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The right place for IL-1 inhibition in COVID-19

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The COVID-19 pandemic, caused by the spread of severe acute respiratory syndrome coronavirus 2, has resulted in more than 1·8 million deaths worldwide as of Jan 7, 2021, a figure that will grow indefinitely until effective vaccines become globally accessible. Two phases are generally recognised in the pathogenesis of COVID-19: an initial viral stage characterised by an appropriate host immune response, mild clinical symptoms, and self-resolution in most patients; and a later phase develops in a minority of patients, and is characterised by maladaptive hyperinflammation, rampant release of cytokines, acute respiratory insufficiency, and considerable mortality. Dampening hyperinflammation in patients with severe COVID-19 via inhibition of cytokines has emerged as a logical therapeutic option.[1]

Corticosteroids, which non-selectively inhibit cytokine production, were assessed in the RECOVERY trial and found to moderately reduce mortality compared with usual care alone in patients with moderate-to-severe COVID-19.[2] Among targeted cytokine inhibitors, IL-6 and IL-1 inhibitors have attracted a lot of clinical attention, for instance in cohort studies of severe COVID-19 IL-1 inhibition with anakinra improved clinical outcomes,[3] whereas IL-6 inhibition yielded more conflicting results.[4] Eventually, controlled evidence became available that IL-6 inhibition is marginally or not effective for COVID-19,[5] which left anakinra as the main candidate among targeted cytokine inhibitors. However, the efficacy of anakinra in COVID-19 had not been tested in controlled settings.

In this context, in *The Lancet Respiratory Medicine* the French CORIMUNO-19 collaborative group report their open-label randomised clinical trial (CORIMUNO-ANA-1) to investigate the efficacy of anakinra in addition to usual care for patients in hospital with COVID-19.[6] The study population consisted of patients with mild-to-moderate disease requiring low-flow supplemental oxygen, and patients receiving further respiratory support were excluded. Notably, enrolment criteria did not include hyperinflammation; although a C-reactive protein concentration of 25 mg/L or higher was required, this threshold is not indicative of hyperinflammation, which is usually defined as greater than 100 mg/L. Anakinra was administered intravenously at a dose of 400 mg per day for the first 3 days (which could be protracted for 3 additional days at physician's discretion), followed by gradual tapering for 2 days before discontinuation. Corticosteroids were not an essential and standardised treatment in the usual care group, with administration instead being at physician discretion. The study was stopped early by recommendation of the data safety monitoring board for futility on the basis of an interim analysis of the first 102 patients, after 116 patients had been randomly assigned to treatment (59 to the anakinra group and 57 to the usual care group), because no significant difference was found between the groups regarding the primary outcomes of 4-day improvement, 14-day ventilation requirement or mortality. Hence, the main finding of this study is that anakinra treatment did not improve clinical outcomes in patients with mild-to-moderate COVID-19.

The study has some limitations, including the small sample size, the non-blinded nature, and the absence of universal standardised corticosteroid regimen. A more critical observation pertains to the choice of the study population. When assessing any immunomodulatory therapy, one needs to be mindful of the specific mechanism being targeted, and the time when such a target mechanism is likely to be driving disease development. Cytokine inhibition has a clear rationale in patients with severe disease with hyperinflammation, a condition caused by excess cytokine production and burdened by considerable mortality. In patients with severe COVID-19 and hyperinflammation, taming excess cytokine production might reduce mortality. However, in this Article, data are only reported for patients with mild-to-moderate disease, and a rather low threshold level for serum C-reactive protein was required for enrolment. One could argue that many patients enrolled in this study had an appropriate immune response to the virus, and mortality in the control group was indeed low compared with previous studies.[3,7] Therefore, the fact that IL-1 inhibition with anakinra in this patient population did not yield a large benefit, which this study was designed to detect, is not surprising. Notably, the RECOVERY trials also found that patients with mild COVID-19 had no difference in outcomes with dexamethasone treatment, which nevertheless is beneficial for severe COVID-19.[2] Therefore, a true test of anakinra would be in patients

with more severe COVID-19, or with evidence of IL-1-mediated hyperinflammation.

As the field of IL-1 inhibition in COVID-19 moves forward, key questions still need addressing. The main challenge is to identify patients who might most benefit from treatment, either through correct timing of administration or through molecular taxonomy of individual inflammatory responses. Because IL-1α and IL-β are notoriously hard to measure in circulation, clinically useful biomarkers for patient selection include C-reactive protein, IL-6, ferritin (all proxies for IL-1 bioactivity),[3] and the soluble urokinase plasminogen activator receptor.[8] Also, since corticosteroids became the standard of care for severe COVID-19, future studies of IL-1 inhibitors will have to prove incremental benefit over corticosteroid treatment. Of related and notable interest is IL-1 inhibition in patients with COVID-19 and with type 2 diabetes: insulin use is associated with increased mortality for COVID-19,[9] and since use of corticosteroids typically results in increased insulin demands, IL-1 inhibition might be a preferable alternative anti-inflammatory strategy for such populations.

Overall, the impression stands that IL-1 inhibition has therapeutic rationale in COVID-19. Besides anakinra, available strategies to inhibit IL-1 include the monoclonal antibody canakinumab and the soluble IL-1 trap rilonacept. Orally available drugs inhibiting IL-1 also hold promise, such as novel and potent inhibitors of the NLR family pyrin domain containing 3 inflammasome.[10] Clinical trials assessing these agents for treatment in patients with severe disease will ultimately determine the right place for IL-1 inhibition in COVID-19.

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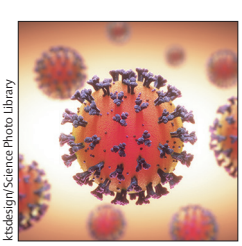
Risks of lung transplantation in the SARS-CoV-2 era



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As the COVID-19 pandemic has swept the world, the provision of health care for conditions that are unrelated to COVID-19 has been extensively disrupted. This is especially the case for patients in need of solid organ transplantation, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections have complicated the approach that transplant centres must take to ensure that recipients are not placed at risk of potentially fatal outcomes or severe allograft dysfunction should they become infected with SARS-CoV-2.

Many DNA and RNA viruses pose both immediate and delayed-onset, potentially serious risks for lung transplant recipients,[1] and disruption of host–virus relationships after solid organ transplantation can lead to both reactivation of latent viruses residing in donor tissues and new infections. Additionally, lung transplant recipients who have had successful transplantations are at risk of developing community-acquired respiratory virus infections, which have been linked to both acute and chronic lung allograft dysfunction.[2]

Infection with the novel SARS-CoV-2 is associated with substantial morbidity and mortality, and many survivors of COVID-19 have long-term or permanent detrimental health effects.[3] Airborne transmission is