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REVIEW ARTICLE

Survival Benefit of High Dose Versus Usual Dose of Baricitinib in Hospitalized Patients with COVID-19: A Systematic Review

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ABSTRACT:
Baricitinib is an oral selective Janus kinase 1 and 2 inhibitor with known anti-inflammatory and anti-viral properties. In patients hospitalized for coronavirus disease 2019 (COVID-19), baricitinib has shown to reduce the risk of death in line with dexamethasone and tocilizumab. However, the most effective and safe dose or optimal dose of baricitinib in severe COVID-19 was not addressed.
We conducted this systematic review to assess whether higher than usual dose could further improve survival as primary outcome. The need of ICU (Intensive care Unit) and Invasive or non-invasive positive pressure ventilation, time to wean from oxygen, length of stay at hospital and adverse events were analyzed as secondary outcome.
We included 10,032 patients in 5 studies (2 randomised control trials and 3 high quality clinical trials). Among them,5,071 patients received baricitinib at different dosage (4909 patients received 4 mg once daily and 162 patients got more than 4 mg daily) and 4961 received standard of care. Baseline characteristics including mean age, sex, co-morbidities, inflammatory marker (C-reactive protein/CRP) were similar across the intervention and standard care groups.
4 out of 5 trials showed significant survival benefit in baricitinib group usual to higher dose (4 to 8 mg daily). Use of higher dose in 3 controlled trials was associated with significant reduction in admission to ICU and requirement of invasive or non-invasive ventilation support, shortening of hospital stay and earlier stabilization of oxygen status which was not evident in two randomized control trials using usual dose (4 mg daily). There was no significant difference in any serious adverse events or opportunistic infections between higher dose versus usual dose group.
Therefore, baricitinib in higher dose could be a potent, highly effective and safe immunomodulatory drug in hospitalized patients with severe COVID-19.
Keywords: *baricitinib, high dose, COVID-19, efficacy, JAK-inhibitor, safety*

1. Introduction:

In late 2019, a novel coronavirus was identified as the cause of cluster pneumonia cases in China. The "deadly" virus was the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) pandemic worldwide[1]. It took a heavy toll of 6.38 million confirmed death globally and around 29 thousand demises in Bangladesh till to date [2].

COVID-19 disease typically involves three clinical phases. Initially, there is a viral response phase where patients mostly have mild constitutional symptoms. Then a pulmonary phase where there is an overlap of host inflammatory response and viral replication effects. Finally, there is a hyperinflammatory phase due to dysregulated host immune response which leads to organ failures, such as hypoxic respiratory failure that may require mechanical ventilator support or may lead to death [3]. Literature showed that the use of dexamethasone or other corticosteroids reduces the risk of death in patients with severe hypoxic COVID-19 [4]. The addition of an interleukin-6 (IL-6) receptor blocker (Tocilizumab etc.) further reduces the risk of death in these patients. [5-6].

Baricitinib is an oral inhibitor of Janus kinase (JAK1 and JAK2). The JAKs are a family of four transmembrane protein kinases (JAK1, JAK2, JAK3 and TYK2) that mediate intracellular signaling of a range of extracellular cytokines and interferons. JAK inhibition prevents activation of signal transducers and activators of transcription (STAT). Since the JAK-STAT pathway mediates the effect of several cytokines, including IL-6, that are raised in severe COVID-19, JAK inhibitors have been proposed as a potential therapeutic option for severe COVID-19 [7,8].

Recently Baricitinib was approved on May 10,2022 by the US Food and Drug Administration (FDA) for the treatment of hospitalized adult patients with severe COVID-19 requiring supplemental oxygen, invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) [9]. The FDA first issued an EUA (emergency use authorization) for baricitinib on November 19, 2020, for its use in combination with remdesivir to treat COVID-19 among hospitalized adult and pediatric patients. [10] Then it was revised on July 28, 2021, to allow baricitinib as a stand-alone treatment. Subsequently it became the first FDA approved COVID-19 immunomodulatory treatment [9]. This approval was supported by three landmark RCTs (randomized control trials) Adaptive Covid-19 Treatment Trial-2 (ACTT-2), COV-BARRIER and RECOERY which showed significant mortality benefit [10,11,12].

Most of the trials mentioned the dosage of Baricitinib of 4 mg daily for 10 to 14 days as a standard treatment, however, could higher dosage result in better efficacy in COVID-19 who were hospitalized, was not assessed. There is evidence that in higher concentrations, baricitinib can also inhibit JAK3 and TYK2 activity which may lead to further control of hyperinflammation in COVID-19 [13]. There are reports showing better disease control in higher dosage of baricitinib (up to 10 mg daily) in several other conditions such as psoriasis [14], atopic dermatitis [15] and rheumatoid arthritis [13,16]. Few studies found additional benefit while using extra loading dose or higher than usual dose of baricitinib in severe COVID-19 [17,18,19]. There are previous systematic reviews and meta-analysis revealing the benefit of baricitinib in usual dose than no baricitinib in SARS Cov-2, however nothing was mentioned about the optimal or ideal dosage which could be used safely for better clinical outcome.

The primary objective of this systematic review is to assess whether higher dose of baricitinib further improve survival than usual dose without causing significant adverse events in hospitalized severe Covid-19.

2. METHODS:

We conducted a systematic review of clinical trials and observational studies and followed the PICO framework as follows, (P) Populations—hospitalized severe coronavirus disease 2019 patients; (I) Interventions—treatment with higher dose (>4 mg daily) and usual dose (4 mg daily) of baricitinib along with standard of care in COVID-19,(C), Comparator/Control—a group of patients who received usual dose (4 mg) baricitinib or none along with standard of care as control/placebo and another group who received treatment with additional or higher than usual dose (>4 mg daily) of baricitinib along with standard of care; (O), Outcomes-primary outcome was survival benefit. Secondary outcome was the admission to intensive care unit, the requirement for invasive mechanical ventilation, the oxygenation index and the risk of adverse events. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria (Figure-1) were followed.

2.1: Inclusion and exclusion criteria:

Studies that met all the following criteria were included:

1. The studies were in the English language and baricitinib was used alone or with other therapies in patients admitted to hospital for severe COVID-19.
2. The efficacy and safety of baricitinib were investigated in adults with COVID-19.
3. Clinical outcomes of interest (all-cause mortality, disease severity, intensive care unit [ICU] admission, invasive mechanical ventilation, and adverse events) were reported.
4. Case-control, cohort, and randomized or non-randomized clinical trial research was contained.

Articles with the following criteria were excluded:

1. Correspondence or review articles, case-series, or case reports,
2. Studies reported other than in English language,
3. Research focusing on children below 18 years old

Definition of severe COVID-19 pneumonia:

The severe stage of COVID-19 infection in a patient is determined with the evidence of bilateral lung infiltrates in chest imaging (usually > 50%) and other (one or more) signs of disease severity, including dyspnoea, fast breathing rate (≥30 breaths/min) and SpO2 < 94% on room air (RA) or getting supplemental oxygen [20].

Usual Dosage and higher dosage criteria:

Baricitinib 4 mg daily for 10 to 14 days were considered standard or usual dose. More than 4 mg daily (8 mg /day) or additional loading dose (8 mg single loading or 8 mg for 2 days followed by a maintenance dose of 4 mg daily) were considered higher dosage. The dose had to be reduced for patients with eGFR <60 mL/min/1.73m2 or receiving probenecid and for children aged <9 years who were excluded from the study [12].

2.2. Search strategy and study quality assessment:

PubMed- MEDLINE was searched from inception to June 30, 2022, by mentioned investigators who completed literature searching and screening and analyses from May,2022 up to July,2022. We used the keywords "baricitinib" OR "Janus kinase inhibitor" OR "JAK inhibitor" AND "SARS-CoV-2," OR "coronavirus disease 2019" OR "Covid-19" AND "higher dose" or "optimum dose" or "usual dose" or "standard dose". These investigators independently screened titles and abstracts generated by the search. After selection, full electronic articles were then carefully evaluated for data extraction.

3. RESULTS:

3.1. Design and quality assessment of included studies:

The PRISMA flow diagram is shown in Figure 1. We initially identified 284 articles. We then identified 17 highly relevant articles by searching titles and abstracts and eliminating repetitions. After examining the content further 5 articles were finally selected for systematic review. The studies included data on the first author, publication year, study type, number of total participants, number of attendees receiving baricitinib with different dosage used and getting other treatments (Table-1).

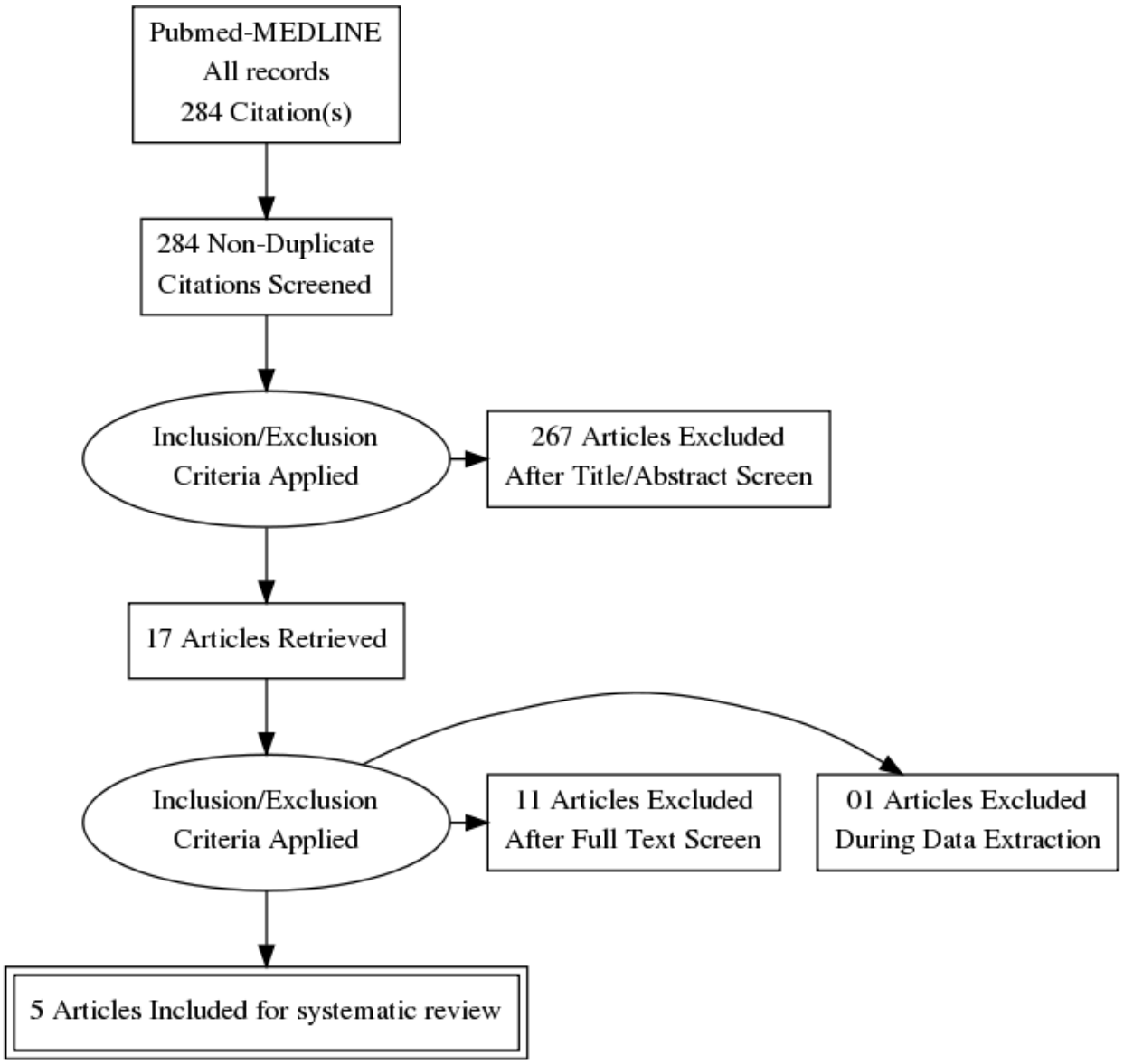

Figure-1: PRISMA Flow Diagram

A total of 10,032 patients were included in 5 studies, of which 5,071 patients received baricitinib at varying dosage and 4961 received standard of care. In total,4909 patients received 4 mg once daily,162 patients got additional or higher dose (8 mg daily)
baricitinib. Baseline characteristics including mean age, sex, co-morbidities, inflammatory marker (C-reactive protein/CRP) were similar across the intervention and standard care groups. Detailed characteristics of the studies are described in Table-1.

All trials included in the analysis studied hospitalized patients with severe COVID-19 who required oxygen support at the time of admission to hospital.
Two trials were double-blinded, and placebo controlled while one had open label, platform design. Three were prospective cohort study. Detailed study designs and study criteria are described in Table-1.

3.2: Assessment of outcomes:
Primary outcome, Survival benefit:

Two randomized controlled trials [11,12] and three clinical trials [17-19] considered 28-day & 30-day mortality respectively with baricitinib in hospitalized COVID-19. Among them, 2 RCTs and two clinical trials [11,12,17,18] found significant mortality benefit. The RECOVERY trial with large number of populations found that 513 (12%) of 4148 patients allocated to baricitinib 4 mg daily versus 546 (14%) of 4008 patients allocated to usual care died within 28 days (age-adjusted rate ratio 0·87; 95% CI 0·77-41 0·98; p=0·026) which is 13% proportional reduction in mortality [12]. Another RCT

reported 162 participants had died (8%) of 764 in the baricitinib 4 mg daily plus usual care group and 100 (13%) of 761 in the placebo group. So, 28-day all-cause mortality was 38% lower in the baricitinib group than in the placebo group (HR 0 · 57 [95% CI 0 · 41–0 · 78] [11]. One trial found using higher dose of baricitinib (8 mg daily in divided dose) further reduced 30-day mortality rate than usual dose (4 mg daily) 3.3% versus 6% respectively which was statistically significant (p=.001) [18]. Here supportive care including dexamethasone, remdesivir and anticoagulation was received by both higher dose baricitinib and usual dose group as standard of care. Another previous study by the same author observed decreased progression of disease, however, didn't find any significant survival benefit between the additional loading dose (8mg) of baricitinib group (5%) versus usual dose (4 mg daily) group (5.9%) [19]. Although one earlier trial in 76 patients showed significant decrement in death rate in baricitinib loading dose followed by usual dose group (5%) in comparison to supportive care only (45%). However, in this study no steroid or baricitinib used in control group [17]. Combined data showed 681 patients expired in 4 to 8 mg dose of baricitinib group (n=5071) whereas 679 died in control group (n=4961) showing odd ratio 0.981 95%CI (0.876-1.098) [Figure-2]

Table-1:

First Author	Year	Study Types	Total number of patients	Baricitinib in higher dose group	control group; lower dose or no baricitinib	Results
Peter Horby et al. RECOVERY [12]	March 2022	RCT	8156	n = 4148 4 mg daily for 10 days	n= 4008 Standard of care	Odd ratio (age adjusted rate) 0.87 95%CI 0.77-0.98. p=.026
Vincent C Marconi et al. (COV-BARRIER) [11]	Dec 2021	RCT	1525	n= 764 4 mg daily 14 days	n = 761 Standard of care	The 28-day all-cause mortality was 8% (n=62) for baricitinib and 13% (n=100) for placebo (hazard ratio [HR] 0·57 [95% CI 0·41–0·78]; nominal p=0·0018)
Md Jahidul Hasan et al. [18]	May 2021	Clinical trial	238	n = 122 8 mg daily in two divided dose for 14 days	n = 116 4 mg daily for 14 days	Odds ratio 0.5278 95 % CI: 0.1504 to 1.8531 Significance level P = 0.3186
Vincenzo Bronte et al. [17]	November 2020	Clinical trial	76	n = 20 4 mg twice daily (8 mg daily) for 2 days then 4 mg once daily for another 7 days	n = 56 No baricitinib nor steroid	Odds ratio 0.0653 95 % CI:0.0082 to 0.5218 Significance level P = 0.0101
Md Jahidul Hasan et al. [19]	Oct 2020	Clinical trial	37	n =20 8 mg loading then 4 mg once daily for 14 days	n =17 No loading, only 4 mg/day for 14 days	Odds ratio 0.8421 95 % CI: 0.0487 to 14.5658 Significance level P = 0.9059

Table-2:

Variables		*Peter Horby et al* [12]	*Voncent C Marconi et al.* [11]	*Md Jahidul Hasan et al.* [18]	*Vincenzo Bronte et al.* [17]	*Md Jahidul Hasan et al.* [19]
Mean Age	Case	58.5	57.8	63	68	59
	Control	57.7	57.5	59	77.5	52
M/F	Case	66/34%	64/36%	68/32%	35/65%	80/20%
	Control	66/34%	68/32%	66/34%	55/45	76/24%
Co-morbidities:						
DM	Case	23%	29%	77.9%	20%	85%
	Control	23%	31%	75.9%	16%	82%
HTN	Case	19%	48%	70.5%	80%	60%
	Control	18%	48%	69.8%	48%	76%
CKD	case	2%	0	17.2%	5%	15%
	control	2%	0	19.8%	10%	11%
Asthma/ COPD	Case	21%	4%	35.1%	10%	30%
	Control	20%	4%	31%	0	23.5%
CRP mg/L	Case	84	67.5	179	53	77.1
	Control	87	62	159	64	43.5
Other supportive care used	Case	Steroid 95%	Dexamethasone in 92%	Dexamethasone in 100% case	Remdesivir in 40% Anticoagulation in 100% No steroid	Steroid+ Baricitinib
	Control	Steroid 96%	Dexamethasone in 90%	Dexamethasone in 100%	Remdesivir in 46% Anticoagulation in 96%	yes
Primary Outcome: Survival benefit						
Mortality	Case	12% (p=.026)	8% (p=.0018)	3.3% (30d) (p=.001)	5%	5 (30d)
	Control	14%	13%	6%	45%	5.9% (30d)
Secondary Outcome						
ICU need	Case	16%	27.8%	11 (p=.020)	15% develop ARDS	10% (p=.005)
	Control	17%	30.5%	20	27% develop ARDS	29.4%
Positive pressure ventilation	Case	20%	27.8%	5%(p=.001)	15	5%
	Control	21%	30.5%	13%	27	11.8%
Normalization of oxygen	Case		10	5 (p-.001)	7-day P/F above 300	5 d (p=.001)
	Control		11d	8	>7 days	8 d
Duration of hospital stay	Case	8	12.9d	12	19d	12 d(p=.028)
	Control	8	13.7d	15	31d	15 d
Safety profile						
Opportunistic infection	Case	<1% (0.12%) (n=5)	9%	0	0	0
	Control	Nil	10%	0	Nil	0
Other adverse effects	Case	n=8	3%	Thrombocytosis=9.8% Mouth sore=2.4%	0	0
	Control	Nil	3%	Thrombocytosis=2.6% Mouth sore=0.08%	0	0

Primary Outcome, survival benefit:

Study Author	Odds ratio	Lower 95%CI	Upper 95% CI
Peter Horby 2022 [12]	0.87	0.77	0.98
Vincent C Marconi 2021 [11]	0.57	0.41	0.78
Md Jahidul Hasan 2021 [18]	0.52	0.15	1.85
Vincenzo Bronte 2020 [17]	0.065	0.0082	0.5218
Md jahidul Hasan 2020 [19]	0.8421	0.048	14.56
Combined	0.981	0.876	1.098

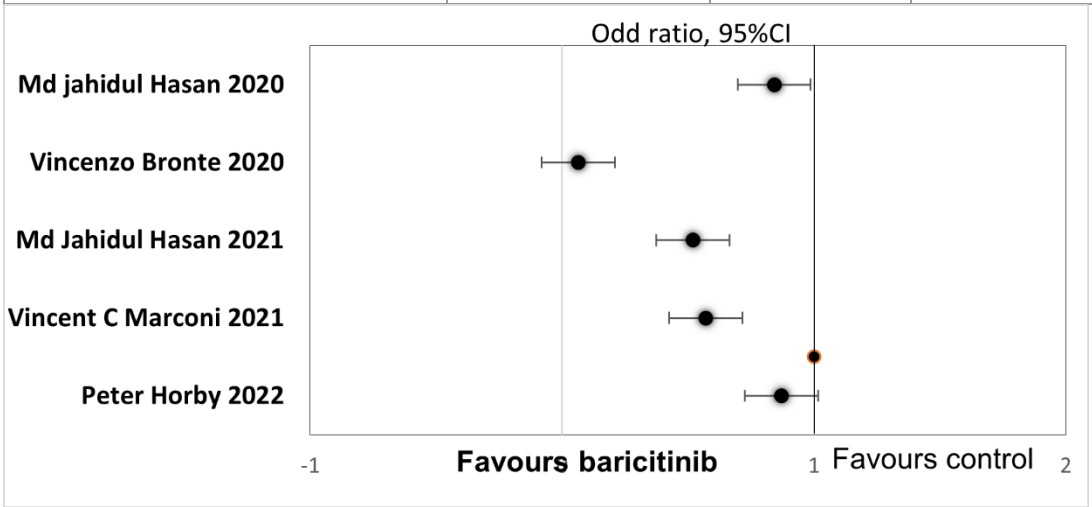

Figure-2: Forest Plot (Baricitinib 4 to 8 mg daily along with standard of care improve mortality than standard of care alone in severe COVID-19)

Secondary Outcome:

Usual dose of baricitinib in 2 RCTs [11,12] revealed a lower trend to progression to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, in other words, lower risk of ICU requirement than control group which was 27.8% versus 30.5% (p=0.18) and 16% vs.17% respectively. However, this secondary outcome was not statistically significant. In rest of the 3 trials [17-19], use of higher dose of baricitinib (>4 mg daily) was associated with significant reduction in admission to ICU and requirement of invasive or non-invasive ventilation support, shortening of hospital stay and earlier stabilization of oxygen status which was not evident in two RCTs [11,12] using usual dose (4 mg daily) [Figure-3].

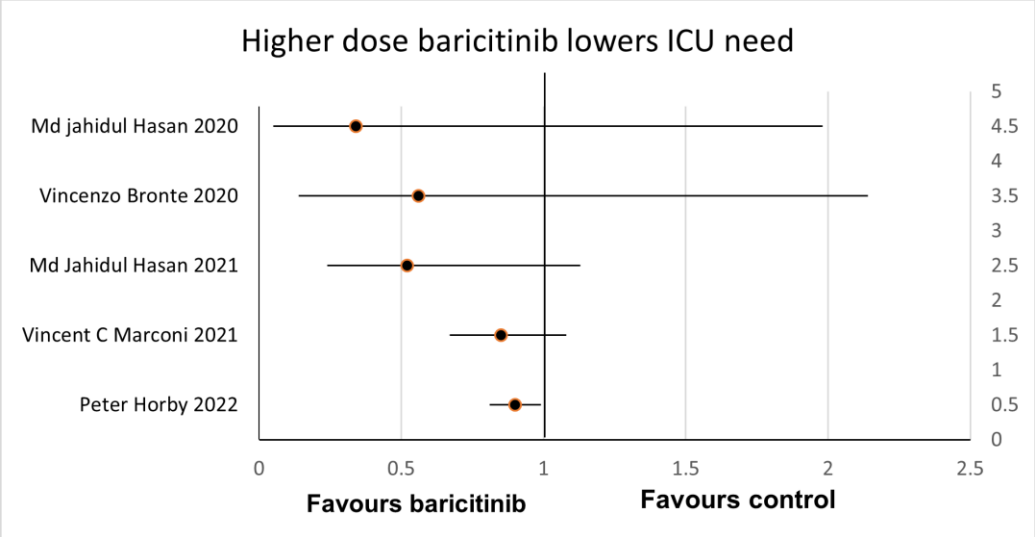

Figure-3: Higher dose (8 mg daily) baricitinib significantly lowers requirement of ICU support in severe COVID-19 than usual dose (4 mg daily).

3.3: Safety Profile of baricitinib:

In the largest RCT [12], use of baricitinib at 4 mg daily for 10 days in 4148 patients reported <1% non-coronavirus infection and other 3 trials [17-19] on 162 patients using higher dose 8 mg daily for 14 days or additional loading dose didn't find any serious or opportunistic infections while on treatment. Another RCT [11] on 764 patients did observe non-covid infections however it was not significant, baricitinib 4 mg daily for 14 days (9%) versus control group (10%).

Regarding thrombotic events, higher than usual dose baricitinib group showed thrombocytosis [18] however no thrombo-embolic events (Pulmonary embolism, deep vein thrombosis) were reported. In 2 RCTs [11,12] baricitinib group showed <1% and 3% thrombotic events respectively which were not significantly different from control group.

4. DISCUSSION:

This systematic review focused on the optimal dose and duration of baricitinib in hospitalized patients with severe COVID-19. Previous reviews and meta-analysis [21,23,24] summarized the studies on the efficacy and safety of JAK inhibitors in COVID-19 up to September, 2021.These trials included fairly large number of patients;,n=1363 [21] and n= 4363 [23] n=2367 [24] respectively. They highlighted the mortality benefit of baricitinib or other JAK inhibitors in hospitalized COVID-19 however, they didn't enlighten us about the ideal dose of baricitinib in severe COVID-19 whether higher dose could be more effective in hyperinflammatory state. We included the latest and the largest multi-center randomized control trials along with high quality smaller clinical trials which assessed the impact of different dosage of baricitinib in COVID-19 admitted to hospital. We found that baricitinib in usual dose (4 mg daily) was associated with a significant reduction in 28- or 30-day mortality in patients hospitalized with COVID-19 [11,12]. However, increasing the dose to 8 mg daily in two divided dose or giving a loading dose of 8 mg or 8 mg for initial 2 days followed by maintenance dose of 4 mg daily could further enhance its anti-inflammatory effects and greater chances of survival [17,18,19].One meta-analyses [22] including n=3564 reported that the higher dose group appeared to have additional benefits for clinical efficacy in COVID-19 which was similar to the findings of our systematic review. Moreover, between the higher dose baricitinib group and control group, there was no significant difference in mean age, co-morbidities, initial inflammatory marker (C-reactive protein) and the supportive treatment received [Table-2]. The use of concomitant therapy varied among trials.4 out of 5 trials used corticosteroid in both case and control groups (except Vincenzo Bronte et al [17]). Most of our studied population received anti-viral and anti-coagulation as standard of care. [Table-2] IL-6 (interleukin-6) receptor blocker Tocilizumab was used in 23% cases of baricitinib group in one study [12].

In a recent meta-analysis [3] including around 10 thousand patients, baricitinib (usual dose) group did show survival benefit however didn't find any statistically significant improvement in secondary outcome such as progression to mechanical ventilation. In contrast, our systematic review discovered a favorable trend in secondary outcome in higher dose population [Figure-3] which was statistically significant. We observed that the risk of ICU admission, the requirement for invasive mechanical ventilation and the discharge oxygenation index were significantly improved after using baricitinib in higher dose (>4 mg) in comparison to usual dose (4 mg daily) in COVID-19 admitted to hospital.

We also found no clinically meaningful differences in safety between the increased dose baricitinib group and the routine dose groups. [Table-2]. Previous studies [21-24] have suggested that new-onset infections and thrombo-embolic events were the main adverse events with baricitinib. However,they didn't find any higher risk of adverse events in baricitinib (usual dose) than control. Furthermore, even with the addition of steroids (which were allowed for >80% study population in COV-BARRIER [11] and >90% in RECOVERY [12]) and tocilizumab (23% patients in RECOVERY [12]), baricitinib was not associated with more infections. Likewise, our review showed no significant difference in terms of serious opportunistic infections or thrombotic events between usual to higher dose (4 mg to 8 mg daily) of baricitinib treatment and controls. This may be due to the accelerated recovery of patients using baricitinib or to the fact that the included studies used baricitinib for a short period of time. Because adverse effects were observed mostly in long term use of baricitinib in diseases other than COVID-19 [30]. We look forward to more studies in the future.

Baricitinib, an adenosine triphosphate competitive kinase inhibitor that selectively, firmly, and reversibly inhibits JAK1 and JAK2 enzymes, was envisaged to be a potential therapeutic option against SARS-CoV-2 using artificial intelligence algorithms [8]. JAK inhibitors (JAKinibs) are biological agents that inhibit Type I/II cytokine receptors. Baricitinib, fedratinib,tofacitinib and ruxolitinib are highly potent selective JAK inhibitors approved for indications such as rheumatoid arthritis (RA) and

some serious skin diseases [14-16]. Current studies show that baricitinib is the most suitable for the treatment of COVID-19 in terms of its clinical efficacy and few side effects. Due to the low plasma protein binding rate (only 50%) of baricitinib, (ruxolitinib: 97% and fedratinib: 95%) and the least interaction with cytochrome P450 enzymes and drug transporters, it has great potential in combination with other drugs to treat COVID-19.

The systemic exposure of orally taken baricitinib is dose-dependent [18] and it has a good oral bioavailability (79%) [19]. Baricitinib has a short half-life (12.5 hour) and acts on targeted critical pathways to reduce inflammation while minimizing biologic redundancy with less immunosuppression [8.10]. Additionally, Baricitinib, an IL-6 receptor antibody, exhibits anti-viral activity in tolerable therapeutic dose ranges and clinically relevant serum concentrations [28]. It does this by inhibiting upregulated INF-1 caused by the ACE-2 receptor, thereby blocking the cell entry of viruses. Therefore, it can block inhibit cell entry through clathrin-mediated endocytosis inhibition [29].

In February 2022, the National Institutes of Health (NIH) updated its guidelines recommending the use of baricitinib for patients on dexamethasone who have rapidly

increasing oxygen needs and systemic inflammation. [25,26] Again, in January 2022, the World Health Organization (WHO) included a strong recommendation for using baricitinib as an alternative to an IL-6 receptor blocker, in combination with corticosteroids, in patients with severe or critical conditions COVID-19 [27]. Our meta-analysis considerably strengthens the evidence that baricitinib in usual to higher dose (4-8 mg daily) when used along with dexamethasone and/or IL-6 inhibitors in hospitalized COVID-19, can further improve survival, time to discharge, progression to mechanical ventilation without any significant difference in adverse outcomes [11,12,17-19]. Furthermore, baricitinib has the advantages of a low cost, easy production, and convenient storage. Therefore, baricitinib in higher dose could be tocilizumab sparing agent in hospitalized patients with severe COVID-19 particularly in low economic countries where shortage and higher cost of IL-6 inhibitor, tocilizumab could be a vital issue.

There are certain limitations to our study as follows. First, although two high-quality, multicenter RCTs were included, we also included some high-quality smaller studies. More multicenter, double-blind, randomized trials are required to substantiate our results. Second, the effect of baricitinib treatment may be affected by other drugs taken simultaneously, and the results do not only reflect the clinical effect of baricitinib. Third, most of the current studies on the safety of baricitinib were short-term. Therefore, the incidence of more long-term adverse reactions still needs to be further investigated Finally, there have been only few studies on the optimal dose of baricitinib for SARSCoV-2. This optimal dose needs to be further explored in future studies.

5. Conclusion

Our systematic review suggests that the higher dose of baricitinib in hospitalized severe COVID-19 infection improves survival rate, early normalizes respiratory function, decreases the need of ICU and mechanical ventilation support rather than usual dosage

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