Original Research Article

An early experience of Itolizumab with best supportive care in the treatment of moderate to severe COVID-19 patients: A retrospective study

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A B S T R A C T

Introduction : Cytokine release syndrome caused by excessive release of cytokines due to activation of T-cells and monocytes is directly associated with COVID-19 disease severity. Itolizumab, an anti-CD6 monoclonal antibody, basis its mechanism of action might have a potential role in reducing inflammatory markers and thereby improving clinical outcomes in moderate to severe COVID-19.

Materials and Methods: We retrospectively examined records of patients with moderate or severe COVID-19 disease who were treated with Itolizumab. Eligible patients were those deteriorating clinically, requiring oxygen support or showing rapid rise in inflammatory markers and administered Itolizumab along with best supportive care. Clinical manifestations (oxygen requirement) and laboratory parameters (CRP and ferritin) were studied pre- and post-treatment.

Results: A total of 27 patients with mean age of 55.63 years (81.5% male) were included. Most common comorbid conditions were hypertension (48.1%), diabetes (44.4%), and coronary artery disease (11.1%). The mean CRP from baseline reduced by 52.68% (91 mg/L pre dose to 43mg/L post dose) at an average time of 6.4 ± 2.5 days. The mean Ferritin levels reduced by 17.41 % (407 ng/ml pre dose to 336 ng/ml post dose) at an average time of 4.6 ± 2.2 days. Mean baseline oxygen saturation improved from 93.4% to 96.1%. All patients showed clinical improvement and got discharged. The mean hospitalization time was 12.2 ± 3.9 days. No serious adverse events or infusion related reactions were reported.

Conclusions: Treatment of moderate to severe COVID-19 disease with Itolizumab along with best supportive care showed reduction in inflammatory markers and improvement in oxygen saturation levels. Itolizumab has shown potential to accelerate recovery time in hospitalized patients with COVID-19.

1. Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a novel strain of Severe Acute Respiratory Syndrome-related Coronavirus (SARS-CoV), was first discovered in Wuhan, China in December 2019. SARS-CoV-2 belongs to the family Coronaviridae, which is enveloped, positive-sense, single-stranded RNA virus.[1]

On 30th January 2020, SARS-CoV-2 was designated as a Public Health Emergency of International Concern and on 11th March 2020 it was declared as a pandemic by WHO. As of December 2020, over 80 million people have been infected with COVID-19 worldwide and over 1.7 million deaths have been reported, with close to 10 million patients infected in India alone.[2] About 15-20% of the infected patients develop pulmonary symptoms such as breathing difficulties and require hospital admission for oxygen support and supportive care.[3,4] Out of these, some patients progress rapidly (within 48 to 72 hours) into a

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severe acute respiratory distress syndrome (ARDS) and multi-organ failure complications.[3]

1.1. Cytokine release syndrome or cytokine storm

It is now well understood that respiratory complications are the consequence of an exaggerated host immune response which produces a pro-inflammatory cytokine storm (i.e. IL-6, TNF) or Cytokine Release Syndrome (CRS) and cytopenias resulting in a high mortality rate. With a deep understanding of COVID-19 pathophysiology and mechanistic links of CRS, various drugs have been repurposed to block the inflammatory cascade in CRS.

The CD6 gene is constitutively expressed mainly on the effector T cells (T_{eff}) and is hardly expressed on the regulatory T cells (T_{regs}). CD6 stimulates the immune response and is overexpressed after lymphocyte activation. CD6 expression helps these T-cells in homing to lesions where its ligand ALCAM is upregulated after activation in the inflamed tissues.[5–7] Itolizumab is an anti-CD6 humanized IgG1 mAb immunomodulatory molecule. Use of this anti-CD6 monoclonal antibody is hence proposed for the prevention and treatment of CRS due to COVID-19.

Itolizumab is approved for use in Psoriasis and has been also evaluated in other inflammatory diseases, such as Rheumatoid Arthritis, with a good safety profile as a monotherapy or in combination with other drugs. It has a potent anti-inflammatory effect and reduces the production of pro-inflammatory cytokines IL-6, TNFα, IFNγ, IL-17 and IL-1.[8–10] It binds to domain 1 of CD6 thereby modulating T_{eff} cells, which is responsible for T cell differentiation. It spares T_{regs}, preserving the anti-viral response. Itolizumab selectively modulates T cell co-stimulation lowering pro-inflammatory cytokine release by Th1 and Th17 pathways.[3]

The current experience, presented here, is based on the hypothesis that use of Itolizumab in COVID-19 patients will control the pro-inflammatory CRS, by immunomodulation of the T_{eff} function and its trafficking to the inflammation site, sparing T_{regs} cells and preserving the anti-viral response eventually resulting in reduced morbidity and mortality due to COVID-19.

2. Materials and Methods

We retrospectively examined records of patients with moderate or severe COVID-19 disease who were treated with Itolizumab in a tertiary care hospital in Mumbai, Maharashtra from May to July 2020. Eligible patients were those deteriorating clinically, requiring oxygen support or showing rapid rise in inflammatory markers and administered Itolizumab along with best supportive care.

The analysis was conducted adhering to ethical principles, including maintaining patient confidentiality. For diagnosis, specimens were obtained by throat swabs under aseptic operation and tested with real-time RT-PCR assay.

Data was obtained retrospectively from hospital records. Clinical parameters such as body temperature, concentration of oxygen inhalation, and oxygen saturation levels were recorded before and after treatment with Itolizumab. Duration of hospital admission, change in SpO2 and inflammatory markers; CRP and ferritin were studied. Pre-dose dose values are defined as data available before Itolizumab infusion and post-dose value as the last value available during the hospital stay. Mean and percentage change was calculated for parameters at pre and post dose.

An informed consent for publication could not be taken from the patients because of the pandemic situation and constraints in resources and access. However, a no objection certificate was obtained from hospital ethics committee on 9th October, 2020. EC NO: ECR/388/Inst/MH/2013/RR-19

3. Results

An early user experience of Itolizumab in 27 patients diagnosed with moderate or severe COVID-19 is presented in this retrospective analysis. Along with Itolizumab all patients received best supportive care (e.g., antipyretics, Vitamin C, Remdesivir, hydroxychloroquine, steroids). Depending on the clinical condition and oxygen saturation of the patients, various oxygen delivering techniques were employed as per hospital protocol.

If the condition of patients deteriorated, they were intubated and put on a ventilator as per hospital protocol. A premedication of 100 mg Hydrocortisone and 30 mg Pheniramine (I.V) was given 30 minutes before Itolizumab infusion. Itolizumab was infused over a period of 5-6 hours.

The average age of the patients was 55.63 ± 13.87 years and ranged from 26 to 82 years (Table 1). Of the 27 patients, 22 were males (81.5%) and 5 were females (18.5%). Out of 27 patients, majority of the patients presented with fever (21, 77.7%) as the first symptom followed by dyspnoea (17, 62.9%), cough (16, 59.2%) and fatigue (12, 44.4%). The most prevalent comorbid conditions were hypertension (48.1%), diabetes (44.4%), and established coronary artery disease (11%). Thirty-four percent of patients reported having two or more comorbidities. Out of 27 patients, 23 patients were on non-invasive ventilation for oxygen support, 12 patients were on nasal cannula/nasal prong, 9 patients were on NRBM/RBM and 2 patients were on AIRVO. Four patients (14.8%) were on room air and they did not need oxygen support. All the patients were administered a single dose of Itolizumab (1.6 mg/kg) over a period of 5-6 hours, except one patient who was administered second dose.

Treatment with Itolizumab plus best supportive care was associated with decrease in pro-inflammatory biochemical parameters such as CRP and ferritin. The mean CRP from baseline reduced by 52.68% (91 mg/L pre dose to 43 mg/L post dose) at an average time of 6.4 ± 2.5 days (Figure 1).

The mean Ferritin levels reduced by 17.41 % (407 ng/ml pre dose to 336 ng/ml post dose) at an average time of 4.6 ± 2.2 days (Figure 2). Low oxygen saturation (<90%) was found in 55.5% patients; mean baseline oxygen saturation was 93.4% pre-dose which improved to 96.1% post treatment at an average time of 8.3 ± 3.5 days (Figure 3).

Among 27 hospitalized patients with COVID-19, 3 patients (11.1%) were transferred to the ICU but after treatment, they showed improvement and were shifted back to general ward with a mean ICU stay of 5 ± 2.2 days. Patients were followed up until discharge. All patients were alive and got discharged including the three patients who received critical care. The mean hospitalization time was 12.2 ± 3.9 days.

Transient lymphopenia (Grade III) was observed in one patient post treatment with Itolizumab, but the lymphocyte count improved within 4-5 days without any active intervention. Itolizumab infusion was well tolerated in all patients. No serious adverse events or infusion related reactions were reported.

**Table 1:** Demographic characteristics of the patients on presentation

| Characteristic	Patients (n=27)
Age in years (Mean ± SD)	55.63 ± 13.87
Age ≥ 60 years	11/27 (40.74%)
Gender	
Male	22/27 (81.48 %)
Female	5/27 (18.51 %)
Chronic medical illness	
Hypertension	13/27 (48.1%)
Diabetes	12/27 (44.4 %)
CAD	3/27 (11.1 %)
Hyperthyroidism	3/27 (11.1 %)
Stroke	1/27 (3.7 %)
Symptoms	
Fever	21/27 (77.7 %)
Dyspnoea	17/27 (62.9 %)
Cough	16/27 (59.2 %)
Fatigue	12/27 (44.4 %)
Oxygen Therapy	
Nasal cannula/Nasal prong	12/27 (44.4%)
NRBM / RBM Mask	9/27 (33.3%)
Room air	4/27 (14.8%)
AIRVO	2/27 (7. 4%)
Clinical Outcome	
Discharge from hospital	27/27 (100%)
Hospitalization days (Mean ± SD)	12.2 ± 3.9
ICU Admission	3/27 (11.1%)
ICU stay in days (Mean ± SD)	5 ± 2.2

4. Discussion

Lack of effective treatment options in COVID-19 has led to increased fear and improper management of the disease. While research and development on COVID-19 vaccine
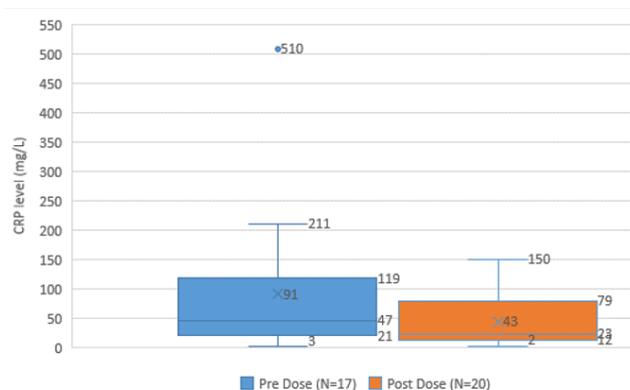
Fig. 1: Change in CRP levels post treatment (Itolizumab + best supportive care)
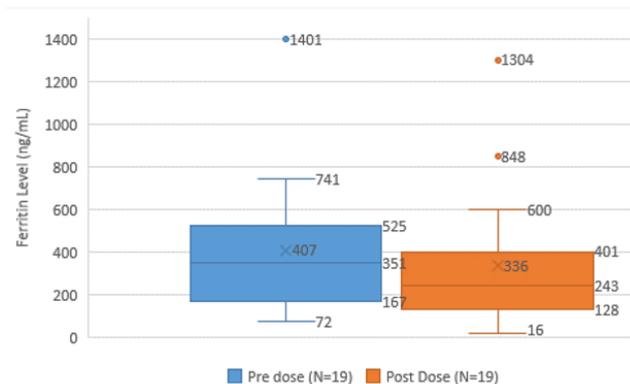
Fig. 2: Change in Ferritin levels post treatment (Itolizumab + best supportive care)
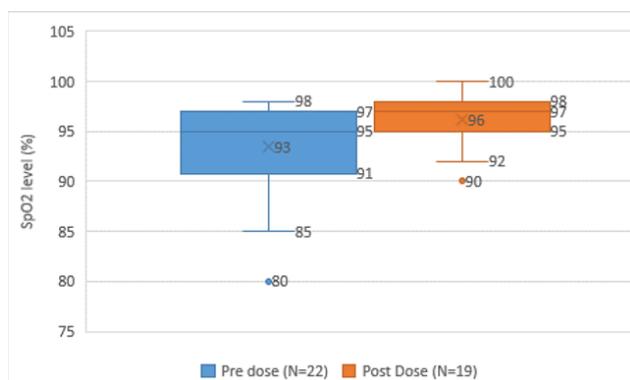
Fig. 3: Change in SpO2 Levels post treatment (Itolizumab + best supportive care)

is ongoing, an alternative approach could be repurposing of existing drugs with known safety profile. Itolizumab is one such immune-modulating anti CD6 monoclonal antibody, with a unique mechanism of action, could be a potential option in the management of moderate to severe immuno-inflammatory complications experienced by COVID-19 patients. On 10th July 2020, Drugs Controller General of India (DCGI) granted Itolizumab approval for restricted emergency use for the treatment of cytokine release syndrome in moderate to severe ARDS in patients with COVID-19.[11]

Age, presence of underlying diseases and secondary infections along with low lymphocyte count and elevated serum levels of CRP, D-dimers, ferritin, cardiac troponin and IL-6 are generally considered in risk stratification to predict severe and fatal COVID-19 in hospitalized patients.[12,13] In this study, 11 patients (40.74%) patients were $\geq$ 60 years of age and existing co-morbidities including hypertension (48.1%), diabetes (44.4%), and coronary artery disease (11.1%). Nine patients (33.3%) had both diabetes and hypertension.

During the course of inflammatory diseases, increase in ferritin production has been observed.[14] CRP is a non-specific acute-phase protein induced by IL-6 and the levels increase rapidly and significantly during acute inflammatory responses.[15,16] Individuals with CRP levels > 41.8 mg/L were more likely to develop COVID-19 complications.[17] In this study, patients showed elevated levels of CRP and ferritin with mean baseline values of 91 mg/L and 407 ng/ml, respectively. The mean CRP and ferritin post treatment showed a decline of 52.68% and 17.41%, respectively.

Severity of COVID-19 disease is characterized by ARDS. Patient SpO2 level is an important parameter to determine the need oxygen support and ICU admission. This analysis showed that 23 (85.2%) required a form of oxygen support. Post treatment the mean SpO2 increased from 93.4% (pre-dose) to 96.1% (post-dose) in an average time of 8.3 $\pm$ 3.5 days. Three patients (11.1%) required ICU admission with a mean duration of stay of 5 $\pm$ 2.2 days compared to mean length of stay for 18.4 days as reported by Turacoote et al.[18] All patients were eventually off oxygen and got discharged, with a mean hospitalization time of 12.2 $\pm$ 3.9 days. A retrospective study in Karnataka, India showed a median length of hospitalization of 17 days.[19] The median length of hospitalization in our cohort was found to be 12 days.

Recent study by Gore V et al., which incorporated Itolizumab in the treatment of moderate to severe COVID-19, also showed a decline in IL-6, CRP and Ferritin by 85.4%, 86.96 % and 55.61%, respectively. Median oxygen saturation also improved from 88 % (pre-dose) to 96% (post-dose). In addition to percent change in parameters, our study also presents the average time taken for improvement in each parameter. Mean hospitalization and ICU time was found to be 14 and 8 days compared to 12 and 5 days in our analysis, respectively. The all-cause mortality was 8%, while there were no deaths reported in our study.[20]

Apart from its retrospective nature, this analysis has other limitations including low patient numbers, single arm evaluation, inflammatory markers like IL-6 and D-Dimer not studied, radiological findings were not reported and effect of concomitant medication with or without Itolizumab not being evaluated. While this is an early experience of Itolizumab with best supportive care in treatment of moderate to severe COVID-19, the authors however, believe that Itolizumab has a definitive role to play in reducing the inflammatory markers based on its mechanism of action.

5. Conclusions

Itolizumab can be considered a possible therapeutic option, adding to best supportive care in moderate to severe COVID-19 patients, based on its effect of reducing inflammatory markers, improving oxygen saturation and favourable safety profile. It has also shown potential to accelerate recovery time in hospitalized patients with COVID-19. Further research evaluating clinical, laboratory and radiological findings in a randomized control setting against best supportive care is required to validate these results.

6. Acknowledgement

7. Source of Funding

8. Conflict of Interest

The authors declare that they have no conflict of interest.

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