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Mini Review

A Novel Potential Therapeutic Tool to Increase Efficiency of Available COV-19 Vaccines

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Abstract

A side from the activation of the immune cells and the noticed increase of cytokine levels in COVID-19 patients who have cytokine storm, it has been proved that they have multiple clinical and laboratory irregularities as renal dysfunction and CRP, in addition hyper-inflammation and tissue damage that found to predict worse effects of COVID-19. Over production of cytokines during SARS-CoV-2 can result in damage of lung tissues, ARDS and death. Many studies recently reported that severity of the disease was significantly lower in the vaccinated individuals who get infected with COVID-19 compared to non-vaccinated ones. There are contradictory data with regard to the immunological effect of COVID-19 vaccines. No evidence of raised cytokines levels was shown in vaccinated people with Moderna and Pfizer-BioNTech. On the other hand, Covaxin increases plasma levels of some cytokines like IFNγ, IL-2, TNFα, IL-4, IL-5, IL-10, IL-13 and others but reduced levels of other cytokines as IL-25, IL-33 and GM-CSF. Pfizer reduced the production of the pro-inflammatory cytokines, TNF-α and IL-1β. The current review highlights updates on the immunological aspects of COVID-19 and its vaccines. After elaborating advanced research studies, cytokine inhibitors and JAK inhibitors could be used in adjunct with available vaccines or as promising therapeutic target for severe cases of COVID-19.

Keywords: COVID-19; Cytokine inhibitors; JAK inhibitors; Vaccines

Abbreviations

ARDS: Acute Respiratory Distress Syndrome; CRS: Cytokine Release Syndrome; CSF: Colony Stimulating Factor; DIC: Diffused Intravascular Coagulation; G-CSF: Granulocyte Colony-Stimulating Factor; GM-IP-10: 10 kD Interferon-Gamma-Induced Protein; GM-CSF: Granulocyte-Macrophage Colony Stimulating Factor; HGF: Hepatocyte Growth Factor; IL-1β: Interleukin 1β; IL-2R: Interleukin 2 Receptor; IL-2: Interleukin 2; IL-4: Interleukin 4; IL-6: Interleukin 6; IL-7: Interleukin 7; IL-10: Interleukin 10; M-CSF: Macrophage Colony-Stimulating Factor; MCP-1: Monocyte Chemoattractant Protein-1; MIP 1-α: Macrophage Inflammatory Protein 1 Alpha; PARs: Proteinase-Activated Receptors; TNF-α: Tumor Necrosis Factor α; VEGF: Vascular Endothelial Growth Factor

Introduction

Advanced COVID-19 syndrome is characterized by the uncontrolled and elevated release of pro-inflammatory cytokines and suppressed immunity, leading to the cytokine storm; cytokines are small glycoproteins produced by various types of cells through the body but in cytokine storm various inflammatory cytokines are produced at much higher rate than normal, causes positive feedback on other immune cells to occur, which causes another immune cells recruitment to the site of injury and leads to organ damage (Figure 1).

It was observed that certain cytokines such as IL-6, IL-10 and TNF-α in COVID-19 patient were elevated. Also, severe cases of COVID-19 which require entering ICU were found to have elevated serum levels of cytokines like IL-2, IL-7, IL-10, M-CSF, G-CSF, GM-CSF, IP-10, MCP-1, MIP 1-α, MIP1-α, HGF, VEGF and tumor necrosis factor-alpha (TNF-α) [1-5]. In general, these cytokines are polypeptide signaling molecules that regulate many biological processes through cell surface receptors [6]. SARS-CoV-2 activates IL-1β which has a role in cytokines storm produced by COVID-19 , then IL-1β in turn activates another cytokines such as IL-6 and TNF-α [1,2,5]. It was reported that elevated levels of IL-2 or its receptor (IL-2R) in COVID-19 patients raise the severity of the disease [7-13]. Some studies show that IL-4 levels increase in cytokine storm cause severe respiratory symptoms in COVID-19 patients [1,5,14,15]. Also, elevated levels of IL-6 in COVID-19 patients are associated with severe symptoms and poor prognosis [9].

The current review highlights the role of cytokines during COVID-19 infection and after vaccination. Additionally, it illustrates the potential use of cytokine inhibitors as a part of COVID-19 therapeutic protocols to alleviate its severity.

COVID-19 and Cytokines

SARS-CoV-2 elicits an innate immune response and causes an immediate rise in the neutrophils and other immune cells along with a marked reduction in the T cells (CD4+ and CD8+). However, the reduction of T cells along with the enhanced production of interleukin6 (IL-6) and interleukin 8 (IL-8) has been reported as a remarkable characteristic of SARS-CoV-2 infection [16], this increase in cytokine production is associated with a high degree of pyrexia, blood leakage, the formation of multiple blood clots, and pleural effusion with the result of acute respiratory distress syndrome (ARDS); a common adverse effect of COVID-19 based on

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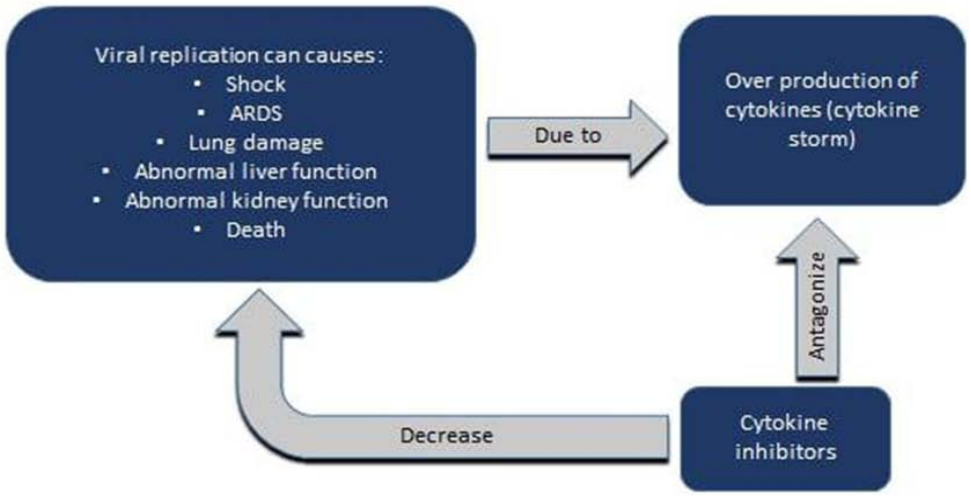

Figure 1: COV-19-induced cytokine storm.

excessive cytokine production [17,18]. Also, a high concentration of interleukins may lead to diffused intravascular coagulation (DIC), a characteristic phenomenon of extreme cytokine release syndrome (CRS) [19]. Activation of coagulation pathways during the immune response to infection results in overproduction of proinflammatory cytokines leading to multiorgan injury. Although the main function of thrombin is to promote clot formation by activating platelets and by converting fibrinogen to fibrin, thrombin also exerts multiple cellular effects and can further augment inflammation *via* proteinase-activated receptors (PARs), principally PAR-1 [20]. A clinically approved PAR-1 antagonist was shown to reduce levels of proinflammatory cytokines, neutrophilic lung inflammation, and alveolar leak during bacterial pneumonia and lipopolysaccharide-induced lung injury in murine models [20,21].

TNFs and colony stimulating factor (CSFs) are the major cytokines involved in the generation of cytokine storms during COVID-19 [22]. Each one of them has its role, for example excessive IFN-γ secretion, resulting in headaches, chills, dizziness, fatigue, and fever. Like IFN-γ, TNF-α causes flu-like symptoms along with fever, fatigue, and malaise, but can also lead to lung damage, vascular leaking, heart failure, and synthesis of acute-phase protein [23].

Elderly patients are more prone to get the sever forms of COVID-19 infection and more likely to have cytokine storm , Immunosenescence makes the innate immune response become more active, increasing the number of natural killer cells (NK) and releasing pro-inflammatory cytokines, such as Interleukin 6 (IL-6), TNFα and CRP. In turn, this results in a chronic, low-grade inflammation, a phenomenon that has been termed as "inflammaging [24], A recent study on the inflammatory biomarkers deduces that the geriatric population with high IL-6 baseline levels and high increment scale of overtime IL-6 levels are more prone to multiple systemic diseases than with low overtime increment of IL-6 with high baseline IL-6 titers. The soaring IL-6 levels during SARS-CoV-2 infection activate CRP, another inflammatory culprit to COVID-19-based multiple systemic disorders and pneumonia [25].

SARS-CoV-2 activates IL-1β which has a role in cytokines storm produced by corona virus infection, then IL-1β in turn activate another cytokines such as IL-6 and TNF- α [26-29]. It was reported that elevated levels of IL-2 or its receptor (IL-2R) in COVID-19 patients which directly proportional raise the severity of the disease [30,31]. Some studies show that IL-4 levels increase in cytokine storm cause severe respiratory symptoms in COVID-19 patients [32]. Also, elevated levels of IL-6 in COVID-19 patients are associated with severe symptoms and poor prognosis [33].

Potential Therapeutic Role of Cytokine Inhibitors in COVID-19

Cytokines inhibitors are a good choice to treat patients with COVID-19 especially those with severe symptoms like tocillizomab which is a monoclonal antibody to IL-6 receptor and it is significantly reduced the risk of mechanical ventilation and death. Also, it was demonstrated that fever is rapidly controlled and respiratory functions are efficiently improved in severe COVID-19 cases and all patients recovered [34,35]. Sariluzomab is another example of IL-6 signaling pathway inhibitor that is used in corona virus [36]. JAK (Janus kinase/signal transducers and activators of transcription) is intracellular trans-kinase that mediates signaling from cytokines, hormones and growth factors. Anti-inflammatory agents such as Baricitub, fedratinib and ruxolitinib are JAK pathway inhibitor which will be effective against high cytokines level as in corona virus. Combination of baricitub with antiviral drugs (lopinavir, ritonavir, remdesivir) showed reduced viral replication in COVID-19 patients [37-39].

Dexamethasone is an example of corticosteroids act as anti-inflammatory and immunosuppressive agent and it's showed the effective against corona virus recently by reduces the mortality rate among severe COVID-19 cases. Low dose dexamethasone is effective in the fight against corona virus [40].

In severe cases of Corona virus which are caused by cytokine storm. Therapeutic plasma exchange (TPE) is used to treat cytokine storm to remove inflammatory cytokines for example Inhibition of IL-1 signaling. Anakinra, a recombinant IL-1 receptor antagonist, used to treat cytokine storm. Anakinra is modified form of a human

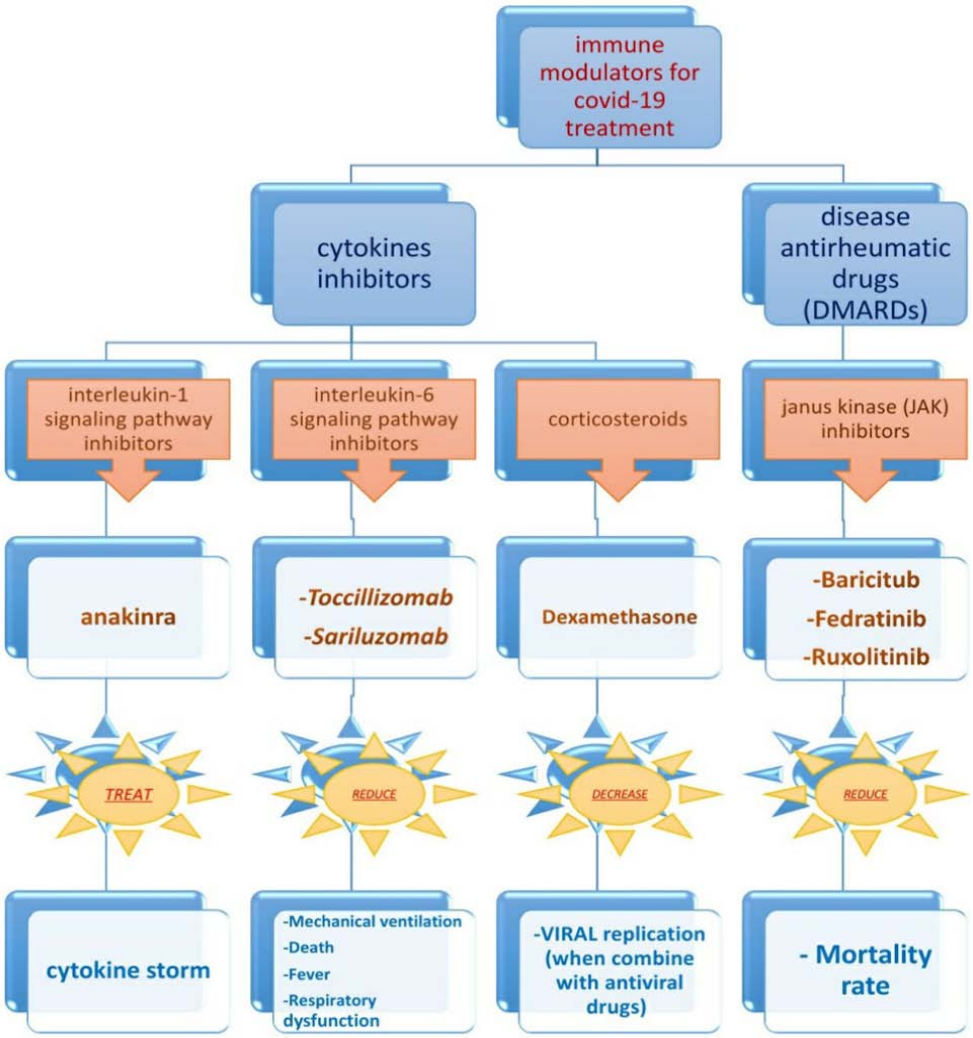

Figure 2: Potential role of cytokine inhibitors in combating cytokine storm.

IL-1 inhibitor. The action of anakinra is safe because it is similar in its physiological mechanism without serious side effects [41,42].

COVID- 19 patients admitted to the Renmin Hospital (Wuhan, China) were classified according to their symptoms. A study showed that patient's cytokine and C-reactive protein levels were higher than those of the control group. Compared with healthy control individuals, patients appear to have higher amounts of cytokines (TNF-α, IFN-γ, IL-2, IL-4, IL-6, and IL-10) and C-reactive protein [43].

For critically ill patients in the intensive care unit (ICU), the peripheral IL-10 concentration is significantly higher than that of non-ICU patients. In addition, IL-10 concentration is closely related to IL-6 and other inflammatory markers (such as C-reactive protein). Like IL-6, high IL-10 levels indicate a poor prognosis for COVID-19 patients, a meta-analysis of COVID-19 patients with and without severe illness successfully predicted IL-6 and IL-10 levels, a mild rise in levels of IFN-γ was seen in severe group with moderate significance [44,45].

Hence, in COVID-19 patients, IL-10 levels rise earlier than IL-6. Tocilizumab has been shown to reduce mortality in potential COVID-19 treatment, while other trials have failed to reduce mortality in studies testing the effectiveness of blocking IL-6/IL-6R, while other clinical trials proposes that blocking of IL-1 is subjected to significant concerns [44,46,47]. Contrary to this, highly elevated levels of IL-10 in serum of COVID-19 patients are generally considered to be anti-inflammatory or immunosuppressive mechanisms (and biomarkers), in the form of a negative feedback loop, rapid accumulation of pro-inflammatory cytokines [44]. IL-6 and IL-10 could be an important precursor in determining the disease severity according to many researches.

Cytokine Levels after COVID-19 Vaccination

Compared to the raised levels of cytokines observed in severe cases of COVID-19 patients, no evidence of raised cytokines levels was shown in vaccinated people with Moderna and Pfizer-BioNTech- the two biopharmaceutical companies that produced mRNA COVID-19 vaccines. Furthermore, it has been noticed that rates of severity of the disease were significantly lower in the vaccinated group than

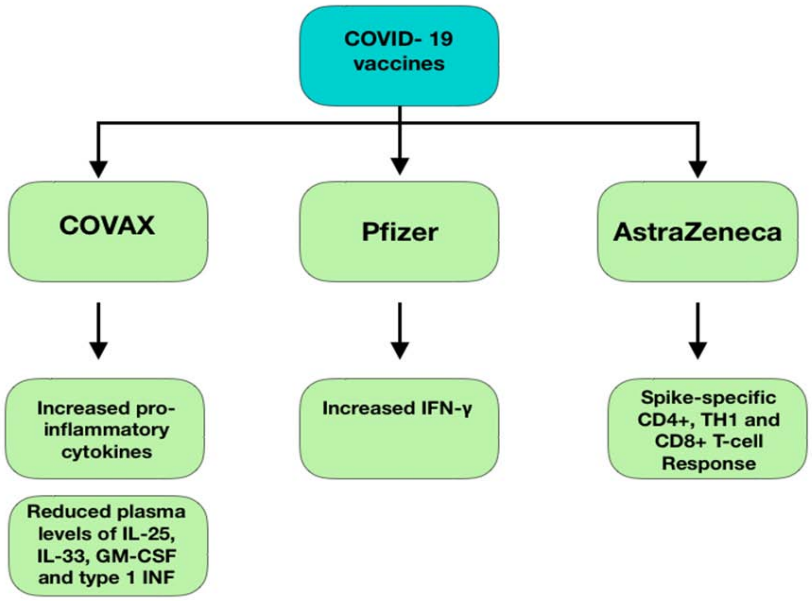

Figure 3: Immunological effect of COVID-19 vaccines.

in the placebo group [42,48]. Covaxin induces enhanced plasma levels of Type 1 cytokines (IFNγ, IL-2, TNFα), Type 2/regulatory cytokines (IL-4, IL-5, IL-10 and IL-13), Type 17 cytokine (IL-17A), other pro-inflammatory cytokines (IL-6, IL-12, IL-1α, IL-1β) and other cytokines (IL-3 and IL-7) But it reduced the plasma levels of IL-25, IL-33, GM-CSF and type 1 IFN [48]. After stimulation with standard COVID- 19 strains or different Toll-like receptor ligands, Pfizer reduced the production of the pro-inflammatory cytokines, TNF-α and IL-1β. The production of the anti-inflammatory cytokine IL-1Ra is reduced in response to Toll-like receptor 4 but IFN-γ production by at least 50% in 37.5% of the samples stimulated with the standard SARS-CoV-2 strain has increased after vaccination [49]. An international team of scientists has discovered that AstraZeneca COVID-19 vaccine can cause substantial spike-specific CD4+, Th1 and CD8+ T-cell responses in vaccinated people [50].

Conclusion

No doubt that severity of COVID-19 cases with consequent higher mortality rates is associated with raised levels of proinflammatory cytokines and on the other hand reduced anti-inflammatory ones. Data are contradictory regarding effect of available vaccines on cytokine levels and more studies are recommended in this field. Cytokine inhibitors like anakinra, tocilizumab in addition to Janus kinase inhibitors as baricitub, fedratinib and ruxolitinib; could be used in adjunct with available vaccines or as promising therapeutic target for severe cases of COVID-19 after elaborating advanced human RCTs to increases the efficiency of COVID-19 vaccines.

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