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Ronapreve for prophylaxis and treatment of covid-19

Equitable allocation is a priority

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On 20 August 2021, Ronapreve received conditional marketing authorisation for the prevention and treatment of covid-19 in the UK.¹ Ronapreve (REGEN-COV in the US) comprises two monoclonal antibodies, casirivimab and imdevimab, that target the SARS-CoV-2 spike protein to reduce the risk and severity of covid-19 in selected patients.^{2–5} Although Ronapreve's approval represents a welcome expansion in the armamentarium against covid-19, it also brings difficult questions about who should be eligible for treatment.

The conditional marketing authorisation was based on two pivotal trials.^{2–4} The first randomised 4567 outpatients with covid-19 to placebo or intravenous Ronapreve.^{2,3} Eligible patients had at least one risk factor for severe disease, symptom onset within 7 days, and a positive SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) result within 72 hours. One-off treatment with 1200 mg or 2400 mg Ronapreve reduced the composite primary outcome of hospital admission or death by around 70% (1% v 3.2% of controls, $P=0.0024$ for 1200 mg; 1.3% v 4.6%, $P<0.0001$ for 2400 mg) and the median time to symptom resolution from 14 to 10 days.

The second trial evaluated prophylactic subcutaneous administration of 1200 mg Ronapreve versus placebo in people without antibodies to covid-19 (seronegative) who had been exposed to SARS-CoV-2 by someone in their household.⁴ Those who initially had a negative PCR result were less likely to develop disease when administered Ronapreve within 96 hours of contact (relative risk reduction 66%, $P<0.001$), while any consequent symptomatic infections also resolved faster (1.2 weeks versus 3.2 weeks). In asymptomatic individuals with an initial positive PCR result, treatment with Ronapreve reduced the development of symptomatic disease by 31% ($P<0.038$).¹

The UK based Randomised Evaluation of Covid-19 Therapy (Recovery) trial also investigated Ronapreve, randomising 9785 hospital patients with covid-19 to usual care or usual care with 8000 mg intravenous Ronapreve administered once only.⁵ Time from admission to treatment ranged between 1 and 4 days, and a prespecified subgroup analysis found Ronapreve reduced mortality among patients without detectable antibodies (rate ratio 0.80, 95% confidence interval 0.70 to 0.91) but not seropositive patients (1.09, 0.95 to 1.26).

The trial data collectively support the use of Ronapreve for post-exposure prophylaxis and treatment of covid-19 in seronegative people, in both hospital and outpatient settings. However, given the variation in efficacy between seronegative and seropositive patients, antibody testing will be

paramount for optimising its allocation. Care is needed to avoid repeating previous mistakes regarding assay selection.⁶ Although the trials varied in their choice of antibody tests,^{2,4,5} widely available commercial assays may be able to achieve sensitivity and specificity of at least 98%.⁷

Patient selection

NHS resources are finite, and the limited supply of Ronapreve will need to be allocated to those who stand to gain most benefit. This is particularly important given that indiscriminate use risks driving SARS-CoV-2 escape mutations.⁸ Despite high levels of vaccine uptake and seropositivity in the UK,⁹ some people are still susceptible to severe disease. Older people and those with multimorbidity mount weaker antibody responses to vaccination.¹⁰ Immunosuppressed people are at particularly high risk.^{11,12} Furthermore, vaccine efficacy is expected to wane over time.¹³ Such factors will need to be coupled with antibody status when prioritising the most vulnerable patients for treatment. In the community, fast, coordinated pathways will have to deliver antibody testing and administer Ronapreve soon after viral exposure or disease onset.¹

The disproportionate effect of covid-19 on poorer families, older people, and ethnic minorities is well documented.¹⁴ National coordination will be essential to facilitate equitable access to Ronapreve and minimise the unwarranted variation in care that has become commonplace in the NHS.¹⁵ The National Institute for Health and Care Excellence must step up once again to guide frontline clinicians in their decision making processes.¹⁶ Guidance should balance resource availability against anticipated benefits in distinct population subgroups. Living guidelines that are constantly reviewed and refined must take centre stage to ensure that practice matches emerging evidence.¹⁷

The conditional marketing authorisation of Ronapreve is an important development in the prevention and treatment of covid-19 but also creates notable challenges, including a requirement for scalable antibody testing, appropriate patient selection, and time critical treatment delivery. Clinical pathways established for Ronapreve through iterative development may also be transferable across emerging SARS-CoV-2 antibody therapies.¹⁸ Just as practice for other aspects of managing covid-19 have developed through the course of the pandemic,¹⁹ the approach for allocation of Ronapreve will have to be continually refined.

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