Outcomes and Adverse Effects of Baricitinib Versus Tocilizumab in the Management of Severe COVID-19

Supplemental Digital Content

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Supplemental Table S1. Characteristics of Total Population

Characteristic	**Baricitinib** **n = 665**	**Tocilizumab** **n = 291**	**Total** **n = 956**	***P* value**
Age, median (IQR), y	58 (46.0-67.0)	55 (44.0-65.0)	57 (46.0-66.5)	0.09
Sex, n (%)				0.54
Female	308 (46.3)	141 (48.5)	449 (47.0)	
Male	357 (53.7)	150 (51.5)	507 (53.0)	
BMI, median (IQR)	33.1 (28.7 – 40.3)	34.5 (29.2 – 40.7)	33.5 (28.8 – 40.5)	0.16
Vaccination, n (%)				0.62
Yes	32 (4.8)	17 (5.8)	49 (5.1)	
No	633 (95.2)	274 (94.2)	907 (94.9)	
Pre-existing Conditions, n (%)	527 (79.2)	231 (79.4)	758 (79.3)	0.96
Diabetes Mellitus	360 (54.1)	174 (59.8)	534 (55.9)	
Essential Hypertension	350 (52.6)	127 (43.6)	477 (49.9)	
Kidney Disease	68 (10.2)	47 (16.2)	115 (12.0)	
Immunocompromised state	1 (0.1)	2 (0.7)	3 (0.3)	
Pregnancy	4 (0.6)	7 (2.4)	11 (1.2)	
Sickle cell disease	2 (0.3)	1 (0.3)	3 (0.3)	
Neuro-developmental disorder	3 (0.5)	1 (0.3)	4 (0.4)	
Presence of Risk Factor(s)*, n (%)	620 (78.2)	274 (94.2)	894 (93.5)	0.71
0	45 (6.8)	17 (5.8)	62 (6.5)	
1	131 (19.7)	58 (19.9)	189 (19.8)	
2	216 (32.5)	88 (30.2)	304 (31.8)	
3	208 (31.3)	99 (34.0)	307 (32.1)	
4	64 (9.6)	27 (9.3)	91 (9.5)	
5	1 (0.1)	2 (0.7)	3 (0.3)	
Ordinal Scale on Day 1, median (IQR)	6.0 (6.0 – 6.0)	6.0 (6.0 – 6.0)	6.0 (6.0 – 6.0)	1.00
Laboratory Values on Day 1, median (IQR)**				
CRP, mg/dL	10.6 (6.2 – 16.4)	12.2 (7.5 – 20.2)	11.3 (6.6 – 17.5)	NA
Ferritin, ng/mL	951.0 (506.0 – 1589.0)	1013.5 (567.0 – 1842.5)	973.0 (532.0 – 1688.0)	NA

Characteristic	**Baricitinib** **n = 665**	**Tocilizumab** **n = 291**	**Total** **n = 956**	***P* value**
LDH, IU/L	506.0 (378.0 – 648.0)	589.0 (445.0 – 784.0)	521.0 (397.0 – 681.0)	NA
D-dimer, ng/mL	605.0 (330.0 – 1460.0)	656.0 (376.0 – 2810.0)	619.0 (341.0 – 2030.0)	NA
WBC, 10^9/L	10.5 (8.1 – 13.9)	11.1 (8.0 – 14.7)	10.7 (8.1 – 14.2)	NA
Absolute Lymphocyte Count, 10^9/L	0.6 (0.4 – 0.9)	0.6 (0.4 – 0.8)	0.6 (0.4 – 0.8)	NA
PCT, ng/mL	0.2 (0.1 – 0.4)	0.3 (0.1 – 0.6)	0.2 (0.1 – 0.4)	NA
ALT, IU/L	45.0 (28.0 – 71.0)	46.0 (28.0 – 76.0)	45.0 (28.0 – 71.0)	NA
AST, IU/L	55.0 (39.0 – 80.0)	61.0 (41.0 – 98.0)	57.0 (39.0 – 85.0)	NA
Hospital Admission to Drug Initiation (days), median (IQR)	2.0 (1.0 – 3.0)	1.0 (1.0 – 3.0)	NA	0.02
ICU at Baseline, n (%)	263 (39.6)	191 (65.6)	454 (0.47)	<0.01
Remdesivir, n (%)	563 (85.6)	249 (84.6)	812 (84.9)	0.72
Steroids, n (%)	658 (98.9)	291 (100.0)	949 (99.3)	0.08
Length of Therapy				
1 dose	NA	286	NA	NA
2 doses	NA	5	NA	NA
Days, median (IQR)	8.0 (5.0 – 13.0)	NA	NA	NA

ALT – alanine transaminase, AST – aspartate aminotransferase, BMI – body mass index, CRP – C-reactive protein, LDH – lactate dehydrogenase, WBC – white blood cell count, IQR – interquartile range

*Risk factors include: Age ≥ 65, BMI ≥ 30, pre-existing conditions.

**N for this data point differs from that listed in the column header.

Missing values – CRP 36%, Ferritin 19%, LDH 28%, D-dimer 40%, WBC 1%, Absolute lymphocyte count 2%, Procalcitonin 15%, ALT 0.5%, AST 0.5%

Appendix 1.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2, 3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5, 6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6, 7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6, 7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8, 9 Supplement
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8, Supplement
Bias	9	Describe any efforts to address potential sources of bias	9
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	15
		(*e*) Describe any sensitivity analyses	N/A

	Item No	Results	Page No
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	10
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders	10
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarize follow-up time (eg, average and total amount)	11, Table 3
Outcome data	15*	Report numbers of outcome events or summary measures over time	11, 12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	9, 10
Discussion			
Key results	18	Summarize key results with reference to study objectives	13, 14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15, 16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13, 14
Generalizability	21	Discuss the generalizability (external validity) of the study results	14, 15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	N/A

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Appendix 2. Data Points and Definitions

- Demographics
    - Age (years)
    - Sex
    - Body mass index (BMI)
- Vaccination status
    - Yes: completed a full primary series of COVID-19 vaccine(s)
    - No: no COVID-19 vaccines received, received only one dose of a two-dose primary COVID-19 vaccine series, or has not reached time required for full immunity after vaccination
- Pre-existing conditions
    - Limited to diabetes mellitus, essential hypertension, immunocompromised conditions, kidney disease, neurodevelopmental disorders, and sickle-cell disease
    - Determined by the presence of diagnosis codes in the electronic medical record. Manually reviewed for accuracy and to remove redundancies.
- Admit date
- Discharge date
- Hospital location (acute care vs ICU)
    - Highest level of care required on the day that treatment was initiated
- Symptom onset date, as reported by patient and documented in progress notes
- Treatment start date
- Treatment end date
- Number of doses of baricitinib or tocilizumab administered
- Level of respiratory support at treatment initiation and each day of therapy through day 14. If multiple types were used on a particular day, the highest level of support was documented.
- Ordinal scale at drug initiation and each day of therapy through day 14
    - Based on The National Institute of Allergy and Infectious Diseases ordinal scale
        - 8 = death
        - 7 = hospitalized, on MV or ECMO
        - 6 = hospitalized, on HF or NIV
        - 5 = hospitalized, on supplemental oxygen via nasal cannula
        - 4 = hospitalized, no supplemental oxygen but not ready for discharge
        - 3 = hospitalized, no supplemental oxygen, ready for discharge
        - 2 = ambulatory with limitation of activities
        - 1 = ambulatory with no limitation of activities
    - Patients with OS 1-4 were analyzed collectively
- Laboratory values
    - C-reactive protein (CRP), mg/dL
    - Ferritin, ng/mL
    - Lactate dehydrogenase (LDH), IU/L
    - D-dimer, ng/mL
    - White blood cells (WBC), 10^9/L

    - Absolute lymphocytes, 10^9/L
    - Procalcitonin (PCT), ng/mL
    - Alanine transaminase (ALT), IU/L
    - Aspartate (AST), IU/L
    - Glomerular filtration rate (GFR), mL/min/1.73m^2
- Concomitant medications of interest which included steroids and remdesivir
    - Non-dexamethasone steroids were converted to dexamethasone equivalents
- Amounts of concomitant medications received
- In-hospital mortality
- Incidence of adverse effects after initiation of baricitinib or tocilizumab
    - Limited to incidence of secondary infection, venous thromboembolism, hypersensitivity, gastro-intestinal perforation, acute kidney injury, or acute liver injury
    - Determined via clinician chart review
    - Secondary infections were determined via clinician chart review to avoid inclusion of potential colonizing bacteria and strictly empiric antibiotic use
    - Acute kidney injury was defined according to the RIFLE criteria and was assessed by review of glomerular filtration rate (GFR) on days 1, 5, 14, and 30, with day 1 being the date of therapy initiation
    - Acute liver injury was defined as AST or ALT increase to > 5 x ULN (>160 for AST, >165 for ALT) and was determined by review of AST and ALT in the same manner as GFR
- Hospital length of stay (LOS)
- ICU LOS