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Is IL-6 a key cytokine target for therapy in COVID-19?

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The identification of elevated IL-6 levels in patients with severe COVID-19 led to the rapid development of clinical trials targeting this cytokine. Overall, these trials do not support the widespread use of IL-6 antagonists in hospitalized patients with mild-to-moderate disease, but IL-6 antagonists may be beneficial when rapidly deployed in patients with severe COVID-19, as we discuss here.

At the start of the pandemic, elevated cytokine levels (notably IL-6, GM-CSF, TNF, IFNs and IL-18) were commonly reported in severely ill COVID-19 patients. These cytokines were often portrayed as part of a dysregulated host response to SARS-CoV-2 that promoted severe disease. However, poor patient outcomes most closely correlate with persistent viral titres and pre-existing health conditions that affect vascular health. Nevertheless, the efficacy of corticosteroids in managing severe COVID-19 supports the idea that an immune component contributes to disease severity. Elevated levels of IL-6 are associated with a wide variety of inflammatory states, including sepsis[1]. Moreover, IL-6 blockade has been used to manage cytokine-release syndromes following CAR T cell therapy in certain cancer patients[2]. Thus, it made sense to perform clinical trials to determine if IL-6 blockade in hospitalized COVID-19 patients would mitigate IL-6-mediated pathology, reduce systemic inflammation and improve patient outcomes[3,4]. However, although IL-6 is frequently described as a pro-inflammatory cytokine in COVID-19, this description de-values the wider properties of IL-6 in health and disease[1]. IL-6 has important roles in promoting resistance to different pathogens, but also the maintenance of tissue homeostasis[1]. Therefore, it was not clear whether the dominant role of IL-6 in COVID-19 would be to promote viral containment or to contribute to local immune pathology and systemic complications[1-4].

[H1] COVID-19 is a complex clinical landscape

To date, multiple studies have examined IL-6 blockade in COVID-19, but the outcome of these trials is often difficult to compare due to small sample sizes and methodological differences. These findings should also be framed in the context of dexamethasone therapy, which has shown 50% efficacy in large patient cohorts and is used as an adjunct in combination with biological drugs. Perhaps the unifying message from all of the studies is that, in contrast to dexamethasone, there is no broad-based benefit of IL-6 blockade in COVID-19. Nevertheless, in two of the larger trials there was a clinical benefit in 15-20% of patients if IL-6 blockade was administered early after hospitalization and used in combination with dexamethasone (compared with dexamethasone alone)[5,6]. Thus, the efficacy of IL-6 targeting depends on the underlying health status of the patient, the severity of the disease, and the timing of the intervention. So, where do we go now? We should first acknowledge the complex biology of IL-6 and consider at least two distinct settings in which IL-6 directs inflammation in infectious diseases. IL-6 drives the host response to local tissue infection, but IL-6 is also involved in systemic inflammation during infection, which is likely influenced by any pre-existing health complications. This might account for the differences in the clinical presentation of COVID-19, which can be sub-grouped based on the incidence of lung-dominant hyperinflammation associated with pneumonia, secondary haemophagocytic lymphohistiocytosis, cardiac and renal injuries, and post-viral consequences including vasculitis and paediatric multisystem inflammatory-like syndromes in adults. Another way to think about this issue is in the instances where IL-6 blockade was beneficial. Did IL-6 inhibition correct an adverse anti-viral response, or impact the underlying or established pathological processes that pre-dispose a patient to severe disease? To address this knowledge gap, we need a more considered view of IL-6 biology to understand how this cytokine affects disease outcome.

[H1] Are all IL-6 targeted interventions equal?

Biological drugs against IL-6 can target the cytokine (clazakizumab, olokizumab, sirukumab and siltuximab), its cognate receptor (tocilizumab and sarilumab), or inhibit IL-6 trans-signalling by blocking the soluble IL-6 receptor (IL-6R) system (olamkicept) (Fig 1). During the current pandemic, these drugs are often considered interchangeable, and access depended on local availability. These inhibitors target the IL-6 cassette in different ways and display distinct pharmacokinetics and pharmacodynamics. For example, biological drugs that prevent IL-6 binding to IL-6R typically trap IL-6 in circulation and increase the systemic concentration of IL-6. This issue is

less problematic with IL-6R blockers or therapies such as olokizumab that target IL-6 to prevent the docking of IL-6 and IL-6R into a functional receptor complex with gp130. Here, it is important to ascertain whether therapeutic inhibitors of IL-6 or IL-6R have different effects. Biological drugs targeting IL-6 fundamentally deal with the flare or sharp increase in IL-6 commonly associated with infection. In contrast, IL-6R blockers engage membrane-bound IL-6R and circulating sIL-6R, which is maintained at high concentrations (25-75 ng/ml) in human sera and increased 2-3-fold during inflammation[1]. Thus, a different biological drug regime maybe required to sustain global IL-6R inhibition. Further side-by-side comparisons are, therefore, required to identify potential differences in the clinical efficacy of IL-6 blockers.

[H1] What governs IL-6 bioavailability?

Almost all stromal and haematopoietic cells produce IL-6, and its expression is highly regulated by microRNAs, RNA-binding proteins, RNases, and circadian response factors[1]. Physiological concentrations of IL-6 in human serum are normally low (1–5 pg/ml), but during disease, IL-6 is rapidly induced and in extreme circumstances (such as septic shock or cytokine-release syndrome) reaches μg/ml quantities[1]. Data from COVID-19 patients show that IL-6 concentrations in SARS-CoV-2 infection are comparable to those in patients with other forms of sepsis or acute respiratory distress syndrome but are far lower than those observed in cytokine-release syndromes associated with polyclonal T cell activation[7]. Thus, the use of IL-6 as a biomarker of disease severity does not accurately identify IL-6 as a unique contributor to patient outcomes in COVID-19. The ability to discern the role of IL-6 in COVID-19 is also complicated by the presence of soluble cytokine receptors (sgp130 and sIL-6R), which affect the bioavailability and signalling properties of IL-6 (Fig 1). A greater appreciation of how these factors shape IL-6 activities in COVID-19 will help establish whether IL-6 activities are abnormally regulated in COVID-19 or if the maintenance of circulating IL-6 is more significant. This is emphasised by genetic studies of patients with COVID-19. Genome-wide association studies and functional analyses of SNPs identify disease susceptibility loci affecting the IL-6 cytokine cassette. For example, a specific *IL6R* mutation (rs2228145), which results in elevated circulating sIL-6R, protects patients from SARS-CoV-2 infection and reduces the need for hospitalization[8]. These results could be viewed as surprising, as sIL-6R maintains the circulating half-life of IL-6 and drives inflammatory signals *via* IL-6 trans-signalling (Fig 1). However, the IL-6-sIL-6R complex is also susceptible to antagonism by sgp130, inhibiting IL-6 trans-signalling and sequestering IL-6 from the membrane-bound IL-6R. There are also IL6ST polymorphisms affecting sgp130 levels, which often associate with indices of cardiometabolic disorders, but it is not clear if they have any impact on COVID-19. Thus, there is genuine complexity that makes it difficult to determine whether genetic mutations influence underlying health conditions or enhance early IL-6 production that promotes viral control. These considerations may provide additional support for the idea that IL-6 blockade can be beneficial. Here, clinical trials with olamkicept (derived from sgp130) might offer additional insights by targeting IL-6 trans-signalling as opposed to a more global IL-6 blockade (Fig 1). Despite multiple trials in the past 12 months, it is still difficult to judge who will benefit from IL-6 blockade in COVID-19. This type of more nuanced approach may help to identify patients that would respond to IL-6 targeted therapy. Unlike IL-6 and sIL-6R, sgp130 is less prone to inflammatory regulation and changes in the circulating IL-6:sIL-6R:sgp130 ratio may offer a more informed view of IL-6 bioactivity.

[H1] Do no harm

Clinical experience tells us that adverse events associated with IL-6 blockade tend to occur in settings where IL-6 controls tissue homeostasis or barrier immunity[1]. For example, tocilizumab treatment of atopic dermatitis is associated with increased skin infections, and gastric complications are contraindications for therapy. Infections associated with IL-6-directed therapies typically arise in the upper and lower respiratory tracts and in the urinary and gastrointestinal tracts, and also occur in patients with rare genetic disorders that affect the IL-6R system or in children with inhibitory autoantibodies against IL-6. As IL-6 promotes immune processes associated with resistance to infection, there are real concerns that IL-6 neutralization could interfere with anti-viral responses or increase susceptibility to secondary respiratory infections in hospitalized COVID-19 patients[9,10]. Encouragingly, the incidence of adverse events in relevant trials appear minimal and these have not been a major concern, likely due to the targeted (1-2 doses) use of these antagonists in COVID-19. It will be interesting to establish whether patients routinely receiving IL-6 antagonists for other forms of disease display improved clinical outcomes in COVID-19.

[H1] Conclusions for the long haul

In many respects, the results in the clinical trials of IL-6 blockade have been disappointing as it was hoped that this intervention would show widespread efficacy. With hindsight, perhaps we should not be surprised — IL-6 antagonists and cytokine blockade in general has not been effective in other forms of sepsis where levels of IL-6 are comparable with COVID-19. Nevertheless, the valuable experiences gained by intensive care specialists and practicing clinicians during this global pandemic may provide impetus to better understand the effects of IL-6 on the vascular compartment, complement activation and coagulation. This could ultimately improve management of other forms of sepsis. Currently available data are insufficient to extend the discoveries from this clinical indication to the other cytokine release syndromes induced by pathogens, cancer or sterile tissue injury[2]. This is not dissimilar to what is seen in autoimmune diseases, where patients respond with varying efficacies to routinely prescribed biological drugs. These differences have fuelled diagnostic advances in patient stratification and teach us that similar approaches may benefit patients with sepsis. Finally, patients that survive sepsis (including COVID-19) are characterized by long-

term adverse consequences and the immune mechanisms involved are poorly understood. It is unclear whether IL-6 blockade at peak of disease impacts post-viral complications such as chronic fatigue, 'brain fog', anxiety and stress. Clinical studies in rheumatoid arthritis often describe improvements in fatigue (potentially linked to the control of iron metabolism and anaemia) and mental wellbeing following IL-6 blockade[1]. Thus, IL-6 antagonists may have added benefits for patients with long COVID or recovering from chronic infectious diseases. The debate around whether IL-6 targeted therapies improve patient outcomes in COVID-19 patients will certainly continue. It is clear that cytokines contribute to immunopathology, and that targeting these proteins can redirect the course of disease. The challenge for the scientific community is to define the best course of therapy for an infectious disease based on the genetic and pre-existing health of the infected patient, as this will ultimately inform the targeted use of cytokine antagonists.

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Competing interests

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Figure 1: Targeting the IL-6 signalling pathway

(a) The figure depicts the three modes of IL-6 signalling and the biological outcomes associated with each that may be relevant to COVID-19. The biological significance of IL-6 trans-presentation requires further evaluation. (b) Drugs targeting the IL-6 pathway can bind to IL-6 to stop interactions with IL-6 receptor (IL-6R) or gp130, target IL-6R to block IL-6 binding or target the IL-6–soluble IL-6R (sIL-6R) complex to inhibit trans-signalling.

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