Targeting the interleukin-17 pathway to prevent acute respiratory distress syndrome associated with SARS-CoV-2 infection

Key words: acute respiratory distress syndrome, COVID-19, cytokine.

The novel coronavirus causing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for coronavirus disease 2019 (COVID-19) pandemic. This is spurring a global response and accelerating trials of a panoply of antivirals, antibiotics, cell therapies, anticoagulants, convalescent plasma infusion and immune modulation using steroids and anti-cytokine therapies. In the absence of SARS-CoV-2-specific interventions to treat the infection, there are urgent needs to identify adjunctive treatments that prevent or counteract the 'cytokine storm' underlying the severe acute respiratory distress syndrome (ARDS) manifestations.1,2 Trials underway using immune modulation focus on targeting interleukin (IL)-6, IL-6 receptor (IL-6R), tumour necrosis factor-alpha (TNF-α), IL-1R, granulocyte-macrophage colony-stimulating factor (GM-CSF) and janus kinase (JAK) inhibition among others. Here, we provide the rationale for considering clinical trial testing of IL-17 blockade as a therapeutic strategy for overt pulmonary inflammation caused by SARS-CoV-2 infection.

IL-17 plays a key role in the cytokine storm observed in ARDS of any cause and is associated with alveolar inflammation and a poor prognosis.3–5 In mouse models, both the direct IL-17 blockade and the upstream blockade of histone acetyltransferase p300 and transcription factor retinoic acid receptor-related orphan receptor gamma t (RORγt), which upregulate IL-17 production, resulted in an attenuation of the lung injury.6,7 Consistently, peripheral blood mononuclear cells (PBMC) from ARDS patients have an increased expression of p300 and RORγt, especially among non-survivors.7

In severe compared to non-severe COVID-19, different studies found increased levels of IL-17-regulated cytokines, including IL-6, monocyte chemotactic protein-1 (MCP-1), IL-8, granulocyte colony-stimulating factor (G-CSF), macrophage inflammatory protein (MIP)-1α and TNF-α; however, IL-17 was only increased in severe cases compared to non-infected controls.2,8,9 Another study observed that IL-17 distinguished between mild and severe cases and correlated positively with an increased lung injury severity score.10 A pathological assessment found a high frequency of peripheral T-helper (Th) 17 in a patient with severe COVID-19 who did not survive.11 Furthermore, IL-17 plays a role in facilitating early neutrophil recruitment into the lungs, a detrimental phenomenon associated with poor prognosis in severe cases of COVID-19.12

Activation of the IL-17 pathway is also a marker of severity in various other known viral infections. Infections due to the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in 2012 were associated with a pro-inflammatory Th1 and Th17 cytokine profile and IL-17 responses.13–15 In the 2009 influenza A (H1N1) pandemic, the IL-17 response played a detrimental role in lung injury and was higher in patients with ARDS who did not survive.16,17 In childhood respiratory syncytial virus (RSV) infections, high IL-17 expression was associated with a poor interferon (IFN) production, abrogated type I IFN (IFN-I) responses and RSV infection severity.5,18,19 IFN-I is implicated in reducing viral spread, and high levels of IFN-I seem particularly relevant in the early infection phase for disease control. Indeed, in mice, early IFN-I administration was protective against MERS-CoV lung disease.20,21 Noteworthy, our observations revealed that IL-17A decreased IFN-I responses in intestinal epithelial cells, thus favouring human immunodeficiency virus type 1 (HIV-1) cell-to-cell spread.22 Similarly, in simian...
immunodeficiency virus (SIV) infections, mucosal IFN-I responses only developed at late time points post-infection and coincided with a vanished IL-17 response.23 These results point to the detrimental role of IL-17 in mounting a rapid IFN-I-mediated antiviral response. However, the beneficial impact of IFN-I on human lung diseases remains under investigation. A recent trial in ARDS patients reported an absence of benefit,24 although this was not in the context of a viral infection.

Finally, while IL-6 has garnered much interest as a potential target to improve COVID-19 outcomes,25,26 it is important to emphasize that it has interdependent relationships with IL-17. IL-6, along with pro-inflammatory IL-23 and other molecules, are upstream inducers of Th17 differentiation and subsequent IL-17 production. IL-17 then has diverse downstream pro-inflammatory effects increasing neutrophil activity, TNF-α secretion and inducing IL-6 production.5 This all leads to a positive inflammatory feedback loop.27 In fact, the rationale for the current interest with JAK blockade in COVID-19 derives from its role in mediating cytokine production, with JAK 2 mediating Th17 responses.28 Moreover, IL-17 and IL-6 synergistically promote viral persistence.29 In mice, IL-17 blockade improved H1N1-induced acute lung injury and decreased the levels of cytokines IL-1β, G-CSF, MCP-1, MIP-1-α, MIP-1-β and TNF-α.10 Additionally, in viral myocarditis, IL-17 blockade abolished viral replication and decreased levels of IL-6.30 Noteworthy, in COVID-19, myocarditis was observed in the context of ARDS.31 Thus, IL-17 blockade may be beneficial in controlling the cytokine storm while boosting antiviral IFN-I responses during SARS-CoV-2 infection (Fig. 1). Consideration of IL-17 blockade is strengthened by the relative absence of adverse inflammatory lung manifestations when these therapies are used for autoimmune conditions such as psoriasis.32,33 Since the initial submission of this commentary, other groups supported the idea of blocking IL-17 for controlling overt inflammation in COVID-19 patients.26,34 In addition to its pro-inflammatory role, our most recent studies originally support a pro-viral role of IL-17 by interfering with IFN-I production/responses.22 Therefore, we consider that early IL-17A blockade will also boost the control of viral replication by the host.

In conclusion, as we rapidly explore existing immunotherapies to be repurposed as adjunctive treatments for SARS-CoV-2-associated ARDS, IL-17 blockade may represent an interesting avenue that deserves testing, especially in people with pre-existing pathologies associated with exacerbated IL-17 responses. Monoclonal antibodies against IL-17A (secukinumab and ixekizumab) and IL-17r (brodalumab) may represent possible therapeutic options.

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