South African National Department of Health
Rapid Review Report
Component: COVID-19

TITLE: Should baricitinib be used to treat COVID-19?

Date: 6 May 2022 (second update of original 15 October 2021 rapid review report)

Key findings

- We updated the rapid review report with additional evidence regarding the benefits and harms of baricitinib for treating patients hospitalised with COVID-19 on supplemental oxygen.
- We identified three randomised placebo-controlled trials (RCTs) pooled in a Cochrane living review (https://covid-nma.com/)
- Overall, amongst adult patients, baricitinib reduced progression to mechanical ventilation with/without additional organ support (ECMO, vasopressors or dialysis) or death (WHO progression score (level 7 or above) by day 28: relative risk (RR): 0.87, 95% confidence interval (CI) 0.78 to 0.97); high certainty evidence. The number needed to treat to prevent one patient from deteriorating clinically was 52 (95% CI 30 to 214).
- Baricitinib reduced all-cause mortality at Day 28 (risk ratio (RR) 0.75; 95% CI 0.58 to 0.98) (moderate certainty evidence). The number needed to treat to prevent one death was 50 (95% CI 30 to 146).
- There were no differences in adverse events (RR 0.98; 95% CI 0.88 to 1.05, moderate certainty evidence), but possibly less serious adverse events associated with baricitinib compared to control (RR 0.77; 95% CI 0.64 to 0.94, moderate certainty evidence).
- Overall, the trials were assessed as high quality and the benefits of baricitinib outweighed the risks.
- Baricitinib is contraindicated in pregnancy – refer to Addendum A (Management of severe COVID-19 in pregnancy) for guidance on the use of immunomodulators in pregnancy.
- There is uncertainty regarding use of baricitinib in children.

NEML MAC ON COVID-19 THERAPEUTICS RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
					X

Recommendation: The Committee recommends baricitinib for use in hospitalised patients with confirmed COVID-19 who require supplemental oxygen. This recommendation is dependent on baricitinib being accessible to all eligible public sector patients in South Africa*.

Rationale: Baricitinib reduced mortality, and was not associated with an increased risk of adverse events. It is cheaper than tocilizumab, and may be administered orally (or via nasogastric tube). However, the committee is concerned that cost may result in inequitable access, and there is uncertainty regarding supply.

Level of Evidence: Moderate to high certainty evidence

Review indicator: Equitable funding; results of further RCTs; confirmation of adequate supply

*** *Note:* *Real-world rates of hospitalisation are likely to be more modest than the modelled basic budget impact analysis- Provinces to monitor local hospitalisation rates to determine local budgetary impact/affordability.*

(Refer to appendix 2 for the evidence to decision framework)

NEML MAC on COVID-19 Therapeutics: Andy Parrish (chair), Gary Reubenson (vice-chair), Marc Blockman, Karen Cohen, Andy Gray, Tamara Kredo, Renee De Waal, Jeremy Nel, Helen Rees. Secretariat: Trudy Leong, Milli Reddy.

Note: Due to the continuous emergence of new evidence, the rapid review will be updated if and when more relevant evidence becomes available – see table 3 for planned and ongoing registered studies.

PROSPERO registration: CRD42021286710

BACKGROUND

In patients infected with SARS-CoV-2, disease severity and outcomes are related to the characteristics of the immune response. [1-6] The median time from onset of symptoms of COVID-19 to the development of acute respiratory distress syndrome (ARDS) is as short as 8 days. [7] Interleukin (IL)-6 and other components of the inflammatory cascade play an important role in the inflammatory reaction and immune response.[8] However, excessive cytokine production ('cytokine storm') as part of a hyperinflammatory response has been suggested as a cause of severe COVID-19. [1-3]

Baricitinib is a Janus kinase inhibitor that has anti-inflammatory properties.[8] Baricitinib is registered for the treatment of several dermatological conditions, rheumatoid arthritis and COVID-19.[9-10] Several observational studies of hospitalised patients with COVID-19 showed evidence of clinical improvement with baricitinib. [11-13] It reduces levels of multiple cytokines associated with the pathophysiology of COVID-19 disease, as well as having anti-viral activity.[14] Furthermore, in a phase 3 double-blind, randomised controlled trial in hospitalised COVID-19 patients, treatment with baricitinib plus remdesivir was found to reduce time to recovery (rate ratio 1.16; 95% CI 1.01 to 1.32) and was associated with fewer adverse events compared to treatment with remdesivir alone, although there was no significant difference in mortality at 28 days between the two groups (5.1% with baricitinib and remdesivir vs 7.8% with remdesivir); Hazard ratio 0.65; 95% CI 0.39 to 1.09.[15] Subsequently, additional RCT data has been published, warranting the updating of the rapid review report (see Appendix 3).

RESEARCH QUESTION: What is the efficacy and safety of baricitinib for the treatment of hospitalised patients with confirmed COVID-19 regardless of their oxygen requirements?

METHODS

This is the second update of the initial review conducted in 2021, where four electronic databases were searched: Cochrane Library COVID-19 study register, PubMed, and the Epistemonikos LOVE platform and the COVID-NMA Living review database on 7 September 2021. The full search strategy can be found in Appendix 1. The retrieved records were imported into the Covidence software for title and abstract, and full text, screening. Screening of records, selection of articles and data extraction was done independently and in duplicate by two reviewers with conflict resolution by a third reviewer The Cochrane ROB 2.0 tool was used to appraise the risk of bias of the included trial and results were presented, available or from the Living Systematic Review on the www.covid-nma.com website. GRADE was used to assess the overall confidence of the evidence considering various factors that may decrease our confidence in the trial finding including risk of bias, inconsistency, imprecision, publication bias and indirectness. [16]

On 11 April 2022, an updated search of two electronic databases, Epistemonikos LOVE platform and the COVID-nma.com Living review, was conducted (see Appendix 1 for the full search strategy). Records were screened to identify new RCTs evaluating the effect of baricitinib compared to standard of care or placebo in the management of COVID-19. The evidence (3 RCTs) from the Cochrane living review was synthesised and the study characteristics, study outcomes, risk of bias assessment and appraisal of the quality of evidence were reported in the updated rapid review. Table 1 describes the study characteristics and Table 2 summarises the evidence profiles.

Eligibility criteria for review

Population: Hospitalised patients with COVID-19 (whether requiring oxygen therapy or not); no restriction to age or co-morbidity.

Intervention: Baricitinib, alone or in combination with any other agent; no restriction on dose, frequency, or timing with respect to onset of symptoms.

Comparators: Standard of care +/- placebo.

Outcomes: Mortality; duration of ventilatory support including mechanical ventilation; duration of ICU stay; progression to ICU admission, progression to mechanical ventilation or requiring oxygen, clinical outcome on an ordinal scale, adverse events, adverse reactions.

Study designs: Randomised controlled trials and systematic reviews of randomised controlled trials.

RESULTS

Results of the search

Initial search: The initial search, conducted in September 2021, identified 127 records. Following the removal of duplicates, 107 titles and abstracts and then 43 potentially eligible full-text records were screened against the PICO. Of the 43 full-text records, 42 were excluded. One RCT[17] was eligible for inclusion in the review. Study selection is shown in the Prisma flow graphic as Figure 1.

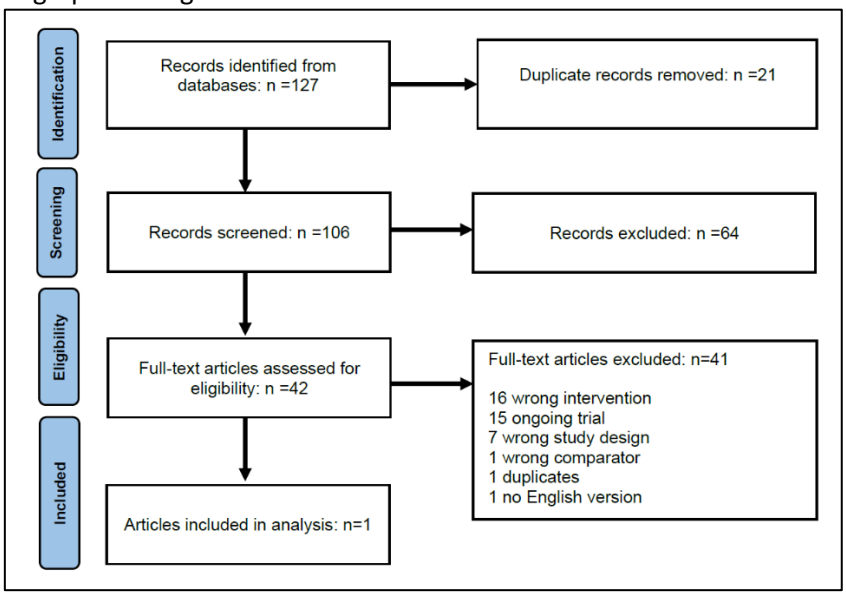

Figure 1: PRISMA flow diagram for the initial review

Updated search: On 11 April 2022, two electronic databases, Epistemonikos LOVE platform and the COVID-nma.com Living review, were searched. The full search strategy can be found in Appendix 1. Thirty records were retrieved, of which 4 were duplicates. Screening of the remaining 26 records identified two additional RCTs.[18, 19] Furthermore, the living review of baricitinib identified in the COVID-NMA database was a systematic review of the 3 RCTs selected for evidence synthesis.[17-19] Thus, the updated Cochrane-supported living review[20]and the 3 RCTs have been included in this review update.

Excluded studies

In the initial search, 41 studies were excluded, mostly because they didn't evaluate baricitinib, they were ongoing studies, or they were the wrong study design.

In the updated search conducted on 11 April 2022, 26 records were excluded as they did not meet the eligibility criteria or the systematic review was not current (see Table 3).

The ACTT-2 trial,[15] which evaluated baricitinib plus remdesivir compared with remdesivir was excluded. Steroid use was allowed only if part of a written treatment policy at the hospital, or for indications other than COVID-19. Steroids were used by 56/515 (11%) patients in the baricitinib plus remdesivir arm and 67/518 (13%) patients in the remdesivir arm. The study was excluded as it involved an active comparator that is not the standard of care in South Africa, and the majority of the patients did not receive current standard of care (corticosteroids for those who require oxygen).

Effects of intervention(s)

The COVID-NMA living review[20] pooled data from 3 RCTs trials (n=9782)[17-19] conducted in hospitalised patients, comparing either baricitinib to standard of care/placebo:

- **Mortality**

The risk of 28-day all-cause mortality was reduced with baricitinib by 25% (RR 0.75, 95% CI 0.58 to 0.98), equivalent to 35 fewer per 1000 (from 59 fewer to 3 fewer). The absolute risk reduction (ARR) is 2.02% (95% CI 0.69 to 3.35%) and one additional death would be prevented per 50 participants treated with baricitinib (95% CI 30 to 146). This evidence was considered to be of moderate certainty due to considerable heterogeneity, I^2=67.3% (see figure 2).

There was a 31% reduction in 60-day all-cause mortality with the use of baricitinib (RR 0.69; 95% CI 0.56 to 0.86), with an absolute risk difference of 5.61% (95% CI 2.12 to 9.1%). The evidence was downgraded to moderate certainty evidence for imprecision due to the low number of participants (n=1626, 2 RCTs).

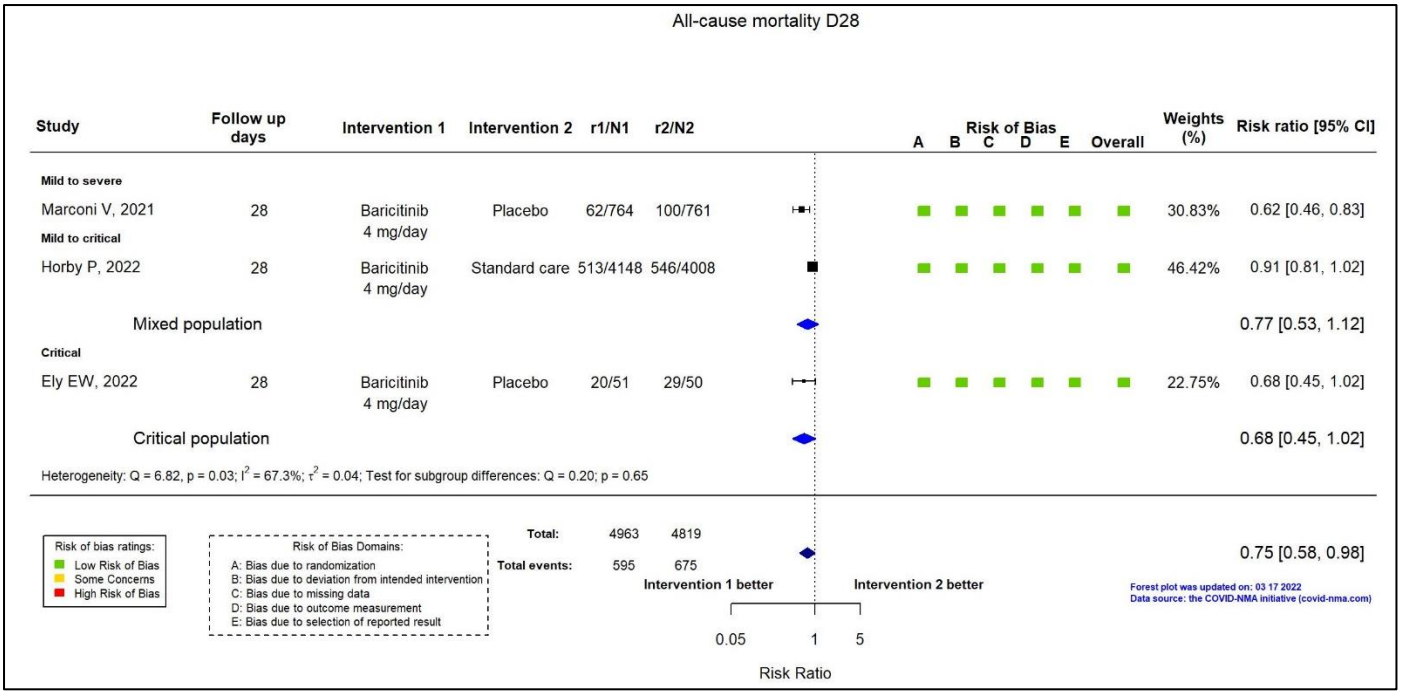

Figure 2: Forest plot of Day 28 all-cause mortality (COVID-nma living review)

- **Clinical deterioration - mechanical ventilation +/- additional organ support (ECMO, vasopressors or dialysis) or death** [WHO progression score level 7 or above]

  Baricitinib reduced the risk of progression to WHO progression score level 7 or above by day 28 (761/4963 (15.33%) compared to placebo 832/4819 (17.26%); RR 0.87; 95% CI 0.78 to 0.97 (high certainty evidence). This is equivalent to 22 fewer per 1000 (from 38 fewer to 5 fewer) amongst those who received baricitinib with a NNT of 52 (95% CI 30 to 214), see figure 3. Note that individual outcomes of duration of hospitalisation, duration of ICU stay or duration of respiratory support was not reported separately in the COVID-NMA living review.

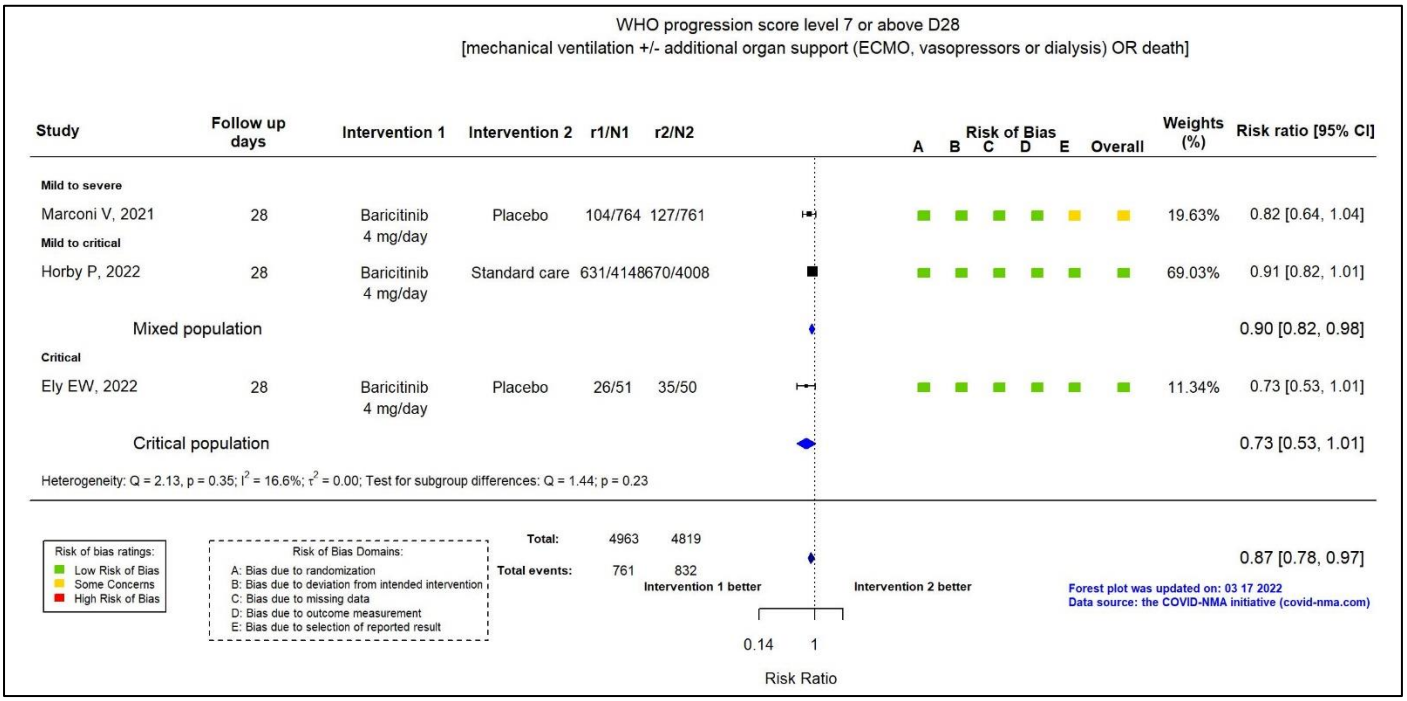

Figure 3: Forest plot of WHO progression score level 7 or above at day 28 Day 28 (COVID-nma living review)

- **Clinical improvement at day 28**
  There was no difference in clinical improvement at day 28 among those receiving baricitinib compared to the control group (RR 1.02, 95% CI 1.00 to 1.05), high certainty evidence. The mean difference was 0.02 days (95% CI -0.62 to 0.65). This was assessed as high certainty evidence.

- **Adverse events**
  There was no difference in the number of adverse events between the baricitinib group compared to the control group (RR 0.96; 95% CI 0.88 to 1.05). This was assessed as moderate certainty evidence for concerns of imprecision due to the low number of study participants (n=1626, 2 RCTs).

- **Serious adverse events (SAEs)**
  There were marginally fewer SAEs in the baricitinib arm (135/812; 16.63%) compared to the standard of care arm(170/811; 20.96%); RR 0.77, 95% 0.64 to 0.94, assessed as moderate certainty due to imprecision and low number of study participants (n=1626, 2 RCTs). There were 48 fewer SAEs per 1000 people treated with baricitinib (ranging from 75 fewer to 13 fewer per 1000) with a number needed to harm (NNH) of 24 (95% CI 13 to 185). See figure 4.

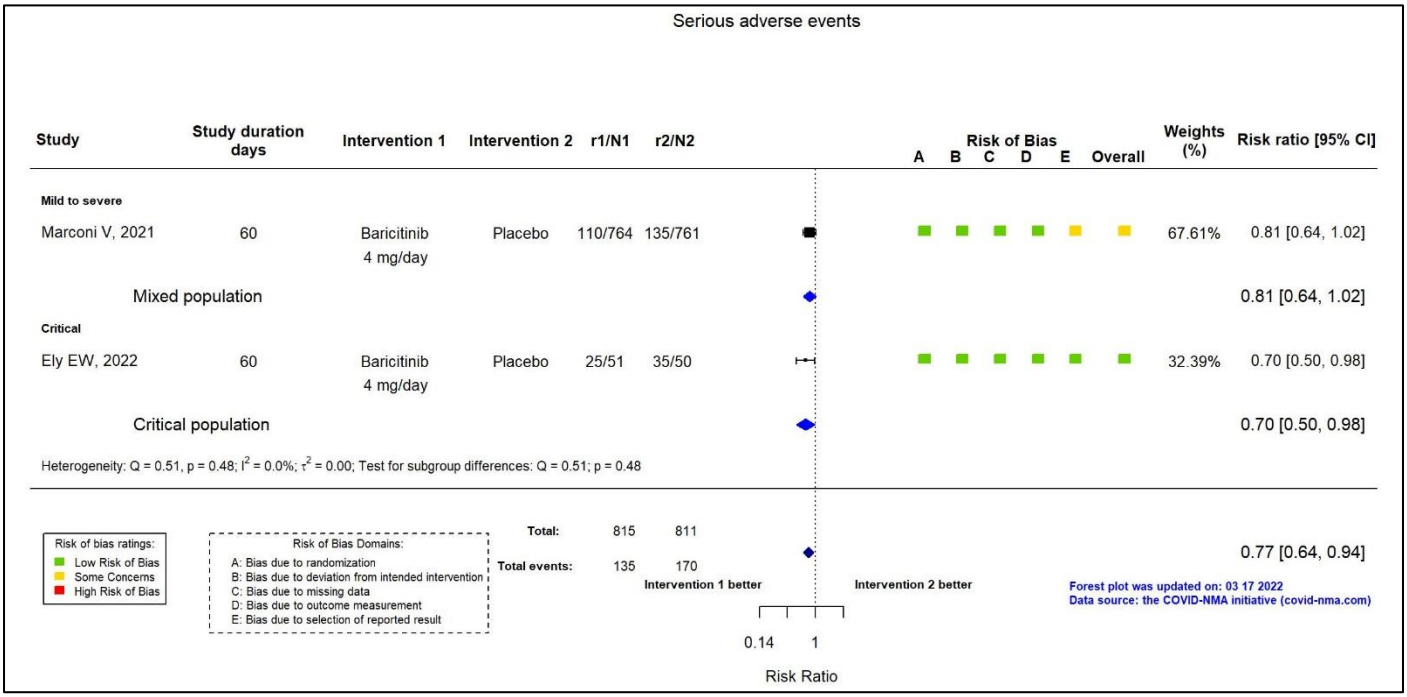

Figure 4: Forest plot of SAEs (COVID-nma living review)

CONCLUSION

A living review of three RCTs showed that baricitinib reduced the risk of 28-day mortality (RR 0.75, 95% CI 0.58 to 0.98) compared to standard of care with an absolute risk reduction of 2.02% (95% CI 0.69 to 3.35%) and number needed to treat to prevent 1 death of 50 (95% CI 30 to 146). However, the evidence was appraised as moderate certainty as the pooled data was heterogeneous (I^2=67.3%) comprising of hospitalised study populations with varying severity of disease ranging from mild, moderate, severe to critical. Likewise, baricitinib reduced the progression to invasive mechanical ventilation with/without organ support or death (WHO progression score level 7 or above). Adverse events and serious adverse events were not increased in study participants on baricitinib.

Reviewers:

Updated review, May 2022: Trudy Leong, Marc Blockman, Jacqui Miot, Halima Dawood.

Initial review, October 2021: Marc Blockman, Renee de Waal, Ntombifuthi Blose, Veranyuy D Ngah, Tamara Kredo.

Declaration of interests: MB (Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town), RdW (Centre for Infectious Disease Epidemiology and Research, University of Cape Town), HD (Greys hospital, University of Kwa-ZuluNatal), JM (HE^{2}RO, University of Witwatersrand) and TL (Essential Drugs Programme, National Department of Health) have no interests to declare in respect of baricitinib. TK (Cochrane South Africa, South African Medical Research Council (SAMRC); Division of Clinical Pharmacology, Department of Medicine and Division of Epidemiology and Biostats, Department of Global Health, Faculty of Medicine and health Sciences, Stellenbosch University; TK is co-director of the South African GRADE Network and TK, NB and VDN are partly supported by the Research, Evidence and Development Initiative (READ-It) project and the Collaboration for Evidence Based Health Care and Public Health in Africa COVID-19 project funding (CEBHA+). READ-It (project number 300342-104) is funded by UK aid from the UK government; however, the views expressed do not necessarily reflect the UK government's official policies.)

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Table 1. Characteristics of included trials

Citation	Study design	Population (n)	Treatment and comparison	Main findings	Risk of Bias
Marconi V, et., al[17] COV-BARRIER (NCT0441027) Lancet Respiratory Medicine, 2021	Randomised (1:1) double-blinded, placebo-controlled, parallel-group, phase 3 trial Date: June 11, 2020, to Jan 15, 2021 Setting: Multicentre (Argentina, Brazil, Mexico, USA) Follow up: 14 days	Asia, Europe, North America, and South America. Population 1: All randomly allocated participants Population 2: Subpopulation on oxygen and not receiving steroids at baseline n=1525 [Baricitinib group (n=764), placebo group (n=761)] Mean (sd) age: 57.6 (14.1) Baricitinib 57.8 (14.3); Placebo 57.5 (13.8) <65 years: 508/764 (66%) in baricitinib and 518/761 (68%) placebo ≥65 years: 256/764 (34%) in baricitinib and 243/761 (32%) placebo Sex: Overall-: 963 (63.1%) were male. baricitinib (males: 490/764 (64%) females: 274/764 (36%); placebo (males: 473/761 (62%) females: 288/761 (38%)	**Intervention:** Baricitinib at 4 mg/day; however, 2 mg/day to patients with baseline eGFR of 30 to less than 60 mL/min/1.73 m² + SOC (corticosteroids, antivirals, prophylaxis for venous thromboembolic events) Delivery: oral or crushed for nasogastric tube **Comparison:** Placebo + SOC	28-day all-cause mortality: Population 1: 8% (n=62) for baricitinib and 13% (n=100) for placebo (hazard ratio [HR] 0·57 [95% CI 0·41–0·78]; nominal p=0·0018), a 43% relative reduction in mortality; one additional death was prevented per 20 baricitinib-treated participants. Population 2: 28-day all-cause mortality was 5% (five of 96 participants) in the baricitinib group and 15% (16 of 109) in the placebo group, equating to a 69% relative reduction (HR 0·31 [95% CI 0·11–0·88], nominal p=0·030 60-day all-cause mortality: was 10% (n=79) for baricitinib and 15% (n=116) for placebo (HR 0·62 [95% CI 0·47–0·83]; p=0·0050) Serious adverse events: (110 [15%] of 750 in the baricitinib group vs 135 [18%] of 752 in the placebo group), serious infections (64 [9%] vs 74 [10%]), and venous thromboembolic events (20 [3%] vs 19 [3%]) were similar between the two groups. Progression to high-flow oxygen &Non-invasive ventilation & mechanical ventilation (MV) or extracorporeal membrane oxygenation (ECMO): "the	**Risk of Bias:** Overall assessment: MODERATE RISK • *Randomisation:* LOW RISK – Random allocation sequence that was probably concealed. Imbalances in baseline characteristics appear to be compatible with chance. • *Deviations from intervention:* LOW RISK – Probably blinded study (participants and personnel/carers). Data analysis was done using intention-to-treat analysis which is appropriate. • *Missing outcome data:* LOW RISK – 1525 participants randomised; 1502 to 1525 participants analyzed (depending on the outcome). Data available for all or nearly all participants randomized. Risk assessed to be low for the outcomes: Mortality (D28). Mortality (D60 or more). Time to death. Clinical improvement (D28). Time to clinical improvement. WHO score 7 and above (D28). Adverse events. Serious adverse events. • *Measurement of outcome:* LOW RISK – Method of measuring the outcome probably appropriate. Measurement or ascertainment of outcome probably does not differ between groups. Probably blinded study (outcome assessor). • *Selection of the reported results:* MODERATE RISK – Mortality outcome pre-specified and analysed as pre-specified. However, mortality (D60 or more), time to death, clinical improvement (D28), time to clinical improvement, WHO score 7 and above, adverse events, serious

Citation	Study design	Population (n)	Treatment and comparison	Main findings	Risk of Bias
				proportion of patients who progressed to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, or death by day 28 (the composite primary endpoint) was 27·8% in the baricitinib group and 30·5% in the placebo group (odds ratio [OR] 0·85 [95% CI 0·67–1·08], p=0·18" - all randomly allocated participants	adverse events were not prespecified. Uncertain whether these results were selected from multiple outcome measurements or analyses of the data.
Ely EW et al.,[18] COV-BARRIER (NCT04421027) – critically ill cohort - Lancet Respiratory Medicine, 2022	Double-blind, RCT Setting: Multicentre (Argentina, Brazil, Mexico, USA) Follow up: 60 days	Adult patients with critical disease (n= 101), randomised to baricitinib (n1=51) or placebo (n2=50) Study achieved it's sample size 55 males, 56 females Mean age not reported *Severity:* Critical *Inclusion criteria:* ≥18 years of age; hospitalized with laboratory-confirmed SARS-CoV-2 infection; use of invasive mechnanical ventilation or ECMO at study entry and randomisation; evidence of pneumonia or clinical symptoms of COVID-19; at least one elevated inflammatory marker above the upper limit of normal range based on the local laboratory result (C-reactive protein, D-dimer, lactate dehydrogenase, or ferritin). *Exclusion criteria:* Receiving high dose corticosteroids (>20 mg per day [or prednisone equivalent] administered for >14 consecutive days in the month before study entry, unless indicated per standard of care for a concurrent condition, such as	**Intervention:** Baricitinib at 4 mg/day; however, 2 mg/day to patients with baseline eGFR of 30 to less than 60 mL/min/1.73 m² + SOC (corticosteroids, antivirals, prophylaxis for venous thromboembolic events) Delivery: oral or crushed for nasogastric tube **Comparison:** Placebo + SOC	**Exploratory primary outcomes:** *Baricitinib vs placebo* 28-day cause mortality: 20 (39%) vs 29 (58%); HR 0.54 (0.31 to 0.96) Ventilator-free days: 8.1 (10.2%) vs 5.5 (8.4%); least square mean difference 2.36 (–1.38 to 6.09); ns ≥1-point improvement on NIAID-OS or live discharge from hospital (D28): 23 (45%) vs 15; OR 1.80 (0.78 to 4.14) (30%); ns Duration of hospital stay (days) 23.7 (7.1%) vs 26.1 (3.9%); least square mean difference –2.30 (–4.59 to 0.00); ns	ITT analysis of an exploratory RCT of critically ill cohort not included in the main COV-BARRIER trial **Risk of Bias:** Overall assessment: **LOW RISK** • *Randomisation:* **LOW RISK** – Random allocation sequence that was probably concealed. • *Deviations from intervention:* **LOW RISK** – Blinded study (participants and personnel/carers); ITT analysis. • *Missing outcome data:* **LOW RISK** – 101 participants randomised; 97 participants analysed for worsened clinical progression or death, but 101 analysed for other outcomes. • *Measurement of outcome:* **LOW RISK** – Blinded study outcome assesors. • *Selection of the reported results:* **LOW RISK** – Outcomes pre-specified and trial analysed as pre-specified.

Citation	Study design	Population (n)	Treatment and comparison	Main findings	Risk of Bias
		asthma, chronic obstructive pulmonary disease, or adrenal insufficiency), immunosuppressants, biologics, T cell or B cell-targeted therapies, interferon, or JAK inhibitors; receipt of convalescent plasma or intravenous immunoglobulin for COVID-19; suspected serious active bacterial, fungal, or other infection, or untreated tuberculosis infection.			
Horby P et al., [19] RECOVERY (NCT04381936; EudraCT2020-001113-21; ISRCTN50189673) medRxiv, 2022	Open-label, unblinded, RCT Setting: Multicentre (UK) Follow up: 28 days	n=8156 (Baricitinib=4148; SOC=4008) 5378 males, 2778 females Mean age not reported *Severity:* Mild=465 Moderate=5513 Severe=1927 Critical=251 *Inclusion criteria:* Patients aged at least 2 years admitted to hospital; clinically suspected or laboratory confirmed SARS-CoV-2 infection; no medical history that might, in the opinion of the attending clinician, put the patient at significant risk if they were to participate in the trial; written informed consent from all patients, or a legal representative if patients were too unwell or unable to provide consent *Exclusion criteria:* Aged <2 years; eGFR <15 mL/min/1.73m^2 or on dialysis or	**Intervention:** Baricitinib 4 mg orally per day x10 days or discharge (reduced for patients with impaired renal function or children <9 years) **Comparison:** SOC	**Primary outcome:** *Baricitinib vs SOC* 28-day all-cause mortality 513/4148 (12%) vs 546/4008 (14%); age-adjusted rate ratio 0·87; 95% CI 0.77 to 0.98; p=0·026. **Secondary outcomes:** *Baricitinib vs SOC* Median (IQR) time to being discharged alive, days: 8/4148 (95% CI 5 to 17) vs 8/4008 (95% CI 5 to 20) Discharged from hospital within 28 days: 3337/4148(80%) vs 3137/4008 (78%); RR 1.10 (95% CI 1.04 to 1.15; p<0.001. Receipt of invasive mechanical ventilation or death: 631/4014 (16%) vs 670/3891 (17%; RR 0.90 (95% CI 0.81 to 0.99); p= 0.026	Preprint was analysed, as peer-review publication pending. Pre-print article, the registry, protocol, statistical analysis plan and supplementary appendices were used in data extraction and assessment of risk of bias. The primary outcome in the article reflects the registry and protocol. Recruitment to the trial was terminated after a planned interim analysis on the decision of the Trial Steering Committee when a statistically significant reduction in all-cause mortality was detected. Inclusion criterion patients ≥2 years of age, and 33 children were randomised, but outcome data was not stratified for children. **Risk of Bias:** Overall assessment: MODERATE RISK • *Randomisation:* LOW RISK – Random allocation sequence that was probably concealed. Imbalances in baseline characteristics appear to be compatible with chance. • *Deviations from intervention:* LOW RISK – Unblinded study (participants and personnel/carers); Minor deviations did not arise because of the

Citation	Study design	Population (n)	Treatment and comparison	Main findings	Risk of Bias
		haemofiltration; neutrophil count <0.5 × 109/L; evidence of active TB infection; pregnant or breastfeeding			trial context; and analysed as ITT analysis. • *Missing outcome data:* **LOW RISK** – Data available for all or nearly all participants randomized. Risk assessed to be low for the outcomes: Mortality (D28). Clinical improvement (D28). WHO score 7 and above (D28). • *Measurement of outcome:* **MODERATE RISK** – Unblinded study outcome assessors. For outcomes of mortality and WHO score 7 and above (D28), risk assessed as low as objectively assessed; but clinical improvement (defined as discharged alive) requires clinical judgement and there is some concern of risk of bias. • *Selection of the reported results:* **LOW RISK** –Trial analysed as pre-specified in the registry protocol.

Table 2: Summary of findings

Question: Baricitinib compared to standard care for COVID-19

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	baricitinib	SOC	Relative (95% CI)	Absolute (95% CI)	
Mortality (follow-up: 28 days)											
3	RCTs	not serious	serious [a]	not serious	not serious	none	595/4963	675/4819	**RR 0.75** (0.58 to 0.98)	**35 fewer per 1,000** (from 59 fewer to 3 fewer)	⊕⊕⊕◯ Moderate
Mortality (follow-up: 60 days)											
2	RCTs	not serious	not serious	not serious	serious [b]	none	102/815	147/811	**RR 0.69** (0.56 to 0.86)	**56 fewer per 1,000** (from 80 fewer to 25 fewer)	⊕⊕⊕◯ Moderate
Clinical deterioration - mechanical ventilation +/- additional organ support (ECMO, vasopressors or dialysis) or death [WHO progression score level 7 or above]											
3	RCTs	not serious	not serious	not serious	not serious	none	761/4963	832/4819	**RR 0.87** (0.78 to 0.97)	**22 fewer per 1000** (from 38 fewer to 5 fewer)	⊕⊕⊕⊕ High
Clinical improvement (follow-up: 28 days)											
3	RCTs	not serious	not serious	not serious	not serious	none	3953/4963	3744/4819	**RR 1.02** (1.00 to 1.05)	**16 more per 1000** (from 0 fewer to 39 more)	⊕⊕⊕⊕ High
Adverse events											
2	RCTs	not serious	not serious	not serious	serious [b]	none	378/815	381/811	**RR 0.96** (0.88 to 1.05)	**19 fewer per 1,000** (from 56 fewer to 23 more)	⊕⊕⊕◯ Moderate
Serious adverse events											
2	RCTs	not serious	not serious	not serious	serious [b]	none	135/812	170/811	**RR 0.77** (0.64 to 0.94)	**48 fewer per 1,000** (from 75 fewer to13 fewer)	⊕⊕⊕◯ Moderate

CI: confidence interval; **RCT:** randomised control trial; **RR:** risk ratio

Explanations

a. Inconsistency downgraded by 1 level: I^2=:67.3%

b. Downgraded by one level due to low number of participants

Table 3. Excluded studies/ records (updated search of 11 April 2022)

Study/ record	Reason for exclusion
1. RECOVERY Trial Investigators. New RECOVERY trial result: baricitinib reduces deaths in patients hospitalised with COVID-19. Press release - RECOVERY trial - 3 March 2022	Press release
Duplicate record	
3. Horby PW, et al Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. medRxiv. 2022	Duplicate record
4. Eli Lilly and Company. Lilly and Incyte's baricitinib reduced deaths among patients with COVID-19 receiving invasive mechanical ventilation. Press release - PR Newswire - Aug 03, 2021, 06:00 ET. 2021	Press release
Press release	
6. Marconi VC, et al, COV-BARRIER Study Group. 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. The Lancet. Respiratory medicine. 2021	Duplicate record
7. Marconi, VC, et al. Efficacy and safety of baricitinib in patients with COVID-19 infection: Results from the randomised, double-blind, placebo-controlled, parallel-group COV-BARRIER phase 3 trial. medRxiv. 2021	Preprint, peer reviewed publication published
8. Kalil, AC, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. New England Journal of Medicine. 2021;384(9):795-807	PICO eligibility criteria not met
9. Ely WE et al. Baricitinib plus Standard of Care for Hospitalised Adults with COVID-19 on Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation: Results of a Randomized, Placebo-Controlled Trial. medRxiv. 2021	Preprint, peer reviewed publication published
10. Eli Lilly and Company. Baricitinib in Combination with Remdesivir Reduces Time to Recovery in Hospitalized Patients with COVID-19 in NIAID-Sponsored ACTT-2 Trial. Press release - lilly.com. 2020	Press release
11. Eli Lilly and Company and Incyte. Baricitinib Receives Emergency Use Authorization from the FDA for the Treatment of Hospitalized Patients with COVID-19. Press release - lilly.com. 2020	Press release
More recent living review identified.	
13. Comisión Nacional de Evaluación de Tecnologías de Salud. Baricitinib for the treatment of patients with COVID-19. 2022	Spanish publication
14. Getso MI, et al. Therapeutic strategies for COVID-19 patients: An update. Infectious disorders drug targets. 2022	Narrative review & PICO eligibility criteria not met
More recent living review identified.	
16. Zhiwei Lin, et al. Clinical Efficacy and Adverse Events of Baricitinib Treatment for Coronavirus Disease-2019 (COVID-19): A Systematic Review and Meta-Analysis. SSRN. 2021	More recent living review identified.
More recent living review identified.	
18. Alunno A, et al. Immunomodulatory therapies for SARS-CoV-2 infection: a systematic literature review to inform EULAR points to consider. Annals of the rheumatic diseases. 2021	More recent living review identified.
19. Wijaya I, et al. The use of Janus Kinase inhibitors in hospitalized patients with COVID-19: Systematic review and meta-analysis. Clinical epidemiology and global health. 2021;11:100755	More recent living review identified.
20. Atzeni F, et al. The Rheumatology Drugs for COVID-19 Management: Which and When?. Journal of clinical medicine. 2021;10(4):1-21	PICO eligibility criteria not met
21. Atzeni F, et al. The Rheumatology Drugs for COVID-19 Management: Which and When?. Journal of clinical medicine. 2021;10(4):1-21	Duplicate record
22. Patoulias D, Doumas M, Papadopoulos C, Karagiannis A. Janus kinase inhibitors and major COVID-19 outcomes: time to forget the two faces of Janus! A meta-analysis of randomized controlled trials. Clinical rheumatology. 2021;	More recent living review identified.
23. Chen CX, et al. JAK-inhibitors for coronavirus disease-2019 (COVID-19): a meta-analysis. Leukemia. 2021;35(9):2616-2620	More recent living review identified.
24. Ngamprasertchai T, et al. Efficacy and Safety of Immunomodulators in Patients with COVID-19: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials. Infectious diseases and therapy. 2021	More recent living review identified.
25. Ananyan S et al. Use of Baricitinib in Treatment of COVID-19: A Systematic Review. medRxiv. 2021	More recent living review identified.
26. Lin Z, et al. Clinical efficacy and adverse events of baricitinib treatment for coronavirus disease-2019 (COVID-19): A systematic review and meta-analysis. Journal of medical virology. 2021	More recent living review identified.
27. Alunno A, et al. Immunomodulatory therapies for the treatment of SARS-CoV-2 infection: an update of the systematic literature review to inform EULAR points to consider. RMD open. 2021;7(3)	More recent living review identified.
28. Cantini F, et al. Immune Therapy, or Antiviral Therapy, or Both for COVID-19: A Systematic Review. Drugs. 2020;80(18):1929-1946	PICO eligibility criteria not met
29. Zhang C, et al. A Systematic Review and Network Meta-Analysis for COVID-19 Treatments. medRxiv. 2020	PICO eligibility criteria not met
30. Karatee DE, et al. Иммуномодулирующая медикаментозная терапия при заболевании, вызванном инфекцией SARS-CoV-2 (COVID-19). Almanac of Clinical Medicine. 2020;48	PICO eligibility criteria not met

Table 4. Characteristics of planned and ongoing studies (source: www.covid-nma.com 12 April 2022)

Treatment (per arm)	n	Severity at enrollment	Sponsor/funder	Reg. Number	Full text link
(1) Baricitinib vs (2) Tocilizumab	184	Severe	University Hospital of Patras	NCT05082714	https://clinicaltrials.gov/show/NCT05082714
(1) Tocilizumab vs (2) Baricitinib + tocilizumab	60	Severe	Shahid Beheshti University of Medical Sciences	IRCT20151227025726N30	http://en.irct.ir/trial/61974
(1) Baricitinib vs (2) Standard of care	260	Moderate	PGIMER Chandigarh	CTRI/2021/11/037866	http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=62438
(1) Baricitinib vs (2) Placebo	100	Moderate/severe	Oslo University Hospital	EUCTR2021-000541-41-PT	https://www.clinicaltrialsregister.eu/ctr-search/trial/2021-000541-41/PT
(1) Baricitinib vs (2) Placebo	1900	Moderate/severe	Oslo University Hospital	NCT04891133	https://clinicaltrials.gov/show/NCT04891133
(1) Imatinib vs (2) Baricitinib vs (3) Standard of care	168	Moderate	Hospital Universitario de Fuenlabrada	NCT04346147	https://clinicaltrials.gov/show/NCT04346147
(1) Baricitinib vs (2) Ravulizumab vs (3) Standard of care	1167	Moderate	Cambridge University Hospitals NHS Foundation Trust	NCT04390464	https://clinicaltrials.gov/show/NCT04390464
(1) Baricitinib vs (2) Placebo	480	Moderate/severe	Incepta Pharmaceuticals Ltd	NCT05056558	https://clinicaltrials.gov/show/NCT05056558
(1) Baricitinib vs (2) Placebo	500	Moderate/severe/ critical	OSLO UNIVERSITETSSYKEHUS HF	EUCTR2021-000541-41-IT	https://www.clinicaltrialsregister.eu/ctr-search/trial/2021-000541-41/IT
(1) Baricitinib + remdesivir vs (2) Dexamethasone + remdesivir	382	Moderate/severe	Bangladesh Institute of Research and Rehabilitation in Diabetes, Endocrine and Metabolic Disorders	NCT04970719	https://clinicaltrials.gov/show/NCT04970719
(1) Baricitinib + dexamethasone vs (2) Dexamethasone vs (3) Emtricitabine + tenofovir vs (4) Standard of care	2193	Mild/moderate	Instituto de InvestigaciÃ³n Hospital Universitario La Paz	NCT04890626	https://clinicaltrials.gov/show/NCT04890626
(1) Baricitinib vs (2) Remdesivir vs (3) Baricitinib + remdesivir vs (4) Standard of care	4000	Moderate/severe	ASST Fatebenefratelli Sacco	NCT04832880	https://clinicaltrials.gov/show/NCT04832880
(1) Baricitinib + remdesivir vs (2) Remdesivir + tocilizumab	150	Severe/critical	M Abdur Rahim Medical College and Hospital	NCT04693026	https://clinicaltrials.gov/show/NCT04693026
(1) Baricitinib vs (2) Standard of care	126	Severe	Azienda Ospedaliero, Universitaria Pisana	NCT04393051	https://clinicaltrials.gov/show/NCT04393051
(1) Hydroxychloroquine vs (2) Baricitinib + hydroxychloroquine vs (3) Hydroxychloroquine + tocilizumab vs (4) Hydroxychloroquine + sarilumab vs (5) Hydroxychloroquine + siltuximab vs (6) Canakinumab + hydroxychloroquine vs (7) Hydroxychloroquine + methylprednisolone	1400	Moderate/severe	SOCIETA' ITALIANA MALATTIE INFETTIVE E TROPICALI	EUCTR2020-001854-23-IT	https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001854-23/IT

Appendix 1: Search strategy

Search strategy 1: September 2021 (Initial search)

Database: Cochrane COVID-19 Study Register (https://covid-19.cochrane.org/)
Search strategy: baricitinib or azetidines or sulfonamides or purines or pyrazoles or Olumiant
Filtered by: Study type – interventional; Study Aim – treatment and management; Study design – parallel/crossover; Intervention Assignment - randomised
Output: 15 studies with 32 references (16 duplicates)
Date: 7 September 2021

Database: LOVE Platform (https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d?utm=aile)
Search strategy: (baricitinib OR azetidines OR sulfonamides OR purines OR pyrazoles OR olumiant)
Filtered by: Systematic reviews and Primary studies (RCTs and Pending)
Output: 33 studies (0 duplicates)
Date: 7 September 2021

Database: PubMed
Search strategy: see table below
Output: 62 studies (4 duplicates)
Date: 7 September 2021

Search	Query	Results
#3	Search: #1 AND #2 Filters: Meta-Analysis, Randomized Controlled Trial, Systematic Review	62
#2	Search: baricitinib OR azetidines OR sulfonamides OR purines OR pyrazoles OR olumiant Filters: Meta-Analysis, Randomized Controlled Trial, Systematic Review	25,281
#1	Search: Coronavirus[mh:noexp] OR coronavirus*[tiab] OR corona virus*[tiab] OR COVID-19[mh] OR covid-19[tiab] OR covid19[tiab] OR covid 2019[tiab] OR SARS-Cov-2[mh] OR SARS-CoV-2[tiab] OR SARS-CoV2[tiab] OR SARSCoV2[tiab] OR SARsCov-2[tiab] OR SARS-coronavirus*[tiab] OR severe acute respiratory syndrome coronavirus 2[nm] OR severe acute respiratory syndrome coronavirus 2[tiab] OR 2019-nCov[tiab] OR 2019nCov[tiab] OR nCov2019[tiab] OR nCOV-2019[tiab] OR hCOV*[tiab] OR n-cov[tiab] OR ncov*[tiab]	184,185

Search strategy 2: 11 April 2022 (Updated search)

Database: Living review of COVID-19 studies – COVID-nma (https://covid-nma.com/)
Search strategy: Baricitinib vs Standard of care/Placebo
Output: 3 RCTs
Date: 11 April 2022

Database: LOVE Platform (https://app.iloveevidence.com/loves/5e6fdb9669c00e4ac072701d?utm=aile)
Search strategy: "prevention or treatment" AND "baricitinib" – restricted to RCTs reporting data
Filtered by: Primary studies (RCTs reporting data) and systematic reviews
Output: 30 records (4 duplicates)
Date: 11 April 2022

Appendix 2: Evidence to decision framework

Desirable Effects

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small **X Moderate** ○ Large ○ Varies ○ Don't know		

№ of studies	Study design	Relative (95% CI)	Absolute (95% CI)	Certainty
Mortality (follow-up: 28 days)				
3	RCTs	**RR 0.75** (0.58 to 0.98)	**35 fewer per 1,000** (from 59 fewer to 3 fewer)	⊕⊕⊕◯ Moderate
Mortality (follow-up: 60 days)				
2	RCTs	**RR 0.69** (0.56 to 0.86)	**56 fewer per 1,000** (from 80 fewer to 25 fewer)	⊕⊕⊕◯ Moderate
Clinical deterioration - mechanical ventilation +/- additional organ support (ECMO, vasopressors or dialysis) or death [WHO progression score level 7 or above]				
3	RCTs	**RR 0.87** (0.78 to 0.97)	**22 fewer per 1000** (from 38 fewer to 5 fewer)	⊕⊕⊕⊕ High
Clinical improvement (follow-up: 28 days)				
3	RCTs	**RR 1.02** (1.00 to 1.05)	**16 more per 1000** (from 0 fewer to 39 more)	⊕⊕⊕⊕ High
Adverse events				
2	RCTs	**RR 0.96** (0.88 to 1.05)	**19 fewer per 1,000** (from 56 fewer to 23 more)	⊕⊕⊕◯ Moderate
Serious adverse events				
2	RCTs	**RR 0.77** (0.64 to 0.94)	**48 fewer per 1,000** (from 75 fewer to13 fewer)	⊕⊕⊕◯ Moderate

Refer to table 2: Summary of findings for detailed information.
Mortality benefit associated with baricitinib amongst hospitalised adult COVID-19 patients on supplemental oxygen (including patients on invasive mechanical ventilation and ECMO).

Undesirable Effects

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate **X Small** ○ Trivial	See figure above. There was no difference in the number of adverse events between the baricitinib group compared to placebo (378/815 vs 381/811; RR 0.96; 95% CI 0.88 to 1.05); but possibly less serious adverse events associated with baricitinib compared to placebo (135/812 vs 170/811; RR 0.77; 95% CI 0.64 to 0.94).	

○ Varies ○ Don't know		
Certainty of evidence: What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Very ○ Low **X Moderate** ○ High ○ No included studies	There is overall moderate certainty evidence for the outcomes of interest. Moderate certainty for overall mortality at day 28 due to inconsistency and heterogeneity of data with I^2=:67.3%. However, for composite outcome of WHO progression score level 7 or above and for clinical improvement outcome certainty of evidence was high.	
Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Important uncertainty or variability ○ Possibly important uncertainty or variability **X Probably no important uncertainty or variability** ○ No important uncertainty or variability		Despite the lack of research evidence from stakeholders, the benefit of survival is likely to be considered of value.
Balance of effects: Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison **X Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know	The Committee considered that the balance of effects probably favours the intervention.	
Resources required: How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
X Large costs ○ Moderate costs ○ Negligible costs and	**Baricitinib: estimated budget impact** • **Cost per patient for 14 days**: (Single exit price) R4220* • **Criteria** - Age ≥18 years	The Committee considered the direct medicine price of baricitinib, noting that baricitinib may be administered orally and via the nasogastric tube.

savings
○ Moderate savings
○ Large savings
○ Varies
○ Don't know

- On supplemental oxygen (including invasive mechanical ventilation and ECMO)

** SEP database, 24 December 2021*

DATCOV data, public sector hospitals *(patient numbers)*:

	Wave 1	Wave 2	Wave 3	Wave 4
Total admissions	39904	65210	84993	46077
On oxygen	16994	26789	40709	27826

Reporting improved between Wave 1 and 2. By Wave 3, includes data from all public sector hospitals in SA.

- Potential impact of vaccinations on hospital admissions and disease severity not taken into account.

Budget impact (Rands) ranges based on above assumptions

	Wave 4	20% lower	20% higher
Patients on oxygen	27826	22261	33391
Budget impact range	**R 117 426 000**	**R 93 941 000**	**R 140 911 000**
	Wave 3	**20% lower**	**20% higher**
Patients on oxygen	40709	32567	48851
Budget impact range	**R 171 792 000**	**R 137 434 000**	**R 206 151 000**

Note: Estimates of hospital admissions or severity of disease in the future are uncertain given the current high levels of seroprevalence through vaccination or COVID infections. If an assumption is made of 5000 admissions, the incremental cost of using baricitinib would be in the region of R21 million. The current budget impact does not take into account any savings that may be generated through reduced length of stay or progression to ventilation.

Assumptions for the model:

- Patients eligible for baricitinib if they require oxygen
- Single exit prices used
- Baricitinib would be readily available (currently SAHPRA registered)

Cost effectiveness: Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies **X No included studies**	There are no included studies on this. However, the estimated ICER for baricitininb (using Wave 4 estimates) was calculated as R15 488 per life year saved. Reducing the cost of a course of baricitinib by 50 % (R2 110) results in a lower ICER of R7 744 per life year saved.	

Equity: What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ Reduced **X Probably reduced** ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	No research evidence is available.	The Committee considered that affordability would probably impact equity. National Treasury funding would reduce inequitable access across provinces. Supply constraints would also result in inequitable access.
Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no **X Probably yes** ○ Yes ○ Varies ○ Don't know	No research evidence is available.	The committee considered that given the potential benefit, this medicine would be acceptable to most stakeholders affected by this intervention (healthcare providers and patients).
Feasibility: Is the intervention feasible to implement?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies **X Don't know**	Baricitinib is SAHPRA registered (in combination with remdesivir) to treat COVID-19 in those who require supplemental oxygen. Although the originator branded remdesivir has also been registered by SAHPRA, access is currently dependent on generic remdesivir, imported as section 21 medicine. Medicine availability: the product is not listed on the EML and is not available on tender in the public sector. Use of the medicine does not require special training for use as it can be given orally or via a nasogastric tube.	Single supplier to satisfy global demand is a concern. Baricitinib was first registered in South Africa in January 2021 and is available only from the single source (Eli Lilly SA (Pty) Ltd). There are concerns about the volumes that would be accessible, in the light of increasing global demand. Shortages have already been reported in high-income countries (https://www.pharmacytimes.com/view/newest-covid-19-surge-leads-to-shortages-in-therapeutics; https://www.healio.com/news/rheumatology/20210916/cascade-of-impact-covid19-surge-again-threatens-patient-access-to-maintenance-drugs). Eli Lilly has already licensed a number of Indian generic versions (https://investor.lilly.com/news-releases/news-release-details/lilly-accelerating-baricitinibs-availability-india-following; https://www.business-standard.com/article/companies/eli-lilly-signs-licensing-pact-with-cipla-sun-lupin-for-covid-19-drug-121051100039_1.html). However, access to generic versions will require either section 21 approval or registration by the generic firms involved (Sun Pharma, Cipla, Lupin).

Appendix 3: Updating of rapid report

Date	Signal	Rationale
4 February 2022	Publication of RCT data by Ely et al	New RCT data (3 February 2022) suggesting benefit amongst critically ill patients (on invasive mechanical ventilation or extracorporeal membrane oxygenation). Subsequent publication of RECOVERY Preprint on 3 March 2022 suggesting mortality benefit in all hospitalised patients (mild/moderate/severe/critical COVID-19 disease).

Version control:

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	15 October 2021	MB, RdW, TK, VN, NB	Baricitinib recommended for use in hospitalised COVID-19 patients on oxygen and who have at least one raised inflammatory marker on specialist motivation/ consultation. This recommendation is conditional on baricitinib being accessible to all eligible public sector patients in South Africa. Baricitinib reduced mortality in a single study, and was not associated with an increased risk of adverse events; cheaper than tocilizumab, and may be administered orally (or via nasogastric tube).
Second	19 November 2021	MB, RdW, TK, VN, NB	Recommendation updated without the need for specialist motivation/ consultation, as patients would be treated at secondary level facilities. Basic incremental cost-effectiveness ratio included.
Third	6 May 2022	TL, MB, JM, HD	Baricitinib recommended for use in hospitalised COVID-19 patients on oxygen, irrespective of presence of inflammatory markers. Recommendation is dependent on baricitinib being accessible to all eligible public sector patients in South Africa – Provinces to monitor budget impact and affordability.

For internal NDoH use:
WHO INN: Baricitinib
ATC: L04AA37
ICD10: U07.1/U07.2

ADDENDUM A: MANAGEMENT OF SEVERE COVID-19 IN PREGNANCY: TOCILIZUMAB AND BARICITINIB

Date: 6 April 2022 (Addendum to baricitinib and tocilizumab rapid reviews)

Background

COVID-19 during pregnancy is associated with an increased risk of adverse maternal and neonatal outcomes.[1]

Previously, the NEML MAC on COVID-19 Therapeutics issued a conditional recommendation in support of baricitinib in hospitalised patients with confirmed COVID-19 who required oxygen and had at least one raised inflammatory marker.[2] Although the recommendation did not specifically consider the suitability of baricitinib in pregnant women, the current professional information (PI) is explicit that baricitinib is contraindicated in pregnancy.[3] The PI states that "The JAK/STAT[1] pathway is involved in cell adhesion and cell polarity which can affect early embryonic development. Animal studies have associated baricitinib with reproductive toxicity as well as adverse effects on *in utero* bone development at higher dosages. Furthermore, baricitinib was teratogenic in rats and rabbits." Therefore, although the MAC recommended baricitinib in the management of severe COVID-19 because of mortality benefit, baricitinib is contraindicated in pregnant women with severe COVID-19 because of serious concerns of foetal harm.

Tocilizumab is an alternative immunomodulator that could potentially be used in combination with corticosteroids in this patient group. Tocilizumab was reviewed by the NEML MAC on COVID-19 Therapeutics in May 2021[4] and a conditional recommendation not to use tocilizumab was made, in view of the unaffordable price and concerns about supply constraints. This addendum has been produced in response to a request for guidance on the use of tocilizumab, specifically in the management of pregnant women with severe COVID-19, where baricitinib cannot not be used.

Method

On 06 April 2022, both PubMed and the Epistemonikos L*OVE evidence platform (https://app.iloveevidence.com/) were searched for publications relevant to this subgroup of patients. The search strategy is represented in Appendix 1.

Results

We did not find any randomized controlled trials investigating the use of TCZ in pregnant women with COVID-19. Data that were available was limited to observational studies in small numbers of patients. The bulk of data on use of TCZ pregnancy comes from patients treated for rheumatological conditions.

We identified a 2021 narrative review which included observational data from 610 TCZ-exposed pregnancies, of which 20 were pregnant women with COVID-19.[5] The authors did not identify any serious safety signals, but concluded that there were insufficient data available to adequately characterize the safety of TCZ in pregnancy. Most TCZ exposures in this review were during the first trimester, with very little data on TCZ exposure in the second and third trimesters, when transplacental transfer of TCZ is likely to be higher than in the first trimester. The effects of TCZ on development of the foetal immune system are not known. The bulk of the data included in the narrative review comes from Roche's Global safety database (180 prospective and 108 retrospective reports) and the European League against Rheumatism (EULAR) taskforce reports (218 reports derived from registration data and conference abstracts). Both of these studies found that rates of prematurity were higher than in the general population (31% vs 10-15%), and there was a lower mean birthweight which was only partially explained by gestational age. The extent to which the underlying rheumatological condition and/or other concomitant medicines contributed to these findings is not clear. All of the 17 patients from the Roche Global database with TCZ exposure after the first trimester gave birth to live neonates; half were preterm deliveries.

[1] *Janus kinase-signal transducer and activator of transcription*

Conclusion

Although no randomized controlled trial data was found to support the safe and effective use of TCZ in pregnant women with severe COVID-19, there is no evidence to suggest these patients would respond differently when compared with other adults.[6] No serious safety signals have been identified to date, but data are limited. The number of TCZ-exposed pregnancies was small, and most exposures were in the first trimester. TCZ may be associated with increased rates of premature deliver, but it is not clear to what extent underlying rheumatological disorders and/or concomitant medicines contributed to this finding .[5]

Although the use of tocilizumab in pregnant women with severe COVID-19 is not recommended, clinicians should assess the individual risk-benefit in each case, and can consider the addition of this agent to an appropriate parenteral corticosteroid (such as hydrocortisone).

Reviewers: Roger Wiseman (Liberty Health (Pty) Ltd, South Africa), Marc Blockman (Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town) have no interests pertaining to tocilizumab.

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Appendix 1 (Addendum A): Search strategy

Date: 06 April 2022

PubMed

(("tocilizumab"[Supplementary Concept] OR "tocilizumab"[All Fields]) AND ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 serotherapy"[Supplementary Concept] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication])) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields] OR "pregnancies"[All Fields] OR "pregnancy s"[All Fields])) AND (humans[Filter])

Records retrieved: 21 (0 RCTs or systematic reviews, 3 case studies, 1 narrative review)

Epistemonikos L*OVE evidence platform:

Tocilizumab for pregnant women

Records retrieved: 17 (0 RCTs or systematic reviews, 2 case reports, 1 retrospective review).

Appendix 2 (Addendum A): GUIDELINE CONSIDERATIONS

1. Australian guidelines for the clinical care of people with COVID-19. Version 53.1 (updated 08 March 2022)[7]

6.1.6.3.2 Tocilizumab for pregnant or breastfeeding women

Conditional recommendation: Consider using tocilizumab for the treatment of COVID-19 in pregnant or breastfeeding women who require supplemental oxygen, particularly where there is evidence of systemic inflammation.

In patients hospitalised with COVID-19 who require supplemental oxygen, tocilizumab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for tocilizumab both within and outside the context of a randomised trial unless contraindicated (e.g. patients with other active, severe infections).

In accordance with the RECOVERY trial, tocilizumab should be administered as a single intravenous infusion over 60 minutes. The suggested dose is dependent on body weight:

- Patients > 90 kg: 800 mg tocilizumab
- Patients 66–90 kg: 600 mg tocilizumab
- Patients 41–65 kg: 400 mg tocilizumab
- Patients ≤ 40 kg: 8 mg/kg tocilizumab

In pregnant and breastfeeding women, dosing should be based on body weight at time of clinical need.
In the RECOVERY trial, 29% of patients received a second dose 12–24 hours after the first dose, although results were not reported separately for this population. The decision to administer a second dose of tocilizumab should take into consideration its availability.

For the babies of women who received tocilizumab during pregnancy (after 20 weeks of gestation), live vaccines (rotavirus and BCG) should be avoided in the first six months of life. All non-live vaccinations are safe and should be undertaken (see factsheet).

In women who receive tocilizumab while breastfeeding only, live vaccines (rotavirus and BCG) can be given to the baby (see factsheet).

In addition, the RECOVERY and REMAP-CAP trials have demonstrated a significant benefit when using corticosteroids in conjunction with tocilizumab. Use of combined tocilizumab and corticosteroids should be considered in patients hospitalised with COVID-19 who require oxygen, however the optimal sequencing of tocilizumab and corticosteroid use is unclear.

As tocilizumab inhibits the production of C-reactive protein (CRP), a reduction in CRP should not be used as a marker of clinical improvement.