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REVIEW ARTICLE

Potential of IL-10 as Targeted Therapy in Severe COVID-19 Patients

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ABSTRACT

A brand new virus that is known as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is the cause of this new disease called Coronavirus Disease 2019 (COVID-19). This new disease may lead to severe illnesses and eventually become fatal due to many complications related to cytokine storms. Cytokine storm could be described as pro-inflammatory cytokine response that is not controlled due to infection and other stimuli. The increase in cytokine levels can cause multiple organ systems damages. To protect the patient from tissue damage caused by the pro-inflammatory cytokine, a balanced immune response is needed. Many efforts have been tested to manipulate or prevent the cytokine storm. One of the potential targets is IL-10. IL-10 is a key role cytokine. The information regarding IL-10 that is currently available will be reviewed in this article, its role in the cytokine storm, and its potential as a curative agent in COVID-19.

Keywords: COVID-19, Cytokine storms, IL-10, Therapeutic target

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INTRODUCTION

In December 2019, a "strange pneumonia" was found in Wuhan, one of city in Hubei Province. From the 18th of December to 29th of December 2019, there were several patients diagnosed with Acute Respiratory Distress Syndrome (ARDS) getting treatment. From the 31st of December 2019 to 3rd of January 2020 these cases have increased rapidly. It is possible for this virus to be disseminated through human to another human being and in less than a month, both in China and a bunch of countries, this brand new virus has been beginning to outspread. Novel coronavirus (2019-nCoV) was initially the name of this new virus. Then on February 11th, 2020, WHO called the new virus as SARS-CoV-2 and then the cause as COVID-19 (1, 2). As of July 6th, 2020, there were about 11.5 million cases and 532,804 deaths worldwide. Meanwhile, in Indonesia currently, there are 64,958 cases of COVID-19 positive and 3,241 deaths (1, 3).

SARS-CoV-2 can increase uncontrolled inflammation, termed as cytokine storms, which can eventually lead to ARDS, respiratory failure, sepsis, and other complications proved to be fatal. Cytokine storms, which are uncontrolled systemic inflammatory responses, could happen because there are huge amounts of pro-inflammatory cytokines and chemokines being released (4, 5-6). There is no doubt that the cytokine storm has contributed to a high death toll.

As of now, effective drugs or vaccine have yet to be found to cure COVID-19 or to avoid the SARS-CoV-2 infection, the only choice for many affected countries is to apply strict limitation on almost all social activities (lockdown) and the attempts to use some antiviral drugs for viral control, as well as some medication to curb or prevent the cytokine storm. The sign of main reaction of normal macrophages in human to lower the dose of intracellular pathogens is IL-10 being produced. IL-10 may defend hosts from a large amount

of inflammatory reactions and tissue injuries secondary causing infections (7). The information regarding COVID-19 and the cytokine storm that is currently available will be reviewed in this article, the available targets for intervention, IL-10's part in cytokine storm, and its potential as a therapeutic agent in COVID-19.

The pathomechanisms of COVID-19 and the cytokine storm

SARS-CoV-2, for the most part, infects the respiratory tract's epithelial cell. SARS-CoV-2 binds to receptors and makes its way into the cell. The glycoprotein in the envelope spike virus will bind itself to the cellular receptor, the shape of it would be ACE2 in SARS-CoV-2. Inside the cell, SARS-CoV-2 releases an RNA genome and synthesizes the proteins needed, and then forms new viral that appears on the cell surface which then more cells would be spread on. While the immune system diagnositcates the antigen of viral, in the conditions of crucial tissue histocompatibility (MHC) antigens APC will be processing viral antigens and presenting both of them to the NK cell and CD8-positive cytotoxic T cells, which occurs at regular intervals. The presentation of antigen then further stimulates humeral also cellular immune responses, the exaggerated of pro-inflammatory cytokines materialized because of them (3) and chemokines (5, 8). Pro-inflammatory cytokines (Interferon-α, Interferon-γ, Interleukin-1β, IL-2, IL-6, IL-7, IL-10, IL-12, IL-18, IL-33, TNF-α, and TGF-β) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, and CXCL10) that came in immoderate amount, responding SARS-CoV-2 is known as a cytokine storm. Whether the inflammation gets out of control, the possible cause of ARDS, sepsis, various organ damages and can even lead one to pass away in serious cases of SARS-CoV-2 infection is cytokine storms (4-6).

The chance of modulating the cytokine storm

It has been shown that cytokine storm is a serious case in COVID-19. Efforts to dampen the cytokine storm are still a subject of ongoing studies. For example, one clinical trial in China (ChiCTR2000029765) discovered high levels of IL-6 in patients that badly suffer COVID-19 and associated those with poor outcome (9). The trial used tocilizumab (a monoclonal antibody that targets IL-6) in 21 patients severely diagnosed with COVID-19. The result shows that all patients without significant side effects were not deteriorating, thus have been released from the hospital. This promising study suggests that it could be beneficial to use neutralizing monoclonal antibodies (mAbs) to dampen inflammatory cytokines in larger trials with other possible targets such as IL-17 or IL-1 with their receptors (9-10). Another trial that is still ongoing is with the use of TNF-α as target and registered as ChiCTR2000030089 (cited by 12). TNF-α has a lot of roles such as mediator of the inflammatory response and promotes other cytokines and chemokines. The spike of SARS-CoV-2 that renders the TNF-α-converting enzyme (TACE), allows the host cell to be infiltrated with the virus and TNF-α levels, is increased if this pathway is facilitated (8, 11-12). TNF-α levels were found to be high in COVID-19 patients and positively have correlation to the seriousness of this disease (13). It could be concluded that TNF-α may be a potential option as treatment for COVID-19. In line with those findings, balancing the inflammatory response may represent an effective treatment for COVID-19. The immunomodulatory treatment has the potential to control cytokine storms.

The role of IL-10 in the cytokine storm

Cytokine synthesis inhibitory factor (CSIF) in human that is also usually called Interleukin-10 (IL-10) (14) and has the ability to suppress Th1 response indirectly. IL-10 has two kinds of receptors that form a heterotetramer, i.e. two chains of IL10R1 and two chains of IL-10R2 (15). The ligand-binding subunit and the signalling subunit are IL10R1 and ILR2, respectively (16-17). Massive amount of immune cells secrete a cytokine specifically IL-10, in which its effect on the immune system and inflammation is pleiotropic. When it comes to immune regulation, IL-10 is proved to have multiple roles. It has shown to inhibit production by dendritic cells and macrophages of many inflammatory molecules such as IL-12, MHC and other costimulatory molecules. It has also shown to have a role in B cell survival, proliferation and antibody production. It also has a role in tumour immunity (17-18). In one hand, IL-10 has the role in remodelling damaged tissues and wound healing, but on the other hand, it can limit antiviral, antibacterial responses (18).

IL-10, as how they have been displayed in several studies, is able to suppress pro-inflammatory cytokine in HIV, HBV, influenza virus, dengue, and other virus infection (19-22). Dendritic, natural killer (NK) cells and cytotoxic T cells are the main immune cells involved in viral detection and elimination during the beginning stage of viral infections. In the first phase, viruses typically trigger the involvement of pathogen recognition receptor (PRR) after a recognition via pathogens-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs). Once virus infects the host cells, PAMPs molecules are recognized by the dendritic cells (DC). These cells can secrete cytokines (Type I IFN, IL-2, and IL-15) in recruiting further cells to the infection's site. These include NK cells. NK cells use their surface receptors to detect foreign molecules in the body such as viruses. DCs that detect viruses also can activate T cells that specifically recognize the virus based on its surface antigens. The antiviral state in antigen-presenting cells (APC) was getting elicited because

of the recognition of PAMP and DAMP, then produces type I IFN, the innate immune response will immediately start (23). In countering or limiting the pro-inflammatory defense that is activated by PRR s ignalling, cytokine IL-10 is induced in DCs. The existence of IFN-γ is possible to antagonize APC that produces IL-10. In the phase of infection that was late, higher levels of IL-10 could be found as a response to a hyperinflammatory state or cytokine storm (24).

The potential of IL-10 as immune modulator

IL-10's effect is depending on the condition. At the time when the inflammation is at a high level, it is important to down-regulate the immune response to keep away from tissue damage. This means that immunopathology occurs when the production of IL-10 is insufficient. However, if it was indicated that the damage risk of immune-mediated as high, IL-10's activity is potentially useful for the host. The activity of IL-10 immunosuppressive could be considered beneficial for the host when the immune response to non-harmful stimuli is overreacting. This is to ensure how the immune response is non excessive but just preservative to the host. In contrast, it is then not appropriate for suppression of IL-10 to be too much and clearing the viral infection sufficiently is failed due to the overall effect, which may lead to infection that is more chronic. Some studies reported that IL-10 was produced by APCs in the late phase of activation (23, 25), suggesting that IL-10 was induced by viral PAMPs to balances the pro-inflammatory signals.

The potential role of IL-10 in COVID-19 cytokine storm

It is well known that COVID-19 patients showed a cytokine profile which is consistent with a hyperinflammatory condition triggered by viral infection (26-28). The excessive release of cytokines and chemokines into the circulation caused some impact on numerous organs that is very much wide and detrimental. When this pathological state or condition occurs, it is important to try to dampen the exaggerated immune response by giving immunosuppressive cytokine such as IL-10 or induce its secretion by the immune cells, in order to produce an immune response that is not damaging the host in the process but enough to clean the pathogen.

Systemic protein of IL-10 administration is not decent because of the rapid breakdown of protein. Fortunately, there have been some developments regarding several methods that is used so that IL-10 can be escalated (e.g. protein administration, viral vectors, naked plasmid DNA, plasmid DNA packaged in polymers to enhance their uptake into target cells, and adenosine 2A agonists) (29). When it is deemed as necessary for something like in the cytokine storm of COVID-19 to be relieved immediately and transiently then it is possible for IL-10 protein administration to be straight up useful in clinical circumstances. Their other use is to be an adjuvant to longer-term gene therapies, they could provide relief immediately during the period exactly when therapeutic onset of the gene therapy got delayed (29).

CONCLUSION

Due to its immunoregulatory and immunosuppressive effects, IL-10 can be seen as an alternative cytokine treatment for patients that suffers badly from COVID-19 with the experience of a cytokine storm. Although several pieces of evidence suggest that IL-10 might be a target that is very much invaluable for the treatment of this disease caused by viral infection (30), further research about this is necessary to determine the appropriate timing and the full scope of impacts related with IL-10-based therapy.

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