Efficacy and Safety of Itolizumab for the Treatment of Coronavirus Disease (COVID-19): A Systematic Literature Review

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Background and objectives

Coronavirus disease (COVID-19) is an infectious disease that leads to a hyperinflammatory state known as cytokine release syndrome. Itolizumab is a humanized recombinant anti-CD6 monoclonal antibody that can reduce serum levels of Interleukin 6 (IL-6), tumour necrosis factor-alpha (TNF-α), and interferon-gamma (INF-γ). This study aims to evaluate the efficacy and safety of Itolizumab in COVID-19 patients.

Methodology

- Embase® and MEDLINE® databases are searched via OVID SP platform on 17th June 2022 for studies assessing the efficacy and safety of Itolizumab in Covid-19 patients.
- No limits were applied for publication year.
- Two reviewers independently searched for articles, reviewed, and extracted data, resolving differences through consensus.
- Quality assessment was performed using Cochrane Risk of Bias tool (RoB 2.0)[1] for randomised controlled trials (RCTs) and Downs and Black checklist for non-randomised studies [2].

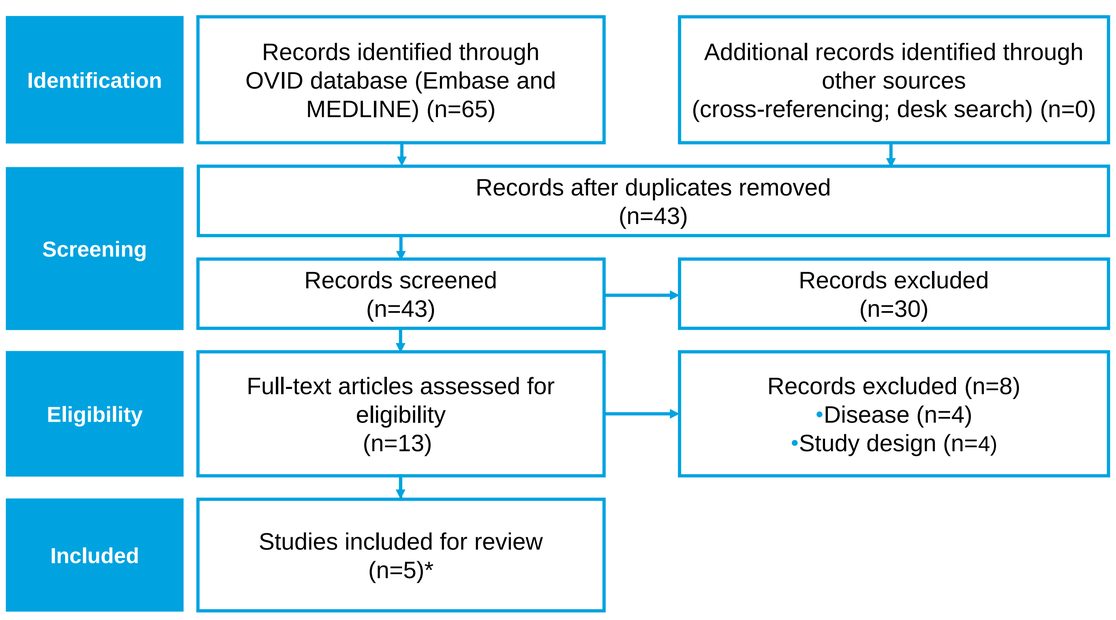
Table 1: *Study eligibility criteria*

PICOS	Inclusion criteria	Exclusion criteria
Populations	Adults (≥18 years old) with Covid-19 patients	Patients below <18 years of age
Interventions	Itolizumab	Interventions not listed in the inclusion criteria
Comparators	No restriction	None
Outcomes	Efficacy and safety outcomes	None
Study designs	Clinical trials/ observational studies	Other studies not listed in the inclusion criteria

Results

- The clinical SLR was conducted in Embase® and MEDLINE® using a pre-designed search strategy applying the PICOS terms, presented in Table 1.
- Out of 43 identified studies, five publications were included (one RCT, three single-arm trials, and one observational study) (Figure 1).

Figure 1: *PRISMA chart of included studies*



*Note: 3 studies (5 publications) included for review

Results

- Kumar et al. 2021 reported no deaths in best supportive care (BSC) plus itolizumab arm compared to BSC alone arm (p=0.0296; 95% CI = -0.3 [-0.61, -0.08])[3].
- Similarly, the combination therapy showed improvements in Oxygen saturation (SpO2) (p=0.0296), partial pressure of oxygen (PaO2) (p=0.0296) and decreased levels of IL-6 (43 vs 212 pg/ml; p=0.0296), TNF-α (9 vs 39 pg/ml; p=0.0253), when compared with BSC alone[3].
- Likewise, single-arm studies of Itolizumab reported a reduction in IL-6: 28.3 pg/mL to 25.9 pg/mL (Diaz et al. 2020)[4], 290.2 pg/mL to 183.1 pg/mL (Saavedra et al. 2020)[5], and 116.3 and 78.8 (Caballero et al. 2020)[6] (Table 2).
- Gore et al. 2020 reported an improved SpO2 from 88% to 96%[7].
- Frequent serious adverse events associated with Itolizumab corresponded to pericardial effusion, hypothyroidism, and airway hyper-reactivity[3].

Table 2: *Serum levels of Interleukin 6 (IL-6)*

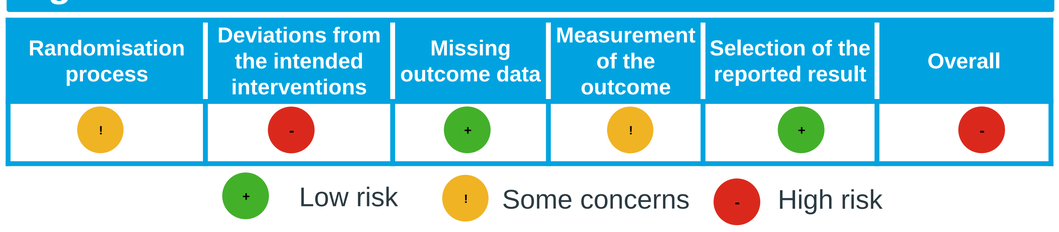
Study Name	Intervention (N)*	Time point (Hours)	Baseline value (pg/ml)	Endpoint value (pg/ml)
Kumar 2021[3]	Itolizumab (20)	48	159.09	43
	Placebo (10)	48	162.16	211.52
Caballero 2020[6] (Diaz 2020[4], Saavedra 2020[5])	Itolizumab (70)[6]	48	28.3	25.9
	Itolizumab (19)[4]	48	290.2	183.1
	Itolizumab (24)[5]	48	116.3	78.8
Gore 2020[7]	Itolizumab (25)	48	113	16.5

* N= Sample size
Note: Kumar 2021 (RCT); Caballero 2020 (Single-arm trial); Gore 2020 (Observational study)

Quality Assessment

- The quality assessment of study NCT04475588 (Kumar et al. (2010))[3] was performed using the revised Cochrane (RoB 2.0) for RCTs (Figure 2). The risk of bias was assessed in five distinct domains, with each answer leading to judgements of “low risk of bias,” “some concerns,’’ or “high risk of bias.’’ The study presented risk of bias stemming from missing outcome data and selection of reported result. High risk of bias was observed in the evaluation of deviations from intended interventions, while some concerns were found in the randomisation process and methods of outcome measurement.
- The overall methodological quality of the single-arm trial (Caballero 2020[6] (Diaz 2020[4], Saavedra 2020[5])) and the observational study (Gore et al. 2020)[7] was “fair” according to the suggested categorisation scheme for the Downs and Black checklist (Supplementary Figure 1).

Figure 2: *Cochrane Risk of Bias*



Conclusion

- Itolizumab demonstrated promising therapeutic activity in reducing hyperinflammatory states in COVID-19 patients along with an acceptable safety profile.
- Further studies in larger populations are needed to ascertain the therapeutic benefit of Itolizumab in COVID-19.

References:
1. Sterne, Jonathan AC, et al. "RoB 2: a revised tool for assessing risk of bias in randomised trials." bmj 366 (2019).
2..Downs, Sara H., and Nick Black. "The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions." Journal of Epidemiology & Community Health 52.6 (1998): 377-384.
3. Kumar, Suresh, et al. "A two-arm, randomized, controlled, multi-centric, open-label phase-2 study to evaluate the efficacy and safety of Itolizumab in moderate to severe ARDS patients due to COVID-19." Expert Opinion on Biological Therapy 21.5 (2021): 675-686.
4. Díaz, Yayquier, et al. "Use of a humanized anti-CD6 monoclonal antibody (itolizumab) in elderly patients with moderate COVID-19." Gerontology 66.6 (2020): 553-561.
5. Saavedra, Danay, et al. "An anti-CD6 monoclonal antibody (itolizumab) reduces circulating IL-6 in severe COVID-19 elderly patients." Immunity & Ageing 17.1 (2020): 1-8.
6. Caballero, Armando, et al. "Treatment of COVID-19 patients with the anti-CD6 antibody itolizumab." Clinical & Translational Immunology 9.11 (2020): e1218.
7. Gore, Vishal, et al. "Itolizumab Treatment for Cytokine Release Syndrome in Moderate to Severe Acute Respiratory Distress Syndrome Due to COVID-19: Clinical Outcomes, A Retrospective Study." J Assoc Physicians India (2021): 13-18.

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