Risk factors for 30-day all-cause mortality in hospitalized patients with COVID-19 receiving immunomodulator therapy: a retrospective cohort study

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Introduction

- The case fatality rate of patients hospitalized with COVID-19 in the pre-vaccine era was estimated at 13-17% with higher rates in the critically ill (37-45%).[1,2]
- Attenuation of the inflammatory cascade has potential to reduce mortality.[3-5]
- Immunomodulators such as tocilizumab and baricitinib may be used for hospitalized patients with significant respiratory compromise (e.g. non-invasive ventilation, mechanical ventilation) and signs of systemic inflammation.[3-6]

Objective

- Primary outcome: evaluate risk factors for 30-day all-cause mortality in hospitalized patients with COVID-19 who received tocilizumab or baricitinib.

Methods

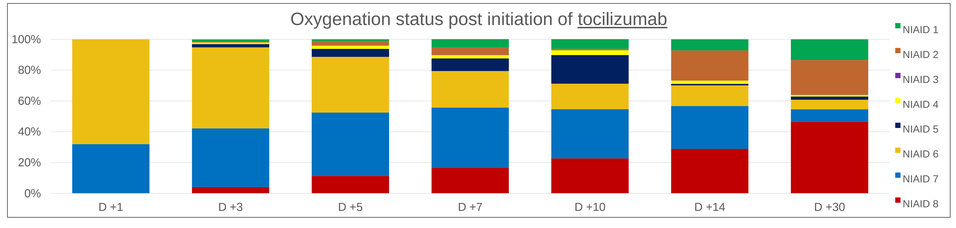
- An interprofessional healthcare team was assembled to create treatment guidelines for patients hospitalized with COVID-19.
- Recommendations were updated based on literature identifying mortality benefits; use of an immunomodulator was suggested for patients who met inflammatory and respiratory requirements.
- Retrospective cohort study evaluating outcomes in patients who received tocilizumab or baricitinib.
  - 30-day all-cause mortality was identified from start of immunomodulator therapy (start date = day 0).
- Inclusion
  - Adult patients (≥ 18 years old).
  - First 100 patients who received tocilizumab or baricitinib after guidelines were updated with use criteria.
- Exclusion
  - Transferred to another facility within 72 hours of initiation.
  - Received monoclonal antibody prior to admission.
- Patient demographics, comorbidities, laboratory results, and clinical management of COVID-19 were evaluated.
- Inferential statistics were used to analyze risk factors associated with 30-day all-cause mortality.
- Variables with p < 0.2 on univariate analysis were analyzed via multivariate logistic regression.

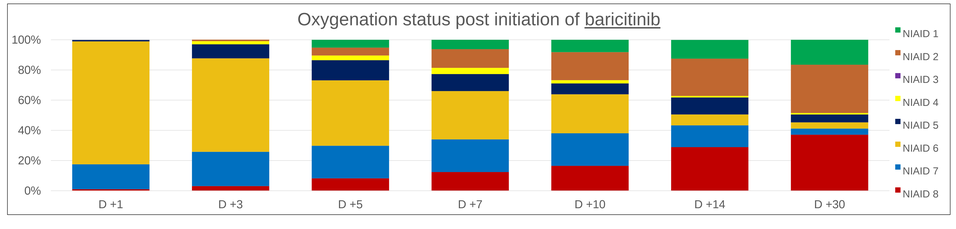
Results

Baseline Characteristics

	Tocilizumab[#] (n = 97)	Baricitinib[#] (n = 97)	p-value
Age; years	66 (57 – 72)	66 (51 – 72)	0.438
Gender; male	51 (52.6)	59 (60.8)	0.246
Received full treatment course of immunomodulator[%]	97 (100)	21 (21.7)	< 0.001*
Days of baricitinib use	---	8 (5 – 13)	---
Vaccine status			
Unvaccinated	83 (85.6)	77 (79.4)	0.257
Fully vaccinated[&]	4 (4.1)	19 (19.6)	0.001*
Partially vaccinated	10 (10.3)	1 (1.0)	0.01*
Oxygenation status at time of ordering immunomodulator			
Optiflow with oxygenation criteria[†]	41 (42.3)	44 (45.4)	0.664
BiPAP or CPAP with oxygenation criteria[†]	26 (26.8)	15 (15.5)	0.053
Mechanical ventilation	23 (23.7)	11 (11.3)	0.023*
Did not meet oxygenation requirements	7 (7.2)	27 (27.8)	< 0.001*
NIAID-OS at time of ordering immunomodulator[‡]			
OS-6	74 (76.3)	86 (88.7)	0.023*
OS-7	23 (23.7)	11 (11.3)	
CRP (mg/L) prior to start of immunomodulator	128 (92.2 – 159)	117 (86 – 174.6)	0.351
Received remdesivir	91 (93.8)	92 (94.9)	0.756
Received corticosteroids	97 (100)	97 (100)	----
Number of inpatient days of corticosteroids	11 (9 – 17)	11 (9 – 14)	0.430
Total amount of dexamethasone (equivalent) received (mg)	94 (73.8 – 146)	92 (66 – 132)	0.418
Average amount of dexamethasone (equivalent) received per day (mg)	8.2 (6.7 – 10.5)	8.4 (6.4 – 10)	0.860
Received convalescent plasma	48 (49.5)	2 (2.1)[#]	< 0.001*
Symptom onset to admission, days	7 (4 – 10)	7 (3 – 8)	0.032*
Admission to initiation of immunomodulator, days	2 (1 – 4)	2 (1 – 4)	0.389
Symptom onset to initiation of immunomodulator, days	10 (7 – 14)	8 (6 – 12)	0.172

Continuous variables are presented as median (IQR) and categorical variables as frequency (%). P-values for continuous variables: Wilcoxon rank-sum test. P-values for categorical variables: chi squared test or Fisher's exact test
* statistically significant
[#] tocilizumab data from February 23, 2021 through June 8, 2021; baricitinib data from August 26, 2021 through September 28, 2021, which coincided with data showing lack of efficacy of convalescent plasma
[%] local treatment algorithm recommended tocilizumab for ICU patients when both therapies were available. Full treatment course: tocilizumab: one time dose; baricitinib: up to 14 days or until discharge (whichever came first)
[&] > 14 days after receipt of dose 2 of mRNA COVID-19 vaccine or dose 1 of Janssen COVID-19 vaccine
[†] oxygenation criteria: Optiflow: > 30 L/min and $PaO_2/FiO_2 \leq 150$; BiPAP: $PaO_2/FiO_2 \leq 150$; CPAP: $PaO_2/FiO_2 \leq 150$
[‡] National Institute of Allergy and Infectious Diseases Ordinal Scale: OS-6: hospitalized, requiring non-invasive or high-flow oxygen; OS-7: hospitalized, requiring mechanical ventilation





30-day all-cause mortality outcome

	Tocilizumab	Baricitinib	p-value
Inpatient mortality	49 (50.5)	39 (40.2)	0.149
Mortality day +7 after initiation of immunomodulator	16 (16.5)	12 (12.4)	0.414
Mortality day +14 after initiation of immunomodulator	28 (28.9)	28 (28.9)	0.999
Mortality day +30 after initiation of immunomodulator	45 (46.4)	36 (37.1)	0.190

Univariate analysis of variables associated with 30-day all-cause mortality

Exposure variable	OR (95% CI)	p-value
Immunomodulator		
Baricitinib	Reference	Reference
Tocilizumab	1.5 (0.8 – 2.6)	0.190
Age (years)		
< 65	Reference	Reference
≥ 65	3.0 (1.7 – 5.5)	< 0.001
Vaccine status		
Unvaccinated	Reference	Reference
Partially vaccinated	0.5 (0.6 – 1.8)	0.262
Fully vaccinated	0.4 (0.2 – 1.2)	0.093
NIAID-OS at time of ordering immunomodulator		
OS-6	Reference	Reference
OS-7	3.1 (1.4 – 6.8)	0.004
Average amount of dexamethasone (equivalent) received per day (mg)	1.2 (1.1 – 1.3)	0.001

Multivariate analysis of variables associated with 30-day all-cause mortality

Exposure variable	OR (95% CI)	p-value
Immunomodulator		
Baricitinib	Reference	Reference
Tocilizumab	1.22 (0.62 – 2.4)	0.558
Age (years)		
< 65	Reference	Reference
≥ 65	3.51 (1.8 – 6.86)	< 0.001
Vaccine status		
Unvaccinated	Reference	Reference
Partially vaccinated	0.30 (0.07 – 1.30)	0.108
Fully vaccinated	0.32 (0.11 – 0.98)	0.047
NIAID-OS at time of ordering immunomodulator		
OS-6	Reference	Reference
OS-7	3.2 (1.34 – 7.62)	0.009
Higher average amount of dexamethasone (equivalent) received per day (mg)	1.15 (1.04 – 1.27)	0.005
Area under the receiver operator characteristic curve: 0.7401		

Conclusions

- In COVID-19 hospitalizations, age ≥ 65, mechanical ventilation (OS-7) at baseline, and higher daily dexamethasone doses were associated with 30-day all-cause mortality.
- Mortality was lower in patients fully vaccinated compared to those unvaccinated.
- Use of a specific immunomodulator did not impact mortality.

References

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