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APPROVAL OF ITOLIZUMAB FOR CORONA: A PREMATURE DECISION OR NEED OF THE HOUR

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Abstract:

Itolizumab is a first-in-class anti-CD6 monoclonal antibody that was initially developed for various cancers and was later developed and approved in India for treatment of moderate to severe chronic plaque psoriasis in 2013. This drug is now being re-purposed for CORONA. The potential utility of Itolizumab in CORONA, based on its unique mechanism of action in ameliorating cytokine release syndrome (CRS), was proposed first in Cuba with approval of a single-arm clinical trial and expanded access use. Subsequently, a phase II, open-label, randomized, placebo-controlled trial has been conducted in 30 CORONA patients in India after receiving regulatory permission. Based on the results, the Indian drug regulatory agency approved itolizumab in July 2020 for 'restricted emergency use' for the treatment of CRS in moderate to severe acute respiratory distress syndrome (ARDS) due to CORONA. This has drawn sharp criticism within the scientific community, with the approval being granted on the basis of a relatively small phase II trial, without conduct of a conventional phase III trial, and lacking availability of the claimed supportive real-world evidence in the public domain to date. In a global scenario where finding a successful treatment for CORONA is of utmost priority, a biologic agent has been re-purposed and approved with a successfully completed RCT, in a country where cases and mortality due to CORONA are growing exponentially. However, instead of welcoming the approval with open arms, many doubts are being raised. This is an issue that needs to be considered and dealt with sensitively, as well as scientifically.

Keywords- Itolizumab, plaque psoriasis, biological therapy,

Introduction:

Amidst the ongoing struggle to find a successful treatment for CORONA, itolizumab became the first novel biologic therapy to be approved in the world for CORONA—for patients with moderate to severe complications [1]. The Indian drug regulatory agency (Central Drug Standard Control Organisation, CDSCO) recently approved itolizumab for 'restricted emergency use' for treatment of cytokine release syndrome (CRS) in moderate to severe acute

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respiratory distress syndrome (ARDS) due to CORONA, followed by a similar approval in Cuba [2]. 'Restricted emergency use' requires fulfilment of certain requirements for practice including written informed consent of patients, explaining risks and benefits of the drug and putting a risk management plan in place to manage any adverse effects [3]. The drug can be given only in hospitals and medical institutions, and is not meant for sale at retail pharmacies. Itolizumab is a first-in-class monoclonal antibody, first developed for auto-immune diseases in India, where it received approval for treatment of patients with active moderate to severe chronic plaque psoriasis in 2013. It has been approved for the same indication in Cuba as well, but not in other countries yet [4].

The potential utility of itolizumab in CORONA, based on its mechanism of action, led to expanded access use and conduct of a trial in Cuba, retrospectively registered with the Cuban regulatory agency (Center for the State Control of Medicines, Equipment and Medical Devices, CECMED) in May 2020 [5]. This trial recruited patients with critical and severe illness, and moderately ill patients with very high risk of developing severe symptoms. Encouraged by the initial promising results with the first few patients seen in this index trial, regulatory permission was received to repurpose the drug for CORONA in India [4]. The drug was studied in an open-label, randomized, controlled, phase II trial at four hospitals in India to assess the safety and efficacy of itolizumab in preventing CRS in moderate to severe ARDS due to corona virus [2]. On the basis of the results of this phase II trial, itolizumab was granted approval for 'restricted emergency use' for its indication in corona virus patients in July 2020 [4]. The data obtained from the Cuban single-arm trial, in conjunction with the Indian data, also led to the drug's approval for the same indication in corona virus in Cuba later in the same month; data on the results submitted to the Cuban authority are not available. On one hand, this is welcome news as a potentially life-saving treatment is now available for an important subset of CORONA patients—those having CRS-mediated ARDS. But, on the other hand, the relative lack of evidence available makes it necessary to carefully evaluate the scientific validity of this approval [4]. Further questions arise as the drug has not been included in the clinical management protocol recommended by the national task force on CORONA in India, despite getting approval from the country's regulator, because of insufficient evidence. The innovator company, Biocon Ltd, claims to have supportive real-world evidence [5].

Discovery of itolizumab:

Itolizumab is a monoclonal antibody that has gained attention in the field of immunotherapy due to its potential therapeutic applications in various autoimmune and inflammatory diseases. Discovered and developed by Biocon, an Indian biopharmaceutical company, Itolizumab has shown promising results in the treatment of conditions like psoriasis and corona virus [6]. Itolizumab works by targeting and blocking a protein called CD6, which plays a crucial role in the activation and regulation of immune responses [5]. By inhibiting the interaction between CD6 and its binding partner, Itolizumab helps modulate the immune system, reducing the excessive immune response seen in autoimmune diseases [7].

One of the most significant breakthroughs for Itolizumab came in the treatment of psoriasis, a chronic inflammatory skin disorder. Clinical trials conducted by Biocon demonstrated that

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Itolizumab effectively reduced the severity of psoriasis symptoms, including scaling, itching, and redness [8]. The drug was found to be safe and well-tolerated by patients, with minimal side effects. These positive outcomes led to the approval of Itolizumab by the Drug Controller General of India for the treatment of moderate to severe psoriasis under the brand name ALZUMAb [9].

In addition to psoriasis, Itolizumab has also shown promise in the treatment of corona virus. As the world faced the unprecedented challenge of the global pandemic, Biocon repurposed Itolizumab to combat the severe immune response seen in critically ill corona virus patients, known as cytokine release syndrome (CRS). CRS can lead to a cascade of inflammatory reactions that damage multiple organs. Itolizumab's ability to modulate immune responses made it a potential candidate for managing CRS in CORONA patients [10].

Initial studies conducted in India showed that Itolizumab significantly reduced mortality rates and improved clinical outcomes in corona virus patients with moderate to severe respiratory distress [7]. The drug was found to suppress the pro-inflammatory cytokine storm, leading to a decrease in lung injury and improved oxygenation. These findings prompted emergency approval by the Drug Controller General of India for the use of Itolizumab in corona virus patients [10].

The discovery and development of Itolizumab highlight the importance of monoclonal antibodies in targeted immunotherapy. By specifically blocking key immune pathways, Itolizumab offers a unique approach to managing autoimmune diseases and hyperinflammatory conditions [11]. The drug's success in psoriasis and corona virus treatment has opened up new possibilities for its application in other inflammatory disorders [12].

However, it is important to note that further research and clinical trials are necessary to fully understand the long-term safety and efficacy of Itolizumab. Ongoing studies are exploring its potential use in conditions like rheumatoid arthritis, multiple sclerosis, and graft-versus-host disease [12].
In conclusion, the discovery of Itolizumab and its subsequent therapeutic applications in psoriasis and corona virus treatment represent significant advancements in the field of immunotherapy. With its ability to modulate immune responses and target specific pathways, Itolizumab offers hope for patients suffering from autoimmune and inflammatory diseases continued research and development will help uncover the full potential of this innovative drug in improving patient outcomes and quality of life [13].

MODE OF ACTION OF ITOLIZUMAB-

Itolizumab is a humanized anti-CD6 monoclonal antibody (mAb), specifically targeting the SRCR–1 (scavenger receptor cysteine-rich like domain 1) of CD6. It has a molecular weight of 148 kDa and contains two heavy chains and two light chains linked with a disulfide bond. The parent antibody of itolizumab is ior T1, a murine mAb, which has shown therapeutic efficacy

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in psoriasis and rheumatoid arthritis. Itolizumab, being a humanized mAb, is less immunogenic and has a better safety profile with the same therapeutic efficacy as ior T1. Itolizumab is a mAb directed against CD6, a surface glycoprotein found on mature T cells, immature B cells, the B1a subset of B lymphocytes, and certain regions of the brain. It plays a pivotal role in cell proliferation, adhesion, differentiation, and survival. Its extracellular region is composed of three SRCR domains [14]. CD6 is a co-stimulatory molecule, and its stimulation is responsible for Th1 activation, and differentiation of T cells, which promotes a proinflammatory response. Thus, by inhibiting CD6, itolizumab down regulates the synthesis of proinflammatory cytokines and adhesion molecules that eventually leads to reduced interferon-γ (IFNγ), interleukin (IL)-6, and tumor necrosis factor-α (TNFα) levels, along with reduced T-cell infiltration at the inflammatory sites [13].

Interestingly, these anti-inflammatory effects are not achieved by inhibiting ligand binding and causing T-cell depletion, but by inhibiting new receptor formation, stimulating loss of existing receptors or by blockade and internalization or downregulation of receptors [3]. In vitro experiments have shown that itolizumab does not cause T-cell depletion but inhibits T-cell proliferation induced in the presence of ALCAM (activated leukocyte cell adhesion molecule or CD 166) and excess IL-2, and downregulates the phosphorylation of intracellular proteins implicated in the CD6-mediated activation pathways [4]. So, it inhibits the downstream inflammatory cascade by a unique mechanism of action [7].

Pharmacological use of itolizumab

Including CORONA virus, Itolizumab is also used in also used in 2 more disease:

1.) Psoriasis

2.) Rheumatoid Arthritis

Psoriasis: [11,12]

Psoriasis is a chronic autoimmune skin disorder characterized by the excessive proliferation of skin cells, leading to the formation of thickened, scaly plaques. It is a multifactorial disease involving genetic predisposition, immune dysregulation, and environmental triggers. Although the exact etiology of psoriasis remains unclear, it is widely recognized that T cells play a crucial role in the pathogenesis of the disease. Pharmacological interventions are essential for managing psoriasis, and one such intervention is Itolizumab, a monoclonal antibody targeting the CD6 receptor. In this response, we will explore in detail the pharmacological use of Itolizumab in psoriasis, including its mechanism of action, clinical efficacy, safety profile, and future perspectives.

Mechanism of Action:

Itolizumab exerts its pharmacological effects by specifically targeting the CD6 receptor, a cell surface glycoprotein expressed on T cells. CD6 plays a significant role in the activation and regulation of T cell-mediated immune responses. It facilitates the formation of the

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immunological synapse and augments T cell signaling pathways, including antigen recognition and co-stimulation.

The binding of Itolizumab to CD6 inhibits the interaction between CD6 and its ligand, primarily activated leukocyte cell adhesion molecule (ALCAM). This interaction is crucial for T cell activation, adhesion, and migration. By blocking the CD6-ALCAM interaction, Itolizumab modulates the activation and proliferation of T cells, leading to a reduction in the inflammatory response observed in psoriasis.

Clinical Efficacy:

The clinical efficacy of Itolizumab in psoriasis has been evaluated in several clinical trials. Notably, a randomized, double-blind, placebo-controlled Phase IIb trial investigated the efficacy and safety of Itolizumab in patients with moderate to severe chronic plaque psoriasis. In this study, patients received either Itolizumab or placebo for a duration of 12 weeks.

The primary endpoint of the study was the proportion of patients achieving a 75% reduction in the Psoriasis Area and Severity Index (PASI 75) score at week 12. The results demonstrated a significantly higher proportion of patients achieving PASI 75 in the Itolizumab group compared to the placebo group. Moreover, Itolizumab-treated patients exhibited a rapid onset of response, with improvement observed as early as week 2.

Further analyses of secondary endpoints, including PASI 50, PASI 90, and Dermatology Life Quality Index (DLQI) scores, also favored Itolizumab over placebo. These findings indicate the clinical efficacy of Itolizumab in improving both disease severity and patients' quality of life.

Safety Profile:

The safety profile of Itolizumab in psoriasis has been assessed in clinical trials and real-world studies. Overall, Itolizumab has demonstrated a favorable safety profile with a low incidence of serious adverse events.

The most commonly reported adverse events associated with Itolizumab treatment are related to the infusion process, including infusion reactions such as fever, chills, headache, and nausea. However, these reactions are generally mild to moderate in intensity and can be managed with pre-medication or by adjusting the infusion rate. Infusion-related reactions are typically transient and decrease in frequency with subsequent infusions.

In terms of long-term safety, data from open-label extension studies have shown that Itolizumab can be well-tolerated with continuous treatment. The incidence of adverse events does not appear to increase with long-term use, and there have been no reports of serious infections or malignancies associated with Itolizumab use in psoriasis.

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Rheumatoid Arthritis: [13, 14]

Rheumatoid arthritis (RA) is a chronic autoimmune disease that affects millions of people worldwide. It is characterized by inflammation of the joints, leading to pain, stiffness, and progressive joint damage. The advent of biologic therapies has revolutionized the treatment of RA, and one such emerging therapy is itolizumab. Itolizumab is a monoclonal antibody that targets CD6, a co-stimulatory molecule involved in T-cell activation. This article provides a comprehensive review of the pharmacological use of itolizumab in rheumatoid arthritis, focusing on its mechanism of action, clinical efficacy, safety profile, and future prospects.

Rheumatoid arthritis is a complex autoimmune disease characterized by chronic inflammation and joint damage. Traditional disease-modifying antirheumatic drugs (DMARDs) and biologic therapies have improved patient outcomes, but there remains an unmet need for more effective and safer treatment options. Itolizumab, a humanized monoclonal antibody, has shown promise in the management of RA. This review aims to evaluate its pharmacological use in RA, including its mechanism of action and clinical applications.

Mechanism of Action:

Itolizumab selectively targets CD6, a co-stimulatory molecule expressed on T-cells. By binding to CD6, itolizumab inhibits T-cell activation, reduces the production of pro-inflammatory cytokines, and modulates immune responses. The downregulation of T-cell activation and cytokine production attenuates the inflammatory response in RA, leading to a reduction in joint damage and symptoms.

Preclinical Studies:

Preclinical studies evaluating the efficacy of itolizumab in animal models of RA have demonstrated its ability to reduce joint inflammation, prevent cartilage destruction, and inhibit bone erosion. These findings support the potential of itolizumab as a therapeutic option for RA.

Clinical Trials:

Several clinical trials have evaluated the safety and efficacy of itolizumab in RA patients. These trials have demonstrated that itolizumab, when used as monotherapy or in combination with conventional DMARDs, improves disease activity, reduces joint pain and swelling, and improves physical function. Moreover, itolizumab has shown to be well-tolerated with a favorable safety profile.

Comparative Studies:

Comparative studies have compared itolizumab with other biologic agents commonly used in the treatment of RA. These studies have shown similar or superior efficacy of itolizumab in terms of disease activity reduction, clinical response rates, and improvement in patient-reported outcomes. However, more head-to-head trials are required to establish its comparative effectiveness conclusively.

Safety Profile:

The safety profile of itolizumab has been favorable in clinical trials, with the most common adverse events being mild to moderate infusion reactions. Serious adverse events are

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infrequent, and long-term safety data are promising. However, further research is needed to evaluate the potential risks associated with long-term use and its effects on other organ systems.

Future Prospects:

The emerging role of itolizumab in the treatment of RA opens up new possibilities for targeted therapies. Ongoing research aims to explore its potential in combination therapy, dose optimization, and personalized medicine approaches. Additionally, investigations into its effects on biomarkers and long-term outcomes will help establish its place in the treatment.

Itolizumab, a monoclonal antibody targeting CD6, shows promise as an effective and safe therapeutic option for rheumatoid arthritis. Clinical trials have demonstrated its ability to improve disease activity, reduce joint inflammation.

Safety data for itolizumab has been derived mainly from the two multicenter clinical trials of patients with chronic plaque psoriasis, and from a study of patients with rheumatoid arthritis. No treatment-related severe adverse effects (AEs) were noted in these trials. The various AEs observed with itolizumab were infusion-related reactions (such as nausea, rash, urticaria, flushing, cough, wheezing, dyspnea, dizziness, and headache), pyrexia due to infections, pruritus, antidrug antibody formation, and transient decrease in mean lymphocyte count. Infusion reactions, the most common adverse event, have been reported in 12–15% of patients. The frequency and severity of infusion reactions were noted to decrease with subsequent infusions. Other frequent adverse events (> 5%) are diarrhea, pyrexia, upper respiratory infections, and pruritus.

Clinical Trials of Itolizumab for the Treatment of CORONA-

A phase II, multi-centric, open-label, two-arm, randomized, pivotal clinical trial was conducted in 30 patients in India . The trial included adults aged > 18 years of either sex with a confirmed virological diagnosis of SARS-CoV-2 infection with reverse transcription polymerase chain reaction (RT-PCR) assay who were hospitalized due to clinical worsening of CORONA infection with an oxygen saturation at rest in ambient air ≤ 94%. Patients had moderate to severe ARDS, as defined by a ratio of arterial oxygen partial pressure and fractional inspired oxygen (PaO2/FiO2) of < 200, or > 25% deterioration from the immediate previous value [14]. In case of a delay in RT-PCR results, biomarker data—either baseline serum ferritin level ≥ 400 ng/mL or IL-6 levels > 4 times the upper limit of normal (ULN)—was required for inclusion of the patient into the study. Patients with known severe allergic reactions to mAbs; known history of hepatitis B, hepatitis C, or HIV; active tuberculosis (TB) infection or having a history of inadequately treated or latent TB; absolute neutrophil count (ANC) < 1000/mm3, platelet count < 50,000/mm3, and absolute lymphocyte count (ALC) < 500/mm3; those on immunosuppressant drugs in the past 6 months; and those who had participated in other clinical drug trials using anti-IL-6 therapy were excluded [15]. Itolizumab was administered at a loading dose of 1.6 mg/kg, chosen as it is the approved dose in patients with chronic plaque psoriasis and has been administered as an intravenous (IV) infusion in several phase II and III clinical trials, without any evidence of dose-limiting

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toxicities [16]. An additional dose of 0.8 mg/kg was administered after 1 week in some patients, if required, based on the physician's discretion; up to four weekly doses were allowed in the study [17].

With a 2:1 randomization, 20 patients were randomized to receive itolizumab plus supportive care, while 10 patients received supportive care alone in the control arm. The primary outcome was comparison of the 1-month mortality rate between the two arms [18]. The secondary outcomes were plasma levels of biomarkers, lymphocyte count, C-reactive protein (CRP), PaO2/FiO2, radiological response, duration of hospitalization, and remission of respiratory symptoms. All patients receiving itolizumab recovered fully and were discharged from hospital, whereas three out of ten patients (30%) in the control arm died [19]. There was also significant improvement in key efficacy parameters of lung function such as PaO2and SpO2 (oxygen saturation) without increasing oxygen flow in the itolizumab arm. All patients on itolizumab were weaned off oxygen by day 30, and none needed ventilator support, unlike the control arm [20]. Key secondary endpoints of the clinical markers of inflammation such as IL-6, TNFα, serum ferritin, d-dimer, lactate dehydrogenase (LDH), and CRP showed clinically significant suppression after itolizumab dosing and correlated well with clinical and radiological improvement in symptoms and chest X-ray images, respectively. Itolizumab was well tolerated overall and found to be safe, with the infusion reactions manageable with slowing the infusion rate [21].

These results are in line with the findings of the Cuban study, a single-arm, non-controlled clinical trial, where 80 CORONA patients were treated with itolizumab . It has been claimed that 79% of severely ill patients were discharged from the intensive care unit (ICU) after 14 days of treatment, while moderately ill patients showed a reduction in the rate of disease progression. However, no further details about this trial are available. Two studies on pre-print servers are available presently; both are from the same Cuban trial (RPCEC00000311) [22]. One study shows that a single dose of itolizumab decreased the serum IL-6 levels after 48 h of administration in 24 moderate to critically ill elderly corona virus patients. In another study, the authors concluded that in 19 moderately ill elderly corona virus patients, itolizumab treatment was associated with a significantly reduced risk of admission to ICU and a 10 times lower risk of death [23].

Approval for Corona Virus-

The approval of itolizumab for restricted emergency use to treat corona virus patients with the complication of moderate to severe ARDS comes at a time when cases and hospitalizations are increasing alarmingly; the mortality has exceeded 80 thousand in India [24]. This approval presumably comes with the intention of providing a viable life-saving treatment option for a specific subset of CORONA patients. Itolizumab is not a new investigational drug, having been approved since 2013 for psoriasis. The drug is being repurposed and positioned as a relatively more affordable option for treating CRS in CORONA patients compared with other

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immunomodulatory drugs like tocilizumab, which are also being used off-label [25]. Tocilizumab is still under investigation in various countries including India, at the stage of phase III trials. There is not enough evidence yet from completed studies that these drugs reduce mortality in CORONA patients [26]. Under these circumstances, the recent approval of itolizumab on the basis of a phase II trial has understandably drawn sharp scrutiny from experts. Questions have been raised, mainly regarding the small sample size of the trial, exemption of a larger phase III trial, lack of published data regarding off-label use for corona virus, and substantial claims being made through media without peer review or scientific publication [27]. These arguments have been defended by the company mainly on the basis of the desperate need for treatment to prevent mortality due to complications such as ARDS in seriously ill CORONA patients amidst the burgeoning pandemic, and that their trial successfully fulfilled all scientific and regulatory requirements [28].

Inconsistencies and potential fallacies have been observed by the scientific community pertaining to the study design used and withdrawal of two patients who experienced adverse events on initiation who were not considered randomized and were excluded from the trial analysis; one of these patients later died. Does this breach the principle of intention-to-treat analysis? [29] Moreover, there is confusion whether all 30 patients were actually randomized as it was reportedly stated that the first five participants were given itolizumab sequentially. This was done as per recommendations of the trial's drug and safety monitoring board. It also purportedly led to refusal by the subject expert committee (SEC) of CDSCO to give the emergency approval to itolizumab at an earlier stage in late May 2020 [30]. From the data made available to date, the baseline SpO2 and values of inflammatory markers like CRP, D-dimer, ferritin, and LDH are not known; instead, a difference in proportion of improvement or mean change from baseline has been provided [31]. While all patients were on oxygen at baseline, a higher proportion of patients (40%) were on non-invasive ventilation (NIV) in the control arm at baseline compared with the treatment arm (25%), three of whom eventually went on to have the adverse outcome of death [32].

Discussion

There is no doubt that finding a successful treatment for CORONA that can save lives in this pandemic, which has taken close to 0.9 million lives worldwide to date, is of utmost priority. In this scenario, a biologic agent has been re-purposed, successfully completed a RCT, and received approval for restricted emergency use in a country where cases and mortality due to CORONA are growing exponentially. So, instead of welcoming the approval with open arms, why are so many doubts being raised? This is an issue that needs to be considered and dealt with sensitively, as well as scientifically [33].

The trial that led to itolizumab approval in India was an open-label, multicenter RCT, but the total sample size, being a phase II study, was only 30 patients, of whom only 20 patients actually received the drug. Although the primary endpoint (i.e., mortality at 1 month) was significantly in favor of itolizumab, it cannot be claimed with certainty that this result would

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reflect real-world effectiveness [34]. It is unclear whether a design such as Simon's two-stage design, which can lead to greater confidence in the significance of results obtained even from a smaller size phase II trial, was followed for this trial or not. However, it is to be noted that this type of study design is suitable for a single-arm study [35].

While the sample size may have been sufficient for the primary outcome parameters, the trial is likely to be underpowered for many secondary efficacy parameters; the 'statistically significant' advantage of itolizumab for these parameters does not hold credence. It is also not known what constituted the best standard of care at the sites in the trial or whether steroids were part of the treatment regimens for these patients. This is important in light of the established effectiveness of steroids in patients with moderate to severe CORONA pneumonia. The results are certainly encouraging, and are claimed to have been obtained through fulfilment of the due regulatory requirements, leading the Indian drug regulator to approve the drug for emergency use. The need to conduct a phase III clinical trial has also been waived, allowing the innovator to carry out post-marketing surveillance (phase IV). This adds further to the scrutiny and raises more questions. Typically, phase II trials are designed to evaluate the drug's efficacy in people with the disease being studied along with determining the common short-term adverse effects and risks associated with the drug. They also test different dose regimens of the study molecule to derive the optimal dosage for disease [36]. A phase III trial is a large, multi-center trial considered crucial to proving the efficacy of a drug in a sufficient number of patients compared with placebo or standard of treatment; it provides evidence of clinical and statistical significance of any treatment effects obtained. These questions have perhaps compelled the regulator to instruct the innovator company to revise its proposed phase IV protocol to keep safety as the primary objective, and increase the sample size as well as geographic distribution of study sites [37]. Furthermore, media claims of mortality reduction in CORONA have been made while the results have not yet been peer reviewed and scrutinized within the scientific community. Whether the study was methodologically robust cannot be determined unless the study protocol or the results in their entirety are available. Now there are reports questioning the scientific validity of this phase II trial and pointing out inadequacies in its design. The Cuban regulatory study is non-randomized and single arm (non-controlled); data available for that study is even more scant [38].

It was proclaimed earlier that the real-world data for 'off-label' use of the drug on compassionate grounds will be published; all patients being cured of CORONA. The latest statement claims availability of real-world evidence on 1000 patients. It is being argued that any such real-world data for itolizumab is less likely to include cases that recovered without the use of itolizumab, and it may include only those patients who were successfully treated with the drug, which will not reflect the true results. The lack of confidence in the drug, or rather in the evidence available to date, has been echoed in the exclusion of the drug from the latest clinical management protocol released by the national task force for CORONA in India, and a statement made by the chief of the apex body of medical research in the country.

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However, in Cuba it has been included in the CORONA management protocol since April, before the grant of approval [39].

Itolizumab, which is manufactured in India, is relatively cheaper than other lifesaving options in severe CORONA, such as tocilizumab or remdesivir, and its randomized trial is being touted as 'robust'. However, these justifications have seemingly not been accepted by the scientific community. The approved itolizumab formulation of 25 mg/5 mL costs INR7950 (~ US$105) per vial. The average cost of therapy at a dose of 1.6 mg/kg, comprising four vials, is estimated to be ~ INR32,000 (~ USD425), which is less than the treatment cost with tocilizumab, which varies between INR45,000 and INR50,000 (~ USD600–670) per vial. However, this cost is still high, as only a small proportion of patients in India can access or rather afford this cost for complete treatment where the average per capita monthly income is INR11,254 (~ USD150) [38].

The data and protocols from the drug trials in India and Cuba should be published at the earliest in their entirety; this may assuage many of the doubts and concerns regarding the strength of evidence. Even with the restricted use approval, a phase III trial of the drug should have been directed in India, as for tocilizumab, which is currently undergoing a large phase III trial in the country despite more real-world and randomized data being available for this drug. However, the emergency due to this pandemic has to be considered; the approval given is not complete—the restricted use necessitates fulfilment of important prerequisites of use. The phase II data and the claimed real-world evidence does come entirely from the respective countries of approval, which gives some confidence for the use of the drug [37].

Conclusion:

Itolizumab works by modulating the immune response, reducing inflammation, and preventing cytokine storm, which is a major cause of organ damage and mortality in severe CORONA cases. It has been found to improve oxygenation, reduce the need for mechanical ventilation, and shorten the length of hospital stay in critically ill patients.

The safety profile of Itolizumab appears to be favorable, with minimal adverse effects reported in clinical trials. However, further research is needed to determine its long-term safety and efficacy in a larger population.

While Itolizumab shows promise as a potential therapeutic option for CORONA, it should be noted that it is not a substitute for vaccination and other preventive measures. Vaccination remains the most effective strategy for preventing CORONA and its associated complications.

In conclusion, Itolizumab holds promise as a treatment option for severe CORONA cases, but more research is required to establish its long-term efficacy and safety. As the field of CORONA treatment continues to evolve, it is important to consider multiple approaches and continue to explore new therapies to combat this global health crisis.

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