CASE REPORT

Off-label Use of Itolizumab in Patients with COVID-19 ARDS: Our Clinical Experience in a Dedicated COVID Center

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Abstract

Severe acute respiratory syndrome coronavirus 2 has affected millions of people worldwide. This pandemic requires newer medical management strategies to control the morbidity and mortality associated with the disease. Several approaches, including global targeting of inflammation or neutralizing a single key inflammatory mediator, are being employed to cope with cytokine storms in coronavirus disease-2019 (COVID-19). The role of anti-inflammatory biologics, such as acalabrutinib, tocilizumab, anakinra, and itolizumab can become relevant. Itolizumab is a humanized recombinant immunoglobulin G1 monoclonal antibody. It targets the extracellular, scavenger receptor cysteine-rich (SRCR) distal domain 1 of CD6 and is responsible for priming, activation, and differentiation of T-cells. Itolizumab has been approved by the Drug Controller General of India for the treatment of COVID-19 in India. Here, we share our clinical experience of 20 patients having moderate acute respiratory distress syndrome (ARDS) due to COVID-19 on treatment with itolizumab. We observed the mortality benefit with single-dose itolizumab (1.6 mg/kg) in patients having moderate COVID-19 ARDS.

Keywords: Acute respiratory distress syndrome (ARDS), COVID-19, Cytokine storm, Itolizumab, Monoclonal antibody.

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Highlights

• Fifteen percent of coronavirus disease-2019 (COVID-19) patients who develop acute respiratory distress syndrome within a week after the appearance of symptoms.
• Cytokine storm is a life-threatening acute systemic inflammatory syndrome, which is characterized by multiorgan failure and fever.
• Itolizumab is an anti-CD6 receptor monoclonal antibody which seems to be the possible strategy for patients with cytokine storm.
• We used Itolizumab off-label in patients with severe COVID-19 from August to September 2020 based on its hypothetical benefit and report the experience in our institute AIIMS, Patna.

Introduction

Severe acute respiratory syndrome (SARS) coronavirus 2 (CoV-2) has affected millions of people worldwide. This pandemic requires newer medical management strategies to control the morbidity and mortality associated with the disease. About 15–20% of the affected patients develop pulmonary symptoms, such as breathing difficulty, and require hospital admission for oxygen therapy and supportive care.1 There is a marked increase in the level of cytokines (e.g., interleukin(IL)-1B, IL-6, and IL-12) and chemokines and this is referred to as “cytokine storm.”2 There is an elevation of other markers of inflammation, coagulation, and organ damage, such as C-reactive protein (CRP), D-dimer, lactate dehydrogenase, ferritin, and troponin-I. Hence, anti-inflammatory agents, such as acalabrutinib, tocilizumab, anakinra, and itolizumab might have a role to play in this disease.3-6 Itolizumab is a humanized recombinant immunoglobulin G1 monoclonal antibody. It targets extracellular, scavenger receptor cysteine-rich distal domain 1 of CD6 and is responsible for priming, activation, and differentiation of T-cells.7 Drug Controller General of India (DCGI) has approved itolizumab for the treatment of COVID-19 in India. Here, we share our single-center clinical experience of off-label use of this drug in 20 patients with acute respiratory distress syndrome (ARDS) due to COVID-19.

Materials and Methods

This is our single-center clinical experience of patients infected with COVID-19 and treated with itolizumab between August and September 2020 at All India Institute of Medical Sciences, Patna. We recorded various clinical and biochemical parameters every day from the day of admission to 14 days after administration of itolizumab. Clinical parameters, such as respiratory rate and oxygen supplementation, were measured daily. Laboratory parameters...
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From August 1, 2020, to September 30, 2020, totally 150 patients were included in our study. Of these 150, 20 received injection itolizumab (1.6 mg/kg) following the fulfillment of inclusion criteria. Among these patients who received itolizumab, seven patients were not survived and 1-month mortality rate was 35%. Among these patients who have not received itolizumab were 130 and 1-month mortality was 60%.

Adverse Effects
We detected infusion-related adverse reactions in eight patients; six patients have mild shivering and other two patients noted tachycardia and oxygen desaturation, for which they required increment of oxygen support.

Discussion
There are various drugs like tocilizumab, itolizumab, and anakinra used in the treatment of COVID-19. Among these, itolizumab is a new biological agent that has been approved in India for the treatment of psoriasis. It acts by immunomodulating T-effector function and its migration to the inflammation site, sparing Tregs, and preserving the antiviral response. It acts upstream at the Th1 and Th17 pathways, i.e., at the T-effector cells. Thus, it decreases the release of multiple cytokines and cell signaling transduction factors primarily involving the Th17 and Th1 pathways. Other drugs, such as tocilizumab or anakinra, block cytokines at a downstream level. Itolizumab also binds to CD6 receptor and blocks activated leukocyte cell adhesion molecule–mediated T-cell activation. For this reason, it is used in the treatment of COVID-19 patient clinical trial done in Cuba. Tocilizumab was another used in the treatment of COVID-19 patients with moderate-to-severe ARDS, in an observational study over off-label use of tocilizumab concluded that tocilizumab appears to be effective in decreasing oxygen withdrawal time and respiratory failure symptoms, avoiding mechanical ventilation, and stopping the biological inflammatory process of COVID-19 pneumonia in hospitalized patients, especially in those with >50% of initial lung lesions on computed tomography scan. It is important to mention that IL-6 is not the appropriate marker of disease improvement as the soluble IL-6 receptor immune complex has a long half-life. It remains in the serum for a long time because of its long half-life after tocilizumab administration. IL-6 levels might also increase after tocilizumab administration because of less consumption of IL-6.

We observed mortality benefit (35 vs 60%) in moderate COVID-19 ARDS patients who have received single-dose itolizumab 1.6 mg/kg in comparison to patients who have not received immunomodulator therapy (tocilizumab/itolizumab) in the course of COVID-19 disease. In India, the mortality rate in moderate-to-severe COVID-19 pneumonia is 42%. Tocilizumab was another immunomodulator used at our center. In our experience, despite giving two doses within 12 hours we have found no improvement. We also observed cost benefit in patients receiving itolizumab, as a single dose was sufficient.

A randomized, controlled, open-label study was conducted by Biocon at four hospitals in India, in moderate-to-severe COVID-19 ARDS patients. As reported by Biocon, the mortality benefit observed in the itolizumab arm was statistically significant than the only supportive care group.

Limitations
Here, we have shared our clinical experience with moderate COVID ARDS patients on treatment with itolizumab. We have not compared the clinical outcome of patients on treatment with other...
drugs like tocilizumab. It would be difficult to comment on or to speculate that itolizumab has better survival benefits without a well-conducted randomized controlled trial, comparing various modalities. Nonetheless, this clinical experience does make us consider itolizumab the treatment option. We have not included patients with mild and severe ARDS (\(\text{PaO}_2/\text{FiO}_2 \leq 100\) with PEEP \(\geq 5\)). Due to unequal distribution of comorbidities among patients, we acknowledge that our results should be interpreted with caution as significant heterogeneity exists within these factors.

**Conclusion**

We observed mortality benefit with single-dose itolizumab (1.6 mg/kg) in patients having moderate COVID-19 ARDS. A well-structured comparative study is required to validate our result and to find superiority over tocilizumab. Use and recommendations for itolizumab in COVID-19 moderate/severe disease should be taken with caution as not only the supportive data are lacking but also long-term outcomes of itolizumab in COVID-19 diseases are yet to be known.

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