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REVIEW

Perspectives on the use and risk of adverse events associated with cytokine-storm targeting antibodies and challenges associated with development of novel monoclonal antibodies for the treatment of COVID-19 clinical cases

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ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the novel coronavirus disease 2019 (COVID-19) pandemic that lacks globally accessible effective antivirals or extensively available vaccines. Numerous clinical trials are exploring the applicability of repurposed monoclonal antibodies (mAbs) targeting cytokines that cause adverse COVID-19-related pathologies, and novel mAbs directly targeting SARS-CoV-2. However, comorbidities and the incidence of cytokine storm (CS)-associated pathological complexities in some COVID-19 patients may limit the clinical use of these drugs. Additionally, CS-targeting mAbs have the potential to cause adverse events that restrict their applicability in patients with comorbidities. Novel mAbs targeting SARS-CoV-2 require pharmacological and toxicological characterization before a marketable product becomes available. The affordability of novel mAbs across the global economic spectrum may seriously limit their accessibility. This review presents a perspective on antibody-based research efforts and their limitations for COVID-19.

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Introduction

With the exception of the swine influenza pandemic of 1918, the novel coronavirus disease 2019 (COVID-19) pandemic has thus far caused one of the greatest humanitarian and public health challenges worldwide. The severe damage inflicted on the world economy by the COVID-19 pandemic has initiated a global recession precipitated by the necessity to place at least one-third of the global population under lockdown.[1,2] The origin of the pandemic has been linked to a "wet market" that sold seafood, wild animals, and/or their products in Wuhan, Hubei Province, China. Following the initial outbreak of the disease, the Chinese Center for Disease Control and Prevention isolated the novel virus from a bronchoalveolar lavage sample taken from a patient in Wuhan.[3] The virus was later confirmed to be a novel enveloped RNA coronavirus (CoV); however, little was known then about the gravity of the public health disaster that was to follow [3]As of 28-February -2021, approximately 114 million COVID-19-positive cases have been reported globally, and more alarmingly, more than 2.5 million lives have succumbed to COVID-19.[4]

While the standard of care is continuing to evolve, there is currently no cure for COVID-19. As of 2 March, 2021, monoclonal antibodies – Bamlanivimab, Casarivimab – Imdevimab combination have been granted Emergency Use Authorization approval from the US-FDA, of which two are monoclonal antibody (mAbs) based treatment options for the nonhospitalized patients with mild to moderate COVID-19[5]). Whereas three vaccines have been authorized by the CDC, as of 2 March, 2021,[6] however, worldwide availability of efficacious vaccines will likely take several years before the pandemic may be stopped in its tracks.[7] Sustained efforts from many researchers worldwide are rapidly yielding prospects of successful vaccines, antiviral agents, and potentially efficacious supportive therapies.[8–10]

Scientific advancements over the past several decades have proven that antibody-based therapeutics can be a panacea for many serious diseases. Historically, convalescent blood-based products (CBPs) have been used effectively during pandemics; there is evidence of clinical successes based on a meta-analysis of CBP usage to control the Spanish flu stands as a positive testament.[11] Although the advent of antibiotics has supplanted the use of CBPs for bacterial disease outbreaks, the successful use of immunotherapeutic strategies was yet again evidenced during the H5N1 swine flu pandemic of 2009.[12] However, the inconclusive therapeutic benefits of CBPs for the MERS, SARS, and Ebola outbreaks cast doubts on their usage.[11] More recently, considering the development of immensely powerful *in vitro* screening and selection methods, in addition to the availability of engineered mAbs, several unmet medical needs and a number of diseases, particularly cancer, can now be successfully treated using an immunotherapeutic approach.[13] As such, there is sustained interest in antibody-based therapeutics as an option for treating dangerous infectious diseases, including those that eventually lead to pandemics. The successful treatment of the COVID-19-stricken ex-president of the United States – Donald Trump – who received a cocktail of SARS-CoV-2-specific mAbs, and thereafter other high-profile COVID-19 patients, reinforces the faith in ongoing research efforts on this treatment option.[14–16] However, this approach

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has serious limitations that may impede clinical development and universal applicability, particularly when fighting recently emerged viral pandemics. [17] The advantages and disadvantages of development and application of mAb-based therapeutic strategies for tackling a pandemic is summarized under Table 1

This review presents asummarized perspective on the background of SARS-CoV-2, comorbidities in COVID-19 patients, CS and adverse events associated with mAbs targeting Cytokine Storm (CS), when administered for the clinical management of COVID-19 patients with preexisting illnesses.

Virology, pathogenesis, and clinical symptoms

As a virus group, CoVs possess a linear positive-stranded RNA genome of ~30 kb in size and ~125 nm in diameter. There are four known CoV genera. α-Coronaviruses include human coronavirus NL63 and viruses that cause porcine epidemic diarrhea, canine coronavirus disease, and transmissible gastroenteritis.[18] β-Coronaviruses include SARS-CoV, MERS-CoV, mouse hepatitis virus, and SARS-CoV-2, and γ- and δ-coronaviruses are associated with avian diseases and porcine deltacoronavirus, respectively.[19–21] Although most CoVs have been identified in animals, three have successfully crossed into humans. Those viruses that have crossed into humans, and particularly SARS-CoV, have been associated with potentially fatal pneumonias and rapidly spreading respiratory infections,[22] MERS,[23] and SARS-CoV-2.[24]

It is widely accepted that SARS-CoV-2 enters host cells by binding to the angiotensin converting enzyme-2 (ACE2) receptors in the nasal epithelium, and mucous membrane of the lower respiratory tract and lungs; however, other host factors such as the presence of sialic acid in the host cell membranes also positively influences S protein–receptor interactions. Additionally, CoVs penetrate host cells at neutral- or low-pH environments, followed by passage of the nucleocapsid and release of the viral genome. This event initiates the virus replication cycle, which leads to the viremic phase of the infection.[25,26] Clathrin-mediated endocytosis has also been shown to play a role in the mechanism of virus entry into host cells.[19–21,27] Interestingly, both SARS-CoV and SARS-CoV-2 have affinity for the human ACE2 (hACE2) receptor, which facilitates host cell invasion. A furin cleavage site detected within the SARS-CoV-2 S protein is speculated to be the basis for the comparatively more extensive tissue tropism observed with this virus arguably makes SARS-CoV-2 more pathogenic than SARS-CoV.[28]

Many investigations have postulated that, similar to SARS-CoV, the S protein in SARS-CoV-2 is the major pathogenic factor responsible for attachment preceding host cell invasion.[29] To further lend support to this hypothesis, these authors have used computational studies and identified 24 stretches of conserved peptides within the SARS-CoV -2-derived S protein.[29] These conserved peptides also appear to be common across other related CoV strains. Of these peptide stretches, 20 bear important B and T cell epitopes that are predicted to be relevant for immunoprotection.[29] The pathogenicity of SARS-CoV-2 is also explained by the partially open conformation of S protein trimers. SARS-CoV and SARS-CoV-2 have a shared sequence homology of 75%, and additional findings suggest that neutralizing antibodies against the former may cross-protectively prevent host cell attachment and entry of SARS-CoV-2.[28,30,31] Compelling evidence from numerous COVID-19 vaccine research studies have corroborated the immunogenicity and potential immunoprotective properties of several epitopes located within the S protein.[32,33] Moreover, structural analysis and studies into the molecular pathogenesis of SARS-CoV-2 suggest the presence of two virus-binding hotspots in the S protein receptor-binding domain (SARS-CoV-2-RBD). Additionally, the ACE2 binding ridge within RBD has a compact conformation and is accompanied by several residue changes that indicate the significantly higher binding affinities of SARS-CoV-2-RBD to the ACE2 receptor. The uniqueness of RBD is considered a major factor contributing to the infectivity and host range of SARS-CoV-2.[34,35] Early investigations that focused on identifying anti-SARS-CoV-2 neutralizing antibodies suggested that RBD-binding antibodies are strongly correlated with virus neutralization capability.[36,37] Collectively, these studies explain the predominant molecular clues that elucidate the efficiency with which both viruses can easily spread among humans. In summary, these findings suggest that the S protein RBD is among the most suitable antigenic candidates, and it is being targeted for generating potentially neutralizing antibodies against SARS-CoV-2.

The prominent clinical symptoms in patients with COVID-19 include fever (98%), cough (76%), and myalgia or fatigue (44%).[38,39] Less prominent symptoms include sputum production (28%), headache (8%), hemoptysis (5%), and diarrhea (3%). Furthermore, 50% of COVID-19 patients develop dyspnea, which has been consistently reported alongside fever and cough.[38,39] Additionally, atypical symptoms, such as headaches, confusion, rhinorrhea, sore throat, delirium, hemoptysis, gastrointestinal bleeding, vomiting, and

Table 1. Summary of advantages and disadvantages of mAb-based therapeutic strategies.

	Advantages	Disadvantages	References
Monoclonal Antibodies (mAbs)	(a) Specificity in molecular interactions and engagement with therapeutic targets (b) Long plasma half-life facilitating fewer dosing repeat (c) Shorter timelines for testing and approval when compared to small therapeutic molecules. (d) Marked improvements in respiratory function in COVID-19 patients. (e) Rapid defervescence.	(a) Possible resistant viral mutations can alter mAb affinities and efficacy (b) Adverse drug reactions are severe and often life-threatening (c) Varying bioavailabilities may affect effectivness (d) Affordability and accessibility across global economic spectrum and lower income countries is questionable	112,167–171

diarrhea have been reported in patients with comorbidities such as heart disease, preexisting lung disease, diabetes mellitus, severe obesity, chronic kidney, or liver disease, and compromised immune system.[40–44] In the following sections, we review the comorbidities associated with patients with COVID-19 and emphasize on neurological and pediatric patients.

Comorbidities associated with COVID-19

With no established standard of care and most treatment choices being either supportive or investigational, the most worrying aspect of the COVID-19 pandemic is the significant incidence of comorbidities in patients requiring intensive care.[45,46] Early reports of pervasive mortalities in elderly patients with comorbidities (8 out of 10) such as diabetes and heart and lung diseases underscored the apparent vulnerability of elderly individuals.[47,48] Other clinically significant comorbidities include but are not limited to chronic lung disease or moderate-to-severe asthma; serious heart conditions; immunosuppression, including cases of poorly controlled human immunodeficiency virus (HIV) or AIDS; prolonged use of corticosteroids; and severe obesity (body mass index ≥40).[49] During the course of the ongoing pandemic, several studies have focused on cohorts of COVID-19 patients who died from severe pneumonia.[50] In a cohort study of 1,591 COVID-19 patients from Italy, the median age of the patients was 63 (56–70) years; 1,304 (82%) were male, and 509 (49%) had hypertension.[51] Similarly, in another cohort study conducted in the USA, the median age of the patients was 63 years; 60.6% were males.[52] In this study, the most common comorbidities were hypertension (n = 3,026, 56.6%), obesity (n = 1,737, 41.7%), and diabetes mellitus (n = 1,808, 33.8%).[52] Ghisolfi et al. presented an intriguing analysis of predicted COVID-19 fatality rates, wherein higher case fatality rates were more likely to be seen in higher-income countries.[53] An analysis by Hashim et al. based on a survey of COVID-19 mortalities across 93 countries provided compelling evidence on the association between higher case mortalities and preexisting health complications such as Alzheimer's disease, lung cancer, asthma, and chronic obstructive pulmonary disease in addition to advancing age.[54] These findings reaffirm the similarities between COVID-19 and MERS and SARS with respect to the occurrence of more serious clinical outcomes in individuals with co-existing conditions.[55–57] These authors also reported that men exhibit a higher susceptibility to these infections than women. Overall, these findings suggest that emergency medical support and treatment choices for COVID-19 patients with chronic comorbidities remain a serious challenge.[49] This may complicate the standard of care for patients with COVID-19 who are receiving multiple prescriptions for their preexisting medical conditions.

Vulnerability of children

Although COVID-19 is frequently asymptomatic in children, some of the pathological manifestations that have been observed thus far are quite different from those observed witnessed in adults, which warrants further investigation. One of the most comprehensive studies on pediatric COVID-19 reported clinical symptoms that are considerably different from those observed in adults, include vomiting, colic, and diarrhea. Of the 58 children investigated in one study, 29 developed shock and required intensive clinical interventions such as inotropic support and fluid resuscitation.[58] Although most cases of pediatric COVID-19 were initially mild, a more severe clinical presentation termed "multisystem inflammatory syndrome" in children (MSI-C) has since been documented. Furthermore, recent reports suggest that some children who recover from SARS-CoV-2 infection develop pediatric MSI-C, which is characterized by clinical presentations such as Kawasaki disease shock syndrome, toxic shock syndrome, myocarditis, and macrophage activation syndrome.[59–61] A recent report indicated that a low number of pediatric COVID-19 cases were associated with severe pulmonary complications that required intensive care during hospitalization.[62]

COVID-19 is spawning a neurological pandemic

Recent clinical observations indicated that some severely ill and recovering COVID-19 patients may manifest neurological signs,[63–65] including minor central nervous system manifestations such as headache and dizziness and more serious symptoms such as impaired consciousness, ataxia, acute cerebrovascular disease, and epilepsy. A study of 37 patients with COVID-19 in France reported neurological manifestations of altered consciousness (73%), confusion (37%), and agitation (19%).[66] The most striking pathological finding observed in 54% of the patients was intracerebral hemorrhagic lesions.[66] Peripheral nervous system manifestations such as hypogeusia, hyposmia, neuralgia, and skeletal muscular symptoms have also been reported.[63–65] A recent hypothesis attributed more serious neurological outcomes such as acute necrotizing encephalopathy (ANE),[67] ischemic stroke,[68] encephalopathy,[69] meningoencephalitis,[70] and Guillain–Barré syndrome (GBS)[71] to CSs and/or a compromised blood–brain barrier that developed during disease progression. However, unlike in the case of SARS-CoV, there is still no empirical evidence that has definitively corroborated the entry of SARS-CoV-2 into the brain. Clinical studies involving patients with SARS-CoV infection have shown the presence of virus particles in brain specimens; these particles are mostly localized in neurons.[72] Unlike SARS-CoV, the detection of viral RNA in the cerebrospinal fluid has thus far been demonstrated in only a single-case report in which SARS-CoV-2 infection was associated with ANE.[73] Based on statistical data from MERS and SARS as a prediction model for the association of neurological involvement and infection with SARS-CoV-2, the possibility of a neurological pandemic is imminent.[74] This finding adds to the uncertainties that could have a bearing on the prognosis of patients with COVID-19. In the near future, it is likely that neurological and other complications will further aggravate the burden on healthcare systems due to the extra patient care and management needs.

Cytokine storm, comorbidities and COVID-19

In COVID-19 patients, the severity of the disease correlates well with the onset of exaggerated immune response that is characterized by higher concentrations of circulating cytokines.[75,76] The trigger for such CSs (CS) is an uncontrolled

immune response resulting in continuous activation and expansion of effector immune cells like lymphocytes, and macrophages. The exaggerated activation induces these cells to produce enormous amounts of pro-inflammatory cytokines and related molecules thus resulting in dire immunological events. The severity of disease manifestation is consistently attributable to the actions of heightened levels of circulating pro-inflammatory cytokines – IL-1, IL-6, IL-18, IFN-γ, and TNF-α.[77] Assessment of cytokine levels in a cohort of 41 COVID-19 patients indicated high circulating levels of IL1β, IFNγ, IP10, and chemokine – MCP1.[24] These cytokines along with related pro-inflammatory molecules are predominantly linked to activation of T-helper-1 (Th1) cell responses[24] . Especially patients with excessive circulating levels of cytokines and chemokines – G-CSF, IP-10, TNFα, MCP1, MIP1 required intensive care hospitalization clearly associating the link between CS and disease severities.[24] Whereas CSs are not novel to COVID-19 infections, they have previously been observed during SARS-CoV[78] and MERS-CoV pandemics as well.[79] The uniqueness of CS during COVID-19 infection is an increased secretion of T-helper-2 (Th2) related cytokines (viz.) – IL4 and IL10, which are known to suppress inflammation. Such a phenomenon was not observed in SARS-Co-V patients.[24] Moreover, numerous multi-centric retrospective studies have observed that increases in the pro-inflammatory cytokine IL-6 correlating with increased severity in COVID-19 patients.[80–82] Alarmingly, eight critically ill pediatric (2 months to 15 cases) COVID-19 cases in China demonstrated increased levels of the cytokines – IL-6, IL-10, and IFN-γ[83] . This has been further corroborated in similar studies done elsewhere.[84]

While CSs have been previously reported during SARS-CoV and MERS, this is neither novel nor unique to Co-V infections alone.[85] Cytokine storms have been reported in several viral infections including influenza infection caused by H5N1[86] H1N1 viruses.[87] While the severity of COVID-19 disease manifestation is more commonly seen in immunosuppressed individuals, and elderly patients with history of obesity, diabetes, renal failure, lung diseases and other comorbidities, the molecular undercurrents that contribute to disease severity is beginning to be understood.[88] For instance, obese COVID-19 patients with an ongoing CS additionally release a larger subset of pro-inflammatory molecules – particularly, the adipokines from their visceral fat deposits.[89] Adipokines are known to affect the immune response, impair chemotaxis, and alter the differentiation of macrophages. The imbalance between the levels of anti- and pro-inflammatory adipokines produced from thoracic and visceral fat deposits are well linked to other comorbidities including but not limited to cardiovascular disease,[90] nonalcoholic fatty liver disease, and type 2 diabetes.[91] Adipose tissue also expresses the cytokine – IL-6 receptor, as well as produces IL-6, which, obviously may be contributing factors to exaggerated disease manifestation in COVID-19-stricken obese patients.[92]

Abnormalities in blood coagulation pathways have also been reported in some COVID-19 patients leading to the coining of the term – COVID-19-associated coagulopathy (CAC).[93–95] Elevated circulating levels of prothrombin, fibrinogen and D-dimer, in addition to elevated pro-inflammatory markers such as C-reactive protein (CRP) and IL-6, are now widely accepted as the markers of CAC.[96] Concomitantly, a heightened risk for inflammatory events, CS and CAS due to increased levels of IL-6 and CRP levels explained the linkage to increased mortalities in diabetic COVID-19 patients.[97]

The advancing age and disease severity is another undisputed factor in COVID-19 disease severity. This is explainable by a differential expression of toll-like receptors (TLRs) with advancing age. TLRs in the host tissue bind and interact with components from invading pathogens and trigger host defense responses. However, with advancing age, the changes in TLR expression and polymorphism are implicated in altered and often inadequate response to vaccines in older adults. The paradoxical increases in basal levels of pro-inflammatory cytokines – IL-8 and IL-6 which are amongst the important components of the CS during COVID-19, further lending support to altered disease manifestation with advancing age.[98–100]

Interestingly, in the pediatric cases of COVID-19, prominently pathological manifestations resemble Kawasaki-like disease. Recent investigations point to differences in T cell subsets, elevated interleukin (IL)-17A levels coinciding with high levels of matrix metalloproteinase-1 (MMP-1), and MMP-10 levels suggesting that arterial inflammation is a prominent pathological feature in this sub-population.[101] Additionally, significant neurological characteristics were documented in a pediatric COVID-19 patient in which the symptoms appeared to correlate with a CS and reduced levels of brain-derived neurotrophic factor.[102]

Emerging approaches with antibody-based treatments

Given the rapid generation of new research data, COVID-19 treatment is a fast-evolving topic. In the absence of efficacious antiviral drugs at the start of pandemic, much of the options were supportive or adjunct therapies. However, recently, US-FDA has granted emergency use authorization approvals for more treatment options, of which two are novel virus-neutralizing mAbs. The most current updates on the standard of care for COVID-19 are available at NIH.[5] Approximately 3,600 clinical trials are currently underway worldwide. Despite this however, the most urgent missing link in the effective control of the COVID-19 pandemic is an effective and affordable antiviral drug of choice as well as supportive therapy for the clinical management of different stages of the disease.[103] At present, it is widely believed that an effective treatment for SARS-CoV-2 infection will emerge from a combination of the following strategies: repurposing previously approved and well-characterized antiviral drugs and/or novel and specific therapeutic molecules that directly disrupt different stages of the viral life cycle; deactivating receptor proteins located on host cells; administering fusion inhibitor peptide and protease inhibitors; administering neutralizing antibodies against SARS-CoV-2; and administering anti-ACE2 mAbs.[104–106]

Ejaz et al. have comprehensively reviewed ongoing clinical trials for different COVID-19 treatments.[107] Other researchers have extensively reviewed repurposed antiviral drugs,[108,109] novel antiviral agents,[110,111] and SARS-CoV-2-targeting mAbs.[112–114] The present review partly focuses on the status, merits, and challenges associated with mAbs targeting CSs, and challenges associated with the development of novel antibodies targeting SARS-CoV-2.

mAbs targeting components of the cytokine storm and related pro-inflammatory mediators

Cytokines are diversified groups of small proteins that mediate intercellular signaling and communication by evoking various specific cellular responses as part of the innate or adaptive immune response.[115] To achieve this, cytokines act through paracrine, endocrine, and autocrine activities and receptor binding on target cells. For instance, some of the specific responses arising from cytokine stimulation include cell proliferation and differentiation, immune and inflammatory reactions, and angiogenesis.[115] Although most of these effects are desirable, the excessive production of cytokines such as interferons (IFNs), interleukins (ILs), and TNF-α, along with other related groups of molecules such as chemokines and colony-stimulating factors (CSFs) may constitute "CSs," which often lead to pathological and clinical manifestations.[116] Some of these effects may become life-threatening or are associated with unfavorable clinical outcomes in patients.[116] Typically, these exaggerated inflammatory responses rapidly involve multiple organs, ultimately leading to complications such as hyperthermia, widespread fibrinous microthrombosis or disseminated intravascular coagulopathy (DIC), and eventually multiple-organ failure. Genome-wide association studies (GWAS) have provided a deeper insight into the individual differences linked to CSs. GWAS analyses suggest that polymorphisms within toll-like receptor 4 might play a role in increased susceptibility to certain pathogens and the severity of disease manifestation in some individuals. In fact, GWAS have identified a strong association between increased susceptibility to bacteremia, tuberculosis, and severe malaria in patients from The Gambia, Hong Kong, Kenya, Malawi, and Vietnam.[117] As noted in some studies, polymorphisms in the cytokine-inducible SRC homology 2 domain protein may negatively impact cytokine signaling.[118] A previous GWAS showed that certain variants in IFN-λ3 are associated with better treatment outcomes and spontaneous resolution of hepatitis C virus infections in patients of European ancestry compared with that in patients of African ancestry.[119] Interestingly, comparative studies between patients with H5N1 and H1N1 infection reported elevated levels of several cytokines and related molecules, including MCP-1 (also known as CCL2), IFN-γ-inducible IP-10, MIG protein, and IL-8.[120] In this study, upregulated cytokine expression during H5N1 infections was strongly correlated with adverse clinical outcomes. As a result of CSs, pathogen-induced pulmonary injury often progresses to acute lung pathology or its more severe form, acute respiratory distress syndrome.[121] These complications often warrant intensive care during hospitalization of patients with more severe SARS-CoV-2 syndromes.[121] One of the key drivers of proinflammatory activities during lung injury in patients is IL-1β, which is often associated with downstream mechanistic events that ultimately manifest in the form of severe bronchoalveolar pathology and edema.[122] With respect to excessive cytokine release, IL-1β and TNF-α are the two perpetrator cytokines that regulate downstream molecular processes that ultimately cause severe damage to endothelial cells and associated extravasation of inflammatory cells as well as the production of secondary cytokine waves. This elevated inflammation causes widespread damage to tissue parenchyma and epithelial cells, which leads to the systemic release of large amounts of secondary cytokines, resulting in multiple organ dysfunction syndrome.[123] Previously, CSs in six healthy volunteers in a clinical trial resulted in the need for emergency and intensive medical care.[124] This observation warrants that new COVID-19 drugs under clinical investigation must be closely monitored for such adverse events. Small-molecule drug – Anakinra, an IL-1 receptor antagonist and several mAbs that are discussed in the later sections and listed in Table 2 can manage COVID-19 associated CSs and therefore alter the course of disease and outcomes.[112]

Initial investigations in China have suggested that IL-6 is a key driver of dysregulated inflammation in COVID-19 patients, thereby implicating IL-6 as a pharmacological target for the treatment of SARS-CoV-2 infection.[172,173] Other cytokines and growth factors have also been evaluated for their potential as drug targets, including granulocyte-macrophage CSF (GM-CSF),[174] TNF-α,[175] vascular endothelial growth factor (VEGF),[176] and IL-1β.[177] The significance of CSs (Figure 1) during COVID-19 has been reviewed in greater detail elsewhere.[76,121]

Using therapeutic mAbs to target CSs is now recognized as a disease course-altering and viable immunotherapeutic strategy for the clinical management of critically ill patients with COVID-19, as evidenced by several clinical trials (summarized in Table 2 and Figure 2). Humanized mAbs possess high epitope specificity and clinically favorable pharmacokinetic properties and are therefore ideal therapeutic tools for tackling the pathological and clinical effects associated with CSs.[75] Recently, a clinical trial demonstrated that lenzilumab, a class IgG1 kappa humanized mAb targeting CSF2/G-CSF, is associated with improved clinical outcomes in patients with SARS-CoV-2 infection with preexisting conditions.[178] Similarly, clinical investigations involving tocilizumab, an IL-6-targeting humanized mAb, showed remarkable clinical progress in 91% of patients with COVID-19.[112] Interestingly, most of these patients only received a single dose which was followed by marked improvements in respiratory function, rapid defervescence, and successful discharge.[112] However, cytokine-targeting mAbs are also documented to be potentially associated with adverse events.[169] This may impact both the outcomes of clinical trials and post-approval use in critically ill COVID-19 patients, particularly those with comorbidities.

Adverse events caused by cytokine and related pro-inflammatory mediators-targeting mAbs

A questionnaire-based survey involving 1,355 patients who were undergoing treatment with cytokine-targeting mAbs for immune-mediated inflammatory diseases identified several risks associated with the immunotherapy.[169] Those patients were treated with various therapeutic mAbs including adalimumab, canakinumab, infliximab, rituximab, sarilumab, and tocilizumab. In several patients, the treatment was associated with minor adverse events such as respiratory disorders, nervous system disorders, or cancer in patients with no comorbidities.[169] However, in patients with preexisting comorbidities such as inflammatory rheumatic diseases, 49% (665/1,355) reported adverse drug reactions (ADRs).[169] In total,

Table 2. Summary of ongoing salient COVID-19 clinical trials with mAbs-targeting cytokine storms and the known adverse events of these mAbs from other approved clinical uses.

Sl. no	Name of the innovator brand of the mAb	Target mechanism	Status in clinical trial	Name of the approved biosimilars (country of origin)	Salient adverse effects	References
1	HUMIRA (Adalimumab)	Inhibits tumor necrosis factor-alpha	(1) Adalimumab for coronavirus in community care: Phase 2 (2) Evaluation of adalimumab regarding clinical symptoms, including respiratory distress, oxygen saturation, and lung involvement in patients with COVID-19: Phase 2	(1) Amjevita (US)/ Amgevita (EU)/ Solymbi (EU) (2) Cyltezo (Germany) (3) Idacio/Kromeya (Germany) (4) Mabura (India) (5) Mraldi (S. Korea, USA) (6) Halimatoz (EU)/ Hefiya (EU)/ Hyrimoz (EU/US) (7) Exemptia (IND)	Lymphoma of the liver, spleen, and bone marrow; heart failure	125–128
2	Avdoralimab	Binds and blocks C5a receptors	(1) Avdoralimab, an anti-C5aR antibody in patients with COVID-19 severe pneumonia: Phase 2	None	Decreased lymphocyte count, urinary tract infections	129,130
3	AVASTIN (Bevacizumab)	Targets vascular endothelial growth factor	(1) Bevacizumab in severe or critically severe patients with COVID-19 pneumonia: RCT (BEST-RCT)– (2) Bevacizumab in severe or critical patients with COVID-19 pneumonia (BEST-CP): Phase 2 COMPLETED (3) Trial evaluating the efficacy and safety of bevacizumab (Avastin®/Zeribev®) in patients with COVID-19 infection, nested in the Corimmuno-19 cohort (CORIMMUNO-BEVA): Phase 2	(1) Mvasi (USA) (2) Lumiere (Argentina) (3) Cizumab (India) (4) Bevax (Argentina) (5) Zirabev (USA) (6) Bevacirel (India) (7) Avegra (Russia)	Serious bleeding, severe high blood pressure, GI perforation, severe stroke, or heart problems	131–135
4	Clazakizumab	Binds and blocks human interleukin-6	(1) Study on the use of clazakizumab in patients with life-threatening COVID-19 infection: Phase 2 (2) Clazakizumab vs. placebo for COVID-19 infection: Phase 2 (3) Randomized placebo-controlled safety and dose-finding study for the use of clazakizumab in patients with life-threatening COVID-19 infection: Phase 2 (4) Use of clazakizumab in patients with life-threatening COVID-19 infection: Phase 2 (5) Clazakizumab vs. placebo for COVID-19: Phase 2 (6) A randomized placebo-controlled safety and dose-finding study for the use of the Il-6 inhibitor clazakizumab in patients with life-threatening COVID-19 infection: Phase 2	None	Under investigation	136–142
5	REMICADE (Infliximab)	Inhibits tumor necrosis factor-alpha	(1) Phase 2 trial of infliximab in COVID-19: Phase 2 (2) Cohort of patients with inflammatory bowel disease during the COVID-19 pandemic (IBD-COVID-19)	(1) Remsima/ Inflectra/ Flammegi (S. Korea, USA) (2) Ixifi (S Korea, USA) (3) Infimab (USA) (4) Infliximab BS (Japan) (5) Zessly (Switzerland) (6) Flixabi (EU)/ Renflexis (US) (7) Avsola (Infliximab-axxq)	Immunosuppression in elderly patients and hepatosplenic T cell lymphoma among younger adults	143–147

(*Continued*)

Table 2. (Continued).

Sl. no	Name of the innovator brand of the mAb	Target mechanism	Status in clinical trial	Name of the approved biosimilars (country of origin)	Salient adverse effects	References
6	TAKHZYRO (Lanadelumab)	Inhibits plasma kallikrein	(1) Lanadelumab for treatment for COVID-19 (COVID_LAN): Phase 1/2 (2) Lanadelumab in participants hospitalized with COVID-19 pneumonia: Phase 1 - WITHDRAWN	None	Injection-site reactions and upper respiratory infection	148–150
7	ILSIRA (Levilimab)	Interleukin 6 receptor antagonist	(1) Clinical trial of the efficacy and safety of levilimab (BCD-089) in patients with severe COVID-19 (CORONA): Phase 3 – COMPLETED	None	Under investigation	151,152
8	ARTLEGIA (Olokizumab)	Binds and blocks human interleukin-6	(1) Study of the efficacy and safety of a single administration of olokizumab vs. placebo in addition to standard treatment in patients with severe acute respiratory syndrome coronavirus 2 infection (COVID-19): Phase 2/3 (2) An International, Multicenter, Randomized, Double-blind, Adaptive Placebo-controlled Study of the Efficacy and Safety of a Single Administration of Olokizumab and RPH-104 With Standard Therapy in Patients With Severe SARS-CoV-2 Infection (COVID-19): Phase 2/3 – COMPLETED	None	Increase in hepatic transaminases, neutropenia, and leukopenia	153–155
9	Otilimab	Binds and blocks granulocyte-macrophage colony-stimulating factor	(1) Investigation of otilimab in patients with severe pulmonary COVID-19-related disease (OSCAR): Phase 2	None	Under investigation	156,157
10	SYLVANT (Siltuximab)	Interleukin-6 antagonist	(1) Efficacy and safety of siltuximab vs. corticosteroids in hospitalized patients with COVID-19 pneumonia: Phase 2 (2) Observational study of the use of siltuximab (SYLVANT) in patients with COVID-19 infection who have developed serious respiratory complications (SISCO)	None	Lowers ability to fight infections, upper respiratory tract infection, and gastrointestinal perforation	158–160
11	Canakinumab	Blocks interleukin-1β	(1) Study of the efficacy and safety of canakinumab for CRS in participants with COVID-19-induced pneumonia (CAN-COVID): Phase 3 (2) Canakinumab MAP in COVID-19 pneumonia with CRS (3) Canakinumab in COVID-19 cardiac injury (the Three C Study): Phase 2 (4) Canakinumab in patients with COVID-19 and type 2 diabetes (CanCovDia): Phase 3 (5) Observational study on the use of canakinumab administered subcutaneously in the treatment of patients with COVID-19 pneumonia.	None	Immunosuppression, risk of infection with live vaccine, and allergic reaction	42,161–166

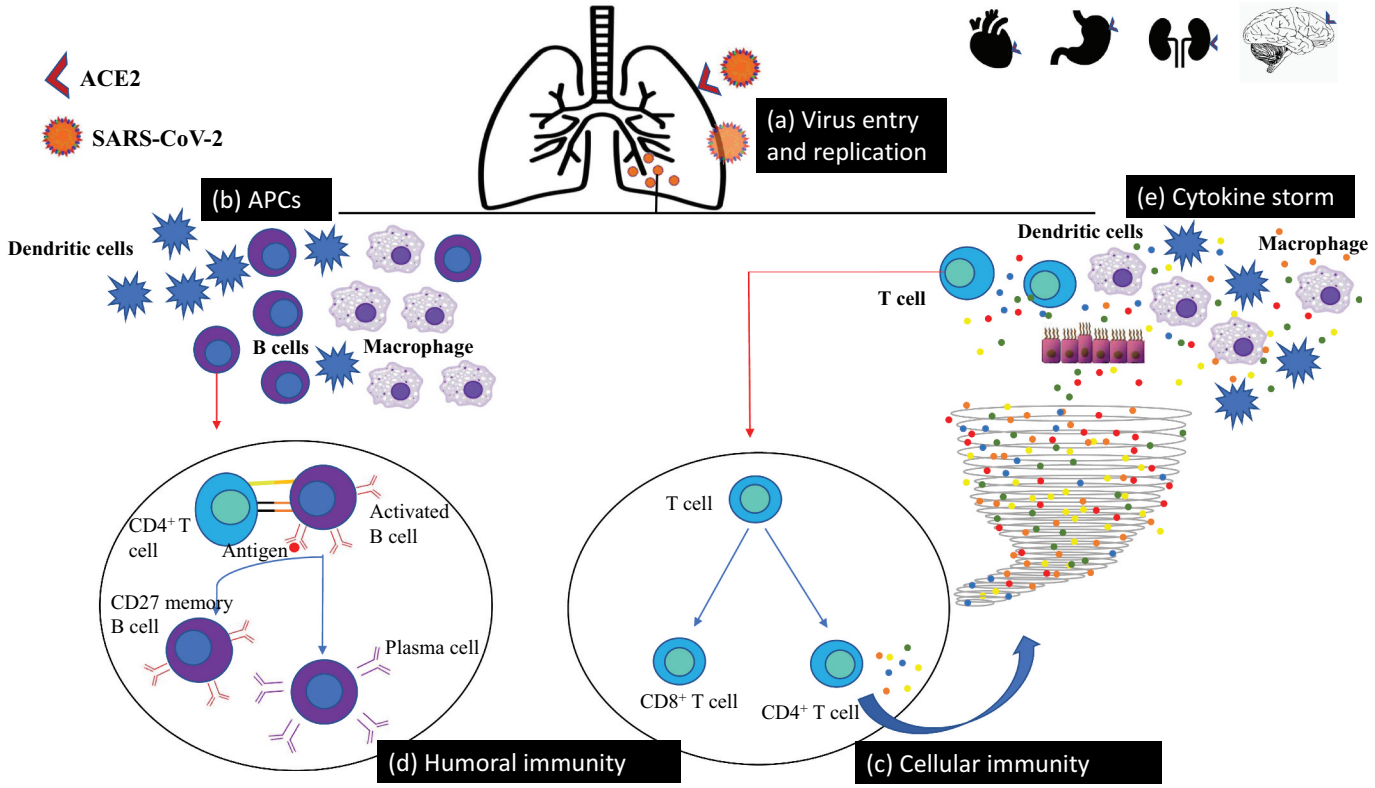

Figure 1. Simplified representation of COVID-19 pathogenic phases. (a) SARS-CoV-2 may pass through the mucous membrane of the nasal epithelium and lungs by binding to the ACE2 receptor and multiply upon entry. (b, c) The entry and replication of the virus primes antigen-presenting cells such as macrophages, B lymphocytes, and dendritic cells, which process and present viral antigens to T cells to trigger cellular immunity. Phagocytes, antigen-specific cytotoxic T cells (CD8+), and T helper cells (CD4+) interact to produce a stream of cytokines (cytokine storm). (d) T helper cells (CD4+) and naive B cells interact and process SARS-CoV-2-specific antigens to mount an antibody response. (e) Simultaneously, large-scale replication of SARS-CoV-2 in the lungs leads to immune cell infiltration, causing an increased level of cytokines in the area of infection. This pathologically manifests as vasodilation and increased capillary permeability, causing a phenomenon called cytokine storm. Vital organs of the body such as the heart, kidney, and brain also express ACE2 receptors at significant levels, which are implicated in the disease manifestation in patients with SARS-CoV-2 infection.ACE2: Angiotensin converting enzyme-2; APCs: Antigen-presenting cells; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2

approximately 1,720 ADRs were reported in patients with comorbidities, with 65% (1,116 ADRs) being musculoskeletal complaints, injection-site reactions, infections, skin reactions, fatigue, and gastrointestinal complications.[169] Moreover, of the patients who developed treatment-associated ADRs, 29 (4%) required hospitalization. Patients with the following ADRs required hospitalization: infections (n = 5), cardiovascular reactions (n = 5), benign or malignant tumors (n = 4), gastrointestinal complaints (n = 2), and skin reactions (n = 2). The authors also reported a higher burden of ADRs in patients with smoking habits and in those with other comorbidities such as respiratory and psychiatric complaints.[169] Collectively, the study findings suggest that ADRs develop during the clinical application of cytokine-targeting mAbs as a treatment option for COVID-19. Thus, ADRs may impede the choice of such immunotherapeutic agents for the treatment of critically ill COVID-19 patients, particularly those with comorbidities. Therefore, the use of cytokine-targeting therapeutic mAbs may require constant monitoring for ADRs, thereby posing a serious challenge to the already stretched healthcare systems during the ongoing COVID-19 pandemic.

The following sections describe each cytokine-targeting mAb currently under evaluation for the treatment of COVID-19 and provide a summary of the current clinical status and a description of the adverse events associated with these mAbs. This information is also summarized in Table 2.

Adalimumab

There are ongoing phase 3 trials investigating the anti-TNF-α mAb adalimumab (Humira®) for the treatment of patients with COVID-19. Humira® was originally developed for the treatment of rheumatoid arthritis and other inflammatory conditions.[125] Notably, Humira® is the innovator brand of adalimumab and has at least six biosimilars.[179] Although the potential benefits of adalimumab as an investigative strategy for COVID-19 treatment cannot be overemphasized, adalimumab is not without associated adverse effects, particularly in patients with comorbidities such as diabetes mellitus and cardiovascular and liver complications. A quick review of the safety information datasheet for adalimumab suggests that refinement of the dosage and other precautions can circumvent potential adverse events associated with the drug.[180] Some adverse events that have been reported in association with adalimumab treatment include a rare type of lymphoma of the liver, spleen, and bone marrow as well as heart failure.[180] Furthermore, adalimumab is potentially associated with hypersensitivity reactions, reactivation of hepatitis B virus in carriers, and adverse neurological and hematological reactions.[180] The co-administration of abatacept with ada-

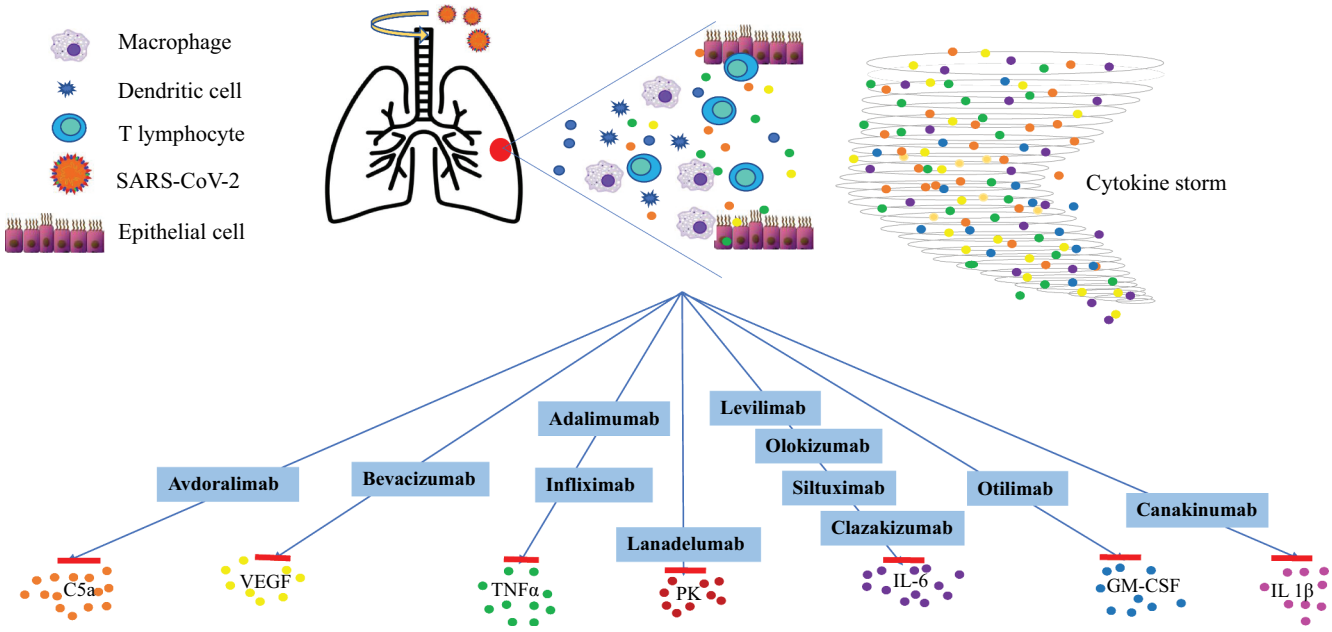

Figure 2. A simplified schematic illustrating the cytokine storm and monoclonal antibody (mAbs) therapeutics targeting cytokines. In response to an infectious stimulus in tissues, lymphocytes, macrophages, dendritic cells, and endothelial cells produce cytokines as a proinflammatory response. The exaggerated output of cytokines, termed as cytokine storm, is observed during illnesses such as viral infections, sepsis, multiple organ failure, and cancer. Targeting the cytokine storm is postulated as a disease-course altering immunotherapeutic strategy for the clinical management of critically ill patients with COVID-19. This illustration depicts a mAb targeting a specific cytokine or growth factor implicated in the pathogenesis of COVID-19.C5a: Complement component 5a; GM-CSF: Granulocyte-macrophage colony-stimulating factor; Interleukin-6; IL-1β: Interleukin-1 *beta*; PK: Plasma kallikrein; IL-6: TNFα: Tumor necrosis factor-alpha; VEGF: Vascular endothelial growth factor

limumab has been shown to lead to serious infections.[180] Based on these observations, a multiplicity of ADRs could become a limiting factor in the clinical use of adalimumab in patients undergoing treatment with abatacept for rheumatoid arthritis.[180] Moreover, adalimumab could potentially revive cytochrome P450 activity in patients. Therefore, it is likely that the clinical use of adalimumab for patients with COVID-19 could enhance the adverse effects of other co-administered drugs whose metabolism is dependent on the cytochrome P450 system.[180]

Infliximab

Infliximab (Remicade®) is a TNF-α-targeting chimeric mAb with at least seven known biosimilars.[179] Infliximab has previously been administered to patients with autoimmune conditions, such as Crohn's disease, rheumatoid arthritis, ulcerative colitis, psoriatic arthritis, and ankylosing spondylitis.[143] Infliximab is associated with serious adverse events in patients who have recovered from tuberculosis or those with the latent form of the disease, those living in regions endemic to histoplasmosis, coccidioidomycosis, and other fungal diseases, and those with diabetes mellitus or immune system problems. Following treatment of patients with COVID-19 with infliximab, adverse events ranging from recurring infections to cardiac failure and ailments, hepatitis B infections, and disorders of the nervous system such as multiple sclerosis and GBS have been reported. These events could be associated with potentially fatal side effects. Considering the potential serious nature of its ADRs, infliximab is contraindicated for use with other TNF-α-based immunotherapies such as anakira, abatacept, and tocilizumab.[143] These limitations severely affect the use of infliximab as a therapeutic choice for critically ill patients with pneumonia, thereby curtailing the wide adoption of the drug as a standard of care for patients with COVID-19.

Bevacizumab

Bevacizumab is mAb that inhibits VEGF, one of the most potent growth factors that increases vascular permeability such as that observed in exudative pneumonia. Bevacizumab has entered the fray of therapeutics undergoing clinical trials for the treatment of patients with COVID-19 with severe pneumonia.[131,132] Furthermore, in combination with other anti-cancer drugs such as fluorouracil, fluoropyrimidine/irinotecan, and fluoropyrimidine/oxaliplatin, bevacizumab is indicated for the treatment of certain malignancies.[133] The innovator brand for the drug is Avastin, which has at least seven biosimilars.[179]

A review of the prescribing information has highlighted several adverse events that may potentially limit the clinical use of bevacizumab.[134] Because of the wide spectrum of such adverse reactions, bevacizumab has been contraindicated in patients undergoing major surgical procedures and in pregnant and breastfeeding women as well as those planning to get pregnant.[134] Adverse events that might lead to treatment discontinuation include hypertensive crisis/hypertensive encephalopathy, congestive heart failure, and thromboembolic events.[134]

Lanadelumab

Lanadelumab is a human IgG1 kappa class mAb that targets plasma kallikrein and thus inhibits the generation of inflammation mediators via the kinin system.[148] The FDA has designated this drug as

a breakthrough therapy for the prevention and management of patients with hereditary angioedema. Pulmonary edema symptoms are often reported during the early stage of respiratory distress in patients with COVID-19, and the kallikrein–kinin pathway, specifically the generation of bradykinin, has been implicated during such pathologies in these patients.[181] As previously mentioned, studies are targeting this pathway with lanadelumab as an investigational option in adult patients with COVID-19 with less than 90% oxygen saturation and an oxygen dependency of at least 3 L/min.[149,150]

A review of Takhzyro's webpage on safety information indicates that injection-site reactions are the most commonly reported adverse effect in patients treated with lanadelumab.[148] Other common side effects include hypersensitivity reactions, dizziness, maculopapular rashes, myalgia, and elevated serum levels of alanine aminotransferase and aspartate aminotransferase. Although lanadelumab has favorable pharmacokinetic properties, the emergence of anti-drug antibodies is possible, which thus far has not been shown to impact the PK profile. However, lanadelumab is also known to produce additive effects when co-administered with C1-esterase inhibitor drugs.[148]

Clazakizumab

Clazakizumab is a genetically engineered and IL-6-targeting humanized IgG1 mAb that typically attains picomolar target affinities.[136] Currently, clazakizumab is under investigation for blocking IL-6 to preserve renal function and minimize renal allograft loss due to antibody-mediated rejection.[136] Clazakizumab is an interesting investigational drug used for the treatment of patients with COVID-19 with severe-to-critically severe pneumonia.[137–140] Recently, clazakizumab was successfully used to treat a 61-year-old patient with COVID-19, and this antibody remains a hopeful choice.[182] Nevertheless, the adverse events associated with the drug remain largely uninvestigated.

Levilimab

Levilimab (BCD-089), which was developed by JCS BIOCAD (Russia), is another IL-6-targeting mAb that has been used for the treatment of several autoimmune disorders, such as rheumatoid arthritis. Although levilimab was previously evaluated for the treatment for various autoimmune diseases, it recently passed phase I clinical studies as a treatment for COVID-19.[183] However, results from the trials of the drug for patients with arthritis remain unavailable. Nevertheless, levilimab continues to be investigated as a treatment choice for patients with severe COVID-19-related pathology.[151]

Olokizumab

Olokizumab is another humanized IL-6-targeting mAb that has been indicated for the treatment of rheumatoid arthritis in patients who are unresponsive to TNF inhibitor therapy.[153] In combination with the IL-1β inhibitor RPH 104, olokizumab is currently being evaluated in clinical trials involving patients with COVID-19.[184] A study evaluating the safety and efficacy of olokizumab in patients with rheumatoid arthritis showed that patients experienced chest pain, pneumonia, perineal abscess, abnormal liver function as per test results, back pain, basal cell carcinoma, mania, and other minor adverse events.[153]

Siltuximab

Siltuximab is an IL-6-targeting chimeric mAb that is currently an immunotherapeutic choice for the treatment of multicentric Castleman disease in human herpesvirus-8 and HIV-negative patients. Siltuximab is currently under investigation in patients with SARS-CoV-2-associated respiratory complications.[158] Some of the serious adverse events associated with siltuximab include immunosuppression that may lead to superinfections along with back and chest pain or tightness, nausea and vomiting, flushing, erythema, irregular heartbeat, breathing difficulties, wheezing, dizziness or light-headedness, lip swelling, skin rash, headache, and itching.[158]

Otilimab

The humanized mAb otilimab, which targets GM-CSF, is under investigation for the treatment of multiple sclerosis and rheumatoid arthritis.[156] Otilimab has emerged as an exciting investigative therapeutic alternative for TNF-α inhibitory drugs in the clinical management of severe COVID-19. However, the efficacy and safety of otilimab remain under investigation.[156]

Canakinumab

Canakinumab is a humanized mAb targeting IL-1β that is indicated for the treatment of systemic juvenile idiopathic arthritis and Still's disease. Currently under investigation as a combinatorial treatment for COVID-19-associated pneumonia,[129,156,161–164,185–189] canakinumab may inadvertently induce cytokine release syndrome.[165] Additional data are expected from ongoing clinical trials in which canakinumab is being tested as combinatorial therapy with several unspecified standard of care agents for the treatment of COVID-19.[185] However, as a result of IL inhibition, canakinumab is known to predispose patients to serious infections and can increase the risk for developing malignancies. Other adverse events include nasopharyngitis, diarrhea, rhinitis, nausea, headache, bronchitis, gastroenteritis, pharyngitis, musculoskeletal pain, vertigo, and weight gain.[165]

Avdoralimab

Avdoralimab is an mAb that targets the complement system and specifically binds and inhibits the C5a receptor, which is often overexpressed in certain tumors. Mechanistically, avdoralimab suppresses T and NK cells and ultimately impedes the activities of programmed death ligand-1 checkpoint blockers.[190] C5a attracts and causes the accumulation of subsets of myeloid-derived suppressor T and NK cells.[129] As an inhibitor of the C5a receptor, avdoralimab may therefore favor the anti-tumor activities of T and NK cells. As an investigational drug of choice for the treatment of COVID-19, avdoralimab is hypothesized to reduce the inflammatory responses

in the lung tissue of advanced cases, potentially alleviating severe pneumonia. Several adverse events have been reported for the combination of avdoralimab and durvalumab, including fatigue, headache, hypertension, diarrhea with colic, urinary tract infections, dyspnea, muscle weakness, decreased lymphocyte counts, and anemia.[129]

SARS-CoV-2-targeting monoclonal antibodies

The entry of SARS-CoV and SARS-CoV-2 into host cells is enabled by the interaction of the RBD of the outer membrane-based S protein and ACE2 receptors on the host cell.[113,186] As the mechanism of pre-entry viral attachment is currently universally accepted and known to involve the S protein, therefore, the S protein has inevitably become a potential target for experimental immunotherapeutic agents. Most of these agents are currently undergoing clinical trials. To date, prior research experience and abundant SARS-CoV-related data continue to inform the identification and development of efficacious SARS-CoV-2-targeting mAbs.[187–189] With advances in research, it will be important to ensure that the novel therapeutic mAbs specifically target the SARS-CoV-2-derived S protein or its recombinant versions. This is important because some potent SARS-CoV-specific neutralizing antibodies such as CR3014 and m396 have demonstrated poor avidity against the SARS-CoV-2 S protein.[104,186] Compelling evidence from many COVID-19 vaccine research studies has corroborated the immunogenicity and potential immunoprotective properties of several epitopes located within the S protein.[32,33] Early investigations on the affinity of neutralizing antibodies to SARS-CoV-2 suggest that RBD-binding antibodies are strongly correlated with the virus neutralization capability.[36,37] Data from an investigation involving three antibody subsets purified from the plasma of convalescing COVID-19 patients demonstrated that virus neutralization is directed at the SARS-CoV-2-RBD.[191] Collectively, these findings suggest that the S protein RBD is among the most suitable antigenic candidates and should be targeted to generate potentially neutralizing antibodies against SARS-CoV-2. Moreover, mAbs typically have a shorter timeline than small molecules (chemical compounds) both in terms of their development, testing, and approval.[168] As research into the pathophysiology of COVID-19 continues to reveal multiple pharmacological targets, bispecific mAbs representing dual specificities, through the simultaneous combination of different antigens or epitopes, could potentially serve as viable immunotherapeutic agents.[40] However, the therapeutic development and application of novel SARS-CoV-2-targeting mAbs or any disease area to produce a marketable drug product requires the fulfillment of several pharmacological and regulatory criteria.[192,193] We discuss some of the key challenges facing these requirements in the later sections of this review.

Pharmacological challenges associated with the development of mAbs as drugs

When hybridoma technology was invented in 1975, it ushered in a new era of mAb development based on antibody generation from a single cell line bearing identical binding affinities for specific targets.[194] Although mAbs were then perceived to be the magic bullet for the treatment of many severe diseases and disabilities, it soon became clear that they were also associated with therapeutically unfavorable pharmacokinetic properties some of which had potential for serious side effects in humans. Furthermore, as most mAbs were of murine origin, the constant region (Fc region) did not ideally engage with the human immune system to fully exert the anticipated pharmacological benefits.[195] With scientific advancements, techniques that manipulated the antibody domains led to the advent of chimeric and humanized immunoglobulins with better druggable properties.[196] The development of SARS-CoV-2-targeting mAbs for the clinical management of COVID-19 therefore require to meet multiple optimization criteria beyond efficacy alone.

As therapeutic molecules, mAbs are typically of xenogeneic origin and are widely known to cause hypersensitivity reactions.[197] In turn, this may additively affect the pharmacokinetic parameters of therapeutic mAbs.[197] Although therapeutic mAbs are systemically administered, their bioavailability is typically poor compared with that of other small molecules.[170] This is possibly due to the proteolytic cleavage of mAbs within the interstitial fluid and lymphatic system. Among the various immunoglobulin isotypes, IgGs have better bioavailability because their Fc region specifically binds to Fc receptors (FcRn) to form the IgG–FcRn complex. This in turn facilitates the release of mAbs back into circulation, thereby ensuring optimal antigen–antibody interactions.[170,197]

mAbs are large therapeutic molecules (~150 kDa) that are typically administered systemically by intravenous, subcutaneous, or intramuscular injections. From the injection site, absorption is achieved through lymphatic uptake, and the distribution is therefore largely restricted to vascular and interstitial fluids. Unlike small molecules, proteolysis is the process of metabolic clearance with excretion largely mediated by the FcRn receptor.[197] The pharmacokinetic behavior of mAbs differs from small molecules and is typically both dose-dependent and non-linear.[198] This makes the pharmacokinetic predictions for mAbs challenging. Target-mediated drug disposition (TMDD) is another key parameter that complicates the development of mAbs as antiviral therapeutic agents. The binding affinities of mAbs to their target, antigen density, and antigen turnover rate could be significantly impacted by the different stages of viremia in patients with COVID-19. The uncertain factors in these patients cause a significant challenge in refining the dose as a way of achieving a therapeutically favorable pharmacokinetic profile. TMDD may also lead to extremely unpredictable and rapid removal of mAbs from circulation at non-saturable dose ranges. Additionally, the PK profiles of mAbs could be mediated by nonspecific mechanisms such as pinocytosis and phagocytosis.[197] All these factors explain the extremely wide range of clearance values (90–560 mL/day) and therefore half-lives (11–30 days) of marketed mAbs. Additionally, it is challenging for mAbs to achieve a favorable distribution from the blood compartment to the peripheral tissue, making it harder to attain therapeutic concentrations. Compartmental (population) analyses of mAb pharmacokinetics have shown small values for intercompartmental clearance (Q = 20–40 mL/h), suggesting that distribution to

peripheral tissues progresses slowly.[199] Challenges faced in the optimization of pharmacodynamics and pharmacokinetic parameters for mAbs are discussed elsewhere in greater detail.[170,197,200] Because of the multiple hurdles that must be overcome for a mAb to obtain approval as a therapeutic agent for the clinical management of patients with COVID-19, information obtained from the development of mAbs for other infectious diseases suggest that TMDD is a key determinant.

Challenges in global affordability of mAbs as drugs of choice

The cost-effectiveness of mAbs for the treatment of critical patients with COVID-19 and in general for the control of the pandemic is another significant concern, particularly in low-income countries; furthermore, whether health insurance providers will agree to insurance cover the treatment remains a concern. For instance, the annual cost for treating a patient with cancer with antibodies is approximately USD 35,000. Although the use of antibodies for critically ill patients with COVID-19 may not be as extensive, the pricing and affordability of mAbs across the economic spectrum is highly questionable.[201] According to a conservative estimate from 2007, pharmaceutical companies typically invest USD 40 USD–$650 M toward the development of mAbs as therapeutic molecules.[202] A retrospective analysis demonstrated that the development of mAbs typically takes approximately 7–8 years and another year for obtaining approvals from the FDA, with a possibility of priority review potentially shaving off approximately 8 months for approval.[203]

Generally, therapeutic mAbs for the treatment of viral diseases demonstrate a high median total cost of care, which could be another prohibitive factor. For example, palivizumab, a mAb targeting respiratory syncytial virus, has a median cost of care ranging from British £1361–£2630.[204] Although palivizumab is an extremely effective drug, its availability as a prophylaxis or standard of care is unlikely in low-income countries.[205]

Experiences from precision medicine-based screening for Kirsten *ras* oncogene mutation in metastatic colorectal cancer have demonstrated that mAb-based treatments with cetuximab and panitumumab are cost-effective.[206]

Concluding remarks

The COVID-19 pandemic has dealt humanity a serious challenge and expediting research efforts toward development of efficacious vaccines and antivirals are the most promising options that will enable humanity to prevail over this pandemic. As we witness the approvals of many promising COVID-19 vaccine candidates, the duration it is likely to take to scale up and administer the vaccine to cover the humanity is a core challenge. Despite of vaccination coverage, there is high likelihood of COVID-19 to become established as a sporadic disease, arguably needing efficacious antiviral drugs, including therapeutic antibodies as an integral strategy for clinical management of severe COVID-19 cases. Convincing investigational evidence on the therapeutic promise of antibody-based options for controlling the viremic phase and alleviating the disease-associated pathologies suggests that this approach will be pharmacologically viable. However, an essential strategy involves the research and development of a treatment paradigm that will cluster patients with COVID-19 with preexisting conditions for the use of approved anti-SARS-CoV-2 mAbs or repurposed mAbs targeting cytokines. As numerous investigations continue to validate the therapeutic success of mAbs, the cost-effectiveness of the production of these drugs, the development of biosimilars to novel mAbs without patent restrictions, continuous and effective research in identifying reservoir species of CoVs, and financial support or affordable accessibility to therapeutic mAbs will dictate the global utility of these therapeutic magic bullets in controlling this pandemic.

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The authors declare no conflict of interest

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