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Contents lists available at ScienceDirect

Biosafety and Health

journal homepage: www.elsevier.com/locate/bsheal

An update to monoclonal antibody as therapeutic option against COVID-19

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ARTICLE INFO

Article history:

Received 9 December 2020

Received in revised form 2 February 2021

Accepted 6 February 2021

Available online xxxx

Keywords:

SARS-CoV-2

Coronavirus

Monoclonal antibody

mAb

Antibody therapy

ABSTRACT

With the number of COVID-19 cases soaring worldwide and limited vaccine availability for the general population in most countries, the monoclonal antibody (mAb) remains a viable therapeutic option to treat COVID-19 disease and its complications, especially in the elderly individuals. More than 50 monoclonal antibody-related clinical trials are being conducted in different countries around the world, with few of them nearing the completion of the third and fourth phase clinical trial. In view of recent emergency use authorization (EUA) from the FDA (Food and Drug Administration) of casirivimab and imdevimab, it is of importance that mAbs, already used to treat diseases such as Ebola and respiratory syncytial virus (RSV), are discussed in scientific communities. This brief review discusses the mechanism of action and updates to clinical trials of different monoclonal antibodies used to treat COVID-19, with special attention paid to SARS-CoV-2 immune response in host cells, target viral structures, and justification of developing mAbs following the approval and administration of potential effective vaccine among vulnerable populations in different countries.

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1. Introduction

Since the emergence of novel coronavirus SARS-CoV-2 in late December 2019, morbidities and fatalities are still increasing worldwide, with reports of re-infections coming along [1]. In spite of significant efforts that have been directed towards developing an effective therapeutic intervention against COVID-19, no therapeutic agent has been approved for treating COVID-19 as of writing this review. Even though several vaccines have received EUA in different countries, people in general in most countries still have to rely on traditional medications and symptomatic management of

the disease. Recent underwhelming results of the World Health Organization (WHO) solidarity trial has again proved our helplessness against this disease with our existing medications [2]. The invention of new modalities of treatment, in addition to a safe and effective vaccine, is now an urgent need to combat this pandemic.

Immunotherapy in the form of vaccine or antibody therapy etc. has proved its effectiveness against viral infectious diseases in earlier cases. Intervention with convalescent plasma from recovered patients or hyper-immune immunoglobulin from the patients who were previously infected with influenza, SARS, MERS, and Ebola, which contains a sufficient amount

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<http://dx.doi.org/10.1016/j.bsheal.2021.02.001>

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of antibody is likely to reduce the viral load and ultimately lead to reduced disease mortality [3]. However monoclonal antibodies (mAbs) represent a form of passive immunotherapy, which can provide an efficient therapeutic intervention against a particular disease. Besides, mAbs are far more specific, precise, and safe in comparison to conventional convalescent plasma therapy as these antibodies can be isolated from the blood of the infected patients or can be engineered in the laboratory [4]. While a safe and effective COVID-19 vaccine, to date, remains the best option to fight off this pandemic, mAbs can be helpful, especially in settings such as care homes and places where rapid dissemination of infection is taking place [5]. This brief review discussed different mAbs including a brief account of the immune response in SARS-CoV-2, the spike protein structure of SARS-CoV-2 – the principal target of the mAbs, mechanism of action of mAbs, how they fare against an effective vaccine and update to COVID-19 clinical trials involving mAbs.

2. Methodology

For this brief review, articles discussing mAbs in regards to COVID-19 treatment were searched and downloaded from publicly available databases including PubMed and Google Scholar. Key search terms and phrases included: SARS-CoV-2, COVID-19, coronavirus, mAb, monoclonal antibody, antibody treatment, monoclonal antibody clinical trial, etc. Key search terms were used both separately and in combination with other ones. Articles deemed relevant to the topic, published up to December 30, 2020 were included in this review. There was no specific requirement regarding article formats, so that all relevant literatures including comprehensive review, original study, clinical trials, perspectives, and editorials were considered as long as their topic was within the scope of this review. Regarding clinical trials involving mAbs, registries such as www.clinicaltrials.gov were searched by the authors, and mAbs undergoing phase 2, 3, and 4 clinical trials were included within this review.

3. Monoclonal antibody against SARS-CoV-2: update to clinical trials

The mAbs are likely to aid in reducing viral load by interfering with virus entry into a cell by binding to viral spikes and thus inhibiting virus attachment to cell surface receptors or by targeting host cell receptors or co-receptors, thereby making the binding sites of host cells unavailable for SARS-CoV-2. Alternatively, they can act as immunosuppressive agents, limiting immune-mediated damage, and play a role in reducing morbidity and mortality [6]. In the following section the review will discuss mAbs directed against different parts of SARS-CoV-2 that received current EUA or undergoing various stages of the clinical trials.

3.1. Antibodies targeting SARS-CoV-2 spike protein

After entering the body, SARS-CoV-2 first activates the innate immune response, and then the adaptive immune responses after a few days. According to immune responses, clinical phases of SARS-CoV-2 infection are the viremia phase, the acute phase (also known as pneumonia phase), and the recovery phase. Studies showed that in the high-risk group with COVID-19, local tissue inflammation and systemic cytokine storm is responsible for the sepsis caused by the virus, and pneumonitis, inflammatory lung injury, acute respiratory distress syndrome (ARDS), respiratory failure, shock, organ failure, and potential death are the consequences of aberrant host immune response [7–10].

The S proteins of SARS-CoV and SARS-CoV-2, two similar viruses, have an amino-acid sequence identity of around 77% with around 89.8% sequence identity in S2 subunits [8,11]. These similarities have helped researchers in repurposing neutralizing mAbs directed against SARS-CoV S-protein or host angiotensin-converting enzyme 2 (ACE-2) receptors for SARS-CoV-2, although several studies showed a range of discrepancies about how these neutralizing antibodies work. For example, antibodies, CR3002, and F26G19 interact with SARS-CoV by binding with their receptor-binding domain (RBD), whereas, in SARS-CoV-2 they target

epitopes other than the RBD, which compete with ACE2 and neutralize the virus more potently than SARS-CoV [12,13]. Several such antibodies are now as work in progress for SARS-CoV-2, namely, 2B2, 1A9, 4B12, and 1G10, S309 [14].

Apart from repurposed drugs, currently several novel humanized or bioengineered mAbs, targeting different parts of S-protein of SARS-CoV-2, have been enrolled in clinical trials. One such mAb cocktail therapy comprising casirivimab and imdevimab (REGN-COV2), which bind to non-overlapping epitopes of the spike protein RBD of SARS-CoV-2 and thereby block virus binding to the human ACE2 receptor, has been developed by Regeneron Pharmaceuticals and approved for EUA by the FDA on November 21, 2020 [15]. The recommended dose is 1200 mg for both mAbs as a single intravenous infusion dose for the treatment of adults and pediatric patients suffering from mild to moderate COVID-19, as well as those who are at high risk of progressing to severe COVID-19. But patients who are hospitalized due to COVID-19 or who require oxygen therapy due to COVID-19 or any other underlying non-COVID-19 related comorbidity were excluded from receiving the cocktail therapy as study findings demonstrated limited benefits of the drug in patients suffering from severe disease [15]. The authorization is based on positive phase-2 data announced in September and October from 799 adults in an ongoing randomized, double-blind, placebo-controlled trial of non-hospitalized patients (“outpatients”) with COVID-19, in which significant reductions were observed in the level of the virus along with significantly fewer medical visits within 28 days of receiving the combination treatment [15]. On further analysis, interim results from phase 1–2 trials in 275 patients published in December corroborated previous findings and demonstrated improved results in patients in whom endogenous immune response had not been initiated and patients who had high viral load at the start of mAb therapy [16].

Like casirivimab and imdevimab, bamlanivimab (LY-CoV555), another anti-spike neutralizing mAb, granted EUA by FDA on November 2020 is restricted to use only in newly diagnosed mild to moderate COVID-19 patients, who are not yet hospitalized but at high risk for developing severe disease [17]. The EUA was granted after it was observed that disease progression was slower in patients who received bamlanivimab than that in those receiving placebo in phase two randomized, double-blind, placebo-controlled clinical trial in 465 non-hospitalized adults [18].

Two other anti-spike mAbs, which are now in phase 3 clinical trials, are LY3819253 + LY3832479, and VIR-7831/GSK4182136. The first one has enrolled 2,400 healthy staff or residents of a nursing facility and 10,000 hospitalized patients as their study population. The second one has enrolled 1,360 non-hospitalized high-risk patients as the receiver of antibody doses. There are several other mAbs targeting S-protein are now in the phase-1 trials, namely, BGB-DXP593, JS016, CT-P59, BRII-196 and 198, SCTA01, MW33, COVI-GUARD/STI-1499, AZD8895 + AZD1061, and HLX70 [19].

3.2. Antibodies regulating immune microenvironment

In the case of SARS-CoV-2, granulocyte-macrophage colony-stimulating factor (GM-CSF) produced by activated CD4⁺ T cells and interleukin-6 (IL-6) play a central role in immunopathogenesis [20]. After binding of SARS-CoV-2 to alveolar epithelial cells, production of a range of proinflammatory cytokines and chemokines, including GM-CSF and IL-6 occur, which in turn recruit more monocytes and macrophages and lead to a subsequent cytokine storm [21]. A great number of studies showed a raised level of various cytokines and chemokines including IL-2, IL-6, IL-7, IL-10, IL-17, G-CSF, GM-CSF, IP-10, MCP1, MIP1A, TNF α , IFN- γ , VEGF, CCL2, etc. in more severe patients with COVID-19 [22–25].

Although complete characteristics of cytokine storm in COVID-19 are yet to be specified, anti-cytokine mAb could play a crucial role in the case of severe COVID. Multiple IL-6 inhibitors including tocilizumab (phase-4), sarilumab (phase-3), and siltuximab are currently under investigation in clinical trials in several concerned groups. Among them, tocilizumab showed immediate improvement in the clinical outcomes of severe and critical patients, which proved to be an effective treatment for reducing mortality [26]. A randomized, double-blinded study for evaluating tocilizumab in hospitalized

patients with severe COVID-19 pneumonia has just been completed, in which 450 participants were included from Canada, Denmark, France, Germany, Italy, Netherlands, Spain, United Kingdom, United States (1 IV infusion of TCZ, dosed at 8 mg/kg, up to a maximum dose 800 mg and 1 additional dose if no improvement) [27]. Currently, several other international clinical trials (phase 4/2) are ongoing including patients entering the ICU with severe acute respiratory failure COVID-19 disease (8 mg/kg up to a total dose of 800 mg) and adult patients hospitalized with COVID-19 either diagnosed as moderate or severe pneumonia requiring no mechanical ventilation or critical pneumonia requiring mechanical ventilation (8 mg/kg D1 and if no response, a second fixed dose of 400 mg at D3) [28].

Lenzilumab, a GM-CSF antagonist, as part of BETB/ Big Effect trial conducted by the National Institute of Allergy and Infectious Disease (NIAD), USA among adult hospitalized patients at as many as 40 US locations for severe COVID-19 disease, along with Risankizumab, humanized mAb against interleukin-23 (IL-23), is now at phase-2 [29]. A case-control study showed 80% reduction in relative risk of invasive ventilation and/or death in patients treated with lenzilumab compared with the control group [30]. In addition, the median time to resolution of ARDS reduced to one day along with early discharge from the hospital for patients treated with lenzilumab versus eight days to resolution, and double-time before discharge for the control group was observed [30]. Apart from these, Gimsilumab (KIN-190 N), Mavrilimumab/KPL 30D, and TJ003234 – three other anti-GM-CSF mAbs are going through phase-2 and phase-3 clinical trial by Kinevant sciences and I-Mab Biopharma Co. Ltd. respectively [31].

A study conducted on 10 terminally ill COVID-19 patients observed complete CCR5 receptor occupancy by leronlimab (CCR5 antagonist) on macrophage and T cells, resulting in a rapid reduction of plasma IL-6, restoration of the CD4/CD8 ratio, and a significant decrease in SARS-CoV-2 plasma viremia [32]. A novel approach using leronlimab thus could play an important role in resolving unchecked inflammation, restoring immunologic deficiencies, and reducing SARS-CoV-2 plasma viral load via disruption of the CCL5-CCR5 axis [32].

Several other mAbs are now being tested in different phases of clinical trials, such as Canakinumab (Anti IL-1 β), CPT-006 and AK119 (Anti CD73), Garadacimab/ CSL312 (F. XIIa antagonist), Pamrevlumab (mAb against connective tissue growth factor), Bevacizumab (Anti VEGF), Cizanolizumab (Anti P-selectin), Ravulizumab (Anti C5) and Emapalumab (IFN γ antagonist) and Anakinra (IL-1 antagonist) combination therapy. A brief description of monoclonal antibodies that are currently going under phase 2/3/4 clinical trial is given in Table 1.

4. Future prospect of monoclonal antibodies

Development procedures of any mAb need to follow a stringent guideline approved by the World Health Organization (WHO). In all cases, both non-clinical (in-vitro and in-vivo animal model study) and clinical evaluations should be performed. The focus of these studies primarily remains on pharmacokinetics (PK), pharmacodynamics (PD), and safety, and when passed, leads into pivotal clinical trials. Antibodies act through a variety of mechanisms ranging from receptor blockade to apoptosis by immune-mediated mechanisms (e.g. CDC, ADCC, and regulation of T cell function) [33]. Therefore, researchers have to take several factors into consideration before using them in any clinical setting. A homogeneous group of patients with the same line(s) of therapy or severity or stage of disease progression, and those receiving first-line therapy are considered to be the ideal candidate for mAb therapies. Another main attraction for mAb therapy is “target specificity” and hence optimum timing of therapy for a specific disease with a mAb must be validated based on clinical stages of that certain disease [33]. For instance, bamlanivimab, the target of which is SARS-CoV-2 spike protein, has been recommended for use within 10 days after onset of symptoms but best suited for use in patients immediately after confirmed virological diagnosis of SARS-CoV-2 [17,18]. On the other hand, Tocilizumab, anti-IL-6 mAb, is indicated for use in more critical patients with COVID-19 pneumonia and those requiring ventilator support [34]. On a general note, when considering infectious diseases, three particular indications are here for their use, namely; treatment

of infected individuals, prophylaxis for high-risk individuals (e.g. pregnant women in the Zika endemic regions) for the patient-level outcome, and prophylaxis to interrupt transmission in average-risk population to achieve population-level outcomes [35].

Although mAbs are one of the fastest-growing drug classes in the modern era, the precise mechanism by which they achieve their therapeutic effect is yet to be known. Any biological response or outcome with therapeutic mAb depends on several variables. Among them, antigen cell-surface density, their tissue distribution along with specificity, avidity, and isotype of any given mAb play a major role. To overcome limitations and to improve therapeutic effects relentless efforts are being made and hence, after chimeric and humanized mAb, bioengineered human antibodies are showing new prospects [36].

As of writing this paper, more than 75 monoclonal antibodies have been developed and approved by the FDA for use in different diseases [5]. But only three of them are being used to treat infectious diseases: RSV, anthrax, and *Clostridium difficile* [5]. More recently, two monoclonal antibodies (MAB114 and REGN-EB3) were tested against Ebola virus disease and the results were encouraging [37]. The reason behind such slow speed in developing monoclonal antibodies against virus diseases include unreasonable costing associated with research and development, especially when compared with alternative preventive and therapeutic strategy such as small molecule drugs and vaccines. Additionally, the complexity and ambiguity of viral pathogenicity and infections as well as the rapid mutation of virus make it harder for researchers to formulate effective and long-lasting mAb therapy against viral diseases [38].

Very recently, two mRNA based vaccines developed by Pfizer-BioNTech and Moderna received EUA by FDA with 95% and 94.1% efficacy rate respectively; one adenovirus vectored vaccine ChAdOx1 nCoV-19 (AZD1222) developed by Oxford-AstraZeneca with 70.4% efficacy rate received approval from the UK; and lastly one inactivated virus vaccine developed by Sinopharm received approval from China, with 79.34% efficacy rate in The United Arab Emirates (UAE) and Bahrain [39–41]. Although these vaccines have been approved for mass vaccination, their long-term effectiveness, any vaccine-related side effects as well as production ability to meet the need of the world population are still to be answered. As a result, monoclonal antibodies will remain a viable alternative to the COVID-19 vaccine for the foreseeable future.

There are more than 50 monoclonal antibodies in different phases of clinical trials in different countries and recently FDA has given emergency use authorization to several monoclonal antibodies including bamlanivimab, casirivimab, and imdevimab – mAbs targeting the spike protein of SARS-CoV-2 virus. One might assume that mAbs are here to stay for the long run but, like most other therapeutic options to treat viral diseases, mAbs have several limitations. Firstly, developing an effective mAb against SARS-CoV-2 requires extensive labor and substantial financial investment, even if a substantial proportion of groundwork regarding monoclonal antibody development was carried out during the original SARS-CoV epidemic in 2003 [42,43]. Nevertheless if mAbs are developed, their application might become limited once those vaccines are widely available. The primary group for mAb therapy would be a small group of people unable to mount an immune response even after administration of a suitable vaccine such as the elderly population or immune-compromised patients, which might not justify the large financial outlay [44]. Secondly, viruses are prone to frequent mutations as experienced in cases of HIV and HCV. Hence, monoclonal antibodies directed against the S-protein and the receptor-binding domain (RBD) might lose their efficacy if there is a mutation followed by a conformational change in antigen epitope, resulting in reduced inhibition of viral replication [45]. In addition to that, establishing a target population has proven to be troublesome with most people with clinical infections who recovered without administration of mAb, making it harder for researchers to establish a clinical endpoint compared with placebo [19]. Besides, in patients suffering from severe diseases, reducing viral replication might not always be the priority as other pressing issues such as inflammation and coagulopathy which might require urgent attention [19]. To summarize, monoclonal antibodies are effective, as evidenced from studies conducted on plasma therapy against COVID-

Table 1

Monoclonal antibodies currently ongoing phase-2, 3 and 4 trial.

Donor/ sponsor	Product	Clinical stage	Trial ID	Study
Regeneron Pharmaceuticals	REGN10933 + REGN10987 combination therapy (Directed against RBD of S-protein of SARS-CoV-2)	Phase 1/2	NCT04425629	2,014 ambulatory patients with COVID-19
Regeneron Pharmaceuticals	REGN10933 + REGN10987 combination therapy (Directed against RBD of S-protein of SARS-CoV-2)	Phase 1/2	NCT04426695	2,970 adult Hospitalized COVID-19 patients
Sorrento Therapeutics, Inc.	COVI-AMG (mAb targeting S-protein epitope, specifically D614G variant)	Phase 1/2	NCT04584697	50 SARS-CoV-2 RNA positive asymptomatic/mild symptomatic participants
University of Cologne/ZKS Kohn/Boehringer Ingelheim	human monoclonal antibody DZIF-10c	Phase 1/2a	NCT04631666	69 SARS-CoV-2 RNA negative and positive individuals
Swedish Orphan Biovitrum	Emapalumab (Anti-interferon gamma mAb) or Anakinra (Interleukin-1 Receptor Antagonist)	Phase-2	NCT04324021	54 hospitalized COVID-19 patients with respiratory distress and hyper inflammation
Assistance Publique - Hôpitaux de Paris	Tocilizumab (Anti IL-6 mAb)	Phase-2	NCT04331808	228 COVID-19 patients included in CORIMUNDO-19 cohort
CytoDyn, Inc.	Leronlimab (CCR-5 receptor inhibitor)	Phase-2	NCT04347239	390 hospitalized severe or critically ill COVID-19 patients
Kinevant Sciences GmbH/Roivant Sciences, Inc.	Gimsilumab (mAb against GM-CSF)	Phase-2	NCT04351243	227 with lung injury or ARDS secondary to COVID-19
Maria del Rosario Garcia de Vicuña Pinedo/Instituto de Investigación Sanitaria Hospital Universitario de la Princesa	Sarilumab (human IgG1 mAb that inhibits IL-6 mediated signaling)	Phase-2	NCT04357808	30 patients with moderate-severe COVID-19 infection
Implicit Bioscience/University of Washington	IC14(antibody to CD14 pattern recognition receptor)	Phase 2	NCT04391309	300 adult Hospitalized COVID-19 patients
Ospedale San Raffaele	Mavrilimumab (mAb against GM-CSF receptor alpha)	Phase-2	NCT04397497	50 participants hospitalized with COVID-19 induced pneumonia
CSL Behring	Garadacimab, (Factor XIIa antagonist)	Phase-2	NCT04409509	124 COVID-19 positive severe patients with interstitial pneumonia
Hospices Civils de Lyon	Nivolumab (Anti-PD1 antibody)	Phase-2	NCT04413838	120 SARS-CoV-2 positive hospitalized obese individual with risk of severe infection
Fibrogen	Pamrevlumab (antibody against connective tissue growth factor)	Phase-2	NCT04432298	130 acute COVID-19 hospitalized patients
Johns Hopkins University/ Novartis/ Socar Research SA/ Brigham and Women's Hospital	Crizanlizumab (mAb that reduced inflammation by binding to p-selectin)	Phase-2	NCT04435184	40 SARS-CoV-2 positive hospitalized acute COVID-19 patients
Assistance Publique - Hôpitaux de Paris/ Institut National de la Santé Et de la Recherche Médicale, France	Tocilizumab (Anti IL-6 mAb)	Phase-2	NCT04476979	120 COVID-19 patients included in the CORIMUNO-19 cohort
Rapa Therapeutics LLC/ Hackensack Meridian Health	RAPA-501-Allo	Phase-2	NCT04482699	88 hospitalized, severe, post-intubation COVID-19 patients
National Institute of Allergy and Infectious Diseases (NIAID)	Risankizumab (IL-23 inhibiting mAb)	Phase-2	NCT04583956	200 SARS-CoV-2 positive hospitalized adult patient
National Institute of Allergy and Infectious Diseases (NIAID)	Lenzilumab (mAb targeting GM-CSF)	Phase-2	NCT04583969	200 SARS-CoV-2 positive hospitalized adult patients
Eli Lilly and Company/AbCellera Biologics Inc./ Shanghai Junshi Bioscience Co., Ltd.	LY3819253 or LY3819253 + LY3832479 (mAb targeting S-protein epitope)	Phase-2	NCT04634409	500 non-hospitalized mild to moderate COVID-19 patients
Assistance Publique - Hôpitaux de Paris	Sarilumab (human IgG1 mAb that inhibits IL-6 mediated signaling)	Phase 2/3	NCT04324073	239 COVID-19 patients included in CORIMUNO-19 cohort
I-Mab Biopharma Co. Ltd.	TJ003234 (Anti-GM-CSF mAb)	Phase 2/3	NCT04341116	384 severe COVID-19 patients under supportive care
Eli Lilly and company/ AbCellera Biologics Inc./Shanghai Junshi Bioscience Co., Ltd.	LY3819253 and LY3832479 (mAb targeting S-protein epitope)	Phase 2/3	NCT04427501	2,450 participants with mild to moderate COVID-19 illness
Alexion Pharmaceuticals	Ravulizumab (prevent activation of complement component-5)	Phase-3	NCT04369469	270 hospitalized COVID-19 patients with severe pneumonia, acute lung injury, or ARDS
Regeneron Pharmaceuticals	REGN10933 + REGN10987 (mAb targeting S-protein epitope)	Phase-3	NCT04452318	2,000 participants including household contacts of COVID-19 patients
Brigham and Women's Hospital	Ravulizumab (mAb targeting C5 complement inhibition)	Phase-3	NCT04570397	32 SARS-CoV-2 positive patients with thrombotic microangiopathy
AstraZeneca/QuintilesIMS	AZD7442 (combination of AZD8895 and AZD1061 targeting S-protein of SARS-CoV-2)	Phase-3	NCT04625725	5,000 participants as pre-exposure prophylaxis
AstraZeneca/QuintilesIMS	AZD7442(combination of AZD8895 and AZD1061 targeting S-protein of SARS-CoV-2)	Phase-3	NCT04625972	1,125 participants with exposure history within preceding 8 days
Hadassah Medical Organization/ Sheba Medical Center/ Wolfson Medical Center	Tocilizumab (Anti IL-6 mAb)	Phase-4	NCT04377750	500 participants with severe COVID-19 disease and suspected hyper-inflammation
Cambridge University Hospitals NHS Foundation Trust	Ravulizumab (prevent activation of complement component-5) + Baricitinib (acts as inhibitor of janus kinase)	Phase-4	NCT04390464	1,167 SARS-CoV-2 positive hospitalized pre-ICU patients

19, as post-exposure prophylaxis to prevent severe diseases or complications. Hence, mAbs may still have important roles, albeit in a small group of people, in treating patients admitted to intensive care units or for those who did not respond to a vaccine [19]. But for that funding must be secured from non-profit donors or else, the development of SARS-CoV-2 specific mAbs can come to a halt sooner than expected.

5. Conclusion

In conclusion, monoclonal antibodies are, and will most likely continue to be, important therapeutic options going into the 21st century, not just for SARS-CoV-2 but also for other infectious pathogens too. Efforts should be directed towards developing monoclonal antibodies that are highly effective, can be developed by a fraction of a current cost, and for whom there is a specific beneficiary group.

Author contributions

Paroma Deb: Conceptualization, Data curation, Writing- Original draft. M.D. Maruf Ahmed Molla: Conceptualization, Data curation, Writing - Original draft. K. M. Saif-Ur-Rahman: Conceptualization, Methodology, Writing- Reviewing and Editing.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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