以第六介白質為標的之治療

IL-6 as a Target of Treatment

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Interleukin-6 (IL-6), originally identified as a B-cell stimulatory factor in the 1970s, is now a well-recognized pleiotropic cytokine. The different signaling pathways of IL-6, including classic signaling, trans-signaling, and trans-presentation, exert various effects on inflammation and homeostasis. Biologics targeting IL-6 as well as membrane-bound and soluble IL-6 receptors have been approved for several inflammatory rheumatic diseases, of which rheumatoid arthritis (RA) being the most widely applied. In RA, tumor necrosis factor alpha (TNF-α) and the downstream IL-6 activate fibroblast-like synoviocytes and promote destructive pannus formation. An overproduction of IL-6 and soluble IL-6 receptors stimulates RANKL expression, causing osteoclastogenesis and bone resorption. However, simultaneously stimulating bone marrow-derived macrophages with IL-6 and TNF-α in mice also induces bone destruction in a RANKL-independent fashion. IL-6 also negatively impacted the differentiation and proliferation of osteoblasts. Therefore, IL-6 inhibition not only protects from bone destruction, but also promotes bone repair.

In a phase 3 clinical trial of systemic sclerosis, though IL-6 inhibition only showed a trend of reducing skin scores, significantly less worsening of the forced vital capacity predicted was found. Tocilizumab was then approved by the U.S. Food and Drug Administration (FDA) for interstitial lung disease due to systemic sclerosis.

In giant cell arteritis (GCA), IL-6 inhibition alleviates excessive T cell-mediated inflammation. In a phase 3 trial of GCA, IL-6 inhibition led to a more sustained remission and a lower cumulative dose of corticosteroids. In Japan, IL-6 inhibition has also been approved for Takayasu arteritis and adult-onset Still's disease based on positive results from clinical trials. Rheumatologists are also becoming increasingly familiar with the use of IL-6 inhibition to treat macrophage activation syndrome of systemic juvenile idiopathic arthritis and other rheumatic diseases in adults. Recently, markedly elevated IL-6 levels were found in cytokine release syndrome (CRS) following chimeric antigen receptor T-cell therapy in patients with relapsed hematologic malignancies. IL-6 inhibition stabilized this life-threatening cytokine storm and enhanced survival. Similarly, in CRS induced by COVID-19, IL-6 inhibition reduces mortality rate at day 28 in those receiving corticosteroids; the U.S.

FDA thus issued an emergency use authorization in June, 2021.

This talk summarizes the pathogenic roles of IL-6 in inflammatory rheumatic diseases and CRS and reviews the approved indications of IL-6 inhibition.