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Is antibody cocktail offering the right mix?

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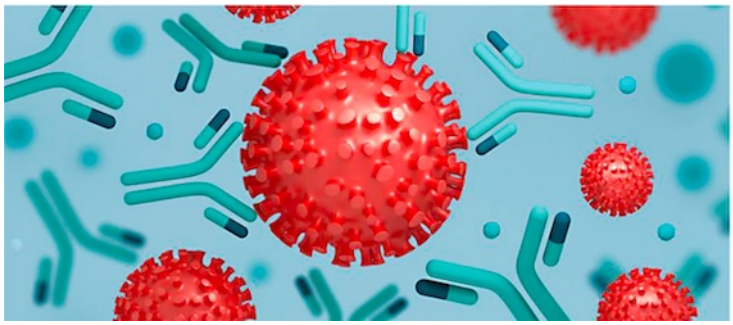

India continues to roll out vaccines for the prevention of COVID-19. While the vaccination drive continues, India has been considering alternative therapies for the treatment of COVID-19. On May 5, 2021, the Central Drugs Standards Control Organisation (CDSCO) provided emergency use authorisation for the antibody cocktail (casirivimab and imdevimab) in India. Former US President, Donald Trump was administered the experimental Regeneron antibody treatment in October 2020, when he tested positive for COVID-19.

The antibody cocktail has been developed by US biotechnology company Regeneron, in association with Roche Pharma. The antibodies bind themselves to two different sites on the SARS-CoV-2 spike protein, neutralising the ability of the virus to infect human cells.

Cipla is marketing the drug manufactured by Roche Pharma in India. The drug is accessible through hospitals and COVID-19 treatment centres. It can in total potential benefit 200,000 patients as each of the 100,000 packs that will be available in India offers treatment for two patients. Cipla is distributing the product by leveraging its strong distribution strengths across the country. The drug will be available through leading hospitals and COVID-19 treatment centres.

The cocktail is to be administered for the treatment of mild to moderate COVID-19 in adults and paediatric patients (12 years of age or older, weighing at least 40 kg) who are confirmed to be infected with SARS-COV-2 and who are at high risk of developing severe COVID-19 disease and do not require oxygen. The pharma majors (Cipla, Roche) claim that it has can help these high-risk patients before their condition worsens, reducing the risk of hospitalisation and fatality by 70 per cent and shortening the duration of symptoms by four days.

Each pack of antibody cocktail contains one vial of casirivimab and one vial of imdevimab totalling 2400 mg of the antibody cocktail (one vial of casirivimab (1200 mg) and one vial of imdevimab (1200 mg). Each pack can treat two patients as the dosage per patient is a combined dose of 1200 mg (600 mg of casirivimab and 600 mg of imdevimab) administered by intravenous infusion or subcutaneous route. The vials need to be stored at 2°C to 8°C.

If opened for the first patient' dose, a vial can be used for the second patients' dose within 48 hours if stored at 2°C to 8°C. The price for each patient dose [a combined dose of 1200 mg (600 mg of casirivimab and 600 mg of imdevimab)] will be Rs 59,750 inclusive of all taxes. The maximum retail price for the multi-dose pack is Rs 119,500 inclusive of all taxes.

The Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial has demonstrated that the investigational antibody combination developed by Regeneron reduces the risk of death when given to patients hospitalised with severe COVID-19 who have not mounted a natural antibody response of their own.

Previous studies in non-hospitalised COVID-19 patients have shown that the treatment reduces viral load, shortens the time to resolution of symptoms, and significantly reduces the risk of hospitalisation or death.

In a small trial in hospitalised patients, preliminary evidence suggested a clinical benefit in patients who had not mounted a natural antibody response of their own when they entered the trial (were seronegative). RECOVERY is the first trial large enough to determine definitively whether this treatment reduces mortality in patients hospitalised with severe COVID-19.

“The hope was that by giving a combination of antibodies targeting the SARS-CoV-2 virus we would be able to reduce the worst manifestations of COVID-19. There was, however, great uncertainty about the value of antiviral therapies in late-stage COVID-19 disease. It is wonderful to learn that even in advanced COVID-19 disease, targeting the virus can reduce mortality in patients who have failed to mount an antibody response of their own,” states Sir Peter Horby, Professor, Emerging Infectious Diseases, Nuffield Department of Medicine, University of Oxford, and Joint Chief Investigator, RECOVERY trial, UK.

On the other hand, Dr D Nageshwar Reddy, Chairman, AIG Hospitals, Hyderabad said that the real-world evidence of these monoclonal antibodies (mAb) is yet to be established but the clinical studies published in peer-reviewed journals including the New England Journal of Medicine are encouraging.

“The timing and patient selection becomes extremely important. Patients over 65, obese patients, with uncontrolled diabetes, cardiovascular patients, those who are under immunosuppressants like cancer patients are ideal candidates for this treatment. The timing also has to be appropriate where it needs to be given within three to seven days at max,” Dr Reddy added. This can be given to patients above 55 if they have heart-related issues like hypertension.

He further added, “Within one week, this treatment can help patients become RT-PCR negative. Pregnant women are not supposed to be given this treatment as we don’t have enough safety data for this subset of patients. There is also a possibility to explore the prophylactic usage of this combination especially among the high-exposure groups like healthcare workers. This to be highlighted that as per US FDA, benefits of this antibodies cocktail have not been observed in patients hospitalised due to COVID-19; moreover, if this combination is administered on patients requiring high-flow oxygen or mechanical ventilation then the clinical outcomes can become worse.”

While speaking at a webinar recently organised by the Federation of Telangana Chambers of Commerce and Industry (FTCCI) Dr Reddy shared that the cost could further come down to Rs 15000 for treatment with the antibody cocktail.

The Brihanmumbai Municipal Corporation (BMC) in Mumbai has carried out a pilot study to check the efficacy of the antibody cocktail. The study was carried out at BMC-run Seven Hills Hospital. The study included 74 patients with each patient suffering from at least one comorbidity and a CT score of 25. Fever in all patients subsided within 48 hours and only one patient required oxygen. BMC officials also shared that hospital stay was reduced to five-six days. A similar study was carried out among patients admitted to the private ICU at Seven Hills and NSCI dome managed by HN Reliance Hospital, the study has been conducted on 70 patients.

West Bengal’s state health department will be using the cocktail for mild to moderately infected patients in four state-run hospitals — Medical College Hospital, ID Hospital, MR Bangur Hospital and Sambhunath Pandit Hospital. Earlier six patients were treated in the state at private hospitals. The state has 300 vials of the drug. Recently AIIMS-Rishikesh began antibody cocktail therapy to treat COVID-19 patients, the hospital has successfully treated six patients.

On June 14, 2021, Sangita Reddy, Joint Managing Director, Apollo Hospitals, Chennai shared a personal experience on the impact of the cocktail treatment on her body. She tweeted, “After 500 days of dodging COVID-19, I tested positive on June 10. My initial reaction was of shock and dismay - Why me? I was careful and vaccinated. Hospitalised with a high fever I took the cocktail Regeneron therapy within the early window period and it has made a dramatic difference.”

Sir Ganga Ram Hospital, Delhi recently administered the cocktail to two patients and there was significant improvement in COVID symptoms within 12 hours. Studies have suggested that the antibody cocktail can prevent the escalation of COVID-19 symptoms which could prevent hospitalisation.

Multiple SARS-CoV-2 variants are circulating worldwide, one of them being B.1.617, which has been detected in India as

well. Some evidence suggests that the virus has evolved to a sub-lineage B.1.617.2, also known as the Delta variant, which is more transmissible. This variant has further mutated to form Delta plus/AY.1 variant. The Delta plus variant is considered to be resistant to the monoclonal antibody (mAb) cocktail treatment.

Dr Vinod Scaria, Scientist, Institute of Genomics and Integrative Biology (IGIB), New Delhi recently tweeted, “One important point to consider regarding K417N (B.1.617.2 with the new K417N mutation) is evidence suggesting resistance to mAbs casirivimab and imdevimab.”

On this note, Roche Pharma has issued a statement saying, “Based on in-vitro assays, we can confirm that the K417N mutation which is present in the so-called ‘Delta plus variant’ has no impact on the neutralising activity of Roche’s antibody cocktail - casirivimab and imdevimab. The casirivimab and imdevimab cocktail retained its neutralising activity against all variants tested.”

Early in June Eli Lilly’s bamlanivimab and etesevimab also received similar emergency approval. The cocktail is to be administered to those with mild to moderate COVID-19 who do not require oxygen and those patients that are at a high risk of progressing to severe disease. On May 26, 2021, GlaxoSmithKline received US FDA’s emergency use approval for Sotrivimab, the company is exploring options to make the monoclonal antibody therapy available for India. Zydus Cadila plans to take an antibody cocktail, ZRC-3308, through trials in India.

Clinical outcomes, as well as clinical trials, have been very promising for patients treated with the antibody cocktail so far. Even though some of the variants that are resistant to the antibodies, currently they are very few. This needs to be addressed immediately. Another point of consideration is the price involved. The treatment along with the antibody cocktail is very expensive and may not be affordable to the masses.

Also, there isn’t enough evidence on the impact this has on the patients who have been administered the cocktail. Utmost caution is a necessity as this could lead to further complications or another crisis could be looming around the corner.

Experts have voiced concerns about reduction in the efficacy of vaccines, therapies for treatment of COVID-19 with newer variants of SARS-CoV-2. Further studies need to be conducted to determine the impact (reduction in efficacy/ escaping immune response) of the newer variants on mAb cocktail treatment.

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