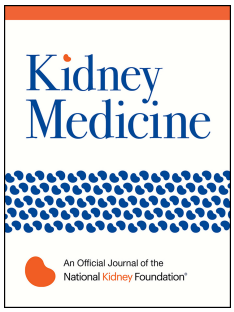
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Monoclonal Antibody Therapy in Kidney Transplant Recipients With Delta and Omicron Variants of SARS-CoV-2: A Single-Center Case Series

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Monoclonal Antibody Therapy in Kidney Transplant Recipients With Delta and Omicron Variants of SARS-CoV-2: A Single-Center Case Series

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G. F. and A. D. contributed equally to this study.

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Abstract

Rationale & Objective: Neutralizing monoclonal antibody treatments have shown promising preliminary results in kidney transplant recipients infected with SARS-CoV-2. However, their efficacy in kidney transplant recipients infected with Omicron variant has not been reported yet.

Study Design: Single-center retrospective study.

Setting & Participants: We included all consecutive kidney transplant recipients treated with monoclonal antibodies for SARS-CoV-2 infection (positive polymerase chain reaction on nasopharyngeal swab) between June 10th 2021 and January 14th 2022. Forty-seven kidney transplant recipients were included. All patients had symptoms evolving for ≤ 7 days and no oxygen therapy need at monoclonal antibody infusion.

Results: Symptoms at diagnosis were mainly cough (n=25 [53%]) and fever (n=15 [32%]). Eighty-three percent of the cohort (n=39) had been vaccinated with at least 2 doses before infection, of whom 77% (n=30) had demonstrated a vaccine-induced humoral response. They were treated with either casirivimab-imdevimab (n= 16 [34%]) or sotrovimab (n= 31 [66%]) a median of 2 (ranges 0-6) days after the onset of symptoms. Except for one mild allergic reaction during casirivimab-imdevimab infusion, no side effects were reported. Median viral loads at admission (day 0) and 7 days after mAb infusion were 2,110,027 (ranges 1000-153,798,962) copies/mL and 1,000 (ranges 0-10,000,000) copies/mL, respectively. Genotypes were available for 22 kidney transplant recipients (47%). Omicron, Delta, and Gamma variants were identified in 13 (59%), 8 (36%), 1 (5%) patients, respectively. In kidney transplant recipients infected with Omicron variant, the median viral loads at day 0 and day 7 were 752,789 (ranges

4000-12,859,300) copies/mL and 1,353 (ranges 0-1,211,163) copies/mL, respectively. Two kidney transplant recipients required hospitalization immediately after sotrovimab perfusion for oxygen therapy that was weaned in 3 days allowing patients' discharge. None were admitted to the intensive care unit or died.

Limitations: Small sample-size, no control group.

Conclusions: Neutralizing monoclonal antibody therapy is associated with positive outcomes in kidney transplant recipients with mild COVID-19, including those infected with the Omicron variant.

Keywords: SARS-CoV-2, COVID-19, kidney transplant, ESKD, monoclonal antibody, hospitalization, Omicron

Plain language summary:

Neutralizing monoclonal antibody treatments have shown promising preliminary results in kidney transplant recipients with SARS-CoV-2. However, its efficacy in kidney transplant recipients infected with the emerging Omicron variant has not been reported yet. This single-center retrospective study describes our experience with monoclonal antibody therapy in 47 kidney transplant recipients with mild COVID-19 (including 13 Omicron variant). Patients were treated with either casirivimab-imdevimab (n= 16) or sotrovimab (n= 31) between 2021/06/10 and 2022/01/14. mAb therapy was associated with a 4% rate of hospitalization for oxygen therapy, without major side effects. The 13 kidney transplant recipients with Omicron variant SARS-CoV-2 infection were all treated with sotrovimab with no need for subsequent hospitalization, a significant drop in SARS-CoV-2 viral load 7 days after treatment.

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Introduction

As of January 2022, more than 356,000,000 cases and 5,600,000 deaths have been reported by the World Health Organization due to COVID-19 pandemic and the numbers continue to rise.[1] Solid organ transplant recipients- including kidney transplant recipients – were recognized early as a particularly vulnerable population to SARS-CoV-2 infection with increased mortality rates around 20-30%.[2,3] These excess deaths are most likely triggered by the maintenance immunosuppressive treatments received to prevent graft rejection[4] and the co-morbidities affecting kidney transplant recipients.[5,6]

Since the onset of the outbreak, an unprecedented rapid development of therapeutic options occurred aiming to improve the outcome of patients infected with COVID-19. Among them vaccines have proven to be efficacious in reducing the risk of both severe disease and mortality in the general population.[7] Unfortunately, emerging evidence has revealed that kidney transplant recipients actually display a reduction in vaccine-induced humoral responses.[8] Moreover, the clinical benefit of vaccine to protect against severe COVID-19 has appeared lower in solid organ transplant recipients compared to the general population.[9]

Taken together, these data suggest that alternative strategies are required for kidney transplant recipients.[10] Among them, neutralizing monoclonal antibody therapy deserves consideration. Indeed, casirivimab-imdevimab[11] and sotrovimab[12] were recently reported to be safe and effective in reducing a composite endpoint combining hospitalization and mortality in two phase 3 placebo controlled trials including immunocompetent patients infected with SARS-CoV-2 at risk of progression. Unfortunately, kidney transplant recipients were excluded from the studies. Nevertheless, we and others[13-17] have reported case-series suggesting that neutralizing monoclonal

antibody therapy may be used safely in kidney transplant recipients with mild forms of COVID-19. However, concerns were recently raised regarding the efficacy of monoclonal antibody therapy in patients infected with the B.1.1.529 (Omicron) variant SARS-CoV-2. Indeed *in-vitro* investigations have suggested that some antibodies used in clinic might lose affinity and efficacy against this variant.[18,19] Moreover, to the best of our knowledge, the efficacy of monoclonal antibody therapy in kidney transplant recipients infected with Omicron variant SARS-CoV-2 has not been investigated yet.

This single-center retrospective study describes our experience with neutralizing monoclonal antibody therapy in kidney transplant recipients infected with SARS-CoV-2, including 13 patients with the Omicron variant. Of note, preliminary results of this study have previously been published.[13]

Methods

Patient selection and study design

Soon after the onset of the outbreak, all kidney transplant recipients were informed to contact our center in case of possible SARS-CoV-2 infection (because of symptoms or high-risk contact). Since the availability of monoclonal antibody therapy in Belgium (June 2021), all kidney transplant recipients with possible infection (or confirmed infection based on an antigen or polymerase chain reaction [PCR] test performed outside of our clinic) are clinically evaluated by a physician from our team and systematically tested (or retested) for SARS-CoV-2 (PCR on naso-pharyngeal swab-day 0). Neutralizing monoclonal antibodies are then locally administrated in all kidney transplant recipients who meet the following criteria: laboratory-confirmed SARS-CoV-2 infection (positive polymerase chain reaction on nasopharyngeal swab) < 5 days,

symptom evolving for ≤ 10 days, and maintain oxygen saturation ≥93% breathing room air according to the Belgian guidelines.[20]

Baseline characteristics at monoclonal antibody infusion (including data regarding vaccination and clinical symptoms), immunosuppression management, and outcomes were retrospectively recorded form the numeric file of patients. Data were collected until 30 days after Mab infusion (to collect potential COVID-19 linked complication) or death.

This study was conducted with the approval of our institutional ethics review board (2021/12NOV/470; B403/). The need for informed consent was waived due to de-identified information.

Management of patients

Patients were given monoclonal antibodies intravenously in our COVID-19 unit before being discharged after a 2-hour surveillance. The study was conducted from June 10th 2021 to January 14th 2022. Two different monoclonal antibodies were used during this period depending on their availability in Belgium: casirivimab 1200mg and imdevimab 1200mg, (Regeneron, USA) from June 10th 2021 to November 11th 2021 and then sotrovimab (GlaxoSmithKline and Vir Biotechnology) 500mg onwards. The last patient included in the present study was treated on January 14th 2022. We repeated viral load measurements 7-8 days after monoclonal antibody infusion according to previously published studies reporting on monoclonal antibody therapy.[21,22]

In COVID-19 not requiring oxygen therapy, our protocol regarding immunosuppression management consists of a withdrawal of the antimetabolite drug for 10 days after the onset of symptoms in all patients or a 50%-dose decrease in high risk patients (first year of transplantation, recent history of acute rejection). The doses of

calcineurin inhibitors and steroids remain unchanged. In patients with mild-COVID-19 (no need for oxygen) transplanted within the month, the immunosuppression regimen is not modified.

Microbiology

The vaccine-induced humoral response was measured using an immunoassay detecting antibodies against the spike protein receptor-binding domain (Elecsys anti-SARS-CoV-2, Roche Diagnostics GmbH, Mannheim, Germany - positive threshold >0.8 BAU/mL).

The detection of SARS-CoV-2 on nasopharyngeal swab was performed using the Alinity m SARS-CoV-2 assay (Abbott Molecular Inc., Des Plaines, IL, USA). This real-time reverse transcription polymerase reaction test is a dual target assay for the RdRp and N genes. To detect and identify SARS-CoV-2 variants of concern (VOCs), RNA extracted from nasopharyngeal swabs stored in a deep freezer were subject to the Allplex SARS-CoV-2 Variants I and II assays (Seegene, Seoul, South Korea) using the CFX96 real-time PCR detection system (Bio-Rad, Hercules, Ca, USA). These assays enable the simultaneous amplification and detection of target nucleic acids of Spike protein mutations (N501Y, E484K, W152C, K417N, K417T, L452R mutations, and HV69/70 deletion) as well as RdRp gene and an endogenous internal control. Data analysis and results interpretation were achieved with the Seegene Viewer Software.

Genotype assessment was not conducted between September 18th 2021 and December 10th 2021 (because of staffing issues and because the B.1.617.2 (Delta) variant was detected in more than 98% of SARS-CoV-2 infections in Belgium during this period of time).[23]

Results

Baseline characteristics and vaccination status

Forty-seven kidney transplant recipients infected with SARS-CoV-2 met the criteria to receive neutralizing monoclonal antibody treatment in our center.

As summarized in Table 1, median age at diagnosis was 50 (ranges 19-78) years with 55% (n=26) of male patients. Median time from transplantation was 61 (ranges 1-348) months. Hypertension and diabetes (66% [n=31] and 34% [n=16]) were the two most prevalent comorbidities among infected kidney transplant recipients.

Eighty-three percent (n=39) of patients had received at least 2 doses of anti-SARS-Cov-2 vaccine and 43% (n=17) of them had received a third dose. Last dose was administered a median time of 113 (ranges: 29-274) days, 171 (range: 39-274) days, and 82 (range: 29-115) days before infection, in all patients, in kidney transplant recipients who were only vaccinated twice, and in those who had received a booster dose, respectively. BNT162b2 (Pfizer-BioNTech) vaccine was administered in all but three kidney transplant recipients [ChAdOx1 nCoV-19/AZD1222 vaccine (AstraZeneca) in 2 and Ad26.COV2.S vaccine (Janssen/Johnson & Johnson in 1)].

Among vaccinated patients (n=39), 77% (n=30) were seropositive (anti- receptor-binding domain antibody titer > 0.8 BAU/mL). The 2 kidney transplant recipients who required hospitalization were seronegative. The median anti-SARS-CoV-2 antibody titer among responders was 257 (ranges 1-257) BAU/mL a median time of 54 (ranges 0-243) days after the last dose and 8.5 (ranges 0-126) days before infection.

Presentation at diagnosis

Most common symptoms were cough and fever (53% [n=25] and 32% [n=15]); dyspnea was uncommon (6% [n=3]) (Table 2).

Among the 22 SARS-CoV-2 available genotypes, Omicron variant was the most prevalent (59%, n= 13) followed by Delta (36%, n=8) and P.1 (Gamma) variants (5%, n=1). The last Delta variant was identified on December 17th 2021 and Omicron has been detected since then (Table 2, Figure 1).

Median viral loads at diagnosis were 2,110,027 (ranges 1000-153,798,962) and 752,789 (ranges 4000-12,859,300) copies/mL for the all cohort and the Omicron variant cohort, respectively (Table 2, Figure 2).

Management and outcome

At day 0, the antimetabolite drug was interrupted or decreased by 50% in 34 (83%) and 6 (15%) patients, respectively. The dose was unchanged in one patient who had been transplanted 22 days prior infection.

Monoclonal antibodies were given immediately after diagnosis, a median time of 2 (ranges 0-6) days after symptoms onset.

Casirivimab/imdevimab was administered in the first 16 patients (34%). One patient reported a mild allergic reaction at infusion characterized by skin flush, pruritus and fever, rapidly resolved after antihistamine and steroids administration, allowing the completion of monoclonal antibody infusion. Of the 6 available genotypes, Delta and Gamma variant SARS-CoV-2 were detected in 5 and 1 patients, respectively (Figure 1). Sotrovimab was used in the following 31 patients (66%). No side effects were reported. Of the 16 available genotypes, Omicron and Delta variant SARS-CoV-2 were identified in 13 (81%) and 3 (19%) patients, respectively (Figure 1).

Median viral loads at day 7 after monoclonal antibody infusion were 1,000 (ranges 0-10,000,000) copies/mL and 1,353 (ranges 0-1,211,163) copies/mL in the whole

and in the Omicron variant cohorts, respectively (Table 2, Figure 2). Of note, 10 (21%) patients did not perform a day-7 PCR: 1 with Omicron variant, 1 with Delta variant, and 8 without available genotype at diagnosis. Six patients (13%) displayed a negative PCR at day 7 (including 2 patients with the Omicron variant).

Immediately after monoclonal antibody perfusion, two patients required hospitalization for oxygen therapy that was weaned in 3 days allowing patients' discharge. Both patients had received two doses of mRNA vaccine before infection but did not exhibit a humoral response. Genotype was not available for them but the infection occurred during the Delta-prevalent SARS-CoV-2 wave in Belgium) and they were both treated with sotrovimab.

One patient was infected in the first month (22 days) after kidney transplantation. He was a 24-year old man who had received 2 doses of the BNT162b2 (Pfizer-BioNTech) vaccine, the second 171 days before infection. He mounted a serological response with anti-SARS-CoV-2 antibody titer of 257 BAU/mL measured 52 days prior infection. He did not require hospitalization and there was no adjustment in his immunosuppression regimen.

No patient required further hospital readmission. None was admitted in intensive care unit (ICU) or died during the study period.

Discussion

We herein report reassuring data regarding both the efficacy and safety of neutralizing monoclonal antibody treatment use in kidney transplant recipients with mild to moderate COVID-19 (with no need for oxygen therapy). Indeed, out of the included 47 patients, only two (4%) required short hospitalization for oxygen supply after monoclonal

antibody treatment and none died or required ICU admission within a 30-day follow-up time. These results are in line with previous observations.[13-17] Moreover, the 30-day hospitalization rate after monoclonal antibody infusion in our cohort seems lower than those reported in two recent case-series (8.7% and 15%, respectively[24,25]).

No major side effects were observed. Interestingly, the use of sotrovimab in infected kidney transplant recipients has been poorly reported so far. In this study, we provide reassuring data as 66% of our cohort was treated with sotrovimab with no safety concerns. However, the only two patients who needed hospitalization were treated with sotrovimab. They became hypoxic soon after monoclonal antibody infusion. Although a direct side effect of monoclonal antibody therapy cannot be totally excluded, oxygen therapy was weaned after three days only, which seems like a long period for allergy. In our opinion, these two seronegative patients had infection already too advanced for the monoclonal antibody therapy to prevent hospitalization, but their infusion most likely participated in the rapid recovery.[26] Both patients were quickly discharged and did not require rehospitalization.

Another important original aspect of the present study is the reassuring information about monoclonal antibody (sotrovimab only) use in cases of the Omicron variant. Indeed, all patients displaying the Omicron variant SARS-CoV-2 were treated with sotrovimab and were discharged after monoclonal antibody infusion without any complication. In addition, a significant drop in viral load 7 days after treatment was observed. Recent *in-vitro* investigations have suggested that antibodies used in clinic might lose affinity and efficacy against this variant.[18,19] VanBlargan et al. tested several monoclonal antibodies in clinical practice for their ability to neutralize infectious

Omicron isolates.[18] They found that neutralizing activity of sotrovimab against this variant was less affected compared to other antibodies. Although this requires validation in a larger scale study, our data seem to confirm this finding in real-life practice. Consequently, sotrovimab might currently be the monoclonal antibody therapy of choice given the massive prevalence of the Omicron SARS-CoV-2 variant worldwide today.

The rate of vaccination in our cohort was high (83% of the cohort had received at least 2 doses of vaccine before infection) possibly contributing to the good outcomes observed in our patients treated with neutralizing monoclonal antibody therapy. However, the impact of vaccination in kidney transplant recipients in protecting against severe forms of COVID-19 is a matter of debate. Indeed, a recent large multicenter study showed that compared to 101 million fully vaccinated adults in the United States, fully vaccinated solid organ transplant recipients (n =18,215) had a 82-fold higher risk of breakthrough infection and a 485-fold higher risk of breakthrough infection with associated hospitalization and death.[27] Aslam et al reported in a single center US retrospective study including 2,151 solid organ transplant recipients that vaccinated patients had a significant decreased risk of developing symptomatic COVID-19.[28] On the other hand, a recent analysis from the UK registry including 43,481 solid organ transplant recipients showed that vaccination was associated with a much lower protection against severe disease compared to those achieved in the general population.[9] Recently, Yetmar et al published a case-series of 32 solid organ transplant recipients diagnosed with COVID-19 at least 14 days after completing SARS-CoV-2 vaccination, demonstrating that COVID-19 breakthrough occurs in immunocompromised populations even after full vaccination.[17] However, 28 patients with mild- to moderate infection received

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casirivimab/imdevimab, with only one requiring further hospitalization, and no ICU admission nor death was reported. Similar to our findings, these results suggest that monoclonal antibody therapy might have an additional impact to protect –even vaccinated- SARS-CoV-2 infected transplant patients against the development of severe COVID-19. However, as in our study, the lack of control group does not allow for drawing firm conclusions. Nevertheless, the combination of both strategies (vaccine and early use of monoclonal antibody therapy in case of infection) is most likely the most effective strategy for this particularly vulnerable population.

An interesting perspective is the use of monoclonal antibodies as a prophylactic strategy in kidney transplant recipients. Indeed its use in immunocompetent patients after a household contact has been shown to reduce the risk of asymptomatic and symptomatic infections as well as a reduced duration of symptoms.[29] Some countries (such as in France) have authorized the use of monoclonal antibodies for prophylaxis in immunocompromised patients (including kidney transplant recipients) with no antibody response after 3 doses of anti–SARS-CoV-2 vaccine administration. Ducloux et al have recently published their experience of casirivimab/Imdevimab as pre-exposition prophylaxis in 91 patients who did not show antibody response after 3 doses of mRNA vaccine.[30] After a 3-month period, no patient experienced COVID-19 infection, compared to a 16% rate of infection in kidney transplant recipients without vaccine-induced response who had refused the monoclonal antibody prophylaxis. If confirmed on larger scale and with longer follow-up, this strategy might become the more efficient preventive measure against COVID-19 in kidney transplant recipients.

Our study has limitations. First, its retrospective design makes it subject to collection bias. Second, the sample size is small. Third, the rate of unavailable genotypes is high (53%). However, systematic genotype assessment was no longer performed in our center during a period of time when the Delta variant SARS-CoV-2 was highly prevalent in our country and was resumed when Omicron variant emerged in Belgium. Consequently, it is highly plausible that a vast majority of unavailable genotypes in our study were actually Delta variants and that we did not miss any Omicron variant. Fourth, we have used Casirivimab-Indevimab and Sotrovimab as monoclonal antibody therapies. The first has shown no efficacy on the omicron variant and the second may be less active against the BA-2 omicron subvariant. Nevertheless, it is highly likely that no patient with the omicron variant was actually treated with casirivimab-indevimab as Sotrovimab had been exclusively used before the emergence of the Omicron variant. However, it is possible that some patients with the BA-2 omicron subvariant were treated with sotrovimab as not all genotypes were available. Fifth, as we included only kidney transplant recipients with mild to moderate COVID-19, our observations cannot be extrapolated for more severe clinical situations (*e.g.* oxygen supplementation needed at admission). Of note, a recent study showed no clinical benefit of sotrovimab in immunocompetent adults hospitalized for severe COVID-19.[31] Also, as we did not include patients with severe disease, the clinical severity of the Omicron variant SARS-CoV-2 in kidney transplant recipients could not be evaluated. In the general population, Omicron variant might be associated with less severe outcomes compared to previous variants, especially in previously immunized population.[32,33] However, the clinical impact of this variant in kidney transplant recipients has not been reported yet. Finally, the lack

of control group does not allow to clearly assess the clinical impact of neutralizing monoclonal antibody therapy. Two studies so far have compared outcomes among solid organ transplant recipients who received monoclonal antibodies vs those who did not and found contrasting results. Sarrell et al compared the outcomes of 93 solid organ transplants treated with monoclonal antibody therapy for mild to moderate COVID-19 (between November 22, 2020 and February 2, 2021) vs 72 solid organ transplants who did not. After adjustment for age, 30-day hospitalization rate was not statistically different between both groups (Odds Ratio 0.49, p=0.16).[24] Klein et al reported on 95 kidney transplant recipients (including 20 who received monoclonal antibody therapy) with COVID-19 between March 1,2020 and April 30, 2021. After adjustment for potential confounders, monoclonal antibody administration was associated with significant decrease in hospitalization rates (adjusted hazard ratio 0.216, p=0.04).[25] Interestingly both study periods occurred before Omicron wave onset.[24,25]

In conclusion, our study provides reassuring data about the efficacy and safety of neutralizing monoclonal antibody treatment in kidney transplant recipients with mild COVID-19, including those infected with the Omicron variant SARS-CoV-2. Larger controlled studies are required to confirm our observations.

Article Information

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Table 1. Baseline characteristics

Characteristics	Casirivimab/Imdevimab N= 16 (34%)	Sotrovimab N= 31 (66%)	Total cohort n=47
Age, years, median (ranges)	48.5 (21-78)	50 (19-70)	50 (19-78)
Male, n (%)	8 (50%)	18 (58%)	26 (55%)
Time from KT, months, median (ranges)	57.5 (1-348)	70 (1-279)	61 (1-348)
Comorbid condition			
Hypertension, n (%)	9 (56%)	22 (71%)	31 (66%)
Diabetes, n (%)	8 (50%)	8 (26%)	16 (34%)
Cardiovascular history, n (%)	1 (6%)	4 (13%)	5 (11%)
Obesity, n (%)	1 (6%)	4 (13%)	5 (11%)
Baseline eGFR, mL/min/1.73 m^2, median (ranges)	51.5 (10-105)	56 (11-121)	56 (10-121)
Maintenance immunosuppression			
Tac-MMF-steroids, n (%)	11 (69%)	23 (74%)	34 (72%)
Prior anti-SARS-CoV-2 vaccination			
At least two doses*, n (%)	13 (81%)	26 (84%)	39 (83%)
Three doses, n (%)	1 (6%)	16 (52%)	17 (36%)
Time from the last dose, days, median (ranges)	117 (39-211)	103.5 (29-274)	113 (29-274)
Documented humoral response, n (%)**	10 (77%)	20 (77%)	30 (77%)
Anti-RBD antibody titer, BAU/mL, median, (ranges)	199.7 (1-257)	257 (1-257)	257 (1-257)

Abbreviations: eGFR, estimated glomerular filtration rate ; KT, kidney transplantation ; MMF, mycophenolate mofetil ; RBD, receptor-binding domain ; Tac, tacrolimus.
*One patient received one dose of the Ad26.COV2.S vaccine (Janssen/Johnson & Johnson)
**Percentages were calculated among vaccinated patients (at least two doses, n=39). Positivity, anti-RBD antibody titer > 0.8 BAU/mL

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Table 2: Characteristics at admission for monoclonal antibody treatment

Characteristics	Total cohort n=47
Symptoms	
Fever, n (%)	15 (32%)
Cough, n (%)	25 (53%)
Shortness of breath, n (%)	3 (6%)
Diarrhea, n (%)	7 (15%)
SARS-CoV-2 viral load*	
Day 0, copies/mL, median (ranges)**	2,110,027 (1,000-153,798,962)
Day 7, copies/mL, median (ranges)***	1,000 (0-10,000,000)
Monoclonal antibody treatment	
Casirivimab-imdevimab, n (%)	16 (34%)
Sotrovimab, n (%)	31 (66%)
SARS-CoV-2 variant	
Delta, n (%)	8 (17%)
Omicron, n (%)	13 (28%)
Gamma, n (%)	1 (2%)
Not available, n (%)	25 (53%)

*Polymerase chain-reaction
**Day of monoclonal antibody treatment
***Seven to eight days after treatment

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Figure Legends

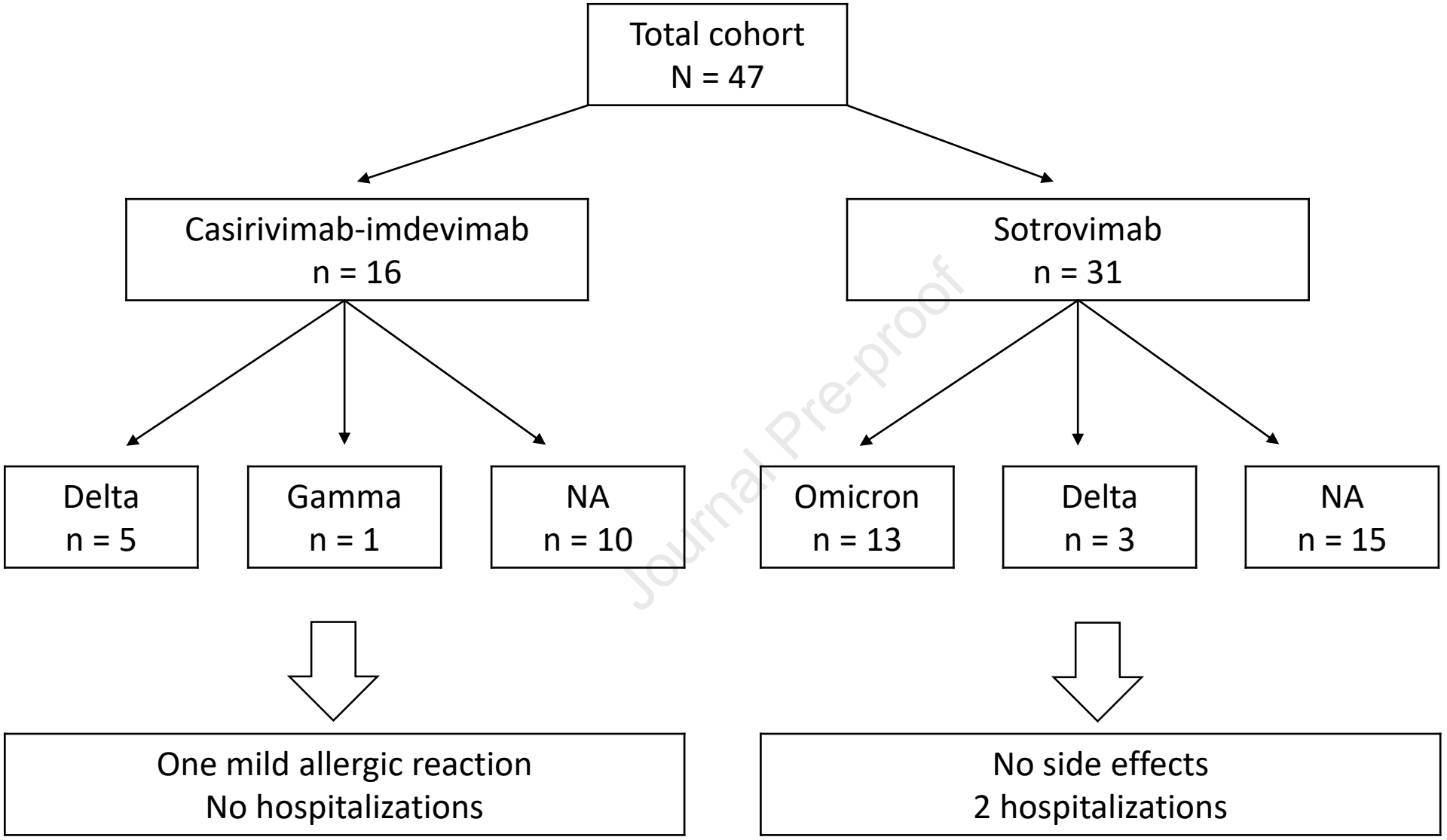
Figure 1: Description of the cohort.

Abbreviation: NA, not available

Figure 2: Evolution of SARS-CoV-2 viral load between the day of monoclonal antibody perfusion (day 0) and 7 days after (day 7) in patients treated with casirivimab/imdevimab (A) and sotrovimab (B).

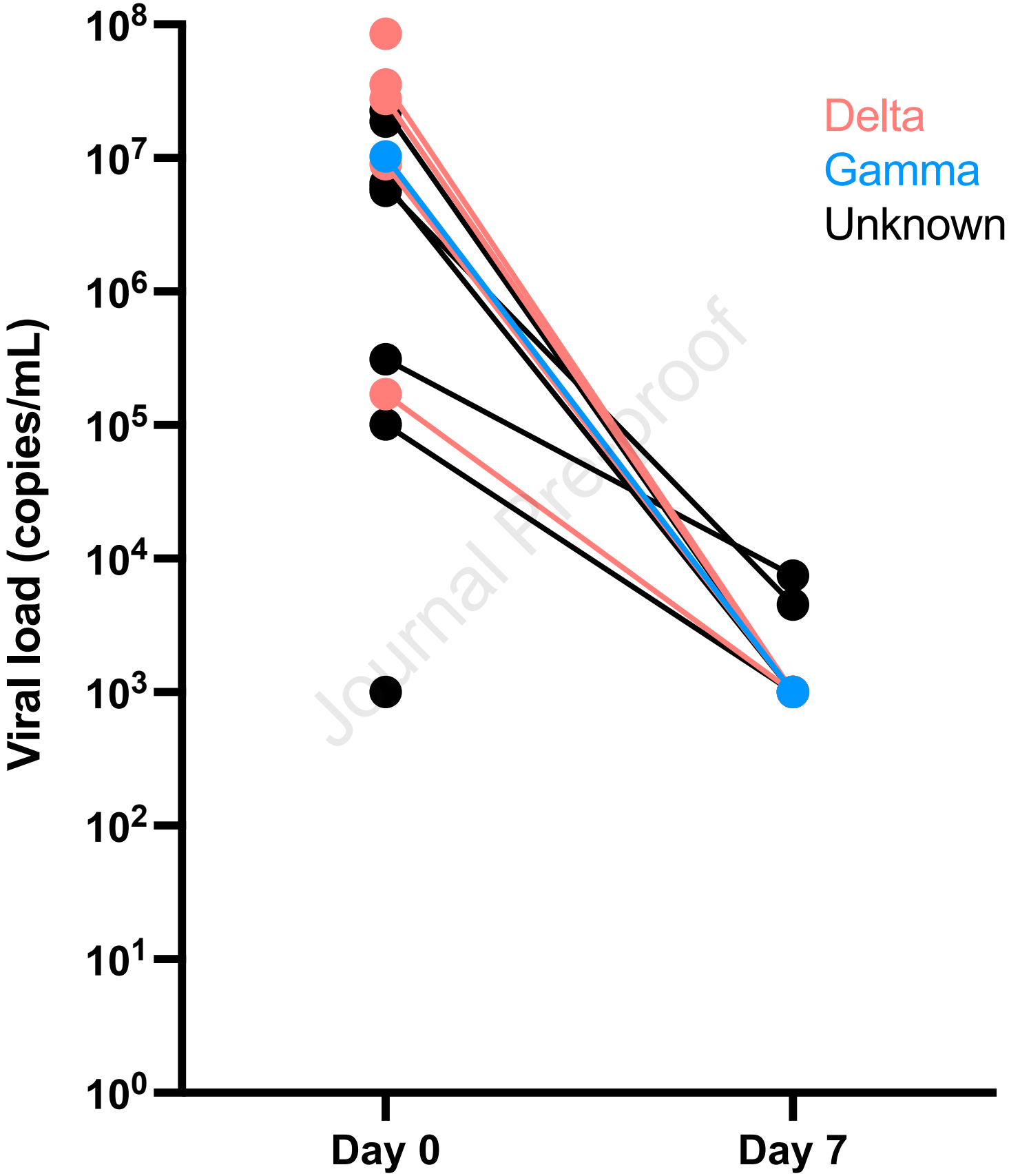
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