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Review Article

Internal Medicine Section

Immunomodulators and SARS-CoV-2: Management of the Dysregulated Immune Response

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ABSTRACT

The Coronavirus Disease 2019 (COVID-19) pandemic caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) resulted in millions of deaths worldwide. In adults, it can lead to serious complications such as Acute Respiratory Distress Syndrome (ARDS), renal failure, encephalitis, acute cardiac illness, thromboembolism, and multiorgan failure. However, in infants and children, it causes mild illness. The current evidence showed hyperinflammatory syndrome is the reason for most of the deaths in patients with severe COVID-19. There are increasing research activities around immunomodulatory drugs to manage SARS-CoV-2 induced dysregulated immune response. However, these immunomodulatory drugs are currently approved by FDA for the prevention and treatment of certain inflammatory disorders, such as rheumatoid arthritis, gout, recurrent pericarditis, and multiple sclerosis. Here, we summarise the drugs studied in several randomised clinical trials to demonstrate the efficacy and safety in treating the uncontrolled immune response of COVID-19 patients.

Keywords: Cytokine storm, Hyperinflammation, Randomised clinical trial, Severe acute respiratory syndrome coronavirus-2

INTRODUCTION

The Coronavirus Disease (COVID-19) pandemic has resulted in 6.6 million deaths globally [1]. Genetic variation or polymorphism within the human population appears to be the determinant factor for susceptibility to infection, host immune response, and fatality to the evolving Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) variants and subvariants. COVID-19 follows a destructive inflammatory response with the release of abundant proinflammatory cytokines, including IL-6, Interferon-α (IFN-α), Tumour Necrosis Factor (TNF), and more in a situation known as a "cytokine storm." Cytokines are associated with Disseminated Intravascular Coagulation (DIC), vascular leak, activation of the complement and coagulation cascade, acute phase protein production, lung injury, and cardiomyopathy. The cytokine storm eventually leads to Acute Respiratory Distress Syndrome (ARDS), multiorgan failure, and unfavourable prognosis [2]. The dysregulated immune response plays a key role in the clinical deterioration of COVID-19 patients. Here, we review the latest evidence-based practices on the usage of drugs that regulate the hazardous immune response in the management of COVID-19.

Hydroxychloroquine (HCQ) and Chloroquine

It was the most suggested drug for postexposure prophylaxis and treatment of COVID-19 at the beginning of the pandemic, given evidence of in-vitro inhibition of SARS-CoV-2 and inhibition of Major Histocompatibility Complex (MHC) class II expression, antigen presentation, and immune activation via Toll-like receptor signalling and IFN gene stimulation by cyclic GMP-AMP Synthase (cGAS) [3]. Thus, it can decrease the production of the proinflammatory cytokines implicated in a cytokine storm. The Solidarity Trial, RECOVERY Trial (UK), ORCHID Trial, and other Randomised Controlled Trials (RCTs) showed that HCQ does not have mortality benefits in hospitalised patients with COVID-19 compared to Standard of Care (SOC) [4-7].

The potential toxicity of HCQ includes QTc prolongation, arrhythmias, and neuromyotoxicity. HCQ may increase the risk of nausea, vomiting, abdominal pain, drowsiness, and headache in patients with COVID-19. However, HCQ is considered safe for treating patients with autoimmune diseases or malaria [8].

Colchicine

It is one of the oldest anti-inflammatory drugs. Only oral formulations are currently approved by FDA for the prevention and treatment of gout and familial mediterranean fever [9,10]. Colchicine is also used in various conditions (off-label), including Behcet syndrome, recurrent pericarditis, calcium pyrophosphate crystal arthritis (pseudogout), postpericardiotomy syndrome, and secondary prevention atherosclerotic cardiovascular events, Sweet syndrome, cutaneous small-vessel vasculitis. Colchicine inhibits microtubule polymerisation, inflammasome activation, neutrophil chemotaxis, and the release of Interleukin-1 (IL-1) beta [11-14].

Colchicine for Community-treated COVID-19 patients (COLCORONA), a placebo-controlled, RCT involving 4,488 non hospitalised patients, showed that the colchicine arm failed to reach its primary outcome of reducing hospitalisation and death with increased gastrointestinal side-effects compared to the placebo arm [15]. In Randomised Evaluation of COVID-19 Therapy (RECOVERY) Trial it was observed that there was no noticeable difference in the 28-day mortality between colchicine and placebo groups [16]. However, a prospective, randomised Greek Study of Colchicine effects on COVID-19 complications (GRECCO-19), involving 105 hospitalised patients, demonstrated a significant decrease in the primary clinical outcome of a two-point deterioration on a seven-point clinical status scale [17].

The minor adverse events of colchicine are nausea, vomiting, abdominal bloating, diarrhoea, loss of appetite, and the major adverse events include neuromyotoxicity and blood dyscrasias [18,19].

Fluvoxamine

It is a Selective Serotonin Reuptake Inhibitor (SSRI) with a high affinity for the sigma-1 receptor in immune cells, resulting in a reduced inflammatory response during sepsis and decreased shock in murine sepsis models. An in-vitro study showed that fluvoxamine brought down the inflammatory gene expression in human endothelial cells and macrophages [20]. In a randomised, placebo-controlled clinical trial involving 152 non hospitalised symptomatic COVID-19 patients, there was no clinical deterioration in patients treated with fluvoxamine compared to six (8.3%) patients in the placebo arm over 15 days [21]. In a prospective, non randomised, observational study

involving 113 non hospitalised patients with COVID-19, there was no hospitalisation in the fluvoxamine group, compared to six patients in the observation group who were treated without fluvoxamine, including Intensive Care Unit (ICU) treatment for two patients [22].

Corticosteroids

In a multicentre, randomised, open-label trial of dexamethasone (RECOVERY trial), it was noted that 6 mg of dexamethasone daily for 10 days in patients who were on either oxygen alone or invasive mechanical ventilation, showed a reduction in the 28-day mortality but the survival benefit was not observed in patients who were not on oxygen support [23]. In a phase II b, randomised, placebo-controlled trial (Metcovid), methylprednisolone was given to hospitalised patients with COVID-19 as adjunctive therapy, which showed no mortality benefits at 28 days in both methylprednisolone and placebo arms. However, in subgroup analysis, low mortality rate was observed at day 28 among patients aged above 60 years in the methylprednisolone arm [24]. The Randomised, Embedded, Multifactorial Adaptive Platform trial for Community Acquired Pneumonia (REMAP-CAP) studied the effect of hydrocortisone in patients with severe COVID-19 and showed no significant benefit in both groups including hydrocortisone given at a fixed dose and the shock-dependent hydrocortisone [25].

The National Institutes of Health (NIH) treatment guideline for COVID-19 recommends dexamethasone along with remdesivir for hospitalised patients who require supplemental oxygen or dexamethasone alone when remdesivir is not available or contraindicated. There is no recommendation for the use of glucocorticoids in hospitalised COVID-19 patients who are not on oxygen therapy. The glucocorticoids that can replace dexamethasone are methylprednisolone, prednisone, and hydrocortisone at a dose of 32 mg, 40 mg, and 160 mg, respectively equivalent to 6 mg of dexamethasone [26].

Interferons (IFNs)

The IFNs are proteins produced by various cells in response to infections. They have antiviral, antitumour, and immunomodulatory effects. IFNs therapeutic use is already known and currently used in treating multiple sclerosis. It has been reported that IFNs inhibit SARS-CoV-2 replication in-vitro, mainly IFN-beta [27].

A randomised, phase II clinical trial involving hospitalised patients with COVID-19 treated with a three-drug combination including IFN beta-1b, ribavirin, and ritonavir/lopinavir showed substantially shorter median time from the initiation of triple therapy to negative nasopharyngeal swab in the combination group than in the control group [28]. In an open-label, RCT, IFN beta-1a was studied in hospitalised COVID-19 patients, and it demonstrated that there was no noticeable benefit observed in the primary outcome of time to clinical response and length of hospital stay, including ICU stay [29]. A phase II, randomised clinical trial of Pegylated IFN alfa-2b (PEG-IFN alfa-2b) in hospitalised patients with moderate COVID-19, showed considerable improvement in clinical condition on day 15 in the PEG IFN alfa-2b group (n=20) than the control group (n=20) [30].

Interleukin-1 (IL-1) Inhibitors

The IL-1 is a potent proinflammatory cytokine. Anakinra is a recombinant human IL-1 receptor inhibitor. FDA has approved it for patients with moderate to severe rheumatoid arthritis, cryopyrin-associated periodic syndromes, gout flares, and idiopathic recurrent pericarditis resistant to colchicine [31-33].

A RCT was conducted on hospitalised patients with mild to moderate COVID-19 pneumonia (CORIMUNO-ANA-1) to study the efficacy of anakinra. The study showed that anakinra had no significant benefit in improving the clinical outcomes of these patients [34]. In a retrospective cohort study, the use of high-dose anakinra in patients with severe COVID-19, showed clinical improvement in 72% of patients treated with high-dose anakinra than the control group [35]. In a cohort study of anakinra for severe COVID-19, it reduced the necessity of invasive mechanical ventilation and also lowered the mortality without serious adverse events [36].

The NIH treatment guideline for COVID-19 does not recommend IL-1 inhibitors for treating hospitalised COVID-19 patients as there is no sufficient evidence [37].

Interleukin-6 (IL-6) Inhibitors

The IL-6 is one of the prime inflammatory mediators in COVID-19, produced by macrophages, lymphocytes, and fibroblasts. The agents that block the IL-6 pathway include IL-6 receptor antagonists such as tocilizumab, sarilumab and direct IL-6 inhibitors (siltuximab). Currently, FDA has approved tocilizumab for treating patients with rheumatic diseases and cytokine release syndrome, sarilumab for patients with rheumatoid arthritis, and siltuximab for patients with multicentric Castleman disease [38-40].

In the REMAP-CAP study, hospitalised patients with severe COVID-19 who were treated with IL-6 receptor antagonists showed survival benefits [41]. In an open-label, randomised, platform trial that included hospitalised COVID-19 patients (RECOVERY), tocilizumab improved survival and other clinical outcomes [42]. In addition to that, a randomised, double-blind, placebo-controlled trial, including hospitalised COVID-19 patients (EMPACTA), showed reduced probability of progression in the clinical status that necessitates the use of mechanical ventilation, but failed to improve survival in the tocilizumab group [43].

The NIH COVID-19 treatment guidelines panel recommends tocilizumab or sarilumab along with dexamethasone in recently hospitalised patients within three days of admission who require ICU care, including High-Flow Nasal Oxygen (HFNO), Non Invasive mechanical Ventilation (NIV), or invasive mechanical ventilation, and who are not admitted to ICU but had rapidly increased oxygen needs, significantly increased inflammatory markers (CRP ≥75 mg/L), and required HFNO or NIV. The panel does not recommend siltuximab for treating severe COVID-19 disease, except in clinical trials [44].

Janus Kinase (JAKs) Inhibitors

The JAKs are cytoplasmic tyrosine kinases that mediate and augment extracellular signals from cytokines via the JAK-STAT pathway. It has four members in the family such as JAK 1, JAK 2, JAK 3, and tyrosine kinase 2 (TYK2). Inhibitors of Janus-kinases hinder the Signal Transducer and Activator of Transcription (STAT) protein activation. JAK inhibitors are effective in treating patients with inflammatory diseases [45]. Among JAK inhibitors, baricitinib has antiviral activity theoretically in addition to immunomodulatory effects [46]. Adverse effects of JAK inhibitors include infection, reactivation of herpes viruses, venous thromboembolism, myelosuppression, and gastrointestinal perforation [47-49].

In a double-blind, placebo-controlled, RCT, the combination therapy of baricitinib and remdesivir in hospitalised COVID-19 patients had reduced recovery time and accelerated the clinical recovery, notably among those receiving High-Flow Nasal Cannula (HFNC) or NIV compared to placebo plus remdesivir [50]. In a multinational, placebo-controlled, randomised trial of baricitinib plus SOC in hospitalised COVID-19 adults who were not on invasive ventilation (COV-BARRIER study), baricitinib with SOC significantly reduced 28-day mortality [51]. A prospective cohort study, conducted on 238 hospitalised COVID-19 patients to correlate the clinical outcome of baricitinib at a high dose with its usual dose, showed reduced requirement of critical care support and rehospitalisation with mortality, compared to those with mortality to its usual dose [52].

In another placebo-controlled, RCT, tofacitinib was studied in patients who were hospitalised for COVID-19 pneumonia, showing that the studied drug reduced the composite outcome of respiratory failure and death at 28 days compared with the placebo [53]. A multicentre, single-blind, RCT of ruxolitinib in treating severe COVID-19, showed statistically insignificant clinical outcomes [54].

The NIH treatment guideline for COVID-19, recommends baricitinib or tofacitinib along with dexamethasone, and remdesivir in recently hospitalised patients who require HFNC or NIV. The other JAK inhibitors are not recommended, except in clinical trials [55].

Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) Inhibitors

The GM-CSF is a haematopoietic growth factor and proinflammatory cytokine that plays an important role in immune-mediated diseases. It is produced by various cells including macrophages, endothelial cells, fibroblasts, neutrophils, eosinophils, T-cells, mast cells, and Natural Killer (NK) cells. GM-CSF-derived signals regulate macrophage number and function, including alveolar macrophages [56]. Increased GM-CSF levels have been reported in patients with COVID-19, and inhibition of GM-CSF signals by anti-GM-CSF monoclonal antibodies may help reduce the hazardous immune response. The direct GM-CSF inhibitors include lenzilumab, gimsilumab, namilumab, and otilimab. GM-CSF receptor inhibitor includes mavrilimumab, which targets its alpha subunit [57,58].

In a phase II, placebo-controlled, RCT, involving patients hospitalised for severe COVID-19 pneumonia were treated with otilimab (OSCAR trial), didn't show any significant outcomes in the otilimab group compared to the placebo group [59]. In a randomised, phase III, placebo-controlled trial, lenzilumab efficacy and safety were studied in recently hospitalised COVID-19 patients (LIVE-AIR trial). Lenzilumab showed significant ventilator-free survival benefits in hypoxaemic patients who were not on mechanical ventilation [60]. In a multicentre, randomised, placebo-controlled trial, mavrilimumab was studied in patients who were hospitalised for severe COVID-19 pneumonia and systemic hyperinflammation (MASH-COVID). There were no significant clinical outcomes in the mavrilimumab arm compared to the placebo arm [61].

The NIH COVID-19 guidelines panel does not recommend GM-CSF inhibitors for the management of COVID-19 as there are no sufficient data [62].

Intravenous Immunoglobulins (IVIG): Non SARS-CoV-2 Specific

In a multicentre, retrospective cohort study, the clinical efficacy of IVIG was analysed in patients hospitalised for severe COVID-19 pneumonia [63]. The interpretation of the study results was hard as there was no randomisation of patients to receive either IVIG or SOC without IVIG, and both groups were treated with concomitant therapies for COVID-19.

Investigational Immunotherapy Drugs

Vilobelimab is an antihuman complement factor 5a monoclonal antibody. It was studied in phase III, multicentre, double-blind, placebo-controlled, RCT involving critically ill patients with COVID-19 on invasive mechanical ventilation (PANAMO trial), and showed a consistent decrease in 28-day all-cause mortality in vilobelimab arm compared to the placebo arm [64].

Peg IFN lambda, a type 3 IFN, has innate antiviral properties with activity against respiratory pathogens. In a double-blind, placebo-controlled, RCT involving 60 non hospitalised patients with COVID-19, on day 7, 24/30 (80%) patients had an undetectable viral load in the peg IFN lambda group compared to 19/30 (63%) patients in the placebo group (p=0·15). Hence, it has the potential to shorten the duration of viral shedding and prevent clinical deterioration [65].

In a phase II, double-blind, placebo-controlled, RCT, inhaled nebulised IFN beta-1a (SNG001) was studied in 101 patients with COVID-19. On day 15 or 16, patients treated with SNG001 showed a greater clinical improvement on the WHO Ordinal Scale for Clinical Improvement (OSCI) than the placebo group [66].

Bucillamine is an oral antirheumatic drug. Currently, a multicentre, randomised, phase III trial of bucillamine for outpatients with mild-to-moderate COVID-19 is going on; results are awaited [67]. The other immunotherapy drugs under investigation include Mesenchymal Stem Cell (MSC) therapy, NK cells, and more [68,69].

A brief description of selected clinical data on immunomodulators in COVID-19 is presented in [Table/Fig-1] [4,15-17,21-25,28-30,34,36,41-43,50,51,53,59-61].

Drug name	Study design	Authors, year, and place of study	Methods	Results	Interpretation	Ref
Hydroxychloroquine (HCQ)	Randomised, open-label platform trial of 4716 hospitalised COVID-19 patients (RECOVERY trial)	Horby P et al., 2020 UK	1561 patients in HCQ and 3155 in Standard of Care (SOC) group Primary outcome: 28-day mortality	28-day mortality in HCQ was 27% and 25% in the SOC group. 95% CI, 0.97-1.23	No mortality benefit at day 28 in the HCQ group	[4]
Colchicine	Phase III, a multicentre, double-blind, adaptive, placebo-controlled, RCT involving 4488 community-treated patients with COVID-19 (COLCORONA)	Tardif JC et al., 2021 Canada, Brazil, Spain, Greece, South Africa, and USA	Colchicine (n=2235) and placebo (n=2253) Primary endpoint: a combined hospital admission or death due to COVID-19	The primary endpoint was 4.7% and 5.8% in the colchicine and placebo group. Odds Ratio (OR), 0.79 95% CI, 0.61-1.03; p=0.081)	Colchicine does not have statistically significant clinical benefits in COVID-19 patients	[15]
Colchicine	Open-label, RCT trial involving 11340 hospitalised patients with COVID-19 (RECOVERY)	Horby P et al., 2020-2021 UK	Colchicine (n=5610) and SOC (n=5730) Primary outcome: 28-day mortality	In both colchicine and SOC arm, mortality within 28 days was observed in 21% of patients (rate ratio 1.01, 95% CI, 0.93-1.10; p=0.77)	Colchicine failed to decrease the 28-day mortality, total duration of hospital stay, and need for invasive mechanical ventilation	[16]
Colchicine	A prospective, open-label, RCT involving 105 hospitalised COVID-19 patients (GRECCO-19)	Deftereos SG et al., 2020 Greece	Colchicine (n=55) and control (n=50) Primary endpoints: Maximum level of cardiac troponin, time taken for increase in C-Reactive Protein (CRP) value greater than 3 times the upper reference limit and decline by 2 points on a 7-point clinical status scale. Secondary endpoints: 1) the number of patients requiring ventilatory support; 2) all-cause mortality; and 3) adverse events: severity and type	The clinical primary outcome rate was 1.8% in the colchicine group compared to 14.0% in the control group (OR, 0.11; 95% CI, 0.01-0.96; p=0.02). The mean (SD) event-free survival time was 20.7 days (0.31) in the colchicine group compared to 18.6 (0.83) days in the control group	In the colchicine group, there was a significant decrease in two-point deterioration on the seven-point clinical status scale. No statistically significant differences were observed in the cardiac troponin or CRP levels	[17]

Fluvoxamine	A placebo-controlled, double-blind, randomised, fully remote clinical trial involving 152 non hospitalised symptomatic patients with COVID-19	Lenze EJ et al., 2020 Eastern Missouri and southern Illinois, USA	Fluvoxamine (n=80) and placebo (n=72) Primary outcome: 1) clinical deterioration defined by shortness of breath or hospitalisation for pneumonia or dyspnoea within 15 days of randomisation 2) oxygen desaturation less than 92% in room air or requiring oxygen therapy to achieve oxygen saturation ≥92%	No clinical deterioration was observed in the fluvoxamine group compared to deterioration of 6 patients in the placebo group (absolute difference, 8.7%, 95% CI, 1.8%-16.4%, p=0.009)	On day 15, patients in fluvoxamine group showed a lower probability of worsening in clinical status compared to the placebo group	[21]
Fluvoxamine	A prospective, non randomised observational cohort study in 113 patients with COVID-19	Seftel D, Boulware DR. 2020 California, USA	Fluvoxamine (n=65) and observation alone (n=48)	No hospitalisation was observed (0 of 65) in patients treated with fluvoxamine compared to 12.5% (6 of 48) hospitalisation in the observation group (p=0.005). On day 14, no patients (0%) in the fluvoxamine group had ongoing symptoms compared to 60% (29 of 48) patients with ongoing symptoms in the observation group (p<0.001)	It is a non randomised trial with a small study sample size and limited data collection	[22]
Dexamethasone	A multicentre, open-label RCT involving 6425 hospitalised patients with COVID-19 (RECOVERY trial)	Horby P et al., 2020 UK	Dexamethasone (n=2104) and placebo (n=4321) The primary outcome was 28-day mortality	In the dexamethasone group, mortality was 482 (22.9%) within 28 days compared to 1110 (25.7%) in the placebo group (age-adjusted rate ratio, 0.83; 95% CI, 0.75 to 0.93; p<0.001)	In patients who were requiring either oxygen support alone or mechanical ventilation, 10 days of dexamethasone 6mg reduced 28-day mortality. However, in patients who were not on oxygen therapy did not show survival benefit	[23]
Methyl Prednisolone (MP)	A phase IIb, double-blind, placebo-controlled, RCT involving 647 patients hospitalised for COVID-19 pneumonia	Jeronimo CMP et al., 2020 Brazil	MP (n=194) and placebo (n=199) The primary outcome: 28-day mortality	In the MP group, overall 28-day mortality was observed in 72 patients (37.1%) (p=0.629) compared to 76 (38.2%) patients in the placebo group	The study showed no statistically significant difference between the groups in the primary outcome. However, in subgroup analysis MP showed lower mortality in patients aged more than 60 years on day 28	[24]
Hydrocortisone	An international, multicentre, open-label, RCT involving 384 patients with severe COVID-19 (REMAP-CAP trial)	Angus DC et al., 2020 Australia, Canada, the Netherlands, New Zealand, France, Ireland, USA, and UK	Hydrocortisone, fixed-dose (n=137), shock-dependent (n=146), and no hydrocortisone group (n=101) Primary outcome: organ support-free days up to day 21	The median organ support-free days on day 21 were zero for all three groups. (composed of 30%, 26%, and 33% in-hospital mortality rates respectively)	No statistically significant difference noted between the groups in the primary outcome of the study. The trial was stopped early and no treatment strategy met the prespecified criteria for statistical superiority	[25]
Interferons (IFNs)	A phase II, open-label, RCT involving 127 patients hospitalised for COVID-19, treated with a combination of IFNβ-1b, ritonavir/ lopinavir, and ribavirin	Hung IF et al., 2020 Hong Kong	Combination group (n=86) and control group (n=41) Primary endpoint: time to attain a negative RT-PCR nasopharyngeal swab test for COVID-19	The primary outcome of a negative nasopharyngeal swab was achieved on day 7 from the initiation of therapy in the combination group compared to that on day 12 in the control group. Hazard Ratio (HR) 4·37 (95% CI, 1·86-10·24), p=0.001). The total length of hospital stay was 9 days in the combination group compared to 14.5 days in the control group; p=0.016	Early therapy with IFNs along with antivirals has the benefits of faster recovery and shorter length of hospital stay in mild to moderate COVID-19	[28]
IFNβ -1a	Open-label, RCT involving 81 patients, hospitalised for severe COVID-19	Davoudi-Monfared E et al., 2020 Iran	IFN β-1a (n=42) and control group (n=39) Primary outcome: time for clinical response. Secondary outcomes: total length of hospital stay including ICU stay, and 28-day mortality	No statistically significant difference in the primary outcome between the IFN (9.7±5.8 days) and the control group (8.3±4.9 days), p=0.95. In the IFN and control group 66.7% and 43.6% of patients were discharged respectively at day 14, (OR, 2.5; 95% CI, 1.05 to 6.37). The 28-day mortality was 19% and 43.6% in IFN and control groups respectively, p=0.015. (OR, 13.5; 95% CI, 1.5 to 118)	In the study groups, there was no statistically significant difference in the primary outcome. In the IFN β-1a group, two patients died before receiving the second dose and another two died before the third dose which was excluded from the analysis. Hence, it is difficult to interpret these study results	[29]

IFN-α2b	A phase II, open-label, RCT involving 40 patients hospitalised for COVID-19 to assess the efficacy and safety of pegylated IFN-α2b (PEG IFN-α2b)	Pandit A et al., 2020 India	PEG IFN-α2b arm (n=20) and SOC arm (n=20) Primary endpoint: on day 15, clinical improvement was assessed by the WHO 7-point ordinal scale	On day 15, clinical improvement was achieved in 19 (95.00%) patients treated with PEG IFN-α2b compared to 13 (68.42%) patients in the SOC arm (p<0.05)	Significant improvements in clinical status on day 15 in the PEG IFN α2b group than the control group	[30]
Anakinra	An open-label, multicentre, Bayesian RCT involving 116 patients hospitalised for mild-to-moderate COVID-19 pneumonia (CORIMUNO-ANA-1)	Tharaux PL et al., 2020 France	Anakinra (n=59) and SOC group (n=57) Primary outcomes: on day 4, number of patients who required non-invasive ventilation or died. On day 14, number of patients survived without mechanical ventilation (including high-flow oxygen)	In the anakinra group, the primary outcome of a WHO-CPS score of >5 at day 4 was observed in 36% of patients compared to 38% in the SOC group (median posterior absolute risk difference (ARD) -2·5%, 90% credible interval (CrI) -17·1 to 12·0). In both groups, 28 patients (47%; 95% CI, 33 to 59 and 51%; 95% CI, 36 to 62) needed mechanical ventilation or died on day 14	No significant clinical outcomes in the anakinra group	[34]
Anakinra	A cohort study involving 96 patients with a severe form of COVID-19	Huet T et al., 2020 Paris, France	Anakinra (n=52) and control cohort (n=44) Primary outcome: admission to ICU for mechanical ventilation or death	The composite outcome of either ICU admission for mechanical ventilation or death was observed in 13 (25%) and 32 (73%) patients in the anakinra and the historical group respectively HR 0.22, 95% CI, 0.11-0·41; p<0.0001)	The clinical implications of the study results are uncertain as there are limitations in the study design including unmeasured confounding variables	[36]
Tocilizumab, Sarilumab	Randomised, international, multifactorial, adaptive platform trial involving 803 hospitalised patients with severe COVID-19 (REMAP-CAP trial)	Gordon AC et al., 2020 UK	Tocilizumab (n=353), sarilumab (n=48), and control group (n=402) Primary outcome: respiratory and cardiovascular support free days	The primary outcome of organ support-free days was 10,11,0 in the tocilizumab, sarilumab, and control arm respectively. OR, 1.64, (95% CrI, 1.25 to 2.14) for tocilizumab, and 1.76 (95% CI, 1.17 to 2.91) for sarilumab	Patients treated with IL-6 receptor antagonists showed survival benefits	[41]
Tocilizumab	A randomised, controlled, open-label, platform trial involving 4116 patients hospitalised for COVID-19 (RECOVERY trial)	Abani O et al., 2020-2021 UK	Tocilizumab group (n=2022) and SOC group (n=2094) Primary outcome: 28 days all-cause mortality. Secondary outcome: length of hospital stay	Mortality on day 28 was 31% and 35% in the tocilizumab and SOC groups respectively. (rate ratio 0.86; 95% CI, 0.77-0.96). Discharge from the hospital within 28 days was observed in 57% and 50% of patients in the tocilizumab and SOC groups, respectively. (rate ratio 1·22; 1·12-1·33; p<0.0001)	Tocilizumab reduced all-cause mortality, and length of hospital stay	[42]
Tocilizumab	A multinational, phase III, double-blind, placebo-controlled, RCT involving 389 patients hospitalised for COVID-19 pneumonia. (EMPACTA)	Salama C et al., 2020 USA, South Africa, Mexico, Kenya, Peru, and Brazil	Tocilizumab (n=249) and placebo (n=128) Primary outcome: composite of either need for invasive ventilatory support or Extracorporeal Membrane Oxygenation (ECMO) or death by day 28	The composite outcome was observed in 12% and 19.3% of patients in the tocilizumab (95% CI, 8.5 to 16.9) and placebo group respectively (95% CI, 13.3 to 27.4) (HR for mechanical ventilation or death, 0.56; 95% CI, 0.33 to 0.97; p=0.04)	Tocilizumab reduced the composite outcome of either need for invasive ventilatory support, ECMO, or death by day 28, but it failed to improve the overall survival	[43]
Baricitinib	A double-blind, placebo-controlled, RCT involving 1033 patients hospitalised for COVID-19 to evaluate baricitinib plus remdesivir	Kalil AC et al., 2020 USA, Singapore, South Korea, Mexico, Japan, Spain, UK, and Denmark	Baricitinib+remdesivir (n=515) and placebo (n=518) Primary outcome: time taken for recovery. Secondary outcome: Clinical condition on day 15	The recovery time was 7 days in the combination arm (95% CI, 6 to 8) and 8 days (95% CI, 7 to 9) in the control arm (rate ratio for recovery, 1.16; 95% CI, 1.01 to 1.32; p=0.03). In the combination arm, the improvement in clinical status at day 15 was 30% higher as compared to the control arm (OR, 1.3; 95% CI, 1.0 to 1.6). In the combination arm, the 28-day mortality was 5.1% compared to 7.8% in the control arm (HR for death, 0.65; 95% CI, 0.39 to 1.09)	The combination therapy of baricitinib and remdesivir is superior to remdesivir alone in shortening recovery time and hastening clinical improvement in COVID-19 patients who are on oxygen therapy or Non Invasive mechanical Ventilation (NIV)	[50]
Baricitinib	A phase III, double-blind, placebo-controlled, RCT involving 1525 patients hospitalised for COVID-19 pneumonia	Marconi VC et al., 2020 Europe, Asia, North and South America	Baricitinib (n=764) and placebo (n=761) Primary endpoint: composite of either requiring High-Flow Nasal Oxygen (HFNO), NIV, invasive ventilatory support or death by day 28. Secondary endpoint: 28-day all-cause mortality	The composite outcomes were observed in 27.8% and 30.5% of patients in the baricitinib and placebo arm respectively (OR, 0.85, 95% CI, 0.67-1.08; p=0.18). The 28-day all-cause mortality was 8.1% in the baricitinib arm compared to 13.1% for the placebo arm (HR 0.57, 95% CI 0.41-0.78; nominal p=0.002)	The addition of baricitinib to SOC significantly reduced 28-day mortality	[51]

Tofacitinib	A randomised, placebo-controlled trial involving 289 hospitalised patients with COVID-19	Guimarães PO et al., 2020 Brazil	Tofacitinib (n=144) and placebo (n=145) Primary outcome: respiratory failure or death by 28 days. Secondary outcome: death from any cause in 28 days	The primary outcome was observed in 18.1% and 29.0% of the patients in the tofacitinib and placebo group, respectively (risk ratio, 0.63; 95% CI, 0.41 to 0.97; p=0.04). Secondary outcomes manifested in 2.8% and 5.5% of patients in the tofacitinib and placebo groups, respectively. (HR, 0.49; 95% CI, 0.15 to 1.63)	Tofacitinib reduced the composite outcome of respiratory failure or death on day 28	[53]
GM-CSF inhibitors-Otilimab	A multicentre, double-blind, placebo-controlled, RCT involving 806 patients hospitalised for severe COVID-19 pneumonia	Patel J et al., 2020 India, Argentina, Canada, Belgium, Brazil, Chile, France, Japan, Poland, Mexico, the Netherlands, Peru, Poland, Russian Federation, South Africa, Spain, UK, and USA	Otilimab (n=395) and placebo (n=398) Primary endpoint: on day 28, the number of patients alive or free of respiratory failure. Secondary endpoint: all-cause mortality at day 60	The primary outcome was observed in 71% and 67% of patients in the otilimab and placebo group, respectively. (95% CI, -0.8, 11.4; p=0.09). However, patients aged ≥70 years had a benefit (model-adjusted difference 19.1% [95% CI, 5.2, 33.1]; nominal p=0.009); these patients also had a 14.4% decrease in model-adjusted all-cause mortality on day 60 (95% CI, 0.9, 27.9%; nominal p=0.04)	No differences in outcomes were noted between the otilimab and placebo groups, except for patients aged ≥70 years	[59]
Lenzilumab	A phase III, double-blind, placebo-controlled, RCT involving 520 patients newly hospitalised for COVID-19 (LIVE-AIR trial)	Temesgen Z et al., 2021 USA, Brazil	Lenzilumab (n=261) and placebo (n=259) The primary endpoint: ventilator-free survival by day 28	Lenzilumab improved the primary outcome of ventilator-free survival by 54% in the modified intent to treat population (mITT) (HR: 1.54; 95% CI, 1.02-2.31, p=0.041) and by 90% in the Intention-to-Treat (ITT) population (HR: 1.90; 1.02-3.52, nominal p=0.043) compared to placebo	In hospitalised COVID-19 patients, lenzilumab significantly improved ventilator-free survival	[60]
Mavrilimumab	Multicentre, double-blind, placebo-controlled, RCT involving 40 patients hospitalised for severe COVID-19 pneumonia and systemic hyperinflammation (MASH-COVID)	Cremer PC et al., 2020 USA	Mavrilimumab (n=21) and placebo (n=19) Primary endpoint: on day 14, the number of patients alive or free of oxygen support	On day 14, 57% and 47% of patients achieved the primary outcome in the mavrilimumab and placebo group, respectively (OR, 1·48 (95% CI, 0·43-5·16); p=0·76)	No statistically significant clinical outcomes were noticed in the mavrilimumab arm compared to the placebo arm	[61]

[Table/Fig-1]: A brief description of clinical trials done on immunomodulators [4,15-17,21-25,28-30,34,36,41-43,50,51,53,59-61].

CONCLUSION(S)

Glucocorticoids, JAK inhibitors such as baricitinib or tofacitinib, and IL-6 inhibitors like tocilizumab or sarilumab suppress the hazardous immune response and improve the clinical outcome of COVID-19 patients when used judiciously. However, other agents need to be studied in larger, well-designed studies for their effectiveness.

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