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Persistent SARS-CoV-2 infection: the urgent need for access to treatment and trials

Lancet Infect Dis 2021
Published Online
August 16, 2021
https://doi.org/10.1016/
S1473-3099(21)00464-3

The management of patients presenting to health-care services with SARS-CoV-2 infection has developed rapidly over the past year, driven by the findings of high-quality randomised trials. These trials have been justifiably focused on preventing severe disease in patients with very early infection and on the treatment of acutely unwell patients. However, although applicable to the majority of patients, it has become apparent that there are specific patient cohorts not well served by these studies, to whom their conclusions might not apply, and who as a consequence risk missing out on access to potentially beneficial treatments.

Patients with persistent SARS-CoV-2 infection are one such cohort. Persistent SARS-CoV-2 infection can occur in certain immunocompromised people, such as those with primary immunodeficiency or recipients of immunosuppressive therapy (eg, B cell-depleting anti-CD20 treatment or chimeric antigen receptor T-cell therapy following bone marrow transplantation). These individuals are well known to be at risk of other chronic viral infections, including norovirus and rhinovirus.

Although some patients might experience severe disease and fatal outcomes, many others might not require hospitalisation but are unable to clear their coronavirus infection. They experience months of cough, fever, breathlessness, and debilitation, often with episodes of apparent clinical recovery followed by deterioration. Reports have confirmed that viable virus can be cultured from such individuals, many months after the initial infection, and they commonly do not develop an anti-SARS-CoV-2 antibody response. The antiviral drug remdesivir can ease symptoms and has been associated with viral clearance and sustained improvement in some patients, yet in others it appears to produce only a transient drop in viral load, with recrudescence once treatment stops.[1] Antibody therapy, whether with convalescent plasma or synthetic monoclonal antibody cocktails, holds promise. There are convincing reports of complete symptom resolution and sustained viral clearance after receipt of these therapies in patients who have had many months of illness.[2] Over 30 such cases have been reported in the UK, but the total number of affected individuals is not known. Data collated from these cases confirm the clinical impression that remdesivir monotherapy is associated with frequent relapses or persistent PCR positivity, but monoclonal antibody therapy combined with remdesivir has been associated with near-universal viral clearance and clinical recovery.

There is currently no access to these treatments in the UK for patients with persistent infection. There does not appear to be support for compassionate use access from pharmaceutical companies, and convalescent plasma has been withdrawn following demonstration that it is ineffective in immunocompetent hospitalised patients.[3] Synthetic antibody therapy has already been authorised for emergency use in the EU and the USA for patients with mild or moderate disease, and work is in progress to define the criteria for access to these therapies in the UK, in light of the preliminary results of the casirivimab plus imdevimab (REGN-COV2) arm of RECOVERY.[4] These results do provide a way forward. Although this trial was not designed to address treatment strategies in patients with persistent infection, it did find a mortality benefit in seronegative patients. This finding supports the rationale for benefit in patients who are unlikely to generate an antibody response, although no randomised controlled trial conducted specifically within this patient group has been published, and such a trial would be challenging given small patient numbers.

It is important that any potential benefit for this small but important cohort is not overlooked. Beyond treatment of sick individuals trapped in hospital or at home in perpetual self-isolation with a risk of developing chronic lung disease, there are compelling public health arguments for attempting a cure. Analysis of viral sequences obtained from such patients over time suggests ongoing viral evolution within immunosuppressed individuals, potentially facilitating the emergence of new strains within the wider population.[5]

It has been suggested that such treatments could themselves risk driving the selection of resistance, and thus any treatment regimen would require close monitoring of viral evolution and early recognition

of any unintended consequences.[5] We agree that such monitoring is mandatory and deliverable for these patients regardless of treatment. However, rapid viral elimination using a combination of antivirals and high-titre antibody-based therapy would prevent any further evolution. The small patient number need not be an impediment to delivery of well designed trials of potential therapies. In the absence of such trials, a rigorously overseen national treatment protocol incorporating the collection of virological and clinical outcome data could be delivered safely. Whatever route is chosen to develop and deliver therapies, a strategy to reduce morbidity and protect public health is needed urgently.

ALG reports grants from Novavax to run vaccine trials and non-commercial funding from the INSIGHT network (NIH-TICO trial) to her institution outside of the submitted work; ALG is also named as an inventor on a patent issued to the University of Oxford covering use of a promotor construct incorporated in the ChAdOx1 nCoV-19 vaccine developed by AstraZeneca and the University of Oxford. RKG reports personal fees from GlaxoSmithKline, Johnson & Johnson, and UMOVIS Lab, and a research grant from Invisi Smart Technologies, outside of the submitted work. SJ reports grants from CSL Behring and Takeda and personal fees from CSL Behring, Octapharma, Pharming, Takeda, LFB, Grifols, Biotest, and UCB pharma, outside of the submitted work; SJ also served on advisory boards for CSL Behring, Octapharma, Pharming, LFB, Grifols, and Biotest, and on data and safety monitoring boards for Biotest and UCB Pharma, outside of the submitted work. DKM served as one of the principal investigators for the UK Convalescent Plasma Trial in critically ill patients with COVID-19, conducted as part of the REMAP-CAP Trial. MS-H reports a grant from the National Institute for Health Research (NIHR Clinician Scientist Fellowship; NIHR-CS--2016-16-011), during the conduct of the study, and served as Clinical Lead for the UK Convalescent Plasma Trial in critically ill patients with COVID-19, conducted as part of the REMAP-CAP Trial. DML reports non-financial support (travel and subsistence costs) from CSL Behring, personal fees from Merck, and grants from LifeArc, the British Society for Antimicrobial Chemotherapy, Blood Cancer UK, Bristol Myers Squibb, and the UK Medical Research Council, outside of the submitted work. All other authors declare no competing interests.

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1 Helleberg M, Niemann CU, Moestrup K, et al. Persistent COVID-19 in an immunocompromised patient temporarily responsive to two courses of remdesivir therapy. *J Infect Dis* 2020; **222:** jiaa446.
2 Hueso T, Pouderoux C, Péré H, et al. Convalescent plasma therapy for B-cell-depleted patients with protracted COVID-19. *Blood* 2020; **136:** 2290–95.
3 RECOVERY Collaborative Group. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021; **397:** 2049–59.
4 RECOVERY Collaborative Group, Horby PW, Mafham M, et al. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *medRxiv* 2021; published online June 16. https://doi.org/10.1101/2021.06.15.21258542 (preprint).
5 Kemp SA, Collier DA, Datir RP, et al. SARS-CoV-2 evolution during treatment of chronic infection. *Nature* 2021; **592:** 277–82.