

Popular Article

Scope of Cytokine based Therapy in COVID-19

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Abstract

COVID-19 pandemic caused deaths of millions of humans, worldwide. Besides, loss of lives, COVID-19 caused loss of education, economy, jobs, etc. Vaccine is urgently needed to combat the losses, but which may or may not be effective against this highly mutating virus. So, cytokines-based therapy can be explored as an alternative approach to combat COVID-19. The high levels of cytokines are thought to be responsible for the high mortality rate of infected patients. So, cytokines became a target for developing therapeutic strategies, and they may be a way to combat this pandemic.

Introduction

COVID-19 (Coronavirus disease 2019), the pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) that has caused death of millions of lives worldwide, is well known. The ongoing pandemic is causing enormous loss in terms of lives, education, the economy, jobs, etc. An effective and safe vaccine is urgently needed to combat the losses, but each vaccine has advantages and disadvantages. So, in this hour of crisis, having an alternative is critical. It was discovered that severely infected patients have high levels of various cytokines, indicating a poor prognosis. Increased cytokine levels (cytokine storm) are thought to be responsible for the high mortality rate of infected patients. So, cytokines became a target for developing therapeutic strategies, and they may be a way to combat this pandemic, but the possibilities in terms of safety and efficacy remain unknown.

COVID-19 patients have elevated levels of proinflammatory cytokines such as IL-6 (Interleukin-6), IL-1, IL-2, IL-8, IL-17, IL-4, IL-10, G-CSF (Granulocyte-colony stimulating factor), GM-CSF (Granulocyte monocyte-colony stimulating factor), IP10 (Interferon-gamma induced protein), MCP1 (Monocyte chemoattractant protein (Tumor necrosis factor)). This rapid rise in serum cytokine levels is known as a cytokine storm or cytokine release storm (CRS). The uncontrolled immune response caused by continuous activation and expansion of immune cells (macrophages, dendritic cells, Th17 cells, CD8+ T cells) that produce a large number of cytokines is the cause of cytokine storm. Cytokine storm is a critical life-threatening condition that necessitates intensive care. It is characterized by overwhelming systemic inflammation, hyperserotonemia, hemodynamic instability, and multi-organ failure, and it is fatal if left untreated.

Therapies targeting cytokines

To combat this potentially fatal inflammatory response, scientists are researching anti-inflammatory therapies that target the cytokines that cause cytokine storm. Anakinra, an IL-1 receptor antagonist used to treat rheumatoid arthritis, was discovered to be helpful for cytotoxic histiocytic panniculitis, but its use for COVID-19 has yet to be discovered. Tocilizumab, a recombinant humanized IL-6 receptor antagonist, is another molecule. It is used to treat rheumatoid arthritis, juvenile idiopathic arthritis, giant cell arteritis, and has been shown to be effective in treating cytokine storms caused by CAR-T cell therapy in haematological malignancies. Tocilizumab may be a candidate drug for managing the cytokine storm in COVID-19 patients because IL-6 is the most frequently reported cytokine to be increased and because IL-6 elevated levels have been linked to higher mortality. In China, tocilizumab was used to treat 21 patients with severe and critical COVID-19, with encouraging results. Table 1 lists the other candidates who could potentially be used as COVID-19 therapies. The efficacy of the listed candidates for COVID-19 infection in humans has yet to be determined.

Limitation of cytokines-based therapy

Cytokine therapies are very effective at controlling cytokine-mediated inflammation, but they are ineffective at clearing the virus load from the system. IL-15, IFN-, and type I IFNs are required for viral clearance. Targeted inhibition of some cytokines, such as IL-17, may result in secondary viral, bacterial, or fungal infection. Inhibition may result in *Candida* sp. infection. TNF and IL-6 inhibition may result in secondary bacterial infection as well as hepatitis B virus activation. A significant amount of research is required to find an effective and safe candidate for the COVID-19.

Conclusion

Because COVID-19 is a new infection and cytokine-based therapy is a new noble area of research, there are many possibilities to uncover in order to find a suitable cytokine-based target to combat the ongoing pandemic. The available potential candidates listed in Table 1 have been successfully used for other conditions, but their effectiveness in combating COVID-19 requires a sufficient number of trials. Rather than currently available vaccines, which may or may not be effective against this highly mutating virus, cytokine-based therapy may be a viable option in the near future.

Table 1: Possible suitable candidates targeting various cytokines can be used for COVID-19 treatment (Approved by U.S. FDA)

Biological candidate	Trigger/ associated disease	Mechanism	Status for hypercytokinemia
Siltuximab	CRS (Cytokine release storm)	Anti IL-6 antibody	Preclinical for CRS
Canakinumab	MAS(macrophage activation syndrome)	Human monoclonal anti IL-1 β antibody	Phase 3 for MAS
Rilonacep	MAS	Neutralizing IL-1 α and IL-1 β	Randomized controlled trial for MAS
Tadekinig alfa	NLRC4-associated MAS	Recombinant human IL-18-binding protein (rhIL-18BP) to tightly bind IL-18	Phase 3 for NLRC4-associated MAS
Emapalumab	HLH(HemophagocyticLymphohistiocytosis)	Anti IFN- γ antibody	Approved for primary HLH
Infliximab	HLH, GvHD (Graft versus host disease) and sepsis	Human monoclonal anti-TNF α antibody	Phase 1-2 for GvHD
Ponatinib	Influenza A	Inhibiting breakpoint cluster region-Abelson (BCR-ABL) kinase to regulate type I IFN	Preclinical for cytokine storms in influenza

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