



Are We Jumping the Gun with Itolizumab in India? A Situational Analysis from the Pre-COVID Era

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Abstract

Itolizumab, an anti-CD6 monoclonal antibody, has been recently approved for the off-label indication of cytokine release syndrome in the background of COVID-19, by the Drug Controller General of India. However, this drug has not been included in the National Clinical Management Protocol for COVID-19 yet. The limited-to-no experience of the Indian health workforce with the drug urged us to conduct a situational analysis in the pre-COVID era to analyse the degree of use of the drug and the indications for which it has been employed.

Keywords Itolizumab · Anti-CD6 monoclonal antibody · COVID-19 · Approved indications · Off-label · Cytokine storm

Introduction

With India surpassing Brazil to take the place of the 2nd most affected country in the world, this populous country has recorded over 71,000 coronavirus disease 2019 (COVID-19) deaths since the beginning of the pandemic as of September 7, 2020 [1]. While the majority of these patients are asymptomatic to mildly symptomatic, around 20% of the affected subset develop symptoms of breathlessness that require oxygen and hospital support [2]. A portion of the admitted cases develop acute respiratory distress syndrome and multi-organ dysfunction within 48 to 72 h. While several risk factors that could modulate the severity of the disease have been identified, activation of several inflammatory pathways that contribute to the cytokine storm has been identified as one of the causal mechanisms. The rise in several inflammatory markers,

a hyper-inflammatory reaction, leads to a fall in saturation and lands the patient in multi-organ dysfunction [3]. Therefore, until a vaccine is available for general use, several medications and biologics have been repurposed in an effort to curtail the cascade of the inflammatory response [4, 5].

One such biologic is itolizumab, a humanized recombinant anti-CD6 monoclonal antibody of immunoglobulin G1 isotype binding to the domain of CD6. Developed in the Centre of Molecular Immunology in Havana, Cuba, it is marketed under the trade name Alzumab™ by Biocon Ltd., Bangalore. Selectively targeting CD6, it is a pan T cell marker that is involved in co-stimulation, adhesion and maturation of T cells. Itolizumab, by virtue of its immunomodulation and its trafficking to the inflammation site, spares Tregs and conserves the antiviral response. The signature cytokines that are reduced include IL-2, IFN γ and TNF α through Th-1 pathway and IL-17, IL-6 and TNF α through Th-17 pathway. This is in contrast to biologics like tocilizumab or anakinra which block only the specific cytokines released downstream [6, 7].

It has been used in moderate-to-severe plaque psoriasis in India since its approval in 2013 by Central Drug Standard Control Organization (CDSCO), Ministry of Health and Family Welfare, Government of India [8]. Biocon Ltd., having collaborated with Equillium in 2017, developed itolizumab in Australia and New Zealand for autoimmune diseases. Itolizumab obtained approval by the US Food and Drug Administration (FDA) for treating aGVHD (acute graft-versus-host-disease) and lupus nephritis [9]. Recently, the drug regulatory of India has approved it for “restricted emergency use” in the background of COVID-19-induced cytokine

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release syndrome. This approval occurred after the regulatory body completely waived off a phase 3 trial, sparking controversy [10].

Despite the Drug Controller General of India (DCGI) approving itolizumab for restricted emergency use based on conditional marketing, the National Task Force for COVID-19 has not included the drug in the National Clinical Management Protocol for the indication of cytokine release syndrome. In some high case-load states like Maharashtra, the drug has been sanctioned for use in place of tocilizumab, if the latter is unavailable or unaffordable. The recent approval of the drug both India (2013) and abroad (2017 in USA) for limited indications, alongside its elevated price point, has limited the experience with this drug among the physicians during the pre-COVID era. Owing to the lack of data on the effect of itolizumab in the Indian population, we aim to explore the use of itolizumab in the pre-COVID era in India by conducting a non-systematic critical appraisal of the situation. We also discuss the basic characteristics of itolizumab in an effort to educate the readers about this home-grown drug, which has been in the limelight recently.

Methods

Study Selection

A search was conducted across the PubMed, medRxiv, biorXiv and arXiv databases with a search strategy that employed keywords such as “Itolizumab” and “India”. We included clinical trials, research studies, case reports and randomized control trials that employed the use of itolizumab at any point in the treatment of Indian patients for conditions other than COVID-19, until September 6, 2020.

In addition, we searched the Clinical Trials Registry of India (CTRI) for relevant trials with itolizumab and recorded the details of the same.

Two independent researches were engaged in the process of screening of articles. Articles were first title-screened. Following this, articles were abstract-screened and thereafter full-text screened. Indian origin studies which were used in data generation of meta-analysis and systematic reviews were also included.

Inclusion Criteria

Indian origin studies (clinical trials, original research, case reports) with patients of both adult and paediatric populations, who received itolizumab at any point during their course of treatment for a condition, were included.

Clinical trials where India was part of a multicentre trial were also included in our study.

Exclusion Criteria

Systematic review, meta-analysis and comments by Indian authors were excluded. Studies released in 2020 pertaining to its use in COVID-19-related conditions were also excluded.

Data Extraction (Selection and Coding)

The details extracted from the screened articles were further documented in Google Sheets. Specific study details such as author and journal details, year of publication, sample size, age and sex of patients, indication for use of itolizumab, duration of treatment and adverse effects were included. Once this data was retrieved, we analysed if the indications for which the drug was administered met with the US Food and Drug Administration guidelines and with the Central Drugs Standard Control Organisation (CDSCO) guidelines.

Statistical Analysis

The data were extracted in Google Sheets in numbers and converted later to percentages.

Results

The PubMed search was conducted on September 6, 2020 (Fig. 1). The search strategy was “Itolizumab AND India” and similar such searches. A total of 19 results were recorded. Studies were screened as per the inclusion criteria. Ten articles did not meet the inclusion criteria and were thereby excluded, including 1 duplicate record. Finally, a total of 9 articles were full-text screened. Summing up the 9 articles, 432 patients received itolizumab in the pre-COVID era for a myriad of indications (Table 1). Majority of these patients were

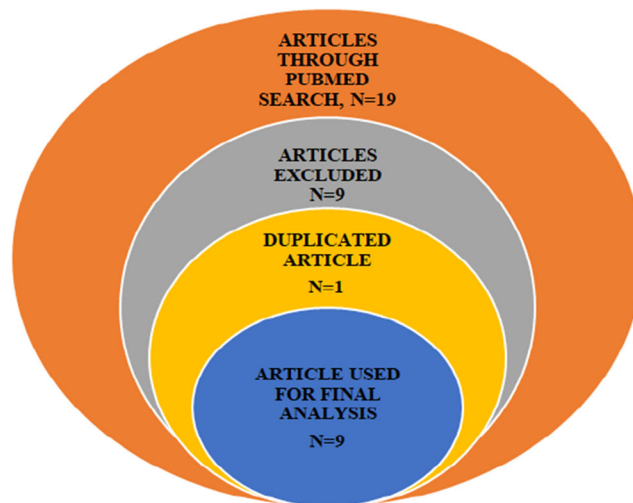


Fig. 1 The search flowchart

Table 1 Articles that met inclusion criteria in PubMed database

S. No	Publication year	Author	Title	Indication
1	2016	Chopra et al. [11]	Itolizumab in combination with methotrexate modulates active rheumatoid arthritis: safety and efficacy from a phase 2, randomized, open-label, parallel-group, dose-ranging study	Active rheumatoid arthritis
2	2017	Pai et al. [12]	Itolizumab - A New Biologic for Management of Psoriasis and Psoriatic Arthritis	Psoriasis and psoriatic arthropathy
3	2014	Krupashankar et al. [13]	Efficacy and safety of Itolizumab, a novel anti-CD6 monoclonal antibody, in patients with moderate to severe chronic plaque psoriasis: results of a double-blind, randomized, placebo-controlled, phase-III study	Chronic plaque psoriasis
4	2016	Parthasaradhi et al. [14]	Safety and Efficacy of Itolizumab in the Treatment of Psoriasis: A Case Series of 20 Patients	Moderate-to-severe psoriasis
5	2017	Parthasaradhi et al. [15]	A Real-World Study to Assess the Effectiveness of Itolizumab in Patients with Chronic Plaque Psoriasis	Chronic plaque psoriasis
6	2017	Parasramani et al. [16]	Itolizumab in the Management of Psoriasis with Metabolic Syndrome	Severe plaque psoriasis
7	2016	Singh et al. [17]	Clinical Outcome of a Novel Anti-CD6 Biologic Itolizumab in Patients of Psoriasis with Comorbid Conditions	Moderate-to-severe psoriasis
8	2019	Gupta et al. [18]	A retrospective case series of 12 patients with chronic reactive arthritis with emphasis on treatment outcome with biologics	Chronic reactive arthritis
9	2016	Gupta et al. [19]	Severe recalcitrant psoriasis treated with Itolizumab, 2a novel anti-CD6 monoclonal antibody	Severe recalcitrant psoriasis

middle-aged with many studies noting a mean age of 40 years. Of the indications, psoriasis was the most commonly noted (plaque psoriasis, recalcitrant psoriasis, psoriatic arthropathy). The only other indications included active rheumatoid arthritis ($n = 60$) and reactive arthritis ($n = 1$). The adverse effects that were noted in these studies are mentioned in Table 2.

The CTRI recorded a total of 2 trials with itolizumab (Titled 1. The use of a novel biological drug to prevent and treat chronic graft rejection in patients who have undergone a bone marrow transplant, 2. Efficacy and safety of itolizumab in COVID-19 complications). However, both the registered trials are yet to be published. Hence, they were not included.

The other databases (medrXiv, arXiv, biorXiv) yielded 0 results as per our search strategy.

Discussion

COVID-19 patients who develop rapid and severe ARDS, organ dysfunction and coagulopathies due to hyperinflammation and cytokine storms currently do not have a definitive cure. Drugs like dexamethasone and biologics like tocilizumab have been approved for an off-label indication of cytokine release syndrome, as they were shown to decrease mortality [20, 21].

A single, repeated-dose toxicity study done in rats revealed that itolizumab was well-tolerated with the no observed adverse effect level (NOAEL) identified as 16 mg/kg/day [22]. The side effect profile of the drug includes infusion reactions, infections, bacterial arthritis, exfoliative dermatitis, erythrodermic psoriasis and anxiety/adjustment disorders. Also, another major limitation that is common to many biologics is the gradual development of anti-idiotypic antibodies leading to decreased serum levels and efficacy of the drug. The use of the drug is avoided in neutropenia, lymphopenia and immunocompromised conditions and contraindicated in the setting of systemic autoimmunity, psoriatic erythrodermic, psoriatic crisis and active or latent tuberculosis [13, 22, 23]. It needs to be borne in mind that guidelines dictate use of the drug only following baseline monitoring including a Mantoux test and routine blood tests. The recommended dosing for its use in treatment in plaque psoriasis is 1.6 mg/kg given as intravenous infusion (mixed with sterile normal saline 250 mL, generally at room temperature) fortnightly for 12 weeks, followed by 1.6 mg/kg every 4 weeks up to 24 weeks [13, 22]. However, for CRS, itolizumab was started at a first dose of 1.6 mg/kg dose, as it showed 99% receptor occupancy. An additional dose of 0.8 mg/kg was administered after 1 week, if needed, to a maximum of 4 weekly doses. The administration of the drug on a need basis was justified owing to the different degrees of host inflammatory response noted

Table 2 Findings in articles that met inclusion criteria

S No	Title	N=	Age	Sex (M/F)	Dose	Duration	Adverse effects
1	Itolizumab in combination with methotrexate modulates active rheumatoid arthritis: safety and efficacy from a phase 2, randomized, open-label, parallel-group, dose-ranging study	60	42–45	F > M	0.2, 0.4, or 0.8 mg/kg; mean dose per week 1.4 mg/week	12 week, 24 week	Pyrexia (14 events), cough (10 events), infusion-related reactions (21 events), anaphylactic reaction, bacterial arthritis, lung infection, hypertension, increase in hepatic enzyme, lupus-like syndrome, decreased appetite, hypernatremia, duodenal stenosis, gastric ulcer, leucopenia and neutropenia No adverse event
2	Itolizumab - A New Biologic for Management of Psoriasis and Psoriatic Arthritis	5	1 M, 4 F	1 M, 4 F	1.6 mg/kg	3 months → maintenance → monthly cycles X 3 months	No adverse event
3	Efficacy and safety of Itolizumab, a novel anti-CD6 monoclonal antibody, in patients with moderate to severe chronic plaque psoriasis: results of a double-blind, randomized, placebo-controlled, phase-III study	182	40–42	M > F	A = 4-week loading dose of 0.4 mg/kg/week followed by 1.6 mg/kg every 2 weeks; B = 1.6 mg every 2 weeks		Infusion reactions and related events, bacterial arthritis, exfoliative dermatitis, erythrodermic psoriasis, adjustment disorder with anxiety, lymph node TB reactivations, exacerbation of psoriasis, neutropenia and depressed mood
4	Safety and Efficacy of Itolizumab in the Treatment of Psoriasis: A Case Series of 20 Patients	20		15 M 5 F	1.6 mg/kg	Fortnight for first X 3 months → by once monthly X 3 months	No adverse event
5	A Real-World Study to Assess the Effectiveness of Itolizumab in Patients with Chronic Plaque Psoriasis	155	40	113 M 42 F	1.6 mg/kg	Every 2 weeks X first 12 weeks → 1.6 mg/kg every 4 weeks for up to 24 weeks	Urticaria (0.64%), nausea (1.29%), vomiting (1.93%), hypertension (0.64%), skin rashes (0.64%), chest pain (0.64%) and fever (1.29%) and diarrhoea.
6	Itolizumab in the Management of Psoriasis with Metabolic Syndrome	1	49	M	1.6 mg/kg	First 7 doses X every fortnight → Last three doses every month	No adverse event
7	Clinical Outcome of a Novel Anti-CD6 Biologic Itolizumab in Patients of Psoriasis with Comorbid Conditions	7	49.8	6 M, 1 F	1.6 mg/kg	Fortnight X first 3 months → monthly for the last 3 months	No adverse event
8	A retrospective case series of 12 patients with chronic reactive arthritis with emphasis on treatment outcome with biologics	1	Na	M	Na	Na	Na
9	Severe recalcitrant psoriasis treated with Itolizumab, a novel anti-CD6 monoclonal antibody	1	22	M	75 mg (1.6 mg/kg in 250 mL of normal saline over 3 h)	Fortnight	No adverse effects

Na Not available

in various patients. Currently, this poses a problem of over-treatment or under treatment as this is at the discretion of the treating physician. This calls for an enhancement in physician's understanding of the drug mechanisms and adverse effects.

However, our study shows that the Indian health workforce has *very* limited experience with the use of itolizumab. While itolizumab seems to have a better safety profile than other biological agents, the safety data has been derived only from two multicentric clinical trials. There exists only a single randomized, double-blind, placebo-controlled comparison study. To fully characterize the drug, larger studies involving bigger sample sizes for longer study duration are needed. In addition, long-term animal studies are pending, which are crucial to assess its carcinogenic or teratogenic potential. Comparison studies with other biological agents are pertinent to better understand the drug's efficacy and use. Safety of itolizumab is not yet established in pregnant and lactating mothers, in children less than 18 years and in patients with significant liver and kidney comorbidities [22].

In the absence of direct head-to-head comparisons, any comments on the safety profile of the drug and its efficacy cannot be made definitively. As the data is too little for the results to be regarded as promising, we exercise caution over the use of this understudied drug and urge clinicians to avoid indiscriminate use based on unwarranted speculations. While the scientific community demands evidence-based recommendations, we need to bear in mind that quality and quantity of evidence are a necessary prerequisite in framing guidelines, even in the most pressing times. As the oath goes, "First, do no harm".

Conclusion

There is an urgent need to enhance the physician's understanding of itolizumab, its mechanisms, actions and side effects, in the background of its use in the pandemic. Owing to its limited use in the past in the Indian scenario and lack of sufficient trials, there might be more to this drug than that meets the eye. This calls for the health workforce to be adequately sensitized about the drug and the reason behind its approval. Lastly, it is the prime duty of all healthcare professionals who choose to employ the drug in the management of COVID-19 cytokine storm, to report any and all adverse events associated with this drug. This will assist in understanding the safety profile of the drug in the Indian subcontinent, anticipate adverse events and aid further change in drug labelling.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent Not applicable; this article does not contain any studies with human participants or animals performed by any of the authors.

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