

# Monoclonal Antibody Cocktail therapy for COVID-19: A Pharmacological innovation

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## Introduction

The novel SARS-CoV-2 infection has ripped through international health systems and protocols causing unprecedented mortality, morbidity and global trade deficits amounting to billions. The extreme speed of the virus coupled with the lack of a prior standardised treatment protocol has culminated into the perfect storm, further allowing the virus to take strongholds in almost every continent globally.<sup>1</sup>

## Evolution of pharmacotherapy in the treatment of COVID-19

The novel nature of COVID-19 and the lack of a pre-established and vetted treatment protocol lead to the use and trials of a very wide array of pharmaceuticals in the onset of the global pandemic. Drugs ranging from corticosteroid therapy to anthelmintic drugs such as ivermectin have been tried and administered throughout the pandemic. Therapeutic plasma exchange therapy (TPE) has shown positive results in severe patients. The majority of the current protocols have recommend initiating treatment with Remdesivir which is to be followed by high doses of the corticosteroid dexamethasone. Despite the use of such drugs, deaths precipitated by COVID-19 remain on the ascent. Newer

## Abstract

The novel SARS-CoV-2 infection has ripped through international health systems and protocols causing unprecedented mortality, morbidity and global trade deficits amounting to billions. Various monoclonal antibodies have been proposed for use in the treatment of COVID-19 infections. One such drug is LY-CoV555 which in an ongoing phase two trial study conducted by Chen P et al, showed to have an elimination of 99.97% of the viral RNA. The monoclonal antibody 47D11 discovered by Wang et al, binds to SARS-CoV-2. The 47D11 has been reconfigured into a human IgG1 isotope. It has shown that the 47D11 mAb effectively neutralizes the SARS-COV-2 virus. The stance and development however for the treatment of COVID-19 with monoclonal antibodies has shifted from a monotherapy to a so-called monoclonal antibody “cocktail” therapy.

REGN-COV2 is such a cocktail developed with the use of two monoclonal antibodies REGN10987 and REGN10933 which have subsequently been named Imdevimab and Casirivimab. REGN-COV2 is currently under study in four phase 2 and 3 trial studies. These studies are multicentric in nature and are being conducted to evaluate the drug’s efficacy, dosing and clinical use as compared to the placebo. The mechanism of action of such monoclonal antibodies is related chiefly to the inhibition of the virus’s ability to perform its invasion and multiplication within the human body.

The severity coupled with the sheer novelty of the SARS-CoV-2 virus demands the use of newer therapies to both decrease the mortality and morbidity in patients suffering from the infection. The use of a combination of monoclonal antibodies is thereby well established and evident to both decrease the viral infection load, but is also useful in disrupting the virus’s life cycle and thus decreases the replication and viral shedding. It is therefore poignant that a combination of monoclonal antibodies, a “cocktail” therapy is employed so as to attack the virus at its various stages and thus this multifaceted approach may enhance the patient’s prognosis.

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monoclonal antibody therapies and drug regimens are under study and may save countless of lives. 2-5

### History of monoclonal antibody drugs

Monoclonal antibodies are produced via the continuous culture of hybridoma cells which allows for a limitless supply of antibodies. Initially monoclonal antibodies were produced via the use of mice; however, the innate human anti-mouse immune reaction has led to the development and production of human monoclonal antibodies which avoids the immunogenicity seen with rodent antibodies. 6-7

The use of monoclonal antibodies has been immeasurable and these drugs have been used in the treatment of a vast array of diseases spanning from various cancers, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, psoriasis to transplant rejection reactions. 8

### Monoclonal antibody drugs for use in COVID-19

Various monoclonal antibodies have been proposed for use in the treatment of COVID-19 infections. One such drug is LY-CoV555 which in an ongoing phase two trial study conducted by Chen P et al, showed to have an elimination of 99.97% of the viral RNA. Patients within the study whom received the LY-CoV555 as opposed to the placebo presented with milder symptoms and only 1.6% of the patients receiving the monoclonal antibody required emergency hospitalization as opposed to the 6% in patients who received the placebo. 9

The monoclonal antibody 47D11 discovered by Wang et al, binds to SARS-CoV-2. The 47D11 has been reconfigured into a human IgG1 isotope. Through the study of 47D11 via ELISA it has been shown to effectively inhibit the Spike protein docking to the angiotensin converting enzyme receptor-2 (ACE2 receptor). It has shown that the 47D11 mAb effectively neutralizes the SARS-COV-2 virus.10

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### Monoclonal Cocktail therapy

REGN-COV2 is such a cocktail developed with the use of two monoclonal antibodies REGN10987 and REGN10933 which have subsequently been named Imdevimab and Casirivimab. This cocktail has been developed by the pharmaceutical company Regeneron. The REGN-COV2 cocktail has been produced through the study of a large heterogeneous set of human antibodies isolated from convalescent patients and engineered mice B cells. The selection of these antibodies was pivoted on their neutralization, binding as well as structural capabilities. By virtue of the above characteristic the most potent pair of mAbs namely imdevimab and casirivimab were identified to develop REGN-COV2. 11

REGN-COV2 is currently under study in four phase 2 and 3 trial studies. These studies are multicentric in nature and are being conducted to evaluate the drug's efficacy, dosing and clinical use as compared to the placebo. The studies are taking place in the USA, Brazil, Chile and Mexico and is expected to enrol 1850 hospitalized and 1050 non-hospitalized subjects. REGN-COV2 has been shown to dramatically reduce the viral load in patients with a drastically improved viral reduction as compared to patients receiving the placebo. COVID-19 positive subjects whom were administered REGN-COV2 were found to record

an average 10-fold diminution in their viral load as when collated to the patients receiving the placebo. The study also depicted a marked decrease in hospitalization of patients being treated with REGN-COV2 as opposed to those receiving the placebo.12

A Phase 3 prevention trial (NCT04452318) testing REGN-COV2 on healthy SARS-CoV-2 negative individuals exposed to a high household risk of exposure to COVID-19 via an infected patient versus a placebo drug in circumventing both symptomatic and symptomatic infections is underway and the results are expected to be positive as it has been noted that REGN-COV2 is more effective in patients who are sero-negative as opposed to sero-positive. 12-14

### Mechanism of action

The mechanism of action of such monoclonal antibodies is related chiefly to the inhibition of the virus's ability to perform its invasion and multiplication within the human body. The virus has a pathognomic structure with various vital proteins namely the nucleocapsid, membrane protein, envelope protein and the spike protein (N, M, E and S proteins respectively) which play a substantial role in the viral entry and replication within the host. The effective specific therapeutic molecules (monoclonal antibodies) can directly interrupt the vital stages of the SARS-CoV-2 lifecycle and/or disrupt the various receptor proteins located on the human host cell surface in order to restrict the binding of the virus and thereby, subsequently blocking the attachment and entry thereof. 15,16

The disruption of the viral cycle can be achieved through the use of fusion inhibitors, protease inhibitors, anti-ACE2 monoclonal antibodies and anti SARS-CoV-2 neutralizing monoclonal antibodies. The drugs mainly focusing on the spike protein and the host cell surface receptor chiefly, Angiotensin converting enzyme 2 (ACE2) receptors; in order to prevent the interaction of the receptor binding domain located in the S protein and target receptor on the host cell surface. This thereby restraining the virus via binding and blocking the virus's attachment and entry. Passive immunization of antibodies that can recognize the specific epitopic sectors in the SARS-CoV-2 particle will inhibit the viral replication and subsequently the disease severity. Such antibodies for passive immunotherapy can be acquired via the isolation of the immunocontents from the blood of infected patients or may be synthesized in a laboratory. 15-17

### Adverse drug reactions

In a double-blinded phase 1-3 trial comprised of outpatients with COVID-19, conducted by Weinreich DM, et al reported that REGN-COV2 were associated with rare and low-grade adverse drug reactions. A low incidence of serious adverse drug reactions that occurred or worsened during the observation period and of infusion-related or hypersensitivity reactions were reported.13

### Conclusion

The severity coupled with the sheer novelty of the SARS-CoV-2 virus demands the use of newer therapies to both decrease the mortality and morbidity in patients suffering from the infection. The use of a combination of monoclonal antibodies is thereby well established and evident to both decrease the viral infection load, but is also useful in disrupting the virus's life cycle and thus decreases the replication and viral shedding. It is therefore poignant that a combination of monoclonal antibodies, a "cocktail" therapy is employed so as to attack the virus at its various stages and thus this multifaceted approach may enhance the patient's prognosis.

**References:**

1. Khan M, Adil SF, Alkhatlan HZ, Tahir MN, Saif S, Khan M, et al. COVID-19: A Global Challenge with Old History, Epidemiology and Progress So Far. *Molecules*. 2020 Dec 23;26(1):39.  
<https://doi.org/10.3390/molecules26010039>

2. Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, et al. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial. *JAMA*. 2020 Oct 6;324(13):1307-1316.  
<https://doi.org/10.1001/jama.2020.17021>

3. Therapeutic Management of Hospitalized Adults With COVID-19 [Internet] [cited 2021 September 12]. Available from: <https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/hospitalized-adults--therapeutic-management/>

4. Kory P, Meduri GU, Iglesias J, Varon J, Marik PE. Clinical and Scientific Rationale for the "MATH+" Hospital Treatment Protocol for COVID-19. *J Intensive Care Med*. 2021 Feb;36(2):135-156.  
<https://doi.org/10.1177/0885066620973585>

5. Remdesivir [Internet]. [cited 2021 September 12]. Available from: <https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/remdesivir/>

6. Nelson PN, Reynolds GM, Waldron EE, Ward E, Giannopoulos K, Murray PG. Monoclonal antibodies. *Mol Pathol*. 2000 Jun;53(3):111-7.  
<https://doi.org/10.1136/mp.53.3.111>

7. Waldmann H. Human Monoclonal Antibodies: The Benefits of Humanization. *Methods Mol Biol*. 2019;1904:1-10.  
[https://doi.org/10.1007/978-1-4939-8958-4\\_1](https://doi.org/10.1007/978-1-4939-8958-4_1)

8. Shepard HM, Phillips GL, D Thanos C, Feldmann M. Developments in therapy with monoclonal antibodies and related proteins. *Clin Med (Lond)*. 2017 Jun;17(3):220-232.  
<https://doi.org/10.7861/clinmedicine.17-3-220>

9. Chen P, Nirula A, Heller B, Gottlieb RL, Boscia J, Morris J, et al. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19. *N Engl J Med*. 2021 Jan 21;384(3):229-237.  
<https://doi.org/10.1056/NEJMoa2029849>

10. Wang C, Li W, Drabek D, Okba NMA, van Haperen R, Osterhaus ADME, et al. Publisher Correction: A human monoclonal antibody blocking SARS-CoV-2 infection. *Nat Commun*. 2020 May 14;11(1):2511.  
<https://doi.org/10.1038/s41467-020-16452-w>

11. Tuccori M, Ferraro S, Convertino I, Cappello E, Valdiserra G, Blandizzi C, et al. Anti-SARS-CoV-2 neutralizing monoclonal antibodies: clinical pipeline. *MAbs*. 2020 Jan-Dec;12(1):1854149.  
<https://doi.org/10.1080/19420862.2020.1854149>

12. Taylor PC, Adams AC, Hufford MM, de la Torre I, Winthrop K, Gottlieb RL. Neutralizing monoclonal antibodies for treatment of COVID-19. *Nat Rev Immunol*. 2021 Jun;21(6):382-393.

<https://doi.org/10.1038/s41577-021-00542-x>

13. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. *New England Journal of Medicine*. 2021 Jan 21;384(3):238-51.  
<https://doi.org/10.1056/NEJMoa2035002>

14. Celltrion accelerates development of COVID-19 antiviral treatment and aims to launch rapid self-testing kit. [Internet]. [cited 2021 September 12]. Available from: [https://www.celltrionhealthcare.com/en-us/board/newsdetail?modify\\_key=174&pagenumber=1&keyword=&keyword\\_type=](https://www.celltrionhealthcare.com/en-us/board/newsdetail?modify_key=174&pagenumber=1&keyword=&keyword_type=)

15. Shanmugaraj B, Siriwattananon K, Wangkanont K, Phoolcharoen W. Perspectives on monoclonal antibody therapy as potential therapeutic intervention for Coronavirus disease-19 (COVID-19). *Asian Pacific journal of allergy and immunology*. 2020 Mar 1;38(1):10-8.  
<https://doi.org/10.12932/AP-200220-0773>

16. Loganathan S, Athalye SN, Joshi SR. Itolizumab, an anti-CD6 monoclonal antibody, as a potential treatment for COVID-19 complications. *Expert Opinion on Biological Therapy*. 2020 Sep 1;20(9):1025-31.  
<https://doi.org/10.1080/14712598.2020.1798399>

17. Deb P, Molla MM, Rahman KS. An update to monoclonal antibody as therapeutic option against COVID-19. *Biosafety and Health*. 2021 Feb 10.  
<https://doi.org/10.1016/j.bsheal.2021.02.001>