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Clinical Profile and Outcome of Severe COVID-19 Patients receiving Bevacizumab in Tertiary Care Hospital in India *(COSCO-B Study)*

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Abstract: ***We hypothesize that the anti-vascular endothelial growth factor (anti-VEGF) drug bevacizumab might be beneficial for treating severe COVID-19, on the basis of COVID-19-induced pulmonary vascular and pathological changes. From April 1 to May 30, 2021, we conducted an observational study and recruited 11 patients in a tertiary care hospital in India, with respiratory rate ≥30 times/min, oxygen saturation ≤94% with ambient air, or partial arterial oxygen pressure to fraction of inspiration O2 ratio (PaO2/FiO2) ratio >100 mmHg and ≤300 mmHg. And followed it up for 14 days. Among these, bevacizumab plus standard care markedly improved the PaO2/FiO2 ratios at Days 1 and 7. After receiving a single dose of bevacizumab, 7 out of 11 patients (63.6%) showed clinical improvement in terms of oxygen-support status and inflammatory markers.63.6% patients were discharged. Of 10 patients with fever, body temperature normalized within 24hrs in 8patients (80%). Relative to non-bevacizumab patients, improvement in oxygenation and shortening oxygen-support duration was observed in patients receiving bevacizumab. Our findings suggest bevacizumab plus standard care is highly beneficial for patients with severe Covid-19. Further studies including randomized and placebo-controlled trials are warranted for validation of bevacizumab monotherapy and combination therapy.***

Keywords: Bevacizumab, anti-VEGF, monoclonal antibody, PaO2/FiO2 ratio, COVID-19

1. Introduction

Coronavirus disease 2019 (COVID-19) is an ongoing pandemic which has devastated the human life in many countries[1]. As developing countries like India were recovering from the first wave of COVID-19, a severe second wave hit the country and claimed many lives. In this disease, dyspnea is a major clinical symptom, caused via inflammatory pulmonary effusion or edema. Dyspnea is present in almost all patients with severe COVID-19, and it instigates pulmonary and systemic hypoxia[2, 3, 4]. Although many brave efforts have been made[5, 6, 7] by the scientific communities all around the globe, not even a single drug against this virus, with significant clinical efficacy is developed yet. The approach of oxygen supplementation, including low flow oxygen, high flow oxygen, non-invasive ventilation and mechanical ventilation became indispensable, causing worldwide shortage of ventilatory devices and other necessary supplies[8, 9, 10]. The current situation poses a world-wide challenge for medical supplies and demands an urgent need for development of efficacious drugs. A novel therapeutic drug called bevacizumab[11] (with concept of blocking vascular endothelial growth factor (VEGF) was proposed for treating severed COVID-19 patients.

A recent study (single arm trial with the recruitment of 26 patients of severe COVID-19) revealed bevacizumab plus standard care markedly improved the PaO2/FiO2 ratios at Day 1 and Day 7[12]. By Day 28, 24 patients (92%) showed improvement in oxygen-support status and 17 (65%) patients were discharged. By day 7, significant reduction of lesion areas/ratios were observed on CT or X-ray films. Fever subsided within 72 hours in 13 out of 14 patients (93%). Relative to comparable controls; bevacizumab showed significant clinical effectiveness in improving oxygen status and shortening the duration of oxygen-support. The findings of this study suggested bevacizumab plus standard care is highly beneficial in patients with severe COVID-19.

On the basis of above experience, bevacizumab was given to 11 severe COVID-19 patients and the outcome was recorded. Acute respiratory distress syndrome (ARDS) and dyspnoea leads to hypoxia in lung tissues and other organs. Hypoxiastimulates VEGF expression via activation of Prolyl-hydroxylase (PHD)-hypoxia-inducible factor (HIF)-1 pathway, which up-regulates VEGF expression via transcription activation. VEGF is a known, potent vascular permeability factor, which accelerates vascular leakiness in the infected lung tissues, resulting in further hypoxia[13, 14]. Furthermore, VEGF takes part in lung inflammation[15]. Blocking VEGF and its receptor (VEGFR-mediated signaling) can augment oxygen perfusion and anti-inflammatory response, resulting in easing of clinical symptoms in severe COVID-19 patients. Thus, we employed bevacizumab, a known anti-VEGF monoclonal antibody, for

treating severe COVID-19 patients and observations were recorded.

Clinical evidence for the bevacizumab therapy hypothesis includes: (1) patients with severe COVID-19suffer from significant hypoxia; (2) VEGF levels are markedly elevated in patients with severe COVID-19[16, 17]; (3) pulmonary oedema is frequently present in COVID-19 patients; (4) autopsy analysis of COVID-19 patients shows excessive extravasates in alveoli[18, 19]; (5) vascular disorganization and endothelial cell proliferation in the infected lung tissues; (6) hyperactive inflammatory response[20]; and (7) Improvement in pulmonary oedema by anti-VEGF therapy has been demonstrated[21, 22] in experimental animal models. In accordance of our hypothesis, vascular dysfunction of the Covid-19-infected tissues have been demonstrated in recent clinical studies[23, 24].

Bevacizumab has been used in medical oncology since years, with considerable reliability and safety. Our study presents the observed clinically efficacy of Bevacizumab in severe COVID-19 patients.

2. Material and Methods

Study Participants: Patients aged 18–80 years with a confirmed Covid-19 diagnosis were eligible if they had respiratory distress with a respiratory rate (RR) of ≥30 times/min, oxygen saturation (SpO2) of ≤94% while they were breathing ambient air, or a partial arterial oxygen pressure to fraction of inspiration O2 ratio (PaO2/FiO2) of >100 and ≤300 mmHg. Patients were made aware of benefits, mechanism of action and adverse effects of Bevacizumab. All 11 patients and attenders consented for Bevacizumab therapy.

Study Design: All 11 patients were admitted during the study period and followed up till discharge. All eligible patients received a single dose (500 mg) of Bevacizumab dissolved in 100ml of saline intravenously in not less than 90 minutes, under electrocardiographic monitoring and standard care. Written, informed consents were obtained from all patients or patient attenders (if the patients were unable to provide consent themselves). All the adverse events were scrutinised and given proper medical treatment to avoid further damage.

Standard Care: Standard care included oxygen-support, non-invasive and invasive ventilation, antibiotics, antivirals, and vasopressor support as necessary. The basic regimens for treating patients with severe Covid-19 included antiviral drugs (Inj. Remdesivir), antibiotics, steroids, antipyretics, anticoagulants, and supportive care.

Outcomes and Measures: Primary outcomes included changes in oxygen support-status at Days 1 and 7. PaO2/FiO2 changes were noted in patients requiring invasive and non-invasive ventilation. Secondary outcomes included the change of fever symptom on Day 7, discharge rates and changes in inflammatory markers.

Clinical, Laboratory and Radiological Data Collection: Arterial blood gas analysis, chest X-ray, and other necessary lab tests were done. The patients' PaO2/FiO2 ratios were assessed at baseline (within 24 h prior to bevacizumab administration), on Days 1 and 7; laboratory tests including blood tests and inflammatory markers. Clinical data including demographic data, presenting symptom, fever symptom as well the changes of status of oxygen-support were recorded using case record forms.

3. Results

3.1 Study Participants

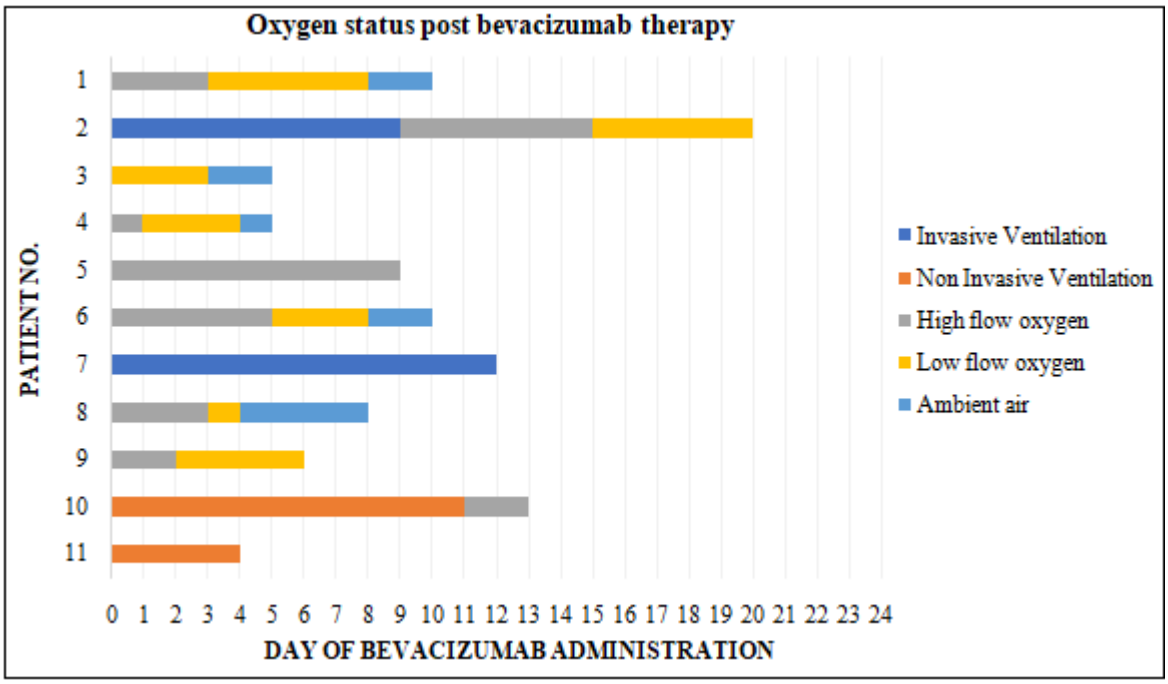
11 patients received a single dose of bevacizumab during stay in the hospital. The median age of the patients is 21.7 years and above, 55% of them were men. The median time from admission to administration of Bevacizumab was 11.5 days. Common onset of symptoms was fever (91%), cough (100%), shortness of breath (54.5%) and loose stools (9%). Among the patients, most common co-morbidity noted was hypertension (45.4%), followed by diabetes mellitus (36.3%).5 patients had each of the following 5 comorbidities individually – parkinsonism, cerebrovascular accident, pulmonary Koch's, epilepsy and obstructive sleep apnoea. One patient presented with symptoms, two weeks after receiving 1st dose of AstraZeneca (ChAdOx1 nCoV-19) vaccine

Baseline demographic clinical characteristics of patients:

Age, median, years	51.7
Sex, no (%)	
• Male	11 (63.6%)
• Female	4 (36.3%)
Symptom onset to admission, median, days	7
Admission to BEVA treatment, median, days	4.5
Medical history, no. (%)	
• Hypertension	5 (45.4%)
• Diabetes Mellitus	4 (36.3%)
• Cerebrovascular Accident	1 (9%)
• Obstructive Sleep Apnoea	1 (9%)
• Epilepsy	1 (9%)
• Parkinsonism	1 (9%)
• Pulmonary Koch's	1 (9%)
Symptoms, no. (%)	
• Fever	10 (90.9%)
• Dry cough	11 (100%)
• Shortness of breath	6 (54.5%)
• Loose stools	1 (9%)

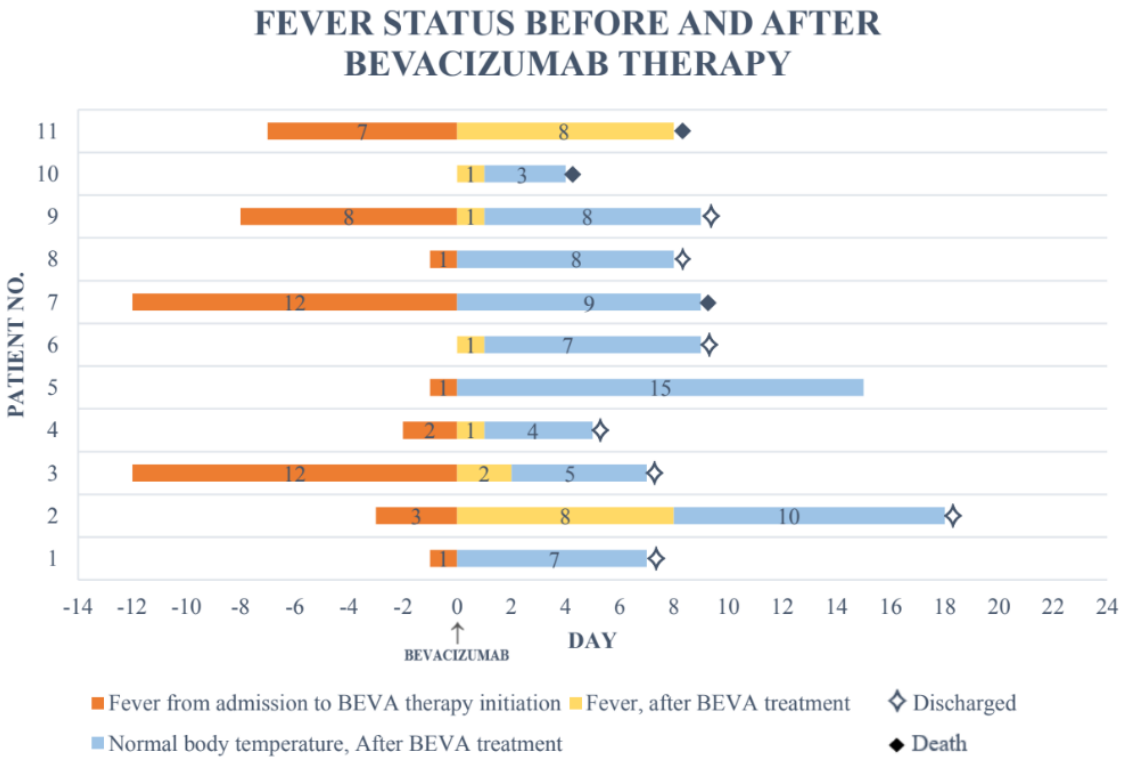
3.2 Oxygen support status and PAO2/FIO2 status:

After receiving a single dose of bevacizumab, 7 out of 11 patients (63.6%) showed improvement and 36.3% (4 out of 11) patients did not show any change in oxygen status. Inspiringly 63.6% of the patients were discharged. Among the patients using invasive, or non-invasive ventilation (2), one of the patients had improved PF ratio on PC mode, while other patient's oxygen status did not improve after initiating Bevacizumab.



Fever Symptom:

Among the treated patients, 91% of the patients had fever at the time of admission to the hospital. Among the patients having fever at the time prior to bevacizumab administration (81.8%), rapid abatement of fever was noticed within 24 hours of receiving bevacizumab in 77.7% (7 out of 9) patients. The remaining two patients had persistent fever, and were diagnosed with sepsis, as evidenced by blood and urine cultures.

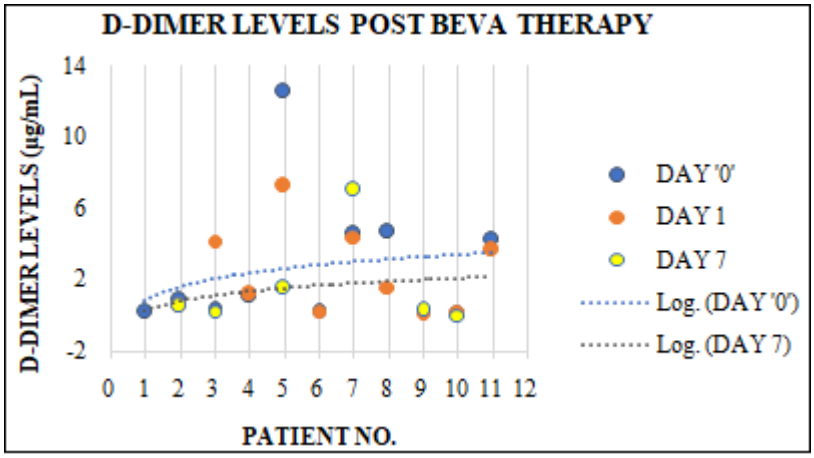


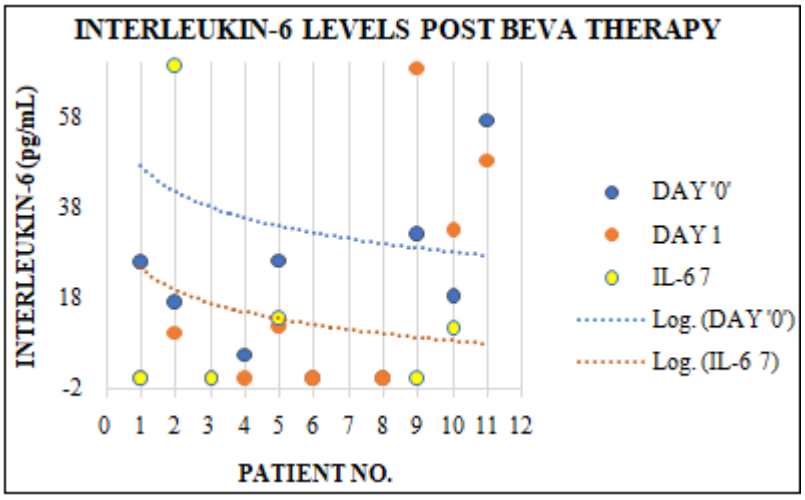
Inflammatory Markers

Significant change in CRP levels was observed before and after administration of bevacizumab.75% of patients CRP levels normalised after receiving bevacizumab, while one patients' CRP level was unchanged. D-DIMER levels showed decreasing trend in 6 of 9 patients, one patient's D-DIMER level was unchanged.

D-DIMER levels were significantly reduced on Day 7 in 4 out of 5 patients, while increasing in one patient by two-fold of Day 1 levels.

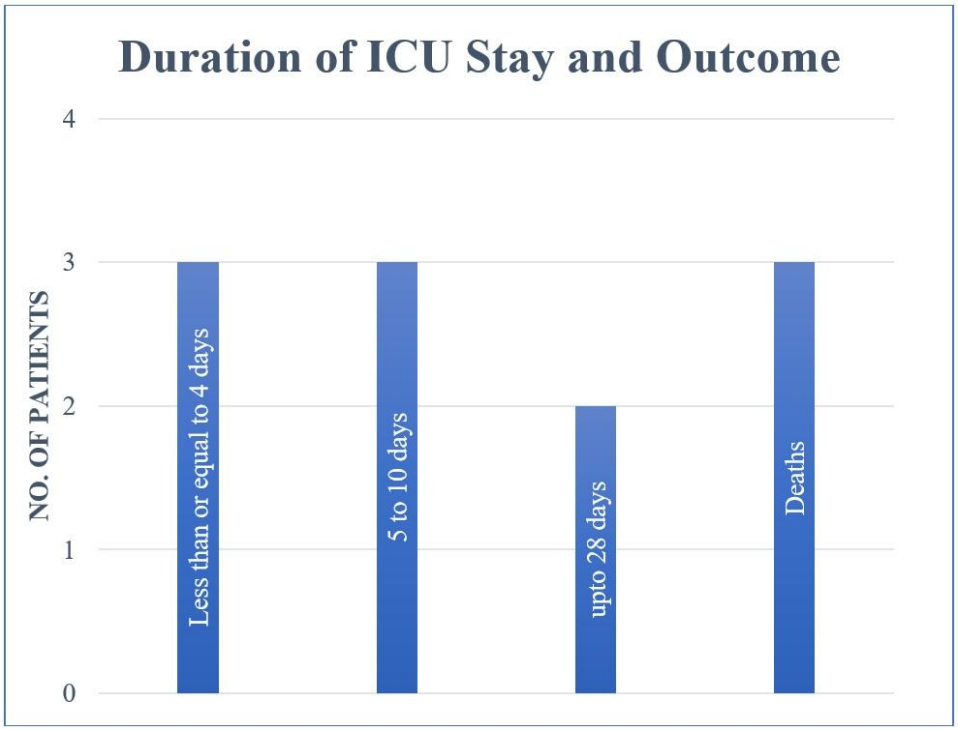
IL-6 levels showed a downward trend in 6 out of 10 patients after one day of receiving bevacizumab and worsened in 2 patients. On Day 7, IL-6 levels were improved in 4 patients while worsening in 1 patient.





Median Duration of ICU Stay and Outcome of Patients

Among 11 patients, 7 were discharged to home among which 5 were discharged on ambient air; and 2 were discharged with minimal oxygen support. Average ICU stay of discharged patients was 8 days.3 deaths occurred due to secondary bacterial infections and septic shock, with their pre-existing comorbidities as major contributing factors in mortality.



4. Discussion

Unfortunately, patients with severe COVID-19 progress downhill, with most cases of this cohort being admitted into Intensive therapy units and being subjected to aggressive medical management modalities, including invasive ventilation, and less proven therapies like stem cell transplantation, plasma therapy, fibrinolytic therapy etc. This treatment reflects an unpleasant period for the patient and lower treatment satisfaction for the attending physicians. Almost no effective therapy for this disease is made available, despite numerous trials. The current scenario demands an urgent need of developing effective, life-saving treatment modalities. The trial done by medical centres of China and Italy had explained the novel treatment of bevacizumab for treating COVID-19 patients (28). With our preliminary experience, we report the clinical findings and outcome in our 11 severe COVID-19 patients in tertiary care hospital, who were administered single dose of bevacizumab.

A single dose treatment with bevacizumab improved the oxygen support status in 64% and improved PaO2/FiO2 values. It has shown excellent response in rapid abatement of fever in 8 out of 11 patients (72.7%) within 24 hours of initiation of treatment. Patients had improvement in clinical condition and decreasing trend in inflammatory markers after initiation of bevacizumab. IL-6 levels showed improvement in 6 out of 10 patients (60%). Patients had shorter duration of ICU stay and 7 of 11 patients were discharged on ambient air or with minimal oxygen support.3 patients succumbed to death due to underlying comorbid conditions, secondary bacterial infections and septic shock. But the initiation of treatment with bevacizumab has remarkably improved overall survival of the patient.

Spontaneous improvement of oxygen support status might reflect the anti-vascular leakiness effect of bevacizumab. It is known that VEGF mobilizes inflammatory cells to infected tissues and anti-VEGF can alleviate fever by counteracting the virus triggered inflammation.

Hence bevacizumab has a major role in improvement of clinical parameters when administered with other standard care modalities including antivirals, anticoagulants and oxygen support.

Bevacizumab at dose range of 5-15mg/kg is routinely used in clinical oncotherapy and about 7.5mg/kg in our study as a lower range. Bevacizumab related serious adverse events such as gastrointestinal perforation, venous thromboembolism (VTE), or haemorrhages were not seen in our study. Only one patient had thrombocytopenia which improved in 72 hours.

5. Conclusion

The study illustrates a basic clinical experience of severe COVID-19 patients treated with bevacizumab. The limitations of this study are-absence of a trial; small intake of patients; short term follow up and unfortunate deaths due to secondary sepsis and comorbid conditions. However, the improvements of multiple clinical parameters in bevacizumab treated patients suggest that anti-VEGFs might benefit patients with COVID-19. In particular, it is worthy to design future trials of bevacizumab with other therapeutic modalities such as anti-viral and anti-inflammatory drugs. Given the limited medical supply and available facility in most medical centres, a single injection of bevacizumab might immediately relieve symptoms and early discharge of patients with severe COVID-19. The therapeutic benefits of bevacizumab monotherapy and combination therapy in patients with severe COVID-19 should be validated in future by randomised and placebo-controlled trials.

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