Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
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EVIDENCE SUMMARY

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

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RECOMMENDATIONS

We suggest the use of baricitinib in addition to dexamethasone and remdesivir as treatment for hospitalized COVID-19 patients who require low-flow oxygen, high-flow oxygen, and non-invasive ventilation. *(Low quality of evidence; Weak recommendation)*

There is insufficient evidence to recommend baricitinib as an alternative to tocilizumab as treatment for hospitalized COVID-19 patients. *(Very low quality of evidence)*

Consensus Issues

The recommendation to give baricitinib in addition to dexamethasone and remdesivir was made based on 2 randomized controlled trials wherein baricitinib was given as an add-on therapy to dexamethasone and remdesivir among hospitalized patients with moderate to severe COVID-19. At present, dexamethasone, a systemic corticosteroid, is considered standard of care for patients requiring oxygen supplementation *(High quality of evidence; Strong recommendation),* while remdesivir may be considered as an additional therapy for patients who require oxygen supplementation but not on invasive mechanical ventilation *(Low quality of evidence, Conditional recommendation).* Although remdesivir is not currently considered standard care, there are studies that show possible synergistic effect in concurrently giving an anti-viral to shorten viral clearance plus an immunomodulator to address impending cytokine storm. Addition of baricitinib is recommended only for non-intubated patients (i.e., on low-flow oxygen, high-flow oxygen, and non-invasive ventilation).

As of writing, the available evidence on baricitinib is not as robust as tocilizumab, and there is only 1 retrospective observational study, which directly compared baricitinib versus tocilizumab. As such, there is insufficient evidence to make recommendations on whether baricitinib may be used as an alternative to tocilizumab. Strategies for conservation of tocilizumab is beyond the scope of the consensus panel, and may be discussed by the local expert group working on COVID-19 treatment algorithms.

PREVIOUS RECOMMENDATIONS

We suggest the use of baricitinib in combination with remdesivir in hospitalized COVID-19 patients requiring oxygen supplementation and who cannot take corticosteroids. *(Low quality of evidence; Conditional recommendation)*

There is insufficient evidence to recommend the use of baricitinib in combination with remdesivir and corticosteroids in hospitalized COVID-19 patients. *(Very low quality of evidence)*

There is no evidence to recommend the use of baricitinib alone in hospitalized COVID-19 patients.

Previous Consensus Issues

These recommendations were made in the context of dexamethasone being considered as a standard of care for severe or critical COVID-19 infection. The incremental benefit of giving baricitinib and remdesivir with dexamethasone remains to be a research gap. Thus, there is insufficient evidence to recommend the use of baricitinib in combination with remdesivir and corticosteroids in hospitalized COVID-19 patients. Caution must be exercised in administering baricitinib in patients who are already taking steroids due to the likelihood of the occurrence of immunosuppression. Results showed that patients who received glucocorticoids had a higher risk of having serious or non-serious infections than those who did not.

Due to supply problems in recent months, baricitinib is currently being used locally to replace tocilizumab in regimens with both remdesivir and dexamethasone. However, using baricitinib for COVID-19 qualifies as off-label use as it is approved only for use in rheumatoid arthritis.

What's new in this version?

This version included data from 1 new randomized controlled trial (RCT).

Key Findings

The evidence on the use of baricitinib comes from 2 RCTs among hospitalized patients with moderate to severe COVID-19. Both studies found that there was a reduction in the all-cause mortalities, progression of oxygen use, and serious adverse events in the baricitinib group compared to the control group. However, there was no significant difference in the duration of hospitalization between the two groups.

Introduction

Baricitinib is an orally administered selective inhibitor of Janus kinase (JAK) 1 and 2 used in the management of rheumatoid arthritis. In vitro studies have shown that it can prevent the entry of SARS-CoV-2 virus to human cells and reduce the levels of cytokines (i.e., Interleukin-2, Interleukin-6, Interleukin-10, G-CSF, and IFN-Y) in COVID-19 patients.[1]

Review Methods

A systematic search was done from the date of the last search April 4, 2021 until September 6, 2021 using Medline, CENTRAL, 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 baricitinib. 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 randomized controlled trials that compared baricitinib against placebo or standard care were included in this review. Only randomized controlled trials were included. No limits were placed on age, COVID-19 severity, and dosing.

Results

There are two (2) published studies that evaluate the use of baricitinib for treating hospitalized moderate to severe COVID-19 patients.[2,3] Both are Phase 3 trials that had a total of 2,558 participants. One study compared baricitinib + remdesivir to remdesivir alone, with all study participants receiving standard supportive care. Glucocorticoids were given only for standard indications such as adrenal insufficiency, asthma exacerbation, laryngeal edema, septic shock, and acute respiratory distress syndrome, but not as a treatment for COVID-19.[2] The other study compared baricitinib to placebo, with all study participants receiving standard care including dexamethasone and remdesivir.[3] The studies reported the following outcomes: all-cause mortality by day 28, duration of hospitalization, and progression to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation or extracorporeal mechanical oxygenation (ECMO).[2,3] One study also reported the time to recovery and time to discharge.[2] The characteristics of the included studies may be found in Appendix 3.

The overall quality of evidence was rated low because of serious imprecision and inconsistency in one important outcome (adverse events). Appraisal of study quality showed no serious risk of bias in the included studies. The risk of bias summary is in Appendix 4. The GRADE evidence profile is in Appendix 5.

Pooled analysis showed a significant decrease in the all-cause mortality by day 28 in the baricitinib group among hospitalized COVID-19 patients compared to the control group (RR 0.64, 95% CI 0.50-0.82; I^2=0%). Both studies evaluated the severity of COVID-19 based on the National Institute of Allergy and Infectious Diseases Ordinal Scale (NIAID-OS) and simplified for clinical purposes (NIAID-OS score of 4: non-oxygen requiring, NIAID-OS score of 5: on low-flow oxygen, NIAID-OS score of 6: on high-flow oxygen or non-invasive ventilation, NIAID-OS score of 7: on invasive mechanical ventilation or ECMO). Subgroup analysis based on severity of the COVID-19 disease revealed that both low-flow oxygen requiring patients (RR 0.62, 95% CI 0.41-0.94; I^2=0%) and high-flow oxygen requiring patients or those on non-invasive ventilation (RR 0.59, 95% CI 0.42-0.85; I^2=0%) had reduced mortality compared to the control group. However, those not requiring oxygen (RR 0.27, 95% CI 0.03-2.39) and those on invasive mechanical ventilation or ECMO (RR 1.06, 95% CI 0.52-2.14) had no significant difference in mortality with the control group.

The progression of the use of oxygen to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation or ECMO (combined endpoint) was significantly decreased in the baricitinib group versus control, although by a small margin (RR 0.87, 95% CI 0.76-0.98; I^2=4%). However, the duration of hospitalization was not significantly different between both treatment groups (MD -0.10 days, 95% CI -1.55 to 1.35; I^2=0%). One study reported no significant difference in the time to recovery of patients between both treatment groups (baricitinib group median 10 days, 95% CI 9-11, control group median 11 days, 95% CI 10-12; RR 1.11, 95% CI 0.99-1.24).[3]

Baricitinib versus tocilizumab

In a retrospective observational study, medical records of 60 patients were reviewed. The population included those with documented interstitial COVID-19 pneumonia with a ratio of arterial

oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) of <300. These patients received baricitinib monotherapy (n = 12), tocilizumab monotherapy (n = 20), a combination of baricitinib and tocilizumab (n = 11) and neither of the 2 drugs (n = 17) aside from anti-virals such as remdesivir and other medications (hydroxychloroquine, azithromycin, and corticosteroids).[4] Appraisal of this study showed serious risk of bias due to imbalance of prognostic factors with no statistical adjustments made. Summary of the risk of bias can be found in Appendix 4.

We compared the groups that received baricitinib only versus tocilizumab only. There was no significant difference in the number of days with symptoms between the 2 groups (MD -0.90, 95% CI -5.54 to 3.74), length of stay in the hospital (MD 0.90 days, 95% CI -1.82 to 3.62), and overall mortality (RR 0.83, 95% CI 0.18-3.88). However, there was significantly reduced need for ICU admission in the baricitinib only group versus the tocilizumab only group (RR 0.06, 95% CI 0-0.92). We also compared the groups that received baricitinib only versus combination baricitinib/tocilizumab. There was no significant difference in the number of days with symptoms (MD -2.10, 95% CI -6.97 to 2.77), length of stay in the hospital (MD -0.30 days, 95% CI -3.20 to 2.60), need for ICU admission (RR 0.13, 95% CI 0.01-2.30), and overall mortality (RR 0.61, 95% CI 0.12-3.00) between the 2 groups.

Safety

There were significantly less serious adverse events in the baricitinib group versus the control group (RR 0.79, 95% CI 0.67-0.94; I2=0%). The most common serious adverse events noted by the studies were development of serious infections, respiratory failure [2,3], and venous thromboembolic events.[3]

There was no significant difference found between the two groups for the number of adverse events (RR 0.91, 95% CI 0.75-1.10; I^2=84%). The most common adverse events noted in one study for the baricitinib group were decrease in glomerular filtration rate, decrease in hemoglobin, decrease in lymphocyte count, and decrease in blood glucose levels.[2]

Recommendations from Other Groups

Table 1. Summary of Recommendations from Other Groups

Regulatory Agency	Recommendation
US Food and Drug Administration (FDA)	Revised the Emergency Use Authorization (EUA) of baricitinib on July 2021. From the previous EUA, allowing the use of baricitinib only in combination with remdesivir, the revised EUA allows the use of baricitinib as monotherapy treatment for hospitalized moderate to severe COVID-19 patients on supplemental oxygen therapy.[5,6] The FDA recommends that baseline laboratory values (estimated glomerular filtration rate, liver enzymes and complete blood count) should be determined prior to administration of the drug to decide the suitability and dose for the patient.
National Institutes of Health (NIH) (as of October 7, 2021)	Recommends the use of baricitinib in addition to dexamethasone or remdesivir for patients who have rapidly increasing oxygen needs, require high-flow oxygen or non-invasive ventilation, and have increased inflammatory markers. However, they recommend against the use baricitinib for those who are stable enough for discharge and do not require supplemental oxygen.[9]

	Recommends against the use of baricitinib in combination with tocilizumab for the treatment of COVID-19. They stated insufficient evidence to recommend one drug over the other.[9]
Australian Guidelines (as of September 29, 2021)	Baricitinib should be considered for adults hospitalized with COVID-19 who require supplemental oxygen, high-flow oxygen and/or non-invasive ventilation.[10]
Infectious Diseases Society of America (IDSA) (as of October 1, 2021)	Suggests baricitinib rather than no baricitinib among hospitalized adults with severe COVID-19 (requiring supplemental oxygen, high-flow oxygen, or non-invasive ventilation) having elevated inflammatory markers but not on invasive mechanical ventilation.[11]
World Health Organization (WHO)	No recommendation on the use of baricitinib as treatment for COVID-19.[12]

Research Gaps

There are currently 10 ongoing clinical trials in *clinicaltrials.gov* on baricitinib for COVID-19 management. One trial (NCT04373044) was terminated after the release of the ACTT-2 data.[2] See Appendix 7 for details.

References

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[10] National COVID-19 Clinical Evidence Task Force. Australian guidelines for the clinical care of people with COVID-19. *Aust Gov*. 2020:215. www.COVID19evidence.net.au.

[11] Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. *Clin Infect Dis*. 2020:0-137. doi:10.1093/cid/ciaa478

[12] 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. Accessed 11 September 2021.

Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion: baricitinib vs control (N = 9)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (9)					• COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity
Benefits	Large (1)	Moderate (7)	Small	Uncertain	Varies (1)		• Significant reduction in all-cause mortality among hospitalized patients on low-flow oxygen (RR 0.62, 95% CI 0.41-0.94), high-flow oxygen or non-invasive ventilation (RR 0.59, 95% CI 0.42-0.85) but no difference in mortality among those not requiring oxygen or on invasive MV/ECMO • 1 panelist answered varies - clear benefit for those requiring oxygen while no benefit for those not requiring or already on invasive MV/ECMO
Harm	Large	Small (8)	Uncertain	No response			• Significantly less serious adverse events (RR 0.79, 95% CI 0.67-0.94)
Certainty of Evidence	High	Moderate (1)	Low (8)	Very low			• Low because of serious imprecision and inconsistency in one important outcome (adverse events)
Balance of effects	Favors drug (8)	Does not favor drug	Uncertain (1)				• Net potential benefit in all-cause mortality especially for those on low-flow oxygen, high-flow oxygen and non-invasive ventilation, as well as progression of oxygen use
Values	Important uncertainty or variability (2)	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability (4)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost (1)	Moderate Cost (7)	Negligible cost	Moderate savings	Large savings (1)	• Php 19,380.48/14-day treatment course (Php 1,384.32 per 4mg tablet)

Certainty of evidence of required resources	No included studies	Very low	Low (3)	Moderate (3)	High (3)		• The cost is based on a DOH memorandum entitled OSEC-HTAC Recommendations on COVID-19 Investigational Drugs
Cost effectiveness	No included studies (4)	Favors the comparison (1)	Does not favor either the intervention or the comparison	Favors the intervention (4)			• None of the included trials assessed cost effectiveness.
Equity	Uncertain (2)	Reduced (3)	Probably no impact (1)	Increased (3)			
Acceptability	Uncertain (3)	No	Yes (5)	Varies (1)			
Feasibility	Uncertain (1)	No	Yes (7)	Varies (1)			

Additional considerations:

- There is need for more data on drug interactions and risk of immunosuppression

Table 2. Summary of initial judgements prior to the panel discussion: baricitinib vs tocilizumab (N=9)

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (9)					• COVID-19 has affected millions of people worldwide and has caused substantial mortality and morbidity.
Benefits	Large	Moderate (2)	Small (4)	Uncertain (2)	Trivial (1)		• No significant difference in the number of days with symptoms (MD -0.90, 95% CI -5.54-3.74), length of stay in the hospital (MD 0.90 days, 95% CI -1.82 to 3.62), and overall mortality (RR 0.83, 95% CI 0.18-3.88) • Significantly reduced need for ICU admission in the baricitinib only group versus the tocilizumab only group (RR 0.06, 95% CI 0-0.92).
Harm	Large (2)	Small (6)	Uncertain	Trivial (1)			• No severe adverse effects were documented in the baricitinib only and tocilizumab only group
Certainty of Evidence	High (1)	Moderate (2)	Low (3)	Very low (3)			• Very low – small retrospective observational study with serious risk of bias due to imbalance of prognostic factors with no statistical adjustments made
Balance of effects	Favors drug (6)	Does not favor drug (1)	Uncertain (2)				• When compared to tocilizumab, baricitinib showed no significant difference in harm or benefit in terms of reducing number of days with symptoms, length of hospital stay and all-cause mortality. • Although majority (6 out of 9) favored the drug prior to the panel discussion, the consensus panel eventually decided that there is currently insufficient evidence to base recommendations on whether baricitinib may be used as an alternative to tocilizumab
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (5)	Possibly NO important uncertainty or variability (3)	No important uncertainty or variability			
Resources Required	Uncertain	Large cost	Moderate Cost (7)	Negligible cost or savings (1)	Moderate savings (1)	Large savings	• Php 19,380.48 for a 14-day oral treatment course with baricitinib
Certainty of evidence of required resources	No included studies (1)	Very low	Low (1)	Moderate (4)	High (3)		• The cost is based on a DOH memorandum entitled OSEC-HTAC Recommendations on COVID-19 Investigational Drugs

Cost effectiveness	No included studies (5)	Favors the comparison	Does not favor either the intervention or the comparison (2)	Favors the intervention (2)		• None of the included trials assessed cost effectiveness.
Equity	Uncertain (5)	Reduced (1)	Probably no impact (1)	Increased (2)		
Acceptability	Uncertain (6)	No	Yes (3)			
Feasibility	Uncertain (3)	No	Yes (6)			

Appendix 2. Search Yield and Results

Comparison 1: Baricitinib compared to standard of care or placebo

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 (Baricitinib) Filters: from April 4, 2021 to September 1, 2021	Sep 6, 2021 9AM	51	1
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 (Baricitinib) Filters: from April 4, 2021 to September 1, 2021	Sep 6, 2021 915 AM	468	0
Google Scholar	Baricitinib AND COVID AND randomized trial	Sep 6, 2021 10 AM	15	2
COVID-NMA initiative	Baricitinib	Sep 6, 2021 1015 AM	2	0
ClinicalTrials.gov	COVID-19 AND baricitinib	Sep 6, 2021 1020 AM	21	0
Chinese Clinical Trial Registry	Baricitinib	Sep 6, 2021 1040 AM	2	0
EU Clinical Trials Register	Baricitinib	Sep 6, 2021 1045 AM	45	0
Republic of Korea - Clinical Research Information Service	Baricitinib	September 6, 2021 1050 AM	2	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Baricitinib	Sep 6, 2021 11 AM	27	0
CenterWatch	Baricitinib	Sep 6, 2021 1115 AM	0	0
chinaxiv.org	Baricitinib	Sep 6, 2021 1120 AM	0	0
Medrxiv.org	Baricitinib Filters: April 4, 2021 to September 6, 2021	Sep 6, 2021 1130 AM	22	1
Biorxiv.org	Baricitinib Filters: April 4, 2021 to September 6, 2021	Sep 6, 2021 1145 AM	23	0

Comparison 2: Baricitinib compared to tofacitinib

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 (Baricitinib) AND (Tocilizumab)	Sep 16, 2021 3PM	48	1
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 (Baricitinib) AND (Tocilizumab)	Sep 16, 2021 330PM	530	0
Google Scholar	Baricitinib AND COVID AND tocilizumab	Sep 16, 2021 4PM	1160	1
COVID-NMA initiative	Baricitinib AND tocilizumab	Sep 16, 2021 415 PM	2	0
ClinicalTrials.gov	Covid-19 AND baricitinib AND tocilizumab	Sep 16, 2021 430PM	1	0
Chinese Clinical Trial Registry	Baricitinib AND Tocilizumab	Sep 16, 2021 440 PM	0	0
EU Clinical Trials Register	Baricitinib AND Tocilizumab	Sep 16, 2021 445PM	0	0
Republic of Korea - Clinical Research Information Service	Baricitinib AND Tocilizumab	Sep 16, 2021 5PM	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Baricitinib AND Tocilizumab	Sep 16, 2021 515PM	0	0
CenterWatch	Baricitinib AND Tocilizumab	Sep 16, 2021 520 PM	0	0
chinaxiv.org	Baricitinib AND Tocilizumab	Sep 16, 2021 530 PM	0	0
Medrxiv.org	Baricitinib AND Tocilizumab	Sep 16, 2021 540 PM	0	0
Biorxiv.org	Baricitinib AND Tocilizumab	Sep 16, 2021 6PM	0	0

Appendix 3. Characteristics of Included Studies

Study ID	Patients (n) & Duration of Follow-Up	Interventions	Outcomes	Study Design
Baricitinib compared to standard of care				
Baricitinib plus Remdesivir for Hospitalized Adults with COVID-19 (ACTT-2) *Kalil AC et al. (USA)*	Hospitalized moderate to severe COVID-19 patients (N = 1,033) Duration of follow-up: 28 days	EXPERIMENTAL: Baricitinib (4mg tab daily for 14 days) + Remdesivir (20mg on first day then 10 mg/day for the next 9 days) CONTROL: Remdesivir (20mg on first day then 10 mg/day for the next 9 days)	PRIMARY: Time to recovery SECONDARY: Clinical status at day 15, time to improvement, time to discharge, number of days of receipt of supplemental oxygen, non-invasive ventilation or high-flow oxygen, and invasive ventilation or ECMO, incidence and duration of new use of oxygen, all-cause mortality, and adverse events	Randomized, double-blind, placebo-controlled
Efficacy and Safety of Baricitinib for the Treatment of Hospitalized Adults with COVID-19 (COV-BARRIER): A Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Phase 3 Trial *Marconi VS et al., (Asia, Europe, USA, South America)*	Hospitalized moderate to severe COVID-19 patients (N = 1,525) Duration of follow-up: 28 days	EXPERIMENTAL: Baricitinib 4mg tablet + Standard of care CONTROL: Standard of care	PRIMARY: Proportion of patients who progressed to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation or death SECONDARY: All-cause mortality by day 28 and adverse events	Randomized, double-blind, placebo-controlled

Baricitinib compared to tocilizumab				
Experience with the use of baricitinib and tocilizumab monotherapy or combined, in patients with interstitial pneumonia secondary to Coronavirus COVID-19: A real-world study *Rosas J et al. (Spain)*	Hospitalized COVID-19 patients with documented interstitial pneumonia and PaO_2/FiO_2 <300 (N = 60) <u>Duration of follow-up:</u> 30 days	GROUP 1: Baricitinib monotherapy GROUP 2: Tocilizumab monotherapy GROUP 3: Combined baricitinib/tocilizumab GROUP 4: No baricitinib/tocilizumab	Days with symptoms Days of admission Severe adverse effects Admission to ICU Overall mortality since admission	Retrospective observational

Appendix 4. Study Appraisal

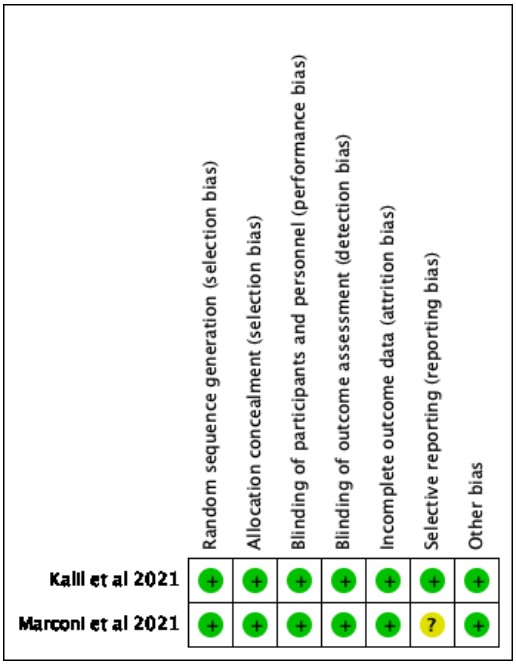

Figure 1. Risk of bias summary for baricitinib only versus standard of care/placebo studies

Table 1. Appraisal for the observational study (baricitinib versus tocilizumab)

Did the intervention in question precede the undesirable outcome?	Yes, the intervention (baricitinib) preceded the outcome
Were important prognostic factors balanced at the time of exposure? If not, were statistical adjustments made for these factors?	No, the baseline characteristics were different and patients were unmatched. There was no mention that statistical adjustments were made to compensate for the differences.
Were unbiased criteria used to determine exposure in all patients?	Yes, the patients received baricitinib, tocilizumab, both baricitinib and tocilizumab, or neither of the 2 drugs.
Were unbiased criteria used to detect the outcome in all patients?	Yes, outcomes were defined.
Was follow-up rate adequate?	Yes, there was no attrition rate since this is a retrospective study.

Appendix 5. GRADE Evidence Profile

Author(s): Isabella S. Ocampo, MD
Question: Baricitinib compared to Standard of care for COVID-19
Setting: In-hospital
Bibliography: 1. [Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. N Engl J Med. 2021;384(9):795-807. 2. Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med 2021. doi:10.1016/S2213-2600(21)00331-3.

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Baricitinib	Standard of care	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (over-all) (follow up: 28 days)												
2	randomised trials	not serious	not serious	not serious	serious [a]	none	86/1277 (6.7%)	137/1274 (10.8%)	**RR 0.63** (0.49 to 0.81)	**40 fewer per 1,000** (from 55 fewer to 20 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Duration of hospitalization (follow up: 28 days)												
2	randomised trials	not serious	not serious	not serious	serious [b]	none	1277	1274	-	MD **0.1 days lower** (1.55 lower to 1.35 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Progression of oxygen use (follow up: 28 days)												
2	randomised trials	not serious	not serious	not serious	serious [c]	none	328/1279 (25.6%)	379/1279 (29.6%)	**RR 0.87** (0.76 to 0.98)	**39 fewer per 1,000** (from 71 fewer to 6 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Serious adverse events (follow up: 28 days)												
2	randomised trials	not serious	not serious	not serious	serious [c]	none	191/1265 (15.1%)	242/1270 (19.1%)	**RR 0.79** (0.67 to 0.94)	**40 fewer per 1,000** (from 63 fewer to 11 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Adverse events (follow up: 28 days)												
2	randomised trials	not serious	serious [d]	not serious	serious [b]	none	602/1257 (47.9%)	661/1261 (52.4%)	**RR 0.91** (0.75 to 1.10)	**47 fewer per 1,000** (from 131 fewer to 52 more)	⨁⨁◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. There is a small number of events.
b. There is a wide confidence interval.
c. Upper limit of confidence interval crosses the threshold for meaningful benefit.
d. There is significant heterogeneity.

Author(s): Isabella S. Ocampo, MD
Question: Baricitinib compared to Tocilizumab for COVID-19
Setting: In-hospital
Bibliography: Rosas J, Liano FP, Canto ML et al. Experience with the use of baricitinib and tocilizumab monotherapy or combined, in patients with interstitial pneumonia secondary to Coronavirus COVID19: A real-world study. Reumatol Clin. 2020. https://doi.org/10.1016/j.reuma.2020.10.009

Certainty assessment							Impact	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Days with symptoms (follow up: 30 days)									
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	There is no significant difference between baricitinib only versus tocilizumab only (MD -0.90, 95% CI -5.54 to 3.74) and baricitinib only versus combination baricitinib + tocilizumab (MD -2.10, 95% CI -6.97 to 2.77).	⨁◯◯◯ VERY LOW	CRITICAL
Length of hospital stay (follow up: 30 days)									
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	There is no significant difference between the baricitinib only versus tocilizumab only groups (MD 0.90 days, 95% CI -1.82 to 3.62) as well as the baricitinib only versus combination baricitinib + tocilizumab groups (MD -0.30 days, 95% CI -3.20 to 2.60).	⨁◯◯◯ VERY LOW	CRITICAL
Need for ICU admission (follow up: 30 days)									
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	There was significantly less ICU admissions in the baricitinib only group versus the tocilizumab only group though with minimal effect (RR 0.06, 95% CI 0-0.92) but there was no significant difference between the baricitinib only group versus the combination baricitinib + tocilizumab group (RR 0.13, 95% CI 0.01-2.30).	⨁◯◯◯ VERY LOW	CRITICAL
Overall mortality (follow up: 30 days)									
1	observational studies	serious [a]	not serious	not serious	serious [b]	none	There was no significant difference between the baricitinib only versus tocilizumab only groups (RR 0.83, 95% CI 0.18-3.88) and the baricitinib only versus combination baricitinib + tocilizumab groups (RR 0.61, 95% CI 0.12-3.00).	⨁◯◯◯ VERY LOW	CRITICAL

CI: Confidence interval

Explanations

a. There is a serious risk of bias due to imbalance of prognostic factors with no statistical adjustments made.
b. There is a small sample size and wide confidence intervals.

Appendix 6. Forest Plots

Baricitinib versus standard of care

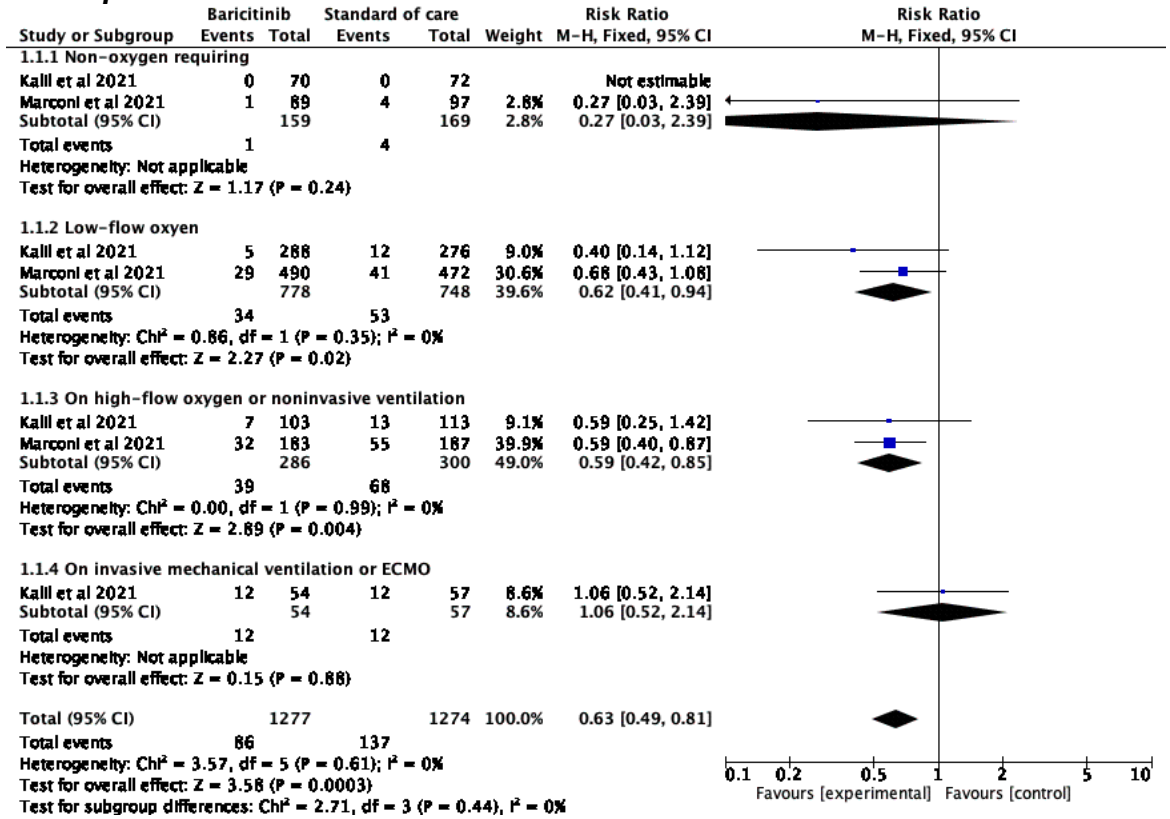

Figure 1. All-cause mortality by oxygen requirement

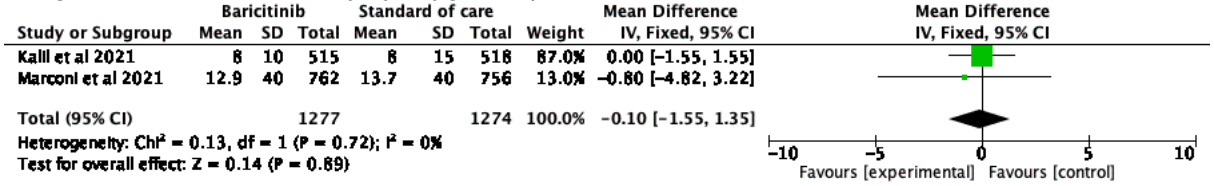

Figure 2. Duration of hospitalization

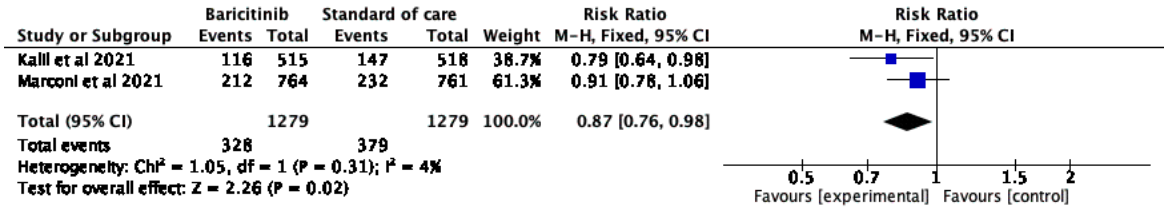

Figure 3. Progression of oxygen use

Figure 4. Serious adverse events

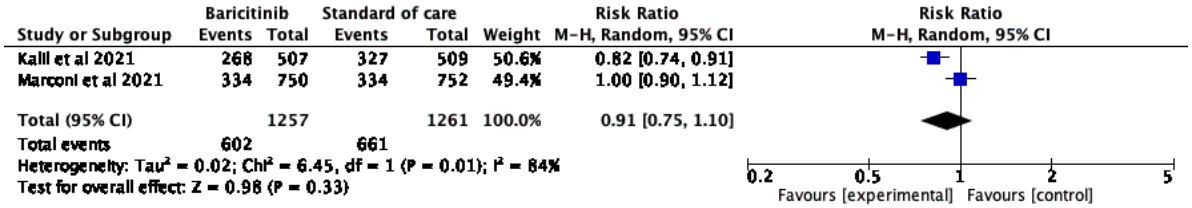

Figure 5. Adverse events

Appendix 7. Table of Ongoing Studies

Clinical Trial Identifier/Title	Participants	Interventions	Outcome
NCT04693026 Efficacy of Remdesivir and Baricitinib for the Treatment of Severe COVID 19 Patients	COVID-19 COVID-19 ARDS	Remdesivir + Baricitinib vs. Remdesivir + Tocilizumab	Time to Clinical Improvement (TTCI) Mortality Rate Duration of ICU stay Duration Total Hospital stay Rate of Daily Supplemental Oxygen Use Time to Clinical Failure
NCT04393051 Baricitinib Compared to Standard Therapy in Patients With COVID-19	COVID-19 Pneumonia	Baricitinib Oral Tablet vs. Standard of care	Need of invasive mechanical ventilation Mortality Time to invasive mechanical ventilation Time to independence from non-invasive mechanical ventilation Time to independence from oxygen therapy Time to improvement in oxygenation for at least 48 hours Length of hospital stay Length of ICU stay Instrumental response Proportion of adverse events
NCT04640168 Adaptive COVID-19 Treatment Trial 4 (ACTT-4)	COVID-19	Baricitinib and Remdesivir vs. Dexamethasone and Remdesivir	The proportion of subjects not meeting criteria for one of the following two ordinal scale categories at any time: 8) Death; 7) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) Change from baseline in alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-reactive protein (CRP), creatinine, d-dimer concentration, glucose, hemoglobin, platelets, prothrombin time (PT), total bilirubin, white blood cell count (WBC) with differential Cumulative incidence of Grade 3 and 4 clinical and/or laboratory adverse events (AEs) Cumulative incidence of serious adverse events (SAEs) Days of invasive mechanical ventilation/ extracorporeal membrane oxygenation (ECMO) Days of non-invasive ventilation/high flow oxygen Days of supplemental oxygen Desirability of Outcome Ranking (DOOR) Duration of hospitalization Incidence of discontinuation or temporary suspension of study product administration 14-day mortality 28-day mortality

			Clinical status Time to an improvement of one category from baseline using an ordinal scale Time to an improvement of two categories from baseline using an ordinal scale Time to recovery
NCT04390464 Multi-arm Therapeutic Study in Pre-ICU Patients Admitted With COVID-19 - Repurposed Drugs (TACTIC-R)	COVID19	Ravulizumab vs. Baricitinib vs. Standard of care	Time to incidence of the composite endpoint of: Death, Mechanical ventilation, ECMO, Cardiovascular organ support, or Renal failure Change in clinical status from baseline Adverse events of special interest in each treatment arm Time to Sp02 >94% on room air Time to first negative SARS-CoV2 PCR Duration of oxygen therapy Duration of hospitalization All-cause mortality at day 28 Time to clinical improvement
NCT04381936 Randomised Evaluation of COVID-19 Therapy	Severe Acute Respiratory Syndrome	Lopinavir-Ritonavir Corticosteroid Hydroxychloroquine Azithromycin Convalescent plasma Tocilizumab Immunoglobulin Synthetic neutralising antibodies Aspirin Colchicine Baricitinib Anakinra Dimethyl fumarate Standard of care	All-cause mortality Duration of hospital stay Composite endpoint of death or need for mechanical ventilation or ECMO
NCT04832880 Factorial Randomized Trial of Remdesivir and Baricitinib Plus Dexamethasone for COVID-19 (the AMMURAVID Trial)	Confirmed COVID-19 patients on oxygen therapy or with documented cytokine storm	Dexamethasone + remdesivir Baricitinib + dexamethasone Remdesivir + baricitinib Standard of care (dexamethasone)	Prevention of very severe respiratory failure or mortality Prevention of mortality (Days 7, 14, 21, 28) Survival analysis Prevention of severe respiratory failure (Days 7, 14, 21, 28) Adverse events Reduction of requirement of tracheal intubation/ECMO Time to clinical improvement Time to discharge
EUCTR2020-001321-31-ES Prospective, phase II, randomized, open-label, parallel group study to evaluate the efficacy of	Confirmed COVID-19 patients with documented pneumonia	Hydroxychloroquine + baricitinib Hydroxychloroquine + imatinib Hydroxychloroquine + lopinavir/ritonavir	Time to clinical improvement Adverse events

hydroxychloroquine together with baricitinib, imatinib or early lopinavir / ritonavir in patients with SARS Cov2 pneumonia (COVID-19 HUF) - COVID-19 HUF		Standard of care	
NCT04346147 Prospective, Phase II, Randomized, Open-label, Parallel Group Study to Evaluate the Efficacy of Baricitinib, Imatinib or Supportive Treatment in Patients with SARS Cov2 Pneumonia	Confirmed COVID-19 patients with documented pneumonia (radiologic or positive detection of SARS-CoV-2 RNA in respiratory sample)	Imatinib Baricitinib Supportive treatment	Time to clinical improvement Adverse events
NCT04321993 Treatment of Moderate to Severe Coronavirus Disease (COVID-19) in Hospitalized Patients	Patients with moderate to severe COVID-19 infection	Baricitinib vs Standard of care	Clinical status Length of time to clinical improvement Development of ARDS after treatment Time to clinical progression Duration of hospitalization and mechanical ventilation (if applicable) Adverse events
NCT04891133 European DisCoVeRy for Solidarity: An Adaptive Pandemic and Emerging Infection Platform Trial	Patients with moderate to severe COVID-19 infection	Baricitinib vs Placebo	Occurrence of death Occurrence of disease progression SpO2/FiO2-ratio Time to sustained recovery Time to first hospital discharge Viral clearance during hospitalization Adverse events