Real-world Efficacy of Baricitinib Among Patients with Severe and Critical COVID-19 Pneumonia Admitted in Ospital ng Makati from December 2020 to May 2021: A Case-Control Study

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Abstract

Background. Management of COVID--19 patients during surges have been a challenge as hospitals have to deal with staff, room, and medication shortages. Among these medications is tocilizumab which is given to patients with severe/critical conditions. In Ospital ng Makati, patients are given baricitinib as alternative immunomodulator to prevent possible cytokine storm during tocilizumab shortages. The current recommendation for baricitinib is to give it in addition to dexamethasone and remdesivir for hospitalized COVID-19 patients requiring low to high-flow oxygen, and non-invasive ventilation. However, there is not enough evidence to recommend it as an alternative to tocilizumab in COVID--19 patients. This study aims to find out the real-world efficacy of baricitinib in addition to standard of care among admitted patients with severe COVID-19 pneumonia admitted in Ospital ng Makati.

Methods. This is a retrospective, case control study that reviewed records of adult patients admitted at Ospital ng Makati from December 2020 to May 2021 due to severe COVID-19. Patients who were given standard of care was compared to those who were given baricitinib by measuring the duration of clinical improvement, in-hospital all-cause mortality, number of hospital stay, and progression to acute respiratory distress syndrome (ARDS) and need for mechanical ventilator.

Results. The use of baricitinib led to a faster improvement time (10 vs 12 days) however did not reach level of significance (*p=0.069*). There was also no significant difference in the mortality, number of hospital days, and progression to ARDS between the two groups.

Conclusion. There is not enough evidence to recommend baricitinib as an alternative to tocilizumab in patients with severe COVID--19 infection.

Keywords: COVID-19, baricitinib, tocilizumab, standard of care

Introduction

Coronavirus disease 2019 (COVID-19) posed a formidable challenge on established health systems worldwide. This led to multiple trials and investigational studies to develop effective control and treatment of symptoms prior to the development and distribution of vaccines. One of the breakthrough trials which showed promise against COVID-19 is the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial which showed that dexamethasone compared to placebo led to significant reduction in mortality rate from COVID-19 (22.9% vs 25.7%) leading to the establishment of dexamethasone as standard of care.[1] Another drug which showed promise against COVID-19 based on its mechanism of action is remdesivir, a nucleotide analogue prodrug with in vitro effect against RNA virus. Multiple clinical efficacy trials yielded conflicting results and the safety and efficacy were not examined when co-administered with other drugs. The Adaptive COVID-19 Treatment Trial (ACTT-1) showed faster time to recovery and trend towards lower 29-day mortality leading to its approval for use in hospitalized patients by the US Food and Drug Administration.[2]

On the other hand, the SOLIDARITY trial showed little or no effect of remdesivir on the overall mortality, initiation of ventilation, and duration of hospital stay.[3] Hence, the World Health Organization (WHO) recommended

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against it use.[4] This is however recommended for use by the United States Center for Disease Control and Prevention/National Institute of Health (US CDC/NIH) in COVID-19 patients in need of high flow oxygen or noninvasive mechanical ventilation.[5]

In Ospital ng Makati, in addition to oxygen support and antibiotics for bacterial pneumonia coverage, dexamethasone and remdesivir are being given to patients with severe and critical COVID-19 pneumonia as part of standard of care. However, despite the benefits of dexamethasone and to some extent, remdesivir, significant morbidity and mortality due to COVID-19 remained. This led to multiple studies which observed the cause of the disease, its progression, pathophysiology, and resistance to approved treatments. One of the proposed mechanisms associated with its severity is the host's unregulated immune response, which, when minimized, may prevent a hyperinflammatory state that could lead to improved clinical outcomes.

One of the proposed drugs that addresses this dysregulated immune response is tocilizumab, an interleukin IL-6 inhibitor. The pro-inflammatory cytokine IL-6 was shown to be associated with critical and fatal COVID-19. The result of the RECOVERY trial showed that adding 1 to 2 doses of weight-based tocilizumab to the standard of care resulted in a reduced 28-day mortality rate compared to the standard of care.[6] This led to the recommendation by the Infectious Diseases Society of America (IDSA) suggesting adding tocilizumab to the standard of care (dexamethasone and supportive treatment) in patients with severe or critical COVID-19 infection.[7]

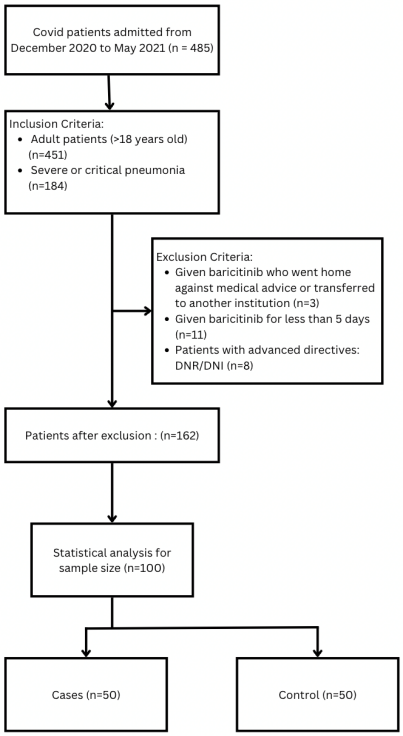

Figure 1 Flowchart outlining patient sample collection

In Ospital ng Makati, tocilizumab is given to patients with severe and critical COVID-19. The challenge however was that aside from being expensive, there was a limited supply of tocilizumab not just in Ospital ng Makati but across the country, especially during the surge of cases.

With this, baricitinib was given as an alternative to severe and critical COVID-19 patients at Ospital ng Makati since it became available last Mar 29, 2021. It is an orally administered, selective inhibitor of Janus kinase (JAK) 1 and 2 acting against the virus by inhibiting the intracellular signaling pathway of cytokines known to be elevated in severe COVID-19. Kalil et al. (2020) reported that the use of baricitinib 4mg daily dose in combination with remdesivir in patients classified as severe COVID-19 showed a trend towards decreased mortality, higher likelihood to have clinical recovery at day 28, and less likely to require initiation of mechanical ventilation.[8] In this study however, the use of dexamethasone has not yet been established as part of COVID-19 management and therefore not part of the standard of care at that time.

Currently, only the IDSA guidelines recommend routine use of baricitinib on COVID-19 patients with high inflammatory markers and not on invasive mechanical ventilation. There is no recommendation for or against by the Philippine Society for Microbiology and Infectious Diseases (PSMID) and WHO guidelines.[9,10]

At Ospital ng Makati, baricitinib is being given 4mg/tab 1 tablet once a day for 14 days or until the patient is non-oxygen requiring on top of dexamethasone and remdesivir.

One recently published randomized trial by Marconi et. al. 2021, reported that adding baricitinib to standard of care reduced 28-day mortality.[11] Of note, the patients in this study were already receiving dexamethasone as part of the standard care in contrast to the earlier trial conducted, hence these patients were similar to the patients being managed at Ospital ng Makati. With this, the investigators would like to look further at the real-world efficacy of baricitinib in severe and critical COVID-19 patients who were given dexamethasone and remdesivir admitted in Ospital ng Makati.

Methods

This is a retrospective, case-control study that reviewed patient records of adult patients admitted in Ospital ng Makati (tertiary hospital) from December 2020 to May 2021 due to severe and critical COVID-19. Subjects were divided to baricitinib plus standard of care (dexamethasone plus remdesivir) group versus standard of care alone. The latter was assigned as a control group which included patients who were admitted before baricitinib became available.

We included adult patients (>18 years old) admitted at Ospital ng Makati from December 2020 to May 2021 treated as a case of confirmed severe or critical pneumonia as defined by the WHO guidelines (RT-PCR

Table I. Baseline Characteristics

Characteristics	Standard of care group (n=50)		Baricitinib + standard of care group (n=50)		P-Value Chi-Square Test
	f	%	f	%	
Age (years)					
19 to 30	1	2.00%	3	6.00%	0.13
31 to 40	2	6.00%	11	22.00%	
41 to 50	5	10.00%	5	10.00%	
51 to 60	17	34.00%	9	18.00%	
61 to 70	11	22.00%	12	24.00%	
Above 70	13	26.00%	10	20.00%	
Sex					
Female	22	44.00%	22	44.00%	1.00
Male	28	56.00%	28	56.00%	
Co-morbidities					
Cancer	2	4.00%	4	6.06%	N/A (No Test applicable due to nominal scale data)
CKD not on dialysis	4	8.00%	2	3.03%	
CKD on dialysis	1	2.00%	0	00.00%	
COPD	2	4.00%	0	00.00%	
HIV	1	2.00%	0	00.00%	
Hypertension	30	60.00%	29	43.94%	
Previous MI	0	00.00%	0	00.00%	
Previous Stroke	0	00.00%	0	00.00%	
Tuberculosis	0	00.00%	0	00.00%	
Type 2 DM	10	20.00%	17	25.76%	
Others	0	00.00%	43	67.19%	
Smoking Status					
Non-Smoker	45	90.00%	41	82.00%	0.45
Previous Smoker	4	8.00%	6	12.00%	
Current Smoker	1	2.00%	3	6.00%	
Vaccination Status					
Not Vaccinated	50	100.00%	39	78.00%	<0.00
Partially Vaccinated	0	00.00%	6	12.00%	
Fully Vaccinated	0	00.00%	5	10.00%	
COVID-19 Severity					
Critical	5	10.00%	2	4.00%	0.24
Severe	45	90.00%	48	96.00%	
None	5	10.00%	1	2.00%	
Supplemental Oxygen on Admission					
Face Mask	22	44.00%	40	80.00%	N/A (No Test applicable due to nominal scale data)
Nasal Canula	17	34.00%	1	2.00%	
High Flow Nasal Cannula	1	2.00%	7	14.00%	
Mechanical Ventilator	5	10.00%	1	2.00%	

CKD, chronic kidney disease; COPD chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; MI, myocardial infarction; DM diabetes mellitus

positive or antigen positive with symptoms suggestive of COVID-19), given either baricitinib plus standard of care or standard of care alone within 24 hours from admission. We excluded patients who were given baricitinib but who went home against medical advice or transferred to another institution; those who were given baricitinib for less than 5 days; and patients who have advanced do not resuscitate (DNR) or do not intubate (DNI) directives.

Procedures. The study protocol was submitted, reviewed and approved by Ospital ng Makati Research Ethics Board. The department's database of daily admissions was reviewed to identify all COVID-19 confirmed severe and critical patients admitted from December 2020 to May 2021. Using the inclusion and exclusion criteria, all eligible patient records were included in the review and were provided with a unique code identifier. A standardized data collection form was used to record the demographic characteristics, comorbidities, personal history, and COVID-19 presenting signs and symptoms. Information on COVID-19 management including daily severity status score, diagnostic tests, treatment, and complications were documented. All qualified patients were classified into two groups based on the treatment received during hospitalization: those given baricitinib + standard of care vs standard of care alone. Severe or critical patients were classified according to the WHO eight-category ordinal scale severity score (*Figure 1*). Outcomes on the survival/mortality status, and the

Table II. Outcomes

Parameter	Standard of Care	Standard of Care + Baricitinib	*p-value*
Average duration of Improvement (days)	12 ± 4	10 ± 4	*0.0686*
Mortality (%)	16 (32%)	9 (18%)	*0.1098*
Average Hospital Duration (days)	13 ± 5	14 ± 6	*0.3502*
Development of ARDS or Progression to Mechanical Ventilation (%)	5 (10%)	7 (14%)	*0.9950*

development of adverse events were reviewed and documented.

We calculated that 100 patients (50 in each group) would provide greater than 80% power to detect an odds ratio of 6 for remdesivir+ baricitinib group vs remdesivir alone using a significance level of 0.05. The odds ratio of 6 was based on projected group sizes at the time of study planning.

Outcomes and Statistical Analysis. The primary outcome of the study is the time to clinical improvement as measured by the number of days from admission to hospital day when the patient had a 2-point reduction in WHO eight-category ordinal scale severity score. This is a classification system used to predict mortality and is used in various studies involving COVID--19 (2,8,12,13). This is an 8-point classification of worsening severity from 1 defined as not hospitalized and no limitations of activities to 8 defined as death (See Appendix Table 1 for the detailed classification). Patients are observed and scored daily depending on their requirement of supplemental oxygen. We used ordinary least squares regression to predict the relationship.

For outcomes in-hospital all-cause mortality and progression to acute respiratory distress syndrome (ARDS) or use of mechanical ventilator, we determined the number of patients who died and those who progressed to use of mechanical ventilatory support. We then used binary logistic regression to identify any relationship.

For the last outcome, the number of hospital days for surviving patients were recorded. Ordinary least squares regression technique was likewise used to identify relationship.

Results

There was a total of 100 patients included in the sample, where 50 belongs to the control group (received Remdesivir treatment only), while the other 50 belongs to the experimental group (received both Remdesivir and Bacritinib treatment).

Baseline Characteristics. The baseline characteristics of our subjects based on their treatment grouping is shown in Table 1. Based on paired t-test analysis, both groups are noted to be similar.

Table II shows the different outcomes of the study. For the first outcome, baricitinib showed earlier time to improvement (10 days vs 12 days). However, the results were not statistically significant. For the second outcome, there was noted a trend toward improved mortality for the baricitinib group, however, was not statistically significant. The baricitinib group had 18% mortality compared to 32% on the control group. For the third outcome which is the number of hospital stay among survivors, there was noted longer duration of hospital stay by one day for the experimental group compared to the control group, however, this is likewise not statistically significant. For the last outcome of the present study, there were more patients noted to develop ARDS or progressed to mechanical ventilation during admission. However, this was likewise noted to be non-statistically significant. In summary, although there was noted better mortality rate, faster improvement, and less patients developing ARDS or needing mechanical ventilators in the baricitinib group, all these are statistically non-significant.

Discussion

The use of baricitinib in this study resulted to a better time to improvement or recovery (10 vs 12 days) which is similar to the results of ACCT-2 trial: 7 days vs 8 days.[8] However, this was noted to be statistically nonsignificant. The possible reason despite the higher difference in the number of days compared to ACTT-2 trial, is the lower number of study subjects. One way to address this is to lengthen the duration of the study covering a longer span of months to include more subjects and increase the power of the study.

For the mortality outcome, the result of this study is similar to the ACCT-2 trial done by Kalil et. al. 2021, which showed an overall trend towards lower 29-day mortality with the addition of baricitinib to remdesivir (5.1 versus 7.8%; HR 0.65, 95% CI 0.39-10.9), and is likewise not statistically significant.[8] This is however contrary to the result of the more recently published trial COV-BARRIER which showed that adding baricitinib to standard of care reduced 28-day mortality (8.1 versus 13.1 percent with placebo) and this reduction in mortality was maintained at 60 days.[11] These two trials differ in the characteristics of enrolled patients. The COV-BARRIER trial enrolled patients like the subjects in our study wherein patients were already being given dexamethasone as part of the

standard of care. More real-world studies are necessary to be able to make a better recommendation regarding the true effect of baricitinib on mortality. Likewise, a meta-analysis summarizing these varying results in the literature including our study would be recommended.

Regarding the hospital stay, the one-day longer duration of stay for the baricitinib group is opposite the result of ACCT-2 trial, but this is likewise statistically not significant.

For the progression to ARDS or need for mechanical ventilator outcome, the result was similar to the findings of the COV-BARRIER trial which did not significantly reduce the progression to increased oxygen support.[11]

This study was conceptualized during the time when no published clinical trial showed improved mortality outcomes for the use of baricitinib in patients who are on corticosteroids as part of the standard of care. The only existing trial at that time was the study by Kalil et. al. 2021, (ACCT-2 trial) a randomized trial of 1033 hospitalized patients which showed improved recovery time.[8] In the ACCT-2 trial, patients were not yet given dexamethasone since the RECOVERY trial was still ongoing when the study was carried out. This then led to the recommendation by IDSA to use baricitinib only for patients who cannot be given dexamethasone, and may use baricitinib in combination with steroids only in the context of clinical trial.[14] At that time therefore, there was a knowledge gap as to whether baricitinib in combination with the current standard of care could result to improved outcomes.

In September 2021, the COV-BARRIER trial, a randomized, double-blind, parallel-group, placebo-controlled phase 3 trial was published, and this trial enrolled patients who were already being given dexamethasone as part of the standard of care.[11] Likewise, the IDSA guidelines updated its recommendation on baricitinib, published in October 2021, adding its recommended use in patients with severe COVID-19.[14] This showed the rapidly evolving nature of the management of COVID-19.

There were several limitations in this study. First, the number of study subjects was limited, and the authors suggest that extending the duration and including more patients may increase the power of the study. Safety outcomes can also be determined; however, not all laboratories were available in the hospital during the study period. Not all patients had monitoring of liver function (AST, ALT) and creatinine. The risk of thrombosis can also be included as part of the safety issues of baricitinib by determining patients who eventually developed thromboembolic disorders. Likewise, the rapidly evolving management of COVID can result in certain differences in the population. Baricitinib only became available at Ospital ng Makati last March 29, 2021 and the authors enrolled patients in the control group for those who were admitted before that time. It was also during that period when vaccines became available, hence some patients in the experimental group had been vaccinated, and this could have affected the outcome.

Conclusion

In summary, the results of this study revealed that baricitinib did not show any statistically significant difference in all the outcomes: time to clinical improvement, all-cause mortality, number of hospital stay, and progression to ARDS or need for mechanical ventilation. Further real world studies involving different patient groups (e.g. different race or ethnicity) or a longer duration of the study to include more subjects are needed to fully ascertain the effect of baricitinib on the subjects as seen in the ACCT-2 and COV-BARRIER trials. As of now, the results of this study is not enough to recommend the use of baricitinib as a substitute for tocilizumab during COVID-19 surges.

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