EVIDENCE SUMMARY

RESEARCH QUESTION: **Among COVID-19 patients, should tofacitinib be used for treatment?**

Update by: Cynric S. Ang, MD, Natasha Ann R. Esteban-Ipac, MD, Mario M. Panaligan, MD, Ivan N. Villespin, MD, Arnel Gerald Q. Jiao, MD, Marissa M. Alejandria, MD, MSc
Initial Review by: Carol Stephanie C. Tan-Lim, MD, MSc (Clinical Epidemiology)

RECOMMENDATIONS

Recommendations	Certainty of Evidence	Strength of Recommendation
We suggest against use of tofacitinib among adult patients with COVID-19.	Low	Weak
We suggest against use of tofacitinib among children with COVID-19.	Very low	Weak

Consensus Issues
The consensus panel maintained its recommendation against the use of tofacitinib in the treatment of adults with COVID-19, due to its lack of benefit in all critical outcomes, except for the composite outcome of death or respiratory failure and the harm due to adverse events. On further analysis by the panel, the perceived benefit was disproportionately driven by respiratory failure, rather than death. Based on current evidence, tofacitinib may be able to prevent respiratory failure but not death, mainly because there are other factors that contribute to COVID-19 deaths. Evidence from adult studies were extrapolated and used by the panel in coming up with a recommendation against the use of tofacitinib in children with COVID-19, hence the certainty of evidence was further downgraded to very low due to indirectness.

KEY FINDINGS

- There are three (3) randomized controlled trials (RCTs) that investigated the effect of tofacitinib compared to placebo or standard of care as treatment for patients with COVID-19.
- Patients treated with tofacitinib had a significant reduction in the composite outcome of death or respiratory failure.
- Tofacitinib did not show significant effect in all-cause mortality, need for mechanical ventilation or extracorporeal membrane oxygenation (ECMO), cure (defined as resolution of fever, cough, or need for ventilatory/oxygen support), length of hospitalization, length of ICU stay, and duration of mechanical ventilation.
- There was no significant increase in serious adverse events and adverse events between the tofacitinib and placebo group. However, two studies showed that there were significant increase in adverse events leading to treatment discontinuation for patients given tofacitinib compared to placebo, with increase in transaminase levels and lymphopenia being the most commonly reported adverse events [3,5].
- The very serious imprecision due to the limited number of events contributed to the downgrading of evidence to a low certainty of evidence.

WHAT'S NEW IN THIS VERSION?

Two new published RCTs [Murugesan 2021, Ferrarini 2022] are included in this update.

PREVIOUS RECOMMENDATION
As of 21 October 2021

We suggest against the use of tofacitinib among hospitalized COVID-19 patients.
(Low quality of evidence; Weak recommendation)

Consensus Issues
The recommendation against the use of tofacitinib among hospitalized patients with COVID-19 was mainly due to the drug's safety issues. Although the study showed that there was benefit in reducing death or respiratory failure, particularly among patients on low-flow supplemental oxygen, patients who received tofacitinib were three times more likely to experience adverse events leading to treatment discontinuation. Furthermore, the US FDA and Health Canada issued safety alert on the use of tofacitinib due to increased risk of serious cardiovascular-related events (heart attack, stroke), cancer (lymphoma, lung cancer), thrombosis, and death.

INTRODUCTION

Tofacitinib is a Janus kinase (JAK) inhibitor that is used for adults with rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, and for children with juvenile idiopathic arthritis. JAK pathways are involved in inflammatory gene expression and perpetuates an inflammatory cycle. Inhibition of JAK leads to an anti-inflammatory effect through decreased production of pro-inflammatory cytokines and increased production of anti-inflammatory cytokines [1]. Mortality in COVID-19 infection has been associated with a cytokine storm characterized by excessive production of proinflammatory cytokines [2]. The action of tofacitinib in inhibiting cytokine production provide the rationale for evaluating its use in COVID-19.

REVIEW METHODS

A systematic search was done last December 13, 2022 from the last search date September 11, 2021 using Medline, Cochrane Library, and Google Scholar with a combined MeSH and free text search using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and tofacitinib. We also looked at the COVID-NMA Living Data and searched for ongoing studies in the NIH clinicaltrials.gov and various trial registries. Preprints were also searched using medrxiv, chinaxiv, and biorxiv. Only RCTs that compared tofacitinib against placebo or standard care were included in this review. Outcomes of interest included mortality, clinical deterioration or improvement, development of acute respiratory syndrome, need for mechanical ventilation, need for hospitalization, duration of hospitalization, time to clinical recovery, improvement of radiographic findings, virologic clearance, or adverse events. No limits were placed on age, COVID-19 severity, and dosing strategy of tofacitinib. Subgroup analysis by disease severity, oxygen requirement, and age was planned.

RESULTS

Characteristics of included studies

Three (3) published RCTs (n=505) evaluated the efficacy of tofacitinib among mild to moderate hospitalized COVID-19 patients compared to placebo or standard of care. One of the articles is a published abstract. Two of the trials were included in the COVID-NMA living data. No available studies were found for children or adolescents.

One study was done in Brazil [3], one was done in India [4], while the other was done in Italy [5]. The study participants in these trials were hospitalized mild to moderate COVID-19 patients aged 18 years and above, with radiologic findings of pneumonia. Treatment group received oral tofacitinib 10mg twice daily for 14 days. In the first study, a reduced regimen of 5mg tofacitinib twice daily was administered for patients with estimated glomerular filtration rate of <50 mL/min/1.73m^2, moderate hepatic impairment or concomitant use of strong CYP3A4 or CYP2C1 inhibitors [3]. All study groups received standard of care, including glucocorticoids, antibiotics, anticoagulants, and anti-viral agents. The control group received placebo or standard of care alone. Appendix 3 summarizes the characteristics of the included studies.

Certainty of evidence

The overall certainty of evidence was rated low because of very serious imprecision due to the small number of events and wide confidence intervals. Appraisal of study showed unclear risk of bias in the one of the included study. The risk of bias summary is in Appendix 4. The GRADE evidence profile is in Appendix 5.

Effectiveness outcomes

Tofacitinib did not significantly reduce all-cause mortality compared to placebo (RR 0.65, 95% CI 0.23-1.87, I^2=6%, 3 studies, n=505). Tofacitinib, however, showed significant reduction in the composite outcome of death or respiratory failure through day 28 among patients who received tofacitinib compared to placebo (RR 0.57, 95% CI 0.39-0.82, 3 studies, n=505, I^2=0%). In one study, a subgroup analysis was done based on supplemental oxygenation status showing benefit among patients on low-flow supplemental oxygen (RR 0.61, 95% CI 0.37-0.99) however, inconclusive results among patients not receiving supplemental oxygen (RR 0.73, 95% CI 0.22-2.35) and high-flow supplemental oxygen (RR 0.57, 95% CI 0.16-2.04) [3].

There was inconclusive results for patients given tofacitinib compared to placebo/standard of care for need for mechanical ventilation or ECMO (RR 0.25, 95% CI 0.03-2.23, 1 study, n=289), and no significant difference in terms of cure, defined as resolution of fever, cough, or need for ventilatory/oxygen support (RR 1.03, 95% CI 0.95-1.10; 1 study, n=289).

There was also no significant difference in median length of hospitalization (tofacitinib group 5.5 days, 95% CI 3.0-8.25; placebo group 6.0 days, 95% CI 3.0-11.0; sub distribution hazard ratio 1.18, 95% CI 0.94-1.48) and median length of ICU stay (tofacitinib group 5.0 days, 95% CI 3.0-11.0; placebo group 5.0 days, 95% CI 2.0-11.5; sub distribution hazard ratio 1.11, 95% CI 0.72-1.70), and duration of mechanical ventilation (median difference 1.00 days, 95% CI -7.0 to 7.0) [3].

Based on one study, Tofacitinib showed significant reduction of inflammatory markers: D-dimer (median percentage reduction tofacitinib 37% vs control 15%, p-value <0.0001), CRP (median percentage reduction tofacitinib 78% vs control 45%, p-value <0.0001) and Ferritin (median percentage reduction tofacitinib 15% vs control 10%, p-value <0.03) from baseline [4].

Adverse events

There is inconclusive results between patients given tofacitinib and placebo or standard of care in terms of adverse events (RR 1.03, 95% CI 0.72-1.48, 2 studies, n=405). The most common adverse events were increase in aminotransferase levels, acute kidney injury, anemia, hyperglycemia, and lymphopenia. However, there is harm for adverse events leading to treatment discontinuation in the tofacitinib group compared to the placebo group (RR 2.23, CI 1.04-4.79, 2 studies, n=405). Increase in transaminase levels and lymphopenia were the most commonly reported adverse events leading to treatment discontinuation [3,5].

In terms of serious adverse events, there was also no significant difference between those given tofacitinib compared to those given placebo (RR 1.18, 95% CI 0.64-2.15; 1 study, n=289). Among the serious adverse events of special interest, deep-vein thrombosis, acute myocardial infarction, ventricular tachycardia, and myocarditis occurred in one patient each in the tofacitinib group. In the placebo group, hemorrhagic stroke and cardiogenic shock occurred in one patient each. One study mentioned that tofacitinib was well tolerated and did not report any serious adverse events [4] while the other study noted that no thrombotic event was observed in the tofacitinib arm [5].

RECOMMENDATIONS FROM OTHER GROUPS

Group or Agency	Recommendation	Strength of Recommendation / Certainty of Evidence
Infectious Diseases Society of America (IDSA) (as of August 21, 2021)	Suggests the use of tofacitinib rather than no tofacitinib among hospitalized adults with severe COVID-19 (severe illness is defined as patients with SpO_2 ≤94% on room air, including patients on supplemental oxygen or oxygen through a high-flow device), but not on non-invasive or invasive mechanical ventilation. Patients treated with tofacitinib should be on at least prophylactic dose anticoagulant, and that these patients should not receive tocilizumab or other IL-6 inhibitor for treatment of COVID-19 [8].	Low certainty of evidence, Conditional recommendation
National Institutes of Health (NIH) COVID-19 Guidelines (as of August 8, 2022)	Recommends tofacitinib in combination with dexamethasone in hospitalized patients with evidence of inflammation and increasing oxygen needs [9].	Moderate recommendation
Australian Guidelines for COVID-19 (as of November 18, 2022)	Does not recommend the use of tofacitinib for the treatment of COVID-19 outside of randomized trials [10].	Low certainty of evidence
World Health Organization (WHO) (as of January 14, 2022)	Suggest not to use tofacitinib for patients with severe or critical COVID-19 [11].	Low to very low certainty of evidence
Surviving Sepsis Campaign Guidelines on COVID-19 (as of January 29, 2021)	No recommendation on tofacitinib for treatment of COVID-19 [12].	

ONGOING STUDIES AND RESEARCH GAPS

As of December 13, 2022, there are nine (9) studies in various clinical trial registries, of which one was withdrawn so that the investigators can pursue other COVID-19 related research. Another trial was terminated due to lack of enrollment. No ongoing studies will include children or adolescents. This review will be updated as soon as full results from these trials become available.

REFERENCES

[1] Hodge JA, Kawabata TT, Krishnaswami S, Clark JD, Telliez JB, et al. The mechanism of action of tofacitinib – an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis. Clin Exp Rheumatol. 2016;34(2):318-28.

[2] Ragab D, Eldin HS, Mohamed T, Khattab R, Salem R. The COVID-19 Cytokine Storm; What We Know So Far. Front Immunol. 2020;11:1446.

[3] Guimaraes PO, Quirk D, Furtado RH, Maia LN, Saraiva JF, Antunes MO, et al. Tofacitinib in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med. 2021;385:406-15.

[4] Murugesan H, Gauthaman CS, Nasreen HS, Santhanam S, Gowrishankar M, et al. An Evaluation of Efficacy and Safetu of Tofacitinib, a JAK Inhibitor in the Management of Hospitalixzsed Patients with Mild to Moderate COVID-19 – An Open- Label Randomized Controlled Study. J Assoc Physicians India. 2022 Dec; 69 (12): 11-12.

[5] Ferrarini A, Vacca A, Solimando A, Tavio M, Acquaviva R, et al. Early administration of tofacitinib in COVID-10 pneumonitis: An open randomized controlled trial. Eur J Clin Invest. 2022 Nov 15;e13898

[6] UptoDate. Tofacitinib: Drug Information. Available from https://www.uptodate.com/contents/tofacitinib-drug-information. Accessed 26 November 2022.

[7] Watsons. Xeljanz Tofacitinib. Available form https://www.watsons.com.ph/tofacitinib-11mg-1-tablet/p/BP_50028739. Accessed 11 September 2021.

[8] Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America 2021; Version 5.1.1. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed26 November 2022.

[9] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 26 November 2022

[10] Australian National COVID-19 Clinical Evidence Taskforce. Australian guidelines for the clinical cure of people with COVID-19 v42.1. Available from https://app.magicapp.org/#/guideline/5596. Accessed26 November 2022.

[11] World Health Organization. Therapeutics and COVID-19 Living Guidelines. 6 July 2021. Available at https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.2. Accessed26 November 2022.

[12] Surviving Sepsis Campaign: Guidelines on the Management of Adults with Coronavirus Disease 2019 (COVID-19) in the ICU: First Update, Accessed 26 November 2022 https://www.sccm.org/SurvivingSepsisCampaign/Guidelines/COVID-19

Appendix 1: Preliminary Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=6/10)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No (1)	Yes (5)					• COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity.
Benefits	Large	Moderate (2)	Small (3)	Uncertain (1)			• Tofacitinib did not significantly reduce all-cause mortality compared to placebo (RR 0.65, 95% CI 0.23-1.87, I^2=6%, 3 studies, n=505). Tofacitinib, however, showed significant reduction in the composite outcome of death or respiratory failure through day 28 among patients who received tofacitinib compared to placebo (RR 0.57, 95% CI 0.39-0.82, 3 studies, n=505, I^2=0%).
Harm	Large	Moderate (5)	Small	Trivial	Varies (1)	Uncertain	• Trend towards harm among those given tofacitinib compared to placebo, but wide confidence interval precludes definite conclusions to be made (RR 1.03, 95% CI 0.72-1.48) • Significant increase in adverse events leading to treatment discontinuation (RR 2.23, 95% CI 1.04-4.79)
Certainty of Evidence	High	Moderate (1)	Low (5)	Very low			• Low because of very serious imprecision due to the small number of events and wide confidence intervals.
Balance of effects	Favors intervention	Probably favors intervention	Does not favor intervention or	Probably favors no intervention (4)	Favors no intervention (1)	Varies	

			no intervention (1)				
Values	Important uncertainty or variability (4)	Possibly important uncertainty or variability (2)	Probably no important uncertainty or variability	No important uncertainty or variability			
Resources Required	Uncertain	Large cost (5)	Moderate Cost (1)	Negligible cost or savings	Moderate savings	Large savings	• ₱32,570.16 to ₱68,381.60 per 14 day treatment course
Certainty of evidence of required resources	No included studies (3)	Very low	Low	Moderate (3)	High		• Based on published online rates of a Philippine drug store website
Cost effectiveness	No included studies (4)	Favors using the comparison (1)	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the invention	Varies (1)	• None of the included trials assessed cost effectiveness.
Equity	Uncertain	Varies (1)	Probably reduced (3)	Probably no impact (1)	Probably increased (1)	Increased	
Acceptability	Uncertain	Varies (2)	No	Probably no (4)	Probably yes	Yes	
Feasibility	Uncertain	Varies (5)	No (1)	Probably no	Probably yes	Yes	
Recommendation	For	Against (6)					
Strength	Weak (6)	Strong					

Additional considerations: None

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 (treatment)	12/13/22 1725h	109	2
CENTRAL	MeSH descriptor: [Coronaviridae Infections] explode all trees OR MeSH descriptor: [Coronavirus] explode all trees 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 {treatment}	12/13/22 1731h	1	0
Google Scholar	Tofacitinib	12/13/22 1736h	1540	2
COVID-NMA initiative	Tofacitinib AND COVID19 AND randomized trial	12/13/22 1750h	2	2
ClinicalTrials.gov	Tofacitinib and COVID19	12/13/22 1755	7	1
Chinese Clinical Trial Registry	Tofacitinib	12/13/22 1758	0	0
EU Clinical Trials Register	Tofacitinib	12/13/22 1800	4	0
Republic of Korea – Clinical Research Information Service	Tofacitinib	12/13/22 1803	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Tofacitinib	12/13/22 1805	0	0
CenterWatch	Tofacitinib and COVID	12/13/22 1809	2	0
WHO Database COVID-19 Studies	Tofacitinib	12/13/22 1812	15	1
chinaxiv.org	Tofacitinib	12/13/22 1818	0	0
Medrxiv.org	Tofacitinib and COVID	12/13/22 1819	95	0
Biorxiv.org	Tofacitinib and COVID	12/13/22 1830	113	0

Appendix 3: Characteristics of Included Studies

Study ID	Patients (n)	Interventions	Outcomes	Method
Tofacitinib in Hospitalized Patients With COVID-19 Pneumonia *Guimaraes et al. 2021 (Brazil)*	N=289 18 years and older with: ● Laboratory-confirmed SARS-CoV-2 infection as determined by RT-PCR ● Evidence of COVID-19 pneumonia assessed by radiographic imaging (CT or radiography) ● Hospitalized for less than 72 hours Exclusion criteria: ● Use of noninvasive or invasive mechanical ventilation or ECMO ● History of thrombosis or current thrombosis ● Known immunosuppression ● Current cancer <u>Duration of follow-up:</u> Up to 28 days after discharge	Experimental: Tofacitinib 10mg twice daily for 14 days or until hospital discharge (N=144) Control: Placebo (N=145)	Primary: Death or respiratory failure until Day 28 Secondary: all-cause mortality, scores of the NIAID ordinal scale of disease severity at day 14 and 28, need for mechanical ventilation or ECMO at day 14 and 28, duration of stay in the hospital, duration of stay in the ICU, cure (resolution of fever, cough, no use of ventilatory or oxygen support), hospital discharge at day 14 and 28, serious adverse events	Randomized, Double-blind, Placebo-controlled, Parallel-design Trial
New Studies				
An Evaluation of Efficacy and Safety of Tofacitinib, a JAK Inhibitor in the Management of Hospitalized Patients with Mild to Moderate COVID-19 – An Open-Label Randomized Control Study Murugesan et al. 2021 (*India*)	N=100 18 to 65 years old with: ● Laboratory confirmed SARS-COV2 infection determined by RT-PCR ● Evidence of Pneumonia by radiological imaging (Chest X-ray or CT Scan) Exclusion criteria: ● On mechanical ventilation at time of admission ● Known allergy to tofacitinib ● Known immunodeficiencies or taking potent immunosuppressants, potent cytochrome P450 inhibitors within past 30 days or received corticosteroids for 14 days prior to screening ● History of major adverse cardiovascular event and/or recent revascularization ● History of deep vein thrombosis or pulmonary embolism ● Pre-existent neurodegenerative disease, severe hepatic or renal	Experimental: Tofacitinib 10mg twice daily completed for 14 days (N=50) Control: Standard of care (N=50)	Primary: Mortality or use of mechanical ventilation or high flow oxygen at day 7 Secondary - Difference in inflammatory markers from baseline - Changes in radiological and clinical presentations	Open label randomized controlled study

	impairment, severe anemia ● History of malignancy or lymphoproliferative disorders Duration of follow-up: Up to 28 days from the last day of treatment			
Early administration of tofacitinib in COVID-19 pneumonitis: An open randomized controlled trial Ferrarini et al. 2022 (Italy)	N=116 Adult patients with: ● SARS-COV2 infection confirmed by RT-PCR ● Mild to moderate COVID-19 pneumonitis (interstitial pneumonia confirmed by CT scan) ● Hospitalized for less than 24 hours ● Not requiring mechanical or non-invasive ventilation to maintain oxygen saturation ≥93% ● Able to provide written consent Exclusion criteria: ● Age >85 years old ● History of major adverse cardiovascular event/s or recent (1 year) revascularization ● History of recurrent deep vein thrombosis and/or pulmonary embolism or established thrombophilia ● History of active malignancy, active bacterial or fungal systemic infection ● Severe hepatic or renal failure Duration of follow-up: Up to 28 days from day of treatment	Experimental: Tofacitinib 10mg twice daily for 14 days + standard of care (N=49) Control: Standard of care (N=58)	Primary: Use of mechanical ventilation or non-invasive ventilation Secondary: - Clinical improvement at Day 7 - Need for ICU or evidence of multiple organ dysfunction - Death	Phase 2, open-label, randomized, multicentre, controlled trial

Appendix 4: Study Appraisal

Figure 1. Risk of bias summary

Appendix 5: GRADE Evidence Profile

Author(s): Cynric S. Ang, MD, Natasha Ann R. Esteban-Ipac, MD, Carol Stephanie C. Tan-Lim, MD MSC
Question: Tofacitinib compared to Placebo/Standard Care for COVID-19
Setting: Hospital Setting

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tofacitinib	Placebo/Standard Care	Relative (95% CI)	Absolute (95% CI)		
Death or respiratory failure (follow-up: 28 days)												
3	randomised trials	not serious	not serious	not serious	serious[a]	none	35/252 (13.9%)	62/253 (24.5%)	**RR 0.57** (0.39 to 0.82)	**105 fewer per 1,000** (from 149 fewer to 44 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
All-cause mortality (follow-up: 28 days)												
3	randomised trials	not serious	not serious	not serious	very serious[b]	none	5/252 (2.0%)	8/253 (3.2%)	**RR 0.65** (0.23 to 1.87)	**11 fewer per 1,000** (from 24 fewer to 28 more)	⨁⨁◯◯ Low	CRITICAL
Serious adverse events (follow-up: 28 days)												
1	randomised trials	not serious	not serious	not serious	very serious[b]	none	20/144 (13.9%)	17/145 (11.7%)	**RR 1.18** (0.64 to 2.15)	**21 more per 1,000** (from 42 fewer to 135 more)	⨁⨁◯◯ Low	CRITICAL
Adverse events leading to treatment discontinuation												
2	randomised trials	not serious	not serious	not serious	serious[c]	none	20/202 (9.9%)	9/203 (4.4%)	**RR 2.24** (1.04 to 4.79)	**55 more per 1,000** (from 2 more to 168 more)	⨁⨁⨁◯ Moderate	IMPORTANT
Adverse events												
2	randomised trials	not serious	not serious	not serious	serious[b]	none	46/202 (22.8%)	45/203 (22.2%)	**RR 1.03** (0.72 to 1.48)	**7 more per 1,000** (from 62 fewer to 106 more)	⨁⨁⨁◯ Moderate	IMPORTANT

Appendix 6: Forest Plots

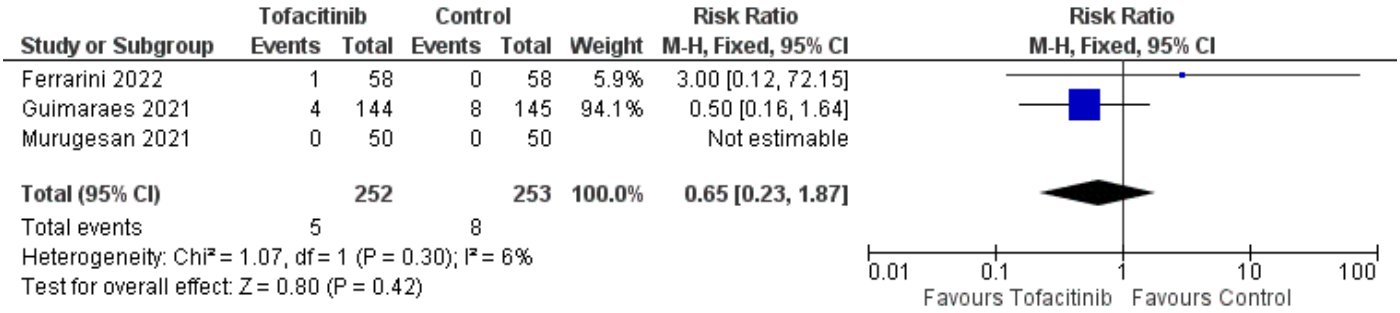

Figure 2. All-cause mortality (day 28)

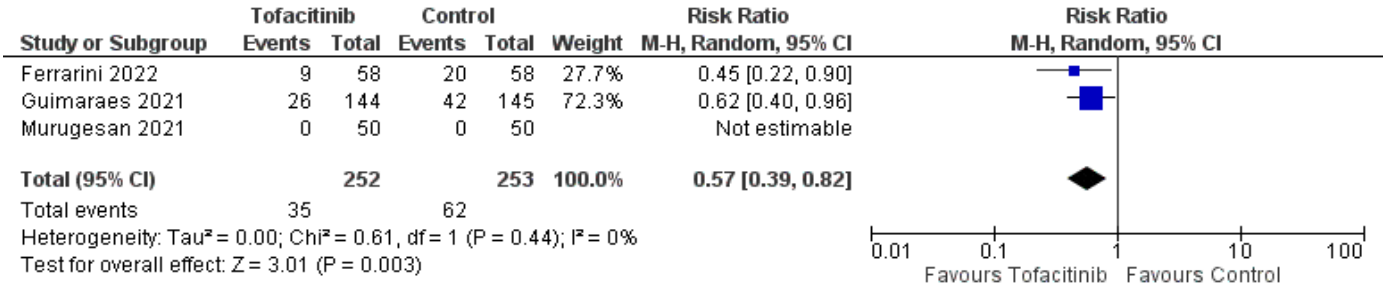

Figure 3. Death or respiratory failure

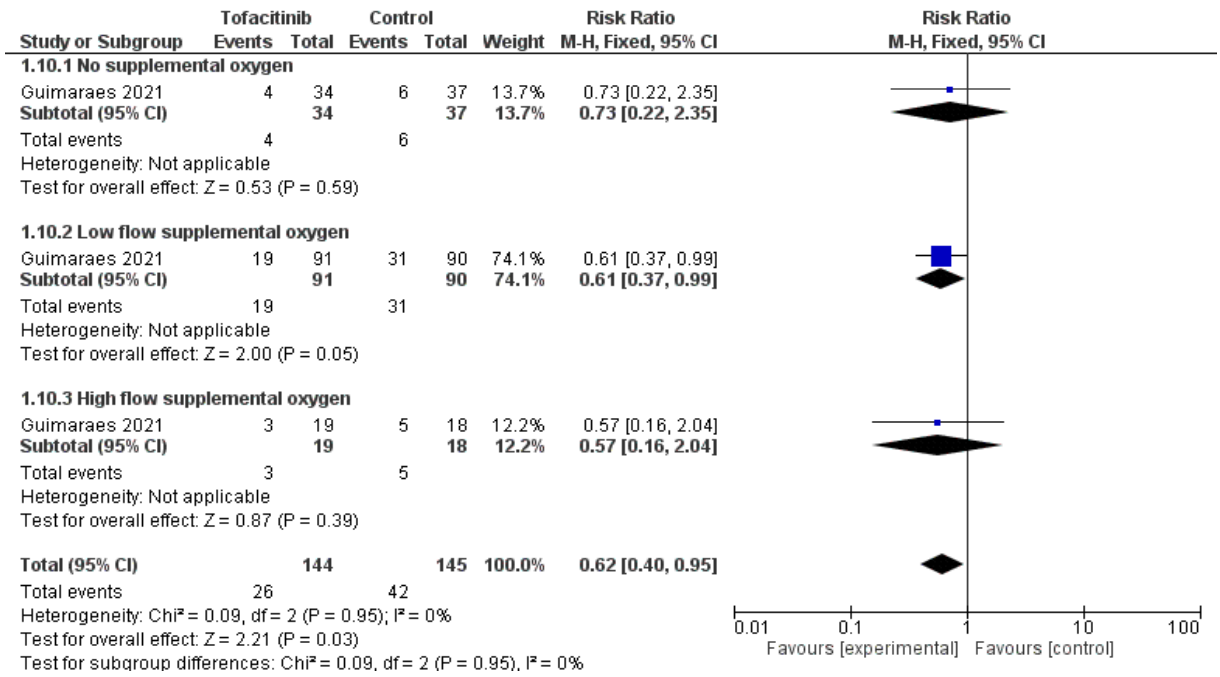

Figure 4. Death or respiratory failure. Subgroup analysis based on supplemental oxygenation status.

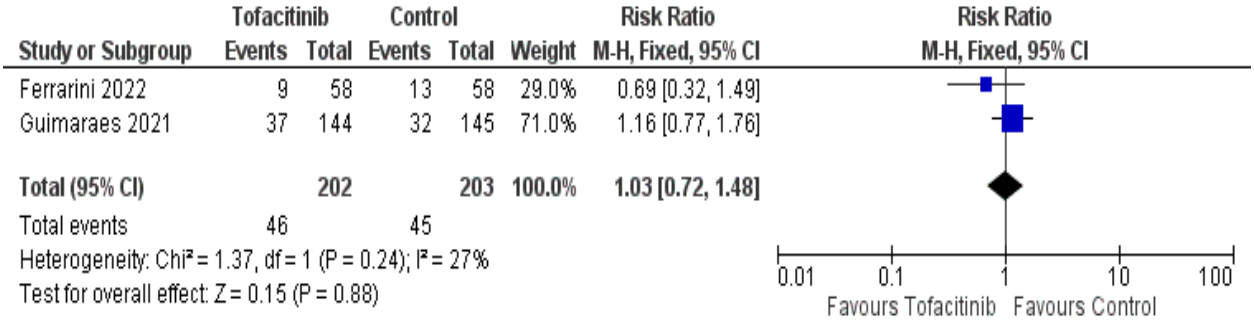

Figure 5. Adverse events

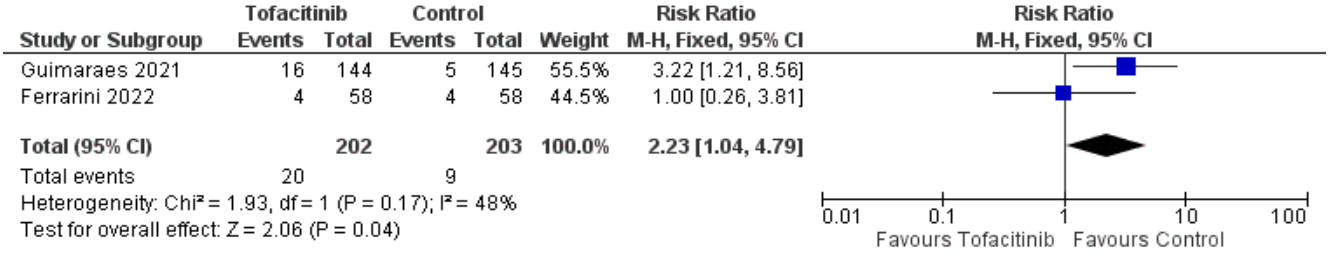

Figure 6. Adverse events leading to discontinuation

Appendix 7: Characteristics of Ongoing Studies

Study Title	Patients (n)	Interventions	Outcomes	Method
1. Tofacitinib for Treatment of Moderate COVID-19 NCT04415151	18 years and older with laboratory-confirmed SARS-CoV-2 infection as determined by polymerase chain reaction, evidence of pneumonia assessed by radiographic imaging, and hospitalized	Experimental: Tofacitinib 10mg PO BID until return to their clinical baseline and then at 5mg PO BID for a total of 14 days Control: Placebo	Disease Severity (Time Frame: 14 days)	Randomized, double blinded, placebo-controlled study
2. Safety and Efficacy of Tofacitinib in Hospitalized Participants With COVID-19 Pneumonia Who Are Receiving Standard of Care Therapy NCT04412252 *Withdrawn to pursue other COVID-19 research*	18 years and older with laboratory-confirmed SARS-CoV-2 infection as determined by polymerase chain reaction, evidence of pneumonia assessed by radiographic imaging	Experimental: Tofacitinib 10mg twice daily for 14 days Control: Placebo	Clinical status using ordinal scale (Time Frame: Day 28)	Randomized, Double-blind, Placebo-controlled, Parallel-group study
3. TOFAcitinib Plus Hydroxychloroquine vs Hydroxychloroquine in Patients With COVID-19 Interstitial Pneumonia (TOFACoV-2) NCT04390061	18 to 65 years old with SARS-CoV2 infection diagnosed by RT-PCR, hospital admission from less than 24 hours, P/F ratio >150 mmHg	Experimental: Tofacitinib 10mg twice daily + hydroxychloroquine 200mg thrice daily for 14 days Control: hydroxychloroquine 200mg thrice daily for 14 days	Prevention of severe Respiratory Failure requiring mechanical ventilation (Time Frame: 14 days)	Randomized, parallel assignment open label trial
4. Evaluation of use and right time identification to initiate Tofacitinib use in the treatment of moderate-severe COVID-19 infection (TOF-RI-TIME) CTRI/2021/06/034162	18 years and older with signs and symptoms consistent with COVID-19 infection confirmed with rapid antigen test (RAT) or RT- PCR and hospitalised with moderate or severe COVID-19 illness	Experimental: Tofacitinib 10mg BID on top of Standard Care for 10 days Control: Standard Care	All-cause mortality up to 28 days of follow-up	Open label randomised, controlled trial
5. Effectiveness evaluation of Tofacitinib plus Remdesivir in comparison with Remdesivir in the treatment of adult patients with severe COVID-19 A randomized double-blind placebo-included clinical trial IRCT20200329046892N2	All patients > 18 years old with severe COVID-19 admitted to the ICU of Razi Hospital in Rasht from March to June 2021	Experimental: Tofacitinib oral tablet 10mg daily + remdesivir IV 100mg daily for 14 days or hospital discharge Control: Placebo oral tablet daily + Remdesivir IV 100mg daily for 14 days or hospital discharge	The time required to improve clinical symptoms and paraclinical measures within 14 days of starting treatment	Double-blind, randomized clinical trial with parallel control group
6. Comparison of the effectiveness of Tocilizumab and Tofacitinib on the outcomes of patients with severe COVOD-19 IRCT20210901052358N3	18 years and older with RT-PCR confirmed COVID-19, hospitalized for severe illness	Experimental: Group 1 Tocilizumab infusion 8mg/kg to a maximum of 800mg + Standard of care Group 2: Oral tofacitinib 10mg every 12 hours for 14 days + standard of care	Admission to intensive care unit, hospital length of stay, use of mechanical ventilation and all-cause mortality until the 14th day of hospitalization / discharge or death	Randomized, parallel group study
7. Evaluation of efficacy of Tofacitinib in COVID 19 patients – A prospective randomized study CTRY/2021/12/038732	18 years and older, RT-PCR confirmed COVID-19, with radiological finding of pneumonia, eGFR 15-30ml/min, PF ratio 100-300mmHg	Experimental: Oral tofacitinib 10mg twice daily for 14 days Control: not in literature	Incidence and duration of invasive and non-invasive ventilation, frequency of kidney adverse events, Length of ICU stay, ICU and hospital mortality	Randomized, parallel group, active controlled trial
8. Efficacy of Tofacitinib/Remdesivir combination therapy compared to Remdesivir treatment on clinical status	18 years and older, RT-PCR confirmed COVID-19 hospitalized for severe illness with CT scan finding of lung	Experimental: Group 1: Oral Tofacitinib 10mg twice daily for 5 days + Remdesivir IV infusion (Day 1: 200mg, Day 2 to 5 100mg)	Comparison of laboratory markers at baseline and 1 day after intervention	Randomized, Double blinded, placebo,

and laboratory findings of patients with severe COVID-19: A double-blind randomized clinical trial study IRCT20200426047212N2	involvement	Group 2: Oral Tofacitinib 10mg twice daily for 5 days + Remdesivir IV (Day 1: 200mg, Day 2 to 10: 100mg) Group 3: Remdesivir IV (Day 1: 200mg, Day 2 -5: 100mg) + placebo twice daily for 5 days Group 4: Remdesivir IV (Day 1: 200mg, Day 2-9: 100mg) + placebo twice daily for 5 days		parallel group clinical trial
9. Randomized controlled trial of Tofacitinib vs standard of care alone for COVID-19 Pneumonia CTRI/2021/11/037898	Adults with RT-PCR confirmed COVID-19, with radiological finding of pneumonia	Experimental: Tofacitinib 5mg twice daily for 14 days + standard of care Control: Standard of care	Proportion of subjects alive at day 14	Randomized, parallel group trial