the time to recovery.

Corticosteroids

Corticosteroids have been widely used for years in autoimmune diseases with great success. A cytokine

storm[32], similar to the hemophagocytic syndrome, may develop in some severe COVID-19 patients. In this setting, immunosuppressive treatments may decrease this hyper-inflammatory state, and this is the rationale for use corticosteroids in SARS-CoV-2 infection. Corticosteroids are hormones that may change the transcription pattern of 20% of the human genome[142], and they act in virtually all immune cells [143]. They inhibit the migration of leukocytes to inflamed tissues, increasing migration from bone marrow to blood and decreasing programmed leukocyte death[144,145]. They also inhibit leukocyte reactive oxygen species secretion, increase anti-inflammatory cytokines like IL-10[146,147], and alter the maturation and differentiation of dendritic cells[148-150]. Corticosteroids modify natural killer (NK) cytolytic activity and monocyte activation[150].

The use of up 100 mg of prednisone or an equivalent dose, acts over cytosolic corticosteroids receptors (cGCR), and we call this the genomic pathway[151,152]. The complex glucocorticoid-cGCR has two actions: Transactivation, which means that the complex promotes anti-inflammatory transcription factors as IL-10 or annexin 1. The other action is transrepression that produces an inhibition of inflammatory transcription factors (IL-1, IL-2, IL-6, IL-8, prostaglandins, TNF-α, and IFN-γ). That modifications happen in hours and may take up to a few days[151].

If we use corticosteroid pulses (doses higher than 100 mg of prednisone), we reach the highest effect of the genomic pathway, but we also obtain additional effects by the "non-genomic pathway"[150]. The non-genomic pathway induces membrane dysfunction in all immune cells and delays the calcium and sodium channel flow through the membrane. This process decreases ATP production. Non-genomic effects induce the bounding to the membrane of glucocorticoid receptors in the T lymphocytes[151]. They also release the Src protein from the complex cGCR-multiprotein, generating anti-inflammatory effects. These mechanisms take effect in hours and are very useful in autoimmune diseases with high disease activity[151].

The effect of corticosteroids depends not only on the dose (as seen before) but also on the timing used. We can preferably use corticosteroids in three moments: The onset of acute lung injury, the initial phase of acute respiratory distress syndrome (ARDS), and when ARDS is refractory to conventional treatment[153-155]. Historically, many studies used corticosteroids for viral pneumonia (including influenza and SARS-CoV-1)[156-161], and ARDS[162-167], with different results. We found no benefit in viral infection, and only a few of these studies demonstrated good results of corticosteroids on mortality [162,166]. Based on these, some authors analyzed the effect of corticosteroids in COVID-19 (see Table 4). Early in the pandemic, initial recommendations were not to use or limit corticosteroids to concrete situations[168-171]. WHO even recommended not to use corticosteroids routinely in COVID-19 pneumonia[172,173]. They base these recommendations on previous bad results in the SARS and Middle East respiratory syndrome (MERS) infections with corticosteroids. Some months later, some observational studies based on the Chinese hospitals' experience recommended using corticosteroids under certain conditions[174-176].

The Recovery trial[177] could demonstrate a mortality improvement with dexamethasone treatment in COVID-19 patients requiring oxygen supplementation, especially in those admitted to ICUs. This improvement does not remain in patients who do not need oxygen supplementation, worsening mortality in this subgroup.

From July to December 2020, several clinical trials demonstrated the benefits of corticosteroids on mortality in COVID-19 associated pneumonia[178-181]. Hydrocortisone, methylprednisolone, and dexamethasone are corticosteroids that demonstrated survival improvement used at a median dose for five to ten days. These corticosteroids at this dose demonstrated moderate mortality reductions. All studies showed that the mortality improvement was more significant in critical patients than in-hospital patients (see Table 4). Corticosteroids can also be used at a higher dose with methylprednisolone pulses for three days (250 mg for three days). One small clinical trial and some observational studies showed essential improvements in mortality using corticosteroid pulses[182-185]. Again using corticosteroid pulses, mortality improvement was more significant in the critical patient subgroup. This regimen (by the non-genomic pathway) showed better results than the median doses of corticosteroids for more extended periods in the few published results. If this regimen is significantly better than lower doses and more prolonged periods must be demonstrated in ongoing head-to-head clinical trials[186].

Progression to MV was lower in the corticosteroid arm in clinical trials and meta-analyses[187,188]. There was a non-significant trend to hyperglycemia and infections in the corticosteroid arm treatment (see Table 4). Results about viral shedding are controversial and different between studies, so we can't extract conclusions. As a final recommendation, corticosteroids should be used in COVID-19 pneumonia requiring oxygen supplementation, including critically ill patients, as proven in the Recovery trial and data obtained with the corticosteroid pulses studies. The 6 mg daily dexamethasone for ten days is the most accepted regimen because it is proven in clinical trials. The 250 mg daily methylprednisolone regimen for three days may be considered as an alternative too.

Intravenous immunoglobulin and hyperimmune immunoglobulin

Intravenous immunoglobulin (IVIG) is a product derived from the plasma of thousands of donors. It contains primarily polyclonal immunoglobulin G [with two functional fragments, the F(ab)2 fragment, for antigen recognition, and the crystallizable fragment (Fc), for the activation of innate immune responses], with small amounts of immunoglobulin (Ig)A and IgM. IVIG provides temporary protection

Table 4 Summary of studies using corticosteroids in coronavirus disease 2019

Ref.	Patients	Treatment regimen	Population	Mortality[2]	ICU administration	In-hospital stay	Secondary infections
RECOVERY Collaborative Group *et al* [177], RCT	11303	DXM 6 mg daily × 10 d	In-hospital	Decrease 2.8% RR 0.83	NS	Increase discharged 28 d (3.7%)	NA
RECOVERY Collaborative Group *et al* [177], RCT	1007	DXM 6 mg daily × 10 d	MV	Decrease 12.1% RR 0.64	NA	Increased discharged 28 d (9.7% RR 1.48)	NA
Tomazini *et al*[176], RCT	299	DXM 20 mg × 5d + DXM 10 mg × 5d	ICU patients	Decrease 2.4% (alive or ventilator-free)		NA	DXM 21.9% *vs* 29.1% standard. (7.9% *vs* 9.5% bacteremia)
Jeronimo *et al*[178], RCT	416	MPD (0.5 mg/kg twice daily) × 5d	In-hospital	NS	NS (MV)	NS	No significant differences
Dequin *et al*[179], RCT	149	HCT 200 mg daily × 7d then decrease dose × 7d (14 d)	ICU patients	NS		NS	NA
Angus *et al*[180], RCT	384	HCT 50 or 100 mg/6 h × 7 d	ICU patients	93% and 80% of superiority in organ support free		NS	NA
Edalatifard *et al*[181], RCT	68	MPD 250 mg × 3 d	In-hospital	Decrease 37%	No patients on MV	Decrease 4.6 d	2.9% (1 pt) in MPD *vs* 0% (0 pt) standard
Corral-Gudino *et al* [188], RCT[1]	85	MPD 40 mg/12 h × 3 d, then MPD 20 mg/12 h × 3 d	In-hospital	Decrease 24% composite death, ICU Adm or NIV		NS	NA
Kim *et al*[186], MA	49569	Variable regimens	ICU patients	OR 0.54 (0.40-0.73)	NA	NS	NA
Van Paassen *et al* [187], MA	20197	Variable regimens	In- hospital	OR 0.72 (0.57-0.87)	RR 0.71 (0.54-0.97)	NS	NA

[1]Preprint, not peer-reviewed.
[2]Absolute risk of mortality reduction in randomized clinical trial or odds ratio in meta-analysis.
ICU: Intensive care unit; RCT: Randomized clinical trial; MA: Meta-analysis; DXM: Dexamethasone; MPD: Methylprednisolone; HCT: Hydrocortisone; NS: Non-significant; NA: Not applicable; Adm: Admission; MV: Mechanical ventilation; NIV: Non-invasive ventilation; RR: Relative risk; OR: Odds ratio.

before being metabolized, requiring several doses over the disease course[189]. IVIG has been used to treat several immunodeficiencies, neurologic disorders, inflammatory and infectious conditions, such as pneumonia by influenza, SARS, and MERS[190].

The rationale for using IVIG in SARS-CoV-2 infection is a modulation of inflammation. The central mechanism of action of IVIG is the inactivation of phagocytes (neutrophils, monocytes, and macrophages) through FCyR. Moreover, it has a neutralizing effect by creating an antibodies-virus complex that prevents the binding of the virus to alveolar epithelial cells. Furthermore, it can also influence the process of lymphocyte differentiation and maturation[191,192].

Xie *et al*[193] conducted a retrospective study among 58 cases of severe or critically ill COVID-19 patients with lymphopenic immunophenotype (absolute lymphocyte count fell under 0.5 × 10^9/L), receiving IVIG (20 g/d), differentiating two groups: Those receiving IVIG early (< 48 h after admission) and after 48 h. There was a significant reduction in 28-d mortality (23% *vs* 57%, P = 0.009), need for MV (6.67% *vs* 32.14%, P = 0.0016) and length of stay (11 ± 1 d *vs* 1696 ± 16 d, P = 0.005) in the < 48 h group. However, a more recent RCT including 84 patients with severe COVID-19 (52 of which received IVIG at a dose of 400 mg/kg/d for three days plus standard care) showed no difference in terms of mortality nor need for MV or admission to the ICU[194]. Finally, an Iranian RCT including 59 patients who did not respond to initial treatments, showed a significantly lower in-hospital mortality (20% *vs* 48.3%, P = 0.025) in those patients (n = 30) receiving IVIG (20 g daily for three days)[195].

Taken together, the results of the studies show some limitations to attribute clinical improvement only to IVIG use (variations in previous/concomitants treatments, a small number of patients, or variations in dosage). So, in conclusion, we can't make a statement recommending its use. Considering its overall safety profile, it may be a promising option at the early stage of severe COVID-19 disease. On the other hand, hyperimmune immunoglobulin (H-IG) is an IVIG obtained from patients with high antibody titers to specific pathogens. Its pharmacokinetic properties are similar to IVIG, suggesting that a single dose may be enough in an acute setting[196,197]. It has been used in previous coronavirus epidemics such as SARS1 in 2003, MERS in 2012, and influenza A[198]. H-IG was used at a dosage of 5 mL/kg with an antibodies neutralizing titer of 1:160, with an optimal administration within the first 7 d. One of its limitations is the generation of neutralizing antibodies in specific individuals who have

passed an infection. Another limitation is that donor availability is limited. A recent Cochrane revision was conducted regarding convalescent plasma and H-IG including 98 ongoing studies[199].

Recently an Indian RCT included 464 moderate COVID-19 patients (PaO_2/FiO_2 between 200-300 mmHg or a respiratory rate higher than 24 rpm with SaO_2 < 93% on room air), 235 of which received convalescent plasma (two doses of 200 mL separated 24 h): No difference was observed with the control group regarding the progression of disease or mortality[200]. Another RCT conducted in Wuhan involved 103 severe COVID-19 patients (44 on NIV or high-flow nasal cannula, 25 on MV or extra-corporeal membrane oxygenation), where 52 received convalescent plasma plus standard therapy, observed an improvement of the negative conversion rate of viral polymerase chain reaction (87.2% *vs* 37.5%, P < 0.001) but did not result in a statistically significant improvement in time to clinical improvement within 28 d or in 28-d mortality[201].

We have limited data regarding critically ill patients. A small case series involving 5 critically ill patients on MV treated with convalescent plasma between day 10 to 22 from admission observed an improvement in their clinical status [increased PaO_2/FiO_2, decreased Sequential Organ Failure Assessment (SOFA) score, and body temperature normalized][202]. Another case report involving 4 critically ill patients (who received 200-2400 mL of convalescent plasma ranging from day 11 to day 18 post-admission) observed lung lesions resolution and decreased SARS-CoV-2 viral load clinical improvement[203]. A summary of RCTs and observational studies, including critically ill patients addressing IVIG and H-IG on COVID-19, is available in Table 5. Therefore, there are not enough data to support the use of H-IG and controversial results on convalescent plasma, so we can't establish a recommendation.

Other potential therapies: Statins and T-lymphocyte restorative therapies

Statins: Statins are potent 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors that prevent the activation of Rho-kinase, and thus, gain cardiovascular protective effects that are low-density lipoprotein-cholesterol independent[204]. The existing published evidence suggests a potential benefit of statins[205,206], despite the higher risk profile of statin-users as opposed to non-users, with some discordant results[207,208].

Statins improve endothelial dysfunction through upregulation of ACE-2 and endothelial nitric oxide synthase, decrease endothelin-1 and reactive oxygen species, and decrease nuclear factor-kB activation as well as proinflammatory cytokine expression[204,209]. Statins might also lessen myocardium injury by increasing nitric oxide, improving coronary perfusion, and decreasing IL-6 synthesis[210-212]. Finally, we can obtain a potential reduction of acute coronary syndromes and cerebrovascular events (both increased in COVID-19 patients)[213,214].

If statins might benefit ARDS due to their pleiotropic properties, it has been evaluated before the current global pandemic. Two RCTs with rosuvastatin and simvastatin did not improve clinical outcomes in ARDS[215,216]. Similar findings were reported in a meta-analysis where stains did not have a clear net benefit among patients with acute lung injury or ARDS[217]. However, a sub-analysis of the HARP-2 trial (HMG-CoA reductase inhibition with simvastatin in acute lung injury to reduce pulmonary dysfunction) observed in the subgroup of patients with hyperinflammatory phenotype a survival benefit of simvastatin that was not observed with rosuvastatin[218]. The presence in most cases of severe COVID-19 both, of hyperinflammation and endothelial dysfunction might theoretically justify why statin treatment showed a protective effect against the need for MV and ICU admission in COVID-19 patients[25,28,30,219]. Unfortunately, no studies seem to have explicitly focused on lipid-lowering agents in critically ill patients with COVID-19. The lack of prospective data on this subset of patients does not allow us to provide a recommendation. However, several ongoing clinical trials will give us evidence-based insights about statin efficacy in severe COVID-19 (NCT04486508; NCT04390074). Until then, the decision about continuation should be individualized.

T-lymphocyte restorative therapies: As mentioned before, the presence of hypercytokinemia with lymphopenia represents a biological signature of a pathogen uncontrolled damage in critically ill patients with COVID-19. NK cells and cytotoxic T cells can kill the virally infected cells, whereas the helper T lymphocytes adjust the total adaptive immune response. In this regard, the lymphopenic immunophenotype is considered a bad prognosis factor and targets novel therapies. Several T-lymphocyte restorative treatments as IL-7 or thymosin alpha are under evaluation. IL-7 is a pleiotropic cytokine essential for lymphocyte survival and expansion. Administration of IL-7 invariably increases circulating and tissue lymphocytes and has an excellent safety profile[220,221]. Several trials are evaluating its use among patients with severe COVID-19 (NCT04442178, NCT04379076, NCT04407689). A recent clinical series by Laterre *et al*[222] evaluated the compassionate use of IL-7 in 12 critically ill patients with COVID-19 and severe lymphopenia (defined as two consecutive absolute lymphocyte counts of less than 700/μL). An initial safety dose of 3 μg/kg was followed by a dose of 10 μg/kg by intramuscular injection twice a week for 2 wk. 13 patients with COVID-19 received standard-of-care treatment matched as a comparator control cohort. On day 30, secondary infections occurred in 7 patients (58%) in the IL-7 group compared with 11 (85%) in the control group; 30-d mortality was 42% *vs* 46%, respectively. IL-7 was associated with a restored lymphocyte count, with the IL-7 group having levels more than 2-fold higher than the control group without associated adverse effects noted in the

Table 5 Summary of randomized clinical trials and observational studies including critically ill patients addressing intravenous immunoglobulin and hyperimmune immunoglobulin on coronavirus disease 2019

Ref.	Patients	Intervention	Comparison	Outcome
Xie *et al*[193], observational	Severe/critical pneumonia and. Lymphocyte count < 0.5×10^9/L (18.9% on MV, 13.8% on NIV/HFNC)	IVIG (20 g/d)	> 48 h after admission (n = 28) *vs* < 48 h after admission (n = 30)	Reduction in 28-d mortality (23% *vs* 57%, P = 0.009), need for MV (6.67% *vs* 32.14%, P = 0.001) and LOS (11.5 ± 1.0 *vs* 16.9 ± 1.6 d, P = 0.005) in the < 48 h group
Tabarsi *et al* [194], RCT	Severe pneumonia (36.9% on MV, 78.6% ICU-admitted)	IVIG (400 mg/kg/24 h for 3 d) (n = 52)	Standard care (n = 32)	No difference in mortality (46.1% *vs* 43.7%, P = 0.83), need for MV (40.4% *vs* 31.2%, P = 0.39) or ICU admission (75% *vs* 84.4 %, P = 0.3)
Gharebaghi *et al* [195], RCT	Severe pneumonia with persisting symptoms or need for supplementary oxygen to maintain SaO_2 > 90% after 48 h of treatment	IVIG (20 g daily for three days) (n = 30)	Standard care (n = 29)	Lower in-hospital mortality (20% *vs* 48.3%, P = 0.022). Mortality. IVIG: OR = 0.003 (95%CI: 0.001-0.815, P = 0.042)
Agarwal *et al* [200], RCT	Moderate pneumonia	Convalescent plasma (200 mL, 2 doses) (n = 235)	Standard care (n = 229)	Disease progression or mortality: No difference
Li *et al*[201], RCT	Severe/critical pneumonia (NIV/HFNO: 42.7%, MV/ECMO: 24.3%)	Convalescent plasma (4-13 mL/kg) (n = 52)	Standard care (n = 51)	No improvement in time to clinical improvement within 28 d

RCT: Randomized clinical trial; MV: Mechanical ventilation; NIV: Non-invasive ventilation; LOS: Length of stay; HNFO: High nasal flow oxygen therapy; ICU: Intensive care unit; OR: Odds ratio; IVIG: Intravenous immunoglobulin; ECMO: Extracorporeal membrane oxygenation; CI: Confidence interval.

intervention arm.

In a recent Chinese study, thymosin alpha-1 (Tα1), another lymphopoiesis-stimulating drug, was employed in two cohorts of critically ill patients with COVID-19[223]. Compared with the untreated group, Tα1 treatment significantly reduced the mortality of severe COVID-19 patients (11.1% *vs* 30%, P = 0.044). Interestingly, patients with counts of CD8+ T cells or CD4+ T cells in circulation less than 400/μL or 650/μL, respectively, gained more benefits from Tα1. Other drugs targeting lymphocyte apoptosis by suppressing PD1/PD-L1, like nivolumab, are also being studied as potential candidates for treatment COVID-19. Currently, several trials are analyzing the role of these novel drugs. Unfortunately, they only focus on mild and moderate forms of COVID-19.

DISCUSSION

Few treatments proposed in COVID-19 have been evaluated in patients critically ill with COVID-19, despite a high mortality rate (20%-40%)[224,225]. This fact makes it extremely difficult to establish degrees of recommendation regarding the different therapeutic options currently available. Therefore, new studies are needed to analyse the role of these and other novel treatments in this subset of patients. In this sense, future trials must employ a better design and careful selection criteria. It is critical not to consider all patients with severe forms of COVID-19 the same. Some of these patients (but not all) show specific hallmarks characterized by profound immunity alterations, hyperinflammatory states, and even severe endothelial dysfunction that favors progression to different degrees of organ failure. This triad (hyperinflammation, immune dysregulation, and endothelial dysfunction) in presence of organ failure is not restricted to COVID-19, and we can find it in sepsis, which would support the theory that severe COVID-19 is a form of viral sepsis. These alterations allow the classification of critically ill COVID-19 patients into different phenotypes[226-228]. Recently Chen *et al*[229], in a single-center study of critically ill patients with COVID-19, identified by a machine learning approach two phenotypes: One hyperinflammatory, characterized by elevated pro-inflammatory cytokines, higher SOFA score, and higher rates of complications and another hypo-inflammatory. Interestingly, corticosteroid therapy was associated with reduced 28-d mortality (HR = 0.45; 95%CI: 0.25-0.80; P = 0.0062) only in patients with the hyperinflammatory phenotype. These endotypes include clinical and biological characteristics and can constitute specific targets for better select specific therapies based on an individualized approach to treatment.

CONCLUSION

Likely many of the treatments above reviewed in this work might be helpful in specific subgroups of patients with certain clinical, analytical and biological characteristics, as occurs in other pathologies such as cancer, certain autoimmune diseases, or even sepsis. This approach, based on a personalized and precision medicine model, could help to better randomization of new clinical trials targeting the specific treatment of severe and critical forms of COVID-19.

ARTICLE HIGHLIGHTS

Research background

Although most people with coronavirus disease 2019 (COVID-19) have only mild or uncomplicated symptoms, 10%-15% requires hospitalization and oxygen therapy and, from the beginning, a large number of patients presented severe respiratory failure, needing mechanical ventilation (MV) and intensive care unit (ICU) admission. The lack of an available, effective treatment in this setting has led to a spate of treatment recommendations, which are not always backed by sufficient scientific evidence. Particular attention were paid to a presumed specific cytokine storm secondary to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, with a special effort to modulate the inflammatory response of these patients.

Research motivation

Two years after the onset of the pandemic, many questions remain unanswered, and we continue to search for the most appropriate treatment. This review aims to summarize the current evidence regarding the different immunomodulatory strategies tested in critically ill patients with COVID-19. Most of the main trials that have shown benefit of any immunomodulatory therapeutic agent against COVID-19 focus on hospitalized patients but not on critically ill patients. Furthermore, many of these studies consider ICU admission as a primary negative endpoint. Very few studies consider treatment in this setting (ICU) as a starting point, sometimes unavoidable, given that many patients with COVID-19 required admission to the ICU already in the first hours of their hospital admission. Therefore, there is a lack of information on the therapeutic approach in these patients.

Research objectives

To summarize the pathophysiology of SARS-CoV-2, including the normal and pathological inflammatory and immune responses that would justify the use of different immunomodulatory therapies in critically ill patients. To analyze the mechanism of action of the different immunomodulatory agents used against COVID-19. Review the scientific evidence collected so far and issue a recommendation for or against the use of each specific agent in this scenario.

Research methods

A comprehensive literature search was developed by using the keywords: "immunotherapy", "immunosuppressives", "haemophagocytic syndrome", "inflammation", "antimalarials", "hydroxychloroquine", "chloroquine", "anakinra", "canakinumab", "tocilizumab", "sarilumab", "corticosteroids", "dexamethasone", "methylprednisolone", "immunoglobulins or convalescent" "JAK inhibitors", "cyclosporine", "colchicine", "statins", "interleukin 7", "tymosin", "PD1 and PD-L1 blockers". We restricted the search to: "SARS-CoV-2", "COVID-19", "severe COVID-19" and "treatment" to identify articles published in English from MEDLINE, PubMed, and The Cochrane Library (until January 2021). The authors reviewed the selected manuscripts and selected the most appropriate. Finally, we established a recommendation of the use of each treatment based on the level of evidence of the articles and documents reviewed. This recommendation was made based on the consensus of all the authors. We carried out the rest of the work methodology following the PRISMA recommendations.

Research results

Different recommendations regarding the use of these immunomodulatory agents ("antimalarials", "hydroxychloroquine" "chloroquine", "anakinra", "canakinumab", "tocilizumab", "sarilumab", "corticosteroids", "dexamethasone", "methylprednisolone", "immunoglobulins or convalescent", "JAK inhibitors", "cyclosporine", "colchicine", "statins", "interleukin 7", "tymosin", "PD1 and PD-L1 blockers") were performed.

Research conclusions

Until then, although several promising therapies exist, only the use of corticosteroids and tocilizumab (or sarilumab in absence of this) has demonstrated evidence enough to recommend its use in critically ill patients with COVID-19. Probably other treatments of those analyzed could be beneficial in certain

critical patients with COVID-19 if they were administered in a selective and personalized way.

Research perspectives

From this work, two simple and clear messages can be extracted that could guide the future therapeutic approach of severe forms of COVID-19: (1) The critically ill patient constitutes a special subgroup of patients that should be studied differently from other patients, considering the ICU as an initial and not a final stage in the course of the disease; and (2) It is a mistake to administer the same treatments to all patients. It is key to individualize these treatments based on the immunological and clinical phenotypes of each patient.

FOOTNOTES

Author contributions: Andaluz-Ojeda D, Vidal-Cortes P, and Cusacovich I designed the study, developed the material and methods section, the introduction and a global discussion; Aparisi Sanz Á, Suberviola B, Del Río Carbajo L, Nogales Martín L, Prol Silva E, Nieto del Olmo J, and Barberán J carried out a selective bibliographic search in relation to each of the study points and developed a partial discussion; and all authors participated in the final recommendations for each class.

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