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Efficacy, Safety of Baricitinib plus Remdesivir versus Standard Therapy (Remdesivir) in Patients with Severe COVID-19 Infection in Third Wave of Epidemics in Myanmar: Case Control Study

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ABSTRACT

Background: Coronavirus disease 2019 (COVID-19) has been a major threat to health around the world as it causes significant morbidity and mortality. SARS-CoV-2 infection induces severe inflammation in lungs and multi-organs; therefore, the Janus kinase (JAK) inhibitor known as baricitinib was proposed as a treatment for COVID-19 because of its anti-inflammatory and potential antiviral effects. It may improve survival in patients with severe Covid-19 infection. The efficacy and safety of Baricitinib therapy in severe COVID-19 infection in Myanmar was not known clearly.

Methods: A case control study was conducted in COVID-19 treatment centers in Myanmar-Yangon and Nay Pyi Taw, from June to October 2021. Baricitinib 4 mg daily for 14 days was given to the patients with severe COVID-19 infection as an add on therapy to Standard treatment group (Remdesivir). The primary outcome was survival status; survive or non-survive. The secondary outcome was duration of hospital stay, the requirement for oxygen therapy at Day 7 (improved or not), changes in chest radiograph at Day 14 (improved, same or worse), and changes in inflammatory markers (CPR and LDH). Patient data were stratified by age, sex, body weight, co-morbidities and immune status (immunocompromised or normal immune status). Data were collected by using standardized forms and analysis was done.

Results: A total of 64 patients with severe COVID-19 infection were enrolled. Base line characteristics in both groups, Baricitinib group (n =32) and Standard treatment group (n = 32), were comparable. Nearly 53% of patients in Baricitinib group and 59% of patients in Standard treatment group survived; however, mean duration of hospital stay was shorter in Baricitinib group (15.53 ± 6.83 days versus 22.25 ± 11.17 days; $p < 0.001$). Improvement in oxygen supplementation, radiological changes and changes in inflammatory markers were not different in both groups. Minor side effects like giddiness, appetite loss and insomnia were noted in Baricitinib group.

Conclusions: In treating patients with severe COVID-19 infection, the survival rate was not different between Baricitinib group (Baricitinib plus Remdesivir) and Standard treatment group

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(Remdesivir). In survivors, those in Baricitinib group had shorter duration of hospital stays; quick recovery time and accelerating improvement in clinical status

KEY WORDS: Baricitinib, Standard treatment, Remdesivir, severe COVID-19 infection, survival

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) has been spreading worldwide since December 2019; it causes global health threat. Once SARS-CoV-2 virus enters host, there is initial phase of high viral replication; then, it is followed by the host immune response leading to a rapid increase in proinflammatory cytokines, an uncontrolled inflammatory response, acute respiratory distress syndrome (ARDS), and multiple organ failure (G. Chen et al., 2020) (García, 2020). The severity of clinical manifestation and survival depend on protective immunity and immune dysregulation. The better the protective immunity, the less severe the clinical status; and, the host wins the battle. On the other hand, if immune dysregulation dominates, the chances of recovery is less likely; the sequence of acute inflammation, cytokine storm, acute lung injury, ARDS, coagulopathy and multi-organ failure occurs one after another (Wu et al., 2020).

The concentration of pro-inflammatory cytokines was related with clinical severity; thus, prognosis. The high level of cytokines also indicates a poor prognosis in COVID-19. Moreover, postmortem examination revealed that excessive infiltration of pro-inflammatory cells, mainly involving macrophages and T-helper 17 cells in lung tissues of patients with COVID-19 (Bhaskar et al., 2020).

The symptoms of COVID-19 vary from mild to very severe fatal form; the majority of patients infected with COVID-19 are either asymptomatic or mild form and they recover within weeks. The minority of infected patients, moderate, severe and critical form, have clinical features of severe pneumonia, respiratory failure, acute respiratory distress syndrome (ARDS), sepsis with multi-organ dysfunction, septic shock and acute thrombosis: acute coronary syndrome, pulmonary embolism and acute stroke; they require intensive treatment.

Thus, early diagnosis, treatment, and prevention of the cytokine storms are extremely important for the patients. Severe SARS-CoV-2 infection induces hyperinflammation with overproduction of proinflammatory cytokines; elevated serum cytokines, including interleukin-6 (IL-6), IL-10, tumor necrosis factor-α (TNF-α) and interferon-γ, may cause fatal ARDS, sepsis, multi-organ failure and acute thrombosis in COVID-19 patients. Baricitinib, a reversible Janus-associated kinase (JAK)-inhibitor that interrupts the signaling of multiple cytokines implicated in COVID-19 immunopathology and has exhibited dose-dependent inhibition of IL-6-induced STAT3 phosphorylation. It may also have antiviral effects by targeting host factors that viruses rely for cell entry and by suppressing type I interferon driven angiotensin-converting-enzyme-2 upregulation (Jorgensen et al., 2020). Exogenous addition of baricitinib decreases the *in-vitro* SARS-CoV-2-specific response in COVID-19 patients using a whole-blood platforms showing the immune-specific viral response (Petrone et al., 2021). Baricitinib, may decrease inflammation; thus, clinical severity and progression to death. FDA gave emergency use authorization in November 2020; and WHO recommended drug for treatment of COVID-19 in January 2022.

The results of several studies favored the use of Baricitinib in severe COVID-19 infection. Baricitinib plus remdesivir was found to be superior to remdesivir alone in shortening recovery time and accelerating clinical improvement among patients with Covid-19, particularly those receiving high-flow oxygen or noninvasive ventilation (Kalil et al., 2021). In another study, it reduced the requirement for invasive procedures or death (Goletti & Cantini, 2021)(Mahase, 2022). Moreover, prospective cohort study in Bangladesh was positive particularly with high dose of Baricitinib (Hasan et al., 2021). Furthermore, retrospective study done in 2020 where combination of Baricitinib with chloroquine in treating moderate to severe cases was promising (Titanji et al., 2021). In addition, observational retrospective study was supportive (Iglesias Gómez et al., 2021). Besides, Chen et al. (2021) found that JAK inhibitors decreased the need for invasive mechanical ventilation; however, the duration of hospital stay was not shortened. Some studies compared baricitinib plus dexamethasone versus dexamethasone monotherapy; thirty-day mortality was significantly lower in baricitinib plus dexamethasone group. However, no difference was observed in progression to invasive mechanical ventilation and hospital acquired infections (Pérez-Alba et al., 2021).

Nevertheless, in phase 3, global, double-blind, randomized, placebo-controlled trial, including 1525 hospitalized adults with COVID-19 receiving standard of care (systemic steroids) were randomly assigned to once-daily baricitinib 4-mg; no difference was seen (Marconi et al., 2021). The reports mentioned fewer serious adverse events (Marconi et al., 2021). Thus, a case control study was conducted to detect efficacy and safety of Baricitinib in severe COVID-19 infection. This study aimed to assess the efficacy of Baricitinib in severe COVID-19 infection in Myanmar.

METHODS

Study design and participants

A hospital based case control study was conducted among severe COVID-19 patients attending at COVID-19 treatment centers in Myanmar- Yangon and Nay Pyi Taw,

from July 2021 to October 2021. All inpatients with severe SARS-CoV-2 infection confirmed by a positive result on RT-PCR testing of a nasopharyngeal sample and WHO severity score were included in this study.

All adult patients (> 18 years) with severe COVID-19 infection confirmed by positive polymerase-chain-reaction (PCR) assay of nasopharyngeal swab with SaO2 less than 92% were included in this study. Patients were excluded if they have active tuberculosis, pregnancy, active malignancy, ESRD and HIV infection. All patients received standard treatment according to Myanmar National guideline; remdesivir, glucocorticoids, antibiotics, prophylactic enoxaparin, oxygen, and nutritional support and supportive care.

The primary outcome was survival status; survive or non-survive. The secondary outcome was duration of hospital stay, the requirement for oxygen therapy at Day 7 (improved or not), changes in chest radiograph at Day 14 (improved, same or worse), and, changes in inflammatory markers (CPR and LDH). Patient data were stratified by age, sex, body weight, co-morbidities and immune status (immunocompromised or normal immune status). Data were collected by using standardized forms and analysis was done. Informed consent was taken from patients or from the patient's legally authorized representative who could provide oral consent with appropriate documentation by the investigator. This study was approved by the hospital research and ethics committee of No.(1) Defence Services General Hospital (1000-Bedded) Mingalardon, Yangon.

Study area

This study was carried out at three purposively selected treatment centers: Mingaladon hospital (500-bedded) and Nay Pyi Taw hospital (1000-bedded) treatment centers, which were designated for confirmed severe COVID-19 patients. Patients from Yangon Region were treated in Mingaladon hospital, whereas those from Nay Pyi Taw region were hospitalized in Nay Pyi Taw hospital. All treatment centers have ICU facilities and treatment were given by junior physicians, supervised by senior consultant physicians with on line meeting at least daily.

Sample size determination and sampling technique

Sample size calculation

For a case-control study with binary outcome

P(exposure|case) = 0.285

P(exposure|control) = 0.660

Ratio (case:control) = 1.00

Alpha = 0.05, Z(0.975) = 1.959964

Beta = 0.20, Z(0.800) = 0.841621

Sample size: Cases = 27, Controls = 27

Sample size by using a continuity correction: Cases = 32, Controls = 32

When two groups need to be compared, randomized controlled trial for continuous data the following formula was used for sample size determination:

$$n_{case} = \left[\frac{z_{1-\frac{\alpha}{2}} \sqrt{\bar{p}\bar{q}\left(1+\frac{1}{r}\right)} + z_{1-\beta} \sqrt{p_1 q_1 + \frac{p_2 q_2}{r}}}{\Delta} \right]^2$$

$$p_1 = P(exposure|case), q_1 = 1 - p_1$$

$$p_2 = P(exposure|control), q_2 = 1 - p_2$$

$$\bar{p} = \frac{p_1 + p_2 r}{1+r}, \bar{q} = 1 - \bar{p}, r = \frac{n_{control}}{n_{case}}$$

$$p_1 = \frac{p_2 OR}{1 + p_2 (OR - 1)}$$

$$m_{case} = \frac{n_{case}}{4} \left(1 + \sqrt{1 + \frac{2(r+1)}{n_{case} r |p_2 - p_1|}} \right)^2$$

Operational definitions

Body mass index (BMI) was a person's weight in kilograms divided by the square of height in meters and it an indicator of body fatness. BMI was categorized as underweight (< 18.5 kg/m^2), normal weight (18.5 to 24.9 kg/m^2), overweight (25.0 to 29.9 kg/m^2) and (≥ 30.0 kg/m^2) obese. Comorbidity was a presence of more or additional medical conditions or diseases in COVID-19 patients.

Standard treatment group included those receiving dexamethasone, remdesivir, prophylactic enoxaparin, oxygen, and nutritional support. Baricitinib group included those receiving Baricitinib treatment in addition to Standard treatment. This study had two arms: in one arm, Baricitinib

was added to standard treatment (dexamethasone, remdesivir, antibiotics, prophylactic enoxaparin, oxygen, and nutritional support) which was named as "Baricitinib group". In another arm, standard treatment (dexamethasone, remdesivir, antibiotics, prophylactic enoxaparin, oxygen, and nutritional support) alone was given which was named as "Standard treatment group".

Duration of hospital stay was total duration of hospital stay till discharge either in survival state or non-survival state which may be beyond secondary outcome i.e., 28 days.

Primary outcome was survivor state or non-survivor state at day 28 after treatment. Secondary outcome was clinical improvement or deterioration in clinical status at day 28 after treatment and it was assessed by treating physician.

Severity of cardiomegaly in CXR was categorized as **"**0 to 3" depending on degree of cardiac enlargement: (1) "0" if heart size was normal; (2) "1" if there was mild degree of cardiomegaly; (3) "2" if there was moderate degree of cardiomegaly; and, (4) "3" if there was severe or gross cardiomegaly.

Severity of lung parenchyma involvement in CXR was calculated by Brixia Score as "0 to 18". lungs were divided into six zones on a postero-anterior (PA) or antero-posterior (AP) projection. In the second step, a score (0 to 3) is assigned to each zone based on lung abnormalities as follows: (1) "0" if there was no lung abnormalities; (2) "1 "if there was interstitial infiltrates; (3) "2" if there was interstitial and alveolar infiltrates with interstitial predominance; and, (4) "3 " if there was interstitial and alveolar infiltrates with alveolar predominance.Finally, the scores of the six lung zones are then added to obtain an overall CXR score ranging from 0 to 18.

Oxygen requirement was classified as NC (nasal canula), HFM (high flow mask), DFM (oxygen double source with high flow mask), NIV (non-invasive ventilation- CPAP or BiPAP) and, invasive ventilation.

Based on WHO severity score, the clinical severity of COVID-19 infection was classified into four types: mild,moderate, severe and critical. In mild category, patients have symptoms only, CXR is normal and, SaO2 on air is normal. In moderate category, CXR shows pneumonias and SaO_2 on air is $\geq$ 90%. In severe category, respiratory rate is > 30/min and, SaO_2 on air is < 92%. In critical disease category, the patient has ARDS; he may have sepsis with multi-organ dysfunction or septic shock or acute thrombosis (pulmonary embolism, acute coronary syndrome, acute stroke).

The level of ferritin was defined as elevated when it was higher than 400 ng/mL (30 - 400 ng/ml). The level of LDH was defined as elevated when it was higher than 225 U/l (135-225 U/l).The level of D dimer was defined as elevated when it was higher than 0.5 μg/ml (< 0.5 μg/ml). CRP, an acute-phase reactant reflecting the inflammatory activity, was defined as elevated when it was higher than 0.5 mg/L (< 0.5 mg/l).The most recent ferritin, LDH and D- dimer and CRP values before tocilizumab administration was selected as the value of before tocilizumab therapy and the changes of the value after tocilizumab administration was observed for 4 week (24 hour, 72 hour, 1 week, 2 week, 3 week and 4 week).

Data collection and procedures

The data of demographics and comorbidities from confirmed COVID-19 infection by nasopharyngeal swab for PCR were taken on admission; their clinical severity was assessed by WHO severity score. CXR and laboratory tests were done. Severe cases were randomly assigned for one of the treatments after getting informed consent: standard treatment plus Baricitinib (Baricitinib group) or standard treatment alone (Standard treatment group). All severe patients received standard treatment according to Myanmar National guideline; remdesivir, glucocorticoids, antibiotics, prophylactic enoxaparin, oxygen, and nutritional support and supportive care.

Primary outcome was clinical improvement or deterioration in clinical status at day 28 after treatment assessed by treating physician. The secondary outcome was duration of hospital stay, the requirement for oxygen therapy at Day 7 (improved or not), changes in chest radiograph at Day 14 (improved, same or worse), and, changes in inflammatory markers (CPR and LDH).

The blood levels of inflammatory markers (ferritin, LDH, D-dimer and CRP), complete picture, liver enzymes, serum creatinine and sugar were done before and after Baricitinib (24 hour, 72 hour, 1 week, 2 week, 3 week and 4 week). The most recent ferritin, LDH and D-dimer, CRP, complete picture, liver enzymes, serum creatinine and sugar values before Baricitinib administration was selected as the value of before Baricitinib therapy and the changes of the value after Baricitinib administration was observed for 4 week (24 hour, 72 hour, 1 week, 2 week, 3 week and 4 week). The clinical outcome of the patients was evaluated daily till 4 week after treatment. Both clinical, radiological and laboratory data were collected and confidentiality was maintained. The data were checked by two medical officers and then, supervision, completeness, and consistency of collected data were performed by the principle investigator. Patient data were stratified by age, sex, body weight, co-morbidities and immune status (immunocompromised or normal immune status). Data were collected by using standardized forms and analysis was done.

Statistical analysis

The primary statistical analysis was done to find out baseline clinical characteristics of COVID-19 infected patients. For primary end point, Baricitinib group was compared with the standard care group for survival status; and, for secondary end points – oxygenation improvement at Day 7, CXR improvement at Day 14 and hospital stay(days). Relative risk (RR), Relative risk reduction (RRR), Absolute risk reduction (ARR) and number needed to treat (NNT) were

calculated for Baricitinib Group. A *p* value of less than 0.05 was considered statistically significant. The collected data were entered into Microsoft Excel 2019 and exported to IBM SPSS Statistics for Windows, Version 23.0 (Armonk, NY: IBM Corp) for analysis. Descriptive statistics were presented as frequency and percentages for categorical variables and mean (standard deviation, SD) for continuous variables.

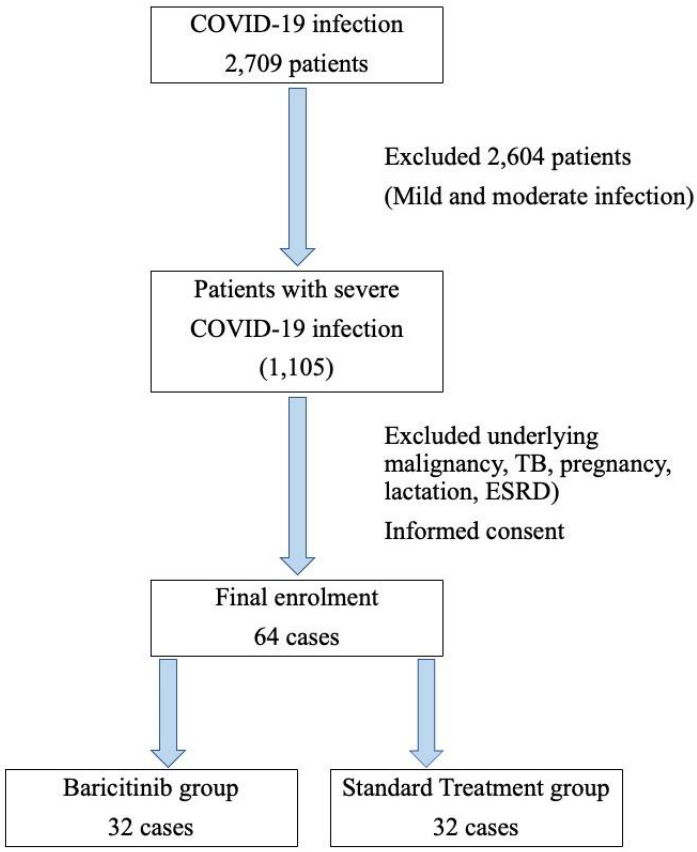

Figure (1) Flow Chart

RESULTS

Although initial enrollment included 2,709 cases with COVID-19 infection, 1,604 cases of mild to moderate infections were excluded. Out of 1,105 cases with severe infection, only 64 cases, 32 patients in Baricitinib group and 32 patients in Standard treatment group, were finally included after obtaining informed consent. Baseline characteristics of patients in two treatment groups including age group, gender, primary endpoint showing survival status and secondary endpoints showing oxygen improvement at Day 7 & CXR improvement at Day 14 were shown in Table (1).

Table (1). Baseline clinical characteristics of study population (n=64)

Clinical characteristics	**Standard Treatment group (n=32)**	**Baricitinib group (n=32)**
Age Group		
<65 years	23 (71.9%)	18 (56.3%)
≥65 years	9 (28.1%)	14 (43.7%)
Gender		
Male	23 (71.9%)	19 (59.4%)
Female	9 (28.1%)	13 (40.6%)

Outcome		
Alive	19 (59.4%)	17 (53.1%)
Death	13 (40.6%)	15 (46.9%)
O2 Improvement at Day 7		
Can't assessed	3 (9.3%)	6 (18.7%)
Yes	17 (53.1%)	15 (46.8%)
No	12 (37.6%)	11 (34.5%)
CXR improvement at Day 14		
Can't Assessed	9 (28.1%)	11 (34.5%)
Improved	6 (18.7%)	6 (18.7%)
Same	12 (37.6%)	11 (34.5%)
worse	5 (15.6%)	4 (12.3%)

Table (2). Comparison of mean clinical characteristics, inflammatory markers between Standard Treatment group and Baricitinib group

Clinical characteristics	**Standard Treatment group**	**Baricitinib group**	**Mean difference (95%CI)**	***t*-test (df)**	***'p'* value**
Age (year)	58.16 ± 14.53	62.44 ± 12.34	4.28 (-2.46, 11.01)	1.27 (62)	0.21
Initial SaO2 (%)	87.72 ± 9.5	89.59 ± 9.9	1.87 (-2.99, 6.74)	0.77 (62)	0.44
CRP (mg/dl) (Before Rx)	18.36 ± 14.11	20.29 ± 25.61	1.92 (-8.6, 12.49)	0.36 (57)	0.7
CRP (mg/dl) (After Rx)	8.8 ± 6.55	14.05 ± 30.74	5.25 (-11.07, 21.57)	0.65 (40)	5.25
LDH (U/L) (Before Rx)	443.69 ±182.27	499.5 ± 189.85	55.81 (-42.40, 154.03)	1.14 (56)	0.26
LDH (U/L) (After Rx)	363.05 ± 134.54	469.92 ± 231.31	102.86 (-11.33, 217.06)	1.82 (37.99)	0.09
**'p'* value by independent samples *t*-test					

Comparison of mean clinical characteristics, inflammatory markers between Standard Treatment group and Baricitinib group was shown in table (2). Mean age of patients in Baricitinib group was 62 years whereas it was 58 years in Standard treatment group. Initial SaO_2 on air was comparable; 89.59 ± 9.9 in Baricitinib group and 87.72 ± 9.5 in Standard treatment group. The oxygen requirement at Day 7 was reduced in half of the patients in both group; and it was not assessed in 10-20% of cases as they expired less than one week during hospital stay.

Chest radiograph changes were compared at Day 14; and, improvement was noted in nearly 20% of cases in both groups. Increasing radiological shadows were recorded in 12-15% of cases; and, no changes was seen in 35% of cases in both groups.

The inflammatory markers, CRP and LDH, dropped after therapy in each group; however, there were not statistically different in comparison.

Primary outcome was to assess mortality at Day 28. In Baricitinib group, 17 cases (53.1%) survived; and, in Standard Treatment group, 19 cases (59.4%) were alive. The survival rate was not different significantly.

Figure (2) Box plot shows mean hospital stay in days; the duration of hospital stay was 15.65 ± 6.15 days in Baricitinib group and 22.05 ± 6.97 days in Standard treatment group. It was statistically different; patients in Baricitinib group recovered one week earlier than those of Standard treatment. Minor side effects like giddiness, nausea, tiredness and insomnia were recorded in both groups. No serious events were seen.

Efficacy of Baricitinib among study population was found as: relative risk (RR) was 1.15, Absolute risk reduction (ARR) was 6.25%, Relative risk reduction (RRR) was 15.3% and number needed to treat was 16. It is shown in Table (4).

Table (3). Comparison of mean inflammatory markers changes before and after treatment within Standard Treatment group and Baricitinib group

Inflammatory Markers	Treatment	Interval	Mean ± SD	Mean Difference	*t*-test	*'p'* value
CRP (mg/dl)	Standard Treatment group	Before	18.93 ± 15.62	10.12 ± 16.12 (1.19, 19.05)	2.4 (14)	0.02*
		After	8.81 ± 6.54			
	Baricitinib group	Before	21.89 ± 26.78	11.35 ± 39.05 (-5.131,27.85)	1.42 (23)	0.95
		After	10.53 ± 28.06			
LDH (U/L)	Standard Treatment group	Before	439.32 ± 174.24	76.26 ± 184.44 (-1.01, 121.04)	1.8 (18)	0.88
		After	363.05 ± 134.54			
	Baricitinib group	Before	487.43 ± 199.13	68.47 ± 168.38 (-6.18, 143.13)	1.91 (21)	0.7
		After	418.95 ± 170.21			

* *'p'* value by paired sample t-test

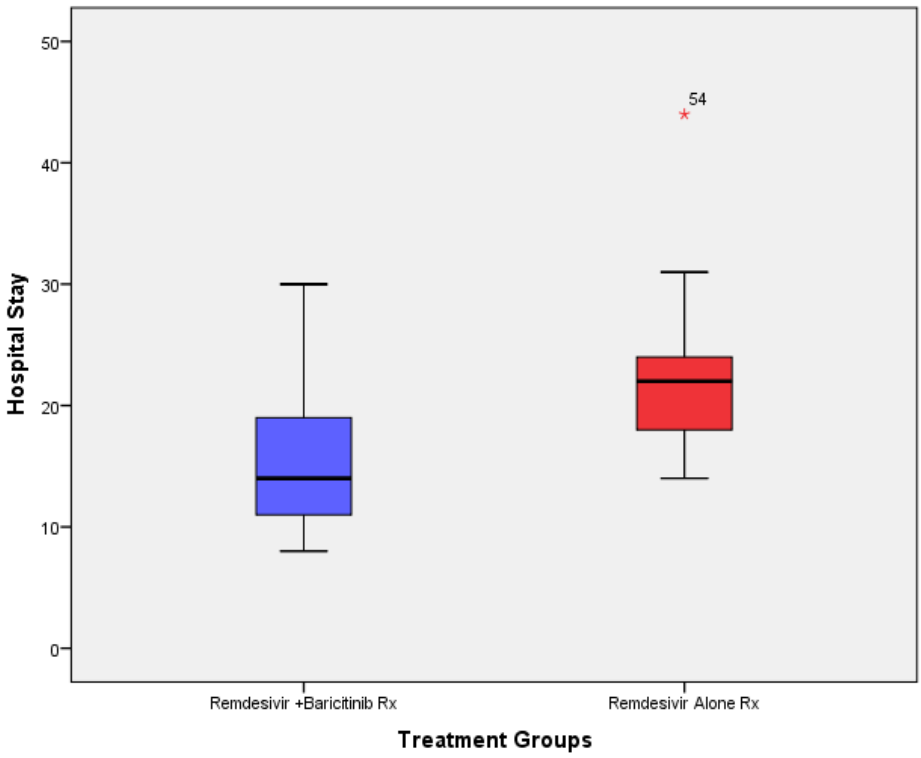

Figure (2) Box plot showing mean hospital stay (days) between treatment Groups

Table (4). Mean hospital stay (days) between treatment groups

	Standard Treatment Group	Baricitinib Group	Mean Difference	t-Test	*'p'* Value
Hospital Stay (Days)	22.05 ± 6.97	15.65 ± 6.15	-6.41	-2.9	0.006*

DISCUSSION

Coronavirus disease 2019 (Covid-19) is associated with immune dysregulation and hyperinflammation, acute respiratory distress syndrome and organ damage. Baricitinib interrupts the signaling of multiple cytokines; thus, ameliorating cytokine release syndrome and hyperinflammatory response. The efficacy of Baricitinib therapy in patients with severe COVID-19 infection was studied in third wave in Myanmar, developing country.

Baseline characteristics, initial SaO_2 on air, oxygen requirement, chest radiograph and inflammatory markers were comparable in both groups. The oxygen requirement at Day 7 as well as chest Xray changes at Day 14 were not different in both groups. Moreover, the reduction in inflammatory markers in each group was the same. Furthermore, the survival rate was not different significantly.

However, the duration of hospital stay was significantly shorter in Baricitinib group. It was clear that Baricitinib promote recovery in severe cases. The immunosuppressive effects of Baricitinib may retard viral clearance (Jorgensen et al., 2020); nevertheless, having significantly shorter hospital stay in this study pay little attention to it.

In one review, *JAK*-inhibitors did not decrease length of hospitalization (C. Chen et al., 2021); however, However, the duration of hospital stay was significantly shorter in Baricitinib group in this study. Regarding viral clearance and Baricitinib, there are two school of thoughts: promoting viral clearance as it has anti-viral action; and, delay viral clearance owing to immunosuppressive effects (Jorgensen et al., 2020).

In the earliest retrospective study where Baricitinib was combined with chloroquine in treating moderate to severe cases of COVID-19, it was found to reduce mortality (Titanji et al., 2021). The survival rate was not different in Baricitinib group in this study; thus, it overlooked previous findings (Kalil et al., 2021) (Goletti & Cantini, 2021). Baricitinib was found to be good; moreover, the effect in saving lives of cases with severe COVID-19 infection in prospective cohort study in Bangladesh (Hasan et al., 2021) (Tziolos et al., 2022). Thirty-day mortality was significantly lower in patients with COVID-19 pneumonia treated with baricitinib plus dexamethasone versus dexamethasone monotherapy. No difference was observed in progression to invasive mechanical ventilation and hospital acquired infections (Pérez-Alba et al., 2021).

The survival rate was not different in Baricitinib group in this study; it provided the evidence for global, double-blind, randomized, placebo-controlled trial. Baricitinib was compared with Standard treatment which included systemic corticosteroids, there was no difference in mortality rate in hospitalized COVID-19 cases (Marconi et al., 2021).

Minor untoward effects were noted in both groups; however, it was difficult to interpret whether the symptoms were due to severe COVID-19 itself or Baricitinib. As the side effects were mild, Baricitinib was safe. It proved the former reports (Kalil et al., 2021). The immunosuppressive effects of Baricitinib may cause secondary opportunistic infections (Jorgensen et al., 2020); however, there was no obvious secondary bacterial or fungal infection in this study. Likewise, no difference was observed in progression to invasive mechanical ventilation and hospital acquired infections in one study where they gave Baricitinib plus dexamethasone in one arm and dexamethasone in another arm in treating patients with COVID-19 pneumonia (Pérez-Alba et al., 2021).

Baricitinib had the risk of increased thromboembolic events (Jorgensen et al., 2020); however, the study done in Bangladesh where they use Baricitinib high dose did not mention it. Also, in this study thromboembolic events were not recorded in survivors.

In facing pandemic disease, all the countries have to face high health care expenditure: preventive measures like personnel protective equipment and vaccination; diagnostic measures like PCR laboratory and chest radiographs; treatment measures like anti-viral drugs, anti-inflammatory drugs, antibiotics, oxygen therapy; rehabilitation measures like physiotherapy; and, human resources. Developing countries have less budget and more difficulties (Thant et al., 2021). Cost-effectiveness is the main issue for all countries even in those doing cost-sharing practice (Vandepitte et al., 2021)(Jo et al., 2021). Thus, cost-effectiveness study from both the payor and the hospital perspectives in hospitalized patients with COVID-19 in the United States was done; the addition of baricitinib to standard care which included steroids and remdesivir was cost-effective (Ohsfeldt et al., 2021) (Kelton et al., 2022).

If we compare the cost of immunomodulatory drugs available in Myanmar, one course of Baricitinib (4 mg daily for 2 weeks) was twenty times cheaper than one dose of Tocilizumab (4 mg containing one vial). Tocilizumab was very expensive, 100 times its original price particularly in third wave of epidemics in Myanmar; thus, most of the patients could not afford to buy as part of cost-sharing therapy and unlikely to repeat second dose or third dose. Therefore, Baricitinib therapy was very economical and cost-effective in treatment of severe COVID-19 infection in Myanmar.

There were several limitations in this study. First, shortage of drug- Baricitinib particularly at the peak of

epidemics. Baricitinib was cheap compared to Tocilizumab; twenty times cheaper. In addition, this study would be stronger if it was a randomized control trial. Moreover, the results may be better if high dose of Baricitinib was used like Bangladesh trial. Furthermore, the sample size was not large though the study covered 1000-bedded and 300-bedded COVID treatment centers. Besides, inflammatory markers-ferritin, LDH, D-dimer and CRP should be measure for better comparison. Finally, observation with a sufficient number of COVID-19 patients in RCT is still needed to document the effectiveness of Baricitinib.

CONCLUSIONS

Though basic clinical parameters were comparable, the survival rate in Baricitinib group was not different from Standard treatment group in treating patients with severe COVID-19 infection. Baricitinib group (Baricitinib plus Remdesivir) had significantly shorter hospital stay than Standard treatment group (Remdesivir); seven days different. Thus, Baricitinib group (Baricitinib plus Remdesivir), Baricitinib, enhanced clinical recovery and probably viral clearance too. The impact of long duration of hospital stay has many sequelae: (1) chances of acquiring hospital opportunistic infections with multi-drug resistant organisms like Pseudomonas species, MRSA and Klebsiella species etc.; (2) burden for health care personnel and patient family; (3) increasing health expenditure for the government; (4) psychological impact on patient himself; and (5) patient turn over rate in pandemic situation. In terms of side effects, Baricitinib was safe with 4mg daily dose. Baricitinib was cheap compared to other anti-inflammatory drugs like Tocilizumab; suitable for developing countries like Myanmar.

RECOMMENDATION

Randomized control trial with large number of cases with higher dosage of Baricitinib are required for better information. Solution for shortage of drugs in clinical trials and treatment should be find out particularly in developing countries. Inflammatory markers like serum ferritin, LDH, D-dimer and CRP can be used as response to treatment in resource poor settings.

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Ethical consideration

The data collection using standardized case report forms was approved by Hospital Ethics Review Committee of Defence Services General Hospital, Mingaladon. Privacy and confidentiality of information were maintained throughout the study process.

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