Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

Immune-based therapeutic approaches in COVID-19

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is a viral disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a member of the Coronaviridae family. On March 11, 2020 the World Health Organization (WHO) has named the newly emerged rapidly-spreading epidemic as a pandemic. Besides the risk-reduction measures such as physical and social distancing and vaccination, a wide range of treatment modalities have been developed; aiming to fight the disease. The immune system is known as a double-edged sword in COVID-19 pathogenesis, with respect to its role in eliminating the pathogen and in inducing complications such as cytokine storm syndrome. Hence, immune-based therapeutic approaches have become an interesting field of COVID-19 research, including corticosteroids, intravenous immunoglobulins (IVIG), interferon therapy, and more COVID-19-specific approaches such as anti-SARS-CoV-2-monoclonal antibodies. Herein, we did a comprehensive review on immune-based therapeutic approaches for COVID-19.

Data availability statement: Not applicable.

1. Introduction

Coronavirus disease 2019 (COVID-19), a viral disease caused by a member of the Coronaviridae family, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has caused one of the greatest global pandemics, as declared by the World Health Organization (WHO) on March 11, 2020 [1]. Lung epithelium damage, hypercoagulability, and vascular leak lead to an important clinical manifestation, named acute respiratory distress syndrome (ARDS). Patients with previously diagnosed hypertension, cardiovascular disease, and diabetes are highly susceptible to ARDS [2]. As of 20 March 2022, more than 468 million confirmed cases and more than 6 million deaths have been reported [3]. As the main route of COVID-19 transmission is via respiratory droplets, social distancing is one of the most important measures for controlling the spread of the virus [4]. In addition to social distancing, developing effective vaccines could be a potent tool in limiting the disease spread and lowering the disease burden [1]. Amongst a variety of treatment approaches, immunotherapy has become an interesting option for COVID-19, although, the treatment results closely depend on choice of the right patient and right timing of drug administration [5]. Herein, we did a comprehensive review on immune-based therapeutic approaches for COVID-19.

2. COVID-19

Coronaviruses, a genus from Coronaviridae family, are pleomorphic, enveloped, positive sense ssRNA viruses, involved in respiratory tract infections [6,7]. Members of this genus cause a wide range of respiratory complications ranging from mild respiratory illnesses, as in HCoV-OC43, HCoV-229E, HCoV-NL63, and HCoV-HKU1 infections, to more severe diseases, such as SARS-CoV-1, SARS-CoV-2, and Middle East respiratory syndrome coronavirus (MERS-CoV) [8].

The viral genome and its surrounding nucleoprotein are wrapped by the viral envelope. The envelope contains structural proteins, matrix protein and spikes [6]. Attachment of SARS-CoV-2 to the cell surface is mediated via interactions between the spike protein and the angiotensin converting enzyme-2 (ACE-2) on the host cell's surface [9]. The mechanism of viral pathogenesis is illustrated in Fig. 1.

The pathophysiology of COVID-19 is divided into four stages; asymptomatic stage, upper respiratory tract involvement, lower

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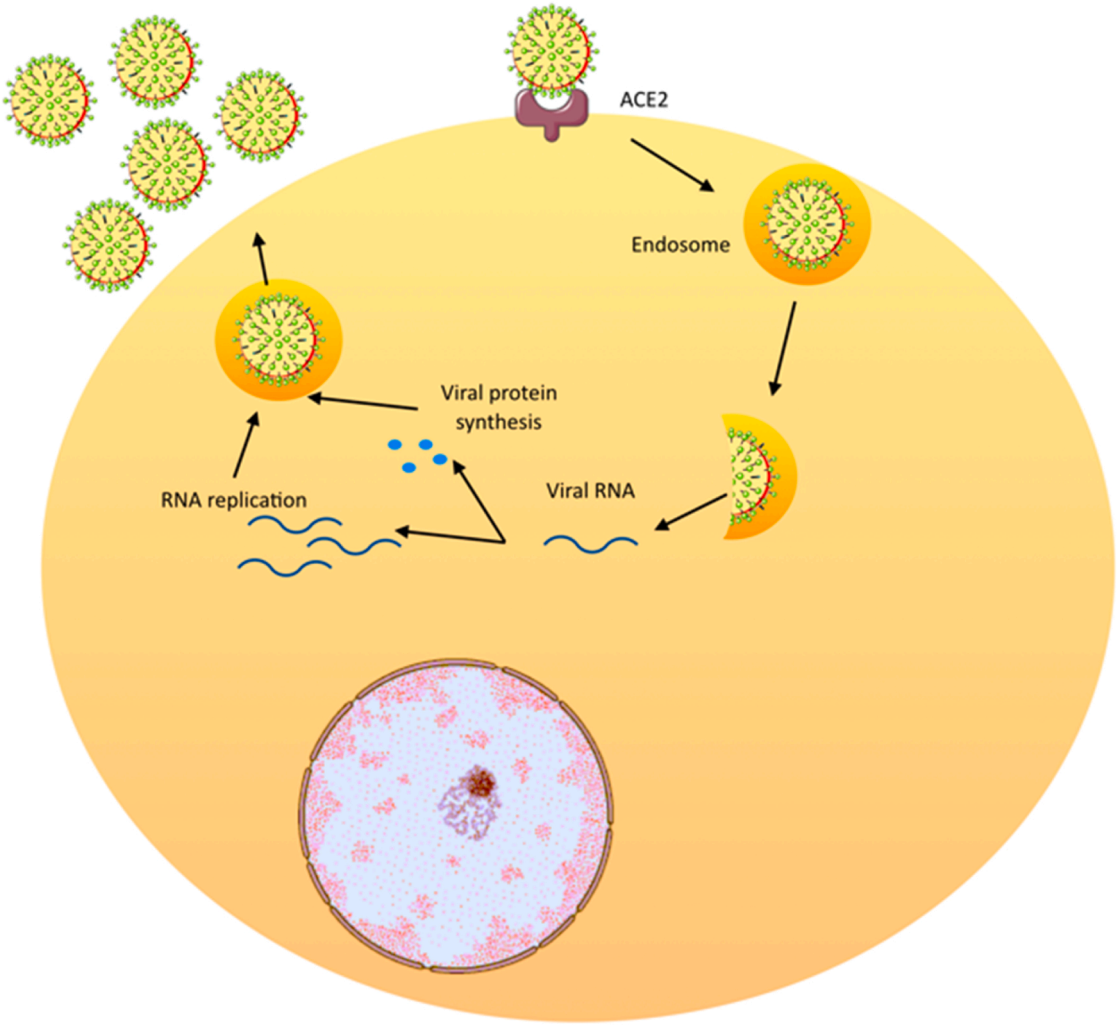

Fig. 1. Cellular mechanism of coronavirus pathogenesis.

Table 1
Pathophysiology, clinical manifestations and immunological characteristics of COVID-19 disease stages(IP-10 =interferon-inducible protein 10, MIG=monokine induced by interferon-γ, IL-8 =interleukin-8, MCP=Monocyte chemoattractant protein, IL-6 =interleukin 6, TNF=tumor necrosis factor, LDH=lactate dehydrogenase, CRP=c-reactive protein).

Stage	Pathophysiology	Clinical manifestations	Immunological characteristics	References
Asymptomatic stage	Virus enters the nasal ciliated epithelial cells via ACE2 and TMPRSS2	Asymptomatic	Mild innate response	[7,11–13]
Upper respiratory tract involvement	Presence of virus in sputum	Cough, sore throat	Strong innate response, higher levels of IP-10, MIG, IL-8, MCP	[7,14,15]
Lower respiratory tract involvement	Virus-associated damage in alveolar cells (mostly pneumocyte II), apoptosis and death in pneumocytes. Alveolar macrophages are also targeted by viruses.	histological findings including hyaline membrane, alveolar damage, pneumocyte II hyperplasia, consolidation	Aggravated immune response (especially T cells), cytokine storm, higher levels of IL-6, TNF	[7,16–19]
ARDS/MODS	hemophagocytic lymphohistiocytosis-like cytokine storm	High cytokine levels, unremitting fever, high ferritin levels, cytopenia, multi-organ damage	Higher levels of ferritin, IL-6, LDH, D-dimer, CRP	[7,17]

respiratory tract involvement, and ARDS/ multi organ dysfunction syndrome (MODS) [7]. The pathophysiological, clinical, and immunological characteristics of these stages are summarized in Table 1.

Also, Turk et al. categorized clinicobiological aspects of the disease into three phases; asymptomatic/pre-symptomatic phase, propagating phase (mild/moderate/severe), and complicating phase (impaired/disproportionate and/or defective immunity) [10].

The pathological manifestations of the disease are mostly noticeable in the lung tissue, including hyaline membrane formation, accumulation of serous, exudate (mostly monocytes and macrophages), and fibrin in alveoli, and hemorrhagic infarction [20,21]. Moreover, inclusion bodies, proliferation, and detachment has been spotted in pneumocyte II cells [22]. Studies on the alveolar septa shows edema, hyperemia, mononuclear cell infiltration, and hyaline thrombose formation [20]. On the other side, some extrapulmonary manifestations have been spotted in spleen (shrinkage, fewer number of T cells), heart (necrosis, leukocyte infiltration), liver (cellular degeneration, hepatomegaly), gall bladder (discoloration to dark-red, volume increase), and kidneys

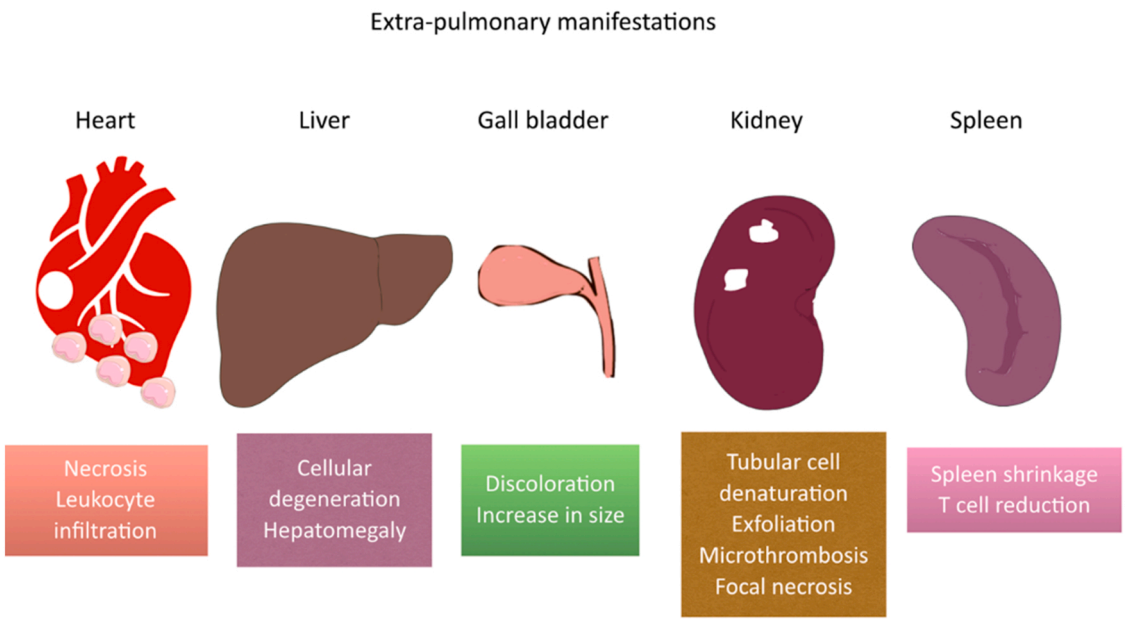

Fig. 2. Extrapulmonary manifestations of COVID-19.

Table 2
Molecular and serological findings in COVID-19 (AST=aspartate amino transferase, ALT=alanine amino transferase, LDH=lactate dehydrogenase, ESR=erythrocyte sedimentation rate, RT-PCR=reverse transcriptase- polymerase chain reaction). * Cytokines including: IL-2, IL-6, IL-7, IL-8, IL-9, IL-10, GM-CSF, MCP-1, MIP-1 α, TNF-α, and basic FGF.

Tests	Findings in patients	References
Blood leukocyte count	Normal / decreased	[28]
Blood lymphocyte count	Decreased	[28]
Liver function tests (AST and ALT levels)	Decreased (in half the cases)	[29]
Creatine kinase	Decreased	[29]
LDH	Decreased	[29]
CRP	Increased	[30]
ESR	Increased	[30]
Cytokine levels *	Increased	[8]
RT-PCR	Presence of virus in pharyngeal swabs, blood, stool	[31]

(tubular cell denaturation, and exfoliation, microthrombi, focal necrosis) [8]. Fig. 2 illustrates these extrapulmonary manifestations.

The extent of abnormalities in chest X-ray (CXR) imaging is of diagnostic and prognostic importance and indicates the severity of the disease [23]. In more than 80% of the cases, the early stage of the disease is characterized by a bilateral multi-lobar ground-glass opacity, mainly distributed in middle-lower lungs [24–26]. In progressive and peak phases, these abnormalities increase in size, along with the appearance of interlobar septal thickening and consolidations. After the 14th day of illness, the radiological abnormalities gradually disappear [23]. In some cases, despite the viral clearance and resolution of the symptoms, some long-term sequelae such as progressive fibrotic abnormalities develop [27].

Laboratory indicators such as serological and molecular indices could be helpful in COVID-19 diagnosis, which are summarized in Table 2.

Management of COVID-19 patients involves both general supportive care and pharmacological treatment [8]. Supportive measures include, bed rest and temperature control in patient's environment. Furthermore, monitoring oxygen saturation, liver and kidney function, electrolyte balance, and blood analyses such as complete blood count, c-reactive protein (CRP), and coagulation state are carried out [32]. In some cases, high-flow oxygen or oxygen-hydrogen mixtures (H^2/O^2: 66.65/33.39%) and rehydration therapy including IV fluid administration could be helpful [8,33].

The effectiveness of some antiviral drugs such as lopinavir/ritonavir, oseltamivir, and ribavirin have been reported [34–36]. Arbidol, chloroquine, and interferon (IFN)-α had been used in Wuhan outbreak and in vitro studies demonstrated their effect on viral load reduction [37–39]. Management of critically ill patients, include respiratory and circulatory supportive care, oxygen therapy and intubation in some cases, besides the preventive and therapeutic measures for secondary complications and infections [8].

3. Corticosteroids

3.1. Mechanism of action

Corticosteroids are a class of substances, either synthetic or naturally expressed in adrenal cortex, which have a wide range of effects on the immune system, inflammation, stress response, metabolism, body fluids, and electrolytes [41]. Corticosteroids induce the production of lipocortin, which inhibits phospholipase A2, an essential enzyme for the production of inflammatory mediators [42].

In most COVID-19 cases, mortality is a result of exaggerated immune response against the infection. Corticosteroids control such responses and subsequently, decrease the time on mechanical ventilations, period of residence in intensive care unit (ICU), and mortality rate in COVID-19 patients [43].

Fig. 3 illustrates the mechanism of corticosteroids' effect of COVID-19.

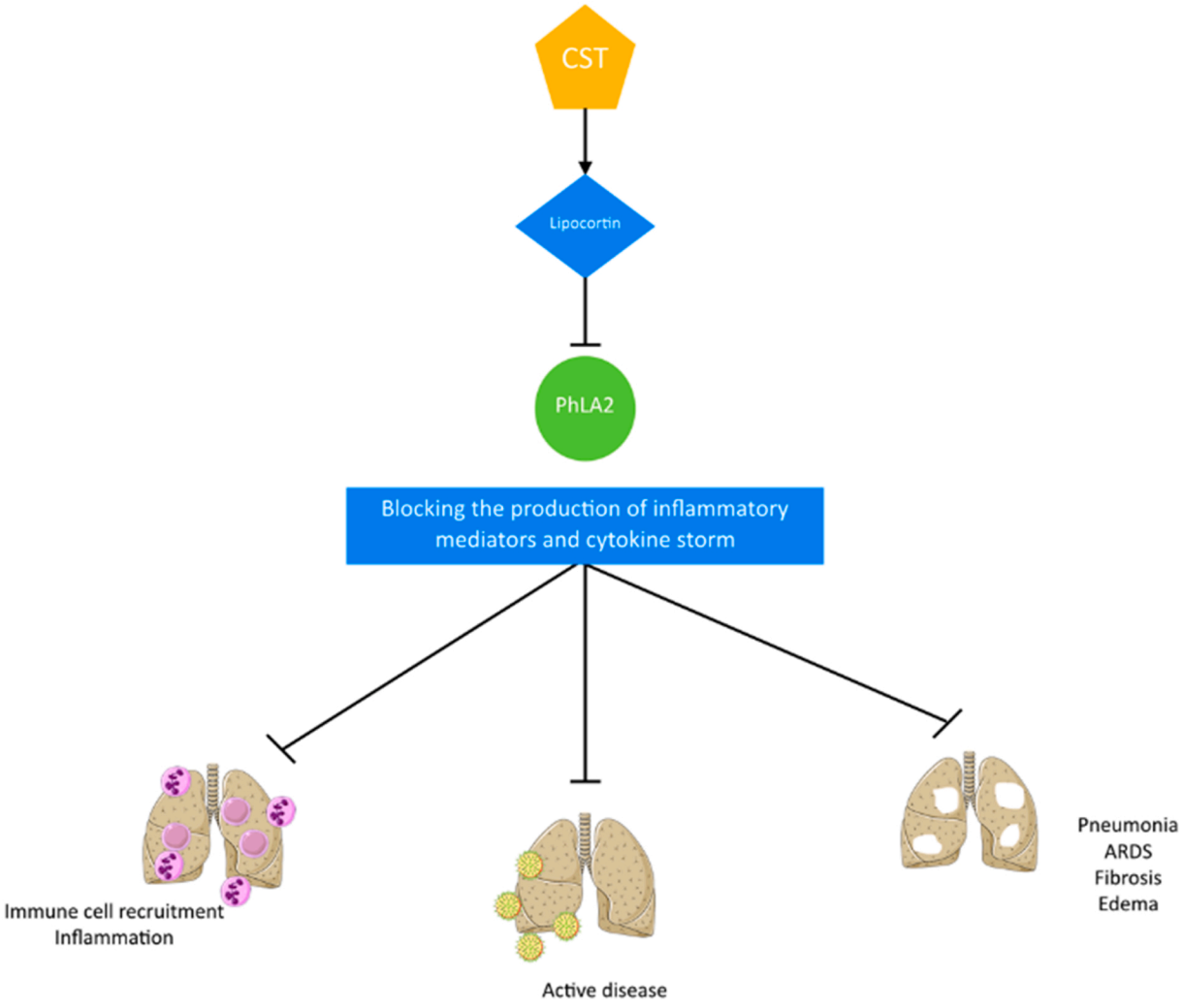

Fig. 3. Mechanism of corticosteroids' effect on COVID-19 (CST=corticosteroid, PhLA2 =phospholipase A2, ARDS= acute respiratory distress syndrome).

3.2. Administration indications and clinical findings

During the SARS outbreak in 2003, corticosteroids, alone or in combination with ribavirin, were extensively used [44,45]. In the current pandemic, a variety of studies have shown the efficacy of corticosteroids in different stages of COVID-19 infection; the results of these studies are summarized in Table 3.

Based on the WHO guidelines on the administration of corticosteroids, there are two recommendations. First recommendation states that systemic corticosteroids are favored in comparison to non-systemic corticosteroids, which is the choice in severe and critically ill COVID-19 patients regardless of their hospitalization status [46]. Severe COVID-19 infection applies to patients with SpO2 $<$ 94% on room air at sea level, respiratory rate of $>$ 30 breaths per minute, PaO2/-FiO2 $<$ 300 mm Hg, or pulmonary infiltrates $>$ 50%. Critical COVID-19 infection applies to patients with conditions requiring life-sustaining procedures (mechanical ventilation, etc.) such as ARDS, multiple organ failure, cardiac failure, exaggerated inflammation, and septic shock [47].

The second recommendation states that it is better not to use corticosteroids in treatment of non-severe COVID-19 patients. Though, in cases of previously initiated treatment for other clinical conditions, corticosteroids should not be discontinued. Corticosteroid therapy, though beneficial in some cases, can cause susceptibility to complicated infections and should be taken into consideration while using this modality [46].

3.3. Challenges

Although the short-term use of corticosteroids has been helpful, high-dose corticosteroids can delay the viral clearance [40]. Based on the current guidelines, the administration of corticosteroids should be limited due to their wide range of side effects. Some of these include increase in mortality rates, diabetes, avascular necrosis, femoral head osteonecrosis, psychosis, and induction of lung injury and shock [66].

Table 3
Recent studies on efficacy and safety of corticosteroids in COVID-19 patients. (MP=methylprednisolone, DX=dexamethasone, CI=confidence interval).

Intervention	Dosage	Population	Study design	Primary outcome	Results	References
Methylprednisolone/ methylprednisolone + tocilizumab	MP 250 mg day 1, 80 mg days 2–5 tocilizumab 8 mg/kg single dosage	Severe COVID-19-associated cytokine release syndrome	Controlled clinical trial (CHIC study)	> =2 stages improvement on a 7 item WHO endorsed scale for trials in patients with severe influenza pneumonia, or discharge from hospital	79% more probability of reaching primary outcome, 65% less mortality, and 71% less invasive mechanical ventilation in treatment group in comparison with controls	[48]
Hydrocortisone	200 mg daily for 7 days	COVID-19 patients receiving > =10 L/min oxygen or on mechanical ventilation	Randomized controlled clinical trial (COVID STEROID study)	days without life support at day 28	Number of days alive without life support at day 28 in treatment and controls groups were 7 and 10 days respectively mortality rate in treatment and controls groups were 6/16 and 2/14 respectively	[49]
Methylprednisolone	0.5 mg/kg	Hospitalized COVID-19 patients ages> =18	Randomized controlled phase IIb clinical trial (Metcovid study)	28-day mortality	No substantial difference in primary outcome between two groups, lower mortality rate at day 28 in > =60 years old patients in treatment group	[50]
Dexamethasone	Group 1: 6 mg/24 h for 10 days (+routine ICU support) Group 2: 16 mg/24 h for 5 days+ 8 mg/24 h for 5 days (+routine ICU support)	Patients with ARDS secondary to COVID-19 infection	Randomized controlled clinical trial	Ventilator-free days at day 28	Trial terminated due to low rate of recruitment	[51]
Hydrocortisone	200 mg/d for 7 days+ 100 mg/d for 4 days+ 50 mg/d for 3 days	Patients admitted to ICU for acute respiratory failure secondary to COVID-19	Multi-center randomized double blind sequential trial	Treatment failure (death, persistent dependence on ventilators or high-flow oxygen therapy) on day 21	Primary outcome occurred in 42.1% in treatment group in comparison with 50.7% in controls	[52]
Hydrocortisone	Fixed 7-day course 100 mg or 50 mg every 6 h, shock dependent course 50 mg every 6 h in case of evident shock	Severe COVID-19	Randomized, controlled trial (REMAP-CAP study)	Organ support-free days in 21 days	Primary outcome median 0 days in all three groups, 30% (fixed-dose), 26% (shock dependent), and 33% (controls) mortality rate, median organ support-free days among survivors 11.5, 9.5, and 6 days, respectively	[53]
Methylprednisolone	250 mg/day, 3 days	Early pulmonary phase COVID-19	Randomized controlled clinical trial	Time of clinical improvement/death (whichever sooner)	Patients improvement 94.1% (treatment) and 57.1% (control), mortality rate 5.9% (treatment) and 42.9% (controls)	[54]
Dexamethasone	20 mg daily for 5 days, 10 mg daily for 5 days (or until ICU discharge)	COVID-19 patients with moderate to severe ARDS	Randomized controlled clinical trial (CoDEX trial)	Ventilator-free days at day 28	6.6 ventilator-free days in dexamethasone group versus 4 ventilator-free days in control group	[55]
Corticosteroids	Corticosteroids regardless of type, dose, and treatment duration	Severe ARDS secondary to COVID-19	Retrospective observational study	28-day all-cause mortality	primary outcome 44.3% (corticosteroids) versus 31% (controls)	[56]
Corticosteroids	Systemic prednisone starting with 1 mg/kg/day and tapering the dose for 15 days + nasal irrigation with betamethasone, ambroxol, and rinazine	> 30 days anosmia or severe hyposmia secondary to COVID-19 infection	Randomized case-control study	–	Higher improvement from baseline in median olfactory score in treatment groups at both 20-day and 40-day checkpoints	[57]
Methylprednisolone	1 mg/kg/day	COVID-19 pneumonia	Randomized controlled clinical trial	Presence of clinical deterioration after 14 days	No substantial difference in primary outcome between two groups, prolonged viral shedding in treatment group	[58]
Methylprednisolone	40 mg bid, 3 days + 20 mg bid, 3 days	COVID-19 pneumonia	Randomized controlled clinical trial (GLUCOCOVID trial)	Death, admission to ICU, requirement for non-invasive ventilation	40% (treatment) versus 48% (control) reached endpoint in intention-to-treat (ITT) analysis	[59]
Dexamethasone	20 mg/day; day 1–5, 10 mg/day; day 6–10	Mild to moderate ARDS secondary to COVID-19	Randomized controlled clinical trial	Need for invasive mechanical ventilation and heath rate	Treatment group: non-invasive ventilation 92%, invasive ventilation 52%, death 64% control group: non-invasive ventilation 96%, invasive ventilation 44%, death 60%	[60]
Methylprednisolone, dexamethasone	MP= 2 mg/day, DX= 6 mg/day	Hospitalized COVID-19 patients		All-cause mortality in 28 days, clinical status	MP group: clinical status day 5 = 4.02, at day 10 = 2.90,	[61]

(*continued on next page*)

Table 3 (*continued*)

Intervention	Dosage	Population	Study design	Primary outcome	Results	References
			Randomized controlled clinical trial	after 5 days and 10 days with 9-point WHO ordinal scale	overall mean score= 3.909, mean length of hospital stay 7.43 ± 3.64 days, need for a ventilator= 18.2% DX group: clinical status day 5 = 5.21, at day 10 = 4.71, overall mean score= 4.873, mean length of hospital stay 10.52 ± 5.47 days, need for a ventilator= 38.1%	
Corticosteroids	–	Mild to critically-ill COVID-19 patients	Retrospective study	Odds ratio for improvement on a 7-point ordinal score on day 15	Primary outcome significantly lower in treatment group (OR, 0.611;95% CI), shorter time to improvement in radiological findings (HR,1.758;95% CI), shorter duration of invasive mechanical ventilation (HR,1.466;95% CI) in treatment group	[62]
Methylprednisolone, dexamethasone	DX 6 mg QD 7–10 days MP 250–500 mg/day, 3 days; then oral prednisone 50 mg for 14 days	Severe COVID-19 pneumonia	Cohort study	Clinical outcome and laboratory differences between two groups (MP and DX)	Lower rate of severe ARDS (17.1% versus 26.1%), more reduction in levels of severity biomarkers such as CRP (2.85 versus 7.2) and D-dimer (691 versus 1083), lower rate of transferring to ICU (4.8% versus 14.4%) and death (9.5% versus 17.1%) in the group receiving MP in comparison with DX group	[63]
Momentsone furoate	100 mcg bid	Non-hospitalized COVID-19 adult patients with severe microsmia or anosmia within 2 weeks	Randomized controlled clinical trial	Improvement of olfactory score	Higher improvement in severe chronic anosmia in comparison with olfactory training	[64]
Methylprednisolone/ methylprednisolone + tocilizumab	MP 40 mg bid 7 days, toilizumabsingle dose 400 mg	Severe COVID-19	Randomized controlled clinical trial	All-cause mortality in 45 days, rate of admission to ICU, length of ICU stay, days on ventilators, length of hospital stay	Rates of ICU admission and invasive mechanical ventilation lowest in MP only group, time on ventilator lowest in MP group, highest in controls, days in ICU in MP group lower than both controls and MP+tocilizumab, mortality 4.3% in MP group and 18.5% in control group	[65]

4. Intravenous Immunoglobulin (IVIG)

4.1. Mechanism of action

Intravenous immunoglobulin (IVIG) is a mixture of human immunoglobulins against microbial infections obtained from the recovered patients; it is administered as an immunomodulatory agent in autoimmune diseases and infections, and as replacement therapy in immunodeficiencies. In viral infections, administration of IVIG induces antibody-dependent cellular cytotoxicity (ADCC) through binding to viruses and inducing phagocytosis via binding to FCγR receptors; IVIG prevents the viral entry to the host cell via blocking viral surface proteins and modulates inflammatory reactions following the blockage of FCγR IIa and FCγR IIIb on leukocytes [67]. Fig. 4 summarizes these mechanisms.

4.2. Administration Indications and Clinical Findings

IVIG administration in SARS patients has improved patient's survival, shortened the viremia period, and led to early discharge [68]. In addition, IVIG can reduce the mortality rate in patients affected with MERS-CoV [69].

Several studies have been conducted to assess the effectiveness of IVIG for COVID-19, which are summarized in Table 4.

High dose IVIG is indicated in all acute severe COVID-19 patients (aimed to reduce post-infection cytokine storm and prevent thrombosis), all patients presented with or developed autoimmune disorders such as Guillain-Barre syndrome, children with multisystem inflammatory syndrome, and patients with primary and secondary immunodeficiencies succumbing to acute COVID-19. Low dose IVIG is indicated in unvaccinated patients with autoimmune disorders or primary and secondary immunodeficiencies for protection against exposure to the virus. IVIG is also helpful in neurological disorders as a result of COVID-19's inflammatory sequelae, including cognitive dysfunction, neuralgia, insomnia, and autonomic nervous system involvement [70].

4.3. Challenges

Some serious adverse effects such as hemolytic anemia, acute lung injury, thrombosis, cardiac arrhythmia, meningitis, and renal

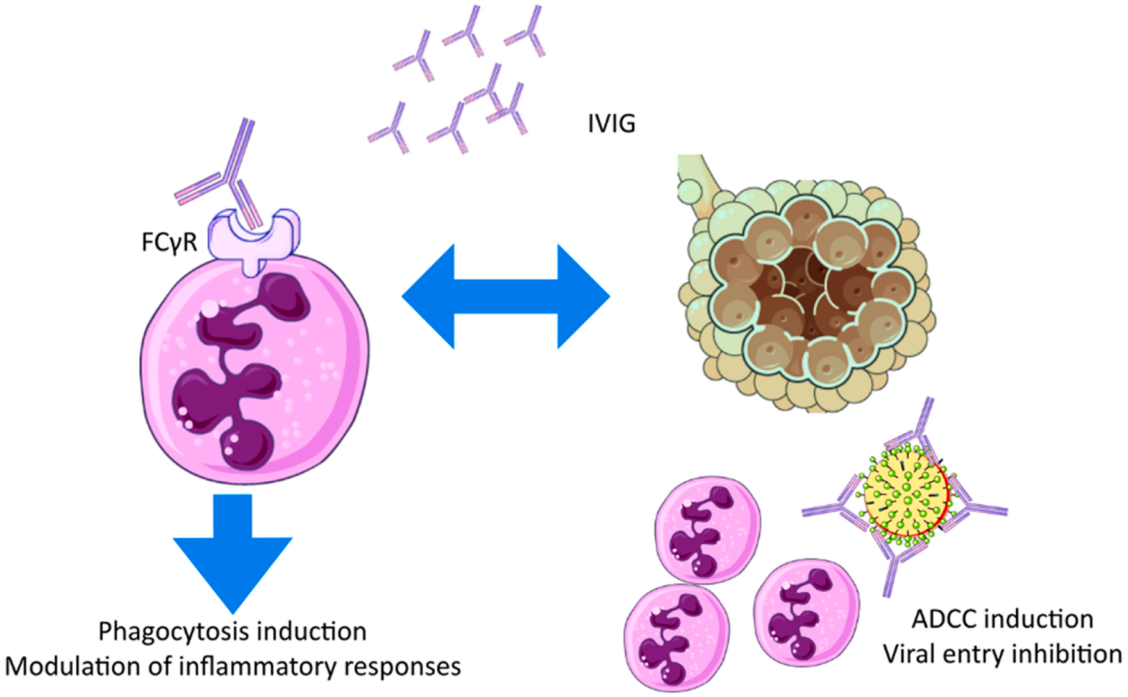

Fig. 4. IVIG mechanism of action in COVID-19.

impairment and lack of sufficient data concerning this therapeutic method have restricted its use in COVID-19 patients; therefore, more studies are necessary in this regard [67].

5. Interferons

5.1. Mechanism of action

Expression of interferon-I (IFN-I) family, including IFN-α and IFN-β, is upregulated following the viral attachment to cell surface receptors and induction of pattern recognition receptors (PRRs). Higher levels of IFN-α and IFN-β, subsequently induce Janus kinase (JAK) signaling pathway and interferon-stimulated genes, providing the first line of antiviral defense [81]. In comparison to other coronaviruses such as SARS-CoV-1, SARS-CoV-2 shows higher efficacy in proliferation and infection with shorter duration to peak levels and higher number of viral particles at the time of peak, which can be a result of insufficient IFN-I response [82–84]. In addition, disease severity can be associated with insufficient innate IFN-I levels, which results in reduction in IFN-stimulated genes expression. Therefore, patients with low IFN-I signaling levels have a poor prognosis [85]. A study by Hadjadj et al. demonstrated that expression of IFN-stimulated genes is upregulated when patients are subjected to IFN-α stimulation, stating that the downstream components of the signaling pathway are not impaired [86]. Fig. 5 illustrates these mechanisms.

5.2. Administration indications and clinical findings

Administration of IFN-I in earlier stages of the disease can reduce the later-coming immunopathologies. Although administration of IFN-I can improve disease outcomes, it can over-activate inflammatory responses, exacerbating the condition. Therefore, IFN-III can be a substitute for IFN-I with similar antiviral characteristics and less toxicity [87]. A study by Jagannathan et al. on administration of pegylated (PEG) IFN-λ1a in mild to moderate COVID-19 patients showed that it can shorten viral shedding and duration of the symptomatic phase, if administered in a period of 72 h after diagnosis [88]. IFN-λ can inhibit the tissue repair as well as the damaging effects of neutrophils on lungs; of note, outcomes of using IFN-λ depend on location, timing, and duration of administration [89].

There is evidence on early administration of interferon in patients receiving glucocorticoids that shorten the duration of hospital stay and symptomatic stage, suggesting a therapeutic synergy [90].

Several studies have been conducted on administration of interferons in COVID-19 patients, some of the most recent of which are summarized in Table 5.

According to the COVID-19 Treatment Guidelines, based on the results from clinical trials, and with respect to the lack of thorough evidence on the occurrence of adverse effects in some patient groups, the Panel recommend against the administration of interferons (α, β, and λ) in hospitalized patients unless in the setting of a clinical trial [33].

5.3. Challenges

The immune system imbalance and the resulting immunopathology has restricted the administration of interferons in COVID-19 patients; in patients receiving interferons, careful patient monitoring during the treatment is crucial [87].

6. Monoclonal antibodies

6.1. Mechanism of action

Monoclonal antibodies target different molecules that are involved in COVID-19 pathogenesis; amongst which there are some of the viral surface proteins such as spike (S) protein and contributors to the

Table 4
Summary of the results of studies on administration of IVIG in COVID-19 patients. (RT-PCR=reverse transcriptase polymerase chain reaction).

Intervention	Dosage	Population	Study design	Results	References
IVIG	4 vials daily for 3 days	Severe covid-19 with no response to initial treatments	Randomized placebo-controlled trial	In-hospital mortality rate lower in treatment group (20% versus 48.3%)	[71]
IVIG	400 mg/kg daily, 3 days	Severe covid-19	Randomized placebo-controlled trial	Length of hospital stay lower in control group ($p = 0.003$), though a positive correlation between the amount of time between admission to hospital and IVIG administration and length of hospital and ICU stay ($p < 0.001$ and $p = 0.01$ respectively), no significant difference between mortality rates ($p = 0.8$) and need for mechanical ventilation ($p = 0.39$) between two groups	[72]
IVIG	0.4 g/kg daily, 5 days	Covid-19 patients with moderate pneumonia	Randomized placebo-controlled trial, phase II	Shorter hospital stay in treatment group (7.7 vs. 17.5 days), shorter median time to RT-PCR negative results in IVIG group (7 vs. 18 days), no significant differences in percentage of mechanical ventilation (24% vs. 38%)	[73]
IVIG	2 g/kg	Severe covid-19	Retrospective	Lower 28-day mortality (more prominently in patients with no other co-morbidities or treated in earlier stages) and lower time to inflammatory biomarker normalization in IVIG group,	[74]
IVIG	–	Covid-19	Meta-analysis	Mortality significantly reduced in critical patients in comparison with controls (RR=0.57), no significant change in mortality of severe and non-severe cases	[75]
High dose polyclonal IVIG	–	Covid-19	Systematic review	No significant reduction in risk of death (RR=0.5), significant reduction in length of hospitalization (only in studies on moderate covid-19)	[76]
IVIG + methylprednisolone	0.5 g/kg/day IVIG, methylprednisolone 40 mg	Covid-19	Prospective randomized controlled trial	Lower need to mechanical ventilation (2/14 vs. 7/12), shorter median length of hospital stay (11 vs. 19 days), shorter length of ICU stay (2.5 vs. 12.5 days), greater improvement in PaO2/FiO2 in 7 days (+131 vs. +44.5)	[77]
IVIG	–	Non-severe covid-19	Retrospective cohort study	Lower progression to severe disease (3.3% vs. 6.6%) and death (0 vs. 2.2%) in IVIG group in comparison with controls	[78]
IVIG	IVIG 5% 30 g/day, 5 days	Critically ill covid-19	Retrospective cohort study	Higher survival rate (61% vs. 38%), longer median survival time (68 vs. 18 days) in IVIG group in comparison with controls	[79]
IVIG	0.1–0.5 g/kg/day, 5–15 days	Critically ill covid-19	Retrospective cohort study	Improvement in 28-day mortality and length of hospital stay in IVIG patients	[80]

cytokine storm syndrome (CSS) such as IL-6, TNF, and IL-1β [107]. The S protein has two subunits; S1 is involved in attachment to ACE2 by means of a receptor binding domain (RBD) and help of the N-terminal domain (NTD) through recognition of sugar moieties, and S2 is involved in fusion of the viral particle. Neutralizing any of these targets can be helpful for the prevention of viral infection [107–109]. CSS is an uncontrolled inflammation especially in critical COVID-19 patients, leading to fever, ARDS, multiple organ failure, and death. Targeting the inflammatory factors involved in CSS can reduce the COVID − 19 mortality rate [110–113].

Fig. 6 illustrates these mechanisms.

6.2. Administration indications and clinical findings

Monoclonal antibodies can be beneficial in the treatment as well as pre-exposure and post-exposure prophylaxis [33]. Administration of monoclonal antibodies cause a better overall survival in hospitalized patients [114]. A variety of clinical and preclinical studies have been carried out to evaluate the effect of administration of monoclonal antibodies in different stages of COVID-19 infection. Table 6 summarizes results of recently conducted clinical trial in this regard.

Among these antibodies, some have been approved by the Food and Drug Administration (FDA). Bamlanivimab plus etesevimab and casirivimab plus imdevimab combination therapies are two of the approved treatment regimens. Though, administration of these products has been paused in the US due to lower susceptibility of the Omicron (B.1.1.529) variant. Sotrovimab is also authorized for administration in both SARS-CoV-1 and different variants of SARS-CoV-2. Combination therapy using tixagevimab plus cilgavimab has also been approved and is used in different variants of COVID-19, including the Omicron variant. This combination can also be used as a pre-exposure prophylaxis and has received an Emergency Use Authorization (EUA) from the FDA in this matter.

The COVID-19 Treatment Guidelines panel recommends administration of single dose sotrovimab 500 mg IV in non-hospitalized mild to moderate infection as soon as possible. Administration of bamlanivimab plus etesevimab and casirivimab plus imdevimab combination therapy is not recommended in omicron variant outbreaks. The panel also recommends against the use of monoclonal antibodies in cases of hospitalized severe infection, and also in immunocompromised patients (due to risk of resistance) [33].

6.3. Challenges

The rapid emergence of various SARS-CoV-2 new variants calls for the need to developing antibodies against the new epitopes and developing tools for timely prediction of the emergence of new variants [107].

7. Cell-based therapy: mesenchymal stem cells (MSCs)

7.1. Mechanism of action

Mesenchymal stem cells (MSCs) are plastic-adherent stem cells with an in vitro differential potential and an ability to express a variety of markers such as CD105, CD90, and CD73, and lack of CD11b, CD14, CD19, CD34, CD45, CD79α, and HLA-DR [145]. MSCs could be an appropriate treatment candidate due to the easy isolation from the donor tissue, as well as lack of expression of HLA markers, rapid proliferation, proper homing capacity of the target site, and persistence in the target lung tissue [146].

The mechanisms involving these cells include immunomodulation and paracrine secretion of cytokines such as, IL-37, keratinocyte growth factor (KGF), hepatocyte growth factor (HGF), lipoxin A4, and angiopoietin-1. In addition, they can induce ATP production in alveoli and enhance phagocytosis by means of mitochondrial transfer. In ARDS

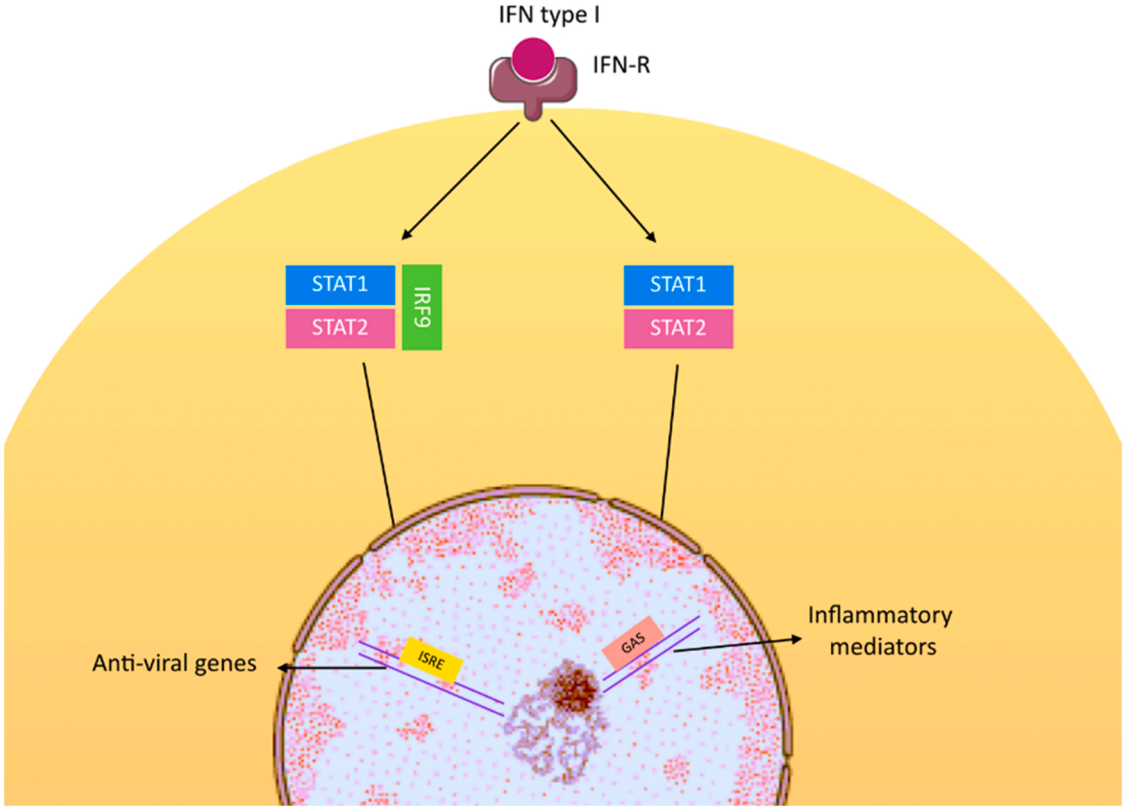

Fig. 5. Interferons in COVID-19.

cases, it can improve the condition by inducing lung permeability, fluid clearance in alveoli, and lung repair in both epithelial and endothelial tissues [146]. Fig. 7 illustrates these mechanisms.

7.2. Administration indications and clinical findings

Since MSCs express low levels of ACE2 and transmembrane protease serine type 2 (TMPRSS2), they are resistant to SASRS-CoV-2 infection regardless of their source [147]. This therapeutic approach has been well tolerated in COVID-19 patients according to the results of the clinical trials. Table 7 summarizes the results of recent studies in this field.

Though promising results have been observed regarding this treatment modality, the COVID-19 Treatment Guideline Panel recommends against the administration of MSCs, unless it is in a clinical trial setting, due to limitation of data [33].

7.3. Challenges

Although recent studies have shown promising results for using MSCs, we still face some problems. Some of such barriers include variability of MSC sources and the need to identify the most suitable source and standardization of the methods of handling MSCs, both in preparation and administration [146].

8. Conclusion

COVID-19 pandemic has caused considerable morbidities and mortalities over the past couple of years. Involvement of the immune system as a double-edged sword, both in constraining the disease and in causing complications such as CSS, has made immune-based approaches a great candidate in combating the disease, amongst which corticosteroids, IVIG, interferon therapy, and monoclonal antibodies are reviewed in this article. Each of these therapeutic approaches are beneficial in specific clinical settings and disease stages to gain the most improvement in clinical conditions with the least adverse effects (susceptibility to infections, etc.). Corticosteroids are advised to be considered in severe or critically ill patients due to their variety of potential side effects. IVIG has shown promising results in trials, though its use is limited and more studies need to be conducted due to the risk of multisystem adverse events. Interferon therapy though considered beneficial in a variety of infectious diseases, including COVID-19, it can cause a range of immune system imbalances; therefore, its usage is currently limited. Monoclonal antibodies are a targeted therapeutic modality and have shown promising results in patients in a variety of disease stages. Nevertheless, due to the rapid emergence of new variants they might lose their efficacy in different outbreaks based on the prevalent variants, hence, it is important to develop antibodies against new epitopes. Overall, in each clinicobiological phase in COVID-19 pathogenesis, some therapeutic agents are indicated. In the asymptomatic phase, monoclonal antibodies can be used; for instance, as mentioned before, bamlanivimab has been used in medical staff as a prophylaxis agent (Table 6). In the propagating phase, different agents can be suitable depending on disease severity. Patients with mild disease, respond to monoclonal antibodies such as bamlanivimab, the combination of bamlanivimab plus etesevimab, MW33, regdanvimab, and sotrovimab (Table 6). In moderately ill patients, monoclonal antibodies (e.g, tocilizumab, itolizumab, bamlanivimab, the combination of bamlanivimab plus etesevimab, MW33, and sotrovimab [Table 6]), interferon therapy (Table 5), and based on results of some trials (Table 4), IVIG can be beneficial. In severely ill patients and patients in complicating phase of the disease, corticosteroids, IVIG, interferons, and monoclonal antibodies can be beneficial. For the administration of monoclonal antibodies, the virus strain is an important factor and it should be taken into consideration in deciding the drug of choice. Although a wide range of pre-clinical and clinical studies have been conducted regarding immune-based approaches, more studies are

Table 5
Summary of the results of studies on administration of interferons in COVID-19 patients.

Intervention	Dosage	Population	Study design	Primary outcome	Results	References
IFN-β1b, lopinavir, ritonavir, Ribavirin	IFN-β1b 3 doses 8 million IU, lopinavir 400 mg, ritonavir 100 mg, Ribavirin 400 mg bid, 14 days	COVID-19 patients	Phase II clinical trial	Time to negative nasopharyngeal RT-PCR test	Shorter time from start of study to a negative RT-PCR test in treatment group in comparison with controls (receiving Lopinavir+ritonavir (7 vs. 12 days)	[91]
IFN-β1a	44 μg SC, every other day, up to 10 days	COVID-19 patients	Prospective non-controlled trial	–	Fiver resolved in 7 days, extension virological clearance in 10 days, recovery in imaging findings in 14-days in all patients	[92]
IFN-α2b, arbidol, IFN-α2b+arbidol	IFN-α2b 5 million IU bid, arbidol 200 mg did	COVID-19 patients	Uncontrolled clinical trial	–	Reduction of the duration of virus detection in upper respiratory tract and elevated blood inflammatory markers in treatment with IFN-α2b with or without arbidol	[93]
IFN-β1a	12 million IU/ml, 3 times a week	Severe covid-19	Randomized controlled clinical trial	Time to reach clinical response	Primary outcome no significantly different, hospital discharge on day 14, 66.7% in treatment group vs. 43.6% in controls, lower 28-day mortality in treatment group (19% vs. 43.6%)	[94]
IFN-β1b	250 μg/day SC, 2 weeks	Severe covid-19	Randomized controlled clinical trial	Time to clinical improvement	Shorter time to clinical improvement (9 vs. 11 days), higher percentage of hospital discharge at day 14 (78.79% vs. 54.55%), lower 28-day mortality (6.06% vs. 18.18)	[95]
IFN-β1b + favipiravir	IFN-β1b 8 million IU bid 5 days favipiravir 1600 mg day 1 + 600 mg bid maximum of 10 days	Moderate to severe covid-19 pneumonia	Randomized controlled clinical trial	Time to clinical recovery, normalization of inflammatory biomarkers, improvement of oxygen saturation, maintained for at least 72 h	No significant difference between length of hospital stay, levels of inflammatory biomarkers, transfer to ICU, discharges, and mortality between two groups	[96]
IFN-β1a	12 million IU	Mild to moderate pneumonia in COVID-19	Randomized controlled clinical trial (INTERCOP)	Time to negative conversion of nasopharyngeal swabs	–	[97]
IFN-α, recombinant super compound IFN-α (rSIFN-co)	IFN-α (2a or 2b) 5 million IU bid, rSIFN-co 12 million IU bid until discharge from hospital	Moderate to severe covid-19	Randomized controlled clinical trial	Time to clinical improvement	Shorter time to clinical improvement (11.5 vs. 14), time to radiological improvement (8 vs. 10 days), and time to virus RNA negative conversion (7 vs. 10 days), higher rate of clinical improvement on day 28 (93.5% vs. 77.1%) in rSFN-co group	[98]
PEG IFN-α2b	1 μg/kg SC single dose	Moderate covid-19	Phase II clinical trial	Clinical status improvement on day 15 (WHO 7-point ordinal scale)	Higher percentage of negative RT-PCR on day 7 (80% vs. 63%) and 14 (95% vs. 68%) and higher percentage of clinical improvement on day 15 (95% vs. 68.42%) in treatment group in comparison with controls	[99]
IFN-β1a, IFN-β1b	IFN-β1a 12,000 IU, IFN-β1b 8 million IU	Severe covid-19	Randomized controlled clinical trial (COVIFERON)	Time to clinical improvement	Significant difference in primary outcome between IFN-β1a group and controls (HR 2.36), no Significant difference in primary outcome between IFN-β1b group and controls (HR 1.42), lower mortality in treatment groups vs. controls (20% IFN-β1a, 30% IFN-β1b, 45% controls)	[100]
Recombinant human IFN-α nasal drop (rhIFN-α)	Nasal drops in low risk group, nasal drops + thymosinα1 in high risk group for 1 month	Medical staff	Prospective clinical trial	New outset of COVID-19 diagnosed by chest CT in 30 days	Negative CT scan in both groups after 1 month	[101]
IFN-based therapy (IFN-β1b+ritonavir/ lopinavir+ribavirin) vs. favipiravir	IFN-β1b 8 million IU, lopinavir 400 mg, ritonavir 100 mg, Ribavirin 400 mg bid, favipiravir 1800 mg/dose bid day 1 + 800 mg/dose bid 7–10 days	Non-critical covid-19	Cohort study	All-cause mortality in 28 days	Lower 28-day mortality (9% vs. 12%), less use of systemic corticosteroids (57% vs. 77%) in IFN-based therapy group in comparison with favipiravir group, no significant different in hospitalization duration between two groups	[102]

(*continued on next page*)

Table 5 (*continued*)

Intervention	Dosage	Population	Study design	Primary outcome	Results	References
IFN-β1a low dose vs. high dose	Low dose 24 million IU, high dose 12 million IU	Severe covid-19	Randomized controlled clinical trial (COVIFERON II)	Time to clinical improvement	Shorter time to clinical improvement in low dose group in comparison with high dose group (6 vs. 10 days), insignificantly higher mortality rate in low dose group (41% vs. 36.5%)	[103]
PEG IFN-α2b	1 μg/kg SC single dose	Moderate covid-19	Phase III clinical trial	Two-point improvement in clinical status on day 11 (WHO 7-point ordinal scale)	Early viral clearance, improved clinical status and reduction of duration of oxygen supplementation in PEG IFN-α2b group	[104]
IFN-β1a + remdesivir vs. remdesivir	IFN-β1a 44 μg, remdesivir 200 mg loading dose day 1, 100 mg/day maintenance dose up to 9 days	Hospitalized covid-19 patients	Phase III clinical trial	recovery (the first day that a patient had a category 1, 2, or 3 score on the eight-category ordinal scale within 28 days)	Time of recovery of 5 days in both groups, no significant difference in 28-day mortality	[105]
IFN-β1a vs. IFN-β1b	IFN-β1a 12 million IU, IFN-β1b 8 million IU	Hospitalized covid-19 patients	Clinical trial	Clinical improvement (rate of hospital discharge)	No significant difference in discharge time, mortality, ICU length of stay, and frequency of mechanical ventilation between the two groups	[106]

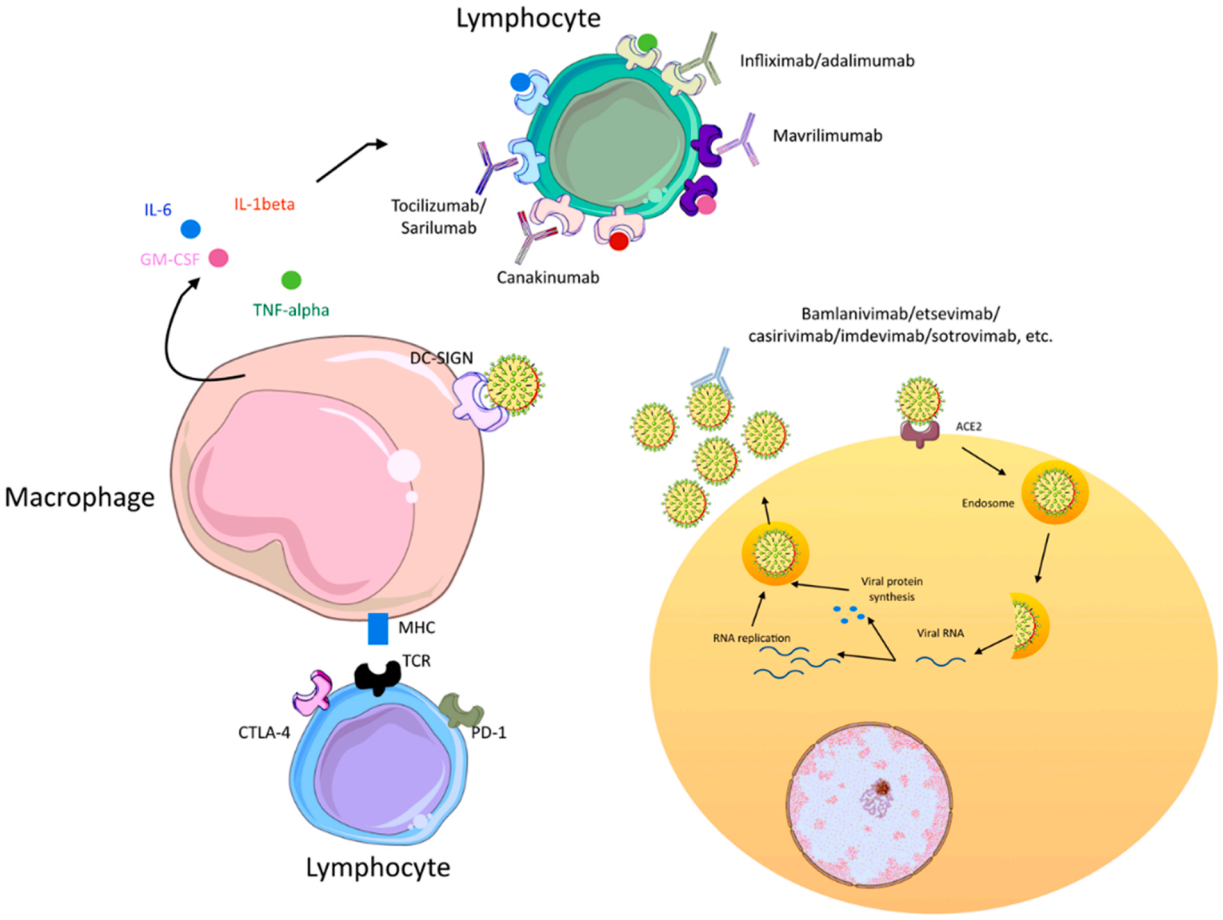

Fig. 6. Monoclonal antibodies in COVID-19.

Table 6
Recent clinical trials on use of monoclonal antibodies in COVID-19.

Monoclonal antibody	Target molecule	Disease stage	Clinical trial number	Results	References
Tocilizumab	IL-6R	Moderate to severe	NCT04331808, NCT04356937 NCT04317092 (TOCIVID-19) NCT04331795 (COVIDOSE) NCT04372186 CTRI/2020/05/025369 (COVINTOC) ChiCTR2000029765 NCT04381936 (RECOVERY) NCT04346355	Reduction in risk of death, mechanical ventilation, non-invasive ventilation, improvement in clinical and laboratory markers of hyper inflammation, reduction in time to negative virus load, though not beneficial in some studies	[115–123]
		Severe / critical	IRCT20150303021315N17 NCT04403685 NCT04320615 NCT04409262 (REMDACTA) NCT04779047	Improvement in risk of death, O2 saturation, required level of oxygenation, respiratory rate, though not beneficial in some studies,	[124–128]
Itolizumab	CD6	Moderate	RPCEC00000311 (VICTORIA)	Improvement in clinical (lower ICU admission), laboratory (reduction in IL-6 levels), and mortality	[129]
Sarilumab	IL-6R	Severe / critical	NCT04327388	Not significantly beneficial	[130]
Bamlanivimab	S protein	Prophylaxis in medical staff	NCT04497987	Reduction in incidence of COVID-19 infection	[131]
		Mild to moderate	NCT04427501 (BLAZE-1)	Not significantly beneficial, slight reduction in neutralizing activity of day 29 serum	[132,133]
		Hospitalized (no organ failure)	NCT04501978	Not significantly beneficial	[134]
Etesevimab	S protein	Healthy adults	NCT04441918	Well-tolerated	[135]
Bamlanivimab+Etesevimab	S protein	Mild to moderate	NCT04427501 (BLAZE-1) NCT04634409 (BLAZE-4)	Reduction in viral load, hospitalization, death,	[132,133, 136,137]
REGEN-CoV (casirivimab+imdevimab)	S protein (RBD)	Outpatients	NCT04425629	Reduction in viral load	[138–140]
		Hospitalized	NCT04426695	Ongoing trial	
MW33	S protein (RBD)	Healthy adults	NCT04533048	Well-tolerated	[141]
		Mild to moderate	NCT04627584	Ongoing trial	
SCTA01	S protein	Healthy adults	NCT04483375	Well-tolerated	[142]
Regdanvimab (CT-P59)	S protein	Healthy adults	NCT04525079	Well-tolerated	[143]
		Mild infection	NCT04593641	More reduction in viral load, shorter duration to recovery	
Sotrovimab	S protein	Mild to moderate	NCT04545060 (COMET-ICE)	Reduction in risk of disease progression	[144]

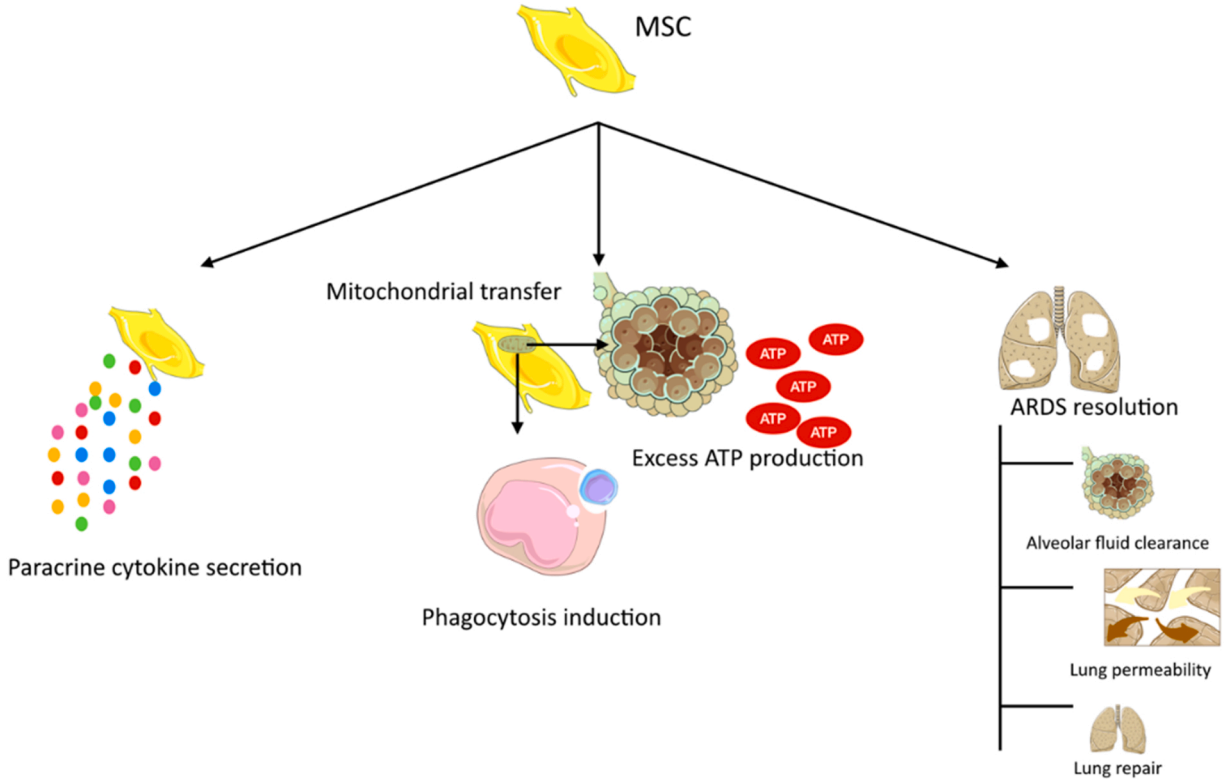

Fig. 7. MSCs mechanism of action.

Table 7
Safety and efficacy data regarding administration of MSCs in COVID-19 patients.

Source of MSCs	Population	Study design	Results	References
Umbilical cord	Hospitalized COVID-19 patients	Phase 1 clinical trial	Safe and well tolerated	[148]
Wharton Jelly	Moderate and critical COVID-19 patients	Prospective double-controlled trial	Significant levels of pro-inflammatory, anti-inflammatory, and growth factors and significant reduction in ferritin, fibrinogen, and CRP levels in MSC receiving group,	[149]
Umbilical cord	Severe/critical COVID-19 patients	Uncontrolled clinical trial	Discharge from ICU 52.5%, mortality 47.5% among critically severe intubated patients, Discharge from ICU 77.5%, mortality 22.5% among critically severe non-intubated patients, higher survival in cases of pre-intubation MSC administration (OR=1.475)	[150]
Umbilical cord	ARDS secondary to COVID-19	Pilot study	Constant rise of PaO2/FiO2 in first 7 days, 3 of the 5 patients survived and were extubated on day 9, the method was relatively well-tolerated	[151]
Perinatal tissue	ARDS secondary to COVID-19	Case series	7 patients showed clinical improvement, 6 of the 7 patients enrolled survived, reduction in levels of TNF-α, IL-8, CRP, IFN-γ, and IL-6, and remarkable signs of radiologic recovery was observed	[152]
Umbilical cord	Severe COVID-19	Randomized controlled trial	Lower incidence of progression, mortality, shorter time to clinical improvement in treatment group, reduction in levels of IL-6 and CRP	[153]
Menstrual blood	Severe/critical COVID-19 patients	Exploratory clinical trial	Lower mortality (7.69% vs. 33.33%) in treatment group in comparison with controls, improvement in SpO2, dyspnea and radiological findings	[154]
Umbilical cord	Severe/critical COVID-19 patients	Pilot study	Improvement in oxygenation index, radiological findings, and lymphocyte count, lower mortality in comparison with historical rate (6.25% vs. 45.4%)	[155]
N/A (ACE2-MSCs)	Severe COVID-19 pneumonia	Pilot study	Clinical improvement, reduction in levels of CRP, over-activated cytokine secreting cells, TNF-α, and increase in levels of peripheral lymphocyte, regulatory DC, IL-10	[156]
Umbilical cord	Critical COVID-19	Randomized controlled trial	2.5 times higher survival rate in treatment group in comparison with controls, no significant difference in length of stay in ICU and ventilator usage, reduction in IL-6 levels	[157]
Umbilical cord	Severe COVID-19	Randomized controlled phase 2 trial	Improvement in radiological findings	[158]
Umbilical cord	ARDS secondary to COVID-19	Randomized controlled phase 1/2a trial	Significant reduction I. Inflammatory cytokines, improvement in patient survival (91% vs. 42%) and time to recovery (P = 0.03)	[159]

needed in order to improve both efficacy and safety of these modalities and the choice of drugs vary based on a wide range of factors including disease stage and availability of agents of choice.

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CRediT authorship contribution statement

Aysan Moeinafshar: Conceptualization, Roles/Writing – original draft, Writing – review & editing. **Niloufar Yazdanpanah**: Conceptualization, Roles/Writing – original draft, Writing – review & editing. **Nima Rezaei**: Conceptualization, Writing – review & editing, Supervision. All the authors have read and approved the final draft of the manuscript.

Conflict of interest statement

The authors report no conflict of interest.

Data availability

No data was used for the research described in the article.

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The authors report no conflict of interest.

Consent to participate

Not applicable.

Authors Contribution

AM conceptualized the title and prepared the first draft. NY conceptualized the title, edited and revised the manuscript and finalized the draft. NR conceptualized the title, critically revised the manuscript, finalized the draft, and supervised the project. All the authors have read and approved the final draft of the manuscript.

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