

Anti-inflammatory agents other than corticosteroid in SARs-CoV-2 pneumonia

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ABSTRACT:

The SARs-CoV-2 results in hyperinflammation among infected patients. This condition leads to serious organ injury, especially in the lungs. Therefore, the main treatment option, in addition to anti-viral agents, is the administration of corticosteroids. However, in many cases, inadequate response to corticosteroids has been observed—other anti-inflammatory agents, such as interleukin-6 inhibitor, kinase inhibitor, etc., play an essential role in reducing this severe complication.

Keywords: COVID-19, SARS-CoV-2, Corticosteroid, Anti-inflammatory agents, Pneumonia

INTRODUCTION

The pandemic of SARs-CoV-2 causes serious illness in many patients. Approximately 80% of patients in the latest wave have progressed to pneumonia rapidly. The specific treatment for this disease involves anti-viral agents, including favipiravir or remdesivir, acting directly against the viral pathogens. However, the virus causes a fatal consequence, leading to the cytokine storm.

The cytokine storm in SARs-CoV-2 constitutes a fatal condition associated with a high level of circulating cytokines produced from dysregulation of the immune system. [1,2] The clinical syndrome of this condition in SARs-CoV-2 disease is characterized by constitutional symptoms, systemic inflammatory response syndrome (SIRS), and multiorgan dysfunction leading to multiorgan failure when treatment is inadequate.[2] The lungs become damaged as a primary target of this condition among patients with the SARs-CoV-2.

Corticosteroid has been approved to alleviate the degree of lung inflammation in SARs-CoV-2 pneumonia. The RECOVERY trial, a randomized controlled study, demonstrated the 28-day mortality benefit, especially among mechanically ventilated patients.[3] However, other anti-inflammatory agents also play a role in treating lung inflammation.

Interleukin-6 Inhibitor

The latest US NIH guidelines recommend using only tocilizumab among hospitalized patients with rapidly progressive pneumonia. [4] The main action of tocilizumab inhibits the production of IL-6 induced by SARs-CoV-2 at the IL-6 receptor. The two largest randomized controlled trials (RCTs) reported survival benefits, including treatment combined with dexamethasone.[5,6]

Tocilizumab should be prescribed within three days of symptom identification among patients with SARs-CoV-2 having the following criteria.

1) Patients requiring intensive care unit (ICU) admission with rapid decompensation in respiration and receiving invasive mechanical ventilation, noninvasive ventilation, or high flow nasal cannula (HFNC) with oxygen flow >30 L/min and FiO₂ >0.4

2) Patients not requiring ICU admission rapidly developing hypoxemia, needing increasing oxygen therapy under noninvasive ventilation or HFNC, and having significant inflammation from c-reactive protein (CRP) ≥ 75 mg/L

The recommended dose of tocilizumab is 8 ml/kg actual body weight. The dose can be titrated up to 800 mg. A repeated dose can be given 24 hours later if no response is observed.

However, this drug is relatively expensive. Therefore, I suggest starting dexamethasone as a first-line treatment in limited resource settings. If patients do not improve within 48 hours, combination therapy with tocilizumab could be given.

Using tocilizumab should be avoided among patients with immune system suppression, elevated liver enzymes, cytopenia, or pregnancy. Physicians should monitor liver enzymes, obtain complete blood count (CBC), and identify opportunistic infection after initializing tocilizumab. The treatment response would be seen within the first week after treatment. Monitoring respiratory rate, the ratio of pulse oximetry (SpO₂), the fraction of inspired oxygen (FiO₂), chest radiography, and CRP are required for evaluating response.

Kinase Inhibitors

The kinase inhibitors prevent signal transduction involving activation of inflammation; currently, we have insufficient data to use these drugs in SARs-CoV-2 pneumonia. An RCT combining baricitinib and remdesivir has provided some benefits in reducing recovery time compared with remdesivir alone among patients receiving high flow nasal cannula or non-invasive ventilation.[7] Similar results were found in a phase II RCT prescribing ruxolitinib as a single therapy in severe cases. [8] The data evaluation of tofacitinib is under ongoing clinical trial. However, some experts in Thailand reported an excellent clinical response in some cases used combined with an anti-viral agent.

Other Anti-Inflammatory Agents

Drugs that potentially prevent inflammation have been proposed in treating SARs-CoV-2 pneumonia. A large RCT studying colchicine among non-hospitalized patients with SARs-CoV-2 has recently shown a trend to reduce hospitalization but without reaching statistical significance.[9]

Fluvoxamine, a selective serotonin reuptake inhibitor, can reduce the production of inflammatory cytokines in sepsis.[10] This drug was researched among patients with mild symptomatic SARs-CoV-2 in a small RCT, but the clinical benefits remain unclear.[11] Antitumor necrosis factor (anti-TNF) has also been proposed to treat SARs-CoV-2.[12] A large international registry of patients with inflammatory bowel disease and SARs-CoV-2 showed corticosteroid, but not anti-TNF, was associated with severe SARs-CoV-2 transmission.[13] Phase II RCT is ongoing in the UK to prove clear benefits.[14]

Finally, the role of other anti-inflammatory drugs or immunomodulators, such as interleukin-1 inhibitors, interferon, and IVIG, are needed to be confirmed.

CONCLUSION

Among drugs containing anti-inflammatory activity, tocilizumab is recommended as the primary option for the second anti-inflammatory agent other than corticosteroid to reduce hyperinflammation induced by SARs-CoV-2. The current evidence confirms that tocilizumab improves survival in severe SARs-CoV-2 pneumonia. Data supporting using other drugs are pending. The results from ongoing large RCTs are required.

KEY MESSAGES:

- Anti-inflammatory agents play a role in treating SARs-CoV-2 pneumonia.
- Tocilizumab has been confirmed with large RCTs regarding survival benefits among severe patients.
- Combination therapy of corticosteroid plus tocilizumab provides a more favorable outcome.

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AUTHORS' CONTRIBUTIONS

Pongdhep Theerawit drafted, approved, and submitted the manuscript, and serves as the corresponding author.

SUPPLEMENTARY MATERIALS

none

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