BARICITINIB

RECOMMENDATION

We suggest the use of baricitinib in combination with remdesivir in hospitalized COVID-19 patients who cannot take steroids and requiring oxygen supplementation. *(Low quality of evidence; Conditional recommendation)*

There is insufficient evidence to recommend the use of baricitinib in combination with remdesivir and corticosteroids in hospitalized COVID-19 patients *(Very low quality of evidence)*

There is no evidence to recommend the use of baricitinib alone in hospitalized COVID-19 patients.

Consensus Issues

These recommendations are made in the context that dexamethasone is being considered as a standard of care for COVID-19. The incremental benefit of giving baricitinib and remdesivir with dexamethasone remains to be a research gap. Thus, there is insufficient evidence to recommend the use of baricitinib in combination with remdesivir and corticosteroids in hospitalized COVID-19 patients. Caution must be exercised in administering baricitinib in patients who are already taking steroids due to the likelihood of increased immunosuppression. Results of the trial showed that patients who received glucocorticoids had a higher risk of having serious or non-serious infections than those who did not.

The panel is cognizant of the current local practice wherein baricitinib is being used off-label as an alternative to tocilizumab in regimens with both remdesivir and dexamethasone among severe to critical COVID-19 patients. This is due to the supply issues with tocilizumab.

EVIDENCE SUMMARY

Should baricitinib with or without remdesivir be used in the management of hospitalized patients with COVID-19?

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Key Findings

One multinational double-blind placebo controlled randomized trial investigated the effect of baricitinib plus remdesivir versus remdesivir alone on 1,033 patients with moderate to severe COVID-19. Based on this RCT, baricitinib plus remdesivir showed benefit in terms of shortening time to recovery by 1 day on average and reducing the incidence of mechanical ventilation or

ECMO. No significant effect on mortality was noted. Significantly fewer serious adverse events were documented in the group given baricitinib plus remdesivir; however, the incidence of infections increased among patients who were taking concomitant glucocorticoids. No other trials were found on baricitinib alone or in combination with other drugs. (i.e., corticosteroids).

Introduction

Baricitinib is an orally administered selective inhibitor of Janus kinase (JAK) 1 and 2 used in the management of rheumatoid arthritis. In vitro studies have shown that it can prevent the entry of SARS-COV-2 virus to human cells and reduce the levels of cytokines (i.e. Interleukin-2, Interleukin-6, Interleukin-10, G-CSF, IFN-Y) in COVID-19 patients [1]. A case series (n=4) and a small open-label, placebo-controlled trial (n=24) showed significant clinical improvement in mild to moderate COVID-19 patients [1, 2].

Review Methods

Studies that evaluated the effectiveness of baricitinib in COVID-19 patients were systematically searched in Medline, clinicaltrial.gov and Medrxiv (Date of last search: April 4, 2021). Free text of *baricitinib* or its brand name *Olumiant* were intersected with prespecified search terms for COVID-19 and the Cochrane maximum sensitivity search for randomized controlled trials. Randomized controlled trials that included baricitinib regardless of dose, concomitant drug interventions, or type of comparator were included. Subgroup analysis according to disease severity or dose were done when possible.

Results

We found only 1 randomized controlled trial (Adaptive COVID-19 Treatment Trial 2 [ACCT-2]) [3] that evaluated the effectiveness of baricitinib as an adjunct to remdesivir in the management of moderate-to-severe COVID-19 patients. No other studies were found that evaluated baricitinib alone or in combination with other drugs for COVID-19 treatment.

The ACTT-2 was as a multinational, double-blind, placebo-controlled randomized trial conducted in the United States, Singapore, South Korea, Mexico, Japan, Spain, United Kingdom and Denmark [3]. The study included 1,033 hospitalized confirmed COVID-19 patients (mean age: 55.4 ± 15.7 years, 63% males) with variable disease severity levels. The treatment group was given baricitinib 4 mg/tab daily for 14 days or up to hospital discharge together with remdesivir (200 mg/ day for first day and 100mg/ for the following days up to 10 days) while the control group was given remdesivir and a placebo. Standard of care also included venous thromboembolism (VTE) prophylaxis. However, glucocorticoid use was prohibited unless clinically indicated (i.e. asthma exacerbation, septic shock, ARDS).

Patients who received baricitinib and remdesivir exhibited a faster time to recovery by an average of 1 day compared to those treated with remdesivir alone (median 7 vs. 8 days; rate ratio for recovery = 1.16, 95% CI: 1.01 to 1.32). When analyzed according to severity, only patients who received noninvasive ventilation or high-flow oxygen (n=216) benefited from the combination (median 10 vs. 18 days; rate ratio = 1.15; 95%CI: 1.10 to 2.08). Baricitinib also did not significantly reduce the time to recovery of patients without oxygen requirement (median 5 vs 4 days; rate ratio = 0.88; 95%CI: 0.63 to 1.23), patients on oxygen but not on non-invasive ventilation or high flow

oxygen (median 5 vs. 6 days; rate ratio = 1.17; 95%CI: 0.98 to 1.39), and patients on mechanical ventilation or ECMO (not estimable median days; rate ratio 1.08, 95%CI 0.59 to 1.97).

There were significantly fewer cases (11.5% vs 19.3%) that progressed to the use of mechanical ventilation or death in the treatment group (RR 0.59, 95%CI 0.44 to 0.80). Incidence of new use of mechanical ventilation or ECMO was also significantly less (10% vs. 15.2%) in the treatment compared to the control group (RR 0.66, 95%CI 0.46 to 0.93).

Mortality rate was not significantly different in both groups (4.7% vs. 7.1%, HR = 0.65; 95%CI: 0.39 to 1.09). Subgroup analysis showed that baricitinib did not significantly reduce mortality in patients with oxygen supplementation (1.0% vs 1.4%, HR = 0.73; 95% CI: 0.16 to 3.26), on non-invasive ventilation or high flow oxygen (1.0% vs 4.4%, HR 0.21; 95% CI: 0.02 to 1.80), and on mechanical ventilation or ECMO (7.4% vs 10.5%, HR 1.08 95%CI: 0.59 to 1.97).

There were fewer serious and non-serious adverse events observed in the baricitinib group compared to the placebo group (40.2 vs. 45.9%, RR 0.76, 95%CI 0.59 to 0.99). Most common adverse events reported were hyperglycemia, anemia, decreased lymphocytes and acute kidney injury. Patients who received concomitant glucocorticoids for other clinical indications had a higher incidence of serious or nonserious new infection. However, it was not specified in the RCT if these patients belonged in the treatment or control group.

Recommendations from Other Groups

Both the US-NIH (11 February 2021) and Infectious Disease Society of America (IDSA) (14 December 2020) recommend giving baricitinib in combination with remdesivir only in cases where corticosteroids cannot be given [4,5]. In contrast, the Australian guidelines (1 April 2021) recommend against the use of baricitinib unless in the context of a clinical trial [6]. All these organizations used the results of the ACTT-2 trial in formulating their recommendations.

The US-NIH *recommends* the use of this treatment for hospitalized, non-intubated COVID-19 patients who require oxygen supplementation and cannot be given corticosteroids. However, they *do not recommend* using baricitinib without remdesivir and other JAK inhibitors unless in the context of a clinical trial [4]. The agency further stated that there is *insufficient data* to recommend either for or against the use of (a) baricitinib plus remdesivir for treating hospitalized COVID-19 patients when corticosteroids can be used, or (b) baricitinib together with corticosteroids. Both baricitinib and steroids are potent immunosuppressants and may increase the risk for infection. [4].

As of December 14, 2020, IDSA suggests the use of baricitinib with remdesivir in severe COVID-19 patients who cannot receive corticosteroids. The combination of baricitinib, remdesivir and corticosteroids can only be done in the context of a clinical trial [5].

Research Gaps

There are 7 ongoing clinical trials in clinicaltrials.gov on baricitinib for COVID-19 management. Four trials compared baricitinib to standard of care while the rest compared it against dexamethasone or tocilizumab in combination with remdesivir. Earliest date of completion is March 2021. See Appendix 3 for details.

References

[1] Tsai YC, Tsai TF. Oral disease-modifying antirheumatic drugs and immunosuppressants with antiviral potential, including SARS-CoV-2 infection: a review. Ther Adv Musculoskelet Dis. 2020;12:1759720X20947296.

[2] Cantini F, Niccoli L, Matarrese D, Nicastri E, Stobbione P, Goletti D. Baricitinib therapy in COVID-19: A pilot study on safety and clinical impact. J Infect. 2020;81(2):318-56.

[3] Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. N Engl J Med. 2021;384(9):795-807.

[4] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines: National Insitututes of Health; 2020 [Available from: https://www.covid19treatmentguidelines.nih.gov/.

[5] Bhimraj A, Morgan RL, Shumaker AH, Baden L, Cheng VC, Edwards KM, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19 2020 [updated December 2, 2020. Available from: www.idsociety.org/COVID19guidelines.

[6] National COVID-19 Clinical Evidence Taskforce. Australian guidelines for the clinical care of people with COVID-19. 2020 [Available from: https://covid19evidence.net.au/.

Appendix 1. Characteristics of Included Studies

Study ID	Population	Intervention	Comparator	Outcomes
ACTT-2 Trial	Moderate to severe COVID-19 patients (N=1,033)	Baricitinib (4mg tab daily for 14 days) + Remdesivir (200 mg on first day then 100 mg/day for the next 9 days) N=518	Remdesivir (200 mg on first day then 100 mg/day for the next 9 days.) N = 514	Time to recovery Clinical status at day 15 Time to improvement Time to discharge Number of days of receipt of supplemental oxygen, non-invasive ventilation or high-flow oxygen, and invasive ventilation or ECMO Incidence and duration of new use of oxygen Mortality

Appendix 2. GRADE Evidence Profile

Author(s): Cabaluna, IG; Burog, I; Bayona, HH

Question: Baricitinib + Remdesivir compared to Remdesivir alone for Hospitalized COVID-19 patients

Setting: Hospital

Bibliography: : Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. N Engl J Med. 2021;384(9):795-807.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Baricitinib + Remdesivir	Remdesivir alone	Relative (95% CI)	Absolute (95% CI)		
Mortality (follow up: 28 days)												
1	randomised trials	not serious	not serious	not serious	serious [a]	none	24/515 (4.7%)	37/518 (7.1%)	**HR 0.65** (0.39 to 1.09)	**24 fewer per 1,000** (from 43 fewer to 6 more)	⨁⨁⨁◯ MODERATE	
Time to recovery												
1	randomised trials	not serious	not serious	not serious	not serious	none	515 participants -	518 participants 78.3%	**Rate ratio 1.16** (1.01 to 1.32)		⨁⨁⨁⨁ HIGH	
New use of mechanical ventilation or ECMO (follow up: 29 days)												
1	randomised trials	serious [b]	not serious	not serious	serious [c]	none	46/461 (10.0%)	70/461 (15.2%)	**RR 0.66** (0.48 to 0.93)	**52 fewer per 1,000** (from 79 fewer to 11 fewer)	⨁⨁◯◯ LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Baricitinib + Remdesivir	Remdesivir alone	Relative (95% CI)	Absolute (95% CI)		
Serious adverse event												
1	randomised trials	not serious	not serious	not serious	serious [c]	none	81/607 (13.3%)	107/609 (17.6%)	**RR 0.76** (0.59 to 0.99)	**42 fewer per 1,000** (from 72 fewer to 2 fewer)	⨁⨁⨁◯ MODERATE	
WHO Progression Score level 7 or above												
1	randomised trials	not serious	not serious	not serious	not serious	none	59/515 (11.5%)	100/518 (19.3%)	**RR 0.59** (0.44 to 0.80)	**79 fewer per 1,000** (from 108 fewer to 39 fewer)	⨁⨁⨁⨁ HIGH	

CI: Confidence interval; **HR:** Hazard Ratio; **RR:** Risk ratio

Explanations

a. Downgraded by 1 level due to imprecision.
b. Not a predefined stratum. Secondary analysis
c. Downgraded by 1 level due to imprecision: low number of events (<300)

Appendix 3. Table of Ongoing Studies

NCT Number	Title	Participants	Intervention	Comparator	Outcome
NCT04421027	A Study of Baricitinib (LY3009104) in Participants With COVID-19	COVID-19	Baricitinib	Placebo	Percentage of Participants who die or Require Non-Invasive Ventilation/High-Flow Oxygen or Invasive Mechanical Ventilation (including extracorporeal membrane oxygenation [ECMO] Percentage of Participants with at Least 1-Point Improvement on NIAID-OS or Live Discharge from Hospital Number of Ventilator-Free Days Time to Recovery Overall Improvement Duration of Hospitalization Percentage of Participants with a Change in Oxygen Saturation from <94% to > 94% from Baseline Mortality Duration of Stay in the Intensive Care Unit (ICU) Time to Clinical Deterioration Time to Resolution of Fever Mean Change from Baseline on the National Early Warning Score (NEWS) Time to Definitive Extubation Time to Independence from Non-Invasive Mechanical Ventilation Time to Independence from Oxygen Therapy in Days Number of Days with Supplemental Oxygen Use Number of Days of Resting Respiratory Rate <24 Breaths per Minute
NCT04373044	Baricitinib, Placebo and Antiviral Therapy for the Treatment of Patients With Moderate and Severe COVID-19	Symptomatic COVID-19 Infection Laboratory-Confirmed	Baricitinib + HCQ	HCQ+ Placebo	Proportion of patients requiring invasive mechanical ventilation or dying Clinical and laboratory features Adverse events
NCT04693026	Efficacy of Ramdicivir and Baricitinib for the Treatment of	Covid19 Covid-19 ARDS	Remdesivir +Barcitinib	Remdesivir + Tocilizumab	Time to Clinical Improvement (TTCI) Mortality Rate Duration of ICU stay Duration total hospital stay

	Severe COVID 19 Patients				Rate of daily Supplemental Oxygen Use Time to Clinical Failure
NCT04393051	Baricitinib Compared to Standard Therapy in Patients With COVID-19	Covid-19 Pneumonia	Baricitinib Oral Tablet	Standard of care	Need of invasive mechanical ventilation Mortality Time to invasive mechanical ventilation Time to independence from non-invasive mechanical ventilation Time to independence from oxygen therapy Time to improvement in oxygenation for at least 48 hours Length of hospital stay Length of ICU stay Instrumental response Proportion of adverse events
NCT04640168	Adaptive COVID-19 Treatment Trial 4 (ACTT-4)	COVID-19	Baricitinib and Remdesivir	Dexamethasone and Remdesivir	The proportion of subjects not meeting criteria for one of the following two ordinal scale categories at any time: 8) Death; 7) Hospitalized, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) Change from baseline in alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-reactive protein (CRP), creatinine, d-dimer concentration, glucose, hemoglobin, platelets, prothrombin time (PT), total bilirubin, white blood cell count (WBC) with differential Cumulative incidence of Grade 3 and 4 clinical and/or laboratory adverse events (AEs) Cumulative incidence of serious adverse events (SAEs) Days of invasive mechanical ventilation/ extracorporeal membrane oxygenation (ECMO) Days of non-invasive ventilation/high flow oxygen Days of supplemental oxygen Desirability of Outcome Ranking (DOOR) Duration of hospitalization Incidence of discontinuation or temporary suspension of study product administration 14-day mortality 28-day mortality Clinical status

					Time to an improvement of one category from baseline using an ordinal scale Time to an improvement of two categories from baseline using an ordinal scale Time to recovery
NCT04390464	mulTi-Arm Therapeutic Study in Pre-ICu Patients Admitted With Covid-19 - Repurposed Drugs (TACTIC-R)	COVID19	Ravulizumab Baricitinib	Standard of care	Time to incidence of the composite endpoint of: Death, Mechanical ventilation, ECMO, Cardiovascular organ support, or Renal failure Change in clinical status from baseline Adverse events of special interest in each treatment arm Time to Sp02 >94% on room air Time to first negative SARS-CoV2 PCR Duration of oxygen therapy Duration of hospitalization All cause mortality at day 28 Time to clinical improvement
NCT04381936	Randomised Evaluation of COVID-19 Therapy	Severe Acute Respiratory Syndrome	Lopinavir-Ritonavir Corticosteroid Hydroxychloroquine Azithromycin Convalescent plasma Tocilizumab Immunoglobulin Synthetic neutralising antibodies Aspirin Colchicine Baricitinib Anakinra Dimethyl fumarate	Standard of care	All-cause mortality Duration of hospital stay Composite endpoint of death or need for mechanical ventilation or ECMO