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IP Indian Journal of Immunology and Respiratory Medicine

Journal homepage: https://www.ijirm.org/

Review Article

Immunomodulation in COVID-19

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ARTICLE INFO

Article history:
Received 29-06-2022
Accepted 03-01-2023
Available online 23-01-2023

Keywords:
Angiotensin converting enzyme
COVID- 19
Cytokines

ABSTRACT

Immunology forms the basis for effective treatment strategies and production of vaccines. In COVID 19 immune insufficiency may increase viral replication while uncontrolled immunity may result in tissue damage. The angiotensin converting enzyme receptors on alveolar type 2 cells of lungs act as target cells are the sites of Corona virus attack. These cells through cytokines or interferons initiate an early local response which may control the infection. However, in COVID-19 this interferon response can be subdued or lagging which may allow the COVID virus to escape detection by the innate immunity or depress the downstream reaction leading to unchecked SARS-COV-2 replication. The suppression of host responses leads to increase in pro-inflammatory cytokines and the resulting inflammatory damage leads to a release of suppressive cytokines as a counter regulatory response. This is the cytokine storm. Thus, immuneregulatory treatments that may succeed are the ones that are in real time tuned to the subject's immunophenotype, where immunosuppression may be helpful at some points while immune-stimulation in others.

1. Introduction

The outbreak of the novel coronavirus disease, COVID-19, caused by SARS-CoV-2 is a pandemic threat to world public health. Till now there is no specific anti-viral agent for COVID 19. The molecular biologists, pathologists and scientists are trying hard to understand this virus, to unravel the pathophysiology of this disease and to discover proper treatment protocols and effective vaccines.

SARS -CoV-2 is difficult to treat, as COVID-19 is an overwhelming immunological response and may damage pulmonary tissue, reduce lung function with a decreased lung capacity.[1] On the contrary, immune insufficiency or misdirection may stimulate the viral multiplication causing lung damage.[2]

2. Early Inflammation

The angiotensin converting enzyme 2 (ACE 2) expressing alveolar type II cells of lungs are the receptors for COVID infection.[3] The cells perform vital function including secretion of lung surfactant, protection of epithelial barrier, and airway recuperation following an insult. Following alveolar damage they secrete cytokines which lead to harnessing of macrophages and immune cells to defend the alveolus. This initial immune response often controls the viral infection and restores the ecology of the respiratory system.

The rolling of type I-III interferon responses and their subsequent signaling effects control the viral infection. The signaling effects also lead to a proper adaptive response.[4] The association of transforming growth factor Beta with IL-6 to initiate the transformation of naive CD4 cells to The 17 cells may be critical at this point.[5] The differentiation and cytolytic potential of CD8 cells may be stimulated by IL-6

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https://doi.org/10.18231/j.ijirm.2022.034

in synergy with IL-7 and IL-15.

3. Immune Escape Phenomenon

In severe COVID infection the interferon response is often depressed or delayed.[6] Thus SARS- COV-2 can escape innate immunity and depress the downstream response. This allows SARS-COV-2 to multiply repeatedly in the respiratory system, leading to high viral load and further person to person transmission before clinical features set in.[7] This is proved by the high frequency of radiological changes in CT images of the lungs of COVID patients, even in the initial days of illness. Autopsies show low counts of CD8 positive T cells in pulmonary tissue.[8] CD4, CD8, NK cells and other immune cells are diminished in peripheral blood.[9] There is reduced production of IL-2, interferon γ, and TNF α.[10] All these suggest T cell depletion.

With their action on Th1 cytokines GMCSF, Corona virus can impair host defense mechanism. Th1 GMCSF is required for development and maturation of alveolar monocytes and they also produce myeloid precursors.[11] This promotes alveolar injury.

In COVID pneumonia increased level of cytokines is inversely related to host immune response. Unchecked viral replication leads to severe lung damage which in turn leads to breakdown of epithelial barrier function causing diffuse alveolar damage with increased microvascular permeability. Pro-inflammatory cytokines IL-6, IL-8 and IL-1β are leaked. Release of suppressive cytokines IL-10 and TGFβ occurs due to a counter regulatory effect.[12] This simultaneous increase of pro-inflammatory and anti-inflammatory cytokine is known as 'cytokine storm'. The pro-inflammatory path causes massive tissue breakdown, organ dysfunction and extinction of alveolar macrophages while the anti-inflammatory arm causes suppression of white cell action or 'immunoparalysis'.[13] Epithelial cell death lays bare the basement membrane to invasion by pathogens offering them an opportunity to enter the systemic circulation.[14]

The main reason for refractory respiratory failure in severe COVID patients is almost the total loss of alveolar macrophages. Corticosteroids improve this inflammation.

Data from RECOVERY trial showed that Dexamethasone can improve outcome in adults of COVID 19 suffering from respiratory failure.[15] Long term treatment with low dose of glucocorticoids[16] has been shown to improve outcome in some studies but the role of steroids in ARDS is still very controversial. Further these trials did not use prior phenotyping to choose patients who were likely to improve with these interventions. Some autopsy studies performed on COVID 19 patients, formation of microthhrombi as well as larger thrombi were seen along with diffuse alveolar damage. Dexamethasone was also found to increase in some of the clotting factor including fibrinogen. In conclusion, role of corticosteroids is still controversial in COVID-19 and should be used carefully.[17]

During the past two decades the focus was more on immunosuppression, but, immuno-stimulation also may be helpful at times. The dilemma in current approach to immune-modulation in hospitalized patients with COVID-19 is shown by the fact that in one trial GM-CSF therapy (NCT04326920) is being used while in another trial GM-CSF blockade (NCT04341116) is being used in a similar population.

No single approach can be taken with regard to immune-modulation in patients with COVID-19. A relatively new immune surveillance trial in COVID-19 patients demonstrated a high degree of heterogeneity of immune phenotypes within the study group.[9] Immunomodulatory treatments that are likely to succeed in COVID-19 patients are those that match the subjects' phenotype in real time. If the immune system is suppressed further it can enhance the risk of viral and bacterial infections, increase the risk of opportunistic infections and stimulate the reactivation of latent viruses. We may also remember that the cytokine levels in peripheral blood do not always mirror systemic leukocyte functions or cytokine profiles at the actual site of pulmonary infection, and may rise after the depth of respiratory function.[18]

To combat COVID long term, besides 'COVID appropriate behavior' we need targeted immunomodulatory therapy, potent antiviral drugs and fast paced vaccine development for the right patient at the right time. A subset of subjects with very high elevations in systemic pro-inflammatory cytokines may improve with medicines such as tocilizumab or anakinra while others may respond to immune-stimulation with GM-CSF which can boost host immunity without worsening cytokine storm.[19]

4. Conflicts of Interests

None declared.

Acknowledgements

None.

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Cite this article: Pal S, Dutta R. Immunomodulation in COVID-19. *IP Indian J Immunol Respir Med* 2022;7(4):151-153.