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REVIEW

Itolizumab, an anti-CD6 monoclonal antibody, as a potential treatment for COVID-19 complications

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ABSTRACT

Introduction: The globally rampant SARS CoV-2 pandemic requires novel medical strategies to control the severity of disease and death due to complications. Of the 15–20% patients that develop pulmonary symptoms, a sub-set develops an acute respiratory distress syndrome (ARDS) rapidly progressing into a critical condition. Marked elevation of cytokines/chemokines is observed with elevation of additional markers of inflammation, coagulation, and organ damage such as CRP, D-dimer, LDH, Ferritin and Troponin-I. This hyperinflammation leads to worsening of oxygen saturation due to pulmonary infiltration and exudation, organ damage, and dysfunction of coagulation pathway and may lead to multi-organ failure.

Areas Covered: The role of anti-inflammatory monoclonal antibodies such as Itolizumab, in cytokine storm.

Expert Opinion: Itolizumab, an *anti-CD6 humanized IgG1* mAb, binds to domain-1 of CD-6 that is responsible for priming, activation, and differentiation of T-cells. Itolizumab significantly reduces T-cell proliferation along with substantial downregulation of the production of cytokines/chemokines. Approved for moderate to severe chronic plaque psoriasis in 2013 it is currently being studied for addressing COVID-19 related cytokine storm and its complications. This article reviews its use in COVID-19 infections; its dose, administration protocol, contra-indications, and safety in treating moderate-to-severe ARDS by preventing and treating the cytokine storm and its complications.

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KEYWORDS
Anti-CD6; monoclonal antibodies; Itolizumab; inflammatory; cytokine storm; plaque psoriasis; COVID-19

1. Introduction

With over 10 million infected with Severe Acute Respiratory Syndrome (SARS) CoV-2 infection worldwide and over 0.5 million deaths [1], we anticipate many more COVID-19 positive patients due to opening of the lockdown and restart of the economy. There is also a likelihood of a second surge of cases after the regular flu season commences. Out of the total infected, most are mildly affected and non-symptomatic. About 15–20% of the patients develop pulmonary symptoms such as breathing difficulties and require hospital admission for oxygen support and supportive care [2]. Out of those that get admitted, some patients progress rapidly within 48 to 72 hours into a severe acute respiratory distress syndrome (ARDS) and multi-organ failure complications [3]. Which patients are susceptible to such a progression and why is an important question being studied across the world, with emerging hypotheses around a genetic/immune predisposition, presence of co-morbid conditions like diabetes and hypertension, age, gender, and viral load at the time of infection [4]. Healthcare systems are now focused on addressing this segment of patients who are prone to severe ARDS and are also trying to understand the causality and treatment modalities in the medical arsenal to prevent the associated mortality. Repurposing the existing approved biologics that address inflammatory pathways may be a novel intervention to manage patients progressing toward ARDS until a vaccine gets available.

2. Hyperinflammation and mortality

While viremia induced cell damage and disease severity is known, another causative mechanism leading to disease severity, complications, and death is an aberrant inflammatory response progressing into a cytokine storm in patients with COVID-19 infection. Several patients with severe ARDS who get treated in an intensive care unit (ICU) setting with oxygen and supportive care have high levels of cytokines and chemokines such as tumor necrosis factor-α (TNF-α), interleukin-2 (IL-2), IL-6, IL-10, macrophage inflammatory protein-1α (MIP-1α), granulocyte-colony stimulating factor (G-CSF), interferon-γ inducible protein-10 (IP-10), interferon-γ (IFN-γ) in the blood [3]. There is a reduction in the absolute lymphocyte count as well as a relative increase in neutrophil-lymphocyte ratio (NLR) in these patients. Elevation in C-reactive protein (CRP) and ferritin is also common. Other markers of coagulation and organ damage such as D-dimer, lactate dehydrogenase (LDH), creatinine, and bilirubin are also observed to be elevated. This hyperinflammatory condition leads to worsening of oxygen saturation due to pulmonary infiltration and exudation, organ damage, and dysfunction of coagulatory pathways.

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Article highlights

- CD6 inhibition has an immunomodulatory effect in activation of T lymphocytes and suppression of pro-inflammatory cytokines
- Anti-inflammatory mAbs are being re-purposed and tested for use in containing the cytokine storm in moderate to severe ARDS patients with COVID-19 complications
- Itolizumab, approved since 2013 for severe plaque psoriasis in India, is being re-purposed for its safe and effective use as a therapeutic modality for COVID-19. Trial results in patients with COVID-19 complications will be published shortly.

This box summarizes key points contained in the article.

This resembles a condition called disseminated intravascular coagulation (DIC) and may lead to a multi-organ system dysfunction. Here is where the role of anti-inflammatory biologics such as Acalabrunitib, Tocilizumab, Anakinra, and Itolizumab can become relevant [5–10].

A recently published retrospective study on Tocilizumab (an IL-6 receptor inhibitor) use in 544 COVID-19 patients reports that, after adjustment for sex, age, recruiting center, duration of symptoms, and sequential organ failure assessment (SOFA) score, Tocilizumab treatment was associated with a reduced risk of invasive mechanical ventilation or death (adjusted hazard ratio 0·61, 95% CI 0·40–0·92; p =0·020) [9].

Anakinra (an IL-1 receptor antagonist) was evaluated in 29 COVID-19 patients. These patients received a high-dose of intravenous Anakinra, noninvasive ventilation, and standard treatment and were compared with 16 patients who received noninvasive ventilation and standard treatment only. At 21 days, treatment with high-dose Anakinra was associated with reductions in serum CRP and progressive improvements in respiratory function in 72% of patients who received the drug, assessed on 7-point ordinal scale [10].

There are no randomized clinical trials published, to date, evaluating the role of Tocilizumab or Anakinra in blocking specific cytokines in COVID-19 complications. All the results on these new agents are preliminary and warrant further confirmatory studies.

Major clinical events usually observed in COVID-19 patients such as high blood pressure, diabetes, thrombosis, kidney disease, pulmonary embolism, cerebrovascular, and neurologic disorders as well as systemic vasculitis (Kawasaki disease in young children) allude to a dysfunctional endothelium that may play an enabling role in furthering the systemic hyperinflammation and causing a shift toward the moderate/severe disease form of COVID-19 [11–13]. The endothelial dysfunction in COVID-19 due to co-morbidities such as diabetes and hypertension could also be the genesis of the systemic hyperinflammation and further be the cause of a DIC like condition with a consequent higher mortality [13]. A multifold increase in cytokines has been observed in patients suffering from COVID-19 along with co-morbid conditions such as hyperglycemia [14,15]. It will be important to assess the beneficial role of anti-inflammatory biologics in these co-morbid conditions [16,17], however, keeping in mind that diabetes and altered glucose homeostasis can be factors limiting the therapeutic response to Tocilizumab and other anti-inflammatory *monoclonal antibody (mAb)* [14].

Systemic hyperinflammation elevates cytokines such as TNF-α, IL-2, IL-7, IL-6, IP-10, MIP-1α, MIP-1β, and monocyte chemoattractant protein-1 (MCP-1). These proteins, in turn, attract monocytes, macrophages, and T-cells to the site of infection, promoting further inflammation (with the addition of IFN-γ produced by T-cells) and establishing a pro-inflammatory feedback loop. These cytokines are indicators of a T-helper-1 (Th1) cell-polarized response, also observed in SARS-CoV and Middle East Respiratory Syndrome (MERS)-CoV.

3. Role of Itolizumab in suppressing the cytokine storm

Itolizumab is an *anti-CD6 humanized IgG1* mAb that binds to domain 1 of CD6, a receptor present on $T_{effector}$ cells, responsible for priming, activation, and differentiation of T-cells [18]. Itolizumab's binding to CD6 domain 1 blocks the co-stimulation pathway and leads to inhibition of proliferation of naïve T-cells. This further leads to a marked reduction in pro-inflammatory cytokines involving the Th-1 and Th-17 pathway – namely, IL-17A, TNF-α, IL-6, IFN-γ, and IL-2. Microarray data also confirm the observation at the protein level and demonstrates an altered expression of other genes involved in the CD6 pathway. Itolizumab acts by immunomodulation of $T_{effector}$ function and its trafficking to the inflammation site, sparing T_{regs} and preserving the anti-viral response, and reducing associated morbidity and mortality. The signature cytokines of hyperinflammation that are reduced by Itolizumab include IL-2, IFN-γ, TNF-α through Th-1 pathway and IL-17, IL-6, TNF-α through Th-17 pathway [18,19]. Itolizumab by acting upstream at the Th-1 and Th-17 pathways, i.e. at the $T_{effector}$ cells, lowers the release of multiple cytokines and cell signaling transduction factors primarily involving the Th-17 and Th-1 pathways and drugs such as Tocilizumab or Anakinra block only the specific cytokines released downstream. The results for Tocilizumab and Anakinra are encouraging and support the hypothesis of containing the cytokine storm syndrome but these results are preliminary and are undergoing further studies. Since Itolizumab acts at Th-17 and Th-1 and downregulates multiple cytokines and chemokines as opposed to Toclizumab or Anakinra, it is being tested for its role in the reduction of systemic hyperinflammation by controlling the cytokine storm syndrome [Figure 1]. Table 1 shows a comparison between anti-CD6 mAb, Itolizumab, anti- IL-6 receptor mAb, Tocilizumab and anti-IL-1 receptor antagonists, Anakinra at the mechanistic level.

If the COVID-19 infection is visualized as an early infection stage, a pulmonary stage, and a hyperinflammation stage, Itolizumab, with its upstream mechanism of action, is

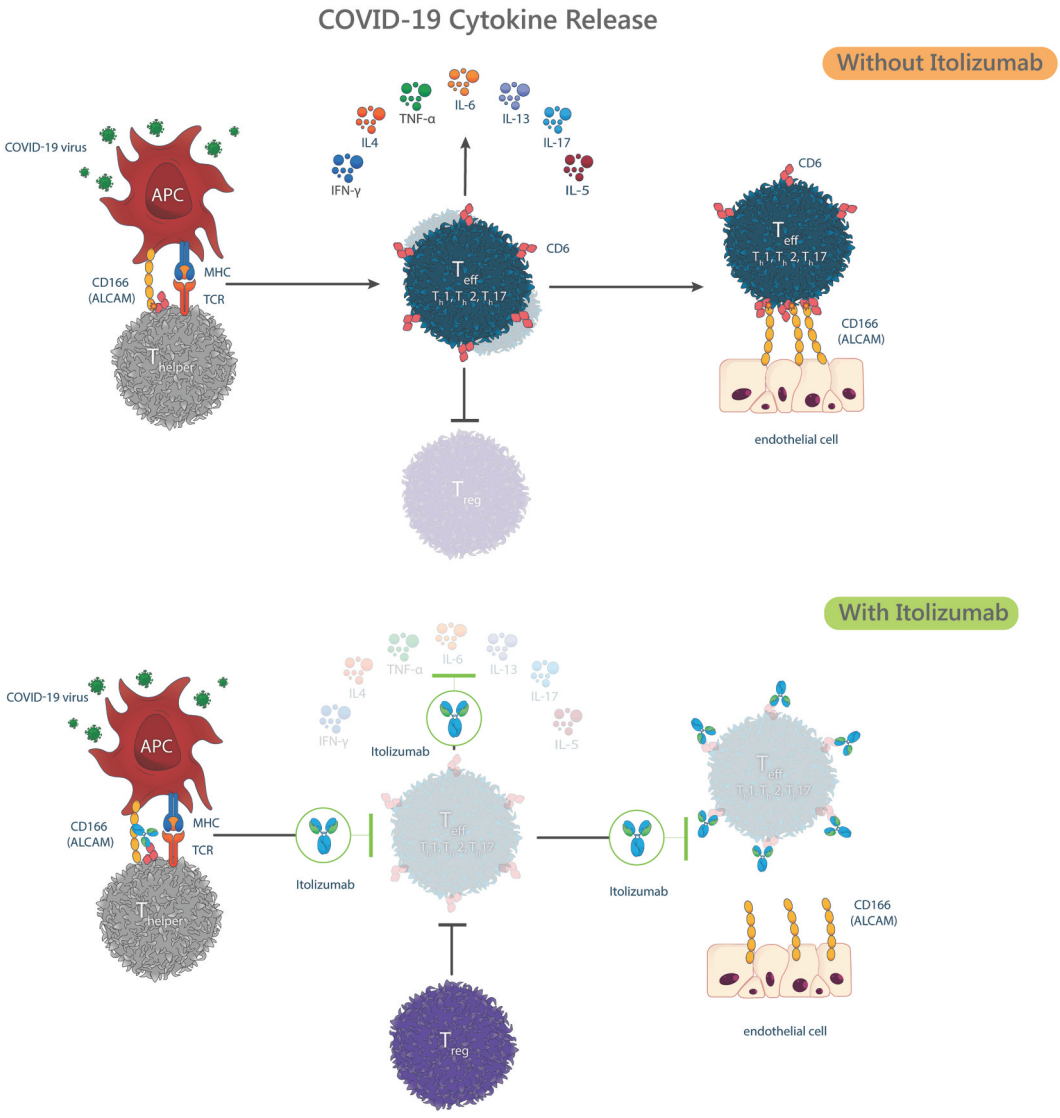

Figure 1. Itolizumab mechanism of action.

Table 1. Comparison of anti-CD6 mAb, Itolizumab and Anti-IL-6 and Anti-IL-1 receptor antagonists, Tocilizumab and Anakinra.

Function	Itolizumab (anti-CD6)	Tocilizumab (anti-IL-6 receptor)	Anakinra (anti-IL-1 receptor)
Mechanism of action	Binds to CD6 receptor and blocks ALCAM mediated T-cell activation	Binds to IL-6 receptor and blocks IL-6 mediated signaling in immune cells	Binds to IL-1 receptor and blocks IL-1 mediated signaling in immune cells
Immuno-modulation by regulatory T- cells	Yes	No	No
Reduction in pro-inflammatory cytokines	Downregulation of IL-6 Downregulation of IL-2 Downregulation of TNF-α Downregulation of IL-17	Blocks signaling of IL-6 alone	Blocks signaling of IL-1 alone
Duration of action	Longer due to upstream effect on the pathway	Shorter due to a more downstream action on the pathway	Short half life of 3–4h [10]

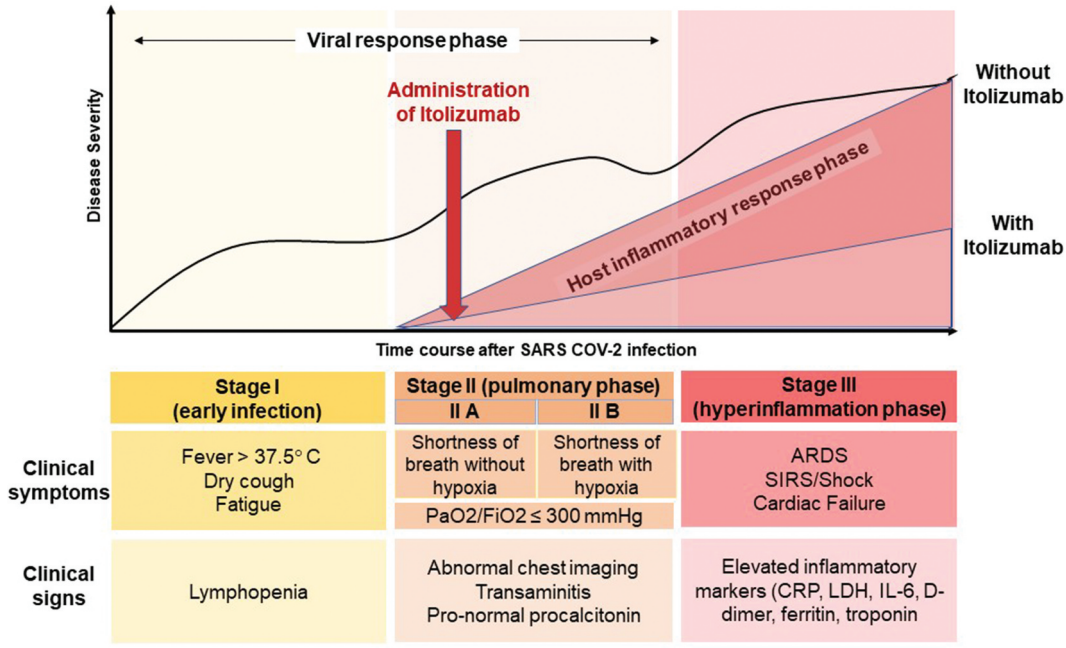

Figure 2. Clinical stages of COVID-19 and timing of administration of Itolizumab.
Adapted from Siddiqi HK, Mehra MR. J Heart Lung Transplantation. 2020;39(5):405–7.

optimally administered before the host systemic inflammatory stage gets initiated [Figure 2].

4. Approval status of Itolizumab

Approved by the Drug Controller General of India (DCGI) in January 2013, Itolizumab has been marketed in India since 2013 for the treatment of moderate to severe chronic plaque psoriasis. Currently, there are trials ongoing in COVID-19 patients, with complications, in India and Cuba.

5. Number of patients treated with Itolizumab till date and its safety profile

Itolizumab has been administered to 338 patients with rheumatoid arthritis or psoriasis in clinical trials and has been found to be well tolerated and efficacious in the patient population. Post-marketing and periodic safety update reports (PSURs) have been generated and submitted to the licensing authority. Based on these periodic reviews of safety data, the overall safety profile evaluation for Itolizumab has remained unchanged. No new clinically significant issues have arisen which would warrant any change to the current reference safety information (RSI).

6. Safety and efficacy of Itolizumab in approved indication (Moderate to severe plaque psoriasis)

6.1. Phase 2 study

A 32-week, randomized, blinded dose range finding study was conducted in 40 patients to assess the safety and efficacy of Itolizumab [20]. Substantial improvement in Psoriasis Area and Severity Index (PASI) scores were observed. The reported adverse events (AEs) included infusion-related reactions such as chills, 5.69% and pyrexia, 4.88%.

6.2. Phase 3 study

A 52-week, randomized, double-blind, placebo-controlled, parallel-arm, one-way crossover study was conducted in 225 patients to assess the safety and efficacy of Itolizumab [21]. There was a significant improvement of PASI scores over time. A total of 27.0%, 36.4%, and 2.3% in Arm A (0.4 mg/kg itolizumab once weekly for 4 weeks, then 1.6 mg/kg once every 2 weeks), Arm B (1.6 mg/kg itolizumab once every 2 weeks) and Arm C (placebo), respectively, achieved a Psoriasis Area and Severity Index-75 (PASI-75; proportion achieving at least 75% improvement in PASI score response) at Week 12. The difference from placebo was statistically significant (P = 0.0172 for Arm A and 0.0043 for Arm B). A total of 46.1%, 45.5% and 41.9% in Arm A, Arm B, and Arm C, respectively, achieved a PASI-75 response at Week 24. A total of 57.6%, 64.4%, and 26.8% in Arm A, Arm B, and Arm C, respectively, showed median percent improvement in PASI score at Week 12. A total of 67.2%, 73.4%, and 70.5% in Arm A, Arm B, and Arm C, respectively, showed median percent improvement in PASI score at Week 24. At Week 12, 27.3% and 9.1% patients achieved improvements in the arthritic parameter, American College of Rheumatology [ACR]-20 and ACR-50, respectively. At Week 24, 27.3% and 9.1% patients achieved ACR-20, ACR-50, and ACR-70, respectively. The reported AEs included infusion-related reactions: acute (on the day of infusion), 17% and delayed (up to seven dose post infusion), 3.6%.

The most commonly reported AEs (occurring in ≥5% patients) in the Phase 3 study were infusion reactions, pyrexia, upper respiratory tract infections, and pruritus. Majority of the events were mild or moderate in severity. Infections were particularly monitored in the clinical studies and, in general, the Itolizumab injection did not appear to increase the rate of infections. Infusion-related reactions were the most common AEs reported in the clinical studies with Itolizumab. Over the duration of the Phase 3 study, acute infusion reactions were experienced by around 15% of patients. In hematological parameters, a transient reduction in the mean absolute lymphocyte count was observed. Most frequently occurring AEs (in >5% of patients) in the Phase 3 study are given in Table 2.

6.3. Other indications/studies with Itolizumab

A randomized, open-label, phase 2 study conducted in India evaluated the safety and efficacy of Itolizumab in combination with methotrexate (MTX) in patients with active rheumatoid arthritis [22]. Itolizumab has been administered and was also found to be safe and efficacious in rheumatoid arthritis in trials performed in Cuba [23]. Additional trials ongoing in US and Australia are in acute graft versus host disease (aGVHD; Phase 1b/2 trial underway in US), uncontrolled asthma (Phase 1b trial in Australia), and lupus nephritis (Phase 1b trial in US). Trials are currently ongoing in COVID-19 patients, with complications, in India and Cuba [24].

7. Current status of Itolizumab in treatment of COVID-19

Itolizumab has completed a trial in COVID-19 patients with moderate to severe ARDS in India. This trial was a multi-centric, open label, randomized, controlled trial to study the efficacy and safety of Itolizumab in COVID-19 complications (CTRI/2020/05/024959). In Cuba, 80 COVID-19 patients with ARDS are being treated with Itolizumab in an interventional trial (WHO Trial ID: RPCEC00000311).

7.1. Key Eligibility criteria of the patients for receiving Itolizumab in COVID-19

The trial included male or female adults above 18 years with a confirmed virological diagnosis of SARS-CoV-2 infection with RT-PCR and requirement of hospitalization due to clinical worsening of COVID-19 infection with an oxygen saturation at rest in ambient air ≤94%. Patients with moderate to severe ARDS, as defined by PaO2/FiO2 ratio of <200, or more than 25% deterioration from the immediate previous value and patients with baseline serum ferritin level ≥400ng/mL or IL-6 levels greater than 4 times the upper limit of normal (ULN) were included. One of the last two conditions was required for inclusion of the patient into the study. To overcome the logistical delay in getting the RT-PCR results on time, the biomarker data was used as inclusion criteria , if known.

7.2. Key exclusion criteria

The following patients were excluded from the study-patients with known severe allergic reactions to mAbs; those with active tuberculosis (TB) infection or having a history of inadequately treated or latent tuberculosis; those who had received oral anti-rejection or immune-suppressive drugs in the past 6 months and those who had participated in other drug clinical trials using anti-IL-6 therapy. Patients with a known history of Hepatitis B, Hepatitis C or HIV, absolute neutrophils count (ANC) <1000/mm^3, platelet count <50,000/mm^3 and absolute lymphocyte count (ALC) <500/mm^3 were also excluded.

8. Monitoring and caution required during the treatment with Itolizumab

Caution was exercised, and risk benefit analysis evaluated before and during treatment in patients with a history of recurrent infections or underlying conditions which may predispose them to serious infections, like HIV, TB, Hepatitis B, Hepatitis C. Caution was exercised in patients on chronic steroid therapy in the preceding 6 months.

8.1. Recommended number of doses of Itolizumab in the treatment of COVID-19

The first dose of Itolizumab was administered at 1.6 mg/kg. This loading dose of 1.6 mg/kg was chosen as it is the approved dose in patients of chronic plaque psoriasis and doses up to 1.6 mg/kg have been administered as i.v. infusion in several phase 2 and 3 clinical trials, without any evidence of dose-limiting toxicities. As Itolizumab is an anti-CD6 antibody, an in-vitro CD6 receptor occupancy was evaluated and as 1.6 mg/kg dose showed a 99% receptor occupancy, it was chosen as the first dose. In some patients an additional dose of 0.8 mg/kg was administered after 1 week, if required. As the patients experienced different degrees of host inflammatory response, subsequent weekly doses were not necessary in all patients. The decision was left to the investigator's discretion based on the clinical condition and markers of inflammation. Up to four weekly doses were allowed in the study.

8.2. Instructions for Itolizumab infusion

Incidence of infusion reactions for the first dose has been observed in 15% plaque psoriasis patients. These reactions are mild to moderate in severity. The pre-medication protocol consisting of Hydrocortisone 100 mg i.v. (or any equivalent short acting glucocorticoid) and Pheniramine 30 mg i.v. was given about 30 ± 10 minutes prior to each infusion.

The first dose of Itolizumab was given at 1.6 mg/kg administered in 250 mL of 0.9% normal saline. The infusion was given over 2 h initiated at 50 mL in the first hour and remainder was given over 1 h. In case of dose interruption due to an infusion reaction, the dosing had to be restarted very slowly following constant monitoring and appropriate management of vitals and symptoms. If the first infusions were well tolerated, then subsequent infusions (at 0.8 mg/kg dose weekly) could be completed over 3–4 h.

Table 2. Most frequently occurring adverse events (in >5% of patients) in the Phase 3 study (Weeks 1–52).

System organ class Preferred term	Number of Subjects, *n* (%)			
	Arm A, *N*=90	Arm B, *N*=90	Arm C, *N*=43	Total, *N*=223
Gastrointestinal disorders				
Diarrhea	0	6 (6.7)	1 (2.3)	7 (3.1)
General disorders and administration site conditions				
Infusion-related reaction (acute)	18 (20.0)	15 (16.7)	5 (11.6)	38 (17.0)
Infusion-related reaction (delayed)	2 (2.2)	5 (5.6)	1 (2.3)	8 (3.6)
Pyrexia	9 (10)	8 (8.9)	5 (11.6)	22 (9.8)
Infections and infestations				
Upper respiratory tract infection	2 (2.2)	10 (11.1)	5 (11.6)	17 (7.6)
Skin and subcutaneous tissue disorders				
Pruritus	3 (3.3)	5 (5.6)	4 (9.3)	12 (5.4)

n = number of patients with response; N = total number of patients.
Patients were randomized in a 2:2:1 ratio to following treatment arms: (Arm A) Itolizumab 0.4 mg/kg every week for 4 weeks, followed by 1.6 mg/kg every 2 weeks for 8 weeks; (Arm B) Itolizumab 1.6 mg/kg every 2 weeks for 12 weeks; (Arm C) placebo for 12 weeks. Arms A and B continued to receive Itolizumab at the dose of 1.6 mg/kg every 4 weeks till weeks 24; Arm C received Itolizumab at 1.6 mg/kg every 2 weeks till weeks 24. Thereafter, arm C received Itolizumab at the dose of 1.6 mg/kg every 12 weeks, and patients in arm A and B were re-randomized based on their PASI response (≥PASI 75 received either Itolizumab 1.6 mg/kg every 12 weeks or placebo till week 52; ≥PASI 50 but <PASI 75 received Itolizumab 0.4 mg/kg every week for 4 weeks followed by 1.6 mg/kg every 4 weeks).

9. Common side effects associated with Itolizumab

9.1. Infusion-related reactions

Presentation of infusion-related reactions to Itolizumab may include chills, rigor, nausea, flushing, urticaria, cough, hypersensitivity, pruritus, rash, wheezing, dyspnea, dizziness, headache, and hypertension. In some cases, severe reactions may be seen leading to a further oxygen decompensation state in COVID-19 infected patients. These occur during the first cycle of dosing and tend to decrease in severity and frequency upon subsequent infusions. Acute infusion reactions should be treated using the standard of care. It is recommended that the infusion be given slower over 5–6 hours to reduce the incidence of infusion reactions and better tolerability.

9.2. Important side effects reported in the clinical studies with Itolizumab

In previous Itolizumab trials, infusion reactions have been reported in 15% of patients. In clinical practice, infusion reactions have been observed to range from 12% to 15%. Other frequently occurring AEs (in >5% of patients) in the Itolizumab Phase 3 study are given in Table 2.

9.3. Contraindications for Itolizumab and limitations of use

Itolizumab should not be administered to patients having a history of severe allergy or known hypersensitivity reaction to any component of Itolizumab or any murine proteins. The safety and efficacy of Itolizumab has not been studied in pediatric patients <18 years old; patients with hepatic and renal impairment; pregnancy and, nursing mothers.

10. Expert opinion

As the number of COVID-19 cases rise all over the world, the hospitals and governments are focusing on having protocols in place to treat severe complications and death as a result of COVID-19 infections. Hospitalized patients that progress rapidly to severe ARDS, organ damage, and coagulation disorders due to systemic hyper-inflammation currently have no approved treatments. Tocilizumab has been used off-label to treat cytokine storm in these patients.

Repurposing of anti-inflammatory biologics such as Itolizumab could play an important role in treating the cytokine storm and complications due to COVID-19 infection and reduce mortality due to cytokine storm complications. Itolizumab is an approved drug in India for psoriasis with a proven safety profile [19–21, 25] and has been used in a clinical trial for treating COVID-19 complications. Itolizumab is being used for compassionate treatment of patients with moderate to severe ARDS due to COVID-19 at several hospitals in India. The trial results will be published shortly.

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