REVIEW

Anti-Inflammation, Immunomodulation and Therapeutic Repair in Current Clinical Trials for the Management of COVID-19

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Abstract: The coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), continues to spread around the world. While prophylactic vaccines against SARS-CoV-2 are making great progress, there is still a need to explore safe and effective therapies with biological products for COVID-19. Currently clinical trial efforts are planned and ongoing using different biological agents for anti-inflammatory therapies, immunomodulation, and therapeutic repair in COVID-19. Targeting inflammatory cytokines with antibodies or inhibitors may be an urgent therapeutic strategy for COVID-19. Importantly, it is critical for an in-depth understanding of these new clinical therapeutic agents in their conditions that are probably involved in both physiological and pathological host responses. In this article, we analyze the potential implications for the current clinical trials of therapeutic biologics and address issues for the development of the COVID-19-related biological therapies.

Keywords: COVID-19, cytokine blockade, immunomodulation, therapeutic repair

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is responsible for coronavirus disease-19 (COVID-19). The increase of COVID-19 cases is of great global concerns. Patients affected by COVID-19 will experience respiratory illness processes and, of note, 26.1% hospitalized patients require to be treated in the intensive care unit due to pneumonia complications, including 61.1% with acute respiratory distress syndrome (ARDS) among these hospitalized patients, 44.4% with arrhythmia and 30.6% with shock.[1] COVID-19 also affects different parts of the body with various clinical manifestations. As a novel infectious disease, safe and effective life-saving antiviral drugs to COVID-19 patients are not enough but expedite the development of treatment options. Vaccines are being developed with unprecedented speed but the translational challenges are still numerous. To ensure the latest information that is available, the WHO is publishing a regularly updated list of COVID-19 vaccine candidates in both clinical and pre-clinical development.[2] Currently, there are 74 candidate vaccines under clinical development and 182 under pre-clinical development.[2] Owing to safe and effective results from clinical trials, the both Pfizer-BioNTech and Moderna COVID-19 Vaccines are early authorized to prevent COVID-19 in persons aged ≥16 and ≥18 years, respectively,[3,4] albeit the main question remains about how long the vaccines will

protect people from COVID-19. Usually, vaccines are being applied to the prophylaxis early in the course of infectious diseases to prevent poor outcomes. Facing the COVID-19 global pandemic, scientists, physicians and government are urged to rework different strategies to combat this disease. To explore novel therapeutic agents become a prompt treatment option for COVID-19. Clinical trials need to establish safety and effectiveness of therapeutic drugs for the management of COVID-19.

To date, treatment of COVID-19 with biologic agents has drawn increasing attention, reflected in the numerous ongoing and planned clinical trials. While a large and growing body of research has demonstrated that conventional drugs such as Dexamethasone and Ribavirin are partly effective, therapies using biologic agents for COVID-19 are not briefly mentioned. For this reason, the current review focuses mainly on different treatment strategies using a variety of biological agents based on clinical trials registered on the clinicaltrials.gov. Given that a huge effort is being put in the development of biological agents, we will briefly summarize our understanding of such agents as well as comment on their pros and cons for the management of COVID-19. Acknowledging multiple aspects of some therapeutic agents, this review also addresses their potential immuno-pathological complications in COVID-19 infection control for the development of more safe and effective biological therapies. In addition, several therapeutic drugs that are not biologic but closely related to the biological signaling cascade such as Janus kinase (JAK) inhibitor and Rapamycin are also discussed and included to this review.

Currently Clinical Trials of Biological Agents for COVID-19

People all around the world are anxiously awaiting the development of more effective and safe biological therapies for the management of COVID-19. In order to get the latest research information from NIH, we recently performed a search at the clinicaltrials.gov in the present article. We used the key search terms "COVID-19", "antibody/immunoglobulin", "Intravenous immunoglobulin (IVIG)", "cytokine", "growth factor", "antagonist/agonist/inhibitor", "mammalian target of Rapamycin (mTOR)" and "complement" and, after selection, comprehensively enumerated the total of 317 clinical investigations worldwide registered on the clinicaltrials.gov through February 28, 2021 (Table 1). The eligibility criteria for considering a clinical trial included in this review belong

to the following categories: a ClinicalTrials Identifier number; the number of participants; a time period; the participants' clinical condition/disease; the nature of intervention/treatment, contact and location. We roughly categorized the selected investigations into anti-inflammatory and immuno-modulatory therapies (282 trials) and therapeutic repair (35 trials) according to the biological agents that are currently being explored. Some of the mentioned therapeutic agents can be ascribed to any of these categories such as JAK inhibitor. Indeed, the issue of separating biological processes is challenging due to the multifaceted roles of these cytokines and growth factors that have been implied within different contexts. We analyzed and assessed their therapeutic potentials and challenges for the treatment and management of patients with COVID-19. Importantly, it would be to quickly determine whether these biological agents are safe and effective in clinical trials. Expectedly, patients with COVID-19 would come forward to take these agents early if clinical data suggest these biologics may be promising.

Anti-Inflammatory and Immunomodulatory Therapies for COVID-19

Interleukin (IL) Receptor Antibody, Interferon (IFN) and Anti-IFN-γ, Anti-Tumor Necrosis Factor (TNF) Agent and p-Selectin Antibody

A subset of patients with severe acute COVID-19 pneumonia develop a hyper-inflammatory state, as is shown significant upregulation of a series of mediators including pro-inflammatory cytokines/chemokines.[5] Some cytokines act as key drivers of COVID-19 pneumonia during the innate immune responses to the SARS-CoV-2. Therefore, targeting cytokine-associated signaling pathway for mitigation of the hyper-inflammatory state could be a therapeutic strategy. Currently, there are certain clinical data available using cytokine antagonists with biological agents for the treatment of COVID-19. One small open-label study has reported that targeting the inflammatory cascade with Anakinra, a recombinant form of IL-1 receptor antagonist, is a safe and effective approach for the treatment of the moderate to severe COVID-19 pneumonia.[6] Another open-label and randomized clinical trial demonstrates that Anakinra does not improve outcomes in patients with mild-to-moderate COVID-19 pneumonia.[7] Interestingly, one trial (NCT04148430) conducted by Memorial Sloan Kettering Cancer Center, New York, is underway to determine whether Anakinra

Table 1 Summary of Clinical Trials of Therapeutic Agents for COVID-19 (n=317, as of February 28, 2021)

Category	Therapeutic Agent		No. of Trials	No. of Phase I	No. of Phase I/ II	No. of Phase II	No. of Phase II/ III	No. of Phase III	No. of Phase IV	No. of Phase N/ A
Anti-inflammatory /Immunomodulation	Anti-IL-1R		27			9	4	7		7
	Anti-IL-6R		66	2		24	9	19	3	9
	Anti-IL-1R and Anti-IL-6R		3			2		1		
	Anti-IL-1R and JAK inhibitor		2			1		1		
	Anti-IL-6R and JAK inhibitor		1					1		
	Anti-IFN-γ		1				1			
	Anti-TNF-α		6			2		2		2
	Anti-P-Selectin		1			1				
	JAK inhibitor		43		2	20	6	8	1	6
	PD-1 blocking		5			5				
	PD-1 blocking and Anti-IL-6R		1			1				
	Anti-CCR5		5			4	1			
	Complement inhibitor		14		1	7		4	1	1
	Neutralizing Ab and Ig		59	12	6	13	9	9	3	7
	IL-2		1			1				
	IFN	IFN-α	11	1	1	2	1	2	1	3
		IFN-β	21			11	1	6	3	
		IFN-λ	5			5				
	Anti-IL-15		2	1	1					
	Anti-IL-17		1					1		
	Anti-IL-23		1			1				
	mTOR inhibitor		6	1	1	4				

(*Continued*)

Table 1 (Continued).

Category	Therapeutic Agent	No. of Trials	No. of Phase I	No. of Phase I/II	No. of Phase II	No. of Phase II/III	No. of Phase III	No. of Phase IV	No. of Phase N/A
Tissue regeneration	Anti-VEGF	6			3	1		1	1
	VIP	4	1		1	1			1
	Anti-CTGF	1			1				
	Anti-GM-CSF	12			8	2	2		
	GM-CSF	9	2	1	4	1		1	
	PGE1 analog	1			1				
	HGF mimetic	1			1				
	EGF	1	1						

Abbreviations: Ab, antibody; CCR5, C-C chemokine receptor type 5; CTGF, connective tissue growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; EGF, epidermal growth factor; HGF, hepatocyte growth factor; IFN, interferon; Ig, immunoglobulin; IL, interleukin; JAK, Janus kinase; N/A, not applicable; PD-1, programmed cell death protein 1; PGE1, prostaglandin E1; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor; VIP, vasoactive intestinal polypeptide.

can prevent the severe side effects caused by CD19-specific CAR-T cell therapy in patients with COVID-19. Additionally, two recent clinical studies show that Tocilizumab, a humanized anti-IL-6 receptor monoclonal antibody, has been proposed the safety and efficacy to treat patients with severe and critical COVID-19.[8,9] However, the mixed results have also been observed in clinical trials with Tocilizumab.[10,11] For example, a randomized trial involving 249 patients hospitalized in the Tocilizumab group and 128 patients in the placebo group demonstrated that the cumulative percentage of patients who received mechanical ventilation or died by day 28 was 12.0% in treatment group and 19.3% in the control, respectively.[10] Serious adverse events occurred in the 15.2% of patients receiving Tocilizumab and the 19.7% of patients receiving a placebo.[10] Currently, there are two clinical trials with anti-IL-15 (NCT04324996 and NCT04385849), one with anti-IL-17 (NCT04724629), one with anti-IL-23 (NCT04583956), one with anti-IFN-γ (NCT04324021), six with anti-TNF-α and one with anti-p-selectin (NCT04435184) to determine the safety and effectiveness for treatment of COVID-19. There are thirty-two clinical trials with type I (eleven with IFN-α and twenty-one with IFN-β) and five with type III (IFN-λ subtype) interferons to test their safety and efficacy in the treatment of patients with COVID-19. However, inflammation, on the other hand, is also necessary for tissue-damaged recovery. Several pro-inflammatory cytokines (eg, IL-1, IL-6, IL-8 and TNF-α) are required in the local to remove virus-infected cells for tissue remodeling, thus facing a double-edged sword for treatment with targeting cytokine-associated signaling pathway.

JAK Inhibitor

JAK is a tyrosine kinase family for the downstream signal cascade of type I and II cytokine receptors bound by over 50 bioactive mediators including cytokines, ILs, IFNs, colony-stimulating factors (CSFs) and hormones.[12] JAK signaling pathways play a key role of cellular proliferation and immune responses. Milara et al have reported that JAK implicates in lung fibrosis in patients with idiopathic pulmonary fibrosis and contributes to alveolar type II (ATII) epithelial cell transformation to mesenchymal transition and fibroblast to myofibroblast.[13] JAK inhibitors (eg, Baricitinib, Ruxolitinib, and Tofacitinib) can inhibit type I/II cytokine receptors and they are currently being used for the treatment of COVID-19. For example, Baricitinib has now been investigating and is suggested as a promising approach as potential treatment for COVID-19.[14–16] A recent pilot clinical study reported that treatment with a JAK inhibitor, Ruxolitinib, was shown to be safe in a subgroup of patients with severe COVID-19.[17] In this study conducted by La Rosée et al, 14 patients with COVID-19 Inflammation Score (CIS) ≥10 of 16 threshold received Ruxolitinib with optimizing therapeutic regimens.[17] These patients achieving the CIS threshold value of ≥10 showed without clinical signs of

sepsis and no uncontrolled active infection. The majority of COVID-19 patients presented with progressive hyper-inflammation governed by Ruxolitinib and the 4/14 patients indicated the viral clearance. During the early stage of infection, IFNs (type-I IFNs) responses are required to prevent viral replication. As the infection progresses, viruses can develop new strategies to counteract effects of IFNs by targeting JAK signaling pathway.[18] Additionally, given the hypercoagulability of COVID-19, the potentially increased inherent thrombotic risk associated JAK inhibitor should be alert for the hospitalized patients with COVID-19.[19] Therefore, JAK inhibitors need to be used cautiously to treat COVID-19.

mTOR Inhibitor

mTOR is involved in regulating cell metabolism, growth and proliferation, survival, and immunity. Several RNA viruses such as influenza virus, SARS-CoV and Middle East respiratory syndrome coronavirus hijack mTOR pathway to promote their own replication.[20] An integrative proteo-transcriptomics analysis is performed by Appelberg et al in SARS-CoV-2 infected human hepatocyte-derived cellular carcinoma cell line Huh7 to map the cellular responses.[20] This study by Appelberg et al[20] suggests a crosstalk between the SARS-CoV-2 and the Akt/mTOR/HIF-1 signaling pathway. Attractively, Akt inhibitor MK-2206 can inhibit mTOR signaling pathway, further decreasing virus production in Huh7. However, using mTOR inhibitor Sirolimus failed to block SARS-CoV-2 infection, albeit it was observed to inhibit MERS-CoV in mice.[21] mTOR inhibitor targeting cell proliferation and suppression of gene expression are being tested in clinical trials. There are six clinical trials for mTOR inhibitors (NCT04341675, NCT04371640, NCT04409327, NCT04461340, NCT04482712, and NCT04584710), as potential treatment options in minimizing the severity of COVID-19.

Neutralizing Monoclonal Antibody/Immunoglobulin

Convalescent plasma (CP) therapy appears to have significantly reduced morbidity and mortality in patients with severe and critical COVID-19 when life-threatening illness condition continues to deteriorate.[22–24] Therapeutic effect of CP on time to clinical improvement in patients with several and life-threatening COVID-19 was also evaluated in one previous clinical trial conducted by Li et al.[25] No significant difference was noted between the CP group and the control group within 28 days.[25] Therefore, the

immediate and urgent challenges have to be addressed at the time of virus outbreak and we would like to extend our discussion in the present paper. First, CP collected from COVID-19 convalescent patients contains a variety of blood-derived components, including nonprotective anti-bodies/immunoglobulins, complements, clotting factors, cytokines and growth factors, in addition to a large quantity of neutralizing antibodies.[26] Second, considering that the mutated virus is able to escape the one type of anti-body therapy, the emergence of resistant SARS-CoV-2 mutations that may diminish the therapeutic efficacy of neutralizing antibodies needs further attention for the effective treatment options. Third, a potential risk during CP therapy has to be alert on the antibody-dependent enhancement due to cross-reactive antibody responses between SARS-CoV-2 and SARS-CoV infections.[27,28] Indeed, non-neutralizing antibodies can also bind to the spike glycoprotein on the surface of SARS-CoV-2 to promote virus uptake into host cells via angiotensin-converting enzyme 2 (ACE2) receptor-mediated viral fusion. Fourth, another potential risk is the transfusion immunoglobulin-related acute lung injury, a severe adverse effect of high doses of intravenous immunoglobulin, with high mortality.[29] Finally, there still exists a potential risk during preparation of anti-SARS-CoV-2 immunoglobulins that needs for viral pathogens inactivation for the safer products. Therefore, CP therapy has safety concerns that still remain under debate.

Immune plasma therapy will be eventually abandoned and replaced by the monoclonal antibody-based therapies. IVIG immunotherapy has been supposed as an efficacious adjuvant with other antiviral drugs in the treatment of COVID-19.[30,31] SARS-CoV-2-neutralizing monoclonal antibodies and enriched immunoglobulins from CP have important advantages over the CP. Currently, fifty-nine clinical trials using neutralizing monoclonal antibodies and immunoglobulins are being performed in combating SARS-CoV-2 infections. Among these, two clinical studies are exemplified as representing new immunotherapeutic approaches. One study (NCT04342195) conducted by Columbia University, New York, is still ongoing to utilize blood specimens from patients who have recovered from COVID-19 infection for isolation of specific monoclonal antibodies from human B cells to potently neutralize the SARS-CoV-2. Purified antibodies will be further assessed using neutralization assays to determine the therapeutic potential of anti-SARS-CoV-2. Another one (NCT04354766) has been conducting to generate human monoclonal antibodies neutralizing SARS-CoV-2 from convalescent patients and antibody

neutralizing capacities would be evaluated among the COVID-19 convalescent donors. Double-filtration plasmapheresis (DFPP), an extracorporeal blood purification technique to reduce hepatitis C viral RNA, is also used to efficiently collect antibodies from COVID-19 convalescent patients (NCT04346589 and NCT04418531). Indianapolis, Eli Lilly and Company announced on June 1, 2020, that patients had been dosed in the world's first study of neutralizing IgG1 monoclonal antibody treatment specifically designed to fight COVID-19.[32] Using combination of antibodies (antibody cocktails), a theoretical treatment strategy, may enhance potential therapeutic efficiency. Antibody cocktail approaches have shown substantial promise in recent in vitro and in vivo studies for preventing SARS-CoV-2 escape.[33,34] Of special notes, one double-blind and Phase I–III trial suggests that an antibody cocktail against SARS-CoV-2 is safe and effective in an individual patient whose immune response has not yet been initiated.[35] Currently, there are eleven ongoing trials (NCT04381936, NCT04425629, NCT04426695, NCT04452318, NCT04519437, NCT04617535, NCT04634409, NCT04666441, NCT04691180, NCT04700163 and NCT04770467) using the synergistic neutralizing antibody cocktails in COVID-19 patients.

Complement Inhibitor/Blockade

Whilst the precise mechanisms of action are unclear, antibodies function as the direct antivirus by the antibody-mediated immunomodulatory processes, including agglutination of virus, opsonization, viral and toxin neutralization. Complement is involved in the immunomodulatory processes. Complement is also a major component of the innate immune system in host that functions to defense against bacterial and viral infection and to maintain immune homeostasis. Excessive complement activation in the lung may contribute to pathologic outcomes.[36] Gralinski et al previously observed that complement component C3 activation in the lung initiated as early as day one following SARS-CoV infection in a C3$^{-/-}$ animal model and C3$^{-/-}$ mice exhibited significantly less respiratory dysfunction.[37] Jiang et al reported in a previous study that the concentration of C5a was increased in sera and lung tissues in MERS-CoV-infected hDPP4-transgenic mice and the blockade of the C5a-C5aR axis with a specific complementary antibody alleviated lung damage.[38] Potential complement component inhibitors with biological agents are currently being tested in patients with COVID-19. One recent clinical study using the combination of an anti-C5a monoclonal antibody (Eculizumab) and a JAK1/2 inhibitor (Ruxolitinib) revealed significant improvement in patients with severe SARS-CoV-2-related ARDS.[39] Another recent investigation indicated Eculizumab, a well-established safety profile, combined with antiviral drugs might work as a therapeutic option for the treatment of patients with severe COVID-19.[40] These safe data collected from clinical studies will support complement inhibition therapeutic potential in treating COVID-19.

Programmed Cell Death Protein 1 (PD-1) and C-C Chemokine Receptor Type 5 (CCR5) Antagonist

PD-1 is often expressed in immune cells including lymphocytes, natural killer cells, and dendritic cells and upregulation of PD-1/PD-1 ligands is generally observed during acute virus infection.[41] T cells from COVID-19 patients have significantly higher levels of PD-1 during the disease progress.[42] Currently ongoing clinical trials of PD-1 blockade (eg, Nivolumab and Pembrolizumab) have also been performing for treatment of patients with COVID-19. Chemokines act as chemo-attractants in the inflammatory cell recruitment during SARS-CoV-2 infection. The chemokine CCL3 and CCL4 are significantly up-regulated in the plasma of COVID-19 patients with a cytokine storm syndrome state compared to healthy controls.[5] Blockade of the CCR5 (receptor for CCL3 and CCL4) with biological agents is proposed. There are currently five initiating clinical trials (NCT04343651, NCT04347239, NCT04475991, NCT04678830 and NCT04710199) to determine whether the CCR5 antagonists Leronlimab and Maraviroc as therapeutic agents work against COVID-19. It would be good to see the beneficial effects on COVID-19.

As aforementioned, a central unanswered question concerns the right timing of administration that is critical and needs to be determined in clinical trials. Currently, the immunopathology of SARS-CoV-2 infection is becoming clearer. There are three stages of the infection's progression, as is recognized as the mild, moderate and severe symptoms in COVID-19 patients, and the optimal times for therapeutic interventions are proposed.[43] Theoretically, cytokine monoclonal antibodies/inhibitors such as JAK inhibitors might be given quickly once the COVID-19 symptoms appear. Thus, assessing clinical progression is urgently needed.

Therapeutic Repair

Vascular Endothelial Growth Factor (VEGF) Antagonist, Vasoactive Agent, and Prostaglandin E (PGE)

Tissue repair and regeneration is a complex process involving a variety of bioactive molecules and enzymes such as VEGF and matrix metalloproteinases.[44] VEGF is known as a key vascular permeability inducer to increase pulmonary edema during infection. VEGF is also involved in the activation of coagulation pathways in severe COVID-19 probably through triggering endothelial cells to upregulate the expression of tissue factor,[45] a potent activator of the extrinsic blood coagulation cascade. Therefore, VEGF is considered as a potential therapeutic target to counteract vessel-permeabilizing effect in the early onset of COVID-19 to reduce the disease severity. Yuksel et al have reported that VEGF antagonist (Bevacizumab) restores epithelial barrier dysfunction in an experimental asthma model.[46] A recent clinical study with Bevacizumab showed therapeutic efficacy by improving oxygenation and shortening oxygen-support duration in patients with severe COVID-19.[47] Likewise, Thalidomide, another angiogenesis inhibitor, has anti-inflammatory and anti-fibrotic effects and is also used for treatment of COVID-19 (NCT04273529 and NCT04273581). Two recent clinical studies suggested Thalidomide combined with low-dose short-term glucocorticoid as an effective therapeutic option in patients with severe COVID-19.[48,49] However, FDA has warned about life-threatening birth defects caused by Thalidomide and risk of blood clots.[50]

VEGF, on the other hand, is essential for the vascular formation and remodeling and critical for restoration of lung homeostasis. A previous study conducted by McClendon et al showed that VEGF signaling may mediate the role of hypoxia-inducible factor in ATII cell proliferation and spreading, the critical stages necessary to restore epithelial structure and function after lung injury.[51] Thus, whether VEGF promotes lung therapeutic repair or exacerbates pulmonary edema remains controversial. The immuno-pathological complications need to be considered cautiously. In addition, four clinical trials (NCT04311697, NCT04360096, NCT04453839, and NCT04536350) describe that Aviptadil, a vasoactive intestinal polypeptide, may restore barrier function at the endothelial/alveolar interface, thus protecting the lung from failure. Alprostadil, a PGE1 analog, is a potent vasodilator agent that increases peripheral blood flow.[52] One Phase II clinical trial (NCT04536363) is ongoing to evaluate the safety and effectiveness of the administration of intravenous PGE1. Although PGE1 may cause bronchodilation and possibly decrease platelet aggregation and intrapulmonary polymorphonuclear leukocyte sequestration for anti-inflammatory treatment and tissue modeling in patients with ARDS, there is an increase in the rate of significant adverse events.[53,54] Together, while some cytokines are responsible to the SARS-CoV-2 infection to play a dual role, it is important to quickly determine whether the potential benefits outweigh the potential risks. Therefore, the plasticity of these therapeutic agents for treatment should be used with great caution.

Connective Tissue Growth Factor (CTGF) Antibody and Hepatocyte Growth Factor (HGF)

CTGF is a secreted glycoprotein, which has been shown to play a role in the chronic process of fibrosis.[55] SARS-CoV-2 infection updates CTGF gene expression in human lung epithelial cells, which may promote lung fibrosis in COVID-19 patients.[56] Anti-CTGF may prevent this cascade. Luca Richeldi et al previously reported the safety and effectiveness of Pamrevlumab, a human monoclonal antibody against CTGF, in patients with idiopathic pulmonary fibrosis.[55] Currently, one phase II clinical trial (NCT04432298) using Pamrevlumab has been conducting for treatment and management of patients with COVID-19. Additionally, HGF has been demonstrated to have a potential role for hastening alveolar repair in patients with acute lung injury (ALI)/ARDS.[57] This in vitro study by Ito et al using primary human alveolar epithelial cells in wound-healing assay shows that HGF released mainly from lung fibroblasts can promote wound closure by accelerating cell motility. Currently, one clinical trial (NCT04459676) of biologics ANG-377, a small molecule HGF mimetic, is already underway to assess its clinical safety and efficacy in the severity and progression of pulmonary and renal dysfunction in patients hospitalized with COVID-19 pneumonia.

Granulocyte-Macrophage CSF (GM-CSF), Granulocyte-CSF (G-CSF) and GM-CSF Monoclonal Antibody

Cytokines are central to the immunopathology of COVID-19 and some play a dual role, as is shown that they may confer detriment and benefit to patients with COVID-19 pneumonia complications. GM-CSF and G-CSF act as the pro-inflammatory cytokine that partially contributes to a hyper-inflammatory state.[5] Mechanistically, downstream signaling cascades of GM-CSF are induced through JAK2

Table 2 Summary of Results of Completed Studies with Therapeutic Agents for COVID-19

Agent Category	Agent Name	Study Category	Therapeutic Effect	Reference
Anti-IL-1R	Anakinra	Retrospective cohort study	Safety and efficacy	[67]
	Anakinra	Randomized and controlled trial	Safety and efficacy	[68]
	Anakinra	Randomized and controlled trial	Ineffectiveness	[7]
	Canakinumab	Cohort controlled trial	Safety and efficacy	[69]
Anti-IL-6R	Tocilizumab	Retrospective study	Safety and effectiveness	[8]
	Tocilizumab	Randomized and controlled trial	Mixed clinical results	[10,11]
	Tocilizumab	Randomized and controlled trial	Improvement of clinical outcomes	[70]
Interferon	Peginterferon lambda	Randomized and controlled trial	Accelerated viral decline	[71]
	IFN-α/Ribavirin	Retrospective study	Mixed clinical results	[72]
	IFN-β1/Lopinavir-Ritonavir	Cohort controlled study	Safety and improvement of clinical outcomes	[73]
JAK inhibitor	Baricitinib	Randomized and controlled trial	Improvement of clinical outcomes	[16]
	Baricitinib	Cohort controlled trial	Decreased SARS-CoV-2 infection	[74]
	Ruxolitinib	Cohort controlled trial	Safety and effectiveness	[17]
	Ruxolitinib+ Anakinra	Randomized cohort study	Safety and effectiveness	[75]
Monoclonal Ab	ChAdOx1 nCoV-19	Randomized and controlled trial	Safety and efficacy	[76]
	CoronaVac	Randomized and controlled trial	Safety and efficacy	[77]
	SCB-2019	Randomized and controlled trial	Safety and efficacy	[78]
	LY-CoV555	Phase II trial	Safety and efficacy	[79]
Ab cocktail	REGN-COV2	Phase I–III trial	Safety and effectiveness	[35]
Complement inhibitor	Eculizumab	Pilot clinical trial	Improvements of clinical outcomes	[39]
	Eculizumab	Phase I/II cohort trial	Safety and effectiveness	[80]
	AMY-101	Cohort controlled trial	Safety and effectiveness	[80]
Anti-VEGF	Bevacizumab	Randomized and controlled trial	Safety and effectiveness	[47]
Anti-GM-CSF	Lenzilumab	Randomized and controlled trial	Safety and improvement of clinical outcomes	[60]

Abbreviations: Ab, antibody; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; JAK, Janus kinase; VEGF, vascular endothelial growth factor.

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pathway, which acts on various downstream cytokines.[58] In this regard, targeting GM-CSF may mitigate the hyperinflammatory state for curbing lung damage. One recent single-centre prospective cohort clinical study showed that administration of Mavrilimumab, an anti-GM-CSF monoclonal antibody, improved clinical outcomes in thirteen non-mechanically ventilated patients with COVID-19 pneumonia and hyperinflammation.[59] Another randomized, placebo-controlled clinical trial demonstrated that Lenzilumab, another anti-GM-CSF monoclonal antibody, was safe and effective for the treatment of severe COVID-19.[60] Currently, there are twelve clinical trials underway to explore a novel approach for the treatment of COVID-19 through targeting of human GM-CSF.

Conversely, GM-CSF, a critical homeostatic factor in lung alveoli, is required in alveolar macrophage homeostasis and lung pathogen clearance to maintain pulmonary function.[61,62] Detailed studies have demonstrated that GM-CSF has been shown to be protective in different preclinical models of pneumonia-associated lung injury and, as compassionate treatment, to improve oxygenation and lung repair in six patients with pneumonia-associated ARDS.[63] Previous investigation demonstrated GM-CSF involvement in lung surfactant homeostasis in GM-CSF-deficient mice.[64] Given the mechanism of action of GM-CSF on neutrophils accumulation in the lung, acute lung injury has been reported in a patient with significant pulmonary comorbidities following the use of GM-CSF.[65] Therefore, monitoring of this immuno-pathological complication together the viral infection progression will be needed with GM-CSF administration in the COVID-19 therapeutic setting. Currently, nine clinical studies using GM-CSF have been performing for prevention and treatment of COVID-19.

Given the immunomodulatory and tissue regenerative properties of mesenchymal stem cells (MSCs), they can secrete a variety of cytokines and growth factors (eg, HGF) and such cells could be used as biological agents for treatment and management of patients with COVID-19 at the time of virus outbreak. Currently, clinical trials using MSCs products as a therapeutic option are ongoing worldwide but potential challenges are numerous. In our recent Commentary to the Drug Design, Development and Therapy, a few important facets, including MSCs fate after systemic infusion, safety issue, MSCs homing and MSCs resistance to the disease microenvironment, would be critically analyzed and addressed for the development of the more safe and effective MSC-based approaches for COVID-19.[66]

Conclusions and Perspectives

There are more and more clinical trials that are being conducted with biological therapeutic agents for treatment and management of patients with COVID-19. Controlled trials of biological agents are needed to determine their safety and effectiveness for therapeutic perspectives. To help speed the clinical research, the data collected in the present study from current clinical studies may contribute to a better understanding of the mechanisms of action of the biological therapeutic agents. Recently published studies have shown that some therapeutic agents play both pathological and beneficial roles in the management of patients with COVID-19 and mixed results have also been obtained in these completed COVID-19 clinical trials (Table 2). We appreciate these clinical trial efforts currently underway for different aspects of COVID-19. While clinical improvement in COVID-19 is the primary outcome measure in most clinical trials of biologics, additional work needs to address safety- and efficacy-related matters in large studies for optimum clinical outcomes. The bottom line is that biological therapeutic agents appear to be safe and clinical efficacy is required more studies. We hope that more and more favorable outcomes of ongoing clinical trials are expected to be observed as quickly as possible.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interests in this work.

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