Antibody Cocktail-Casirivimab and Imdevimab in COVID19

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ABSTRACT

Combination therapy of two neutralizing monoclonal antibody - Casirivimab and Imdevimab also referred to as "Antibody Cocktail" (REGN-COV2) for treatment and prophylaxis of COVID-19 is being evaluated. The rationale for this antibody combination is that it is unlikely that a mutation in the S protein of SARS- CoV-2 will simultaneously render both antibodies ineffective. The Casirivimab/ Imdevimab cocktail has received emergency use authorization (EUA) by the US FDA for the treatment of ambulatory patients with mild to moderate COVID-19 and a high risk of hospitalization .

Introduction :

A variety of prophylactic and therapeutic treatments are being developed or repurposed to battle COVID-19 caused by the severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). One promising approach to combat the COVID-19 pandemic involves development of monoclonal antibodies (mAbs) that can bind to and "neutralize" the virus in infected patients and are a novel class of antiviral intervention[1,2]. Neutralizing mAbs are recombinant proteins that can be derived from the B cells of convalescent patients or humanized mice[3].

Two non-competing, high-affinity human IgG1 anti-SARS-CoV-2 monoclonal antibodies (mAbs) Casirivimab (REGN10933) and Imedevimab (REGN10987) are developed by Regeneron Pharmaceuticals, Inc. and F. Hoffman-La Roche, Ltd (Roche). This combination therapy of Casirivimab and Imdevimab also referred to as "Antibody cocktail" (REGN-COV2) for treatment and prophylaxis of COVID-19 is being evaluated. Casirivimab and Imdivimab are intended to be utilised as a combination treatment and should not be used individually as monotherapy[4]. The rationale for this antibody combination is that it is unlikely that a mutation in the S protein of SARS- CoV-2 will simultaneously render both antibodies ineffective. After extensive in vitro testing, this combination retained its ability to neutralize all known S protein mutations[5]. Further, Casirivimab and Imdevimab combination therapy-initiated antibody mediated cytotoxicity and cellular phagocytosis in virally infected cells in vitro[6].

The Casirivimab / Imdevimab cocktail has received emergency use authorization (EUA) by the US FDA for the treatment of ambulatory patients with mild to moderate COVID-19 and a high risk of hospitalization[7], and the European Medicines Agency (EMA) has similarly recommended Casirivimab/Imdevimab for use in COVID-19 patients who do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19[8]. U.S. Food and Drug Administration (FDA) updated the EUA for Casirivimab / Imdevimab Antibody cocktail, lowering the dose to 1,200 mg (600 mg Casirivimab and 600 mg Imdevimab), which is half the dose originally authorized. As part of the updated EUA, it should be administered by intravenous (IV) infusion; subcutaneous (SC) injections are an alternative when IV infusion is not feasible and would lead to a delay in treatment[9]. Central Drugs Standards Control Organisation (CDSCO) approved the antibody cocktail in May 2021, Roche India received an emergency use authorisation (EUA) for the antibody cocktail to treat mild to moderate Covid-19 in high-risk patients. The CDSCO's authorization was based on the data submitted for the EUA in the US, as well as the scientific opinion of the European Medicines Agency's (EMA)

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Committee for Medicinal Products for Human Use (CHMP)[10,11]. Casirivimab and Imdevimab are available in single-dose vials as a 300 mg / 2.5 mL (120 mg/mL) or 1332 mg / 11 mL (120 mg/mL) sterile, preservative-free aqueous solution to be diluted prior to intravenous infusion[12].

Pharmacology :

Mechanism of Action :

Casirivimab and Imdevimab are two recombinant human neutralized mAbs which are unmodified in the Fc regions. Casirivimab and Imdevimab bind to non-overlapping epitopes of the spike protein receptor binding domain (RBD) of SARS-CoV-2. Casirivimab, Imdevimab and the Casirivimab + Imdevimab combination blocks RBD binding to the human ACE2 receptor thereby blocking viral entry into host cells. The specific engineering of the two neutralising antibodies allows them to bind to different parts of the virus spike. This enables them to remain effective against various existing strains and decrease the risk of losing neutralization potency against new emerging variants[4].

Pharmacodynamics :

Casirivimab and Imdevimab was evaluated in trial R10933-10987-COV-2067 with doses of 1 and 3.33 times the recommended doses (1,200 mg Casirivimab and 1,200 mg Imdevimab; 4,000 mg Casirivimab and 4,000 mg Imdevimab) in ambulatory patients with COVID-19. A flat dose-response relationship for efficacy was identified for Casirivimab and Imdevimab at those two doses, based on viral load and clinical outcomes[13].

Pharmacokinetics :

Pharmacokinetic profiles of Casirivimab and Imdevimab are expected to be consistent with the profile of other IgG1 mAbs. Both Casirivimab and Imdevimab exhibited linear and dose-proportional pharmacokinetics (PK) between (600 mg of Casirivimab and 600 mg of Imdevimab) to (4,000 mg of Casirivimab and 4,000 mg of Imdevimab) doses following intravenous administration of single dose. The effect of different covariates (e.g., age, sex, race, body weight, disease severity, hepatic impairment) on the PK of Casirivimab and Imdevimab is unknown. Renal impairment is not expected to impact the PK of Casirivimab and Imdevimab, since mAbs with molecular weight > 69 kDa are known not to undergo renal elimination. Similarly, dialysis is not expected to impact the PK of Casirivimab and Imdevimab. Interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely[13].

Clinical Aspects :

Casirivimab and Imdevimab - antibody cocktail is authorized for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. It is supplied as individual vials to be administered together[9].

Definition of High-Risk Patients[9] :

The following medical conditions or other factors may place adults and pediatric patients (age 12-17 years and weighing at least 40 kg) at higher risk for progression to severe COVID-19 :

- Older age (age = 65 years of age)
- Obesity or being overweight (for example, BMI >25 kg/m2, or if age 12-17, have BMI =85th percentile for their age and gender based)
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immuno-suppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases, interstitial lung disease, cystic fibrosis and pulmonary hypertension.
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity.

Limitations of Authorized Use[9] :

Casirivimab and Imdevimab antibody cocktail is not authorized for use in patients who are hospitalized or who require oxygen therapy or who require an increase in baseline oxygen flow rate due to COVID-19. Benefit of treatment has not been observed in patients hospitalized due to COVID-19 and may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high-flow oxygen or mechanical ventilation.

Efficacy of treatment in ambulatory patients :

Casirivimab and Imdevimab are being investigated as a cocktail in the ambulatory setting in a phase 1/2/3 trial (NCT04425629) taking place across several countries. Data have been reported from the phase 3 study (N = 4567) evaluating 1200 mg or 2400 mg Casirivimab / Imdevimab versus placebo in patients with more than one risk factor for severe COVID-19. The trial met its primary endpoint and revealed that the Casirivimab / Imdevimab cocktail significantly reduced the risk of hospitalization or death by 70% in the 1200 mg dose arm ($p = 0.0024$) and 71% in the 2400 mg dose arm ($p < 0.0001$) compared with placebo[14]. All key secondary endpoints were also met, including a four-day reduction in the median duration of symptoms (both doses; $p < 0.0001$) versus placebo. An ongoing dose-ranging phase 2 companion trial in low-risk symptomatic or asymptomatic non-hospitalized patients with COVID-19 (NCT04666441) showed significant and comparable viral load reductions across Casirivimab / Imdevimab doses ranging from 300 mg to 2400 mg delivered via intravenous (IV) or sub-cutaneous (SC) routes[14].

Efficacy of Treatment for Hospitalized Patients :

Hospitalized patients with COVID-19 are a difficult-to-treat population that are associated with extremely poor outcomes, including ~ 25% mortality and significant requirements for critical care[15,16]. The Casirivimab / Imdevimab cocktail is being investigated in a placebo-controlled phase 1/2/3 trial of hospitalized adult patients with COVID-19 (NCT04426695). However, following an independent data monitoring committee evaluation, a recommendation was made to proceed with recruitment only in patients requiring no or low-flow oxygen, as the benefitrisk profile for patients requiring high-flow oxygen or mechanical ventilation was considered unfavorable[17]. This trial is ongoing, but a futility analysis was conducted among 217 patients requiring low-flow oxygen who were SARS-CoV-2 seronegative at baseline, a group that were shown to have an increased risk of death compared to those that had already mounted an antibody response[18].

Recently Regeneron Pharmaceuticals announced positive results from the largest trial, "UK RECOVERY trial" assessing any monoclonal antibody treatment in patients hospitalized with severe Covid-19. The UK RECOVERY trial found that adding investigational antibody cocktail of casirivimab and imdevimab to usual care reduced the risk of death by 20% in patients who had not mounted a natural antibody response on their own against SARS-CoV-2, compared to usual care on its own. It is likely that Regeneron will share new data with regulatory authorities immediately and request that the U.S. EUA be expanded to include appropriate hospitalized patients.[19]

Efficacy of Prophylaxis :

Vaccines will remain the most appropriate measure to deliver COVID-19 protection to the majority of individuals. However, it is likely that nAbs will play an important role in providing short-term protection for those who are unvaccinated or do not respond well to vaccination (e.g immunocompromised individuals), as well as during periods when vaccines do not provide sufficient protection from circulating variant viruses[18].

SC injection of the Casirivimab / Imdevimab cocktail is also being investigated for post-exposure prophylaxis in an ongoing placebo-controlled phase 3 trial involving healthy adult household contacts of individuals with a positive SARS-CoV-2 reverse-transcription polymerase chain reaction (RT-PCR) test (NCT04452318). Initial results involving an exploratory analysis of the first ~ 400 participants

showed that Casirivimab / Imdevimab prophylaxis resulted in complete prevention of symptomatic COVID-19 (0/186) among household contacts, compared with a frequency of 3.6% (8/223) among household contacts receiving placebo, and a 51% reduction in PCR-positive infection (5.4% [10/186] vs. 10.3%[20].

Adverse Events :

Data on safety were collected in various trials performed. Targeted adverse events that were collected during the study COV-2067 included grade = 2 infusion-related reactions (urticaria, pruritis, flushing, pyrexia, shortness of breath, chest tightness, nausea, vomiting, rash) through day 4 and grade = 2 hypersensitivity reactions through day 29, and in phase 1 only, all grade 3 and grade 4 treatment-emergent adverse events (TEAEs) occurred[9].

Use in Specific Populations :

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes in pregnancy or presence of Casirivimab and/or Imdevimab in human milk or animal milk, the effects on the breast fed infants[9].

Challenges :

Besides the challenges associated with cost / access, large-scale manufacturing and storage[21], the largest hurdle that currently exists, in both the ambulatory outpatient and prophylaxis settings, is mode of administration and Casirivimab / Imdevimab cocktail that have been granted EUA by the FDA for treatment of COVID-19 in the outpatient setting, but are administered by IV infusion, a procedure that, whilst commonplace in hospitals, creates substantial challenges in a community setting. An alternative to IV infusion for nAb delivery includes SC injection, which is being investigated for the Casirivimab / Imdevimab cocktail in the COVID-19 post-exposure prophylaxis setting (NCT04452318) .

Conclusion :

A number of neutralizing monoclonal antibodies are in various phases of development for COVID-19 treatment and prophylaxis, and several promising candidates have progressed to evaluation in the clinical trial setting. Emerging data suggest nAbs like Caserivimab and Imdevimab are particularly effective in preventing patients with risk factors from progressing to severe disease requiring hospitalization. Studies in hospitalized patients are ongoing. Cocktail therapy may provide a powerful way to minimize mutational escape by SARS-CoV-2 In this respect, future studies investigating the safety and efficacy of different combinations of nAbs will be important.

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