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OPINION

Tocilizumab: A Therapeutic Option for the Treatment of Cytokine Storm Syndrome in COVID-19

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Presently, we need more therapeutic molecules for this COVID-19 outbreak. The severity and mortality of the disease is associated with a high level of release of cytokine in the patients which is known as CRS (cytokine release syndrome) or cytokine storm syndrome. IL-6 is a type of pro-inflammatory cytokine which release in the severe COVID-19 patients. This cytokine initiates CRS the JAK-STAT or MAPK/NF-κB-IL-6 pathway. Tocilizumab, a humanized monoclonal antibody, is designed to bind both mIL-6R (membrane bound receptor for IL-6) and sIL-6R (soluble receptor for IL-6) and inhibit the JAK-STAT or MAPK/NF-κB-IL-6 signaling pathway. It finally stops the cytokine storm syndrome. However, we need to understand that how tocilizumab is bound with mIL-6R or sIL-6R. Similarly, we also need to understand more about the real molecular mechanism of activity of tocilizumab.

Key Words: Tocilizumab, Therapeutic option, Cytokine storm syndrome, COVID-19.

Since December 2019, a deadly viral disease grasps almost the entire world under its pathogenic effect and threatens its civilization with an impact never seen before. The main cause of this disease has been recognized as a new member of the coronavirus family, namely SARS-CoV-2 and the disease is popularly known as COVID-19. The disease was first reported in Wuhan, China and the primary and well-known symptoms of the disease include fever, respiratory distress and inability to breathe spontaneously which ultimately leads to pneumonia (1–3). However, some other symptoms, including different kinds of neurological symptoms (4) and diarrhea could also be considered as clinical signs associated with this disease. Moreover, it has been found that the severity and mortality of the disease is closely associated with high levels of cytokine release in the critical patients which ultimately results in CRS (cytokine release syndrome) or more popularly known as cytokine storm (5). There is a strong correlation between theprogress of the disease from severe to very critical and this cytokine storms. Cytokines are small chemical messengers, specifically meant for immunogenic response, and can induce both adaptive and innate immune response. They are small molecules including interferons (INF), interleukins (IL), growth factors, TNF or tumor necrosis factors and chemokines (6). Surprisingly, the association of CRS or cytokine storm and high morbidity is not something which is unique to SARS-CoV-2, it has also been reported in the previous viral infection caused by other coronaviruses, like SARS-CoV and MERS-CoV (7). It has also been reported from various previous scientific information's that interleukin-6 (IL-6) plays a pivotal role in this kind of elicit immunogenic response. It has been observed that there is a strong involvement of this particular interleukin in inducing CRS which correspond to a higher rate of morbidity associated with different viral infections (SARS CoV and MERS CoV) and also in some other diseases (8). The concentrations of serum IL-6 in normal condition is very less and tends to increases if there is an infection or injury in the human body. IL-6 is a kind of

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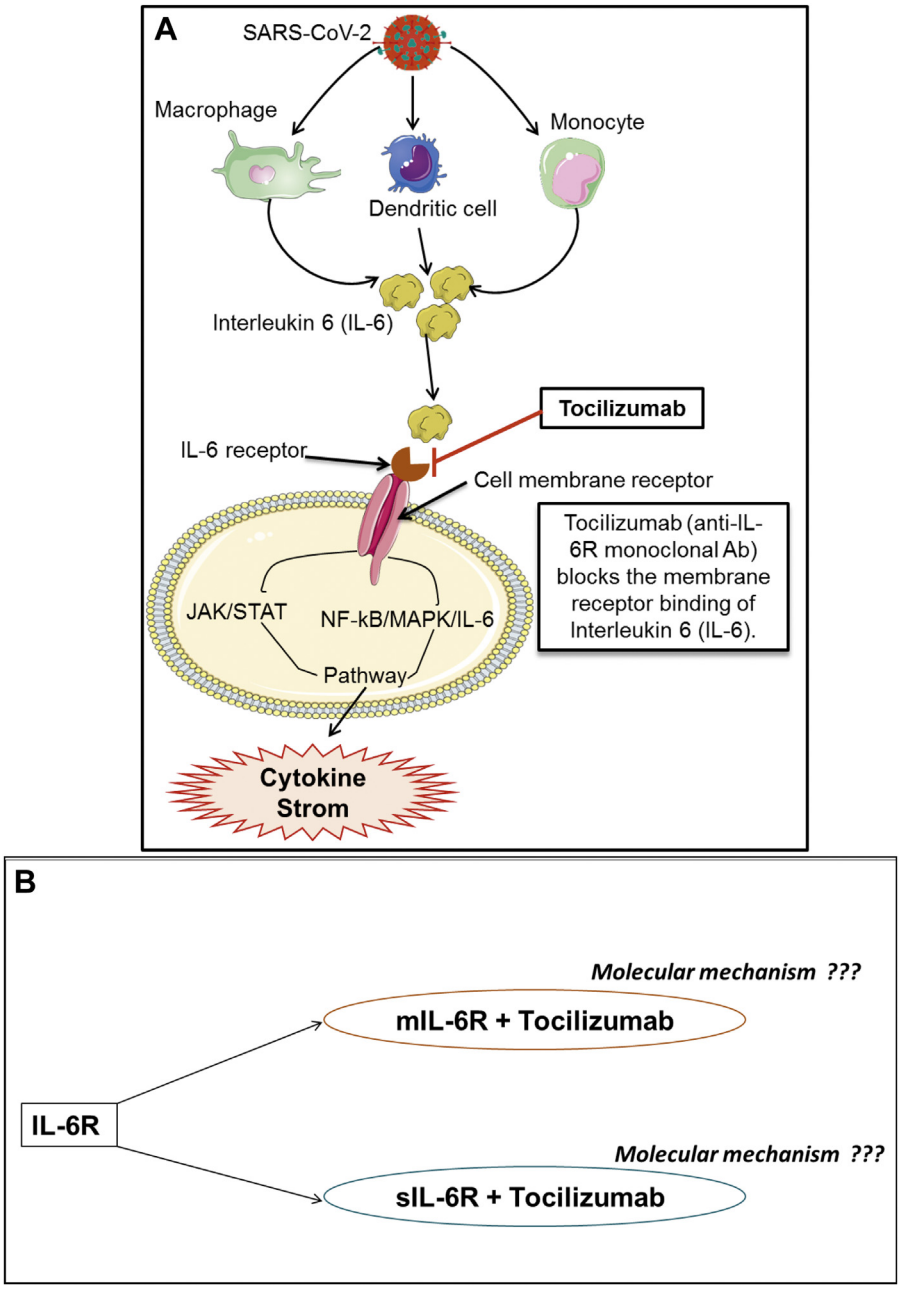

Figure 1. Probable mechanism of action of Tocilizumab, (A) Schematic diagram shows the cytokine storm by SARS-CoV-2 which can be blocked by Tocilizumab. (B) Molecular binding mechanism of Tocilizumab with two types of IL-6 receptor needs to know more.

pro-inflammatory cytokine and there are two types of signaling pathways (classical and trans signaling pathway) have been employed by this interleukin molecule to initiate immune response. In the classical pathway, IL-6 bind to its receptor i.e. mIL-6R (membrane bound receptor for IL-6) present in the cell surface of mainly immunogenic cells, and then this complex bind with anther signaling transducer molecule, glycoprotein 130 (gp-130) and this complex in turn transduce the signaling pathway through JAK-STAT (Janus kinases-signal transducer and activator of transcription) pathway (9) or MAPK/NF-κB-IL-6 pathway, which in turn activate different kinds of inflammatory effects in innate immune system (Natural killer (NK) cells, neutrophils and macrophages) and as well as acquired immune system (B and T cells) (10). But this classical cis signaling pathway is only confined to immunogenic cells, whereas, the IL-6 can also activate a huge pro-inflammatory effect via its other alternative signaling pathway, i.e. trans signaling pathway. In this pathway, the interleukin bind with a receptor which is not present in the cell surface, rather it a

kind of soluble form of the receptor, sIL-6R, and forming a complex with gp-130 dimer, possibly present on all the cell surface, specifically different kinds of endothelial cells (11). So, by this trans signaling pathway IL-6 potentially can induce a pro-inflammatory response possibly in every type of cells present in our system and moreover, it has also been reported previously that IL-6 is almost secreted by all kind of immune and stromal cells (11).

So, it is imperative to note that, the signaling of IL-6 plays an important role in inducing this cytokine storm (both by its classical and trans signaling pathway) in seriously affected COVID patients and in order to check or control the deadly effect of this particular interleukin, some molecules should be present or applied to block both of its signaling pathway. One of this molecule, which can act as an effective antagonist to IL-6 signaling, is tocilizumab, a humanized monoclonal antibody, specifically designed to bind both mIL-6R and sIL-6R (soluble receptor for IL-6) and can inhibit both classical and trans signaling pathway (Figure 1). Though the underlying molecular mechanism of action of this humanized antibody is still not clear, but it has been reported that this drug plays an important role in betterment of serious COVID patients. Currently, the efficacy of this particular drug has been tested globally in different laboratories and has also been approved by US-FDA for its stage III clinical trials, but still a lot of scientific exploration is needed to confirm the real molecular mechanism of its activity.

Conflict of Interest

No potential conflict of interest was declared by authors.

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