ORIGINAL RESEARCH

Outcome of Bevacizumab Use in Moderate to Severe COVID-19 Induced ARDS Patient: A Prospective Study from North India

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ABSTRACT

Background:Atypical pneumonia is caused by the SARS CoV-2 virus in persons who have it. Inflammation is induced by the virus, which aids viral reproduction, dissemination, tissue injury, and hypoxia. Bevacizumab is a prominent anti-VEGF monoclonal antibody that has been approved by the USFDA for colorectal carcinoma, non-small cell lung carcinoma, renal carcinoma, recurrent glioblastoma, cervical carcinoma, and ovarian carcinoma. We conducted this study to look into the clinical benefits of bevacizumab in combination with standard care for patients with moderate to severe COVID-19 disease.

Materials and Methods: The present prospective study was conducted among patients with moderate to severe COVID-19 pneumonia, admitted at CMC MULTISPECIALITY HOSPITAL Hospital during SEP 2020 to june 2021. After taking informed consent from relatives a pretested proforma was used to record the demographic data, presenting symptoms, the changes of status of oxygen-support as well as the symptom. Each eligible patient received two doses (400 mg) of bevacizumab and arterial blood gas analysis, chest computed tomography (CT) scanning, chest X-ray, and laboratory tests were performed at baseline, Day 1 and Day 7 after start of bevacizumab. To compare differences between different time points after intervention and baseline point, a paired t-test or Wilcoxon matched-pairs signed-rank test was used for quantitative data.

Results: In present study, the mean age of patients was 50.2±14.1 years. Majority of enrolled patients were males (80.0%). The fever (85.0%) followed by cough (76.7%) and dyspnoea (70.0%) were the common symptoms among enrolled patients. The mean temperature of the enrolled patients was 99.3±1.4 F. CT chest showed that left lung lesion ratio was 19.7±15.4% at baseline and it showed improvement and reduced to 12.1±4.3% and similar significant improvement was observed for right lung lesion ratio (baseline: 35.2±14.9% vs Day 7: 17.2±13.9%). The discharge rate in our study was 65.0%. Due deteriorating of condition or addition of new complications, 18.3% of patients were referred to higher centres for further management. The death rate was 16.7% in our study.

Conclusion: To reduce mortality in the global COVID-19 pandemic, the necessity for efficient treatment with few complications should be prioritised. These 60 patients also demonstrate bevacizumab's high efficacy in SARS CoV-2 patients.

Keywords: Bevacizumab, COVID-19, Hypoxia-induced factor-1, Chest CT images, Arterial blood gas.

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INTRODUCTION

In 2002 and 2012, the severe acute respiratory syndrome (SARS) and the Middle East respiratory disease (MERS) emerged. Atypical pneumonia is caused by the recently discovered SARS-CoV-2 coronavirus. In December 2019, the first case was recorded in Wuhan, China. On March 11, 2020, the World Health Organization (WHO) classified the novel coronavirus (COVID-19) outbreak a worldwide pandemic.[1] More than 200 million cases have been reported worldwide, with approximately 4.5 million deaths. Over 30 million cases have been reported in India, with more than 0.4 million deaths.[2-3]

Atypical pneumonia is caused by the SARS CoV-2 virus in persons who have it. Inflammation is induced by the virus, which aids viral reproduction, dissemination, tissue injury, and hypoxia. Hypoxia-induced factor-1 (HIF-1) is activated by tissue hypoxia. HIF-1 is a transcription factor that helps cells maintain their oxygen homeostasis. Many genes that promote angiogenesis, such as vascular endothelial growth factor (VEGF) , are activated by HIF-1. HIF-1 also increases the production of ACE-2 receptor genes, which are important in the pathophysiology of COVID-19. Due to rapid cell turnover, cellular hypoxia causes activation of the HIF-1 pathway and angiogenesis in tumour cells, making the HIF-1/VEGF pathway a key target for oncotherapy.[4-5]

Bevacizumab is a prominent anti-VEGF monoclonal antibody that has been approved by the USFDA for colorectal carcinoma, non-small cell lung carcinoma, renal carcinoma, recurrent glioblastoma, cervical carcinoma, and ovarian carcinoma.[6] It is also utilised to inhibit neovascularization in wet age-related macular degeneration (AMD).[7] We conducted this study to look into the clinical benefits of bevacizumab in combination with standard care for patients with moderate to severe COVID-19 diseas.

MATERIALS & METHODS

Study Design and Population

The present prospective study was conducted among patients with moderate to severe COVID-19 pneumonia (aged 18 years and above), admitted CMC MULTISPECIALITY Hospital during SEP 2020 to JUNE 2021. The inclusion criteria were patients with SARS-CoV-2 pneumonia confirmed by RT-PCR of nasopharyngeal swab specimens, together with signs, symptoms and radiological findings suggestive of COVID-19 pneumonia. The patients with severe hepatic dysfunction, severe renal dysfunction, uncontrolled hypertension, poorly controlled heart diseases, hereditary bleeding tendency or coagulopathy, thrombosis within 6 months before enrolment, undergone major surgery, malignant tumours within 5 years of enrolment, patients with untreated active hepatitis or HIV-positive patients, pregnant and lactating women and those planning to get pregnant were not included in the study. No sample-size calculations were performed. All consecutive patients who met the inclusion criteria were assessed for eligibility and recruited until the completion of study period.

Clinical, Laboratory and Radiological Data Collection

After taking informed consent from relatives a pretested proforma was used to record the demographic data, presenting symptoms, the changes of status of oxygen-support as well as the symptom. Arterial blood gas analysis, chest computed tomography (CT) scanning, chest X-ray, and laboratory tests were performed. The patients' PaO2/FiO2 ratios were assessed at baseline (within 24 hours prior to bevacizumab administration) , on days 1 and 7; chest CT were performed at baseline (within 48 hours prior to bevacizumab administration) and day 7 (±1 day), or alternatively performed chest X-ray at baseline (within 48 hours prior to bevacizumab administration) at days 3 and 7; laboratory tests including blood routine and C-reactive protein (CRP) at baseline (within 48 hours prior to bevacizumab administration) and day 7. Chest CT images were quantified to obtain the volume and the ratios of the lesions in

bilateral lungs. X-ray images were semi-quantified to assess the ratios of the lesions in bilateral lungs.

Bevacizumab Intervention

Each eligible patient received two doses (400 mg) of bevacizumab (Qilu Pharmaceutical Co. LTD and Roche Pharmaceutical Co. LTD) dissolved in 100 ml of saline intravenously in no less than 90 min under electrocardiography monitoring and standard care. Standard care included supplemental oxygen, non-invasive and invasive ventilation, antiviral or antibiotic agents, vasopressor support, and extracorporeal membrane oxygenation as necessary. Each patient was followed up for 28 days or until hospital discharge postintervention. The adverse events were monitored and adjudicated by the Safety Monitoring Committee. All the adverse events were handled timely with proper medical treatment to avoid further damage.

Statistical Analysis

The data was coded and entered into Microsoft Excel spreadsheet. Analysis was done using SPSS version 20 (IBM SPSS Statistics Inc., Chicago, Illinois, USA) Windows software program. Primary outcomes were changes of PaO2/FiO2 at day 1 and day 7. Secondary outcomes included change of chest radiological imaging at day 7, as well as oxygen-support status, discharge rate and change of fever symptom during 28 days follow-up. Descriptive statistics included computation of percentages, means and standard deviations. To compare differences between different time points after intervention and baseline point, a paired t-test or Wilcoxon matched-pairs signed-rank test was used for quantitative data. Level of significance was set at $p < 0.05$.

RESULTS

In present study, the mean age of patients was 50.2±14.1 years. Majority of enrolled patients were males (80.0%). Among enrolled patients the most common comorbidity was diabetes mellitus (16.7%), hypertension (16.7%) followed by hypothyroidism (6.7%). The fever (85.0%) followed by cough (76.7%) and dyspnoea (70.0%) were the common symptoms among enrolled patients. The mean temperature of the enrolled patients was 99.3±1.4 F. In our study, the mean duration of onset of symptoms to admission was 11.2±3.4 days and mean duration of admission to bevacizumab treatment initiation was 8.2±4.6 days (Table 1).

Table 1: Baseline demographic and clinical characteristics of the patients (N=60)

Characteristics	**Number/Mean**	**%/SD**
Age (in years)	50.2	14.1
Gender		
Male	48	80.0
Female	12	20.0
Comorbidity		
Coronary artery disease	3	5.0
Dilated cardiomyopathy	1	1.7
Diabetes	10	16.7
Epilepsy	1	1.7
Haemorrhoids	1	1.7
Hypertension	10	16.7
Hypothyroidism	4	6.7
Intra cerebral haemorrhage	1	1.7
Post percutaneous transluminal coronary angioplasty	1	1.7
Cholecystectomy	1	1.7
Sarcoidosis	1	1.7

Obsessive Compulsive Disorder	1	1.7
Symptoms		
Fever	51	85.0
Cough	46	76.7
Dyspnoea	42	70.0
Severe dyspnoea	2	3.3
Malaise	4	6.7
Body pain	4	6.7
Weakness	2	3.3
Chest pain	2	3.3
Sore throat	3	5.0
Throat pain	1	1.7
Nausea	2	3.3
Vomiting	1	1.7
Haemoptysis	1	1.7
Pain abdomen	1	1.7
Sweating	1	1.7
Vertigo	1	1.7
Maximum body temperature (F)	99.3	1.4
Symptoms onset to admission (in days)	11.2	3.4
Admission to Bevacizumab treatment (in days)	8.2	4.6

In present study it is observable that tremendous improvement in the Clinical, Laboratory and Chest Radiological parameters. The duration of fever prior to initiation of bevacizumab was 4.3±1.9 days, which was reduced to 2.0±0.9 days after initiation of bevacizumab. Also, PaO2/FiO2 ratios showed significant improvement on Day 1 (223.7±151.2) and Day 7 (298.3±178.4) after initiation of bevacizumab, when compared to baseline PaO2/FiO2 ratios (184.2±94.5). Improved lymphocyte count was observed on day 7 (1.4±0.6 X 106/L) as compared to baseline (0.9±0.3 X 106/L). Also, CRP level were reduced to 11.3±22.2 mg/L on Day 7 as compared to baseline (66.7 ±74.6 mg/L). CT chest showed that left lung lesion ratio was 19.7±15.4% at baseline and it showed improvement and reduced to 12.1±4.3% and similar significant improvement was observed for right lung lesion ratio (baseline: 35.2±14.9% vs Day 7: 17.2±13.9%). Chest X-ray showed that left lung lesion ratio was 47.2±30.4% at baseline and it showed improvement and reduced to 25.8±23.6% and similar significant improvement was observed for right lung lesion ratio (baseline: 48.9±24.7% vs Day 7: 30.3±26.9%) (Table 2).

Table 2: Clinical, Laboratory and Chest Radiological parameters changes among patients (N=60)

Parameters	**Mean±SD**		**P value**
Duration of fever (n=51)	**Before start of Bevacizumab**	**After start of Bevacizumab**	
	4.3±1.9	2.0±0.9	< 0.0001
PaO_2/FiO_2 ratios	**Baseline**	**Day 1**	
	184.2±94.5	223.7±151.2	0.088
	Baseline	**Day 7**	
	184.2±94.5	298.3±178.4	< 0.0001
	Baseline	**Day 7**	
Lymphocyte (10^6/L)	0.9±0.3	1.4±0.6	< 0.0001

CRP level (mg/L)	66.7 ±74.6	11.3±22.2	< 0.0001
CT chest			
Patchy shadow	2.4±2.9	1.6±2.6	0.161
Ground glass opacity	3.6±2.6	6.4±5.1	0.0002
Total lesion area (cm3)	1043.3±649.3	678.4±392.8	0.0003
Left lung lesion ratio (%)	19.7±15.4	12.1±4.3	0.0004
Right lung lesion ratio (%)	35.2±14.9	17.2±13.9	< 0.0001
Chest X-ray			
Left lung lesion ratio (%)	47.2±30.4	25.8±23.6	< 0.0001
Right lung lesion ratio (%)	48.9±24.7	30.3±26.9	0.0001

PaO2/FiO2=partial arterial oxygen pressure to fraction of inspiration O2 ratio, CRP= C Reactive Protein, CT= Computed Tomography.

In our study, the newly observed complications after start of bevacizumab were raised CT severity score (21.7%), raised total leucocyte count (21.7%) and decreased SpO2 (15.0%). The discharge rate in our study was 65.0%. Due deteriorating of condition or addition of new complications, 18.3% of patients were referred to higher centres for further management. The death rate was 16.7% in our study (Table 3).

Table 3: Complications and outcome of patients (N=60)

Variables	**Number**	**%**
New Complications		
Raised CT severity score	13	21.7
Raised Total leucocyte count	13	21.7
Increased O_2 demand	5	8.3
Decreased SpO_2	9	15.0
Deranged renal functions	1	1.7
Outcome		
Discharge without O_2	31	51.7
Discharge with O_2	(n=8)	13.3
2L	3	5.0
4L	1	1.7
5L	3	5.0
10L	1	1.7
Dead	10	16.7
Referred	11	18.3

DISCUSSION

In present study, the mean age of patients was 50.2±14.1 years. Majority of enrolled patients were males (80.0%). The mean temperature of the enrolled patients was 99.3±1.4 F. The discharge rate in our study was 65.0%. The death rate was 16.7% in our study. SARS-CoV-2 is spread from person to person by respiratory droplets and aerosols. The virus attaches to host receptors and enters cells via endocytosis or membrane fusion once within the body. SARS-CoV-2 possesses a functional receptor called ACE-2, which is extensively expressed on pulmonary epithelial cells and nasal epithelia. The virus then replicates and propagates locally within the cell. Viruses that have just developed invade nearby tissue. Virus particles are spreading from the nasal epithelium to the upper and lower respiratory tract via the respiratory system at this point. Tumour necrosis factor-α (TNF-α), interleukins (IL-1, IL-6,

IL-8, IL-120, and IL-12), interferon-λ and β, CXCL-10, and monocyte chemoattractant protein-1(MCP-1) are only a few of the inflammatory markers and cytokines released by infected pneumocytes. This cytokine storm functions as a chemoattractant, mobilizing neutrophils, CD4 helper T cells, and CD8 cytotoxic T cells to the lung tissue. These cells are in charge of attacking the virus. They produce inflammation and lung damage as a result of this process. Apoptosis occurs when the host cell releases new virus particles, which infect nearby type 2 pneumocytes.[8-12]

In our study, the fever (85.0%) followed by cough (76.7%) and dyspnoea (70.0%) were the common symptoms among enrolled patients. In our study, the mean duration of onset of symptoms to admission was 11.2±3.4 days. COVID-19 has a 4 to 14 days incubation period between exposure and development of symptoms. Fever, cough with or without expectoration, breathing difficulty, weariness, and headache are the most prevalent symptoms, which range from mild to severe. The clinical course is classified as mild, moderate, or severe.[13-14]

In present study it is observable that tremendous improvement in the Clinical, Laboratory and Chest Radiological parameters. The duration of fever prior to initiation of bevacizumab was 4.3±1.9 days, which was reduced to 2.0±0.9 days after initiation of bevacizumab. Also, PaO2/FiO2 ratios showed significant improvement on Day 1 (223.7±151.2) and Day 7 (298.3±178.4) after initiation of bevacizumab, when compared to baseline PaO2/FiO2 ratios (184.2±94.5). Improved lymphocyte count was observed on day 7 (1.4±0.6 X 106/L) as compared to baseline (0.9±0.3 X 106/L). Also, CRP level were reduced to 11.3±22.2 mg/L on Day 7 as compared to baseline (66.7 ±74.6 mg/L). Depending on the severity of the case, patients can be treated in outpatient or inpatient settings. Antiviral Remdesivir, corticosteroids with or without oxygen assistance, and other supportive management are all standard treatments. Newer guidelines evaluate the judicious use of baricitinib, tofacitinib, tocilizumab, and sarilumab for severe diseases.[14-17]

In our study, the CT chest showed that left lung lesion ratio was 19.7±15.4% at baseline and it showed improvement and reduced to 12.1±4.3% and similar significant improvement was observed for right lung lesion ratio (baseline: 35.2±14.9% vs Day 7: 17.2±13.9%). Chest X-ray showed that left lung lesion ratio was 47.2±30.4% at baseline and it showed improvement and reduced to 25.8±23.6% and similar significant improvement was observed for right lung lesion ratio (baseline: 48.9±24.7% vs Day 7: 30.3±26.9%). Hypoxia causes the production of cytokines, inflammatory markers, and vascular endothelial growth factors in COVID-19 patients, which causes endothelial cell proliferation and increased permeability, resulting in pulmonary edoema and a decrease in alveolar ventilation. COVID-19 patients have greater VEGF levels than healthy controls, according to new research.[12,18,19]

CONCLUSION

To reduce mortality in the global COVID-19 pandemic, the necessity for efficient treatment with few complications should be prioritised. Bevacizumab medication was provided to 26 patients in China and Italy from February to April 2020, and all of them improved significantly. These 60 patients also demonstrate bevacizumab's high efficacy in SARS CoV-2 patients. The fact that these patients improved clinically encouraged us to consider the necessity for a bigger bevacizumab investigation.

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