

Review

# Role of Interleukin-6 in Lung Complications in Patients With COVID-19: Therapeutic Implications

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**Abstract.** COVID-19 is viral respiratory infection with frequently fatal lung complications in the elderly or in people with serious comorbidities. Lung destruction appears to be associated with a cytokine storm related to an increased level of interleukin-6 (IL6). Therapeutic targeting of the interleukin-6 signaling pathway can attenuate such a cytokine storm and can be beneficial for patients with COVID-19 in danger of pulmonary failure. This article demonstrates the importance of IL6 in progression of disease and the possibility of inhibition of IL6 signaling in COVID-19 therapy.

COVID-19 is pandemic respiratory infection caused by coronavirus severe acute respiratory syndrome–coronavirus 2 (SARS-CoV-2), which originated in mainland China. The majority of infected persons are asymptomatic or only have a mild course of disease. Unfortunately, the elderly are at particular risk of serious complications associated with damage to the lung resulting in the risk of fatal respiratory failure (1-3). This article demonstrates importance of interleukin-6 (IL6) in progression of this disease and the possibility of inhibiting IL6 signaling in COVID-19 therapy.

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## Cytokine Storm

Serious lung injury is associated with a cytokine storm as was demonstrated in similar diseases SARS and Middle East respiratory syndrome (MERS) (4-6) exhibiting signs of lung fibrosis as was also detected in patients with COVID-19 (7). It can be, therefore, hypothesized that lung injury in COVID-19 may be also associated with this pathology (8). Pedersen and Ho observed increased cytokine levels [IL6, IL10 and tumor necrosis factor  $\alpha$  (TNF $\alpha$ )], lymphopenia (of CD4<sup>+</sup> and CD8<sup>+</sup> T-cells), reduced interferon  $\gamma$  (IFN $\gamma$ ) expression in CD4<sup>+</sup> T-cells, and immunosuppression in patients with severe COVID-19 (8), which fulfil the criteria for the existence of a cytokine storm.

## Interleukin-6

IL6 is critically important for the initiation and progression of a cytokine storm. Primarily, this cytokine stimulates inflammation but it also has other important functions such the stimulation of cell proliferation and migration in wound healing and in cancer, where it increases metastasis. IL6 is recognized by two types of receptors which is important from the functional point of view. However, IL6 also has important metabolic effects, controlling the metabolism of adipocytes, striated musculature and hepatocytes. It can stimulate catabolic pathways to promote senility/cancer wasting and cachexia. Moreover, IL6 crosses the brain–blood barrier and is recognized by neurons that can underlie some psychotic problems and anorexia (10-12). In this aspect, IL6 plays an important role in other pathological situations such as sepsis and syndrome including thrombocytopenia, anasarca, myelofibrosis, renal dysfunction, organomegaly (TAFRO) syndrome (13, 14). The role of IL6–signal transducer and activator of transcription 3 (STAT3) in tissue fibrosis, including lung damage, is well established (15).

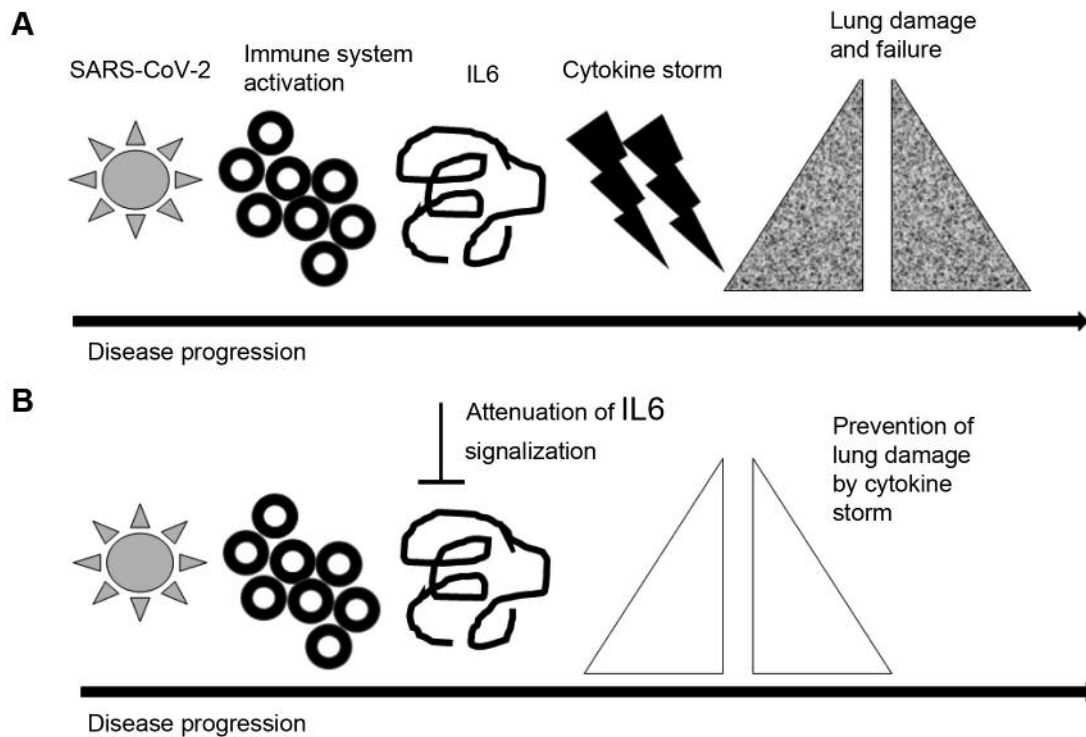


Figure 1. The role of interleukin-6 (IL6) in a cytokine storm. A: Infection by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) activates the immune system, which can produce an extremely higher amount of IL6 than is necessary. The abundant production of IL6 is important for the initiation of a cytokine storm that is subsequently responsible for lung damage and failure. B: Attenuation of IL6 signaling by suppression of its production (antimalarial drugs) or by targeting of its receptor complex (tocilizumab, bazedoxifene) has an inhibitory effect on the cytokine storm and protects the lungs from damage.

### Blocking of IL6 in COVID-19

Therapeutic blocking of IL6 signaling has been successfully used in the therapy of autoimmune diseases. It was also tested in anticancer therapy, but its efficiency was not high when monotherapy alone was employed (16, 17). However, efficiency was improved by simultaneous targeting of other cytokines (18). In the context of this article, blockade of the IL6 signaling cascade can attenuate the cytokine storm (19) in selected patients exhibiting symptoms of cytokine storm, for example monitored by the level of factors such as ferritin (8).

The monoclonal antibody tocilizumab targeted against IL6 receptor has been successfully used for the therapy of rheumatoid arthritis. Preliminary results demonstrated a good effect of this antibody on the treatment of patients with COVID-19 with lung complications (20, 21) resulted in the US Food and Drug Administration approval of phase III clinical study (22). However, a clinical trial is necessary before it can be introduced into the anti-COVID-19 clinical arsenal. Humanized antibodies to IL6 receptor from other companies (sarilumab, siltuximab) are also about to enter

phase I-III clinical trials for the prevention and management of lung damage in patients confirmed to have COVID-19.

Antimalarials such as chloroquine/hydroxychloroquine are used for therapy of parasitic diseases, as well as for therapy of some autoimmune pathologies, such as inflammatory bowel disease and lupus. Their effect is anti-inflammatory where they negatively influence the production of IL6 (23, 24). From this point of view, these substances are also good candidates for treatment of COVID-19-related lung complications (25). Employment of these substances is not without complications but for this indication, the benefit for patients will prevail (26).

Another therapeutic affecting the interaction of IL6 with its receptor, and the glycoprotein 130 (GP130) axis is bazedoxifene. This was designed as an estrogen analog for treatment of postmenopausal osteoporosis. However, this drug also interacts with GP130, part of the IL6 receptor (27, 28), where it prevents the binding of IL6 to the receptor. Bazedoxifene exhibits anti-inflammatory activity in arthritis (29) and due to its anti-IL6 activity was also found to have anticancer effects in various experimental setups (30-34). It has been observed that mortality from COVID-19 is gender-

dependent, whereby men are more sensitive than women (35, 36). This finding has not yet been explained but in this context, the estrogenic activity of bazedoxifene might, hypothetically, also be promising.

It can be hypothesised that bazedoxifene may represent a cheaper and easier alternative to humanized IL6 receptor antibodies for treatment of COVID-19-related lung complications. Moreover, the function of bazedoxifene as an estrogen analog might also be effective against SARS-CoV-2 entry and replication. Consistently, the in vitro preliminary results indicate bazedoxifene activity against COVID-19 (34). The principles of anti-IL6 therapy in COVID-19 are summarized in Figure 1.

## Conclusion

Inhibitors of IL6 signaling represent a promising approach that can be employed for attenuation of a cytokine storm and might be beneficial for patients with COVID-19.

## Conflicts of Interest

The Authors declare no conflicts of interest.

## Authors' Contributions

K.S. and J.B. collected data and prepared the article.

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