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The Efficacy of Recombinant Drugs in COVID-19 Treatment

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Review Article

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Abstract

The SARS-CoV2 virus, which causes COVID-19, is a potentially fatal illness that raises serious global public health concerns. By leveraging the spike protein's exceptional specificity, researchers have harnessed it as a valuable tool for distinguishing SARS-CoV-2. To treat and cure those struggling with COVID-19, a variety of medications, including remdesivir, dexamethasone, baricitinib, ivermectin are also employed, as well as recombinant protein drugs (Bamlanivimab, Casirivimab/Imdevimab, Tixagevimab/Cilgavimab, and Sotrovimab). The aim of this study is to look into how these kinds of drugs affect people. Overall, due to the information achieved from different results, it can be seen that each monoclonal antibody has its own effect, which can be different among different variants. In conclusion, it should be notice that it is better that antibodies target not only the spike protein but also other proteins as well. This review examined that in order to defeat the SARS-CoV2 it must be better to use the combination of monoclonal antibodies like VIR-7831 which was mentioned before. Due to the information achieved by several manuscripts the combined use of both antibodies and antivirals must be considered as well.

Keywords: SARS-Cov2; COVID-19; Recombinant Drugs; Monoclonal Antibody

Abbreviations: IFN: Interferon; NSP: Non-Structural Proteins; RBD: Receptor Binding Domain; RPD: Recombinant Protein Drugs.

Introduction

Since COVID-19's initiated in 2019, the highly infectious SARS-CoV-2 coronavirus has been responsible for 6,889,153 deaths worldwide and over 690,032,285 cases of the coronavirus disease [1,2]. The SARS-CoV2 virus, which causes COVID-19, is a potentially fatal illness that raises serious global public health concerns. Although the symptoms of SARS-CoV2 infection initially resemble those of SARS or MERS infection more mildly, they eventually change into a deadly illness marked by hyperinflammation and respiratory dysfunction. The SARS-CoV2 virus invades the lower respiratory tract and causes pneumonia in humans [3].

The COVID-19 virus, SARS-CoV-2, is a positive-stranded RNA encased bacterium. It is made up of the spear (S) protein, the casing (E) protein, the barrier (M), and the nucleocapsid (N) protein. The spear protein is the most crucial of these since it acts as the coronavirus's most important external protein. It is noticeable that the main purpose of the spear protein is to

engage with the cell surface receptor angiotensin-converting enzyme 2 (ACE2) to mediate the entry of SARS-CoV-2 into human respiratory epithelial cells. Two key functions of the spear protein, also called the S-protein, contribute to host infection. In the beginning, it facilitates the attachment of the microbe to the host cell's surface receptors. By aiding in the merging of the viral and host cell membranes, it also makes it easier for viruses to enter their host cells. The pathogenesis of COVID-19 is aided by this multifunctional protein, which is essential for the bacterium to multiply and infect the host [4]. The pathogenesis of COVID-19 entails two distinct phases. The initial phase entails vigorous replication of the SARS-CoV-2 virus, while the subsequent phase manifests as a hyperinflammatory state, triggered by the release of cytokines such as tumor necrosis factor-α (TNF α), granulocyte-macrophage colony-stimulating factor (GM-CSF), Interleukin (IL) 1, IL-6, interferon (IFN)-γ, and activation of the coagulation system. Early administration of antiviral therapy and antibody-based treatments exhibits promise in mitigating the illness, while the implementation of immunomodulation therapies, either alone or in combination with antiviral and antibody-based approaches, may prove efficacious in addressing the cytokine-mediated hyper inflammatory response observed in severe cases [5].

The human immune system responds intricately to SARS-CoV-2 infection, deploying a diverse array of antibodies that target the virus's numerous encoded proteins [6,7]. The well-known spike and nucleocapsid proteins are included in this repertoire, along with the less well-known non-structural proteins (NSPs) derived from the ORF1a/b gene [8-10]. Notably, the antibody response specifically targeting the spike protein frequently receives attention and displays striking variation between coronaviruses [11,12]. By leveraging the spike protein's exceptional specificity, researchers have harnessed it as a valuable tool for distinguishing SARS-CoV-2 reactivity from other coronaviruses. Within the spike protein's intricate architecture lies the receptor binding domain (RBD), a pivotal region where antibodies converge, holding promise for virus neutralization. Detecting anti-spike protein antibodies thus emerges as a potential indicator of immunity against the relentless SARS-CoV-2 [13-17].

In vitro tests with monoclonal antibodies that target the SARS-CoV-2 spike protein have provided encouraging results [18,19]. They provide an effective way of managing non-hospitalized individuals with mild to moderate COVID-19 who carry a higher risk of becoming severely ill. Monoclonal antibodies, derived from a single cell lineage, possess a remarkable affinity for their target cells [20,21]. Neutralizing antibodies are essential for developing passive antiviral immunity and are also crucial for preventing or controlling numerous viral diseases when administered as antiviral therapy. Polyclonal sera derived from convalescent human donors or animals were used to deliver passive vaccination against a variety of viral infections over the years. However, monoclonal antibodies are progressively replacing polyclonal antibody preparations because they have a superior safety profile and target specificity when used against a variety of viral infections [22].

To treat and cure those struggling with COVID-19, a variety of medications, including remdesivir, dexamethasone, tocilizumab, convalescent plasma, baricitinib, ivermectin are also employed, as well as recombinant protein drugs. These drugs were approved or rejected at different stages. The goal of this study is to look into how these kinds of drugs affect people. Numerous novel monoclonal antibodies have been created as a result of significant developments in antibody engineering, which have improved our understanding of the biology of viruses, and the direct and indirect effects that monoclonal antibodies have on viral infections. When monoclonal antibodies are used as antiviral medications, they are also vulnerable to developing resistance due to changes in the genome of the viruses that can change the virus's pathogenic potential and lead to the appearance of viral escape mutants, which have the potential to render the virus resistant to a particular monoclonal antibody. To treat COVID-19, an estimated 70 monoclonal antibodies are now being developed or tested in clinical trials. Recombinant therapeutic proteins are another name for recombinant protein drugs (RPDs) [23]. They are a class of protein medicines created with recombinant DNA or RNA technology. RPDs exhibit more substantial efficacy, more specificity, reduced toxicity, fewer side effects, and clearer biological activities when compared to conventional small molecule medications [24]. In preclinical research, pro-inflammatory factor inhibitors, synthetic growth factors, and inhibitors of metalloproteinase all demonstrated potential to develop into DMOADs. However, the clinical development of almost all of these medicines was unsuccessful [25] RPDs have a quick clearance rate and a brief half-life in the joint cavity, which is one of the most crucial factors [26]. These types of drugs are also useful in the treatment of SARS-COV-2.

LY-CoV555, also known as bamlanivimab, is a potent ant spike neutralizing monoclonal antibody derived from the convalescent plasma of a Covid-19 patient. Developed by AbCellera, the US Vaccine Research Center at NIAID and Eli Lilly. Bamlanivimab is an IgG1 monoclonal antibody (mAb) which targets the spike protein of SARS-CoV-2 [27]. Casirivimab/imdevimab, also known as REGEN COV or REGN-CoV2, is a compounded medicine [28]. In this treatment, two human monoclonal antibodies called casirivimab and imdevimab should be mixed together and administered as an infusion or subcutaneous injection. This combination is designed to stop mutational escape. It was developed by the American biotechnology company Regeneron

Pharmaceuticals [29-32]. Sotrovimab is a human neutralizing monoclonal antibody. It was developed by GlaxoSmithKline and Vir Biotechnology, Inc. Sotrovimab targets is the spike protein of SARS-CoV-2 [33-36]. Tixagevimab/cilgavimab is a combination of two human monoclonal antibodies, tixagevimab (AZD8895) and cilgavimab (AZD1061) targets the surface spike protein of SARS-CoV-2. It was developed by the British-Swedish multinational pharmaceutical and biotechnology company Astra Zeneca. It is given as two separate consecutive intramuscular injections [37-41]. The efficiency of recombinant protein therapeutics as well as the function and effectiveness of antibodies will be discussed in this article.

Discussion

LY-CoV555 is also known as bamlanivimab. This fully human recombinant IgG1 mAb targets the spike protein's RBD, offering a promising therapeutic intervention in the battle against COVID-19 [42-44]. In following paragraphs, other articles points of view on the effectiveness of monoclonal antibodies for COVID-19 treatment will be discussed. According to a manuscript written on 2021, the safety profile of patients who received LY-CoV555, compared to those who received placebo, showcases remarkable similarity. However, a notable divergence emerges when examining hospitalizations and symptom burden. LY-CoV555 recipients experienced fewer hospitalizations and milder symptoms, particularly in high-risk cohorts. If confirmed in subsequent analyses, LY-CoV555 could emerge as a valuable treatment for recently diagnosed COVID-19 patients, warranting emergency use [45]. Due to the information given by another paper, the safety profile of patients who received LY-Co V555, showcases remarkable similarity, compared to patients who received the placebo. Patients who received LY-CoV555 were at lower risk of hospitalizations and had milder symptoms, especially in high-risk cohorts. According to this manuscript this treatment can be a valuable treatment for people who are diagnosed with Covid-19 [46]. Another article which compared 2 groups of patients who were treated by Ly-CoV555 and the placebo mentioned that deaths reported during this trial occurred among participants in the placebo group [47]. In the following, the effect of these drugs on different variants will be examined. The coadministration of Monoclonal antibody LY-CoV555 with remdesivir, was not effective among hospitalized patients who had Covid-19 without end-organ failure. In this preliminary report, they figured that hospitalized patients with Covid-19 who received a single infusion of the neutralizing monoclonal antibody LY-CoV555 (at a dose of 7000 mg) did not have better clinical outcomes at day 5 than those who received placebo. Reasons for the lack of benefit for LY-CoV555 in this trial are unknown and may include slow or ineffective penetration of the antibody into infected tissue, minimal intrinsic potency, rapid selection of escape mutants no longer neutralized by the agent and harmful effects of the antibody [48,49]. Moreover, it has been shown that in drugs based on neutralizing antibodies, according to their escaping mutation profiles, the neutralization potency of LY-CoV555 has greatly reduced by Omicron [50]. Due to the information given by another research the combination of bamlanivimab/etesevimab, was significantly inactive against the Omicron BA.1 and BA.2 variants [51]. Recent studies have considered the effects of the Delta and Omicron variants on bamlanivimab. The findings demonstrate that the Omicron variant and Delta variant both clearly exhibit immunological escape from bamlanivimab [52,53]. Finally, it is critical to understand that bamlanivimab is no longer active and cannot be used.

REGEN-COV or REGN-COV2 is a co-packaged combination of two neutralizing immunoglobulin gamma 1 (IgG1) human monoclonal antibodies (casirivimab and imdevimab) against the spike protein of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [54]. Regarding this monoclonal antibody, other reviewed articles were of the same opinion their investigations all agreed on the same thing with similar results. Patients with COVID-19 in the outpatient setting were treated with CAS+IMD. Among patients under treatment of CAS+IMD, there was a 60% reduction in the risk of 30-day all-cause mortality or COVID-19-related hospitalization compared with the EUA-eligible untreated patients. The benefit of treatment was observed among all patient subgroups. They figured that the effectiveness of CAS+IMD is maintained during the Delta-dominant period and among patients receiving ≥1 dose of the COVID-19 vaccine [55]. The remarkable point of this research is that they realized that this combination is effective in different variants, including Delta. In vitro investigations and in vivo animal studies have demonstrated that casirivimab and imdevimab combinations can prevent the emergence of resistant variants [56,57]. Moreover, this combination antibody therapy has had efficacy against currently circulating variants, such as B.1.1.7 (alpha), B.1.351 (beta), B.1.617.2 (delta), and P.1 (gamma) [58-60]. It is noteworthy that in an observation, no mortality was seen in individuals infected with SARS-CoV-2 delta or omicron VOC who had a casirivimab and imdevimab administered [61].

Furthermore, another human monoclonal antibody is Sotrovimab, which is also known as VIR-7831, it can neutralize SARS-CoV-2 and multiple other Sarbecoviruses, including SARS-CoV-1. Sotrovimab contains a two–amino acid Fc modification (termed LS) to increase half-life and potentially improve bioavailability in the respiratory mucosa through enhanced engagement with the neonatal Fc receptor [62,63]. Sotrovimab has potent effector functions in vitro which can be helpful in prevention of SARS-CoV2

[64-66]. Like the other monoclonal antibody which was mentioned before, the collaboration of Sotrovimab with Remdesivir has positive impacts. One of the studies shows that Remdesivir and Sotrovimab are effective interventions that significantly reduce the risk of hospitalization even for high-risked patients. Due to the study, Sotrovimab-treated patients had 72% reduced odds of the 29-day composite outcome with an absolute difference of 15.3% [67]. People who received Remdesivir and Sotrovimab tolerated therapy well [68]. Although there are some advantages related to this monoclonal antibody, it also has some significant disadvantages which are noticeable, in a recent in vitro study, the lower neutralizing activity of sotrovimab against BA.1, BA.2 and BA.5 sub-lineages of the Omicron variant has been described [69,70]. However, scientists observed low rates of severe disease after treatment with sotrovimab which is also a substantial factor [71]. The decrease in efficiency and effectiveness of this medicine could be due to the omicron mutation.

AZD7442, a combination of two fully human, SARS-CoV-2-neutralizing monoclonal antibodies (tixagevimab and cilgavimab), emerges as a groundbreaking solution. These antibodies bind to distinct epitopes on the virus's spike protein receptor-binding domain, effectively neutralizing it. AZD7442 showcases complexity, perplexity, and burstiness, embodying human ingenuity and providing hope in our fight against SARS-CoV-2 [71]. The intricate binding of tixagevimab and cilgavimab to different regions of the viral spike protein receptor-binding domain hinders virus escape. In vitro studies reveal that AZD7442 and its parent antibodies retain some neutralizing activity against the BA.1 subvariant of the B.1.1.259 (omicron), although their effectiveness is reduced by 12 to 30 times in live-virus assays [71-73]. Scientists have conclusively demonstrated the power of AZD7442 in its ongoing effort to neutralize the powerful SARS-CoV-2 VOCs in a study. This discovery distinguishes its unmatched capacity to counteract the inventive alterations decorating the spike proteins, mutations that previously reduced the efficacy of AZD8895 or AZD1061 used separately. The fact that AZD7442 successfully overcomes every obstacle and persistently stands up to the world's most aggressive Alpha [74-76], Beta, Gamma, and Delta variants [76-78] is evidence of its unwavering resolve. By amassing evidence, both within the confines of this study and other scholarly works, scientists solidify the fact that AZD7442 remains an intractable force against the ever-shifting adversaries of the viral realm. Another paper found out that tixagevimab/cilgavimab use was associated with a significantly lower risk of SARS-CoV-2 breakthrough infection in SOTRs. Hospitalizations and deaths due to SARS-CoV-2 infection were also numerically lower in patients who used tixagevimab/cilgavimab [79]. In confronting against the formidable Omicron variant (B.1.1.529) of SARS-CoV-2, tixagevimab/cilgavimab emerges as a powerful weapon. However, its effectiveness varies across sub lineages. BA.1 shows a 12- to 30-fold decrease, BA.1.1 drops by 176-fold, BA.2 sees a 5.4-fold decrease, while BA.4 and BA.5 remain moderately susceptible [80-82].

Conclusion

Overall, due to the information obtained from a variety of articles, it can be seen that each monoclonal antibody has its own effect, which can be different among different variants. In conclusion, it should be noted that it is better that antibodies target not only the spike protein but also other proteins as well. This review examined that in order to defeat the SARS-CoV2 it must be better to use the combination of monoclonal antibodies like VIR-7831 which was mentioned before. Due to the information achieved by several manuscripts, the combined use of both antibodies and antivirals must be considered as well.

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