Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

A rapid decline in the anti–receptor-binding domain of the SARS-CoV-2 spike protein IgG titer in kidney transplant recipients after tixagevimab–cilgavimab administration

To the editor: Immunocompromised patients are at high risk of severe coronavirus disease 2019 (COVID-19) and show an impaired anti–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine response, even after 4 vaccine doses.[1,2] In this population, monoclonal antibodies that are used as a preexposure prophylactic treatment significantly reduce the incidence of severe infections. Since the emergence of the Omicron variant and its sublineages, tixagevimab–cilgavimab has been shown to be the only effective monoclonal combination therapy.[3] According to the PROVENT (***Pro***phylaxis Pre***vent***ion) study,[4] the efficacy of tixagevimab–cilgavimab is estimated to last at least 6 months; however, the study was conducted before the Omicron era. Herein, we describe the long-term anti–receptor-binding domain (RBD) kinetics in a single-center cohort of kidney transplant recipients treated with tixagevimab–cilgavimab for preexposure prophylaxis.

Immunocompromised patients with a weak antibody response after a complete vaccine program (anti-spike IgG <264 binding antibody units [BAUs]/ml) or for whom a vaccine administration contraindication was identified were eligible for this treatment. Patients with a history of COVID-19 after tixagevimab–cilgavimab administration were excluded (n = 56). Anti-RBD IgG titers were measured in serum samples collected from 98 adult kidney transplant recipients who received gluteal injections of 150 mg tixagevimab and 150 mg cilgavimab in the Strasbourg University Hospital (Strasbourg, France). Of these patients, 72 had been previously treated with the casirivimab–imdevimab combination before the emergence of the Omicron variant. The kinetics of neutralization against the Omicron BA.2 variant, which was predominant at the time of writing, were investigated in a subgroup of 18 patients. The study protocol was approved by the local ethics committee (identifier: DC-2013–1990), and written informed consent was obtained from all participants.

Patient characteristics are presented in Table 1. A total of 96 of 98 patients were vaccinated with at least 2 doses of anti–SARS-CoV-2 mRNA vaccine. The median time between the last vaccination and tixagevimab–cilgavimab administration was 227 days (interquartile range [IQR], 190−257 days). In the subgroup of 26 patients not previously treated with the casirivimab–imdevimab combination, the median anti-RBD IgG titer was 19 BAUs/ml (IQR, 3−120 BAUs/ml) before tixagevimab–cilgavimab administration, after which it increased to 2753 BAUs/ml (IQR, 2321−3124 BAUs/ml; $P < 0.0001$) after a median of 30 days (IQR, 26−37 days) and then finally decreased to 1293 BAUs/ml (IQR, 1070−1627 BAUs/ml; $P < 0.0001$) after a median of 111 days (IQR, 95−125 days; Figure 1a[5]). The anti-RBD titer decreased by a median of 53% (IQR, 45%−59%). With the exception of 1 patient, all participants had an anti-RBD titer <2500 BAUs/ml, which has been previously associated with the lack of neutralizing activity against the Omicron BA.1 variant.[5]

For the remaining 72 patients, the last casirivimab–imdevimab administration had been performed with a median of 57 days (IQR, 34.8−70.8 days) before the tixagevimab–cilgavimab injection. The median anti-RBD IgG titer was 5500 BAUs/ml (IQR, 3629−8470 BAUs/ml) before tixagevimab–cilgavimab administration; and then it stabilized at 5213 BAUs/ml (IQR, 3897−7269 BAUs/ml; $P = 0.17$) after a median of 33 days (IQR, 28−37 days) and declined to 1824 BAUs/ml (IQR, 1207-2882 BAUs/ml; $P < 0.0001$) after a median of 119 days (IQR, 94−125 days; Figure 1b).

In a subgroup of 18 patients, the neutralizing activity decreased from 2.7 $\log_{10}$ (IQR, 2.59−2.85 $\log_{10}$) to 2.4 $\log_{10}$

Table 1 | Characteristics of kidney transplant recipients who received prophylactic injections of tixagevimab–cilgavimab

Variables	Kidney transplant recipients (n = 98)
Age, yr	55.5 [50.0–67.8]
Male sex	53 (54)
Comorbidities	
BMI, kg/m^2	24.9 [22.2–28.8]
Cardiovascular disease	26 (27)
Diabetes	32 (33)
Hypertension	89 (91)
Time from kidney transplantation, yr	3.69 [1.52–8.25]
First transplantation	74 (76)
Deceased donor	83 (85)
CNI	
Tacrolimus	66 (67)
Cyclosporine	20 (20)
No CNI	12 (12)
MMF/MPA	85 (87)
mTOR inhibitors	9 (9.2)
Belatacept	12 (12.2)
Steroids	77 (79)
Serum creatinine, μmol/L	142 [108–179]
No. of vaccine doses	
0	2 (2)
2	3 (3.1)
3	73 (74)
4	19 (19)
5	1 (1)
Time between the last dose vaccine and tixagevimab–cilgavimab administration, d	227 [190–257]

BMI, body mass index; CNI, calcineurin inhibitor; MMF, mycophenolate mofetil; MPA, mycophenolic acid; mTOR, mammalian target of rapamycin.
Data are expressed as median [interquartile range] or *n* (%).

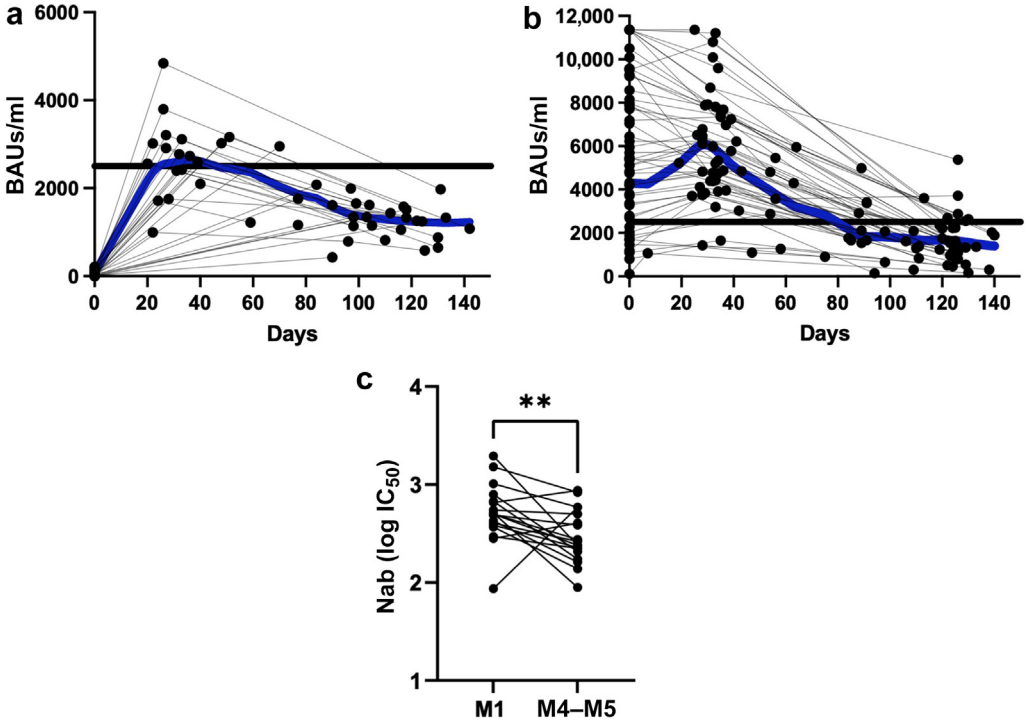

Figure 1 | Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) anti–receptor-binding domain IgG titer kinetics tested by ARCHITECT IgG II Quant test (Abbott). Results in arbitrary units/ml specific of this assay were converted into binding antibody units (BAUs)/ml adapted to the World Health Organization standard for SARS-CoV-2 Ig by multiplying them by the factor 0.142 (assay range, 1–11,360 BAUs/ml). Titers are represented from the day of tixagevimab–cilgavimab administration for patients previously treated with the casirivimab–imdevimab combination (n = 72; **b**) or not (n = 26; **a**). For 28 patients, data were missing around 1 month after antibody administration. The black lines represent the threshold below which no neutralizing activity against the Omicron BA.1 variant was detected in our previous study.[5] The thick blue lines indicate the trend in antibody titer using smoothing splines. The kinetics of neutralization were investigated in a subgroup of 18 patients, and a significant decrease was observed between 1 month (M1) and 4 to 5 months (M4–M5) following tixagevimab–cilgavimab injection (**c**). $^{**}P = 0.007$. IC_{50}, 50% inhibitory concentration; Nab, neutralizing antibody.

(IQR, 2.3−2.72 $\log_{10}$; $P = 0.007$; Figure 1c). The neutralizing activity against the BA.2 variant was positively associated with anti-RBD titers (Spearman $\rho = 0.49$; $P = 0.02$; Figure 2).

In this study, we show, for the first time, a significant decrease of the anti-RBD IgG 4 to 5 months after the administration of 150 mg of tixagevimab and 150 mg of cilgavimab. The PROVENT study demonstrated a persistent neutralizing activity against pre-Omicron variants for 6 months after tixagevimab–cilgavimab administration, despite a progressive decrease in drug concentration.[4] As the neutralizing activity is already reduced against the Omicron variant *in vitro* and *in vivo* 1 month after the injection,[5–7] the significant decrease in anti-RBD titers indicates a potential rapid loss of efficacy and an increased risk of severe COVID-19 in transplant recipients. Despite the fact that all of the sera tested within 4 to 5 months after a 150-mg dose of tixagevimab and cilgavimab each exhibited neutralizing activity against BA.2, it should be kept in mind that the currently predominant variant (BA.5) is characterized by a higher resistance against tixagevimab–cilgavimab. In this regard, the BA.5 variant poses similar concerns as the BA.1 variant in light of their similar escape profile.[8] Unfortunately, we have previously shown that <10% of patients exhibited neutralizing activity against BA.1 1 month after tixagevimab–cilgavimab injection.[5] Moreover, in our cohort, 73 patients (74%) had a titer <2500 BAUs/ml after a median of 117 days (IQR, 94−125 days), which was associated with the

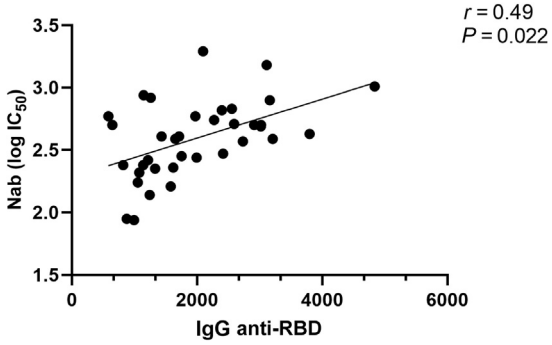

Figure 2 | Scattergram and regression line showing a significant positive correlation between anti–receptor-binding domain (RBD) IgG (Abbott Architect) and neutralizing antibody (Nab) titers (Spearman $\rho = 0.49$; $P = 0.02$). IC_{50}, 50% inhibitory concentration.

absence of neutralizing activity against the Omicron BA.1 variant.[6]

Despite the small sample of our study, our data suggest the necessity to administer another tixagevimab–cilgavimab dose before 6 months, especially when the monoclonal cocktail was given at the dose of 150 mg of each antibody. Additional research is needed to investigate the impact and the antibody kinetic of the higher dose of 600 mg of tixagevimab–cilgavimab, which is currently approved in the United States, but not in European countries. Furthermore, the dose required to reach neutralizing titers against different Omicron sublineages should be determined. Recent evidence indicates that an additional 150-mg dose of tixagevimab and cilgavimab each can improve the neutralizing activity against the BA.2 variant, although this was not the case for the BA.1 variant.[9] This can be attributed to the high resistance of the latter variant to tixagevimab–cilgavimab, which would require even higher antibody doses for neutralization. The BA.5 variant, which is currently predominant, poses the same concern as the BA.1 variant in light of its similar escape profile. There is an unmet need to develop more specific monoclonal antibodies to address this clinical issue. Pharmacokinetic studies will also be needed to support dose selection.

DISCLOSURE

SC reports receiving travel grants from Astellas and Sanofi, consulting fees from AstraZeneca, and lecture honoraria from Alexion. All the other authors declared no competing interests.

1. Caillard S, Chavarot N, Francois H, et al. Is COVID-19 infection more severe in kidney transplant recipients? *Am J Transplant*. 2021;21:1295–1303.
2. Caillard S, Thaunat O, Benotmane I, et al. Antibody response to a fourth messenger RNA COVID-19 vaccine dose in kidney transplant recipients: a case series. *Ann Intern Med*. 2022;175:455–456.
3. Ducloux D, Courivaud C. REGEN-Cov antibody combination to prevent COVID-19 infection in kidney transplant recipient without detectable antibody response to optimal vaccine scheme. *Kidney Int*. 2022;101:645–646.
4. Levin MJ, Ustianowski A, De Wit S, et al. Intramuscular AZD7442 (tixagevimab–cilgavimab) for prevention of Covid-19. *N Engl J Med*. 2022;386:2188–2200.
5. Benotmane I, Velay A, Gautier-Vargas G, et al. Pre-exposure prophylaxis with 300 mg Evusheld elicits limited neutralizing activity against the Omicron variant. *Kidney Int*. 2022;102:442–444.
6. Bruel T, Hadjadj J, Maes P, et al. Serum neutralization of SARS-CoV-2 Omicron sublineages BA.1 and BA.2 in patients receiving monoclonal antibodies. *Nat Med*. 2022;28:1297–1302.
7. Benotmane I, Velay A, Gautier-Vargas G, et al. Breakthrough COVID-19 cases despite prophylaxis with 150 mg of tixagevimab and 150 mg of cilgavimab in kidney transplant recipients. Published online June 17, 2022. *Am J Transplant*. https://doi.org/10.1111/ajt.17121
8. Tuekprakhon A, Nutalai R, Dijokaite-Guraliuc A, et al. Antibody escape of SARS-CoV-2 Omicron BA.4 and BA.5 from vaccine and BA.1 serum. *Cell*. 2022;185:2422–2433. e13.
9. Karaba AH, Kim JD, Chiang TPY, et al Omicron BA. 1 and BA.2 neutralizing activity following pre-exposure prophylaxis with tixagevimab plus cilgavimab in vaccinated solid organ transplant recipients. Preprint. *medRxiv*. 22275467. Posted online May 26, 2022. https://doi.org/10.1101/2022.05.24.22275467

Ilies Benotmane[1,2], Aurélie Velay[2,3], Gabriela-Gautier Vargas[1], Jérôme Olagne[1], Noëlle Cognard[1], Françoise Heibel[1], Laura Braun-Parvez[1], Jonas Martzloff[1], Peggy Perrin[1], Romain Pszczolinski[1], Bruno Moulin[1,2] Samira Fafi-Kremer[2,3] and Sophie Caillard[1,2]

[1]Department of Nephrology Dialysis and Transplantation, Strasbourg University Hospital, Strasbourg, France; [2]Unité mixte de recherche (UMR) S1109 Labex Transplantex, Institut national de la santé et de la recherche médicale (Inserm) Fédération de Médecine Translationnelle, Strasbourg University, Strasbourg France; and [3]Department of Virology, Strasbourg University Hospital, Strasbourg, France

Correspondence: *Ilies Benotmane, Department of Nephrology Dialysis and Transplantation, University Hospital Centre Strasbourg, place de l'hôpital, Strasbourg, bas rhin 67091, France. E-mail: ilies.benotmane@chru-strasbourg.fr*

Kidney International (2022) **102,** 1188–1190; https://doi.org/10.1016/j.kint.2022.07.022

Pregnancy after kidney transplantation: more attention is needed for long-term follow-up of the offspring

To the editor: With great interest we read the article by Gosselink *et al.* on the outcomes of pregnancies after kidney transplantation.[1] However, we feel an important aspect of pregnancy after kidney transplantation is lacking: follow-up of the offspring. In line with the existing literature, the authors report high rates of preterm birth and low birth weight, both of which are associated with reduced kidney development.[2] In addition, about half of mothers used a calcineurin inhibitor during pregnancy, which has been shown in animal research to have an impact on kidney development.[3] No information about the (renal) health of the children at an older age is included in the article.

Overall data on the health of the offspring at an older age are scarce in the existing literature, as pointed out in our recently published systematic review.[4] It is likely that the (kidney) development of the fetus is affected by the pregnancy after transplantation and its consequences such as immunosuppressive medication use and that problems may become apparent later in life, perhaps even in adulthood. Therefore, it would add to the knowledge of such consequences if data on long-term follow-up of the offspring would have been presented, including a risk assessment of factors such as prepregnancy graft function and immunosuppressive use by the mother during pregnancy. We would like to emphasize the value of performing such analyses in detail and include those results in the evaluation of pregnancy after kidney transplantation.