Effectiveness of Corticosteroids in the Treatment of Patients with COVID-19 Infection

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The pandemic caused by the SARS-COV-2 virus was first identified in December 2019. Covid-19 causes illness that is unlike other respiratory infections. Covid-19 pandemic has come as a surprise. It is the most significant pandemic of the 21st century. In fact, only the Spanish flu pandemic almost a century ago can be compared with it. Moreover, it is worth understanding that this pandemic has cost more than 5 million lives till now, despite such progress in medicine during the last century or so. Numbers or mortality are only going to increase as the pandemic is showing no sign to decline. There is no doubt that corticosteroid therapy may significantly reduce covid-19 associated mortality. However, the timings of initiation of such therapy are critical. Therapy initiated too early or in less severe cases may do more harm than good. It appears most beneficial in those with a severe condition, like those requiring invasive mechanical ventilation (IMV). Further, studies seem to show that this approach is also effective in severely ill pediatric patients. However, there are some limitations to present nderstanding, like inadequate data regarding the efficacy of corticosteroids in patients older than 80 years of age. Similarly, data is limited from the pediatric population. Guidelines remain unclear regarding the use of corticosteroids in the delayed multisystem inflammatory syndrome of children and adults.

Keywords: COVID-19, corticosteroids.

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1. BACKGROUND

As the disease has a considerably high mortality rate, especially in older adults, researchers are looking for ways to manage it more effectively. Studies show that adding corticosteroids to disease treatment may help reduce mortality. However, how corticosteroids work and understanding their efficacy requires some understanding of the disease pathogenesis.

COVID-19 disease pattern

In most individuals, it would perhaps cause some mild illness resembling influenza. Thus, it would cause fever, body aches, cough, headaches, changes in taste and smell. However, in a small number of cases, it would cause pneumonia, further complicated by the hyperinflammatory response and multiorgan failure (1)..

Based on the pathogenesis and cells affected, Covid-19 can be divided into three phases (2):

a) Stage 1–is an asymptomatic stage, when the virus attaches to the nasal cavity lining and replicates. This stage continues for 1-2 days.

b) Stage 2 – is when the virus starts invading the upper respiratory tract. This stage continues for the next few days. In about 80% of people, the virus will be eliminated at this stage. Such people only develop a mild illness.

c) Stage 3 – Unfortunately, about 20% of people will progress to the third stage, when the disease starts infiltrating pulmonary cells, causing severe illness. It infects the alveolar cells, causing severe damage. It has an overall mortality rate of about 2%, though it is much higher in older adults[2].

Covid-19 causes a biphasic illness. An increasing viral load causes the first illness, and the second phase is caused by an increased inflammatory response to the virus.

This second phase of illness occurs in some patients only. This second phase of **hyperinflammatory response is also called a cytokine storm**.

In Covid-19, it appears that greater mortality is due to immune dysregulation rather than direct damage caused by the virus. Since more severe illness occurs in the second stage, causing hospitalization, ARDS (acute respiratory distress syndrome), most fatal outcomes happen in this phase. Since, in this stage, viral load is low, targeting the virus with antivirals has limited benefit. Thus, the target of therapy in severely ill patients should be in managing hyperinflammatory response/ cytokine storm and its ill effects (1).

2. CALMING THE CYTOKINE STORM

Hyperinflammatory response or dysregulated immune response or cytokine storm as now most like to

call is a phenomenon known since long. This phenomenon is associated with high mortality related to sepsis, plaque, and other conditions. Researchers think that even the high mortality rate of the 1918-1919 influenza pandemic was associated with this cytokine storm. However, now researchers understand that cytokine storms in response to various infections differ. Thus, its early biomarkers vary, and hence therapeutic approach that worked for cytokine storms caused by other illnesses may not essentially work in Covid-19 (3).

Cytokine is an umbrella term used to describe a severe illness that causes immune dysregulation, high levels of cytokines, systemic inflammation, and multiorgan dysfunction. Its onset may differ and depend on the initial treatment given to patients. However, it has similar signs in later stages like high fever, fatigue, headaches, rashes, diarrhea, joint pains, muscular pains, and neuropsychiatric changes. The disease can progress swiftly, causing coagulopathy, hemorrhages, hypoxia, dyspnea, hypotension, severe changes in hemodynamics, vasodilatory shock, and death (3).

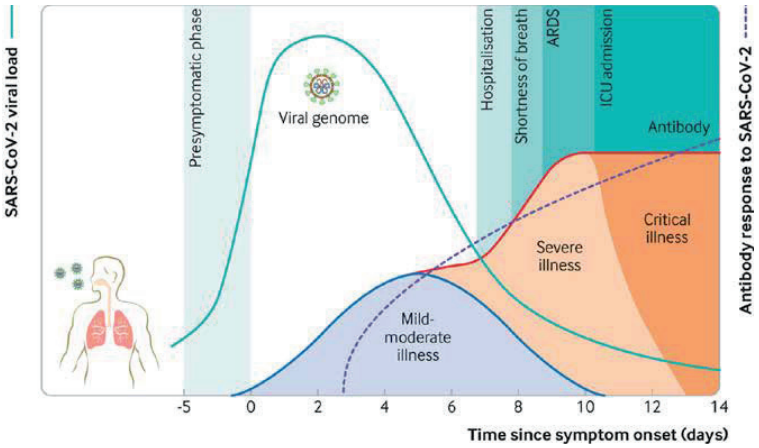

Figure 1 Biphasic response to covid-19

In cytokine storm, related to Covid-19, laboratory findings show an increase in non-specific markers of inflammation like C-reactive protein, abnormalities in blood count, leukopenia, anemia, thrombocytopenia. Among cytokines, IL-6, IL-10, interferon-gamma are elevated in the early phase. Highly elevated IL-6 is especially characteristic of the cytokine storm in Covid-19. In addition, indicators of coagulopathy like elevated D-dimer value plays a vital role in disease prognosis (3, 4).

Since cytokine storm and not damage due to direct viral activity is related to high mortality in the disease, thus the need to calm this cytokine storm. Studies show that using an antiviral drug like remdesivir may help reduce hospital stay, but managing cytokine storm is essential to reduce mortality.

There are two approaches to calming this cytokine storm. The first is to use monoclonal antibodies targeting IL-6 or IL-1β. Another approach is of using corticosteroids. Corticosteroids have some distinct benefits, like they are widely available and are not expensive. Hence, a need to understand their role and efficacy in the condition (4).

3. EFFECTIVENESS OF CORTICOSTEROIDS IN THE TREATMENT OF COVID-19

The recommendation for using corticosteroids for suppressing cytokine storms to reduce mortality comes from the large-scale multicenter clinical trial RECOVERY done in the UK. This has led various guidelines to include the use of corticosteroids in severely ill patients (5, 6).

WHO has two recommendations regarding the use of corticosteroids in Covid-19 (5).

a) **Recommendation** 1: WHO strongly recommends using corticosteroid (i.e., dexamethasone, prednisolone, hydrocortisone) in critically ill patients.

b) Recommendation 2: WHO advises against the use of corticosteroids in non-severe cases of Covid-19.

This recommendation to use corticosteroids is built upon clinical experience accumulated over the decades. There has been extensive research regarding the role of corticosteroids in managing septic shock. Early studies showed that low-dose corticosteroid therapy might help reduce mortality (7).

Although corticosteroids appear to help, they only help when therapy is initiated at the right moment. Moreover, some early studies regarding the use of corticosteroids in Covid-19 failed to show much benefit. Thus, CAPE COVID trial in 149 patients did not show the benefit of corticosteroid therapy (7).

However, the following and much larger clinical trial, REMAP in 903 patients, demonstrated considerable benefit and reduction in mortality by as much as 26%. Another trial, CoDEX, with 299 patients deployed early use of corticosteroids. It found that although corticosteroids increased ventilator-free days, but early use of corticosteroids had no impact on 28-day mortality. These and similar other clinical trials provided some initial information and direction for more extensive clinical trials like the RECOVERY (7).

RECOVERY trial and its success is the basis of recommending corticosteroids in severe Covid-19 patients. It remains the largest of its kind of clinical study. It was a multicenter, open-label adaptive trial done in the UK. It has a sample size of 6425. Out of them, 2104 got dexamethasone along with standard care, and 4321 just got standard care. The mean age of patients was 66 years. The duration of intervention or corticosteroid therapy in the trial was 10 days (6).

The key findings of the RECOVERY trial regarding the effectiveness of corticosteroids in covid-19 were (6).

The mortality rate was 25.7% in the standard care group and 22.9% in dexamethasone and standard care. Thus, it is a statistically significant benefit.

However, effectiveness was highest in those requiring

invasive mechanical ventilation (IMV), with mortality of 29.3% in the dexamethasone group and 41.4% in the non-dexamethasone group. Thus, it clearly shows massive benefits in such a category.

Benefits were lower in those who needed oxygen but not IMV. There was 23.3% mortality in the dexamethasone group in this category against 26.2% in the non-dexamethasone group.

However, there was no survival benefit in less severe cases, and on the contrary, dexamethasone increased mortality. Thus, in those not requiring oxygen, the mortality rate in the dexamethasone group was 17.8% and 14% in the standard care arm.

RECOVERY trial demonstrated that only hospitalized and severely ill patients benefit from corticosteroids. Further, it shows that the timing of initiation of corticosteroid therapy is vital. Thus, therapy started early like those not on IMV had minimal benefit. However, there was a massive benefit in those on IMV. Further, there is no role for corticosteroids in less severely ill patients, and on the contrary, corticosteroid therapy may increase the mortality rate.

Further, there have been trials regarding the use of inhaled corticosteroids. Inhaled corticosteroids may reduce airway inflammation, reduce pulmonary obstruction, and also appear to impair Covid-19 replication. However, the results of inhaled corticosteroids like Budesonide had contradictory results. Thus, there is neither evidence in its favor or against such a use (6).

It is worth noticing that further meta-analysis of clinical trials confirms that corticosteroids only help in severe cases in those requiring oxygen therapy. However, in less severe cases, they prolong viral clearance, hospital stay and increase mortality (8).

4. FUTURE DIRECTION FOR IDENTIFYING THE ROLE OF CORTICOSTEROIDS IN COVID-19

The Covid-19 pandemic is still ongoing, and lots have to be understood about its pathogenesis. Further, it also has many delayed complications. Thus, a delayed multisystem inflammatory syndrome of adults (MIS-A) and children (MIS-C) still remains poorly understood. Although, it is causing significant mortality. In this syndrome, the viral activity does not appear to play any role. It is just another immune dysregulation syndrome. Therefore, researchers are studying the role of IL-6 inhibitors like tocilizumab and corticosteroids in such a group.

5. CONCLUSION

There is no doubt that corticosteroid therapy may significantly reduce Covid-19 associated mortality. However, the timings of initiation of such therapy are critical. Therapy initiated too early or in less severe cases may do more harm than good. It appears most beneficial in those with a severe condition, like those requiring invasive mechanical ventilation (IMV). Further, studies seem to show that this approach is also effective in severely ill pediatric patients.

However, there are some limitations to present understanding, like inadequate data regarding the efficacy of corticosteroids in patients older than 80 years of age. Similarly, data is limited from the pediatric population.

Further, guidelines remain unclear regarding the use of corticosteroids in the delayed multisystem inflammatory syndrome of children and adults.

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