**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*
*Funded by the DOH AHEAD Program through the PCHRD*

## EVIDENCE SUMMARY

# Should Baloxavir be used in the treatment of COVID-19?

Antonio L. Faltado Jr., MD FPCP, FPSEDM, MSc (cand) and Anna Angelica Macalalad-Josue, MD, FPCP, FPSEDM, MSc (cand) and Maria Teresa Sanchez-Tolosa, MD, D Clin Epi, FPDS,

## RECOMMENDATION

We suggest against the use of baloxavir as treatment for COVID-19 infection. *(Very low quality of evidence; Conditional recommendation)*

### Consensus Issues

Only one small study was included in the review, which showed consistent result of no significant benefit across all the outcomes measured (i.e., need for mechanical ventilator/ ECMO, admission to ICU, hospitalization, clinical improvement at 14 days, adverse events and time to clinical improvement). It was noted that baloxavir is a repurposed drug for COVID-19 and is originally indicated for influenza. It costs Php 450 per tablet and is usually given within 48 hours from the onset of symptoms for the treatment of influenza. In terms of health equity, it was raised that since its benefit is yet to be established, resources should be allocated to more known and established drugs where the benefits are certain.

## Key Findings

There was only one randomized controlled trial included in this review. Treatment with baloxavir did not lead to significant reduction in the need for invasive mechanical ventilation, admission to intensive care unit, hospitalization and clinical improvement (very low quality of evidence). There was no report of mortality in any of treatment arms. Currently, there are two ongoing clinical trials on the efficacy of baloxavir as treatment for COVID-19.

## Introduction

Baloxavir is an oral antiviral agent that inhibits the initiation of viral mRNA which is an early step in virus replication [1-3]. Baloxavir marboxil is the prodrug and baloxavir acid is the active metabolite that inhibits cap-dependent endonuclease [4]. SARS-CoV-2 being an RNA virus, baloxavir is considered to be potentially effective against SARS-CoV-2 by blocking its RNA synthesis. Moreover, studies show that baloxavir has antiviral activity against SARS-CoV-2 in vitro [5]

## Review Methods

We performed a comprehensive systematic search of related literature from Medline, CENTRAL, Love Platform App and COVID-19 NMA database. We also searched for ongoing clinical trials

using ClinicalTrial.gov, Clinicaltrialsregister.eu and Chinese Clinical Trial Register. Freehand search using Google was also done to check for other sources of information. Search was conducted using the following search terms: “COVID-19,” “SARS-CoV-2” and “Baloxavir.” There was no limit as to the date, language and country of publication.

Eligible articles were evaluated using the following criteria:

| | |
|---|---|
| Population | COVID-19 patients any age, co-morbidities and severity |
| Intervention/Exposure | Baloxavir or Baloxavir Marboxil |
| Comparison | Usual standard of care, placebo, any active control |
| Outcomes | Mortality, clinical improvement, need for mechanical ventilations and adverse effects |
| Methodological filter | randomized controlled trials (RCT), observational clinical studies, systematic review and meta-analysis available |

## Results

Thirty-one articles were initially screened but only one article matched our criteria. We found two ongoing clinical trials in the searched trial registers. Only one study was included in this review. The study of Lou et al. [5] is an exploratory randomized controlled open label trial. It enrolled 30 patients who were randomized equally into one of three arms. There was no limit in terms of severity in the inclusion criteria, however patients in all of the treatment arms had a National Early Warning Score (NEWS) 2 score of (4 [IQR 4,5]) or low to medium risk. The control group (n=10) was given the institution’s existing antiviral treatment of lopinavir/ritonavir (400mg/100 mg, bid, per orem) or darunavir/cobicistat (800 mg/150 mg, qd, per orem) and arbidol (200 mg, tid, per orem.). All of them were used in combination with interferon-α inhalation (100,000 iu, tid or qid). The baloxavir group (n=10) was given this control treatment plus baloxavir marboxil at a dose of 80 mg once a day per orem on Day 1 and Day 4; the patients still positive virologically could be given again on Day 7. The favipiravir group (n=10) was given the control treatment plus favipiravir, the latter administered as a first dose of 1600 mg or 2200mg orally, followed by 600 mg thrice daily, with duration of administration not exceeding 14 days. In this study, the allocation concealment was unclear. It was unblinded, and the primary outcome of clinical improvement (with the use of the WHO score), as well as report of adverse events, involved clinical judgement that could be influenced by the knowledge of the intervention assignment. There was adequate follow up and there was no report of participant cross-over. There were imbalances among the treatment arms in terms of baseline characteristics: mean age (46.6 [SD 14.1] in control, 53.5 [12.5]) in baloxavir, 58 [8.1] in favipiravir), days from symptoms onset to randomization (13.6 [4.6] in control, 12.7 [SD 3.5] in baloxavir, 8.5 [3.7] in favipiravir) CRP (2.1 [0.32, 79.9] in control, 14.1 [IQR 0.65, 50.9] in baloxavir, 27.3 [0.32, 79.9] in favipiravir and viral load (Ct value) (29.6 [IQR 19.8, 37.1] in control, 28.2 [22.1, 36.8] in baloxavir and 25.4 [19.8, 36] in favipiravir). Time-Dependent Cox proportional hazards model was used to investigate the effects of these covariates and the results showed no association between these covariates and time to viral negativity. There was no report of mortality in any of the treatment arms. Each of the

intervention groups was compared against the control group. The baloxavir group was not compared against the favipiravir group in this study. Baloxavir did not lead to significant reduction in the need for mechanical ventilation or extracorporeal membrane oxygenation (ECMO) (RR 3.0; [95%CI 0.14, 65.9]), admission to ICU (RR 3; [95% CI 0.14, 65.9]), hospitalization (RR 0.67; [95% CI 0.27,1.66]) and clinical improvement at 14 days (RR 1.20; [95% CI 0.54, 2.67]).

## Recommendations from other groups

There was no mention on the use of baloxavir marboxil as treatment for covid-19 in the Infectious Diseases Society of America (IDSA) treatment guidelines (April 14, 2021), World Health Organization (WHO) living guideline (March 31, 2021) and US-NIH treatment guideline (Feb 16, 2021). The Australian Living Clinical Practice Guidelines recommends not to use Baloxavir Marboxil as treatment for COVID-19 outside randomized trials with appropriate ethical approval (May 20, 2021).

## Research gaps

Currently there are two ongoing studies on the efficacy of baloxavir as treatment for COVID-19 (Appendix 3). More randomized controlled trials are needed to examine the use of baloxavir as treatment for COVID-19.

## References

[1] Plotch S, Bouloy M, Krug R. Transfer of 5'-terminal cap of globin mRNA to influenza viral complementary RNA during transcription in vitro. Proc. Natl Acad. Sci. 1979. USA 76, 1618-1622.

[2] Plotch S, Bouloy M, Ulmamen I, Krug R. A unique cap(m7GpppXm) dependent influenza virion endonuclease cleaves capped RNAs to generate the primers that initiate viral RNA transcription. 1981. Cell 23, 847-858.

[3] Reich S. et al. Structural insight to cap-snatching and RNA synthesis by influenza polymerase. 2014 Nature 516, 361-366.

[4] Hayden F, Sugaya N, Hirotsu N et al. Baloxavir Marboxil for uncomplicated influenza in adults and adolescents. 2018. N Engl J Med 379, 913-923. https://doi.org/10.1056/NEJMoa1716197.

[5] Lou Y, Liu L, Yao H. et al. Clinical outcomes and plasma concentrations of baloxavir marboxil and favipiravir in COVID-19 patients: an exploratory randomized, controlled trial. 2020. Eur J of Pharm Sci 157 105631.

## Appendix 1. Characteristics of Included Studies

| Author, Year | Patients (n) | Intervention | Comparator | Outcomes | Study Design |
|---|---|---|---|---|---|
| Lou et al, 2020 [5] | Confirmed COVID-19 patients who are still positive for SARS-CoV-2, they did not restrict inclusion as to severity but patients included had a mean NEWS2 score of 4 or low to medium risk. | The baloxavir group: control treatment plus baloxavir marboxil 80 mg once a day per orem on Day 1 and Day 4; if patients are still positive, they could be given again on Day 7<br>The favipiravir group: control treatment plus favipiravir administered as a first dose of 1600 mg or 2200mg orally, followed by 600 mg thrice day, with duration of administration not exceeding 14 days. | lopinavir/ritonavir (400mg/100 mg, bid, per orem) or darunavir/cobicistat (800 mg/150 mg, qd, per orem) and arbidol (200 mg, tid, per orem.) | Primary:1) percentage of patients with viral negative results at 14 days 2) time from randomization to clinical improvement of two points or live discharge<br>Secondary: 1) percentage of patients with viral negative results at 7 days, 2) incidence of mechanical ventilation by day 14, ICU admission by day 14 and all cause mortality by day 14<br>Adverse events. | RCT |

# Appendix 2. GRADE Summary of Findings (SoF) Table

**Author(s)**: Faltado, Antonio Jr, Anna Angelica Macalalad-Josue
**Question**: Baloxavir compared to Standard of Care for COVID-19
**Setting**:
**Bibliography**:

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Baloxavir | Standard of Care | Relative (95% CI) | Absolute (95% CI) | | |
| **Mortality** | | | | | | | | | | | | |
| 1 | randomised trials | serious [a,b] | not serious | not serious | very serious [c] | none | No mortality reported in the treatment arms | | | | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Need for Mechanical Ventilator/ ECMO** | | | | | | | | | | | | |
| 1 | randomised trials | serious [a,b] | not serious | not serious | very serious [c,d] | none | 1/10 (10.0%) | 0/10 (0.0%) | **RR 3.00** (0.14 to 65.90) | **0 fewer per 1,000** (from 0 fewer to 0 fewer) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Admission to ICU** | | | | | | | | | | | | |
| 1 | randomised trials | serious [a,b] | not serious | not serious | very serious [c,d] | none | 1/10 (10.0%) | 0/10 (0.0%) | **RR 3.00** (0.14 to 65.90) | **0 fewer per 1,000** (from 0 fewer to 0 fewer) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Hospitalization** | | | | | | | | | | | | |
| 1 | randomised trials | serious [a,b] | not serious | not serious | very serious [c,d] | none | 4/10 (40.0%) | 6/10 (60.0%) | **RR 0.67** (0.27 to 1.66) | **198 fewer per 1,000** (from 438 fewer to 396 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Clinical Improvement at 14 days** | | | | | | | | | | | | |
| 1 | randomised trials | serious [a,b] | not serious | not serious | very serious [c,d] | none | 6/10 (60.0%) | 5/10 (50.0%) | **RR 1.20** (0.54 to 2.67) | **100 more per 1,000** (from 230 fewer to 835 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Adverse Events (Respiratory Failure or ARDS)** | | | | | | | | | | | | |
| 1 | randomised trials | serious [a,b] | not serious | not serious | very serious [c,d] | none | 6/10 (60.0%) | 4/10 (40.0%) | **RR 1.50** (0.60 to 3.74) | **200 more per 1,000** (from 160 fewer to 1,000 more) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Time to Clinical Improvement (2 points decrease from baseline score or hospital discharge)** | | | | | | | | | | | | |
| 1 | randomised trials | serious [a,b] | not serious | not serious | very serious [c,d] | none | 10 | 10 | - | SMD **0.56 SD higher** (0.34 lower to 1.45 higher) | ⨁◯◯◯ VERY LOW | IMPORTANT |

**CI:** Confidence interval; **RR:** Risk ratio; **SMD:** Standardised mean difference

**Explanations**

a. unclear allocation concealment
b. Unblinded
c. small sample size
d. wide confidence interval

## Appendix 3. Characteristics of Ongoing Clinical Trials

| Clinical Trial Identifier/Title | Study Design | Country | Population | Intervention | Outcome | Estimated Date of Completion |
|---|---|---|---|---|---|---|
| ChiCTR2000029548 Randomized, open-label, controlled trial for evaluating the efficacy and safety of Baloxavir marboxil, Favipiravir, and Lopinavir-Ritonavir in the treatment of novel coronavirus pneumonia patients | Randomized Controlled Trial, parallel assignment | China | COVID-19 | BaloxavirMarboxil vs Favipiravir vs Lopinavir-Ritonavir | Primary Outcome: All-cause mortality, Time to viral negativity, Time to clinical improvement, incidence of mechanical ventilation, incidence of ICU admission. | unknown |
| ChiCTR2000029544 A randomized controlled trial for the efficacy and safety of Baloxavir Marboxil, Favipiravir tablets in novel coronavirus pneumonia (COVID-19) patients who are still positive on virus detection under the current antiviral therapy | Randomized Controlled Trial, parallel assignment | China | COVID-19 | BaloxavirMarboxil vs Favipiravir vs Control group | Primary Outcome: Clinical Improvement Secondary Outcome: Patient status upgraded to ICU level, Oxygen supplementation, days with fever, days to discharge, SAEs | unknown |