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A NARRATIVE REVIEW OF THE ANTI-SARS-COV2 MONOCLONAL ANTIBODIES COCKTAIL - CASIRIVIMAB PLUS IMDEVIMAB FOR SARS-COV2 INFECTION

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ABSTRACT: Numerous therapeutic and prophylactic interventions are tried being developed and tried for COVID-19, from repurposed drugs, antivirals to immunotherapy including convalescent serum, vaccines and monoclonal antibodies to reduce the global burden of the disease. Vaccine-derived immunity develops over time and remains as the primary option for prophylaxis. Administration of neutralizing mAbs is an immediate and passive immunotherapy with the potential to reduce disease progression, hospitalizations and death. Antibody-based treatments are likely to be more effective if used during the early phase of the illness. Casarivimab together with Imdevimab, holds emergency use authorizations in several countries globally and in India. This review discusses the mechanism of action, current clinical indications, dose, use with other medications and vaccines, duration of protection, protection against variants and evidence of Casarivimab and Imdevimab monoclonal antibody cocktail therapy for mild to moderate COVID-19 patients.

INTRODUCTION: Coronavirus Disease-2019 (COVID-19) cases are soaring sky high worldwide since scientists first identified severe acute respiratory syndrome corona virus-2 (SARS CoV-2) in samples of bronchoalveolar lavage fluid from a patient in Wuhan in December 2019. COVID-19 is characterized by respiratory syndrome with a variable degree of severity, ranging from a mild upper respiratory tract illness to severe interstitial pneumonia and acute respiratory distress syndrome (ARDS) [1, 2]. Even though there was depression in number of cases in between, alarming reports of different variants of the virus are coming along.

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COVID-19 has had an unprecedented impact on the world's population. As of 31 January 2022, more than 376 million cases of COVID-19 and over 5.6 million deaths were reported globally, including over 41 million confirmed cases and over 49000 deaths in India [3]. Numerous therapeutic and prophylactic interventions are being developed and tried for COVID-19, from repurposed drugs, antivirals to immunotherapy including convalescent serum, vaccines and monoclonal antibodies to reduce the global burden of the disease.

Being an RNA virus, SARS-CoV-2 is prone and evolved through random mutations, which is a threat to many therapeutic approaches. B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.617.2 (Delta), B.1.1529 (Omicron) are some important mutant variants detected over time. These new mutations can affect the virus' ability to evade adaptive immune responses from past SARS-CoV-

2 infection or vaccination, which is a real risk for reinfection and decreases vaccines' efficacy [4]. Immunotherapy proved its efficacy in treating viral infectious diseases in the past. Vaccine-derived immunity develops over time and it still remains as the primary option for prophylaxis. But uncertainties remain about the duration of protection and efficacy of current vaccines against emerging SARS-CoV-2 variants. Neutralizing monoclonal antibodies (mAbs) are recombinant proteins that can be derived from the B cells of convalescent patients or humanized mice exposed to SARS CoV-2 antigens. These mAbs block entry of the virus and are therefore termed as 'neutralizing' and can be used as a type of passive immunotherapy in already infected individuals, which rapidly reduces the viral load and controls disease progression, especially in high-risk patients [5]. Today, the process to mass-produce recombinant mAbs has become scalable to meet demand and is cost-competitive with other treatments [6]. This review discusses the mechanism of action, current clinical indications, dose, use with other medications and vaccines, duration of protection, protection against variants and evidence of Casarivimab and Imdevimab monoclonal antibody cocktail therapy for mild to moderate COVID-19 patients in an outpatient/ambulatory setting who are at high risk of developing severe disease.

METHODOLOGY: Articles discussing mAbs in COVID-19 treatment were searched from publicly available databases, including PubMed and Google Scholar. Key search terms and phrases included antibiotics-based treatment for SARS CoV2 infection; Anti-SARS-CoV-2 Monoclonal Antibodies; Casirivimab plus imdevimab; COVID 19; Monoclonal Antibodies; Treatment. Articles published up to January 31, 2022, were included in the review.

Role of Monoclonal Antibodies in SARS CoV-2 Infection: SARS-CoV-2 is a single-stranded RNA virus coming under the same genus beta coronavirus as severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and Middle East respiratory syndrome coronavirus (MERS-CoV) [7]. The pathogenesis of COVID-19 illness occurs in two distinct phases, an early stage characterized by profound SARS CoV-2 viral replication followed by a late phase characterized by a hyper-inflammatory state induced 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 resulting in a prothrombotic state. Antiviral therapy and antibody-based treatments are likely to be more effective if used during the early phase of the illness, and immunomodulating therapies, either alone or in combination with antiviral and antibody-based therapies, may be more effective when used in the later stage to combat the cytokine-mediated hyperinflammatory state that causes severe illness [8]. Preventing the progression of COVID-19 illness in patients with mild to moderate forms of the disease is crucial to improving associated clinical outcomes.

The SARS-CoV-2 genome encodes four major structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N), as well as nonstructural and accessory proteins. The spike protein is further divided into two subunits, S1 and S2. S1 subunit contains two functional domains, the N-terminal domain (NTD) and a receptor-binding domain (RBD). S2 subunit contains three functional domains, fusion peptide (FP), and heptad repeat (HR) 1 and 2. SARS CoV-2 binds the host cell through interaction between its S1-RBD and the cell membrane receptor, following con-formational changes in S2 subunits and result in virus fusion and entry into the target cell. The cell surface angiotensin-converting enzyme 2 (ACE2) receptor expressed abundantly on the respiratory epithelium, such as type II alveolar epithelial cells acts as the main host cell receptor for SARS CoV-2. The host transmembrane serine protease 2 (TMPRSS2) helps in priming of the spike protein for binding of RBD with ACE2 [9, 10, 11]. SARS-induced down-regulation of ACE2 receptors in lung epithelium contributes to acute lung injury and subsequent ARDS pathogenesis.

Previously, Convalescent plasma therapy (CPT) or use of sera containing polyclonal antibodies from recovered SARS CoV-2-infected patients has been used to treat SARS CoV-2 infection. But lack of neutralizing antibodies, logistical difficulties in finding proper donors, and transfusion-related risks came as major drawbacks, and the development of monoclonal antibodies came as an alternative.

The mAbs can reduce the viral load by interfering with virus entry into a cell by targeting viral spike proteins, or limiting immune-mediated damage by regulating various immune mediators involved in pathogenesis. In this review, we focus on mAbs involving the former group. All currently developed anti-SARS CoV-2 mAbs target the viral S protein, including S1-RBD, S1-NTD, or S2 region though RBD-specific antibodies have greater potency to neutralize infection with divergent virus strains. These mAbs directed to the S protein block the binding of RBDs to their respective receptors and interfere with S2-mediated membrane fusion or entry into the host cell, thus inhibiting viral infections. Like other antiviral drugs, monoclonal antibodies when used as antiviral agents are also susceptible to developing resistance. Alterations in the viral genome can change the pathogenic potential of the virus resulting in the emergence of viral escape mutants, which may render the virus-resistant to a specific monoclonal antibody. To counter this viral escape phenomenon, a combination of monoclonal antibodies, commonly referred to as antibody cocktails, have been proposed with the rationale that combining two specific monoclonal antibodies that complement each other can prevent neutralization escape by targeting multiple viral epitopes [12].

Anti SARS CoV-2 Monoclonal Antibodies: Currently, three anti-SARS CoV-2 mAb products have received Emergency Use Authorizations (EUAs) from the Food and Drug Administration (FDA) [13] for the treatment of laboratory-confirmed SARS CoV-2 infection who are at high risk for progressing to severe disease and/or hospitalization.

Bamlanivimab Plus Etesevimab: These are neutralizing mAbs that bind to different but overlapping epitopes in the spike protein RBD of SARS CoV-2. Both the Gamma (P.1) and Beta (B.1.351) variants of the virus have reduced susceptibility to bamlanivimab and etesevimab. This combination has emergency use authorization from the FDA for clinical use in non-hospitalized patients with mild to moderate COVID-19 who are at increased risk for developing severe disease and/or hospitalization and post-exposure prophylaxis (PEP) for appropriate candidates.

Casirivimab Plus Imdevimab (CAS/IMD): These are recombinant human mAbs that bind to non-overlapping epitopes of the spike protein RBD of SARS CoV-2. This combination was granted emergency use authorization from FDA in November 2020 for clinical use in non-hospitalized patients (aged ≥12 years and weighing ≥40 kg) with laboratory-confirmed SARS CoV-2 infection and mild to moderate COVID-19 who are at high risk for progressing to severe disease and/or hospitalization. For appropriate candidates, this combination has also been granted EUA from the FDA for PEP.

Sotrovimab: This mAb was originally identified in 2003 by a SARS CoV survivor. It targets an epitope in the RBD of the spike protein that is conserved between SARS CoV and SARS CoV-2. This monotherapy was granted emergency use authorization for clinical use in non-hospitalized patients (aged ≥12 years and weighing ≥40 kg) with laboratory-confirmed SARS CoV-2 infection and mild to moderate COVID-19 high risk for progressing to severe disease and/or hospitalization.

The high risk category is defined as those with age >=60 years, obesity, cardiovascular disease, including hypertension, chronic lung disease, including asthma, type 1 or type 2 diabetes mellitus, chronic kidney disease, including those on dialysis, chronic liver disease, immunosuppressed, based on investigator's assessment. Examples include cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of AIDS), sickle cell anaemia, thalassemia, and prolonged use of immune-weakening medications [14].

Even though the Delta variant is susceptible to all the above mAbs, the Omicron (a variant of concern at present) is predicted to have markedly reduced in vitro susceptibility to bamlanivimab plus etesevimab and casirivimab plus imdevimab. The FDA revised the authorizations for these two monoclonal antibody treatments to limit their use only when the patient is likely to have been infected with or exposed to a variant that is susceptible to these treatments. Since sotrovimab retains its activity against the Omicron, it can be used [15].

The EUA allows the combination of Tixagevimab plus Cilgavimabto be used as SARS CoV-2 pre-exposure prophylaxis with available in vitro data suggest that the Omicron variant remains susceptible to this combination [16].

The Central Drugs Standards Control Organization (CDSCO) in India, on 5 May 2021, granted an Emergency Use Authorization to Roche (Genentech) and Regeneron for the use of the CAS/IMD cocktail in the country. This came in light of the second wave of the COVID-19 pandemic in India. Roche India maintains a partnership with Cipla, thereby permitting the latter to market the drug in the country [17].

As per the revised treatment protocol to optimize COVID treatment outcomes in Kerala dated 6th August 2021 [18], it was recommended to administer monoclonal antibodies (CAS/IMD) in COVID 19 patients with very high-risk factors in a timely fashion to prevent disease progression.

Casirivimab and Imdevimab (CAS/IMD) Therapy: CAS/IMD (also known as REGN-COV2) are IgG1 mAbs with unmodified Fc regions directed explicitly against the spike protein of SARS CoV-2. These MAbs bind to different parts of the S protein of SAR CoV-2, and it is rare to occur mutations on both sites simultaneously. This helps the antibody combination to escape through viral mutations.

They also retained their ability to neutralize all known S protein mutations in in-vitro studies [12]. In rhesus macaques and golden hamsters models infected with SARS-CoV-2, prophylactic and therapeutic treatment with CAS/IMD reduced viral load. Also, it diminished the incidence and severity of lung disease relative to a placebo [19].

The evidence from various clinical trials and studies is summarized in **Table 1**. The phase 3 double-blind, placebo-controlled randomized trial in outpatients with mild to moderate COVID-19 demonstrated that the CAS/IMD antibody cocktail reduced viral load with a more significant effect in patients whose immune response had not yet been stimulated or who had a high viral load at baseline [20]. There was a reduction in hospitalization or death among patients who received a lower and higher dose of casirivimab plus imdevimab [21].

In a separate trial that evaluated casirivimab plus imdevimab in symptomatic participants, there were similar reductions in viral load in the participants in the intravenous (IV) and subcutaneous (SC) arms of the trial [22]. However, because the safety and efficacy data for casirivimab plus imdevimab administered by SC injection are limited, this route of administration should only be used when IV infusion is not feasible or would lead to a delay in treatment. The real-world clinical data was obtained from a retrospective cohort study [23], done in 696 patients where patients who received casirivimab-imdevimab had significantly lower all-cause hospitalization rates at day 14, day 21 and day 28 compared with controls. In the RECOVERY trial [24] among patients hospitalised with COVID-19, the monoclonal antibody combination of casirivimab and imdevimab reduced 28-day mortality among patients who were seronegative at baseline. Casirivimab and Imdevimab antibody cocktail in the high-risk population reduced the requirement for mechanical ventilation and high flow oxygen [25]. Retrospective studies by Bierle DM *et al.* [26] and Kakinoki Y *et al.* [27] showed lower hospitalization rates in the vaccinated and unvaccinated cohorts during the delta surge and reduced further need for medical interventions in the antibody cocktail group.

Currently, casirivimab plus imdevimab is only authorized for use in non-hospitalized patients with COVID-19. In addition, rapid serology testing that can identify seronegative individuals in real-time is currently not widely available. Various clinical trials are ongoing to evaluate the efficacy and safety of Casirivimab-Imdevimab to prevent COVID-19 in immunocompromised adolescents and adults.

It is not yet known whether these mAb products provide clinical benefits in people with B-cell immunodeficiency or other immuno-deficiencies. Hypersensitivity, including anaphylaxis and infusion-related reactions, has been reported in patients who received anti-SARS-CoV-2 mAbs. Rash, diarrhea, nausea, dizziness, and pruritis have also been reported. Injection site reactions, including ecchymosis and erythema, were reported in clinical trial participants who received casirivimab plus imdevimab by SC administration [22, 28].

TABLE 1: EVIDENCE FROM CLINICAL TRIALS AND STUDIES

Author/ inclusion criteria	Study design/ intervention	Results
Weinreich DM *et al.* [20, 21] Inclusion Criteria: Patients aged ≥18 years who had a positive SARS-CoV-2 polymerase chain reaction result at randomization and who had one or more risk factors for progression to severe COVID-19	Double-Blind, Phase 3 randomised control adaptive trial Intervention: Single IV infusion of CAS 600 mg plus IMD 600 mg (n = 736) or placebo (n = 748) - CAS 1,200 mg plus IMD 1,200 mg (n = 1,355) or placebo (n = 1,341)	Interim results from 275 non-hospitalized patients demonstrated that the CAS/IMD antibody cocktail reduced viral load significantly in patients whose immune response had not yet been stimulated or who had a high viral load at baseline. Compared to placebo, there was 2.2% absolute reduction and a 70% relative reduction in hospitalization or death with receipt of casirivimab 600 mg plus imdevimab 600 mg. Comparable results were observed for IV infusions of casirivimab 1,200 mg plus imdevimab 1,200 mg, which demonstrated a 3.3% absolute reduction and a 71% relative reduction in COVID-19 related hospitalization or all-cause deaths
O'Brien MP *et al* [22] Inclusion Criteria: Participants (≥12 years of age) who were enrolled within 96 hours after a household contact received a diagnosis of SARS-CoV-2 infection.	Double-blind, randomized placebo-controlled trial Intervention: Total dose of 1200 mg of REGEN-COV or matching placebo administered by means of subcutaneous injection.	Overall, REGEN-COV prevented symptomatic and asymptomatic infections (relative risk reduction, 66.4%). Among symptomatic infected participants, the median time to resolution of symptoms was 2 weeks shorter with REGEN-COV than with placebo (1.2 weeks and 3.2 weeks, respectively), and the duration of a high viral load (>104 copies per milliliter) was shorter (0.4 weeks and 1.3 weeks, respectively)
Razonable RR *et al* [23] Inclusion Criteria: 696 patients who received casirivimab-imdevimab between December 4, 2020 and April 9, 2021 was compared to a propensity-matched control of 696 untreated patients with mild to moderate COVID-19 at Mayo Clinic sites in Arizona, Florida, Minnesota, and Wisconsin	A retrospective cohort Intervention: One-hour infusion of casirivimab (1200-mg dose) and imdevimab (1200-mg dose)	Compared to the propensity-matched untreated control, patients who received casirivimab-imdevimab had significantly lower all-cause hospitalization rates at day 14 (1.3% vs 3.3%), day 21 (1.3% vs 4.2%) and day 28 (1.6% vs 4.8%). Rates of intensive care unit admission and mortality at days 14, 21, and 28 were similarly low for antibody-treated and untreated group.s This gives a real world clinical data to support the use of casirivimab and imdevimab in mild to moderate COVID-19 patients.
Horby PW *et al* [24] Inclusion Criteria: 9785 patients with clinically suspected or laboratory confirmed SARS-CoV-2 infection	Randomised, controlled, open-label platform trial Intervention: Single dose of casirivimab 4g and imdevimab 4g by intravenous infusion (REGEN-COV group) were compared with usual care in patients hospitalised with COVID-19	There was no difference in 28-day all-cause mortality between CAS/IMD arm and the standard of care arm; 944 of 4,839 patients (20%) in the CAS/IMD arm died versus 1,026 of 4,946 patients (21%) in the standard of care arm (rate ratio 0.94; 95% CI, 0.86–1.03; P = 0.17). Subgroup of patients who were seronegative for the anti-spike protein antibody, there was a significant reduction in 28-day all-cause mortality in the CAS/IMD arm (396 of 1,633 CAS/IMD recipients [24%] died vs. 451 of 1,520 standard of care recipients [30%]; rate ratio 0.80; 95% CI, 0.70–0.91; P = 0.001).
Joy AP *et a*l [25] Inclusion criteria: Symptomatic COVID19 patients to evaluate the impact of Casirivimab and Imdevimab antibody cocktail in the high-risk population	Retro-prospective comparative observational study Intervention: Test (Casirivimab and Imdevimab treated patients, n = 79) and control (Non- Casirivimab and Imdevimab treated individuals, n = 73) subsets	Lesser requisite for mechanical ventilation (6.3%; p < 0.001), high flow oxygen (5.1%; p < 0.001) and no death during Casirivimab and Imdevimab therapy
Bierle DM *et al* [26] Inclusion criteria: All patients with COVID-19 in the US Midwest to compare the rates of hospitalization between casirivimab-imdevimab treated	Retrospective study Intervention: 630 patients with COVID-19 during the early period of the Delta surge in the community	Among 403 eligible patients for Mab, the 28-day hospitalization rate was 2.6% of 112 patients who received treatment with casirivimab-imdevimab, compared to 16.6% of 291 eligible high-risk patients who did not receive casirivimab-imdevimab (Odds Ratio [OR]: 0.138, 95% confidence interval (CI):

versus untreated patients		0.0426–0.4477, p = 0.001)Casirivimab-imdevimab treatment was associated with lower rates of hospitalization among the vaccinated and unvaccinated cohorts
Kakinoki Y *et al* [27] Inclusion criteria: Covid-19 patients with high-risk factors who underwent the antibody cocktail therapy, compared to those who were not given the cocktail therapy	Retrospective study Intervention: Equal doses of 600mg of casirivimab and imdevimab combined in a 100ml normal saline solution through intravenous infusion over 30 minutes, if applicable 55 patients receiving antibody cocktail therapy and 53 patients within initial isolation into non-medical facilities	Antibody cocktail therapy significantly reduced 70% in need for further medical interventions compared with the isolation (odds ratio=0.30, 95%CI [0.10-0.87], p=0.027)

Recommendations on CAS/IMD Therapy:

Dosage Schedule: Casirivimab 600 mg plus Imdevimab 600 mg administered as an intravenous (IV) infusion or as subcutaneous (SC) injections to treat non-hospitalized adults and paediatric patients (12 years of age and older weighing at least 40 kgs) with mild to moderate COVID-19 who are at high risk of clinical progression. When using anti-SARS CoV-2 mAbs, treatment should start as soon as possible after the patient receives a positive result on a SARS CoV-2 antigen test or nucleic acid amplification test (NAAT) within 10 days of symptom onset [13].

Limitations: Anti-SARS CoV-2 mAbs are not authorized for use in patients hospitalized with severe COVID-19, who require oxygen therapy due to COVID-19, or who require increasing baseline oxygen therapy due to COVID-19 in those who were previously on chronic oxygen therapy at baseline due to non-COVID-19 related comorbidity as it may be associated with worse clinical outcomes [13].

The mAbs must not be administered to patients with known hypersensitivity to either ingredient of casirivimab or imdevimab as hypersensitivity reactions and infusion-related reactions are most commonly encountered adverse events. Data regarding the safety and efficacy of mAbs in patients with renal failure or hepatic impairment are limited. Pregnancy-specific data on the use of these mAbs are insufficient. Therapy should not be withheld in pregnancy but should be used if benefits outweigh the risk.

Vaccination: mAb therapy may interfere with vaccine-induced immune responses, and so SARS-CoV-2 vaccination for people who have received anti-SARS-CoV-2 mAbs be deferred until ≥90 days after the therapy is completed [29]. The rationale for a 90-day deferral is not based on clinical trials but on general assumptions that consider the estimated half-life of such therapies and the premise that reinfection is uncommon for 90 days after initial infection.

Current Scenario: REGN-COV2 (CAS/IMD) is available in India through a tie-up between Swiss drug company Roche and Indian company Cipla. The antibody cocktail is made available through Cipla's distribution network across the country. The private and public healthcare institutions can place an inquiry by reaching out to their nearest Cipla distributor. The antibody cocktail is available in a multi-dose pack, with each suited to treat two patients and costs around 1.20 lakhs. The price for each patient dose [a combined dose of 1200 mg (600 mg of Casirivimab and 600 mg of Imdevimab)] is INR 59,750 inclusive of all taxes [30]. The patient will have to pay for both doses if a second patient is not available. This is because once opened; a vial has to be used for the second patient within 48 hours if stored at 2 to 8 degrees Celsius.

The insurance firms will not reimburse this expensive drug as it is an outpatient procedure where patients are given the drug as an IV infusion for over an hour. No inpatient admission is required. When logistical or supply constraints limit the availability of anti-SARS CoV-2 mAbs and make it impossible to offer the therapy to all eligible patients, triage becomes necessary. The availability and distribution of authorized anti-SARS CoV-2 mAbs should be monitored to ensure equitable access to the products. The COVID-19

treatment guidelines panel (National Institutes of Health) suggests [31] a) Prioritizing the treatment of COVID-19 over post-exposure prophylaxis of SARS CoV-2 infection b) Prioritizing anti-SARS CoV-2 mAb therapy for unvaccinated or incompletely vaccinated individuals and vaccinated individuals who are not expected to mount an adequate immune response (*e.g.,* individuals who are immunocompromised or on immunosuppressive medications or individuals aged ≥65 years). c) Prioritizing the use of anti-SARS CoV-2 mAb therapy for patients at highest risk of clinical progression. The emergency authorization use of monoclonal therapies in combating COVID-19 appears promising. Limited published data regarding the adverse effects and drug-drug interactions with these therapies are available. Hence, its clinical use in patients non-hospitalized with COVID-19 illness who are at high risk of developing severe illness requires a holistic approach and inter-professional communication and care coordination to minimize adverse reactions and improve clinical outcomes. The patient should be monitored closely during the infusion, and at least 1 hour after the infusion is complete to look for infusion-related adverse effects. The hospitals and healthcare communities should have a plan in place to triage moderate and high-risk patients for additional therapy, such as monoclonal antibodies, on an outpatient basis.

CONCLUSION: Though vaccines are the best long-term strategy against COVID-19, mAbs also have potential benefits. Especially the unvaccinated or recently vaccinated high-risk population are benefited. The antiviral activity observed with neutralizing mAb treatment points to the benefits of early intervention. However, mAbs productions are complicated, and supply could be limited during the initial period. The offered protection would be temporary, and the duration of protection is yet to be known. They should be used based on a variant of virus, access, and risk-benefit ratio. The requirement of "the right patients at the right time" still holds, rather than the robust evidence base for universal usage.

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