Medicine / Healthcare, Drug discovery, Life science

Therapeutic efficacy of anti-IL-6 receptor antibody in treatment of cytokine release syndrome

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Abstract

A hyperinflammatory response following infection or trauma can cause the lifethreatening condition cytokine release syndrome (CRS). Our research team found that IL-6 signaling induces the expression of inflammatory cytokines and PAI-1 in CRS patients, causing respiratory distress and multiple organ failure, which are also observed in severe COVID-19 patients. Blockade of IL-6 signaling using a human monoclonal antibody reduced PAI-1 levels and alleviated the clinical manifestations of disease in severe COVID-19 patients.

Background & Results

Overstimulation of the inflammatory response has an array of harmful complications, ranging from asthma to severe autoimmune diseases. One such complication, called cytokine release syndrome (CRS), is seen in patients suffering a hyperimmune response to microbial infection or trauma and can lead to multiple organ failure and even death. Despite knowing which cytokines are involved, there is still no specific immunotherapy for CRS and treatment is limited to supportive care. To better understand the molecular mechanisms of CRS pathogenesis, we first studied the cytokine profiles of 91 patients diagnosed with CRS associated with bacterial sepsis, acute respiratory distress syndrome, or burns. Strikingly, patients from all three groups had elevated levels of proinflammatory cytokines IL-6, IL-8, IL-10, and MCP-10, as well as a protein called PAI-1, which causes small blood clots in vessels throughout the body, including the lungs. Importantly, increased PAI-1 levels are associated with more severe cases of pneumonia, a common cause of death among COVID-19 patients. Because IL-6 was positively associated with the levels of the other cytokines and PAI-1, the researchers concluded that IL-6 signaling is crucial for the development of CRS following infection or trauma, and may play a role in the pathogenesis of COVID-19. Examination of cytokine profiles in severe COVID-19 patients revealed an increase in IL-6 early in the disease process, causing release of PAI-1 from blood vessels. Interestingly, PAI-1 levels were significantly higher in COVID-19 patients with severe respiratory impediment. Most significantly though, when severe COVID-19 patients were treated with a human monoclonal antibody to block IL-6 signaling, PAI-1 levels rapidly declined and severe disease symptoms were alleviated. IL-6 signaling blockade could therefore prove useful for the treatment of both CRS and the severe respiratory complications of COVID-19.

Significance of the research and Future perspective

Based on the results of this research, the administration of anti-IL-6 receptor antibody drastically reduced the symptoms of cytokine storms, and recently it is recommended by WHO as a treatment for new coronavirus infection (COVID-19). Thus, therapeutic effects targeting IL-6 receptors are expected for acute inflammatory diseases such as acute respiratory distress syndrome and sepsis.

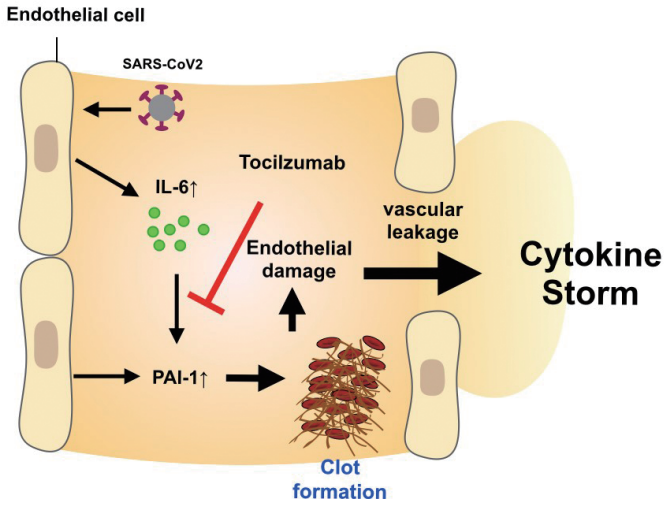

Figure: How Actemra© suppresses inflammation IL-6 in blood promotes thrombus formation via PAI-1. By suppressing IL-6, Actemra reduces the severity of pneumonia caused by the cytokine storm.
Actemra©; An humanized anti-IL-6 receptor antibody (tocilizumab)

Patent
Treatise Kang, S; Tanaka, T; Inoue, H et al. IL-6 trans-signaling induces plasminogen activator inhibitor-1 from vascular endothelial cells in cytokine release syndrome. Proc Natl Acad Sci USA. 2020; 117(36): 22351-22356. doi: 10.1073/pnas.2010229117
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