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Anti-SARS-CoV-2 and anti-cytokine storm neutralizing antibody therapies against COVID-19: Update, challenges, and perspectives

Cassiano Martin Batista, Leonardo Foti *

Laboratory of Trypanosomatids Molecular and Systemic Biology, Brazil

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ABSTRACT

Coronavirus disease 2019 (COVID-19) has been declared by the World Health Organization (WHO) as a pandemic since March 2020. This disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The only available tools to avoid contamination and transmission of this virus are physical distancing, the use of N95 and surgical masks, and hand hygiene. Vaccines are another essential tool to reduce the impact of the pandemic, though these present challenges in terms of production and logistics, particularly in underdeveloped and developing countries. One of the critical early research findings is the interaction of the spike virus protein with the angiotensin-converting enzyme 2 (ACE2) human receptor. Developing strategies to block this interaction has therefore been identified as a way to treat this infection. Neutralizing antibodies (nAbs) have emerged as a therapeutic approach since the pandemic started. Infected patients may be asymptomatic or present with mild symptoms, and others may evolve to moderate or severe disease, leading to death. An immunological phenomenon known as cytokine storm has been observed in patients with severe disease characterized by a proinflammatory cytokine cascade response that leads to lung injury. Thus, some treatment strategies focus on anti-cytokine storm nAbs. This review summarizes the latest advances in research and clinical trials, challenges, and perspectives on antibody-based treatments (ABT) as therapies against COVID-19.

1. Introduction

A pandemic was declared in March 2020 by the World Health Organization (WHO). Since then, coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has intrigued researchers, medical doctors, and the general population.

The first disease cases were characterized as atypical pneumonia in Wuhan, China, in December 2019 [1]. Coronaviruses are known to have caused pneumonia epidemics in humans, such as SARS-CoV (related to SARS-CoV-2) and Middle East Respiratory Syndrome (MERS-CoV) [2,3]. However, the origin of SARS-CoV-2, the most infectious coronavirus known, is still under investigation by the WHO.

Since no specific treatment has been approved so far, the only available tools to prevent the transmission of SARS-CoV-2 are physical distancing, the use of N95 and surgical masks, and hand hygiene [4]. Besides the Regeneron antibody cocktail, which has been approved by the US Food and Drug Administration (FDA) [5], emergency FDA approval has also been issued for an antibody cocktail from Eli Lilly and is now revoked [6]. An equine hyperimmune serum in Argentina has also received emergency approval from the Argentinian regulatory agency [7]. However, these treatments currently lack both usage data and scalability and are not being used for prevention. Currently, health practitioners rely on strategies known to work against other infections, such as dexamethasone [8], oxygen therapy, anti-coagulation drugs, and intensive care unit interventions like tracheostomy and mechanical respiration [9].

Vaccines are another essential tool to reduce the impact of the

Abbreviations: ABT, Antibody-based treatments; ACE2, Angiotensin-converting enzyme 2; ADE, Antibody-dependent enhanced disease; CLO, Chloroquine; COVID-19, Coronavirus disease 2019; CP, Convalescent plasma; FDA, US Food and Drug Administration; HCLO, Hydroxychloroquine; IFN, Interferon; IL, Interleukin; IVHI, Intravenous hyperimmune immunoglobulin; IVIG, Intravenous immune globulin; mAbs, Monoclonal antibodies; MERS-CoV, Middle East respiratory syndrome coronavirus; nAbs, Neutralizing antibodies; NTD, N-terminal domain; RBD, Receptor-binding domain; RBM, Receptor-binding motif; S, Spike virus protein; SARS-CoV, Severe acute respiratory syndrome coronavirus; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; TNF, Tumor necrosis factor; WHO, World Health Organization.

* Corresponding author at: Carlos Chagas Institute/FIOCRUZ, 3775 Professor Algacyr Munhoz Mader St, 81350-010 Curitiba, PR, Brazil.
E-mail addresses: cassiano.batista@fiocruz.br (C.M. Batista), leonardo.foti@fiocruz.br (L. Foti).

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pandemic. As a result of the global race for a vaccine [10], the rate of vaccine development has been the fastest in human history. Some have already been approved, bringing hope for an end to the pandemic. However, vaccinating billions of people represents a production and logistics challenge, particularly in underdeveloped and developing countries, which have the less economic power to purchase vaccine doses [11]. In addition, anti-vaccine and anti-science movements represent a critical risk to the success of vaccination campaigns, as do the denialist positions that some leaders and their followers support [12]. These challenges highlight the ongoing importance of research on COVID-19 in order to save lives, especially in severe cases.

One of the critical early research findings is the interaction of spike virus protein with angiotensin-converting enzyme 2 (ACE2) human receptor, which is more robust against SARS-CoV-2 than SARS-CoV [13]. This characteristic is responsible for SARS-CoV-2 being more infectious and transmissible [13]. Thus, developing strategies to block this interaction can help treat infections. Neutralizing antibodies (nAbs) have therefore emerged as a therapeutic approach since the beginning of the pandemic, and their use continues to the present date.

As of July 27, 2021, COVID-19 was present in 192 countries, with 194,909,258 total cases and 4,171,772 total deaths [14]. Patients infected with SARS-CoV-2 can be asymptomatic or present with mild symptoms, though these may also progress to moderate or severe disease, potentially leading to death [15]. Some severely ill patients experience an immunological phenomenon known as cytokine storm, characterized by a proinflammatory cytokine cascade response that leads to lung injury [16]. Some treatment strategies have therefore focused specifically on anti-cytokine storm nAbs [16–21].

This review summarizes new developments in research and clinical trials, challenges, and perspectives on antibody-based treatments (ABT) as therapies against COVID-19. We separate this review into four major parts: 1) spike virus glycoprotein/ACE2 human receptor interaction nAbs; 2) cytokine storm nAbs; 3) challenges; 4) perspectives.

2. SARS-CoV-2 and the COVID-19 pandemic: A brief characterization

SARS-CoV-2, the etiological agent of COVID-19, belongs to the subfamily of β-coronaviruses that infect humans and may cause severe disease and lead to death [22]. This genome is approximately 80% identical to SARS-CoV, the first coronavirus outbreak in China in 2002 [2], which killed 774 people.

SARS-CoV-2 is 87.23% identical to the corona-like bat virus bat-SL-CoVZXC21, and 87.99% identical to bat-SLCoVZC45, which has led to speculation SARS-CoV-2 originated in bats [23], though its zoonotic origins have yet to be determined. There is evidence that pangolins are an intermediate host, which could have initially transmitted the disease to humans at an open seafood market in Wuhan, China [24]. However, the WHO is still investigating the origins of transmission. Determining the outbreak's origin has proven challenging as some of the first patients did not go to the market.

In terms of clinical presentations, 80% of COVID-19 patients have asymptomatic to mild symptoms (fever, head and body pain, loss of smell and taste, diarrhea), and 20% have moderate to severe symptoms (pneumonia, dyspnea, secondary infections, renal or cardiac failures, and coagulation), which can lead to death [15]. The majority of the virus contamination occurs by aerial transmission, which has been documented more recently, but it also may occur less frequently by fomite droplets and contaminated surfaces [15].

A recent study by Flora and collaborators (2021) [25] at Bauru hospital in Brazil has provided insights into the differential protein expression during each stage of SARS-CoV-2 infection. The authors identified changes in plasma proteins related to complement activation, blood coagulation, antimicrobial humoral response, acute inflammatory, and endopeptidase inhibitor activity. Specifically, patients with mild symptoms had higher levels of the Iron-responsive element-binding protein 2 (IREB2), Gelsolin (GELS), DNA-directed RNA polymerase III subunit RPC 4 (POLR3D), Serum paraoxonase/arylesterase 1 (PON1), and UL16-binding protein 6 (ULBP6) proteins. Increased expression of Galectin-10 (Gal-10) was found in critical and severe patients [25]. In another robust genomic study in 208 intensive care units (ICUs) in the United Kingdom, called the Genetics of Mortality in Critical Care (GenOMICC), by Pairo-Castineira and collaborators (2021) [26], discovered susceptibility markers to severe COVID-19 development: low expression of the interferon receptor gene IFNAR2 and high expression of tyrosine kinase 2 (TYK2), as well as increased expression of the monocyte/macrophage chemotactic receptor CCR2 in the lung [26]. Such studies are critical to new pharmaceutical research and development related to SARS-CoV-2 since they help inform therapies that can target these genetic/blood markers.

In terms of structure and organization, SARS-CoV-2 follows the structural protein forms of coronaviruses: envelope, spike (S) glycoprotein and membrane, and the non-structural nucleocapsid protein plus RNA-positive genome (26.2 to 31.7 kilobases) from the ribonucleocapsid complex (RNP), which are encapsulated in the envelope (Fig. 1) [22].

3. Interaction of the human receptor ACE2 with the virus spike glycoprotein for SARS-CoV-2 virus entry as the primary therapeutic target for neutralizing antibodies (nAbs)

As thoroughly described in the literature, the virus S glycoprotein of SARS-CoV-2 is responsible for host cell entry after interacting with the human receptor ACE2 (Fig. 2A) [13,27–29]. Nevertheless, it is essential to know that inside the S1 monomer, a receptor-binding domain (RBD) is responsible for receptor interaction [26]. More specifically, the receptor-binding motif (RBM) contains the residues that actively bind to ACE2 [29], as in Fig. 2A. Structurally, the spike protein has two conformational states: "up" and "down" [5]. Significantly, the RBD only interacts with and binds to ACE2 when the spike protein is in the "up" conformation state (Fig. 2A) [5].

The interaction of SARS-CoV-2 with ACE-2 is stronger than that of SARS-CoV due to mutations in RBM, such as the insertion of Gly-Val-Glu-Gly (GVEG) in residues 482–485 [13]. Outside of the RBD domain, a Pro-Arg-Arg-Ala-Arg (PRRAR) insertion, a second additional site for protease action and S2 monomer assembly for virus or RNA internalization, is a furin protease site that is another critical difference between SARS-CoV-2 and SARS-CoV and is involved in the increased pathogenesis [30]. Both mutations contribute to the greater transmissibility of SARS-CoV-2 and can be used as targets for treatments.

At the onset of the pandemic, the predominant strategies involved using available medicines to treat or even prevent infection. This strategy had a misleading success at the beginning, as some chemical compounds tested *in vitro* and *in vivo* presented evidence of early treatment and prophylaxis [31], such as the promising and novel use of clofazimine [32] and molnupiravir [33], as well as compounds that have already used for similar applications, such as chloroquine (CLO), hydroxychloroquine (HCLO), ivermectin, azithromycin and some others [8], including ABT [34–38].

However, in human clinical randomized studies, CLO, HCLO, and ivermectin present a risk of substantial collateral effects such as toxic hepatitis, which has been another pandemic burden. Indeed, the pharmaceutical producer of ivermectin, Merck, published a note concluding that the drug should not be used to prevent or treat COVID-19 [39]. Another risk of ivermectin usage is the false sense of protection, which leads people to avoid prevention actions of contamination. Meanwhile, the use of azithromycin can lead to microbial resistance and, ultimately, sepsis [40]. Furthermore, these medicines were found to offer no clinical benefits in randomized studies [41].

The amount of time necessary for widespread, global vaccination and the possibility of spreading novel variants highlights the need for continued research on therapeutic methods. Thus, ABT, which is specific, more manageable, safer, and faster to produce and use, has

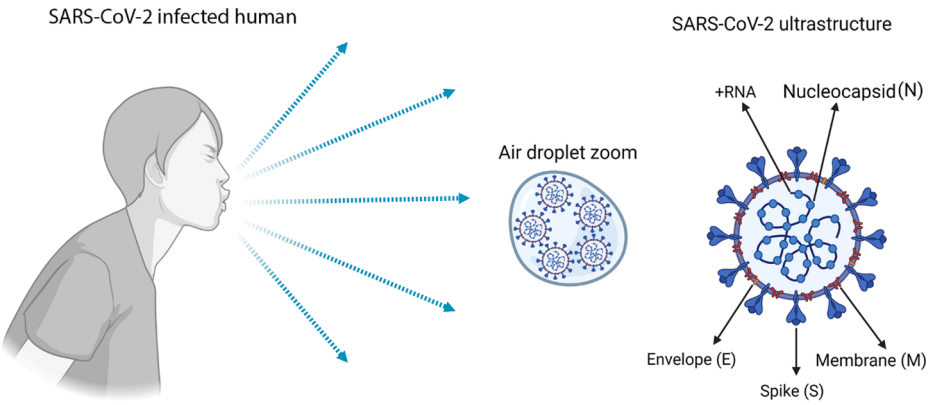

Fig. 1. General SARS-CoV-2 proteins and genomic RNA from an infected human. After coughing in the air, the virus droplets can infect another person. The figure shows the general ultrastructural protein and genomic RNA of SARS-CoV-2, including the nucleocapsid (N), envelope (E), membrane (M), spike (S), and genomic + RNA, respectively. The figure was generated using BioRender software.

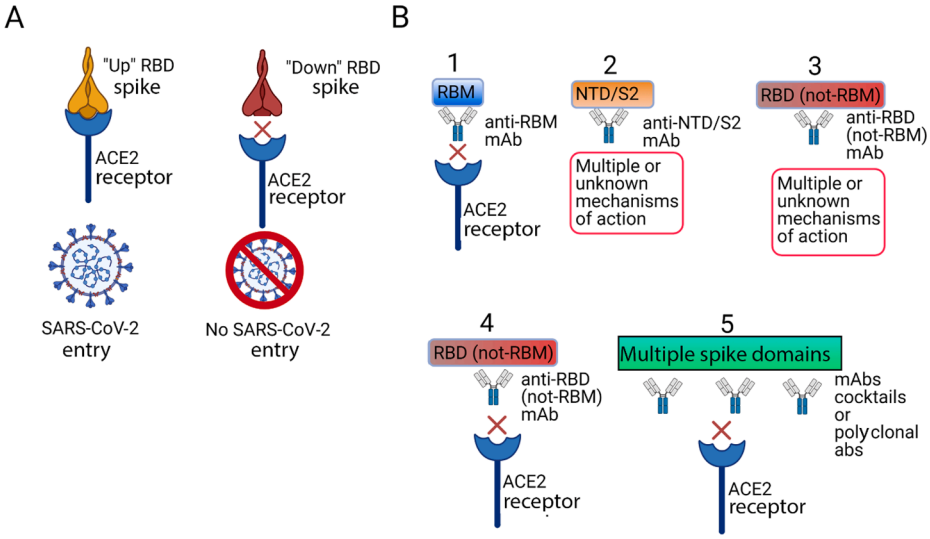

Fig. 2. SARS-CoV-2 spike (S) glycoprotein interaction with ACE2 host receptor and antibodies against S protein can prevent virus entry. A) Spike has two conformational states: "up" and "down." RDB only interacts and binds to ACE2 when spike is in the "up" conformation. B) Types of antibody-mediated blockage of virus entry: 1) nAbs bind to RBM, avoiding interaction with ACE2 and resulting in no entry and no infection; 2) nAbs bind to other spike domains, such as the N-terminal domain (NTD) and S2, with multiple mechanisms of action or with mechanisms of action that remain unknown; 3) nAbs bind to RBD (not RBM) and do not compete with ACE2 binding, with multiple mechanisms of action or with mechanisms of action that remain unknown; 4) nAbs bind to RBD (not RBM) and compete with ACE2 binding, resulting in no entry and no infection; and 5) nAbs bind to two or more regions (cocktails and polyclonal antibodies), resulting in no entry and no infection. The figure was generated using BioRender software.

emerged as a possible alternative against SARS-CoV-2 [35].

ABT passive immunotherapy is based on nAbs to keep pathogens from entering the host cell. ABT can be divided into five categories: convalescent plasma (CP), intravenous immunoglobulin (IVIG), intravenous hyperimmune immunoglobulin (IVHI), monoclonal antibodies (mAbs) – alone or in cocktails – and nanobodies [34–38]. Major nAbs against SARS-CoV-2 act against the S glycoprotein RBD [42]. As postulated by the literature, five possible groups could be used based on the targeting region and mechanism of neutralization [42], as follows: 1) nAbs bind to RBM, avoiding interaction with ACE2 and resulting in no entry and no infection; 2) nAbs bind to other S glycoprotein domains, such as N-terminal binding domain (NTD) and S2, with multiple mechanisms of action or with mechanisms of action that remain unknown; 3) nAbs bind to RBD (not RBM) and do not compete with ACE2 binding, with multiple mechanisms of action or with mechanisms of action that remain unknown; 4) nAbs bind to RBD (not RBM) and compete with ACE2 binding, resulting in no entry and no infection; 5) nAbs bind to two or more regions (cocktails and polyclonal antibodies), resulting in no entry and no infection (Fig. 2B).

Three classes were mentioned in another more recent classification by Finkelstein and collaborators (2020) [34] of SARS-CoV-2 nAbs that mediate RBM biding to ACE2 by epitope blocking: class I, the largest structurally characterized mAbs, which are direct ACE2 competitors that bind only to "up" RBD; class II, which binds to "up" and "down" RBD, and may stabilize spike in a conformation that prevents ACE2 binding; class III, which blocks ACE2 with quaternary epitopes (NTD, non-RBM) by potentially locking the spike in a closed conformation, thus preventing access to the ACE2 binding site [34].

Hence, advances in the technology used to produce nAbs for HIV treatment, such as structural characterization of the host receptor-virus ligand and production of mAbs to block this ligation, allowed the fastest discovery of ABT for SARS-CoV and SARS-CoV-2 in science history [43].

4. Anti-SARS-CoV-2 neutralizing antibodies (nAbs) as a therapeutic approach against COVID-19

4.1. SARS-CoV and SARS-CoV-2 cross-reacted nAbs

Due to their genomic proximity and the similar virus entry mechanism (spike × ACE2 interaction) in SARS-CoV and SARS-CoV-2, one of the first strategies involving ABT to treat SARS-CoV-2 was the usage of mAbs (detailed below) and nAbs against SARS-CoV. As previously reviewed [42], many SARS-CoV nAbs were tested against SARS-CoV-2, both *in vitro* and *in vivo* [44–46]. In these studies, cross-reaction and little or weak neutralization were observed [44–46]. The best result was for VIR-7831, derived from the non-RBM S309 (clinical trial NCT04545060, Vir Biotechnology, and GlaxoSmithKline (GSK) Inc. collaboration, USA), which is currently at the clinical trial stage (Table 1), alone [47] or combination with other antibodies. This antibody is currently awaiting FDA emergency approval after showing 85%

Table 1
Antibody-based treatments against SARS-CoV-2 proteins.

ABT approach	nAb name/target	Stage	Origin	Reference (s)
SARS-CoV cross-reaction with SARS-CoV-2	VIR-7831/spike	Clinical studies, waiting for FDA emergency approval	USA	[47]
CP	-/spike	Clinical studies /FDA emergency approval with some concerns / needs additional results	USA, UK, Italy, Spain, China, India, Brazil, South Africa, and others	[48,53]
IVIG/ IVHG	-/spike	Clinical studies	Various	[51,56]
mAbs	REGNCoV2 cocktail (Regeneron)/ spike	FDA approved	USA	[5]
mAbs	LY-CoV555 in combination with LY-CoV016 (Eli Lilly)/spike	Emergency FDA authorization revoked	USA	[6]
Nanobodies	-/spike	Preclinical studies	Various	[61–63]
Horse hyperimmune serum	-/spike	Preclinical studies	China	[68]
Horse hyperimmune serum	-/spike	Awaiting ANVISA approval to initiate clinical studies	Brazil	[70]
Horse hyperimmune serum	-/whole inactivated virus	Clinical studies	Brazil	[73]
Horse hyperimmune serum	-/spike	Emergency Anmat authorization/ needs additional results	Argentina	[7,69]
Horse hyperimmune serum	-/spike and mix	Preclinical studies	Costa Rica	[71]

efficacy in clinical studies. One accepted explanation of the unsuccessful use of SARS-CoV nAbs against SARS-CoV-2 is the structural differences between the spike and ACE2 interaction.

4.2. SARS-CoV-2 convalescent plasma, purified IgGs and mAbs/nAbs

The use of CP from recovered COVID-19 patients has emerged as a fast and safe treatment strategy due to the presence of nAbs against the spike glycoprotein [48]. The FDA has approved the emergency administration of CP to study its efficacy [49]. Some concerns have to be considered with respect to CP, such as 1) CP nAbs titles should be a minimum of 1:80 [50]; 2) randomized clinical trials should be undertaken to determine CP efficacy [51]; 3) pre-existing infections or diseases in donors should be documented, as well as the time to recover from COVID-19 [52]; 4) clinical structures and specialized nursing staff are required to stock and apply CP [48].

As recently reviewed by Devarasetti and collaborators (2021) [53], few randomized clinical trials focused on the use of CP have been carried out [53], some with contradictory conclusions (Table 1). A recent study from the Indian Council of Medical Research (ICMR) indicated that the best results and benefits were found: 1) in the early administration within five days of the first symptoms; 2) no CP administration to critical patients; 3) when donors exhibited ideal conditions, such as high nAbs titers and donation within 45 days of recovery from SARS-CoV-2 infections [50]. More standardized and multicenter randomized clinical trials should be done to understand the prophylactic benefit of CP therapy for SARS-CoV-2 patients.

Limitations of CP application include the difficulty in storage and donors' availability. Some approaches could help, including IgG-specific S glycoprotein nAbs being isolated and purified from CP, termed IVIG nAbs (or IVHI if isolated from a concentrated pool of CPs) [54]. Due to higher titers, they could be used in a great number of patients. However, these approaches are time-consuming, expensive, and do not offer proinflammatory protection. Moreover, they could lead to antibody-dependent enhanced disease (ADE), such as dengue hemorrhagic fever, due to the presence of non-neutralizing antibodies [55]. As reviewed recently, little new research is available on IVIG or IVHI [51,56], and few clinical studies are currently being performed.

mAbs and nAbs have emerged as promising alternatives that could solve some of the previously mentioned challenges. mAbs mostly come from immortalized hybridoma clones resulting from the fusion of B cell mAb producing cells with myeloma cancer cell lines [57]. The B cells could be obtained from recovered COVID-19 patients (using B cell isolation), phage-display libraries, or immunized animals (mouse, rabbit, and others) [58–59]. Since the cell lines are immortalized, there is no need for other donors/animals. As a result of careful screening of nAb-specific B cell line isolation, ADE is less likely to occur. However, their production is more expensive than the purification of hyperimmune IgGs. Additionally, non-human mAbs need to be humanized in Fc portions for the best avidity results [60]. Another concern about mAbs is the escape of mutant variants due to their unique epitope response, which could be reverted by implementing mAbs cocktails with no competitive epitopes [47].

Two mAbs cocktails recently received FDA approval or emergency use authorization: REGN10933 in combination with REGN10987, named REGNCoV 2 (Regeneron) was approved [5] and, more recently, LY-CoV555 in combination with LY-CoV016 (Eli Lilly, USA) received an emergency use authorization [6] (Table 1). However, the Eli Lilly mAbs emergency approval was revoked after the announcement of the loss of efficacy against variants. Other mAbs (alone or in combination) are in different clinical evaluation phases [61–63]. More long-term studies are needed to verify their effectiveness not only for SARS-CoV-2 but, principally, for the variants. Thus, there is a demand for platforms that could predict mutations and combine them through genetic engineering to produce more efficient mAbs cocktails.

4.3. SARS-CoV-2 camelid nanobodies and equine hyperimmune nAbs

Other technologies to develop therapeutic antibodies could be used for COVID-19 therapies. Nanobodies are smaller than antibodies due to the absence of an Fc domain and are produced primarily in camelids [64]. The advantage of these molecules is the opportunity to produce them recombinantly in bacterial platforms, which is less costly than other approaches. Since they are smaller, they could be administered by inhalation/nebulization and be directed to the lungs [37]. Indeed, nanobodies against S glycoprotein of SARS-CoV-2 have been produced, resulting in powerful nAbs such as synthetic humanized or yeast libraries, which block the interaction of the virus with ACE2 via distinct mechanisms, or camelid immunized with RBD, the epitope of which can recognize both "up" and "down" spike proteins and other non-overlapping epitopes with pico and femtomolar affinities [60,65–67]. In spite of their importance, the technology for producing them has only been recently developed. Therefore, all possible nanobodies are in discovery or preclinical studies at the moment (Table 1).

Another ABT approach for SARS-CoV-2 is hyperimmune serum from horses, recently reviewed by Costa and collaborators (2021) from Vital Brazil Institute, Rio de Janeiro, Brazil [12]. The advantage of using equine serum lies in better production at higher volumes than with other species [12]. To date, four studies have been published: one in China [68], one in Argentina [69], one in Brazil [70], and one in Costa Rica [71]. They all used enzymatically digested IgG with pepsin or papain to obtain Fab or F(ab) 2 fractions, respectively. The nAbs production was

50–150 times higher in titles than CP [68–70]. Argentina's hyperimmune serum has recently received emergency approval, with some caveats, from the country's regulatory agency (Anmat) since clinical studies showed a 45% reduction in mortality [7] (Table 1). Meanwhile, the use of Vital Brazil's hyperimmune serum still requires authorization from Brazil's regulatory agency (ANVISA) to start clinical studies (Table 1). No updates from the Chinese study have been published or announced after the first publication, so we consider it to be in the preclinical stage (Table 1). Furthermore, the Butantan Institute in Brazil is also developing an equine serum against SARS-CoV-2 using the whole inactivated virus as antigen. This study received authorization from ANVISA to start clinical studies (Table 1) [72]. Such an approach could help these countries combat the disease until vaccination rates increase.

5. SARS-CoV-2 cytokine storm and antibody-based treatments against key cytokines

As recently reviewed by Sette and Crotty (2021), rapid viral clearance is due to T cell responses against SARS-CoV-2. An extended period of innate immune response is associated with severe/acute disease [73]. Another critical finding associated with severe/acute disease is the ineffective IFN I and III innate immunity, which leads to innate cell immunopathology and cytokine storm [74,75]. The SARS-CoV-2 cytokine storm, induced by macrophages and other innate immune cells, is characterized by high levels of key cytokines such as TNF-α, IL-1β, and IL-6 [13], as well as IL-7, IL-8, IL-9, IL-10, IFN-γ, TNF, MCP1, MIP1A, MIP1B, G-CSF, GM-CSF (Fig. 3A) [76]. The signature of these proinflammatory cytokines is very clearly observed in COVID-19 pneumonia patients, with other severity-associated symptoms such as coagulation [16]. Furthermore, inflammations may survive for months after virus clearance, as observed in many recovered patients [77] as the so-called "post-COVID-19 syndrome", characterized by the persistence of symptoms such as fatigue and tiredness [78].

Identifying the key cytokines may therefore enable the development of therapies to block them. Indeed, dexamethasone, an anti-inflammatory corticosteroid, has been shown to significantly reduce mortality among patients hospitalized with or without mechanical ventilation [79]. ABT against cytokine storm markers such as TNF-α, IL-1β, and IL-6 is an essential approach at the moment to stop a proinflammatory response to SARS-CoV-2 (Fig. 3B).

Specific particularities of the antibodies mentioned above can be found in the most recent review by Yakota et al. (2021) [16]. Table 2 shows the current clinical stages of these antibodies. Adalimumab, sarilumab, and infliximab are in clinical trials; canakinumab is in clinical trials and needs more randomized studies; and tocilizumab, the most promising, is approved in the UK [37] and a clinical study with remdesivir is ongoing with pneumonia patients in the USA (Table 2).

Table 2
Recent advances in antibody-based treatments against SARS-CoV-2 cytokine storm.

Antibody Name and origin	Target	Stage	Reference(s)
Adalimumab/ Humira®, AbbVie Inc., USA	TNF-α	Clinical trials	[16,17,80]
Infliximab/ Remicade®, Johnson & Johnson, USA	TNF-α	Clinical trials	[16]
Canakinumab/ Ilaris®, Novartis International, Switzerland	IL-1β	Clinical trials need additional randomized studies	[16,18]
Tocilizumab/ Actemra®, Chugai Pharmaceutical, Japan	IL-6 receptor	Approved in the UK; part of a clinical study with remdesivir for pneumonia patients in the USA	[19–21,37,81–85]
Sarilumab/ Kevzara®, Sanofi S.A., France	IL-6 receptor	Clinical trials	[16,20]

6. Challenges

SARS-CoV-2 presents a multitude of challenges, three of which are particularly related to the context of this review: 1) reinfection with SARS-CoV-2 and SARS-CoV-2 variants due to the duration or escape of nAbs or memory cells, respectively; 2) ADE; 3) autoantibodies.

Reinfection, the ability of SARS-CoV-2 to infect previously infected patients, is a significant concern with SARS-CoV-2, as it can promote escape from vaccines and reduce the quality of life of re-infected people [86]. Asymptomatic and mildly symptomatic patients appear to be more susceptible to reinfection due to a lower memory B and T cell response and less long-term duration of nAbs. Moderate and severe patients are less vulnerable to reinfection due to the intermediate to long-term memory or duration of nAbs from 3 to 8 months [87,88]. However, more robust cohort studies are needed to estimate the time of memory and nAbs in recovered patients.

Some SARS-CoV-2 variants that escape from nAbs/memory cells are an emerging issue at the moment. There are a lot of SARS-CoV-2 variants

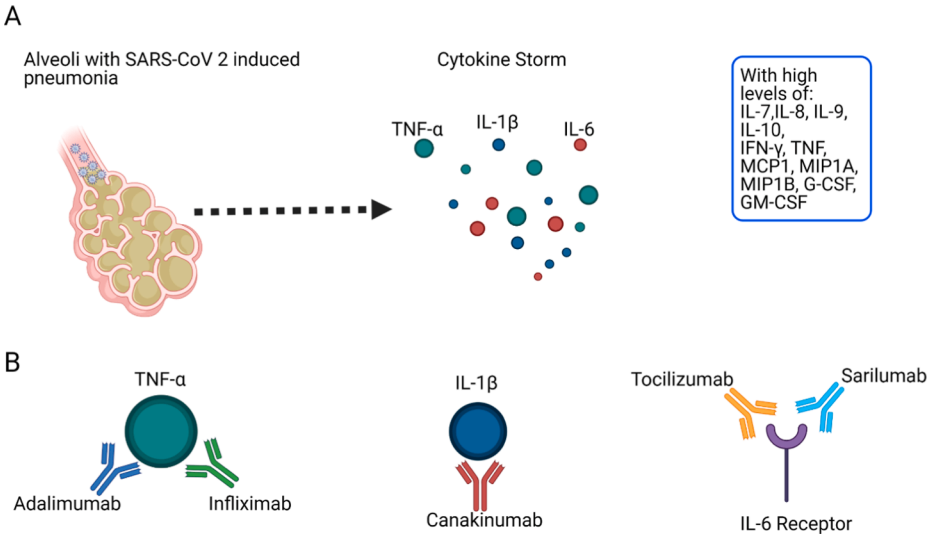

Fig. 3. SARS-CoV-2 alveolar pneumonia induced by Cytokine Storm and antibody-based treatments against crucial cytokines. A) SARS-CoV-2 alveolar pneumonia induced by cytokine storm proinflammatory response caused by macrophages and other innate immune cells. The key cytokines are TNF-α IL-1β and IL-6. B) Antibody-based treatments against the key cytokines: TNF-α (adalimumab and infliximab), IL-1β (canakinumab), and IL-6 receptor (tocilizumab and sarilumab). The figure was generated using BioRender software.

[89], but four are more transmissible and dangerous than the original SARS-CoV-2 and need more concern: B.117 from the United Kingdom (UK), P1 from Brazil, and 501Y.V2 (or B.1.351) from South Africa [89], and the most recently emerged, B.1.617.2 from India [90]. Until now, there has been no evidence of a loss of vaccine efficacy in response to the UK variant [89]. On the other hand, the South African variant could escape from CP [91]. The Brazilian and Indian variants are more recent than others, and little information is available. However, as with B.1.351, the Brazilian variant is highly transmissible and appears to re-infect people who have recovered from the original virus [92]. More studies are crucial to determine whether the variants are more lethal than the original virus and induce more reinfections and escape from vaccines. On May 31, 2021, WHO announced a new and more straightforward nomenclature for the variants, divided into "variants of concern" and "variants of interest". The four above-mentioned variants of concern are now Alpha (former B.117 British variant), Beta (former B.351 South African variant), Gamma (former P1 Brazilian variant), and Delta (former B.1.617.2 Indian variant) [93].

ADE is characterized by a more potent disease after a second exposure to a pathogen [55]. It could be an issue in ABTs, principally those involving CP and hyperimmune serum, due to the presence of non-neutralizing antibodies together with the nAbs [55]. ADE has been observed in MERS and SARS-CoV [55]. However, no ADE has been confirmed for SARS-CoV-2, and IgG isolation, purification, mAb technology, and recombinant modification in glycosylation of the Fc domain could help avoid ADE [56].

Another antibody-mediated pathogenesis in COVID-19 patients is the production of autoantibodies in severe/critically ill patients, as suggested by the observation that these patients were reported to have antiphospholipid and anti-β2-glycoprotein I (β2GPI) IgA, IgM, and IgG antibodies [94–97]. Some autoantibodies or factors related to autoimmune rheumatic diseases have been found in COVID-19 patients without a disease history [95,98]. Another study showed that critically ill COVID-19 patients display lupus-like hallmarks, such as activating extrafollicular B cells [99]. These extrafollicular responses induce antibody-secreting cells. Thus, SARS-CoV-2 infection may lead to autoimmune disease induction by producing and amplifying autoantibodies [56].

As recently shown by Liu and collaborators (2021) [100] in a review, other autoantibodies have also been detected in COVID-19 patients [100], such as cold agglutinins, which cause hemolytic anemia and complicate laboratory assessment and renal replacement therapy [101,102]; anti-Ro/SSA antibodies, which may be associated with severe pneumonia [103]; anti-Caspr2 antibodies [104], anti-GD1b antibodies [103], anti-MOG antibodies [105], and red cell-bound antibodies, associated with the anemia severity [106]. In addition, the American Journal of Nursing published a NewsCAP (March 2021) suggesting that autoantibodies across a wide range of immunological targets in COVID-19 patients are also related to long COVID-19 or post-COVID-19 syndrome [107]. More studies are needed to understand the risks of COVID-19 in patients with pre-existing autoimmune conditions or if COVID-19 disease generated this autoimmune disease.

7. Perspectives

Due to the challenges discussed previously, ABT for SARS-CoV-2 treatment may be discarded. However, as treatments involving ABT have been simpler, faster, and safer than vaccines, ABT using variants as targets could be used as alternative treatment until effective vaccines against variants are developed. In addition, mAbs cocktails or polyclonal antibodies could be used to block virus ABT escape. Research advances in molecular biology could discard ADE induced by ABT. Furthermore, we propose that ABT be used not only for treatment but also for prevention, as reinfection and poorly understood immune responses are significant issues for COVID-19. ABT could also block autoantibodies in severe/critical patients, and more efforts could be made along these lines.

In conclusion, more actions should be taken by the research community and pharmaceutical industry to make ABT less expensive and scalable, which would allow more access to these therapies, principally in underdeveloped countries. This technology could be used for other future pandemics, as ABT could be applied to block the pathogenesis of infection, reinfection, cytokine storm, and autoimmune antibodies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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