

EDITORIAL

COVID-19 treatment: a growing (anti)body of evidence

Our lives changed dramatically eight months ago when we went into a hard nationwide lockdown in a bid to limit the transmission of our new spiky foe, SARS-CoV-2. We endured the uncertainties of autumn, and then the winter and the cold July COVID-19 peak. At this time, Oxford University's RECOVERY Collaborative group first reported on dexamethasone (6 mg daily for 10 days) significantly lowering the 28-day mortality in hospitalised COVID-19 patients on invasive mechanical ventilation or on oxygen alone, by as much as a third and a fifth, respectively.¹ It was hypothesised that glucocorticoids modulate inflammation-mediated lung injury, thus reducing the likely progression to respiratory failure and death in patients with severe illness. This made us perk up because a couple of months earlier, the intravenous antiviral, remdesivir (100 mg), also administered for 10 days, had shown promise in shortening the time to recovery by a median of five days compared to placebo, but not in reducing death in hospitalised COVID-19 patients with lower respiratory tract involvement.² The FDA granted remdesivir Emergency Use Authorization (EUA) in May for the treatment of adults and children hospitalised with suspected or laboratory-confirmed COVID-19 based on this meagre evidence, as there were no other treatment options at the time. Meanwhile, dexamethasone, which is relatively cheap, quickly became the standard care in patients requiring oxygen.

In spring, we were able to surface from that first wave breaking over us: Restrictions were eased to Level 1, which meant that we could go out and about if we were sufficiently robust to brave our new world. Ancillary evidence,³⁻⁶ compelled the WHO to endorse the use of not only systemic dexamethasone (6 mg orally or intravenously daily), but also hydrocortisone (50 mg intravenously TDS), methylprednisolone (10 mg intravenously QID) or prednisone (40 mg orally daily) in patients with severe or critical COVID-19.⁷ Although the body of evidence is growing, the subtleties of dexamethasone therapy are yet to be elucidated, including whether or not recovery is related to viral load, degree of impaired interferon and endogenous immune responses, levels of oxygen support (low- to high-flow nasal), synergy with remdesivir, and the timing of dexamethasone administration – seven or more days after symptom onset appears optimal,⁸ as opposed to remdesivir, where the benefit appears greater when given earlier in the illness.⁹ On 22 October, the FDA approved remdesivir for use in adult and paediatric patients 12 years of age and older and weighing at least 40 kilograms for the treatment of COVID-19 requiring hospitalisation. This is the first COVID-19 drug to receive full FDA approval.¹⁰

The blazing summer is upon us. There are currently several treatment approaches under investigation, including modifiers of the immune response and intrinsic pathways, given alone or in combination. These are exciting, frustrating and busy times for drug discovery. For instance, the monoclonal antibody, tocilizumab, that targets interleukin-6, appears to have been discarded because it lacked evidence of efficacy. Meanwhile, recent research showed that immunoglobulin G auto-antibodies against type I interferons (IFN- α 2 and IFN- ω) were present in about 10% of patients with severe COVID-19.¹¹ This adaptive autoimmunity blocks the innate immune response and impairs intrinsic antiviral immunity. Individuals with inborn errors of type I IFN immunity, who have these anti-IFN auto-antibodies, appear to have the highest risk of life-threatening COVID-19. It stands to reason that an external source of SARS-CoV-2 neutralising antibodies may provide passive protection, complement the innate immune response and aid recovery.

At the beginning of October we received preliminary evidence that Eli Lilly's LY-CoV555 (bamlanivimab), a rapidly isolated potent IgG1 antibody derived from plasma obtained from a convalescent COVID-19 patient, provides protection in a non-human primate model of SARS-CoV-2 infection.¹² By the end of October, Eli Lilly had released the interim analysis of their on-going phase two clinical outpatient study of this anti-spike SARS-CoV-2 neutralising monoclonal antibody that binds to the receptor binding domain, thus preventing cell entry through ACE-2 receptors.¹³ The medium 2 800 mg dose, administered by intravenous infusion, significantly accelerated the natural decline in viral load over an 11 day period. The 700 and 7 000 mg doses did not. This is a classic example of the Goldilocks effect – too much, too little, just right. Noteworthy is that this is the first randomised, controlled trial of a specific SARS-CoV-2- targeted treatment, ultimately intended to alleviate disease progression in patients with early disease. The outpatient study population mostly presented with mild disease, presumably therefore, with no evidence of a counterproductive hyper-immune response that is associated with severe respiratory distress and multi-organ damage. The likelihood was low that the intervention would provide benefit in hospitalised patients. Of interest is that viral load declined in the majority of patients, irrespective of treatment. Patients who received bamlanivimab had marginally lower symptom severity on days 2–6 compared to those who received placebo, while more COVID-19 patients required hospitalisation or needed to visit an emergency room in the placebo group (6.3%) compared to the antibody group (1.6%).

Mild infusion-related reactions were reported in patients in the bamlanivimab group (2.3%) as well as in the placebo group (1.4%), and these included facial swelling, rash, pruritus and flushing. On 10 November 2020, the FDA issued an EUA for the antibody for mild to moderate COVID-19 in those at increased risk for progression to severe COVID-19 or hospitalisation.

Is the natural decline in viral load actually related to humoral immunity? Seroconversion reportedly occurs between one and two weeks following a COVID-19 diagnosis. Previously, it was suggested that many become antibody-negative early during their convalescence, while several have reported higher prevalences and levels of SARS-CoV-2 antibodies in severely ill patients than in those with no or mild symptoms. At the very end of October, an Icelandic study reported on the longitudinal changes in antibody levels within the first four months after SARS-CoV-2 infection in 30 576 people by measuring immunoglobulin (IgA, IgM and IgG) antibodies against the nucleoprotein and the receptor-binding domain in the S1 subunit of the virus's spike protein.¹⁴ The results showed that 0.9% of Icelandic people were infected during the first SARS-CoV-2 wave. Interestingly, more than 90% of quantitative polymerase chain reaction-positive people were also positive for pan-Ig SARS-CoV-2 antibodies, which increased for two months from diagnosis and then plateaued and remained seropositive 120 days from diagnosis, suggesting stability of SARS-CoV-2 humoral immunity.

Antibody kinetics and immune response decay patterns are important for predicting the likelihood of re-infection, as well as potential vaccine efficacy. Vaccines (and infections) generate two waves of antibody responses: an initial short-lived peak, followed by a longer less dramatic wave. It is unknown if persistent anti-SARS-CoV-2 antibodies are protective and if they preserve their neutralising or other protective functions to block (re)infection. The proof of the pudding lies in the decrease in rate of infection following SARS-CoV-2 exposure (or re-exposure). Many argue that a 60–70% decline is sufficient to prove vaccine efficacy.¹⁵ Yesterday (09 November), it was reported that Pfizer and BioNTech's first-of-its-kind mRNA vaccine against COVID-19 exceeded this cut-off, preventing symptomatic COVID-19 in more than 90% in an on-going, unpublished, phase three, placebo-controlled study. Theoretically, host cell ribosomes utilise this artificial mRNA to build components of the viral spike protein. This epitope or antigen then elicits an acquired, possibly in tandem with an innate, immune response. Because it is a trailblazer, the intricacies, duration and adverse effects of the response are not yet known. More evidence, including critical safety data, and efficacy in the comorbid and vulnerable elderly,

is being gathered. We could all do with ending the year on a high note, and this could possibly be it. May we all enjoy our season in the sun.

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