International Journal of Medical Research Professionals
P-ISSN: 2454-6356; E-ISSN: 2454-6364
DOI: 10.21276/ijmrp

Original Research Article.

Use of Baricitinib in the Treatment of Critically ill Covid-19 Patients: A Comparative Study

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ABSTRACT

Background: Severe cases of COVID-19 are associated with dysregulated inflammation. The effects of including Baricitinib in the treatment of COVID-19 is still not widely known. The aim of this study is to compare the outcome of patients treated with and without Baricitinib in the treatment of COVID-19.

Materials and Methods: 145 cases of critically ill COVID-19 patients admitted in ICU were included in this study. Out of them, 85 patients did not receive Baricitinib, while the remaining 60 patients were given Baricitinib on admission. As primary outcome, we compared which group had a better survival rate. Among the patients who survived, we also evaluated the length of stay in hospital for these groups. Along with this, we compared their inflammatory markers to identify any significant differences between the two groups.

Results: Out of 145 cases 122 patients (77.2%) survived while 33 (22.8%) died. Among the patients who survived, 78.3% patients survived in the Baricitinib group while 76.5% survived in the non-Baricitinib group. Patients receiving Baricitinib in combination with Remdesivir and Steroids had a mean length of hospital stay of 9.51± 4.6 days (95% confidence interval [CI], 8.51-10.5) whereas patients who received only Remdesivir and Steroids had a mean length of stay of 10.38±3.9 days (95% CI, 9.37-11.4). A significant difference between the two groups were observed for the parameters neutrophil: lymphocyte ratio (p = 0.001), C reactive protein (p<0.001), d-dimer (p=0.001), Lactate dehydrogenase (p=0.001), serum ferritin (p<0.001), troponin I (p=0.011), serum creatinine (p=0.006) and procalcitonin (p=0.002).

Conclusion: Use of Baricitinib in combination with Remdesivir and steroids gave a slightly better outcome of critically ill COVID-19 patients as compared to patients using only Remdesivir and Steroids. Baricitinib played an important role in reducing the length of hospital stay and the number of deaths among the critically ill patients.

Keywords: Dexamethasone Baricitinib, COVID-19, Remdesivir

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Article History:

Received: 11-06-2022, **Revised:** 06-07-2022, **Accepted:** 29-07-2022

Access this article online	
Website: www.ijmrp.com	Quick Response code
DOI: 10.21276/ijmrp.2022.8.4.003	

INTRODUCTION

COVID-19 is a disease caused by the coronavirus SARS-CoV-2. Since its emergence in the year 2019, multiple research have been conducted to find a treatment protocol for patients suffering from this potentially fatal disease. Based on evidence from prior pandemics caused by respiratory viruses and their association with acute respiratory distress syndrome, the efficiency of using steroids to prevent ARDS, was somewhat established. Studies from Wuhan, the place where COVID19 first started, showed increased survival among critically ill patients who were given steroids such as methyl prednisolone.[1,2]

Further studies showed Dexamethasone to be a better option in increasing survival rates among hospitalized COVID-19 patients.[3]

In case of antiviral drugs, few effective therapies have been found against respiratory viruses and Remdesivir is one of them. Remdesivir, an inhibitor of the viral RNA-dependent, RNA polymerase was introduced as an effective drug for the treatment of hospitalized COVID-19 cases in May 2020.[4]

It had the ability to inhibit SARS-CoV-2 in vitro. When used with the steroid dexamethasone an additive effect was observed.[4] However, despite the use of both remdesivir and steroids to treat

hospitalized patients with COVID-19, survival rates were still low in ICU settings where critically ill Covid-19 patients were placed. In order to improve survival rates, it is necessary to ease the immune responses and prevent hyper inflammation states among patients.

Janus Kinase inhibitors (JAK)are drugs recently indicated for the treatment of inflammatory diseases, such as moderate to severe rheumatoid arthritis, psoriatic arthritis, myeloproliferative malignancies, ulcerative colitis, etc.[5] They work by inhibiting the intracellular pathway of cytokines that are known to be elevated in severe Covid-19 cases. Baricitinib is an oral selective Janus kinase 1 & 2 inhibitor with known anti-inflammatory properties and few studies have been conducted regarding the efficiency of using Baricitinib among patients with Covid-19.[6] Hence, the aim of our study is to verify if Baricitinib is effective in improving survival among severely ill covid-19 patients.

MATERIALS AND METHODS

The study conducted was a prospective observational study among severely ill Covid-19 patients that were admitted to the intensive care unit of Chattogram Maa O Shishu Hospital Medical College. Data was collected from October 2020 to April 2021 and all patients whose relatives gave consent for the study were included.

Patients that were admitted to the ICU from October 2020 to February 2021 were prescribed only Remdesivir and steroids. Patients who approached the hospital for the next two months (March and April 2021) were prescribed Baricitinib along with Remdesivir and Steroids according to the newly set guidelines for treatment of severely ill Covid-19 patients. The outcomes of both groups of patients were compiled and analyzed using statistical software SPSS version 23.

Table 1: Demographic profile of the study subjects

Characteristics		All patients (n=145)	Baricitinib, Remdesivir & steroids (n=60)	Only remdesivir and steroids (n=85)
Age				
	Mean- years	55.13±15	52.2±15.9	59.3±12.8
	<40	30(20.7%)	5(8.3%)	25(29.4%)
	40-64	74(51%)	35(58.3%)	39(45.9%)
	>64	41(28.3%)	20(33.4%)	21(24.7%)
Gender				
	Male	101(69.7%)	39(65%)	62(72.9%)
	Female	44(30.3%)	21(35%)	23(27.1%)
Time from symptom onset to ICU admission		3.73± 0.88	3.59±0.76	3.93±1.01
Comorbidities				
	None	39(26.9%)	9(15%)	30(35.3%)
	One	23(15.9%)	8(13.3%)	15(17.6%)
	Two or more	83(57.2%)	43(71.7%)	40(47.1%)

Table 2: Patient outcome and length of stay among study subjects

Variables		All patients (n=145)	Baricitinib, Remdesivir & steroids (n=60)	Only remdesivir & steroids (n=85)
Outcome				
	Survived	112(77.2%)	47 (78.3%)	65 (76.5%)
	Died	33(22.8%)	13 (21.7%)	20 (23.5%)
Length of stay				
	mean- days	9.87±4.3	9.51±4.6	10.38±3.9
	<7 days	27(18.6%)	5 (8.3%)	22 (25.9%)
	7-14 days	97(66.9%)	46 (76.6%)	51 (60%)
	>14 days	21(14.5%)	9 (15%)	12 (14.1%)

Table 3: Comparison of inflammatory markers between the two groups of patients

Parameters	Non- Baricitinib group	Baricitinib group	*P- Value
N:L ratio	4.4±3.3	6.2±3.2	0.001
CRP	58±42	86.4±35.3	< 0.001
D-dimer	1±0.79	1.4±0.67	0.001
LDH	314.65±131.5	384±123	0.001
S. Ferritin	556.8±283.4	711.2±238.6	< 0.001
Troponin I	4.6±8.6	12.1±25.3	0.011
S. creatinine	1.1±0.38	1.3±0.36	0.006
Procalcitonin	0.39±0.45	0.80±0.95	0.002

*Student's t-test

RESULTS

A total of 145 ICU patients were included in this study. Among them the proportion of patients who survived was 77.2%. Mean age of enrolled patients were 55.13 ± 12.8 and 69.7% of the respondents were male patients. Mean time from symptom onset to ICU admission was 3.73 ± 0.88 days. More than 57% of the patients had at least two comorbidities or more. The mean length of stay was 9.87 ± 4.3days in the ICU. Further details on the demographic profile are given in Table 1.

Among the patients who survived (Table 2), 78.3% patients survived in the Baricitinib group while 76.5% survived in the non-Baricitinib group. The mean length of stay was 9.51 ± 4.6 in the Baricitinib group while the mean length of stay was 10.38 ± 3.9 in the non-Baricitinib group. Although no significant difference was observed between the two groups, mean length of stay among patients receiving Baricitinib were slightly lower than the comparison group. Furthermore, patient survival was slightly superior in the group that received Baricitinib.

On comparing the biochemical and hematological markers among the two groups of patients on admission, it was observed that the group of patients that received Baricitinib had significantly higher markers than the control group. As observed in Table 3, significantly higher values were observed in the parameters N:L ratio (p=0.001), CRP (p<0.001), D-dimer (p=0.001), LDH (p=0.001), S. Ferritin (p<0.001), Troponin I (p=0.011), S. creatinine (p=0.006) and Procalcitonin (p=0.002).

DISCUSSION

Treatment of patients with COVID-19 remains a challenge to this day. With the potential for the virus to develop new strains, surplus number of studies have been conducted worldwide to better understand the disease and discover drugs that would be most effective in managing patients afflicted by the disease. This study focused only on critically ill patients that required ICU admissions for treating the symptoms of COVID-19. While Baricitinib is a drug that was repurposed solely for the treatment of critical cases of COVID-19, the effect of their use among ICU admitted patients in Bangladesh have rarely been reported. Since this JAK inhibitor is comparatively much cheaper than the traditionally used monoclonal antibodies (Tocilizumab), accessing this medication does not put much of a strain on patients who are already overburdened by expensive ICU bills that need to be paid.[7] Hence it is only plausible to further study the efficacy of this medication in treating critically ill cases.

In our study, the mean age of the ICU admitted patients was 55.13±15 years. This somewhat agrees with another study conducted by Saha et al[8] where the highest proportion of ICU admitted patients in Chattogram were between the 50- 60 years age group. Yet another study by Hasan et al[9] reported the mean age of ICU admitted patients to be over 59 years in the two groups of patients. The proportion of males (69.7%) was higher than females in our study just like many others before. On observing patient outcome, critically ill COVID-19 patients in this study had a much better outcome than that reported in the Saha study[8] with a death rate of only 22.8% as compared to 56.5%. Since data for the Saha study was collected earlier during the pandemic, there was a dearth in knowledge on disease treatment and management leading to higher proportions of adverse outcomes. The mean time from symptom onset to ICU admissions was 3.73± 0.88 days. This is also lower than that reported in a few international studies.

The result of this comparative study shows that a combination treatment of Baricitinib, Remdesivir and Steroids is superior to the treatment with Remdesivir and Steroid alone. Among the patients who survived, 78.3% patients survived in the Baricitinib group while 76.5% survived in the non-Baricitinib group. The mean length of stay was 9.51 ± 4.6 in the Baricitinib group while the mean length of stay was 10.38 ± 3.9 in the non-Baricitinib group. This further verifies the claims in another study by Kalil et al[6] where a shorter recovery time and a better survival rate was observed among moderate to severe COVID-19 patients that received Baricitinib. Vitiello et al[10] has also claimed a shorter length of stay with the use of Baricitinib among patients with moderate to severe COVID-19 in their study. In mild cases of the disease, JAK- inhibitors like Baricitiib are redundant since the viral load can usually be cleared through endogenous antiviral mechanisms. However, in moderate to severe cases of COVID-19, the viral load peaks at about seven days from onset of symptoms. Around this time, hyper inflammation leads to the severe phase of the disease (cytokine storm). During this severe phase, there are increased levels of interferonsα,β and interleukin 6 among many others. These require the JAK-STAT pathway to send signals from cell to cell. With the use of Baricitinib, there is a reversible inhibition of the Janus Kinases (JAK), resulting in immunomodulation and control of inflammation and thus preventing a dysregulated response as commonly observed in advanced stages of the disease.[10] When the inflammatory markers of patients were evaluated prior to beginning of treatment, it was observed that the group that received Baricitinib had significantly higher inflammatory markers for C reactive protein (p<0.001), d-dimer (p=0.001), Lactate dehydrogenase (p=0.001), serum ferritin (p<0.001), troponin I (p=0.011), serum creatinine (p=0.006) and procalcitonin (p=0.002). This implied that the cohort that received Baricitinib had a worse clinical presentation on admission as compared to the group that did not receive this drug. Despite this fact, the outcome of patients who received Baricitinib was slightly better than the group that did not receive this drug.

CONCLUSION

Although vaccinations have become a breakthrough in the prevention of COVID-19 infections, research is still being done on the current and potential future treatments for the disease. Since Baricitinib helps reduce the length of hospital stay and increases survival among severely ill COVID-19 patients requiring intensive care, use of this medication among a certain cohort of COVID-19 patients can be very beneficial.

RECOMMENDATIONS

Since the study was conducted for a short period of time with a limited sample size, it was difficult to observe a significant association between the two groups. Conducting a study with a larger sample size may yield better results. Our study shows the benefit of using Baricitinib in severe cases of COVID-19 but does not investigate what dosage of this drug is needed to obtain the best outcome. Hence, further studies on the most effective dose of Baricitinib in the treatment of COVID 19 is necessary.

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Source of Support: Nil.

Conflict of Interest: None Declared.

Cite this article as: Hassan Mahade, Alak Nandy, Sultan Kawsar. Use of Baricitinib in the Treatment of Critically ill Covid-19 Patients: A Comparative Study. Int J Med Res Prof. 2022 July; 8(4): 11-14. DOI:10.21276/ijmrp.2022.8.4.003