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Assessment Of Supplemental Oxygen Requirement With The Use Of Baricitinib As An Adjuvant In The Treatment Of Moderate To Severe Covid-19

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Abstract

Background: In Covid-19 pneumonia there was dysregulated immune system with hyperactive inflammation, due to increased cytokine release, for which IL-6 is considered to be the main culprit leading to severity of the disease and causing multi organ damage and mortality[1]. Here we are observing the use of Baricitinib - Janu kinase inhibitors as an adjuvant in the treatment for COVID-19 which was approved by FDA on November 19, 2020 because they can prevent phosphorylation of key proteins involved in the signal transduction that leads to immune activation and inflammation (e.g., the cellular response to pro inflammatory cytokines such as interleukin [IL]-6). Immunosuppression induced by this class of drugs could potentially reduce the inflammation and associated immunopathologies observed in patients with COVID-19. Additionally, JAK inhibitors, particularly Baricitinib, have theoretical direct antiviral activity through interference with viral endocytosis, potentially preventing entry and infection of susceptible cells.

Aim And Objectives: The aim of this study is to assess the role of Baricitinib, in clinical outcome and supplemental oxygen support at the time of discharge in moderate to severe COVID -19 patients. The primary objective is to evaluate the effect of BARICITINIB on outcome and supplemental oxygen support at the time of discharge.

Materials And Methods: We did a prospective, observational study in patients admitted with moderate to severe COVID-19 pneumonia at Kamineni academy of medical sciences and research center (KAMSRC), L B Nagar, Hyderabad, who met the criteria (Severity graded according to MoHFW). Our study group were subjected to Baricitinib 4 mg once daily for 10 days or until hospital discharge or whichever is earliest along with the antivirals Inj Remdesivir.

Results: Total of 41 subjects are included in the study who have moderate to severe disease which included male and female population of 30 (73.17%) and 11(26.82%) respectively. Out of 41 patients according to MoHFW severity grading, 19 are included in the moderate disease and 22 are included in severe disease which are 46.3% and 53.7% respectively. The mean days of recovery was 11.45 ± 6.17 days, the subjects not requiring or decreased supplemental O2 at the time of discharge have been significantly increased. At the time of discharge, the percentage of cases requiring *supplemental oxygen support* have *decreased* to *31.7%* and the percentage of cases *on room air increased to 43.9%*.

Conclusion: Baricitinib plus Remdesivir reduced the recovery time and accelerated improvement in clinical status among patients with Covid-19, notably among those receiving oxygen or noninvasive ventilation. Few studies were conducted regarding safety and efficiency of Baricitinib with Remdesivir in moderate to

severe disease. In our study, there is a significant decrease in oxygen requirement at the time of discharge and lesser number of subjects required supplemental oxygen support at discharge and a decreased duration of hospital stay is seen. In our study there is mortality. Few cases required prolonged care and oxygen support but eventually recovered and some subjects are dependent on oxygen support. Further confirmatory studies are required to support the data observed in this study. This study provides evidence for the potential use of Baricitinib 4 mg once daily for 10 days in the treatment of moderate to severe COVID-19 disease in early stages. The significant improvement in clinical status is likely due to faster viral reduction.

Keywords: COVID –19, IL-6, Baricitinib ,JAK inhibitors, Supplemental oxygen support.

Introduction

Novel coronavirus disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in December 2019 (COVID-19) in a cluster of patients in Wuhan, China, which has been designated a worldwide pandemic. As of October 2021, there have been 244,536,555 million confirmed cases of COVID-19 worldwide, including 4,966,160 million deaths reported (WHO, 2021)[2]. Pharmacological therapies of proven efficacy in corona virus disease 2019 are still lacking. In covid-19 pneumonia the disease severity may be due in part to a dysregulated inflammatory response[1]. Recently proposed line of therapy showed the use of kinase inhibitors as a treatment for COVID-19[4] because they can prevent phosphorylation of key proteins involved in the signal transduction that leads to immune activation and inflammation (e.g., the cellular response to pro inflammatory cytokines such as interleukin [IL]-6)[2]. Janus kinase (JAK) inhibitors interfere with phosphorylation of signal transducer and activator of transcription (STAT)[3] proteins that are involved in vital cellular functions, including signaling, growth and survival. Immunosuppression induced by this class of drugs could potentially reduce the inflammation and associated immunopathologies observed in patients with COVID-19. Additionally, JAK inhibitors, particularly Baricitinib, have theoretical direct antiviral activity through interference with viral endocytosis, potentially preventing entry and infection of susceptible cells.

Objectives

To evaluate the efficacy and supplemental oxygen support at the time of discharge with oral 4 mg Baricitinib given in moderate to severe COVID-19 disease.

Materials And Methods

Study Design

Our study is a prospective, observational study that evaluated the efficacy of the drug Baricitinib in the treatment of adult subjects diagnosed with SARS-CoV-2. The study is undertaken at Kamineni academy of medical sciences and research center (KAMSRC), LB Nagar, Hyderabad, India. Eligible subjects are assigned to receive Remdesivir along with other standards of care as per guidelines of MoHFW and BARICITINIB have been given as an adjuvant.

Study Population

Individuals with suspected COVID-19 who are admitted in KAMSRC from MAY 2021 to JUNE 2021 are taken into study. Key inclusion criteria are age ≥18 years, suspected or laboratory confirmed COVID-19 in hospitalized adults, requiring supplemental oxygen, or invasive mechanical ventilation with moderate to severe COVID 19 pneumonia's. Total of 41 cases who accepted to receive the treatment are taken into the study.

Key exclusion criteria are alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >5 x ULN, stage IV CKD or requiring dialysis (i.e., estimated glomerular filtration rate < 30 mL/min/1.73 m^2), pregnant or breast-feeding women, systemic disease which had affected the vital organs severely, immunocompromised patients, patients with co-morbid condition like myocardial infarction or heart failure within 90 days of recruitment.

Interventions

The study is initiated in response to the COVID-19 public health emergency, many drugs and treatment approaches were considered but no drugs had mortality benefit. In this study along with antiviral

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therapy, Baricitinib is given and outcomes are assessed. There is no formal calculation of sample size for this study. Forty-one subjects are enrolled in the study and all are given once-daily Baricitinib (4 mg) orally/ nasogastric tube for 10 days or till the date of discharge, whichever comes first. The regulatory recommendations (Clinical Management Protocol: COVID-19[Ministry of Health and Family Welfare,2020])[7], have been followed to categorize moderate and severe COVID-19 subjects and treatment given accordingly. Standard of care included systemic corticosteroids, such as dexamethasone, and antivirals, including Remdesivir intravenously as a 200-mg loading dose on day 1, followed by a 100-mg maintenance dose administered daily on days 2 to 10 or until hospital discharge or death. Venous thromboembolism prophylaxis is given for all the patients without a major contraindication. During the study, all the subjects are given antipyretics, cough suppressants, antibiotics, steroids, vitamins, anticoagulants, as per regulatory recommendation and approval. RT-PCR / Rapid antigen tests, using pharyngeal swabs were performed during screening on all the subjects who are hospitalized and are discharged after clinical cure.

Assessments

Subject's supplemental oxygen support at the time of admission and at the time of discharge were recorded along with the duration of hospital stay.

Safety assessments are based on physical examinations, vitals, laboratory tests, and the incidence and severity of adverse events.

Statistical Analysis

Data is entered into Microsoft excel data sheet and analyzed using SPSS-22 version software. Categorical data is represented in the form of Frequencies and proportions.

Graphical representation of data: MS Excel and MS word are used to obtain various types of graphs such as bar diagram, Pie diagram.

Statistical software: MS Excel**,** SPSS version 20 is used to analyze data.

Results:

Total of 41 subjects are included in the study who have moderate to severe disease.

Table 1: Profile of Subjects Distribution

		Count	%
	21 to 30 years	5	12.19%
Age	31 to 40 years	5	12.19%
	41 to 50 years	4	9.75%
	51 to 60 years	10	24.39%
	61 to 70 years	10	24.39%
	>70 years	7	17.07%
	Mean age (years)	55.02	
	Median	59.00	
	Std. Deviation	15.46	
	Minimum	22	
	Maximum	76	
Sex	Female	11	26.82%
	Male	30	73.17%

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In this study, the mean age of subjects was 55.02 ± 15.46 years, the majority of subjects are in the age group 51 to 60 years and 61 to 70 years (24.39%). Out of 41 subjects 73.17% (30) are males and 26.82% (11) are females. Maximum age of the patient is 76 yrs and minimum is 22 yrs.

Figure 1- Histogram of Age

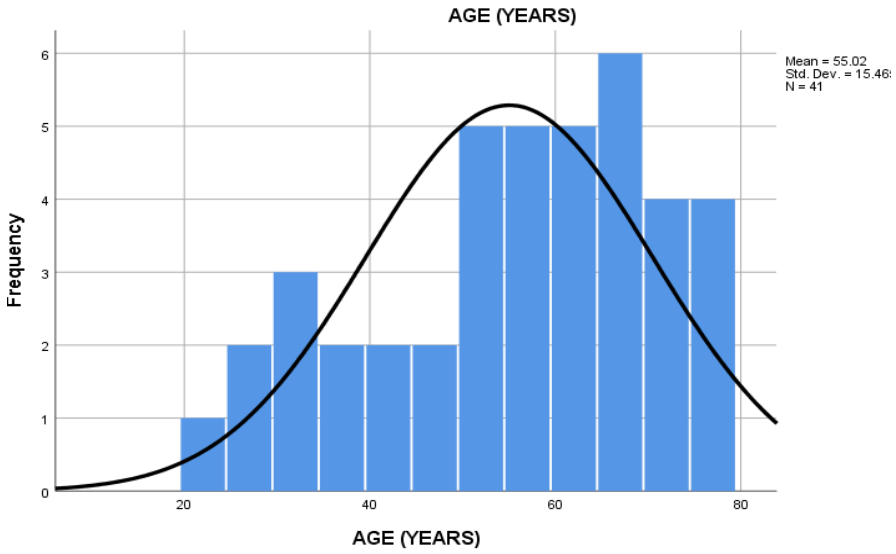
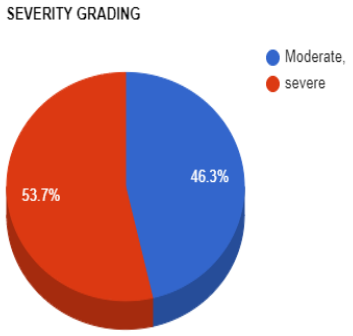


Table 2 - Showing Severity Index According To MoHFW

SEVERITY(SPO2%)	POPULATION(N)	N%
MODERATE (90-94%)	19	46.3%
SEVERE (<90%)	22	53.7%
TOTAL	41	100%

Figure 2-Pie Diagram Showing Severity Index According To MoHFW



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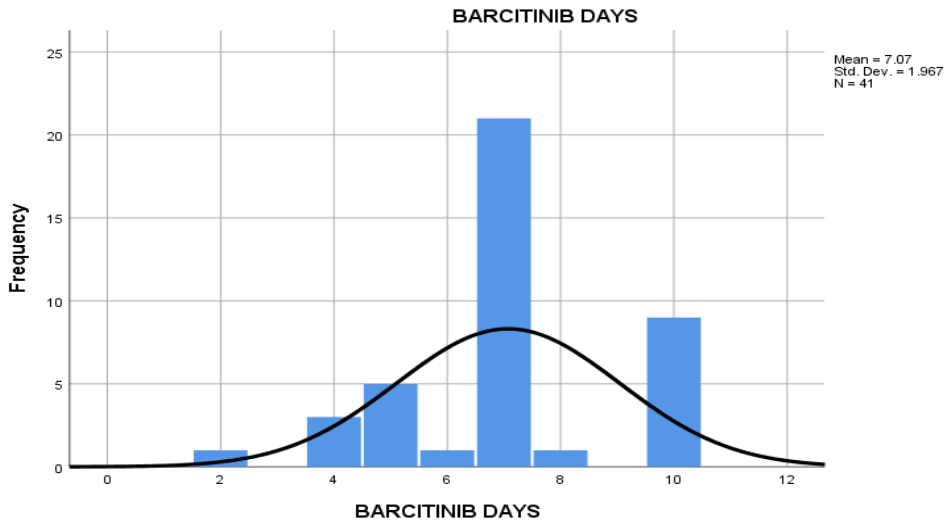
Above table and figure 2 showing that out of 41 patients according to MoHFW severity grading 19 are included in the moderate disease and 22 are included in severe disease which are of 46.3% and 53.7% respectively.

Table 3: Descriptive Profile of Baricitinib Days

	BARCITINIB DAYS
Mean	7.07
Median	7.00
Std. Deviation	1.967
Minimum	2
Maximum	10

Figure 3- Histogram of Baricitinib Days



Above table and figure 3 showing that Mean value of the number of days of Baricitinib are 7.07±1.967 years. Maximum number of Baricitinib days are 10 days and minimum are 2 days.

Table 4-Frequency table of recovered and expired patients

	Frequency	Percent
RECOVERED	35	85.4%
EXPIRED	6	14.6%
Total	41	100%

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Figure 4- Pie Diagram of Recovered and Expired Patients

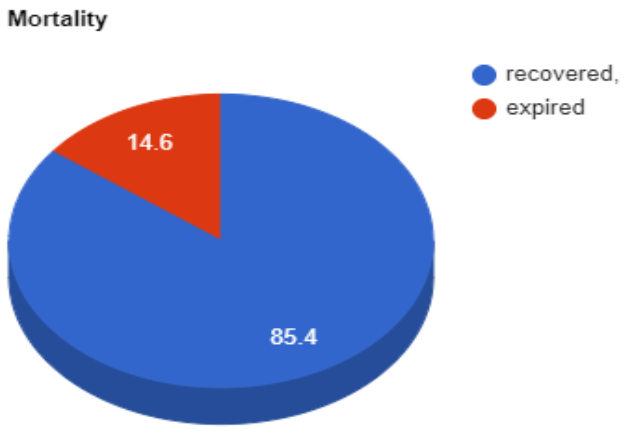

Table 5 - Recovery Days with the Use of Baricitinib

	DAYS OF RECOVERY
Mean	11.45
Median	12
Std. Deviation	6.17
Minimum	3
Maximum	32

Above tables and figures 4, 5 shows that, In the study out of 41 subjects, 35 (85.4%) are recovered and 6 (14.6%) expired. The mean days of recovery are 11.45 ± 6.17 days which excluded the expired subjects.

Table 6: Supplemental Oxygen Requirement at The Time of Admission and Discharge

			OXYGEN REQUIREMENT AT DISCHARGE				Total
			BIPAP	EXPIRED	O2	RA	
O2 REQUIRE-MENT AT	INTUBATED	Count	3	6	4	0	13

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ADMISION		%	23.1%	46.2%	30.8%	0.0%	100.0%
	NIV	Count	0	0	3	1	4
		%	0.0%	0.0%	75.0%	25.0%	100.0%
	O2	Count	1	0	6	16	23
		%	4.3%	0.0%	26.1%	69.6%	100.0%
	RA	Count	0	0	0	1	1
		%	0.0%	0.0%	0.0%	100.0%	100.0%
Total		Count	4	6	13	18	41
		%	9.8%	14.6%	31.7%	43.9%	100.0%

As shown in the above table 6, out of 41 patients initially at the beginning of the study 1 patient is on room air, 23 patients required supplemental oxygen support, 4 patients required NIV support and 13 are intubated. At the end of the study 18 patients are discharged on room air, 13 patients on supplemental oxygen support and 4 patients on BIPAP support and 6 patients expired which are of 43.9%, 31.7%, 9.8% and 14.6% respectively with a conclusion that 6 expired and 35 are discharged.

At the time of admission, subjects requiring supplemental oxygen support/ NIV support are more and the subjects not requiring or decreased supplemental oxygen support at the time of discharge have been significantly increased. The percentage of cases who are initially on supplemental oxygen/NIV requiring supplemental oxygen support at the time of discharge have *decreased to 31.7%,* and the percentage of cases discharged *on room air* have *increased to 43.9%.*

Safety: No relevant clinical examination findings, vital signs were attributed to Baricitinib. Overall use of Baricitinib is safe and well-tolerated in the study. Serial laboratory measurements are monitored closely.

Discussion:

The study conducted is a prospective, observational study which evaluated the efficacy and assessment of supplemental oxygen support with the use of Baricitinib combined with Remdesivir in the treatment of moderate to severe COVID disease. Mitigating the immune response and preventing a hyper inflammatory state may further improve clinical outcomes. On November 19, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the use of Baricitinib in combination with Remdesivir in hospitalized adults and children aged ≥ 2 years with COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[6] The issuance of an EUA does not constitute FDA approval. An EUA indicates that a product may be effective in treating a serious or life-threatening disease or condition. Historically, Baricitinib is an oral Janus kinase (JAK) inhibitor that is selective for JAK1 and JAK2 and FDA approved for the treatment of rheumatoid arthritis. The Janu kinase (JAK) inhibitors are proposed as treatments for COVID-19 because they can prevent phosphorylation of key proteins involved in the signal transduction that leads to immune activation and inflammation (e.g., the cellular response to pro inflammatory cytokines such as interleukin [IL]-6)[4.] In this regard, a Phase 3 study using Baricitinib in treating moderate COVID-19 patients is already in progress in India, where the sample size is 1585 subjects, and the follow-up duration is 29 days[9,10] in which Percentage of Participants who Die or Require Non-Invasive Ventilation/High-Flow Oxygen or Invasive Mechanical Ventilation (including extracorporeal membrane oxygenation [ECMO]) [Time Frame: Day

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1 to Day 28] is the primary outcome treatment with Baricitinib reduced 28-day all-cause mortality. In our study Primary outcome of the study is that a significant percentage of cases requiring supplemental oxygen support have decreased from the time of admission to discharge, and also a significant percentage of cases have been discharged on room air. The mean days of recovery is 11.45 ± 6.17 days which is better than the normal course of the disease. In this study, the mean age of subjects is 55.02 ± 15.46 years. The majority of subjects are in the age group 51 to 60 years and 61 to 70 years (24.39%). Out of 41 subjects 73.17% (30) are males and 26.82% (11) are females. Maximum age of the patient is 76 yrs and minimum is 22yrs. According to MoHFW severity grading 19 are included in moderate disease and 22 are included in severe disease which are 46.3% and 53.7% respectively. Out of 41 subjects, 35 (85.4%) are recovered and 6 (14.6%) expired. At the beginning of the study / at the time of admission, out of 41 patients - 1 patient is on room air, 23 patients required supplemental oxygen support, 4 patients required NIV support and 13 were intubated. At the end of the study 18 patients are discharged on room air, 13 patients with supplemental oxygen support and 4 patients on BIPAP support and 6 patients are expired which is of 43.9%, 31.7%, 9.8% and 14.6% respectively with a conclusion that 6 expired and 35 are discharged. However, a key limitation of the study was the inability to evaluate the treatment effect of Baricitinib in addition to, or in comparison to, corticosteroids which are used as standard treatment for severe or critical COVID-19 pneumonia. But in our study, we found that late administration or patients intubated had no significant change in mortality. This small study clearly showed that treatment with Baricitinib with Remdesivir may have prevented disease progression to severe respiratory disease and averted respiratory disease-related complications. Our study has some limitations, firstly the study cohort was small, with a total of 41 subjects. Second, subjects were followed-up only till discharge. The early administration of antiviral agents in viral infections can accelerate viral clearance and postpone neutrophil infiltration. Considering the dysregulated inflammatory response in the pathogenesis of the late phase of COVID-19, it is not surprising that antivirals do not have immediate effects in relieving the main symptoms at this stage.

Conclusion:

This study is done in the 2nd wave of COVID-19 disease where the role of Remdesivir is of questionable benefit. Baricitinib plus Remdesivir reduced recovery time and accelerated improvement in clinical status among patients with Covid-19, notably among those receiving supplemental oxygen support or noninvasive ventilation. Few studies were conducted regarding safety and efficiency of Baricitinib with Remdesivir in moderate to severe disease. In our study, there is a significant decrease in supplemental oxygen support at the time of discharge and a lesser number of subjects required supplemental oxygen support at discharge and a decreased duration of hospital stay is seen. In our study there is mortality. Few cases required prolonged care and supplemental oxygen support but eventually recovered and some subjects were dependent on supplemental oxygen support. Further confirmatory studies are required to support the data observed in this study. This study provides evidence for the potential use of Baricitinib 4 mg once daily for 10 days in the treatment of moderate to severe COVID-19 disease in early stages. The significant improvement in clinical status is likely due to faster viral reduction.

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