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Neutralizing Antibody Cocktail Approach: Insights from Combination Therapy of Casirivimab and Imdevimab

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Abstract: The combination of Casirivimab and Imdevimab as a neutralizing antibody cocktail therapy has demonstrated significant effectiveness in treating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during the COVID-19 pandemic. By targeting distinct epitopes on the virus's spike protein, this therapy efficiently blocks viral entry into human cells and reduces the likelihood of immune escape, offering a robust defense against SARS-CoV-2. This review explores the underlying mechanisms of action, summarizing clinical outcomes that highlight the therapy's efficacy in reducing severe disease, hospitalization rates, and mortality. Additionally, the review addresses the safety profile and potential adverse events associated with the Casirivimab-Imdevimab cocktail, as well as current limitations such as evolving viral variants that may affect effectiveness and the challenges of large-scale production, cold-chain storage, and distribution logistics. Insights into the future of antibody cocktail therapies are discussed, emphasizing the necessity for innovative solutions to overcome these hurdles. Continued research is essential to refine antibody therapies, ensuring accessibility and sustained efficacy in combating emerging viral threats and optimizing the global COVID-19 response.

Keywords: COVID-19, cocktail, Casirivimab, Imdevimab, SARS-CoV-2

1. Introduction

Starting from late 2019, countries around the world were experiencing unprecedented rates of infection by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus with overwhelming healthcare systems. People experienced high mortality rates, particularly among populations such as the elderly and those with preexisting conditions. The virus was mainly spread by respiratory droplets, and COVID-19 patients start from symptoms such as fever and cough, some may progress into severe respiratory disorder, even death. The virus's high transmission rate and its ability to mutate into various strains created ongoing challenges in managing the disease and developing effective treatments [1].

Throughout the pandemic, different treatment approaches were developed and applied at different periods and regions globally, including antiviral drugs, corticosteroids, and oxygen therapy. Among them, monoclonal antibody (mAbs) therapy was widely adapted as one of the major treatment strategies that played a critical role in interfering with the progress of the disease prognosis, therefore, became a powerful tool to save lives during the COVID pandemic.

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The spike protein provides the spiky appearance to the coronaviruses and is the key element to allow the SARS-CoV-2 virus to enter into human body. By developing mAbs specifically targeting the spike protein, the virus will lose the ability to enter human cells [2]. However, as the virus evolved, so did the need for more targeted approach for antibody development.

During the process of antibody therapy development to treat COVID-19, a cocktail approach is often used by combining different monoclonal antibodies together in treatment of a single patient to maximize the effects of antibody therapy. This strategy was naturally applied stemming from physician's past clinical experience in antibody therapy targeting viruses, such as HIV [3], or SARS (called severe acute respiratory syndrome, which is a viral respiratory disease found in 2003) [4] treatment. Among the monoclonal antibody candidates, the combination of Casirivimab-Imdevimab has been particularly successful in preventing severe clinical outcomes in COVID-19 patients [5]

Casirivimab and Imdevimab are two IgG1 like humanized antibodies that bind at different epitopes on the spike protein, augments their therapeutic effects to its maximum strength in preventing the spike protein from performing its designated function of facilitating the SARS-CoV-2 virus entering human cells, subsequently reducing the likelihood of viral immune escape through mutations. This cocktail antibody approach, which has been used in the treatment of other virus infections, was critical in managing the pandemic's later stages and in combating emerging variants. This review delves into the mechanisms and efficacy of Casirivimab and Imdevimab, exploring their roles in neutralizing the virus and providing insights into the future of monoclonal antibody therapies for COVID-19 treatment, and potentially for other virus infection.

2. Rationale of Monoclonal Antibody Cocktail Therapy

2.1. Mechanisms of Viral Evasion and Mutation in Single-Antibody Therapies

SARS-CoV-2 is 79.6% genetically identical to SARS-CoV, which is responsible for the 2002 SARS outbreak [6]. Both viruses are positive sense viruses with single strand ribonucleic acid (RNA). Both SARS CoV and SARS-CoV-2 use a similar mechanism of virus entry utilizing its spike protein. The spike protein usually forms a dimer or trimer with glycoproteins, and projects from the surface of an virus particle. It binds to human angiotensin-converting-enzyme 2 (ACE2) receptor, which is usually expressed in the kidneys, lungs, heart, and intestines. Once the spike protein binds to the ACE2 receptor, it will help the virus entering into human cells [6]. Common symptoms of COVID include dyspnea, shortness of breath, fever, and cough, sometimes headache or diarrhea. Severe infection of SARS-CoV-2 may cause lungs congestion. With the COVID progression, this may cause lung failure and even death [6-8].

One major challenge in using single-antibody therapies to treat SARS-CoV-2 lies in the fact that the virus can escape from the immune responses by mutating its spike protein. Mutated spike protein can alter its epitopes that are targeted by neutralizing antibodies, reducing the effectiveness of these therapies. As the virus evolves, new variants emerge, making it harder for a single monoclonal antibody to provide long-lasting protection or treatment effects. This is why a cocktail approach using multiple antibodies targeting different regions of the spike protein, is critical for minimizing the risk of viral escape and improving the efficacy of the antibody treatment [8].

2.2. Casirivimab and Imdevimab: Complementary Roles

2.2.1. Benefits of Broader Epitope Coverage in Minimizing Escape Mutations

Casirivimab and Imdevimab utilize the format of recombinant humanized IgG1 like form and bind to non-competitive receptor binding domains of the spike protein in the SARS-CoV-2 virus. This

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binding blocks the virus from binding to the human ACE2 receptor, and consequentially prevents it from entering into human cells [5].

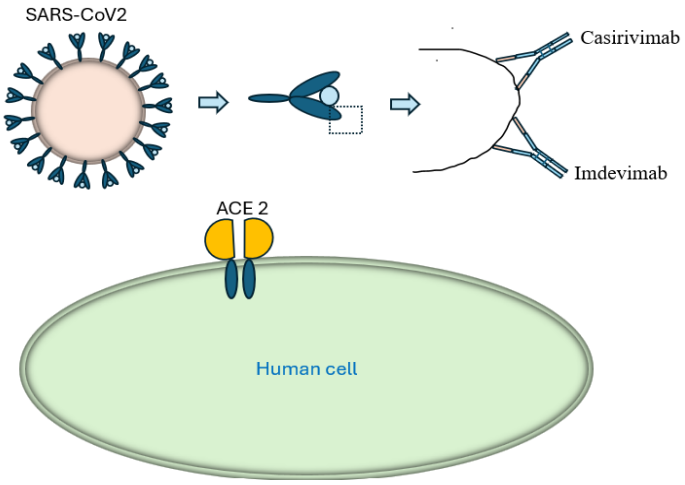

Figure 1: Mechanism of neutralizing monoclonal antibodies inhibition of SARS-CoV-2 targeted human cell engagement. Reprinted from [9]

As illustrated in Figure 1, Casirivimab and Imdevimab targeted non-competitive epitopes on the spike protein from a SARS-CoV-2 virus. The co-binding of both antibodies blocks the virus from engagement to the ACE2 Receptor on the surface of the human cell, therefore, preventing virus from entering to human body.

One of the major challenges for COVID-19 treatments lies in the fact that the ability of the virus to mutate its immunogenic epitopes constantly to escape an epitope-targeted therapy. While developing an epitope-based therapy requires time and resources, the constant changing of SARS-CoV-2's immunogenicity on its surface epitope posed difficulty in the development of a long-term effective antibody therapy. The rapid mutation of virus surface epitopes for immune escape requires medical therapies that can eradicate the virus before it mutates to the next variant or are able to broadly react to different SARS-CoV-2 variants, which calls for the development of a cocktail strategy for antibody therapy. With this principle, multiple combinations of mAbs cocktails therapies for COVID treatment were explored, and the combination of Casirivimab-Imdevimab stood out as one of the top picks [5, 9].

2.2.2. Scientific Basis for Using Multiple Antibodies Targeting Different Epitopes

As long as epitopes from one molecule are separated enough to allow spatial access of different mAbs, this molecule can be bound by more than one mAbs. For this reason, Casirivimab and imdevimab complement each other by binding to non-overlapping epitopes on the spike protein, and therefore, blocking the SARS-CoV-2 virus from binding to the human ACE2 receptor.

A synergistic effect was observed while both Casirivimab and Imdevimab mAbs were used for COVID-19 treatment. Casirivimab is weak to against variant B.1.351 (Beta) as a monotherapy. Alternatively, if Casirivimab is used together with Imdevimab, they will display high therapeutic efficacy [10, 11].

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3. Clinical Evidence for Cocktail Approach Using Casirivimab and Imdevimab

3.1. Clinical Trial Outcomes for the REGN-COV2 Cocktail

Casirivimab and Imdevimab, marketed as REGEN COV, are co-administered as a cocktail antibody therapy for COVID-19 treatment during its pandemic. This dual-antibody regimen demonstrated significant efficacy during clinical trials [5, 12].

On November 8, 2021, Regeneron Pharmaceuticals, Inc. (NASDAQ: REGN) reported that REGEN-COV substantially resulted in less hospitalization or death in COVID-19 patients with high-risk. This finding, detailed by O'Brien et al. (2021), was based on a Phase 3 trial that evaluated the prophylactic and therapeutic effectiveness of subcutaneously administered Casirivimab and Imdevimab [12]. The study was a pioneering step in COVID-19 treatment, offering promising evidence for monoclonal antibody therapies in reducing severe outcomes among COVID patients.

In the Regeneron-COV study (ClinicalTrials.gov number, NCT04452318) [12], COVID-19 patients who were at least 12 years old were enrolled within 96 hours after a diagnosis of SARSCoV-2 infection. A 1:1 randomized ratio was applied to these patients who received subcutaneous injection of REGEN-COV or placebo. The study results showed that with the Regeneron-COV cocktail antibody, a significant difference ($P < 0.001$) of less symptomatic SARS-CoV-2 infection was observed from the REGEN-COV group (1.5%) than the placebo group (7.8%). Between 2 to 4 weeks after injection, symptomatic SARS-CoV-2 infection were observed in only 0.3% participants from the REGEN-COV group (2/753) but 3.6% participants form the placebo group (27/752). The relative risk was reduced by 92.6%.

REGEN-COV can not only prevent people from developing COVID symptoms, but also prevent symptomatic infected participants from prolonged/worsening symptoms. COVID patients with symptoms, when receiving REGEN-COV, resolved the symptoms 2 weeks sooner than the placebo group. The subcutaneous REGEN-COV, therefore, demonstrated that it can prevent both symptomatic and asymptomatic SARS-CoV-2 infection infections. [12].

3.2. Efficacy of Casirivimab/Imdevimab in High-Risk and Immunocompromised Populations

The cocktail of Casirivimab and Imdevimab was used for various COVID-19 positive patients, including high risk patients. A real-world study demonstrated that Casirivimab and Imdevimab can effectively treat mild or moderate COVID patients at home with high-risk characteristics [13].

From December 2020 to April 2021 at Mayo Clinic sites in different states in the US, a 1: 1 ratio retrospective comparison was made between 696 mild or moderate symptomatic COVID patients who were treated by the casirivimab-imdevimab cocktail and 696 mild or moderate symptomatic COVID patients without the antibody therapy. Baseline characteristics of both groups were matched by the method called “propensity-matched”. Both groups have high-risk patients such as hypertension, obesity, diabetes mellitus, or heart failure, chronic kidney and lung diseases, or compromised immune systems [13].

The antibody group, when compared to the control showed significantly less 2-week all-cause hospitalization rates (1.3% vs 3.3%) with a 95% confidence interval (CI) between 0.5 - 3.7%. Similar trends were observed at 3 and 4 weeks. This study demonstrated that Casirivimab and Imdevimab treatment resulted in a significantly less hospitalization than patients with similar disease but without antibody treatment for high-risk patients with mild to moderate COVID-19 symptoms [13].

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4. Effectiveness Against Variants

As the SARS-CoV-2 mutates, it leads to immune escape where the host immune system fails to respond effectively to the pathogen, which is also known as immune evasion or antigenic escape. It is crucial to evaluate the therapeutic efficacy of cocktail antibody treatments across different SARS-CoV-2 variants.

Walinjkar et. al. [14] conducted a study on the real-world effect of Casirivimab and Imdevimab cocktail in treatment with patients who were infected by the SARS-CoV-2 delta and omicron variants. The purpose of this study is to understand the effect of this cocktail therapy on different SARS-CoV-2 variants. This retrospective analysis included 85 patients under 60 years old, with comorbidities and a BMI > 25 kg/m², selected from a larger cohort consists of 871 patients. Majority of the patients in both the variants groups received intravenously equal doses of 600 mg for both Casirivimab and Imdevimab. From day 3, the COVID symptoms started resolving and all symptoms were resolved by 14 days for both variants groups. No significant difference for symptom starts days, or days in hospital were observed between delta vs omicron groups. In conclusion, the Casirivimab and Imdevimab antibody cocktail demonstrated similar efficacy and safety profiles in COVID patients who were infected by either the delta or omicron variants [14].

5. Safety and Adverse Events

Clinical studies focusing on casirivimab and imdevimab cocktail therapy for COVID-19 treatment reported relatively few adverse events. Based on the REGEN-COV study, at least one adverse event happened in 20.2% of the antibody arm and 29.0% of the placebo arm. At least 2% of the participants had adverse events that were symptomatic, injection-site discomfort, or headache Non–COVID-19-related adverse events were observed in 16.0% of the REGEN-COV group and 16.5% of the placebo group [12]. Similarly, Razonable *et. al.* reported mild, non-hospitalization adverse events in 7 out of 696 subjects who received the Casirivimab and Imdevimab cocktail. These findings suggest that the administration of Casirivimab and Imdevimab monoclonal antibodies (mAbs) presents a low risk to COVID-19 patients [13].

6. Challenges and Considerations for Widespread Use

Despite the promising clinical outcomes demonstrated by Casirivimab and Imdevimab cocktail therapy to treat COVID-19, several challenges hinder its rapid expansion and adoption. One major hurdle is the complex and costly manufacturing process of mAbs, which is protected by intelligential property (IP) rights. Production involves high technical barriers, including high technical barrier of expensive producing steps, stringent quality assurance/control process and time-consuming timeline of production. These requirements limit the quantity of supply for the mAbs therapy in general, including the Casirivimab and Imdevimab cocktail, with only numbers of pharmaceutical companies having the capability to meet these demands. In addition, the storage and distribution conditions of mAbs are extremely temperature sensitive, that they require cold-chain transportation and handling, which further limits the rapid adoption of any mAbs therapy in an environment of huge demands under the needs of a global pandemic.

7. Future of Antibody Cocktail Therapies

The successful treatment effects of the Casirivimab and Imdevimab mAbs cocktail therapy underscore the promising potential of mAbs cocktail therapies in the future. Beside this combination, other mAbs cocktail, such as Tixagevimab and Cilgavimab [15], as well as Bamlanivimab and Etesevimab cocktail [16], have been developed and showed efficacy in COVID treatment.

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Importantly, IMM-BCP-01 as a triple antibody therapy, consists of three patient-derived broad neutralizing Abs targeting the spike protein. In IMM-BCP-01, two antibodies block ACE2 binding, with the last antibody chnages the conformation of the spike protein [17]. The effectiveness of a particular mAbs therapy must be demonstrated via clinical studies in both designated and eventually real-world population, with careful monitoring of potential side effects to ensure its safety and efficacy.

For future research, efforts should be focused on enhancing efficacy and safety profile for mAbs cocktail therapies, adopting to the immune escape property of virus for broad neutralization capacities. Additionally, efforts should be directed toward streamline licensing agreement, standardizing manufacturing, transportation and distribution processes to allow wider and faster adoption of the mAbs cocktail therapy in urgent need of pandemic human virus disease.

8. Conclusion

This article summarizes the mechanism, clinical outcomes, side effects, limitations and future considerations of the Casirivimab-Imdevimab cocktail therapy for COVID-19 treatment. The experience and lessons learned from the Casirivimab-Imdevimab cocktail therapy will largely benefit the research and development of future mAbs therapy, allow better and faster adoption of such therapy in any potential events that even with the magnitude of COVID-19, and lead human beings to a promising future of overcoming pandemic diseases.

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