Effects of Infliximab on patients with COVID-19: a systematic review and meta-analysis

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Abstract

Despite the control of the COVID-19 pandemic, it remains one of the main concerns of healthcare systems throughout the world. Inflammation and hyper-reactive immune system play an essential role in developing SARS-CoV-2 infection, particularly in immunocompromised patients. Infliximab, an anti-TNFα antibody that is used in autoimmune disorders, may exert an important role in alleviating inflammation and hyper-reactive immunity. In this systematic review and meta-analysis, we have concluded that Infliximab can significantly decrease the mortality rate in patients with COVID-19. Conversely, it did not have a significant effect on the rate of hospitalization, mechanical ventilation, and adverse events during SARS-CoV-2 infection. More studies on the influence of Infliximab on patients with COVID-19 are warranted.

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Abstract

Despite the control of the COVID-19 pandemic, it remains one of the main concerns of healthcare systems throughout the world. Inflammation and hyper-reactive immune system play an essential role in developing SARS-CoV-2 infection, particularly in immunocompromised patients. Infliximab, an anti-TNFα antibody that is used in autoimmune disorders, may exert an important role in alleviating inflammation and hyper-reactive immunity. In this systematic review and meta-analysis, we have concluded that Infliximab can significantly decrease the mortality rate in patients with COVID-19. Conversely, it did not have a significant

effect on the rate of hospitalization, mechanical ventilation, and adverse events during SARS-CoV-2 infection. More studies on the influence of Infliximab on patients with COVID-19 are warranted.

Introduction

Despite the reduction in the mortality rate of COVID-19, SARS-CoV-2 infection remains one of the major worldwide health concerns, particularly in older adults, unvaccinated individuals, and patients with underlying diseases, or immunocompromised conditions [1]. Few medications with antiviral properties including Nirmatrelvir/Ritonavir (Paxlovid), Remdesivir, and Molnupiravir have been authorized for treatment of mild to moderate COVID-19 in high-risk patients [2]. Because of the detrimental role of inflammation and excessive immune response in COVID-19 patients, it's crucial to lessen the side effects of SARS-CoV-2 infection by pharmacological agents [3]. Accordingly, corticosteroids such as dexamethasone have beneficial effects on hospitalized patients with COVID-19 who need respiratory support [4]. Other therapies for COVID-19 such as monoclonal antibodies, anti-thrombotics, and immunotherapies are also under investigation [5].

Infliximab, a chimeric monoclonal antibody against TNF-α indicated for management of inflammatory/autoimmune disorders like Rheumatoid Arthritis and Psoriasis, has demonstrated promising role in the management of SARS-CoV-2 infection [6].

Current studies on the pathophysiologic mechanisms of COVID-19 propose that hyper-reactive immune response and increased generation of cytokines such as TNF-α, interleukin (IL)-6, IL-2, IL-7, and IL-10 (called cytokine release syndrome) play a pivotal role in worsening the signs and symptoms of this disease [7]. TNF-α, one of the essential pro-inflammatory cytokines during cytokine release syndrome, intensifies the severity of COVID-19 infection mainly through inducing interaction of the SARS-CoV-2 with angiotensin-converting enzyme 2 (ACE-2) in respiratory system, cytokine release syndrome [7], and auto-immune response [8]. Therefore, TNF-α is a potential target in COVID-19 patients with inappropriate activity of immune system and may lead to better management of this infection [9]. Infliximab binds to TNF-α and thereby inhibits the biological activity of soluble and transmembrane forms of this inflammatory cytokine [10]. Infliximab can also lyse inflammatory immune cells through binding transmembrane TNF-α and subsequently impair the excessive inflammatory response [11].

Herein, we set out a systematic review and meta-analysis on the role of Infliximab in terms of its effectiveness, and safety in the management of COVID-19.

Method

This review was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline which is an evidence-based protocol for rapid review of major studies.

Literature search

A literature searches of the full text or abstracts available on PubMed, Cochrane Library, Web of Science, medRxive, and Google Scholar was conducted to identify relevant evidence through September 20, 2023. A reference list of studies was scanned for additional citations. In addition, we searched clinical trial databases including ClinicalTrials.gov and the European Union Register of Clinical Trials to discover additional records. All these steps were conducted by two authors independently. There was no restriction on language. The key search terms used were SARS-CoV-2, COVID-19, Infliximab, safety, and efficacy. The search strategy used in PubMed is as follows: (Coronavirus[Title/Abstract]) OR (Coronavirus [MeSH Terms]) OR (COVID-19 [Title/Abstract]) OR (SARS-CoV-2 [Title/Abstract]) OR (COVID-19[MeSH Terms]) OR (SARS-CoV-2 [MeSH Terms]) OR (2019 novel coronavirus infection[Title/Abstract]) OR (2019-nCoV infection[Title/Abstract]) AND (Infliximab [Title/Abstract] OR (Remicade [Title/Abstract]).

Study selection

We included studies if they fulfilled the following criteria: Patients with a confirmed diagnosis of COVID-19

Intervention: Infliximab

Control: placebo, standard of care (SOC), any treatment

Efficacy outcomes of interest: mortality rate, need for mechanical ventilation, and ICU admission

Safety outcomes of interest: the incidence of any adverse events (AEs)

The studies which conducted on animal models, case reports, case series, and letters to the editor were excluded.

Data Extraction and Quality Assessment

Two of the five review authors extracted data independently and in duplicate, using a customized data extraction form developed in Microsoft Excel (Microsoft Excel). Disagreements during the review process were resolved through discussion between the two review authors. In cases where consensus could not be reached, a third review author was consulted to help resolve the disagreement and make a final decision. The Risk of Bias in Non-Randomized Interventions (ROBINS-I) tool was used to assess the quality of non-randomized studies (table 2). The Risk of Bias (RoB2) tool was also used to assess the quality of randomized studies (table 3). We used the same data extraction form to extract the data. We extracted data including (1) study characteristics (author, year, place, and study design); (2) patient's characteristics (sample size, and sex); (3) intervention and comparison (sample size and treatment dose); and (4) safety outcomes. All steps stated above were performed independently by two authors.

Evidence synthesis

Comprehensive Meta-analysis software is used to compare the efficacy and safety of and control. The Odds ratio (OR) with 95% confidence interval (CI) was used for dichotomous variables. We conducted a pairwise meta-analysis for our analysis and reported summary effect estimates along with 95% confidence intervals (CIs) for each direct comparison. We included studies that provided data for at least two comparisons. The heterogeneity is defined as I2>50% and P <0.1. The random and fixed effect models were used for high and low heterogeneity studies, respectively.

Results

3.1 Search findings

The identification of evidence, removal of duplicated records, screening by title, abstract, and full text, eligibility, and final inclusion process is depicted in Figure 1. A total of 138 articles were identified in the literature search. Following screening by title and abstract, 8 studies underwent full-text review. Three studies were excluded due to combination treatment and irrelevant reported outcomes, resulting in five articles being included in the study. Table 1 presents the main characteristics of the included studies. We implemented a meta-analysis on the role of Infliximab in COVID-19 patients within the investigations of Farrokhpour et. al., and Stallmach et. al., O'Halloran et. al., (randomized double blind clinical trial),

Taleng et. al. (observational studies), Fisher et. al., (randomized open-label clinical trial), (retrospective cohort study) [12] [13] [14, 15]. These studies compared Infliximab with various treatment interventions.

Efficacy outcomes

Mortality rate

A total of five studies involving 1224 patients reported cases of death among COVID-19 patients receiving Infliximab or no Infliximab. The pooled analysis of these studies revealed no significant difference in mortality rates between the Infliximab and no Infliximab groups (RR= 0.70, 95% CI: 0.53 to 0.91; P < 0.001, I2 = 0%) (Figure 2).

Hospitalization rate

The combined estimate from two studies indicated no significant difference in ICU admission between the Infliximab and no Infliximab groups (RR= 0.37, 95% CI: 0.11 to 1.16; P = 0.09, I2 = 20%) (Figure 3).

Need for Mechanical Ventilation

Three studies reported on the need for mechanical ventilation in patients treated with Infliximab and no Infliximab. The meta-analysis demonstrated no significant difference between the Infliximab and no Infliximab groups in terms of need for mechanical ventilation (RR= 0.98, 95% CI: 0.65 to 1.48; P = 0.94, I2 = 30%) (Figure 4).

ICU Admission

The combined estimate from three studies showed no significant difference in ICU admission between the Infliximab and no Infliximab groups (RR= 0.92, 95% CI: 0.67 to 1.26; P = 0.61, I2 = 30%) (Figure 5).

Adverse events

The pooled estimate from two studies indicated no significant difference in the incidence of adverse events between the Infliximab and no Infliximab groups (RR= 1.09, 95% CI: 0.79 to 1.51; P = 0.51, I2 = 56%) (Figure 6)

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Discussion

Other indices including the rate of adverse events, hospitalization, mechanical ventilation, and ICU admission were not statistically significant between the two groups.

The impact of Infliximab on mortality rate of COVID-19 patients:

Our meta-analysis has revealed that Infliximab administration could significantly decrease the mortality rate compared to non-infliximab group in patients with SARS-CoV-2 infection.

According to Kokkotis et. al., meta-analysis, anti-TNFα treatment has helpful effects in terms of reducing the risk of hospitalization and severe COVID-19 in patients with underlying inflammatory disease [16]. Tocilizumab, a kind of anti- TNFα which primarily used in Rheumatoid disorders, could also decrease all-cause mortality in 6481 individuals with generally severe, non-critical COVID-19 infection based on Avni et. al., meta-analysis [17]. Based on Halim et. al., meta-analysis, the mortality rate in COVID-19 patients is strongly correlated with higher levels of serum concentrations of TNF-α. Each 1 picogram (pg)/mL surge in TNF-α level significantly increases the risk of mortality rate in patients with COVID-19 according to this study (with crude hazard ratio = 1.0640; 95% CI: 1.0259–1.1036; p = 0.0009) [18]. Baricitinib, a Janus kinase (JAK) inhibitor primarily used in moderate to severe active rheumatoid arthritis, could significantly decrease the 28-day mortality rate of COVID-19 in hospitalized patients rather than standard treatment (RR, 0.69, 95% CI, 0.50–0.94, p = 0.02, i2 = 64.86%) [19]. According to Amstutz et. al., meta-analysis remdesivir reduces the mortality rate in hospitalized patients with COVID-19 who needed no or conventional respiratory oxygen support. In this study, 662 (12·5%) of 5317 patients of remdesivir group and 706 (14·1%) of 5005 patients of no remdesivir group died (aOR 0·88, 95% CI 0·78-1·00, p=0·045). However, the results of the study were not influential enough to recommend remdesivir for ventilated patients with COVID-19 (aOR 1·10 [0·88-1·38]) [20].

According to Gohda et. al., study which utilized multivariate logistic regression analysis, the mortality rate in patients with COVID-19 were correlated with increased serum levels of TNFR1 and TNFR2 (p value = 0.08, p value = 0.03, respectively) [21]. Combination of Infliximab with tocilizumab has superior therapeutic

function rather than tocilizumab alone in decreasing mortality rate and serum levels of inflammatory factors in hospitalized patients with severe Covid-19 [22]. According to CLARITY study, levels of antibodies against SARS-CoV-2 and anti- SARS-CoV-2 immune reactivity can be declined by administration of Infliximab in patients with inflammatory bowel disease (IBD) [23].

Infliximab and rate of adverse events in COVID-19 patients:

The rate of adverse events was not statistically significant between the two groups according to our study.

According to Hernandez et. al., meta-analysis, the adverse effects of monoclonal antibodies on hospitalized patients with COVID-19 was uncertain (RR 1.31; 95% CI, 1.02-1.67; I2 = 77%). In non-hospitalized patients, monoclonal antibodies could marginally decrease the serious adverse events (RR 0.47; 95% CI, 0.22-1.01; I2 = 33%) [24]. The risk of any adverse events (OR, 0.90; 95% CI: 0.79–1.03; p = 0.14) and drug-related adverse events (OR, 1.43; 95% CI: 0.85–2.41; p = 0.18) in the three groups of non-hospitalized patients with COVID-19 managed by nirmatrelvir plus ritonavir, remdesivir, and molnupiravir were similar to placebo counterparts based on Lai et. al., meta-analysis [25].

Infliximab and rate of hospitalization in COVID-19 patients:

The rate of hospitalization was not statistically significant between the two groups based on our meta-analysis.

Monoclonal antibodies have desirable effects in terms of decline in hospitalization of outpatients with COVID-19 (RR 0.30; 95% CI, 0.17-0.53; I2 = 0%) [24]. Both baricitinib and tocilizumab decrease the length of hospitalization in hospitalized patients with COVID-19 (baricitinib: mean difference, -1.13 days (95% CI, -1.51 to -0.76), $p < 0.001$, i2 = 0.00%; tocilizumab: mean difference, -2.80 days (95% CI, -4.17 to -1.43), $p < 0.001$, i2 = 55.47%) and also result in significant clinical recovery of them by day 28 (baricitinib: RR, 1.24 (95% CI, 1.03–1.48), $p = 0.02$, $i^2 = 27.20\%$; tocilizumab: RR, 1.41 (95% CI, 1.12–1.78), $p < 0.001$, $i^2 = 34.59\%$) in comparison with standard care [19]. Lai et. al., network meta-analysis revealed that nirmatrelvir plus ritonavir treatment had the least risk of hospitalization or death (OR, 0.12; 95% CI: 0.06–0.24), following remdesivir (OR, 0.13; 95% CI: 0.03–0.57) and molnupiravir (OR, 0.67; 95% CI: 0.46–0.99) in non-hospitalized patients with SARS-CoV-2 infection compared with placebo treatment [25].

According to Halim et. al., meta-analysis, the risk of COVID-19 infection severity is insignificantly associated with higher serum levels of TNF-α. The results of this study also indicated that every 1 picogram (pg)/mL surge in TNF-α level is correlated with severity of COVID-19 infection (with adjusted odds ratio = 1.0304; 95% CI: 0.8178-1.2983; p value = 0.80) [18].

Infliximab and rate of ICU admission in COVID-19 patients:

The rate of ICU admission was not statistically significant between the two groups according to our study.

Based on Gohda et. al., retrospective study, the ICU-admitted patients with SARS-CoV-2 infection had significantly increased blood concentrations of Tumor Necrosis Factor receptor 1 and 2 (TNFR1, 2) rather than patients who did not hospitalize in ICU section after adjustment the confounding factors [21].

Infliximab and rate of mechanical ventilation in COVID-19 patients:

The rate of mechanical ventilation was not statistically significant between the two groups according to this meta-analysis.

Monoclonal antibodies could slightly decrease the rate of mechanical ventilation in hospitalized patients with COVID-19 (relative risk 0.74; 95% confidence interval [CI], 0.60-0.9; I2 = 20%) [24].

Infliximab may potentially induce pulmonary complications like non-infectious interstitial lung disease and thereby should be cautiously prescribed in patients with SARS-CoV-2 [26].

Limitations of this study

Interpretive bias may occur due to the different study methods reported in the clinical articles (which are used in our meta-analysis) [27]. The other limitation of our study is the limited numbers of meta-analysis that investigated the impact of infliximab on COVID-19 patients.

Conclusion

We conclude that Infliximab exerts favorable impact in terms of lowering the mortality rate of SARS-CoV-2 infection. More studies on the effects of Infliximab on severe COVID-19 should be conducted [28].

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Table 1

SARS-COV-2 variant	COVID-19 vaccination rate (%)	Control(s)	Intervention	M	N	D
		SOC	Infliximab	17	24	C
		Control; IVIg; infliximab + IVIg	Infliximab	68	104	C
		Placebo	Infliximab	40	69	R
		Placebo	Infliximab	637	1061	R
		SOC	Infliximab	50	190	o

Abbreviations: M, male, N, number; NR, not reported; RCT, randomized controlled trial; SOC, standard of care

Table 2 Risk of bias of included studies (ROBINS-I)

Study	Confounding	Selection	Classification of interventions	deviations from intended interventions	Missing Data	Measurement of outcomes	Reported Result	Overall
Farrokhpour,2021	Serious	Serious	Moderate	Moderate	Low	Moderate	Moderate	Serious
Taleng,2021	Serious	Serious	Moderate	Moderate	Low	Moderate	Moderate	Serious
Stallmach, 2020	Serious	Serious	Moderate	Moderate	Low	Moderate	Moderate	Serious

Table 3 Risk of bias of included studies (RoB2)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blindi
Fisher,2021	Low	Unclear	Unclear	high
O'Halloran,2023	Low	Unclear	Low	Low

Figure 1

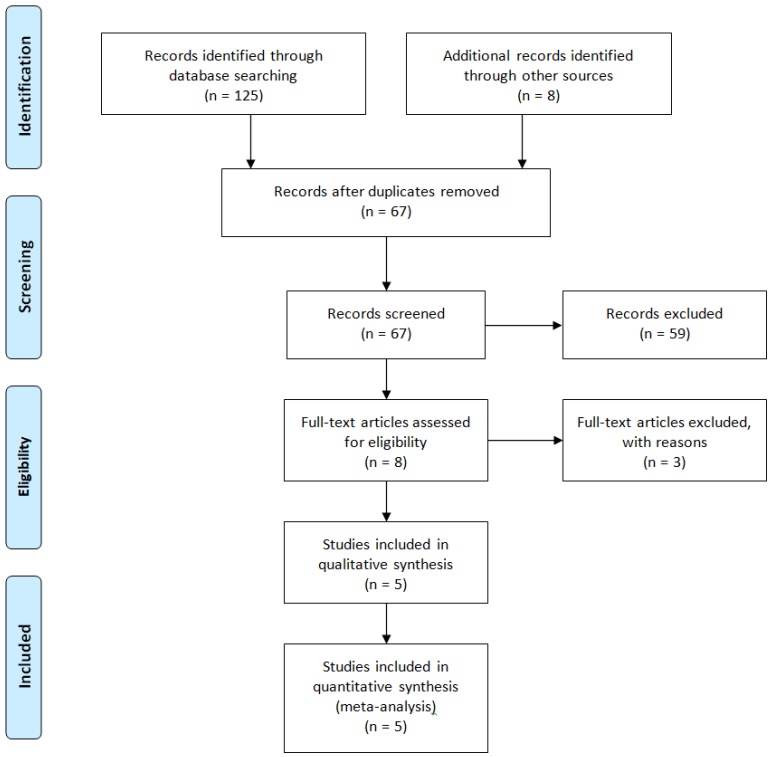

Figure 1. PRISMA flow diagram of study selection process

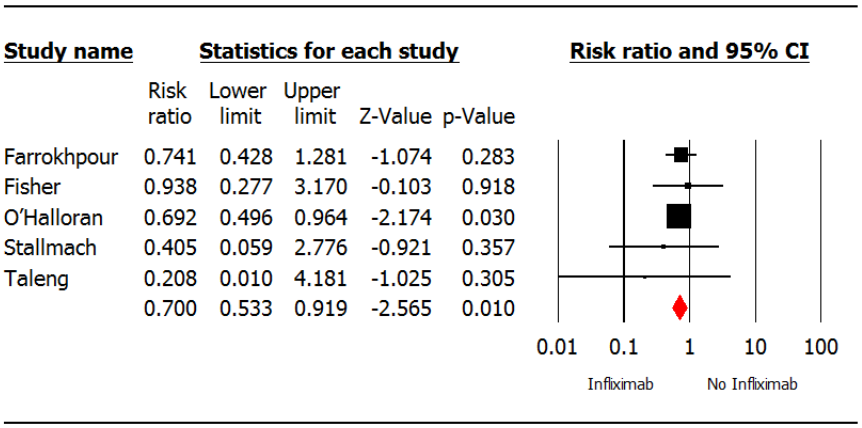

Figure 2 Forest plot of Infliximab versus control group for outcome of mortality rate

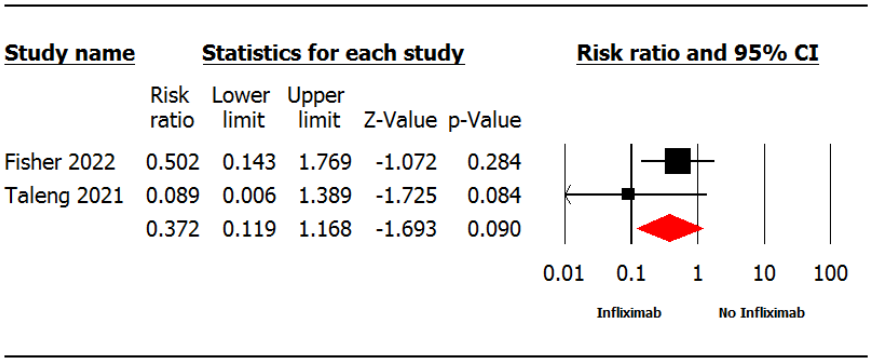

Figure 3 Forest plot of Infliximab versus control group for outcome of hospitalization rate

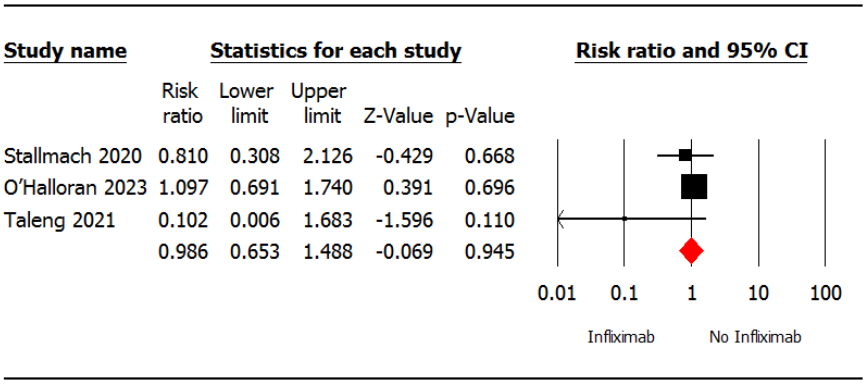

Figure 4 Forest plot of Infliximab versus control group for outcome of Need for mechanical ventilation

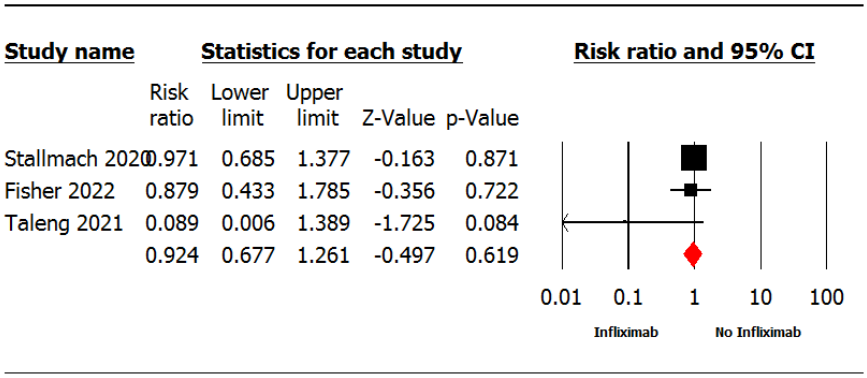

Figure 5 Forest plot of Infliximab versus control group for outcome of ICU admission

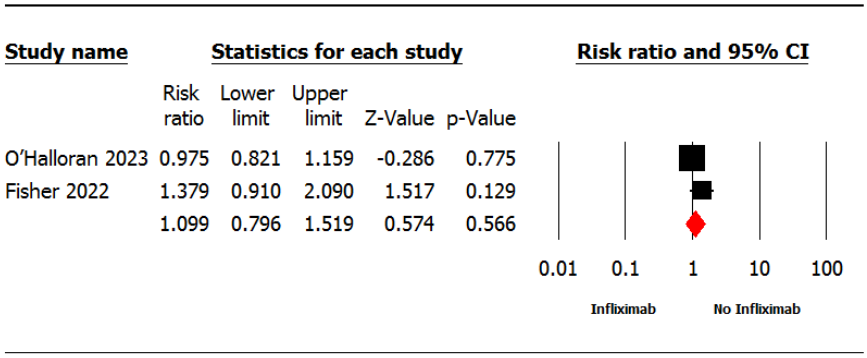

Figure 6 Forest plot of Infliximab versus control group for outcome of Adverse Events