EVIDENCE SUMMARY

Among COVID-19 patients, should infliximab be used for treatment?

Evidence reviewers: Daniel Y. Guevara, MD, Carol Stephanie C. Tan-Lim, MD, MSc (Clinical Epidemiology)

RECOMMENDATION

We suggest against the use of infliximab among patients with COVID-19 infection *(Very low quality of evidence; Weak recommendation)*

Consensus Issues

The recommendation against the use of infliximab among patients with COVID-19 was made based on a small, pre-print randomized controlled trial (n = 63), which did not show any benefit on mortality, hospital discharge within 28 days, and time to clinical improvement. The panel also emphasized that the infliximab arm of the study was prematurely terminated due to futility on interim analysis, explaining its small sample size.

Key Findings

There is one (1) pre-print randomized controlled trial (RCT) that reported the effect of infliximab compared to standard of care as treatment for patients with COVID-19. Results of the RCT showed no significant difference in mortality, hospital discharge in 28 days, and time to improvement in the WHO clinical progression scale. The RCT suffered from lack of allocation concealment, blinding, and poor comparability of treatment groups. It was also terminated prematurely due to futility. The very serious risk of bias and imprecision contributed to the downgrading of evidence to a very low certainty of evidence.

Introduction

Tumor necrosis factor (TNF) plays an important role in the pathogenesis of acute inflammatory reactions.[1] TNF, produced mainly by macrophages, activates signaling pathways that lead to the production of inflammatory cytokines (IL-1, IL-6) and chemokines (IL-8), inhibition of regulatory T-cells, and induction of apoptosis.[1] Infliximab is a TNF-alpha inhibitor approved for the treatment of various inflammatory conditions such as rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and inflammatory bowel disease.[1]

Among COVID-19 patients, levels of IL-6 and TNF-alpha are significantly elevated and are strong predictors of survival.[2-4] Anti-TNF therapy has also been shown to reduce the pathologic changes of viral pneumonia in preclinical studies.[5] These observations provide the rationale for anti-TNF therapy to reduce lung inflammation and improve clinical outcomes in COVID-19.[6]

Review Methods

A systematic search was done in Pubmed, Cochrane Library, and Google Scholar using free text and MeSH terms for coronavirus infections, novel coronavirus, COVID-19, SARS-CoV-2, and infliximab. Preprints were sought using the medrxiv, biorxiv, and chinarxiv databases. Ongoing studies were also searched including *clinicaltrials.gov*, EU Clinical Trials Register, Cochrane

COVID-19 study register, and other trial registries. The COVID-NMA Initiative was also searched. Manual search of cross-referenced materials was also done.

All studies that compared infliximab to placebo or standard of care in treating patients with confirmed COVID-19 infection were included. Eligible studies should have at least one of the following outcomes: mortality, clinical deterioration, development of ARDS, need for mechanical ventilation or ECMO, need for ICU admission, ICU/hospital length of stay, time to clinical improvement/recovery, radiographic improvement, virologic clearance by RT-PCR test, and adverse effects. For this initial review, no limits were placed on disease severity, and age. Subgroup analysis by disease severity, oxygen requirement, and age was planned.

Results

The initial search yielded 77 articles. After review of the search output, we retrieved 1 RCT with a total of 63 patients. The RCT is a pre-print and was done in UK. It involved hospitalized patients with features strongly suggestive of COVID-19 pneumonia, with or without a positive RT-PCR assay. Infliximab (single infusion of 5 mg/kg) as add-on to standard therapy was compared to standard therapy alone. Standard therapy included the administration of corticosteroids, tocilizumab, and remdesivir. Outcomes of interest were mortality, hospital discharge status at day 28, improvement in WHO clinical progression scale, and adverse events.[7] Appendix 3 summarizes the characteristics of the included studies.

The overall quality of evidence was rated very low because of very serious risk of bias and imprecision. The RCT suffered from lack of allocation concealment, blinding, and poor comparability of treatment groups with consequent selection, performance, and detection bias. During the course of recruitment, the RCT also changed one of its inclusion criterion from low oxygenation status to high CRP levels. The authors also changed the primary outcome during the recruitment phase from oxygenation status to CRP levels, stating that oxygenation status was not a viable outcome measure of sickness. On interim analysis, the infliximab arm of the RCT was discontinued due to futility.[7] The GRADE evidence profile is in Appendix 5.

Results of the RCT showed no significant difference in the use of infliximab compared to standard of care in reducing mortality (RR 0.94; 95% CI 0.28-3.17) and hospital discharge within 28 days (RR 1.17, 95% CI 0.85-1.62).[7] There was also no significant difference in the median time to improvement in the WHO clinical progression scale (infliximab group median 15 days, 95% CI 6-21; control group median 10 days, 95% CI 6-14).

Adverse events

There was no significant difference in the risk for adverse events (RR 1.00, 95% CI 0.66-1.51). The most common adverse events noted were hypoalbuminemia, elevated ferritin, azotemia, and leukocytosis.[7]

Recommendations from Other Groups

Table 1. Summary of Recommendation from other Groups

Regulatory Agency	Recommendation
Australian Guidelines for COVID-19 (version 42.0)	Recommends the use of anti-TNF therapy (infliximab) as a third-line option in children and adolescents with Pediatric Inflammatory Multisystem Syndrome who do not respond to intravenous immunoglobulin and corticosteroids.[11] However, outside of this indication, no recommendation exists for infliximab use in COVID-19 infection.[11]
Surviving Sepsis Guidelines	No recommendation for infliximab as treatment in COVID-19 infection.[12]
Infectious Diseases Society of America (IDSA)	No recommendation for infliximab as treatment in COVID-19 infection.[13]
World Health Organization (WHO)	No recommendation for infliximab as treatment in COVID-19 infection.[14]
National Institutes of Health (NIH)	No recommendation for infliximab as treatment in COVID-19 infection.[15]

Research Gaps

There are six (6) ongoing studies registered in different trial registries. Five studies involve adults with severe COVID-19, while one study involves pediatric patients with MIS-C. Infliximab is either a sole intervention or part of a multi-arm treatment group involving other biological therapies such as abatacept, anakinra, cenicriviroc, gemtuzumab, namilumab, and tocilizumab. An update of this review will be done once results of these trials are available.

References

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Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N = 8)

FACTORS	JUDGEMENT					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS	
Problem	No	Yes (8)				• COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity.	
Benefits	Large	Moderate	Small (5)	Trivial (1)	Uncertain (2)	• 1 small pre-print RCT (n = 63) showed that there was no significant difference in the use of infliximab compared to standard of care in reducing mortality (RR 0.94, 95% CI 0.28-3.17) and hospital discharge within 28 days (RR 1.17, 95% CI 0.85-1.62).	
Harm	Large (1)	Small (5)	Trivial (1)	Uncertain (1)		• There was no significant difference in the risk for adverse events (RR 1.00, 95% CI 0.66-1.51).	
Certainty of Evidence	High	Moderate	Low (2)	Very low (6)		• Very low because of very serious risk of bias and imprecision.	
Balance of effects	Favors drug (1)	Does not favor drug (5)	Uncertain (2)			• Although infliximab showed no increase in harm, it had no significant effect on mortality, discharge status within 28 days, and time to clinical improvement. • One panelist also emphasized that recruitment was prematurely terminated due to futility on interim analysis, explaining the study's small sample size.	
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability (3)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost (8)	Moderate Cost	Negligible cost	Moderate savings	Large savings	• For a 5 mg/kg single infusion, 2-3 vials are needed per treatment course, amounting to Php 78,711 (biosimilar) –173,216.40 (Remicade)
Certainty of evidence of required resources	No included studies (1)	Very low (1)	Low (3)	Moderate (1)	High (2)	• Cost is from personal communication with local distributor and outpatient pharmacy of private hospital (available online)	

Cost effectiveness	No included studies (3)	Favors the comparison (4)	Does not favor either the intervention or the comparison (1)	Favors the intervention		• None of the included trials assessed cost effectiveness.
Equity	Uncertain (3)	Reduced (1)	Probably no impact (2)	Increased (2)		
Acceptability	Uncertain (7)	No (1)	Yes			
Feasibility	Uncertain (5)	No (2)	Yes (1)			

Appendix 2. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (“Infliximab” [Mesh] OR infliximab)	Sept. 1, 2021 9:00 PM	57	0
CENTRAL	{MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees OR MeSH descriptor: [COVID-19] OR coronavirus OR novel coronavirus OR NCOV OR covid19 OR covid 19 OR covid-19 OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND MeSH descriptor: [Infliximab] explode all trees OR infliximab	Sept. 1, 2021 9:45 PM	11	0
COVID-NMA Initiative	Infliximab	Sept. 1, 2021 10:00 PM	1	0
Google Scholar	Infliximab AND COVID	Sept. 1, 2021 10:30 PM	8	0
ClinicalTrials.gov	Infliximab AND COVID	Sept. 1, 2021 11:15 PM	8	0
Chinese Clinical Trial Registry	Infliximab AND COVID	Sept. 1, 2021 11:45 PM	0	0
EU Clinical Trials Register	Infliximab AND COVID	Sept. 1, 2021 11:50 PM	5	0
Republic of Korea - Clinical Research Information Service	Infliximab	Sept. 2, 2021 12:00 AM	4	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Infliximab	Sept. 2, 2021 12:15 AM	165	0

CenterWatch	Infliximab AND COVID-19	Sept. 2, 2021 12: 25 AM	2	1
Cochrane COVID-19 study register	Infliximab AND COVID-19	Sept. 2, 2021 12: 30 AM	55	6
chinaxiv.org	Infliximab	Sept. 1, 2021 10:43 PM	0	0
Medrxiv.org	Infliximab AND COVID	Sept. 1, 2021 10:45 PM	59	1
Biorxiv.org	Infliximab AND COVID	Sept. 1, 2021 11:00 PM	13	0

Appendix 3. Characteristics of Included Studies

Study ID	Patients (n) & Duration of Follow-up	Interventions	Outcomes	Method
Namilumab or infliximab compared to standard of care in hospitalized patients with COVID-19 (CATALYST): a phase 2 randomized adaptive trial [7] *Fisher et al, 2021 (UK)* *Pre-print*	N = 63* Patients ≥16 years old with a clinical picture strongly suggestive of COVID-19 pneumonia (with or without a positive RT-PCR) and CRP ≥ 40 mg/L Duration of follow-up: Up to 28 days after discharge	Experimental group 1: Namilumab 150mg Experimental group 2: Infliximab 5 mg/kg Control: Standard care	Primary outcome: change in CRP levels Secondary outcomes: WHO clinical progression scale, mortality, adverse events, and hospital discharge status at day 28	Randomized, open label

**For the infliximab arm and its corresponding control group*

Appendix 4. Study Appraisal

* No p-value for baseline characteristics; number of confirmed COVID-19 patients higher in Infliximab arm; more patients in the control received Remdesivir

Study	Randomization	Allocation concealment	Similar baseline characteristics	Blinding (participants/ personnel)	Blinding of outcome assessment	Intention-to-treat analysis	Adequate follow-up	Other bias
Fisher 2021	Yes	No	No *	No	No	No	Yes	COVID diagnosis may be done through imaging only

Appendix 5. GRADE Evidence Profile

Author(s): Daniel Y. Guevara, MD; Carol Tan-Lim, MD, MSc (clinical epidemiology)
Question: Infliximab compared to Standard care for COVID-19 infection
Setting: In-hospital
Bibliography: 1. Fisher B, et al. Namilumab or infliximab compared to standard of care in hospitalized patients with COVID-19 (CATALYST): a phase 2 randomized adaptive trial. preprint doi: https://doi.org/10.1101/2021.06.02.21258204 2. Farrokhpour M, et al. Infliximab and Intravenous Gammaglobulin in hospitalized severe COVID-19 patients in intensive care unit. Arch Iran Med. February 2021; 24 (2): 139-143 doi: 10.34172/aim.2021.22 3. Stallmach A, et al. Infliximab against severe COVID-19-induced cytokine storm syndrome with organ failure - a cautionary case series. Crit Care. 2020 Jul 17;24(1):444. doi: 10.1186/s13054-020-03158-0

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Infliximab	Standard care	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 28 days)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	4/29 (13.8%)	5/34 (14.7%)	**RR 0.94** (0.28 to 3.17)	**9 fewer per 1,000** (from 106 fewer to 319 more)	⨁◯◯◯ VERY LOW	CRITICAL
Hospital discharge status at 28 days (follow up: 28 days)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	22/29 (75.9%)	22/34 (64.7%)	**RR 1.17** (0.85 to 1.62)	**110 more per 1,000** (from 97 fewer to 401 more)	⨁◯◯◯ VERY LOW	CRITICAL
Time to improvement in WHO clinical progression scale												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	No significant difference in median time to improvement in the WHO clinical progression scale (infliximab group median 15 days, 95% CI 6-21; control group median 10 days, 95% CI 6-14)				⨁◯◯◯ VERY LOW	IMPORTANT
Adverse events (follow up: 28 days)												
1	randomised trials	very serious [a]	not serious	not serious	serious [b]	none	17/29 (58.6%)	20/34 (58.8%)	**RR 1.00** (0.66 to 1.51)	**0 fewer per 1,000** (from 200 fewer to 300 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Lack of allocation concealment, blinding, and poor comparability of treatment groups. Change in primary outcome done during the recruitment phase
b. Wide confidence interval due to very small study size

Appendix 6. Characteristics of Ongoing Studies

Study Title	Patients (n)	Interventions	Outcomes	Method
A Randomized, Controlled, Multicenter, Open Label Phase II Clinical Study to Evaluate Infliximab in the Treatment of Patients With Severe COVID-19 Disease (INFLIXCOVID)	Age ≥ 18 years with severe COVID-19 • Bipulmonary infiltrates • COVID inflammation score ≥ 10 • Ferritin ≥ 500 ng/mL • O2 sat ≤ 93% N = 88	Experimental: Infliximab 5 mg/kg (1 dose) Control: Standard of care	Primary outcome: 28-day mortality Secondary outcomes: • 90-day mortality • ARDS occurence • Ventilation-free days • RRT-free days • Vasopressor-free days • ICU admission • ICU length of stay • Hospital length of stay • WHO COVID-19 progression scale • Incidence of cardiomyopathy • Health-related quality of life index • Changes in IL-6, Ferritin, lymphocyte count • Safety	Randomized parallel assignment, open label
Immune Modulators for Treating COVID-19 (ACTIV-1 IM)	Age ≥18 years with confirmed COVID-19 + one of the following: • Radiographic infiltrates • O2 sat ≤ 94% • O2 requiring (including MV, ECMO) N = 2,160	Experimental group 1: Infliximab 5 mg/kg (1 dose) + remdesivir Experimental group 2: Abatacept 10 mg/kg up too 1000mg (1 dose) + remdesivir Experimental group 3: Cenicriviroc 450mg LD (D1) then 150mg BID (D2-29) + remdesivir Control: Standard of care + matching placebo + remdesivir	Primary outcome: Time to recovery by day 29 Secondary outcomes: • Mortality rate • Number of patients hospitalized on MV • Clinical improvement (8-point clinical scale) • Decline in oxygen supplementation • Number of patients needing non-invasive ventilation/high flow O2	Randomized controlled trial

			• Hospital length of stay • Changes in abnormal WBC counts • Adverse events	
A randomised phase II proof of principle multi-arm multi-stage trial designed to guide the selection of interventions for phase III trials in hospitalised patients with COVID-19 infection (CATALYST)	Age ≥16 years with severe COVID-19 • O2 sat ≤ 94% • PF ratio ≤ 300 • Requiring MV N = 168	Experimental group 1: Gemtuzumab Ozogamicin (3 doses: D1, D5, D10) Experimental group 2: Namilumab Experimental group 3: Infliximab Control: Standard of care	Primary outcome: SpO2/FiO2 ratio Secondary outcomes: • Survival • Hospital discharge • Hospital length of stay • WHO progression scale • RR, Temp • CRP • Adverse events	Randomized controlled trial
Infliximab effectiveness in COVID-19 patients	Confirmed COVID-19 with O2 sat < 88%, high inflammatory markers N = 40	Experimental group: Infliximab 4 mg/kg (1 dose) Control: Matching placebo + usual care	Changes in: Blood oxygen levels, WBC count, ferritin, D-dimer, and CRP	Randomized controlled trial

MIS-C Comparative Effectiveness Study (MISTIC)	Age ≤20 years Current or recent COVID-19, suspected COVID-19 exposure with MIS-C N = 180	Experimental group 1: Infliximab 10 mg/kg (1 dose) Experimental group 2: Methylprednisolone 2 mg/kg IV or orally divided every 12 hours + steroid taper Experimental group 3: Anakinra 8 mg/kg/day IV or SQ (max dose: 100mg q6) Control: standard therapy (including IVIG) Allows for randomization to one of the two remaining arms if clinically warranted	Primary outcome: Treatment with lowest rate of second randomization Secondary outcomes: CRP reduction (50%), return of LV EF, and adverse events	Randomized parallel assignment, Open label