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COMMENTARY

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COVID-19: Consider IL-6 receptor antagonist for the therapy of cytokine storm syndrome in SARS-CoV-2 infected patients

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Abstract

COVID-19 leads to mortality of several patients and the cytokine storm is reportedly critical in the patients. To reduce the cytokine storm, we would like to propose the interleukin (IL) 6 receptor (IL-6R) antagonist therapy for the COVID-19 patients. Two humanized monoclonal antibodies are in clinical trial following IL-6R antagonist therapies namely tocilizumab and sarilumab. However, researchers and physicians should look for more IL-6R antagonists for the therapy of cytokine storm syndrome severe acute respiratory syndrome coronavirus 2 infected persons to enhance the therapeutic options for cytokine storm.

KEYWORDS

cytokine storm, IL-6R antagonist, sarilumab, therapeutic option, tocilizumab

1 | INTRODUCTION

The recently published paper by Zheng et al[1] in this journal provides information on immune-regulation through mTOR inhibitors for the therapy of COVID-19, which we found interesting and timely. The article mentioned about the cytokine release especially proinflammatory such as interleukin 6 (IL-6) during cytokine storm syndrome severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected patients.

The COVID-19 pandemic has killed more than 337 687 patients so far and over 5.2 million cases of infections. Among them, some infections are mild and some severe. Amongst the severe patients, cytokine storm is involved and causes organ failure leading to death.[2,3] The cytokine storm, also called cytokine release syndrome, is the major cause of morbidity for several critical patients of COVID-19. It causes death of several SARS-CoV and MERS-CoV infected patients.[4]

SARS-CoV-2 causes activation of different immune cells like macrophages, monocytes, and dendritic cells. This phenomenon helps to secrete proinflammatory cytokine IL-6 and other inflammatory cytokines. IL-6 binds with the two pathways. First one is noted as classic signaling (also called as classic cis-signaling) pathway and the second one is entitled as trans-signaling pathway.

In the classic signaling pathway, IL-6 bound with the receptor (membrane-bound) which is membrane-bound IL-6 receptor (mIL-6R). This is finally forming a complex with gp130 called IL-6-mIL-6R complex. It activates a downstream signaling pathway through the JAK- STAT pathway that stimulates IL-6-mIL-6R-JAK-STAT pathway/signaling.[5]

On the other hand, in the trans-signaling track, circulating IL-6 attached with the soluble IL-6R (sIL-6R) binds with gp130 dimer forming a complex called IL-6-sIL-6R complex. It activates the downstream signal transduction pathway through JAK-STAT pathway. It also activates the IL-6-sIL-6R-JAK-STAT signaling.[6]

On the other route, IL-6-mIL-6R complex or IL-6-sIL-6R complex may activate the MAPK/NF-κB-IL-6 pathway also. It has been noted that any of the pathway activations can cause cytokine storm. However, in this process, different immune cells may also activate and the activated immune cells include natural killer cells, macrophages, neutrophils, etc.

Conversely, IL-6 receptor (IL-6R) antagonist (anti-IL-6R) is a therapeutic choice for different diseases. IL-6R antagonist is already approved for rheumatoid arthritis.[7] IL-6R antagonist therapy can help in other autoimmune diseases also.[8] Now, IL-6R antagonist may be a choice for the therapy of the syndrome SARS-CoV-2 infected patients. There are at least two monoclonal antibodies are in the clinical trial which may be the therapeutic option for the COVID-19 patients.

2 | TOCILIZUMAB

Tocilizumab can be used to treat cytokine storm of the COVID-19 patients that targets IL-6R.[9] It is a humanized monoclonal antibody (hmAB) and also is an antagonist IL-6R. IL-6 level is significantly increased in serum in COVID-19 infected severe patients. IL-6 is a one of the major cytokines, which can create inflammatory storm. This may consequence of impair oxygen diffusion. Due to this, respiratory muscles become fatigued and that may finally leads to respiratory failure. In this case, Tocilizumab may be the right therapeutic choice to treat critical patients.

A clinical trial study in China found hmAB to be a useful treatment of severely affected COVID-19 patients with augmented IL-6 levels. In this study, the initial dose was used as 4 to 8 mg per kg body weight and consecutive dosage was provided with 400 mg hmAB that can be in mixed with saline and the time of the infusion was approximately 1 hour. In case of poor effectiveness in the patients after the initial dosage, an extra dosage can be applied after twelve hour interval, with an upper limit of two cumulative dose.[10] Conversely, in a single centric study, Luo et al applied Tocilizumab in 15 seriously sick COVID-19 patients where the augmented levels of IL-6 were found. After the Tocilizumab therapy, elevated IL-6 levels reduced in 10 patients.[11] In another study using 21 COVID-19 patients, Xu et al[12] applied Tocilizumab for the treatment to 18 patients as treatment group. Other drug was used for another three patients. It was noted that all patients have been discharged after the application of Tocilizumab. The discharged date was on average lasted 15 days. It can be concluded that Tocilizumab can be used to treat the severe and critical COVID-19 infection and it can serve as an effective therapy to reduce mortality.

3 | SARILUMAB

Similarly, sarilumabcan also be applied for the therapeutic purpose of cytokine storm of the COVID-19 patients. It is also a humanized monoclonal antibody and also is an antagonist IL-6R. Clinical trials of Sarilumab have been initiated for the therapy of the cytokine storm syndrome in SARS-CoV-2 infected victims.[13,14]

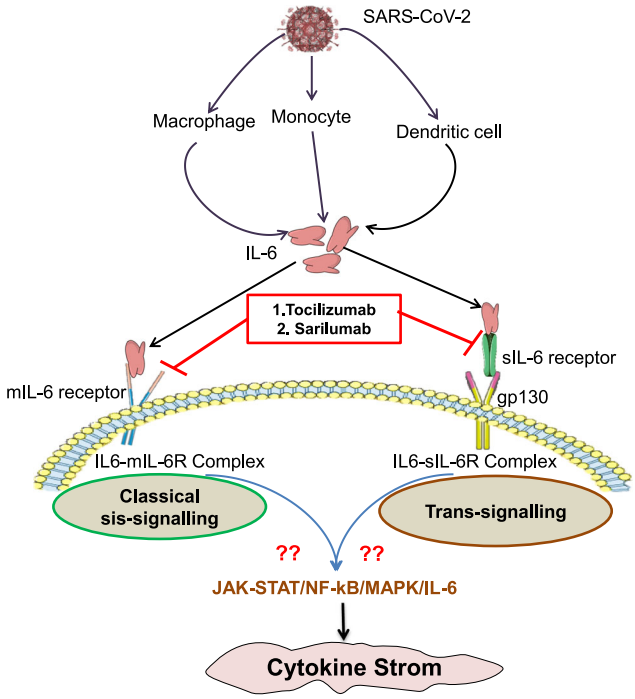

FIGURE 1 Probable mechanism of action of IL-6 receptor antagonist for the therapy of cytokine storm syndrome in SARS-CoV-2 infected individuals. IL, interleukin; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

4 | CONCLUSION

Therapeutic molecules with the IL-6R antagonist property can be applied for the cure of the cytokine storm syndrome in SARS-CoV-2 infected patients. IL-6R antagonist may be one of the best choices to treat severe COVID-19 patients. However, there are some open questions needs to be answered: what is the molecular mechanism of these therapeutic molecules on the antagonist activity of IL-6 receptor? The answers to this query will open a new generation for treating critical COVID-19 patients. Moreover, new IL-6R antagonist molecules are needed for the cytokine storm syndrome in SARS-CoV-2 infected individuals and it will also the door for the improvement of therapeutic options of critical COVID-19 patients (Figure 1).

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Writing-original draft: CC; writing-review and editing: CC, MB, ARS, GS; revising and supervising: CC, SSL, GA. All authors have read and approved the final version of this manuscript.

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