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 bevacizumab be used for treatment?

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RECOMMENDATION

We suggest against the use of bevacizumab as treatment for COVID-19. (*Very low certainty of evidence; Weak recommendation)*

Consensus Issues
Currently available evidence came from one small non-randomized clinical trial with only 27 patients in the treatment group and 26 patients in the external control cohort. Administration of bevacizumab led to net potential harm with unclear potential benefit in only 1 non-critical outcome (i.e., duration of oxygen support). Its cost and potential negative effect on equity, since the drug is also being used as treatment for lung cancer, were also considered by the consensus panel. At present, bevacizumab is not readily accessible due to its limited availability and large cost. Use of bevacizumab among COVID-19 patients when its benefit is still unclear, may lead to even greater difficulty for lung cancer patients to gain access to this drug.

Key Findings

One (1) small non-randomized clinical trial investigated on the potential use of bevacizumab for treatment of COVID-19. The study showed that bevacizumab led to net potential harm with minimal potential benefit only in terms of duration of oxygen support. Evidence was inconclusive for hospital discharge. Adverse events in the bevacizumab group were elevation of liver enzymes (30%), reduced hemoglobin (19%), decreased platelet counts (15%), elevation of blood pressure (11%), elevated blood urea nitrogen (7%), and sepsis (7%).

Introduction

Bevacizumab is a humanized monoclonal antibody that acts as anti-vascular endothelial growth factor (VEGF) and is currently used for treatment of cancers. Its potential use in severe COVID-19 pneumonia has been explored since VEGF is a potent vascular permeability factor that induces vascular leakiness in COVID-19-infected lung tissues. VEGF results in plasma extravasation and pulmonary edema, which further increases tissue hypoxia. VEGF levels have been observed to be markedly elevated in patients with COVID-19. Blocking VEGF and the VEGF receptor (VEGFR)-mediated signaling would potentially improve oxygenation and anti-inflammatory response, thereby improving the clinical symptoms in patients with severe COVID-19.[1]

Review Methods

A systematic search was done from inception up to October 3, 2021 using Medline, Cochrane Library, and Google Scholar with a combined MeSH and free text search using the terms coronavirus infections, COVID-19, severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2, and bevacizumab. 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. Clinical trials that compared bevacizumab against placebo or standard care were searched for in this review. Outcomes of interest included mortality, clinical deterioration or improvement, improvement of radiographic findings, and adverse events. No limits were placed on age, COVID-19 severity, and dosing strategy.

Results

One (1) published study investigated on the efficacy and tolerability of bevacizumab in patients with severe COVID-19 pneumonia.[1] The study is a single-arm, non-randomized, non-blinded, clinical trial which utilized an external control cohort. The treatment arm included 27 patients (13 from China and 14 from Italy) who were given a single 500mg dose of bevacizumab, with 1 dropout. The external control included 26 patients with severe COVID-19 from China and Italy who were admitted in the same center within a similar timeframe (±5 days). Data from the external cohort were collected retrospectively. Patients in the treatment and control groups received standard care, which included anti-viral drugs, hydroxychloroquine, antibiotics, steroids, anti-pyretics, and supportive care. The primary outcome reported was change in PaO2/FiO2 at days 1 and 7. Secondary outcomes included change in chest radiological imaging on day 7, oxygen-support status, discharge rate, and fever resolution during the 28-day follow-up.

The overall certainty of evidence was rated very low because of very serious risk of bias and imprecision. The study had serious risk of selection, performance, detection and reporting bias. The risk of bias summary is in Appendix 4. The GRADE evidence summary is in Appendix 5.

Compared to the control group, patients given bevacizumab had significant increase in PaO2/FiO2 values at day 1 (p-value = 0.0001) and day 7 (p-value = 0.0002) from baseline. Both Chinese and Italian cohorts showed a significant increase of PaO2/FiO2 values at day 1 post-bevacizumab treatment relative to the baseline values, whereas, at day 7, only the Italian cohort had significant increase in PaO2/FiO2 ratio. The bevacizumab group had significantly shorter duration of oxygen support (median 9 days, IQR 5-19 days) compared to control group (median 20 days, IQR 14-28; p-value = 0.003). There was no significant difference in hospital discharge (RR 1.42, 95% CI 0.86-2.34).

Of the eight patients in the treatment group who underwent chest CT scan, there was reported improvement in the total lesion areas (cm^3) and the lesion ratios (%) for both lungs at day 7 relative to baseline. There was observed rapid abatement of fever in 13 out of 14 febrile patients (93%) who had fever within 3 days after bevacizumab treatment.

Safety

Adverse events noted among patients given bevacizumab included elevation of liver enzymes (30%), reduced hemoglobin (19%), decreased platelet counts (15%), elevation of blood pressure (11%), elevated blood urea nitrogen (7%), and sepsis (7%). The following were observed in 1 study participant (4%) each: hemorrhagic urea, diarrhea, skin rash, muscle pains in the lower extremity, superficial phlebitis, and sinus tachycardia with atrial premature beats. Adverse events were not reported in the control group.

Recommendations from Other Groups

There are no recommendations on the use of bevacizumab in COVID-19 from the following organizations: NIH COVID-19 Treatment Guidelines (as of August 25, 2021) [2], Australian Guidelines for Clinical Care of People with COVID-19 (as of September 29, 2021) [3], Surviving Sepsis Campaign: Guidelines on the Management of Adults with Coronavirus Disease 2019 (COVID-19) in the ICU (as of March 2021) [4], Infectious Diseases Society of America Guidelines

on Treatment and Management of Patients with Covid-19 (as of October 1, 2021) [5], and WHO Therapeutics and COVID-19 Living Guideline latest versions (as of September 24, 2021).[6]

Research Gaps

There are 4 ongoing randomized controlled trials evaluating the efficacy and safety of bevacizumab for severe to critical COVID-19 patients.

References

[1] Pang, Jiaojaio, et al. Efficacy and tolerability of bevacizumab in patients with severe COVID-19. Nature Communications (2021)12:814

[2] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed 30 August 2021

[3] Australian National COVID-19 Clinical Evidence Taskforce. Australian guidelines for the clinical cure of people with COVID-19 v43.0. Available at https://app.magicapp.org/#/guideline/5571. Accessed 5 October 2021

[4] Surviving Sepsis Campaign: Guidelines on the Management of Adults with Coronavirus Disease 2019 (COVID-19) in the ICU: First Update, Accessed 30 August 2021 https://www.sccm.org/SurvivingSepsisCampaign/Guidelines/COVID-19

[5] Bhimraj A, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America 2021; Version 5.3.1. Available at https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/. Accessed 5 October 2021

[6] World Health Organization. Therapeutics and COVID-19 Living Guidelines. 24 September 2021. Available at https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2021.2. Accessed 5 October 2021

[7] Maximum Retail Price for Medicines, Department of Health. https://www.doh.gov.ph. Accessed October 3, 2021

[8] World Health Organization. WHO Handbook for Guideline Development. Geneva: World Health Organization; 2012

Appendix 1. Evidence to Decision

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

FACTORS	JUDGEMENT (N = 6)						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (6)					
Benefits	Large	Moderate (1)	Small (2)	Uncertain (3)			• Shorter duration of oxygen support (median 9 days, IQR 5-19 days) compared to control group (median 20 days, IQR 14-28; p-value = 0.003) • There was no significant difference in hospital discharge (RR 1.42, 95% CI 0.86-2.34)
Harm	Large (2)	Small (2)	Uncertain (2)				
Certainty of Evidence	High	Moderate (1)	Low	Very low (5)			• Very low because of very serious risk of bias and imprecision. The study had serious risk of selection, performance, detection, and reporting bias.
Balance of effects	Favors drug	Does not favor drug (2)	Uncertain (4)				• Bevacizumab showed net potential harm with minimal benefit in clinical improvement in terms of oxygen support status and duration
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (5)	Possibly NO important uncertainty or variability	No important uncertainty or variability			
Resources Required	Uncertain	Large cost (6)	Moderate cost	Negligible cost	Moderate savings	Large savings	• Large cost; the maximum retail price of Bevacizumab 100mg/4 ml vial is Php 23,445.90 and the 400 mg/16 ml vial is Php 80,686.97 • The total cost of treatment per patient is Php 117,229.50
Certainty of evidence of required resources	No included studies (3)	Very low (1)	Low (1)	Moderate (1)	High		• The cost of bevacizumab was based from the published list of maximum retail price for medicines from the Department of Health
Cost effectiveness	No included studies (5)	Favors the comparison (1)	Does not favor either the intervention or the comparison	Favors the intervention			
Equity	Uncertain (5)	Reduced (1)	Probably no impact	Increased			
Acceptability	Uncertain (4)	No	Yes (2)				
Feasibility	Uncertain (3)	No (3)	Yes				

Additional comments:

- Very small study, clinically important data such as mortality/clinical progression/prevention or shortening hospitalization is missing
- Basis is from 1 small non-randomized clinical trial investigation (27 patients); adverse effect includes sepsis

Appendix 2. Search Yield and Results

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	{"Coronavirus Infections"[Mesh] OR "Coronavirus"[Mesh] OR coronavirus OR novel coronavirus OR NCOV OR "COVID-19" [Supplementary Concept] OR covid19 OR covid 19 OR covid-19 OR "severe acute respiratory syndrome coronavirus 2" [Supplementary Concept] OR severe acute respiratory syndrome coronavirus 2 OR SARS2 OR SARS 2 OR SARS COV2 OR SARS COV 2 OR SARS-COV-2} AND (bevacizumab OR bevacizumab{Mesh})	October 2, 2021 6:00 pm	26	1
CENTRAL	{"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 (bevacizumab OR bevacizumab{Mesh}	October 3, 2021 10:00 pm	8	1
COVID-NMA Initiative	Bevacizumab	October 3, 2021	0	0
Google Scholar	Bevacizumab AND COVID 19 AND randomized trial	October 2, 2021	1,260	1
ClinicalTrials.gov	Bevacizumab and COVID 19	October 3, 2021	4	4
Chinese Clinical Trial Registry	Bevacizumab and COVID	October 3, 2021	0	0
EU Clinical Trials Register	Bevacizumab and COVID	October 3, 2021	0	0
Republic of Korea - Clinical Research Information Service	Bevacizumab AND COVID	October 3, 2021	0	0
Japan Primary Registries Network/ NIPH Clinical Trials Search	Bevacizumab AND COVID	October 3, 2021	0	0
CenterWatch	Bevacizumab and COVID	October 3, 2021	0	0
Cochrane COVID-19 study register	Bevacizumab	October 3, 2021	15	0
chinaxiv.org	Bevacizumab	October 3, 2021	0	0
Medrxiv.org	Bevacizumab AND COVID	October 3, 2021	20	1
Biorxiv.org	Bevacizumab AND COVID	October 3, 2021	10	0

Appendix 3. Characteristics of Included Studies

Study ID	Patients (n)	Interventions	Outcomes	Method
Efficacy and tolerability of bevacizumab in patients with severe COVID-19 *(Pang 2021)*	Bevacizumab group (n = 27): Patients aged 18 to 80 years old with a confirmed COVID-19 diagnosis and with respiratory distress: respiratory rate (RR) of ≥30 times/min, oxygen saturation (SpO_2) of ≤93% while they were breathing ambient air or a partial arterial oxygen pressure to the fraction of inspiration O_2 ratio (PaO_2/FiO_2) of >100 and ≤300 mmHg, and diffuse pneumonia confirmed by chest radiological imaging External control group (n = 26): Patients with severe COVID-19 from China and Italy who had complete data set available for PaO2/FiO2 and who were admitted in the same center within a similar timeframe (±5 days) Inclusion criteria was similar with bevacizumab group.	Bevacizumab 500mg single dose IV infusion	Primary outcome: Change in PaO2/FiO2 at days 1 and 7 Secondary outcomes: Change of chest radiological imaging on day 7, oxygen-support status, discharge rate, and change of fever symptom during the 28-day follow-up	Non-randomized controlled trial

Appendix 4: Study Critical Appraisal

1. Were the patients randomly assigned to treatment groups?	There was no randomization done. The control group is an external cohort and included patients were screened retrospectively.
2. Was the allocation concealed?	There was no allocation concealment.
3. Were baseline characteristics similar at the start of the trial?	Baseline characteristics were similar for both treatment and control groups.
4. Were the patients blinded to the treatment assignment?	There was no blinding.
5. Were the caregivers blinded to the treatment assignment?	There was no blinding.
6. Were the outcome assessors blinded to the treatment assignment?	There was no blinding.
7. Were all patients analyzed in the groups to which they were originally randomised?	Intention to treat analysis was not applicable.
8. Was the follow up rate adequate?	There was only 1 drop-out in the treatment group.

Appendix 5: GRADE Evidence Profile

Author: Maria Philina P. Villamor, MD, FPCP, FPCCP
Date: October 3, 2021
Question: Should Bevacizumab be used for treatment of covid-19?
Setting: In-patients
Intervention: Bevacizumab
Comparison: Standard of care
Bibiliography: Pang, Jiaojaio, et al. Efficacy and tolerability of bevacizumab in patients with severe Covid-19. Nature Communications (2021)12:814

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bevacizumab	Control	Relative (95% CI)	Absolute (95% CI)		
Improvement in oxygenation (assessed with: PaO2/FiO2 at Day 1 and Day 7)												
1	Non-randomised trial	very serious[a]	not serious	not serious	serious[b]	none	Compared to the control group, bevacizumab was associated with a significant increase in PaO2/FiO2 values at day 1 (p-value 0.0001) and day 7 (p-value 0.0002) from baseline.				⊕◯◯◯ VERY LOW	CRITICAL
Improvement in oxygen-support status (follow-up: 28 days)												
1	Non - randomised trial	very serious[a]	not serious	not serious	serious[b]	none	24/26 (92.3%)	16/26 (61.5%)	**RR 1.50** (1.09 to 2.07)	**308 more per 1,000** (from 55 more to 658 more)	⊕◯◯◯ VERY LOW	CRITICAL
Duration of oxygen support												
1	Non - randomised trial	very serious[a]	not serious	not serious	serious[b]	none	Significantly shorter duration of oxygen support for bevacizumab (median 20 days, IQR 14-28 for bevacizumab; median 9 days, IQR 5-19 days for control; p-value 0.003)				⊕◯◯◯ VERY LOW	CRITICAL
Adverse events												
1	Non-randomised trial	very serious[a]	not serious	not serious	serious[b]	none	Adverse events noted among patients given bevacizumab included elevation of liver enzymes (30%), reduced hemoglobin (19%), decreased platelet counts (15%), elevation of blood pressure (11%), elevated blood urea nitrogen (7%), and sepsis (7%). The following were observed in 1 study participant (4%) each: hemorrhagic urea, diarrhea, skin rash, muscle pains in the lower extremity, superficial phlebitis, sinus tachycardia with atrial premature beats.				⊕◯◯◯ VERY LOW	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations

a.High risk of bias in selection bias, performance bias, detection bias, and reporting bias
b.Small sample size

Appendix 6: Characteristics of Ongoing Studies

Study Title	Patients (n)	Interventions	Outcomes	Method
1. Bevacizumab in Severe or Critical Patients with COVID-19 Pneumonia (NCT04257414)	Patients with severe or critical covid-19 N = 140	Experimental: Bevacizumab 7.5mg/kg + conventional therapy	The time from randomization to clinical improvement	Randomized controlled trial
2. Cohort Multiple Randomized Controlled Trials Open-label of Immune Modulatory Drugs and Other Treatments in COVID-19 Patients CORIMUNO-19-BEVA Trial	Adults with severe COVID-19 admitted in conventional units or ICU	Experimental: Bevacizumab Control: Standard of care	Oxygen saturation Adverse event ARDS Dyspnea Admission to ICU Mechanical ventilation Duration of hospital stay	Phase II Randomized controlled trial Parallel/cross-over
3. Pilot Study of Single Dose Bevacizumab as Treatment for Acute Respiratory Distress Syndrome (ARDS) in COVID-19 Patients	COVID-19 patients with ARDS who have previously received anti-viral and anti-inflammatory treatment	Experimental: Bevacizumab	Mortality	Phase II, multi-centered, randomized, open label, two-armed clinical trial
4. Trial Evaluating Efficacy and Safety of Bevacizumab (Avastin®/Zeribev®) in Patients With COVID-19 Infection, Nested in the Corimmuno-19 Cohort	Adult patients included in the CORIMUNO-19 cohort Hospitalized patients with no acute PE, no superimposed bacterial infection	Bevacizumab: 7.5 mg/kg (with a maximum of 750mg) on day 1 (D1) SOC: patients will receive the best of standard of care including corticosteroids, anticoagulant, antibiotics and tociluzimab	Primary Outcome: The time to recovery for a category 0 to 5 on the WHO Progression scale Secondary Outcomes: 1. Clinical status on the OMS Progression scale 2. Overall survival 3. Ventilator free days 4. High flow free days 5. Time to oxygen supply weaning 6. Changes in VEGF plasma levels 7. Comparison of the incidence of Grade 3 or 4 events 8. Proportion of Adverse Event	Randomized controlled trial Parallel/cross-over