

Role of Corticosteroids and Interleukin-6 Inhibitors in Covid-19

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Abstract

Covid-19 has totally changed the world dynamics in terms of Health Management, economics and travel. Caused by Novel SARS-CoV-2, covid-19 poses immense health burden to all healthcare system across the world. This mini review explains about the basics of covid-19 as well as the inflammatory cascades associated with it. This review also discusses the role of corticosteroids (both systemic and inhaled) and interleukin-6 inhibitors in the management of covid-19. The significance of dexamethasone in the treatment of covid-19 patients is discussed in detail. The essence of key clinical trials and their outcomes involving the use of inhaled corticosteroids in covid-19 patients are provided as well. The results of the trials involving interleukin-6 inhibitors were contradicting and hence a through risk-benefit analysis should be carried out before administering these agents to Covid-19 patients. .

Keywords: Covid-19; Corticosteroids; Interleukin-6 Inhibitors; Dexamethasone; Tocilizumab

Introduction and Background

As of 19 December 2021, there were over 273 million cases of Coronavirus disease 19 (COVID-19), and over 5.3 million individuals succumbed to death globally [1]. Reported first in the Wuhan province of China in the last month of 2019, Coronavirus disease 19 (COVID-19), creates severe and sudden respiratory syndrome through the virus severe acute respiratory syndrome-Coronavirus 2 (SARS-CoV-2) [2]. Then, the virus spread in a pandemic manner and posed severe stress literally on every country's health system and economy [3]. For the ease of discussion and understanding, in this article the word Coronavirus always refers to novel SARS-CoV-2.

The genome sequencing of the pathogen causing Covid-19 was done by various reputed research institutions and the details entire genome sequence were published on GISAID database on 12 January 2021 [4]. The epidemic peak of Covid-19 was observed in China in the month of February 2020 during which at least 3000 new cases were reported every day. This forced the Chinese government to impose national wide lockdown [5]. The nationwide lockdown and stringent health measures implemented by the Chinese government resulted in a steady decrease Covid-19 cases [6]. While the Covid-19 cases in China were declining, elsewhere in the world the virus propagated in an unprecedented manner that forced the World Health Organization (WHO) to announce the outbreak of Covid-19 as a pandemic on 11th March 2020 [7]. Johns Hopkins University announced in the month of August 2020 that almost all countries across all six continents had more than 20 million COVID-19 cases and approximately 733 thousand patients died because of the disease [8].

The corona virus responsible for Covid-19 utilizes the angiotensin-converting enzyme 2 (ACE2) receptors that are identical to SARS-CoV [9]. Genetic studies elucidating RNA sequencing data reported that transmembrane protease serine protease 2 (TMPRSS2) was found in significant numbers in many tissues along with ACE2 receptors in the respiratory system [10,11].

The pathogenesis of Covid-19 expresses initially as mild symptoms but can proceed into severe respiratory failure. The corona virus binds to epithelial cells of the upper respiratory system. It then multiplies and migrates to lower respiratory track and gain access to al-

veoli. The quick reproduction of coronavirus in its target site initiates severe immune reaction which in turn results in cytokine storm. The cytokine storm can precipitate as respiratory failure that is regarded as the primary cause mortality associated with Covid-19 [12,13]. The elderly and patients with concomitant chronic ailments like diabetes and cardiovascular disorders were reported to be more susceptible to serious outcomes such as multi organ failure and death [14,15].

Inflammatory response during Covid-19

Out of all the mechanisms proposed that activate the inflammatory response, two mechanisms have clear scientific merit. According to the first mechanism, Angiotensin II prompts the pro-inflammatory cytokines such as IL-6 and TNF α . This triggers the migration of immune cells to the site of infection and causes vascular injury. Further, the increased levels of Angiotensin II result in inflammatory response and fibrosis. This fact was validated by postmortem reports of COVID-19 casualties showed severe alveolar damage, with the precipitation of blood clots [16]. The second mechanism proposed that the pattern-recognition receptors (PRRs) present in the patients the host senses pathogen-associated molecular patterns (PAMPs) of the coronavirus. This in turn triggers inflammation in the local area through MAPK pathway which eventually pushes the monocytes and macrophages to the affected parts of the respiratory system and causes serious damage [17,18].

Corticosteroids in the management of Covid-19

Individuals in advanced stage COVID-19 can experience a serious inflammatory response in their body that can eventually damage lungs and other organs. Considering the strong anti-inflammatory shown by corticosteroids, it is common logic to use them in an attempt to ease these harmful effects [19]. Many randomized trials indicate that the use of systemic corticosteroid in Covid-19 patients results in better therapeutic outcomes and decreased mortality in hospitalized patients who receives supplemental oxygen [20].

Till date the RECOVERY trial is considered as a significant study. It was a multicenter, open-label study conducted in the UK that randomly assigned 6,425 hospitalized patients. The mortality rate at the end of 28 days was found to be lower in the patients treated with dexamethasone than those who received only standard care. It should be stressed that this therapeutic advantage was detected only in the patients who have received external oxygen support. The study also revealed that the use of systemic corticosteroids did not result in any benefit among the hospitalized patients who do not receive supplemental oxygen [21]. The proof to advocate the usage of methylprednisolone and hydrocortisone is not significant and hence these agents should be administered with caution in Covid-19 patients. The septic shock associated with Covid-19 patients can be managed by i.v. hydrocortisone [19].

Inhaled Corticosteroids were also studied for their efficacy in the treatment of Covid-19. Two randomized controlled trials (STOIC trial and PRINCIPLE trial) evaluated the efficacy of inhaled budesonide in outpatients who had mild symptoms. The STOIC trial with smaller enrollment revealed that the use of inhaled budesonide may decrease the need of emergency care and the PRINCIPAL trial with larger enrolment revealed that the inhaled budesonide did not result in any change in hospitalization rate [22,23]. As the evidence level of both these trials is not significant, these agents should be administered with caution in Covid-19 patients.

IL-6 inhibitors in the management of Covid-19

Cytokines are considered as the chemical messengers between the cells of the immune system. Interleukins are a type of cytokines that assist in communication between leukocytes. The Interleukin-6 (IL-6) family consists 9 receptors and IL-6 league plays an important role in the pathogenesis of rheumatoid arthritis and cytokine release syndrome and hence the inhibition of IL-6 is expected to be beneficial in the treatment of these disorders [24].

As viruses are obligatory intracellular parasites, they rely on their hosts to execute many of their own functions. Viruses often causes organ damage in the individuals with the help of their own immune system through the release of inflammatory mediators. IL-6 plays a

pivotal role facilitating inflammation in covid-19 and the level of IL-6 will be elevated in majority of the patients suffering from Covid-19 [25].

United States- Food and Drug Administration (US-FDA) has approved two different types of IL-6 inhibitors such as anti-IL-6 (e.g. Siltuximab) and anti-IL-6 receptor monoclonal antibodies (e.g. Tocilizumab). The efficacy of these agents in Covid-19 patients with systemic inflammation were evaluated. The two studies Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP) and COVACTA were the two studies published in New England Journal of Medicine revealed contradicting results. REMAP-CAP revealed that the mortality rate of the patients received IL-6 receptor blocker is less (27%) when compared to the patients who had not received IL-6 receptor blocker (36%) [26]. The COVACTA study reported that the mortality of the patients received tocilizumab was fractionally more (19.7%) than the patients who had not received tocilizumab (19.4%) [27].

The light in the tunnel regarding the IL-6 inhibitors are the results published from the RECOVERY study on IL-6 inhibitors. The study found that the tocilizumab administration resulted in better therapeutic outcomes in patients with systemic inflammation and severe breathing difficulties. The study added that these improved outcomes were observed irrespective of the quantum of respiratory support [28].

Conclusion

Finding a perfect cure for covid-19 is still a distant reality. Researches across the globe utilizes their logic and resources to find treatment strategies that can result in better therapeutic outcomes. Dexamethasone is considered to be an efficient agent that can be used in hospitalized patients with ventilator support. Inhaled corticosteroids were used in certain clinical trials but their efficiency cannot be established due to either study design or less number of patient population. There were contradicting reports about the efficacy of interleukin 6 inhibitors in covid-19 patients. A careful of risk benefit analysis should be carried out before administering to the patient population.

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The authors have no financial interest or conflict of interest towards any information discussed in this article.

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