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Clinical and Virological Outcome of Monoclonal Antibody Therapies Across Severe Acute Respiratory Syndrome Coronavirus 2 Variants in 245 Immunocompromised Patients: A Multicenter Prospective Cohort Study

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Background. Immunocompromised patients (ICPs) have an increased risk for a severe and prolonged COVID-19. SARS-CoV-2 monoclonal antibodies (mAbs) were extensively used in these patients, but data from randomized trials that focus on ICPs are lacking. We evaluated the clinical and virological outcome of COVID-19 in ICPs treated with mAbs across SARS-CoV-2 variants.

Methods. In this multicenter prospective cohort study, we enrolled B-cell– and/or T-cell–deficient patients treated with casirivimab/imdevimab, sotrovimab, or tixagevimab/cilgavimab. SARS-CoV-2 RNA was quantified and sequenced weekly, and time to viral clearance, viral genome mutations, hospitalization, and death rates were registered.

Results. Two hundred and forty five patients infected with the Delta (50%) or Omicron BA.1, 2, or 5 (50%) variant were enrolled. Sixty-seven percent were vaccinated; 78 treated as outpatients, of whom 2 required hospital admission, but both survived. Of the 159 patients hospitalized at time of treatment, 43 (27%) required mechanical ventilation or died. The median time to viral clearance was 14 days (interquartile range, 7–22); however, it took >30 days in 15%. Resistance-associated spike mutations emerged in 9 patients in whom the median time to viral clearance was 63 days (95% confidence interval, 57–69; $P < .001$). Spike mutations were observed in 1 of 42 (2.4%) patients after treatment with 2 active mAbs, in 5 of 34 (14.7%) treated with actual monotherapy (sotrovimab), and 3 of 20 (12%) treated with functional monotherapy (ie, tixagevimab/cilgavimab against tixagevimab-resistant variant).

Conclusions. Despite treatment with mAbs, morbidity and mortality of COVID-19 in ICPs remained substantial. Combination antiviral therapy should be further explored and may be preferred in severely ICPs.

Keywords. SARS-CoV-2; monoclonal antibodies; immunocompromised; spike mutations.

Three and a half years into the coronavirus disease 2019 (COVID-19) pandemic, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to evolve genetically. The majority of mutations observed in SARS-CoV-2 are located in the gene that encodes for the spike (S) protein. This ongoing viral evolution has resulted in variants of concern (VOCs) that are more transmissible (eg, Alpha, Delta, and Gamma) and/or show a reduced susceptibility to the neutralizing activity of vaccine-induced or infection-induced antibodies (eg, Beta and Omicron). Moreover, the current dominant variants (eg, XBB and its derivatives) are resistant to all of the approved monoclonal antibody (mAb) therapies [1]. Even antibodies induced by the bivalent booster vaccine (D614G/Omicron BA.1/BA.5) have at least partially lost their neutralizing potential [2].

Immunocompromised patients (ICPs) with COVID-19 have an increased risk for a more severe and prolonged disease course [3]. The inadequate or delayed immune response after infection or even vaccination allows SARS-CoV-2 to replicate longer, sometimes for months[3–6]. In a large prospective cohort of 2204 ICPs, vaccination generated no or very low

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concentrations of spike antibodies in 39% [7]. The delayed clearance of infection in ICPs is hypothesized to facilitate viral evolution and occurrence of S protein mutations, the key target of neutralizing antibodies [4]. In an attempt to prevent progression to severe disease and mortality, antibody-based therapies such as convalescent plasma and mAbs were extensively used in ICPs. Viral evolution in ICPs has been demonstrated in case reports and small case series during treatment with convalescent plasma [8–12]. More recently, mutations in the S protein were described after treatment of ICPs with essentially all of the available mAbs [13–18].

A systematic evaluation of the effectiveness of mAb-based therapy in ICPs with COVID-19 is missing, particularly when these therapies are used in hospitalized ICPs. In this study, we evaluated the clinical outcome, viral clearance, and incidence of resistance-associated mutations that emerged during therapy in a cohort of 245 ICPs with COVID-19 treated with casirivimab/imdevimab, sotrovimab, and tixagevimab/cilgavimab.

METHODS

Setting and COVID-19 Treatment

We conducted a multicenter prospective cohort study at 5 hospitals in the Netherlands (Supplementary Methods 1). Erasmus Medical Center (EMC) acted as the sponsor and coordinator. The institutional review board determined that the study did not fall under the Dutch law on the Medical Research Involving Human Subjects Act. Patients who declined the use of their medical data for research purposes were excluded. Data were collected in accordance with the European General Data Protection Regulation (GDPR) and The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use and Good Clinical Practice regulation (ICH-GCP).

ICPs were followed longitudinally until full recovery from COVID-19. They were recruited during dominance of the Delta and Omicron variants in the Netherlands, when these strains were still sensitive to at least 1 of the available mAbs. The Dutch COVID-19 guideline allowed the off-label use of mAbs for the treatment of hospitalized COVID-19 ICPs and also allowed use outside the window of 7 days after symptom onset. The off-label use of sotrovimab and tixagevimab/cilgavimab in hospitalized patients was based on and therefore extrapolated from the reduced mortality that was observed in the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial on casirivimab/imdevimab in hospitalized SARS-CoV-2 spike antibody-negative patients [19]. See Supplementary Methods 2 for more information on local protocols for mAbs.

Data Collection

Clinical data regarding demographics, medical history, vaccination, immune status, biochemistry, treatment, hospitalization, clinical recovery, and survival were collected. SARS-CoV-2 antibodies were quantified using the LIAISON SARS-CoV-2 TrimericS immunoglobulin G assay (DiaSorin), reported in binding antibody units per milliliter. Key dates included the first positive SARS-CoV-2 polymerase chain reaction (PCR) test and mAb treatment. Virological data (cycle threshold [Ct] values and sequencing results) were only available for patients included at EMC. Data were collected using the online data capture program Castor.

Diagnostic Follow-up

The EMC COVID-19 treatment protocol explicitly recommended weekly monitoring of all ICPs treated with mAbs with a SARS-CoV-2 PCR. Until January 2022, PCR tests were performed on the COBAS 6800 system (Roche Diagnostics), which reported Ct values for the *E gene* as a proxy indicator for viral load. Monitoring was halted when the Ct value was ≥30, preferably on 2 consecutive occasions. From January 2022 until the end of the study, PCR tests were performed on the Hologic Panther (non-Fusion) Aptima platform, which reported viral load in international units per milliliter. Follow-up was halted when the viral load was lower than 4×10^4 IU/ mL, as this correlates with a Ct value ≥30 and negative viral cultures [20]. Therefore, a patient with a negative PCR test or a Ct value ≥30 was considered to have cleared the virus [21]. Sequencing was performed as previously described [22–24]. All sequences are available in the Global Initiative on Sharing All Influenza Data (GISAID) database, and the raw sequence data are available on the European Nucleotide Archive. More information on sequencing methods and the accession numbers of the sequence data are provided in Supplementary Methods 3.

Outcomes

We evaluated hospitalization rates for patients treated as outpatients and duration of hospital stay for those treated during hospitalization, intensive care unit (ICU) admission rate and duration, mode and oxygen flow rate, clinical recovery (disappearance of COVID-19–related symptoms), and mortality within 30 days. Full recovery was defined as disappearance of COVID-19–related symptoms in combination with viral clearance. These data were only available for patients included at EMC, as other centers did not perform a weekly PCR test once patients had recovered clinically. In patients with a Ct value <30 or viral load $>4 \times 10^4$ IU/mL at baseline, time to viral clearance was calculated after administration of the mAb.

When sequencing at any time after treatment was successful, nonsynonymous mutations in the S gene preceding and following mAb treatment were investigated next to mutations in the rest of the genome. The observed amino acid changes in the S protein were compared with mutations associated with antibody immune escape (decreased neutralizing activity) from polyclonal and mAbs derived from the Coronavirus Antiviral

& Resistance Database at Stanford University [25]. More information on how the proportion of patients with resistance-associated mutations was calculated can be found in Supplementary Methods 4.

Statistical Analyses

Statistical analyses were performed with SPSS (IBM SPSS Statistics for Windows, Version 28.0, IBM Corp, Armonk, NY) and R (Version 4.2.2). Baseline characteristics were reported as counts and percentages for categorical variables and as a median with quartiles (interquartile range [IQR]) for continuous variables. Frequencies and percentages for sequencing data were reported. We created Kaplan–Meier curves and performed a log-rank test with viral clearance as outcome based on the presence of relevant mutations known to confer a reduced neutralization capacity of the mAbs as independent variable. Statistical analyses were explorative, and no formal power calculation was performed for determination of outcome effects. Statistical tests were done 2-sided.

RESULTS

Baseline Characteristics

Baseline characteristics (Table 1) for the 245 ICPs included between July 2021 and November 2022 were analyzed. Casirivimab/imdevimab was administered to 142 (58%), sotrovimab to 67 (27%), and tixagevimab/cilgavimab to 36 (15%) patients. Median age was 61 years (IQR, 51–69), and 56% were male. Most patients had a solid organ transplant or a hematological malignancy. Detailed information on the type of immunosuppressive medication was available for 205 patients and is shown in Table 1. B-cell–depleting therapy (eg, rituximab) was administered to 75 (31%) patients. A total of 164 (67%) patients received at least 2 vaccinations at the time of treatment, and 104 (42%) received at least 3. In the 202 patients in whom spike antibodies were measured prior to mAb treatment, 146 (72%) were antibody-negative. Median time from COVID-19 symptom onset to mAb treatment was 6 days (IQR, 3–13). In total, 167 (68%) patients were treated as inpatients, and all but 8 were hospitalized because of COVID-19.

Clinical Outcome

Of the 245 patients included, complete data on clinical recovery within 30 days were available for 225 (92%); 152 (62%) had recovered and 38 (16%) had died. Seventy-eight (32%) patients received mAbs in an ambulatory setting, of whom only 2 required hospital admission for worsening of COVID-19–related symptoms.

Among the 159 patients already hospitalized for COVID-19 at the time of treatment, the median duration of hospital stay was 8 days (IQR, 4–16), with 21(13%) requiring ICU admission. Eleven of 68 (16%) patients hospitalized for COVID-19 and infected with an Omicron variant died within 90 days after treatment. More information on outcomes can be found in Supplementary Data 5, Supplementary Table 1.

Viral Clearance

Data on viral clearance were available for 202 of the 245 patients. Within this subgroup, viral clearance could be documented in 155 of 202 (77%). Seventy-seven were treated with casirivimab/imdevimab, 55 with sotrovimab, and 23 with tixagevimab/cilgavimab. Median time to viral clearance was 14 days (IQR, 7–22). Within the 30-day timeframe, 132 of 155 (85%) patients cleared the virus; 71 of 77 (92%) and 48 of 55 (87%) were treated with casirivimab/imdevimab or sotrovimab, respectively. In contrast, only 13 of 23 (57%) patients treated with tixagevimab/cilgavimab cleared the virus within 30 days of treatment. Eighteen (9%) patients died before viral clearance could be documented.

Of the 152 patients with a clinical recovery within 30 days, data regarding viral clearance were available for 114; the 38 remaining patients were treated outside EMC. Full recovery within 30 days was documented in 108 of 114 (95%) patients (Supplementary Data 5, Supplementary Table 1).

Time-to-event analysis on all patients with at least 1 attempt to sequence the virus post-treatment showed a median duration to viral clearance of 16 days (95% confidence interval [CI], 13–19) versus 63 days (95% CI, 57–69) in patients without and with resistance-associated spike mutations, respectively ($P < .001$; Figure 1). Figure 2 illustrates the time to viral clearance of patients treated with sotrovimab or tixagevimab/cilgavimab depending on their mutational status. An overview of time to viral clearance for casirivimab/imdevimab can be found in Supplementary Data 6 and Supplementary Figure 1.

Sequencing Data and Mutational Analysis

SARS-CoV-2 was sequenced in 162 of 202 (80%) patients and was successful in 133 (82%) before and/or after treatment (Table 2, Supplementary Data 7, Supplementary Table 2). In 83 patients, decreasing viral loads precluded successful sequencing after treatment; in 49 patients, sequencing was successful in at least 1 sample after treatment. Sixty-six patients were infected with the Delta variant, and all were treated with casirivimab/imdevimab. Omicron BA.1 was found in 29, of whom 26 were treated with sotrovimab and 3 with casirivimab/imdevimab. Omicron BA.2 was detected in 12, of whom 7 were treated with sotrovimab and 5 with tixagevimab/cilgavimab. A total of 26 patients were treated with tixagevimab/cilgavimab, of whom 20 were infected with Omicron BA.5, 4 with BF.7, and 1 with BQ.1 and BE.1.1 each. More detailed information on the exact variants that were sequenced can be found in Supplementary Data 8 and Supplementary Table 3.

Mutations in the S protein were found in 12 of 49 patients in whom sequencing was successful after mAb treatment, while mutations known to be associated with a significant increase

Table 1. Baseline Characteristics

Characteristic	Total (N = 245)	Casirivimab/ Imdevimab (n = 142)[e]	Sotrovimab (n = 67)	Tixagevimab/ Cilgavimab (n = 36)
Age (years), median (IQR)	61 (51–69)	61 (51–71)	61 (50–67)	65 (55–73)
Male, no. (%)	138 (56)	80 (56)	36 (54)	22 (61)
Immunocompromised state due to, no. (%)				
SOTx[a]	120 (49)	63 (44)	42 (63)	15 (42)
Hematological malignancy[b]	61 (25)	33 (23)	12 (18)	16 (44)
Autoimmune disease	44 (18)	27 (19)	13 (19)	4 (11)
Hematopoietic stem cell transplant[b]	15 (6)	6 (4)	3 (5)	6 (17)
Solid organ malignancy	7 (3)	5 (4)	1 (2)	1 (3)
Other[c]	26 (11)	19 (13)	3 (4)	4 (11)
Number of comorbidities, median (IQR)	2 (1–3)	1 (0–2)	2 (1–3)	1 (1–2)
Vaccination, no. (%)				
Unknown	39 (16)	20 (14)	6 (9)	13 (36)
No/incomplete vaccination	42 (17)	34 (24)	6 (9)	2 (6)
Complete vaccination series	60 (24)	51 (36)	7 (10)	2 (6)
Complete vaccination + ≥1 booster	104 (42)	37 (26)	48 (72)	19 (53)
B-cell–depleting therapy (eg, rituximab), no. (%)	75 (31)	45 (32)	20 (30)	10 (28)
T-cell–depleting therapy (eg, alemtuzumab), no. (%)	17 (7)	17 (12)	0 (0)	0 (0)
Immunosuppression for SOTx, no. (%)				
Single/duo therapy	54/118 (46)	35/61 (57)	12/42 (29)	7/15 (47)
Triple therapy	64/118 (54)	26/61 (43)	30/42 (72)	8/15 (53)
Antibody severe acute respiratory syndrome coronavirus 2 immunoglobulin G titer prior monoclonal antibody, no. (%)				
Negative or <300 BAU/mL	171 (69)	119 (84)	40 (60)	12 (33)
Positive (≥300 BAU/mL)	13 (5)	0 (0)	10 (15)	3 (8)
Positive, titer unknown	18 (7%)	18 (13%)	0 (0%)	0 (0%)
Unknown	43 (18%)	5 (4%)	17 (25%)	21 (58%)
Laboratory findings, median (IQR)				
Lymphocyte (10^9/L)	0.66 (0.34–1.37)	0.68 (0.40–1.28)	1.14 (0.45–1.50)	0.31 (0.18–1.00)
C-reactive protein (mg/L)	49 (15–105)	49 (12–94)	34 (13–86)	104 (62–177)
Ferritin (µg/L)	366 (134–795)	354 (132–761)	326 (123–981)	794 (521–928)
D-dimers (g/L)	1.23 (0.62–2.65)	1.02 (0.62–2.87)	1.47 (0.68–2.60)	2.24 (0.5–4.13)
Time from first symptoms to monoclonal antibody treatment (days), median (IQR)	6 (3–13)	7 (4–13)	7 (3–13)	10 (3–12)
Treatment in outpatient setting, no. (%)[d]	78 (32)	50 (35)	21 (31)	7 (19)
Admission after outpatient treatment, no. (%)	2 (1%)	1 (1%)	0	1 (3%)

Abbreviations: HM, hematological malignancy; IQR, interquartile range; SOTx, solid organs transplant.

[a]A total of 62 patients received a kidney transplant, 47 received a lung transplant, 3 received a liver transplant, 5 received a heart transplant, and 3 received more than 1 donor organ (2 received lung + kidney, 1 received heart + kidney).

[b]HM is only reported if an active HM was present in the last 5 years prior to inclusion. Only allogeneic stem cell transplantations were registered.

[c]Other diseases included common variable immune disorder (n = 8), hypogammaglobulinemia (n = 6), AIDS (n = 6), Castleman disease (n = 1), and not specified (n = 5).

[d]Seven patients were hospitalized for reasons other than coronavirus disease 2019 infection but were treated in the hospital with monoclonal antibodies.

[e]There were 47, 61, and 29 patients who received 8000 mg, 2400 mg, and 1200 mg, respectively; dose was unknown in 5 patients.

in the inhibitory concentration were found in 9 [25]. A visual representation of the changes in the viral genome can be found in Supplementary Data 9, Supplementary Figure 2 (spike protein), and Supplementary Figures 3 and 4 (the remainder of the genome). Clinical information on these patients can be found in Supplementary Data 10 and Supplementary Table 4. In patients treated with casirivimab/imdevimab, sequencing after treatment was precluded by a low viral load in 53 patients, while 14 were successfully sequenced. In 1 of these patients, resistance-associated mutations (RAMs) were found (G446V and E484Q). RAMs were found in 6 of 21 patients after treatment with sotrovimab. However, because the mutation was already present before treatment in 1 patient, it did not emerge during therapy. These mutations were most frequently situated at position 337 or 340, both in Omicron BA.1 and BA.2. In 3 of 14 patients, mutations were found after treatment with tixagevimab/cilgavimab, all at position 444. The incidence of mutations in all patients with a sequencing attempt after treatment (whether successful or not) is listed in Table 2. Although the time to viral clearance in these patients was significantly longer (see below and Figures 1 and 2), no patients with mutations in the S protein died during follow-up.

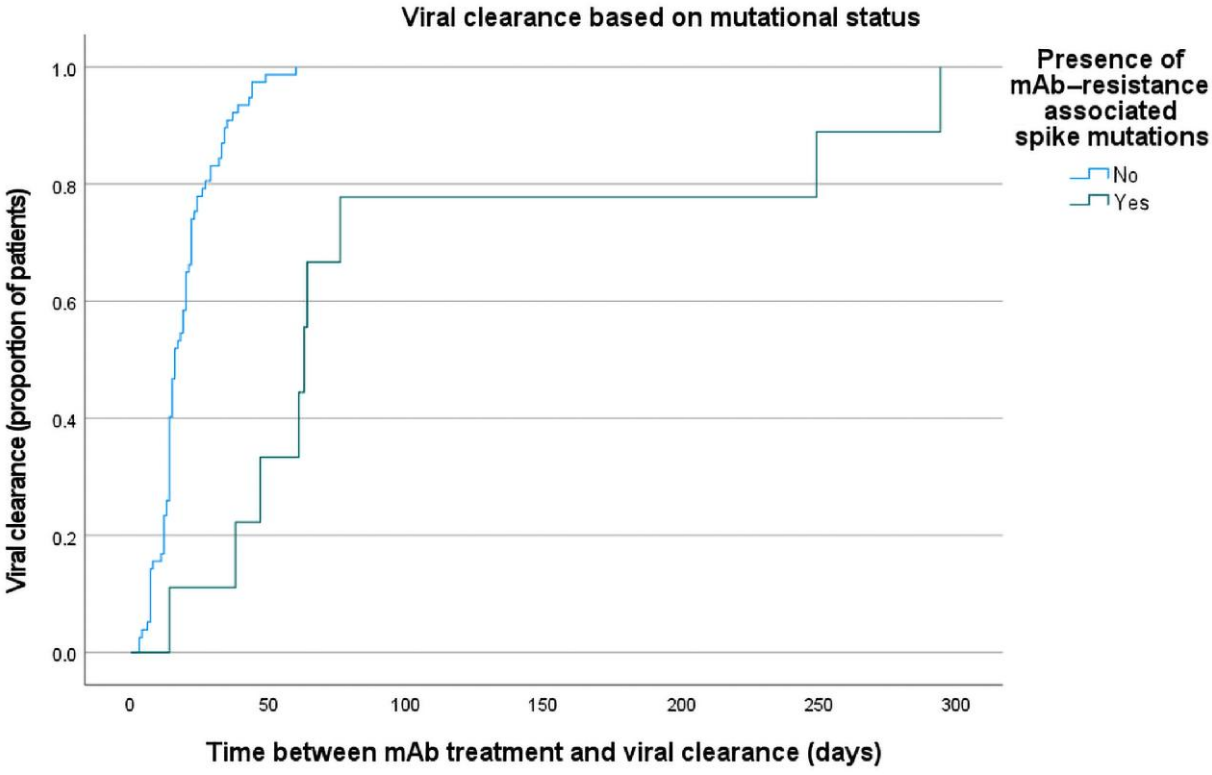

Figure 1. Survival analysis for viral clearance based on the presence of mAb resistance–associated mutations. This figure represents a Kaplan–Meier curve. The *x*-axis represents the time after the day of administration of mAbs. The *y*-axis represents the proportion of patients in whom viral clearance occurred (PCR Ct value ≥30). The blue line represents the patients in whom no resistance-associated spike mutations were found during sequencing. The green line represents patients in whom resistance-associated mutations were found after treatment with mAbs. Abbreviation: mAb, monoclonal antibody.

DISCUSSION

In this cohort of 245 ICPs with COVID-19, 3 mAb therapies were used during dominance of 4 subsequent VOCs. Overall, we observed that spike protein mutations emerged more frequently if patients were treated with only 1 active mAb against the VOC. Despite administration of mAbs, mortality remained substantial in patients who were treated after hospital admission.

Sequencing was successfully attempted in 133 of 162 patients, and RAMs were found in 9 patients post-treatment. A striking observation was that RAMs emerged after treatment in only 1 of 42 (2%) patients treated with 2 fully active mAbs. This contrasts sharply with RAMs observed in 8 of 54 (14%) patients treated with functional or actual monotherapy. Despite the very extensive use of casirivimab/imdevimab worldwide, very few cases in which RAMs were detected after treatment have been published, and we are unaware of cases in which RAMs led to complete loss of casirivimab/imdevimab activity [17]. In a recent systematic review, RAMs were less frequently reported in casirivimab/imdevimab compared with sotrovimab and tixagevimab/cilgavimab (8.6% versus 33.2% and 27.0%, respectively)[26]. The emergence of RAMs that we observed in ICPs after (functional) monotherapy across several SARS-CoV-2 variants is in line with previous reports [27, 28, 29]. For instance, in an unselected group of 18 882 patients treated with sotrovimab for BA.1 or BA.2, RAMs on position 340 or 337 were found in 25 but were only detected in the subgroup of ICPs [30]. Another study sequenced SARS-CoV-2 after functional monotherapy with tixagevimab/cilgavimab in 18 patients infected with BA.2, 14 of whom were immunocompromised; RAMs on position K444 developed in 8 [32]. We also observed that the time to viral clearance was substantially longer when RAMs emerged during therapy. This finding may be subject to bias as it remains unclear whether the presence of RAMs led to a prolonged time to viral clearance or if RAMs are more likely to emerge in patients with a slower viral clearance (similar to "what came first, the chicken or the egg?").

We observed a high overall mortality of 23% in the 154 patients hospitalized for COVID-19 at the time of treatment. Even in patients infected with a SARS-CoV-2 Omicron variant, 11 of 68 (16%) died despite therapy with mAbs and repeated vaccination in most. This was also concluded in a large cohort study performed in the United Kingdom [7]. It is important to interpret our results with the correct context in mind. All patients were immunocompromised. In addition, the Dutch

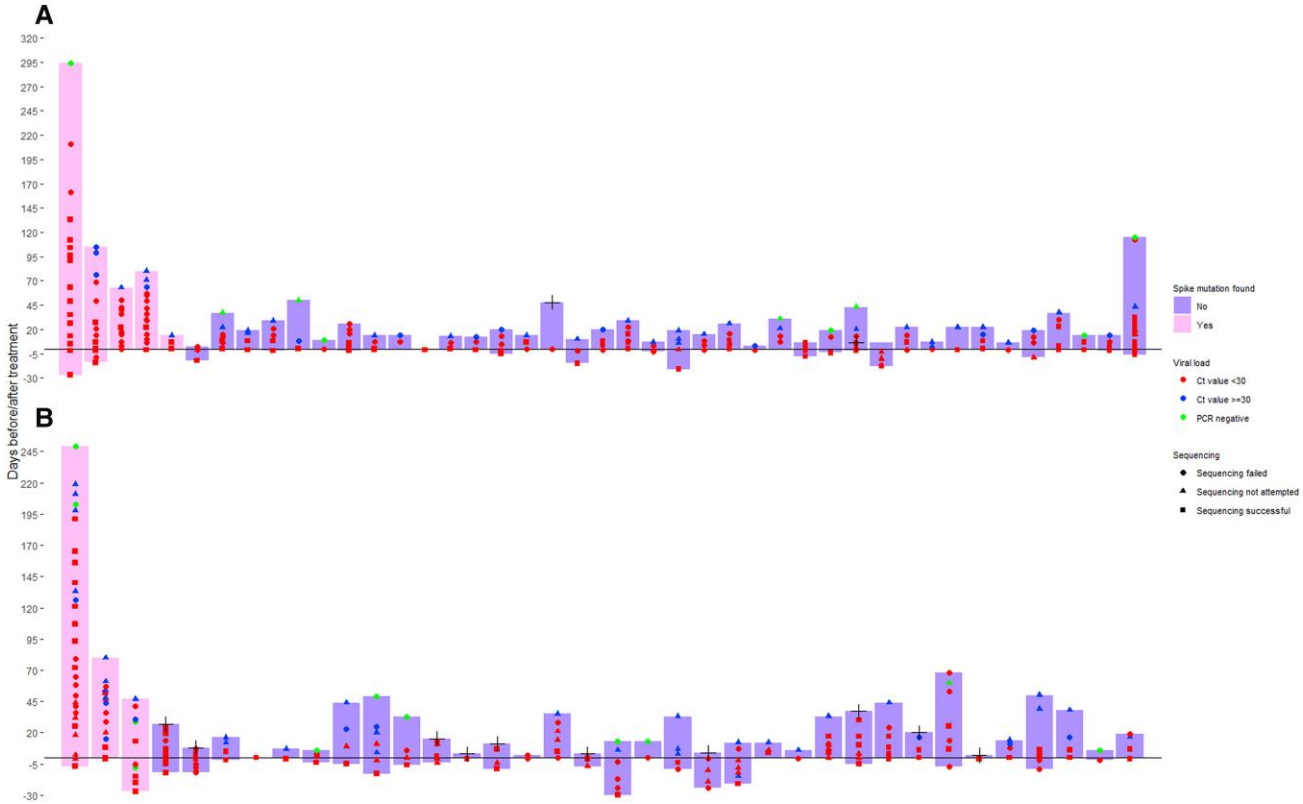

Figure 2. *A*, Overview of virological follow-up of patients treated with sotrovimab (N = 43) in whom sequencing was done after treatment. *B*, Overview of virological follow-up of patients treated with tixagevimab/cilgavimab (N = 36) in whom sequencing was done after treatment. The black crosses represent patients who died during follow-up. Abbreviations: Ct, cycle threshold; PCR, polymerase chain reaction.

COVID-19 guideline limited the use of mAbs in hospitalized patients to those shown or very likely to be seronegative. This was based on the findings from the RECOVERY trial [19]. Later, when casirivimab/imdevimab was no longer active against the first of several circulating Omicron VOCs, sotrovimab (for BA.1) and eventually tixagevimab/cilgavimab (for BA.2 and 5) were used off label in a similar way for ICPs hospitalized for COVID-19. This use of mAbs in a selected group of hospitalized ICPs probably explains why the mortality in our cohort was so high. Furthermore, in contrast to other studies, we excluded patients with nonhematological malignancies and with well-controlled human immunodeficiency virus. Indeed, these patients are typically not very immunocompromised since they have an adequate antibody response after SARS-CoV-2 vaccination [31, 33].

Our study has several strengths. Despite its observational nature, it adds important data to the available literature. First, randomized, controlled trials that focus on mAb treatment in ICPs are lacking. Furthermore, by only including patients with a clear B- and/or T-cell immunodeficiency, we created a large cohort of severely ICPs treated with mAbs with detailed virological outcome data. Second, few studies have described the outcome of therapy with mAbs in hospitalized ICPs, particularly during dominance of the Omicron variants. Third, while treatment with tixagevimab/cilgavimab for early COVID-19 significantly reduced hospital admissions in a phase 3 trial, very few ICPs were recruited, and the drug never became registered for this indication. Therefore, our study is one of the few with outcome data on treatment of ICPs with these mAbs.

This study also has several limitations. First, we had no contemporary control group to compare the outcome with since mAbs were the standard of care at that time. Second, the nonrandomized design of the study may have introduced unknown confounders. For example, ICPs considered at very low risk or terminally ill could have been excluded from treatment. Also, the Dutch guidelines evolved over time and restricted the use of the mAbs sotrovimab and tixagevimab/cilgavimab that became available later during the pandemic to fewer outpatients (eg, only those unvaccinated or with a documented vaccination nonresponse; see Supplementary Methods 1 for more details). We also emphasize that because mAbs were used against different VOCs with dissimilar virulence, our results should not be used to compare the effectivity of the different mAbs. Also, to disentangle the roll of antiviral potency versus the benefit of combination therapy, a comparison of the neutralizing capacity of the patient's serum after mAb treatment would have

Table 2. Sequencing Results (no. (%))

Sequencing characteristics	Total (N = 202)	Casirivimab/Imdevimab (n = 99)	Sotrovimab (n = 67)	Tixagevimab/ Cilgavimab (n = 36)
Sequencing result				
Pre + post-treatment sequence successful	41 (20)	11 (11)	17 (25	13 (36)
Pre-treatment sequence successful	78 (39)	53 (54)	12 (18)	13 (36)
Post-treatment sequence successful	14 (7)	5 (5)	4 (6)	5 (14)
All sequence attempts unsuccessful	29 (14)	14 (14)	10 (15)	5 (14)
Not available	40 (20)	16 (16)	24 (36)	0
Identified variants				
Delta	66/133 (50)	66 (96)	…	…
Omicron BA.1	29/133 (22)	3 (3)	26 (79)	…
Omicron BA.2	12/133 (9)	…	7 (21)	5 (16)
Omicron BA.5	26/133 (19.5)	…	…	26 (84)
Spike mutations associated with resistance detected during follow-up[a]				
Denominator = patients with successful sequence result after mAb treatment	9/49 (18)	1/14 (7)	5/21(24)[b]	3/14 (21)
Denominator = patients with any sequencing attempt after mAb treatment (successful or not)	9/96 (9)	1/42 (2) Patient C1: L18F, S222A, G446V on day 12 (Delta); del145, E484Q on day 21	5/34 (15) Patient S1: E340Q, D796Y on day 8 (BA.2) Patient S2: E340V on day 23 (BA.1) Patient S3: P337S on day 23 (BA.1) Patient S4: D796Y on day –2, P337L, D796Y on day 8; E340A, D796Y, D839N on day 28 (BA.1) Patient S5: A372G on day –2, E340D, A372G, D936H on day 14 (BA.1)	3/20 (15) Patient T1: K444R on day 53 (BA.2) Patient T2: K444N on day 14 (BA.5.2.1) Patient T3: S371F, K444R on day 73 (BA.2)

Abbreviation: mAb, monoclonal antibody.

[a]For this analysis, only the 104 patients in whom at least 1 attempt was made to sequence the virus were included.

[b]In 2 patients, mutations were documented during follow-up that have not been shown to be associated with resistance against sotrovimab: the D796Y in a patient infected with BA.2 and the V483A and S490F in a patient infected with BA.1. In 1 patient with BA.2, a P337S mutation was already observed before treatment with sotrovimab and was therefore not accounted for as a treatment-induced mutation.

been very helpful. Finally, in 20% of the patients, the virological outcome was not available, and in a small subgroup, data on SARS-CoV-2 antibodies at baseline were missing.

Based on our data, we propose that authorities such as the EMA and US Food and Drug Administration require the inclusion of a minimum number (eg, 20%) of severely ICPs in the design of future phase 3 trials on mAbs in the treatment of a viral infection. Our data also show the importance of studying the effects of combination antiviral therapy in ICPs. As far as we know, only one investigator initiated study has started [34] and no industry initiated studies on combination antiviral therapy for COVID-19 are currently ongoing.

Recently, an mAb mimicking angiotensin-converting enzyme 2 with the potential to remain active against future variants was identified. Future trials may show its value for ICPs [35, 36]. Convalescent plasma from donors with very high neutralizing antibody titers against circulating variants may also be part of such a combination therapy [6, 37]. However, it is very difficult to keep a stock of high-titer convalescent plasma "up to date" at a time when variants continue to change rapidly. Finally, we emphasize the need for virological follow-up in ICPs to monitor both clearance and possible selection of RAMs.

In conclusion, we described the outcome of COVID-19 in ICPs treated with 3 mAbs during the dominance of several SARS-CoV-2 variants. We showed that once hospitalization was required, the mortality remained high. In those treated with 1 instead of 2 functional mAbs, RAMs were more frequently observed and associated with a longer time to viral clearance. Prospective studies on combination antiviral therapy in ICPs with COVID-19 are urgently needed.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. Conceptualization: B. R. and B. O. M. Methodology: B. R., B. O. M., and S. H. Investigation: S. H., S. B., N. W., M. B., L. K., R. H., R. F., and H. L. Formal analysis: B. O. M., S. H., and P. M. A. Data curation: S. H. Writing the original draft: B. R., S. H., and A. G. Writing—review and editing: all authors. Supervision of the project: B. R. Funding acquisition: B. R.

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Potential conflicts of interest. B. R. reports membership on advisory boards for AstraZeneca, Roche, and Pfizer; and receipt of consulting fees from Roche, AstraZeneca and Pfizer. All other authors report no potential conflicts.

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