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European Journal of Internal Medicine 100 (2022) 137–139

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Letter to the Editor

Doubtful clinical benefit of casirivimab-imdevimab treatment for disease severity outcome of high-risk patients with SARS-CoV-2 delta variant infection

ARTICLE INFO

Keywords
Casirivimab/Imdevimab therapy
SARS-CoV-2 delta variant
High-risk patients
Severe outcome
BNT162b2 vaccine

To the editor,

The ongoing COVID-19 pandemic continues to be a global threat. Up to 10% of patients initially presenting with mild illness eventually progress to a severe disease, most of them have a least one comorbid condition [1]. REGEN-COV, a combination of 2 neutralizing monoclonal antibodies, Casirivimab and Imdevimab has been shown to reduce the viral load, shorten the symptoms duration, reduce the need for hospitalization and the risk of death in high-risk non-hospitalized patients [2]. Delta variant became a variant of concern by WHO on May 11, 2021 [3], but there are only sparse data [4] on Casirivimab / Imdevimab therapy clinical benefit against the Delta variant and specifically with respect to its effect among vaccinated patients [4]. Bierle et al [4]. found monoclonal antibody treatment to be associated with reduced hospitalization in vaccinated high-risk persons with mild-to moderate COVID-19. However, their study was not focused on the Delta variant. We aimed to assess the "real-life" contribution of Casirivimab/Imdevimab therapy in preventing severe disease outcome, defined as either room air saturation <93% within 14 days of initial presentation or 45-day all-cause mortality [5], in high-risk patients with SARS-CoV-2 Delta variant infection, and to compare that effect between vaccinated and unvaccinated patients.

After receiving an approval from the institutional research ethics board, we conducted a retrospective cohort study at the emergency department (ED) of a tertiary university-affiliated medical center between June 1, 2021 and September 31, 2021. Included were all patients who presented with a positive PCR for SARS-CoV-2 to the ED or were identified as being positive while hospitalized for a non-COVID-19 indication. All of the study participants fulfilled the criteria for receiving Casirivimab/Imdevimab treatment, based upon the FDA (EUA) guidelines [6]:

1 A positive PCR for SAR-COV-2 within 10 days of presentation.
2 High-risk factors for developing severe COVID-19 infection, defined as one of the following criteria (16): age >65 years, age >55 years with a chronic heart condition (including ischemic heart disease, chronic dysrhythmias, heart failure, and valves and structural illness) or a pulmonary disease (defined as chronic obstructive pulmonary disease or heavy smoking over 10 pack years), and older than 12 years of age with any of the following: diabetes mellitus, chronic kidney disease, morbid obesity (defined as body mass index ≥35), being severely immunocompromised (organ transplant patients, bone marrow transplant patients, hematologic malignancy, patients receiving anti-CD20 or Fingolimod, congenital immunodeficiency and acquired immunodeficiency, including HIV with a CD4 count <300), pregnancy patients and those with liver failure.

Patients who were diagnosed with severe COVID-19 infection already at initial presentation (room air saturation <93%) were excluded.

Age, sex, medical history, immunization status (vaccinated patients were defined as those who received at least 2 doses of the BNT162b2 vaccine), Covid-19 related details, vital signs, physical examination, abnormal chest x ray findings (defined as consolidation, ground glass opacities, or nodules, and severe findings defined as those occupying >50% of the lung field) laboratory results, including SARS-CoV-2 IgG antibodies titers (in U/ml), treatment, including Casirivimab/Imdevimab administration as well as implementation of an O2 cannula, non-invasive high flow respiratory support system, or an invasive ventilation and disposition were extracted.

Therapy consisted of a single parenteral injection of 1200 mg Casirivimab and 1200 mg Imdevimab. Patient selection was based upon the clinical decision of both the ED physician and the infection disease specialist, and with the patient's agreement.

The study is reported according to the STROBE guideline. Data entry and analysis were performed with SPSS Statistics, version 26 (SPSS Inc, Chicago, IL). A *P*-value <0.05 was considered statistically significant.

Three-hundred and fifty-nine patients (189 females, 52.6%) were included in the final cohort, with a median age of 63 years (IQR 41.0-75.0), of them, 116 were treated with Casirivimab/Imdevimab ("cases") and 243 were not ("controls"). Two-hundred and three patients (56.5%) received at least 2 doses of COVID-19 vaccine and 57 of them were vaccinated with a 3rd dose. Significantly more patients in the treatment group had a severe outcome (20.7% vs. 10.7%, $P = 0.01$). The patients who were treated with Casirivimab/Imdevimab, compared to

https://doi.org/10.1016/j.ejim.2022.03.001
Received 22 February 2022; Accepted 1 March 2022
Available online 14 March 2022

those who were not, were significantly older (62.2 ± 18.3 years vs. 57.6 ± 22.2 years, $P = 0.03$), had higher rates of immunosuppressive disorders (48.3% vs 24.0%, $P < 0.001$), lower room air saturation levels, albeit within the normal range (95.9% ± 2.9% vs. 96.9% ± 2.1%, $P < 0.01$) and higher rates of abnormal findings on chest x-rays (57.3% vs. 41.2%, $P = 0.02$).

In a secondary analysis of the subgroup of 116 patients who were treated with Casirivimab/Imdevimab, there were no significant differences in the occurrence of severe outcome between those who were vaccinated and those who were not (45.8% vs. 54.3%, $P = 0.49$), nor between those who received the 3rd dose of vaccine and those who did not (12.5% and 15.2%, $P > 0.99$). In addition, no significant difference was observed in the occurrence of severe outcome between seronegative (IgG levels <1 U/ml) and seropositive (IgG levels ≥1 U/ml) patients (24.1% vs. 17.1%, $P = 0.55$) and no significant correlation was found between antibody titers and severe outcome (Spearman correlation 0.04, $P = 0.73$).

Fifty patients had a severe outcome: 7 patients died within 45 days from their initial presentation and 48 had room air saturation <93% within 14 days from their initial presentation. Patients with a severe outcome were significantly older (68.7 ± 19.6 years vs.57.5 ± 20.9 years, $P < 0.001$) and higher rates of the severe outcome group had chronic kidney disease (24.0% vs. 8.1%, $P < 0.001$). Patients in the severe outcome group had significantly higher mean number of days from symptom onset (4.7 ± 3.2 vs. 3.7 ± 2.6, $P = 0.01$), significantly lower mean room air saturation values (94.4 ± 3.5 % vs. 96.9 ± 2.0%, $P < 0.001$), and significantly higher mean body temperature values (37.6 ± 0.9°C vs. 37.3 ± 0.7°C, $P = 0.008$). The neutrophil/lymphocytes ratio and the CRP levels were significantly higher for the severe outcome group (7.0 ± 7.6 vs. 4.9 ± 5.8, $P = 0.03$ and 73.7 ± 57.0 mg/dl vs. 36.3 ± 45.3 mg/dl, $P < 0.001$, respectively), along with abnormal chest- x ray findings at the presentation (77.8% vs. 39.6%, $P < 0.001$). (Table 1).

Independent predictors for severe outcome: factors with significance level of $P < 0.15$ in the univariable analysis (Table 1) and those considered as either risk or protective factors for severe disease outcome were inserted into a multi-regression analysis. Chronic kidney disease (aOR = 3.51 [95% CI: 1.34-9.20], $P = 0.01$), lower saturation (aOR = 0.7 [95% CI: 0.58–0.85], $P < 0.01$), and higher CRP levels (aOR = 1.01 [95% CI: 1.00 – 1.01], $P = 0.008$) emerged as independent risk factors of severe outcome. Positive immunization status was found to be an independent protective factor of severe outcome (aOR = 0.33 [95% CI: 0.14–0.77], $P = 0.01$).

In contrast to previous report (18), Casirivimab/Imdevimab treatment was not found to be an independent protective factor for severe outcome (aOR = 1.54 [95% CI: 0.71–3.34], $P = 0.26$).

Moreover, it had a significant association with severe disease outcome in the univariable analysis.

Several factors may explain our observation. First, our sub-analysis revealed that patients who were treated with Casirivimab/Imdevimab had higher rates of immunosuppressive conditions, which had been reported to be associated with a higher likelihood of hospitalization following monoclonal antibody treatment (7). Moreover, the COVID-19 mRNA vaccine, that was found to be an independent protective factor of severe outcome in our study, have lower effectiveness among immunocompromised patients compared to immunocompetent controls and the ability of the former to develop high neutralizing antibody titers and to be protected against severe COVID-19 outcomes were limited compared to the latter (8). These observations may partially explain the higher rates of severe outcome among patients who received Casirivimab/Imdevimab treatment, compared to those who were not, in our cohort.

We, as others (7), found chronic kidney disease to be an independent risk factor for severe disease outcome. The high prevalence of comorbidities in patients with chronic kidney disease, such as hypertension, cardiovascular disease, and diabetes mellitus, might contribute to the poorer outcomes among those COVID-19 patients.

Table 1
Comparison of epidemiological and clinical characteristics of patients with and without severe disease outcome.

P value	Severe disease outcome ($n = 50$) (N, %)	No severe disease outcome($n = 309$) (N, %)	Characteristic
<0.001	68.7 ± 19.6	57.5 ± 20.9	Age (mean±SD)
0.53	23 (46.0)	167 (53.8)	Sex (female)
			Vaccination status
0.18	26 (55.3)	183 (66.3)	At least one dose
0.12	23 (46.0)	180 (58.3)	≥2 doses
0.53	6 (12.0)	51 (16.5)	3 doses
>0.99	2 (4.2)	10 (3.7)	Recovered
			Risk factors
0.11	17 (34.0)	72 (23.3)	Heart disease
>0.99	8 (16.0)	51 (16.6)	Lung disease
0.05	19 (38.0)	74 (23.9)	Diabetes Mellitus
0.002	12 (24.0)	25 (8.1)	Chronic kidney disease
0.62	14 (28.0)	100 (32.5)	Immunosuppression
0.44	3 (6.0)	32 (10.4)	Pregnancy
0.01	4.7 ± 3.2	3.7 ± 2.6	Days from symptoms onset
0.40	3.0 ± 2.9	2.7 ± 2.6	(mean±SD)
			Days from positive PCR (mean±SD)
0.64	38 (84.4)	266 (86.9)	Symptoms
			Vital signs (mean±SD)
0.06	91.0 ± 13.4	84.1 ± 16.7	Pulse (bpm)
<0.001	94.4 ± 3.5	96.9 ± 2.0	Saturation (%)
0.46	134.4 ± 21.3	132.0 ± 20.8	Systolic Blood Pressure (mmHg)
0.48	73.4 ± 13.1	74.8 ± 12.4	Diastolic Blood Pressure (mmHg)
0.008	37.6 ± 0.9	37.3 ± 0.7	Body temperature (Celsius)
			Laboratory results (mean ±SD)
0.23	9.5 ± 13.8	7.6 ± 9.2	WBC (K/uL)
0.03	7.0 ± 7.6	4.9 ± 5.8	Neutrophil/lymphocytes ratio
<0.001	73.7 ± 57.0	36.3 ± 45.3	CRP (mg/dL)
<0.001	35 (77.8)	80 (39.6)	CXR positive findings at presentation
0.01	24 (48.0)	92 (29.8)	Casirivimab/Imdevimab treatment (yes)
			Other treatment during hospital stay
<0.001	31 (62.0)	24 (7.8)	Anticoagulation
<0.001	16 (34.8)	39 (12.5)	Steroids
<0.001	13 (26.0)	20 (6.5)	Abx
0.01	6.6 ± 6.7	3.7 ± 6.3	LOS (days) (mean±SD)

Greater disease severity was found to be associated with older age in a series of analyses (9). Although age was significantly higher in our severe disease outcome group in the univariable analysis, it was not an independent predictor for severe disease outcome in the multi-regression model, potentially due to co-factors such as chronic diseases. It should be borne in mind that our patients were selected by either older age or chronic disease and that our cohort already represents a high-risk group for severe disease outcome, and that our findings should be interpreted accordingly.

A recent study found that Casrivimab/Imdevinab lost its antiviral activity against the Omicron variant, which quickly became the dominant variant (10). These data, taken together with our results, raise some doubt about the benefit of Casrivimab/Imdevinab for treating new SARS-CoV-2 variants.

To conclude, we found no added benefit to the administration of Casrivimab/Imdevinab monoclonal antibody therapy to a mostly vaccinated high-risk population with an early delta variant of SARS-COVID-19 infection. Additional studies of new variants in the vaccination era are needed to explore the effect of monoclonal antibody therapy on the severity of disease outcome.

Appendix

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Funding

None.

Ethics approval

Approval for this study was obtained from our institutional research ethics board: 0615-21-TLV.

CRediT authorship contribution statement

Noah Shopen: Conceptualization, Visualization, Data collection, Writing – original draft. **Michal Dekel:** Conceptualization, Visualization, Data collection, Writing – original draft. **Michal Mizrahi:** Conceptualization, Visualization, Data collection. **Daniel Talmud:** Conceptualization, Visualization, Data collection. **Neta Cohen:** Conceptualization, Visualization, Data collection, Formal analysis, Data curation, Writing – original draft.

Declaration of Competing Interest

The authors have no conflict of interests to disclose.

References

[1] Docherty AB, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO clinical characterization protocol: prospective observational cohort study. BMJ 2020;369:m1985.
[2] Weinreich DM, Sivapalasingam S, Norton T, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. N Engl J Med 2021;384:238–51.
[3] He X, He C, Hong W, Zhang K, Wei X. The challenges of COVID-19 Delta variant: Prevention and vaccine development [published online ahead of print, 2021 Oct 19] MedComm 2020;2(4):846–54. https://doi.org/10.1002/mco2.95. 2021.
[4] Bierle DM, Ganesh R, Tulledge-Scheitel S, et al. Monoclonal antibody treatment of breakthrough COVID-19 in fully vaccinated individuals with high-risk comorbidities [published online ahead of print, 2021 Nov 16] J Infect Dis 2021:jiab570. https://doi.org/10.1093/infdis/jiab570.
[5] Recovery Collaborative Group, Horby PW, Mafham M, Peto L, et al. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. medRxiv 2021:21258542. 06.15.
[6] An EUA for bamlanivimab-a monoclonal antibody for COVID-19. JAMA 2021;325:880–1.
[7] Ganesh R, Philpot LM, Bierle DM, et al. Real-world clinical outcomes of bamlanivimab and casirivimab-imdevimab among high-risk patients with mild to moderate coronavirus disease 2019. J Infect Dis 2021;224(8):1278–86. https://doi.org/10.1093/infdis/jiab377.
[8] Mair MJ, Berger JM, Berghoff AS, Starzer AM, Ortmayr G, Puhr HC, et al. Humoral immune response in hematooncological patients and health care workers who received SARS-CoV-2 vaccinations. JAMA Oncol 2021:1–8.
[9] Gao YD, et al. Risk factors for severe and critically Ill COVID-19 patients: a review. Allergy 2021;76(2):428–55 (Copenhagen)Web.
[10] Planas D, Saunders N, Maes P, Guivel-Benhassine F, Planchais C, Buchrieser J, et al. Considerable escape of SARS-CoV-2 variant Omicron to antibody neutralization. bioRxiv 2021:472630. https://doi.org/10.1101/2021.12.14.472630. .12.14.

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