RECOVERY
Randomised Evaluation of COVID-19 Therapy

Intervention

Sotrovimab 1000 mg once

Summary of information on sotrovimab in COVID-19

Sotrovimab (VIR-7831) is a neutralising monoclonal antibody targeting the SARS-CoV-2 spike glycoprotein receptor binding domain. It was identified by screening antibodies from a patient who had been infected during the 2003 SARS-CoV-1 outbreak, and its ability to also neutralise SARS-CoV-2 implies that its binding site is highly conserved, maybe meaning mutational escape will be difficult.[1] The Fc portion of the parent antibody has been modified to extend sotrovimab's half-life to around 49 days. It is given as a single intravenous dose and been well tolerated in clinical studies, although occasional serious hypersensitivity reactions have occurred.

It is licenced in the UK for the treatment of COVID-19 in patients who do not require oxygen and are at high risk of developing severe disease (at a 500 mg dose). The COMET-ICE trial, conducted in 583 such patients, showed that when given within five days of symptom onset it reduced the risk of hospitalisation by 85%, from 7% in the control group to 1% in the sotrovimab group.[2] Evidence in hospitalised patients is limited, and the sotrovimab arm of ACTIV-3 was stopped due to futility after recruiting 344 participants, although no safety concerns were raised.[3] However, by recruiting around 10,000 patients, RECOVERY subsequently showed that another neutralising monoclonal antibody treatment (casirivimab+imdevimab) reduced mortality by 20% in hospitalised patients who were anti-spike antibody negative at baseline.

Potential harm

Safety data from COMET-ICE and other studies are reassuring with no excess of adverse events (including infusion-related reactions) among participants allocated sotrovimab compared to placebo.

Frequently asked questions

1. ***What are the contraindications to sotrovimab?***
   - Known hypersensitivity to sotrovimab or its excipients
   - Age <12 years old
   - If age ≥12 <18 years old, weight <40 kg

2. ***Can it be given to pregnant or breast-feeding women?***

Yes, as long as they have had the potential benefits and risks discussed with them.

3. ***Why is RECOVERY using a 1000 mg dose when 500 mg is being used in routine clinical care?***

The Omicron SARS-CoV-2 variant that emerged in late 2021 has multiple spike protein mutations, which have led to its rapid expansion in immune populations. These also appear to cause near complete loss of neutralising activity by the monoclonal antibodies in casirivimab+imdevimab,[4] and reduce the neutralising activity of Sotrovimab about 10-fold.[5,6] Data comparing the peak and day 29

concentrations following 2.4 g casirivimab+imdevimab and 500 mg Sotrovimab demonstrate much lower concentrations of Sotrovimab.[7] These pharmacodynamics and pharmacokinetic considerations underly the selection of a 1000 mg dose in this trial. The published safety of Sotrovimab and higher doses of other anti-spike human monoclonal antibodies (including the 8g dose of casirivimab+imdevimab used in RECOVERY) do not suggest a safety concern with this increased dose.

4. ***Can patients who have already received sotrovimab be recruited into the sotrovimab comparison in RECOVERY?***

Yes.

5. ***Can patients who have received other monoclonal antibodies (eg, Ronapreve, tocilizumab) be recruited into the sotrovimab comparison in RECOVERY?***

Yes.

6. ***Can sotrovimab be given to patients with kidney or liver disease?***

Yes, there are no eligibility criteria based on kidney or liver function.

References

1. Pinto D, Park YJ, Beltramello M, et al. Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. *Nature* 2020; **583**(7815): 290-5.
2. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early Treatment for Covid-19 with SARS-CoV-2 Neutralizing Antibody Sotrovimab. *N Engl J Med* 2021; **385**(21): 1941-50.
3. National Institute for Health. NIH-Sponsored ACTIV-3 Clinical Trial Closes Enrollment into Two Sub-Studies. 2021. https://www.nih.gov/news-events/news-releases/nih-sponsored-activ-3-clinical-trial-closes-enrollment-into-two-sub-studies.
4. Wilhelm A, Widera M, Grikscheit K, et al. Reduced Neutralization of SARS-CoV-2 Omicron Variant by Vaccine Sera and monoclonal antibodies. *MedRxiv* 2021.
5. Cathcart AL, Havenar-Daughton C, Lempp FA, et al. The dual function monoclonal antibodies VIR-7831 and VIR-7832 demonstrate potent in vitro and in vivo activity against SARS-CoV-2. *BioRxiv* 2021.
6. Cao YC, Wang Y, Jian F, et al. B.1.1.529 escapes the majority of SARS-CoV-2 neutralizing antibodies of diverse epitopes. *BioRxiv* 2021.
7. GlaxoSmithKline. Xevudy - summary of product characteristics, 2021.