



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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

COVID-19 morbidity decreases with tixagevimab–cilgavimab preexposure prophylaxis in kidney transplant recipient nonresponders or low-vaccine responders



To the editor: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with high mortality in kidney transplant recipients (KTRs).¹ Unfortunately, they display a poor humoral immune response following coronavirus disease 2019 (COVID-19) mRNA vaccination.² The use of anti-SARS-CoV-2 monoclonal antibodies was therefore proposed for preexposure prophylaxis in individuals who did not exhibit a significant antibody response following vaccination. Tixagevimab–cilgavimab (Evusheld; AstraZeneca) was found to be effective in preventing COVID-19 during Alpha and Delta waves.³ Because it retained a neutralizing activity against the Omicron variants BA.1 and BA.2, it was approved in many countries for preexposure prophylaxis of KTRs with a low anti-SARS-CoV-2 antibody response after vaccination.^{4,5} A recent study of Bertrand *et al.* revealed the potential clinical efficiency of tixagevimab–cilgavimab against Omicron in KTRs with weak or no response to vaccine.⁶ At the same time, Benotmane *et al.* reported serious Omicron infections despite prophylactic therapy using tixagevimab–cilgavimab.⁷ In light of these conflicting data, we report herein the impact of this pre-exposure prophylaxis on the incidence of symptomatic COVID-19; COVID-19–related hospitalizations, including intensive care unit hospitalizations; and death in a cohort of KTRs during the Omicron wave.

KTRs from Bordeaux University Hospital (France) were considered as nonresponders or low responders if they had an anti-spike antibody level of <7 binding antibody units/ml (threshold of detection) or between 7 and 264 binding antibody units/ml, respectively, after at least 3 doses of mRNA vaccines. All patients were to receive i.m. prophylactic injections of tixagevimab–cilgavimab (150 mg tixagevimab and 150 mg cilgavimab) between December 28, 2021, and February 28, 2022 (COVID-19 incidence of 779 of 100,000). This period corresponded to the peak of the Omicron wave observed on January 27, 2022 (COVID-19 incidence of 4021 of 100,000) in our region (<https://www.santepubliquefrance.fr/>). During this study period, BA.1 was the predominant variant until February 14, 2022, when the BA.2 variant became predominant. The last follow-up was on May 5, 2022. Diagnosis of COVID-19 was based on the reverse transcriptase–polymerase chain reaction of nasopharyngeal swabs, and genome sequencing was

performed when suitable samples were available. All the data were recovered from our database (Réseau Aquitain de Néphrologie [R@N]: Commission Nationale de l’Informatique et des Libertés [CNIL] final agreement, decision 2009-413, number 1357154, July 2, 2009). Written informed consent was obtained from all patients.

We identified 430 KTRs who failed to develop a protective humoral response after at least 3 doses of mRNA vaccine against SARS-CoV-2. Among them, 333 received prophylactic injections of tixagevimab–cilgavimab without obvious security concerns (no cardiovascular events or significant adverse events). A total of 97 patients did not receive tixagevimab–cilgavimab for the following reasons: refusal (n = 21 [4.8%]), recent cardiovascular events (which were a contraindication, according to the manufacturer’s recommendations; n = 10 [2.3%]), inability to plan injection in our outpatient clinic during this period (n = 51 [11.9%]), or other reasons (n = 15 [3.4%]). **Table 1** presents the demographic characteristics of patients with and without tixagevimab–cilgavimab. Among the 333 KTRs who received tixagevimab–cilgavimab, 12.3% developed symptomatic COVID-19 compared with 43.3%

Table 1 | Patient characteristics

| Characteristic | Tixagevimab–cilgavimab (n = 333) | No tixagevimab–cilgavimab (n = 97) |
|---|----------------------------------|------------------------------------|
| Age, yr | 60 ± 14.4 | 58.3 ± 14.3 |
| Time from kidney transplantation, mo | 92 ± 91.1 | 108 ± 58.2 |
| Body mass index, kg/m ² | 25.2 ± 5.3 | 25.4 ± 5.2 |
| Male sex | 204 (61.2) | 63 (64.9) |
| Immunosuppressive drugs at inclusion | | |
| Mycophenolic acid | 254 (76.2) | 84 (86.6) |
| Azathioprine | 10 (3) | 1 (1.03) |
| Corticosteroids | 256 (76.9) | 82 (84.5) |
| mTOR inhibitor | 43 (12.9) | 6 (6.2) |
| Tacrolimus | 248 (74.5) | 73 (75.2) |
| Ciclosporin | 44 (13.2) | 14 (14.4) |
| Belatacept | 25 (7.5) | 11 (11.3) |
| Weak responder/nonresponder ^a | 57 (17)/276 (83) | 9 (9)/88 (91) |
| Previous treatment with REGEN-CoV antibody combination | 137 (41.1) | 43 (44.3) |
| Serum creatinine, μmol/l | 167 ± 134 | 161 ± 55 |
| History of cardiovascular event | 25 (7.5) | 19 (19.5) |
| Cardiovascular event in the last 3 mo | 0 (0) | 10 (10.3) |
| Follow-up, d | 116 ± 14 | 117 ± 13 |
| Symptomatic COVID-19 | 41 (12.3) | 42 (43.3) |
| COVID-19–related hospitalization | 4 (1.2) | 11 (11.3) |
| COVID-19–related hospitalization in intensive care unit | 2 (0.6) | 6 (6.2) |
| COVID-19–related death | 1 (0.3) | 2 (2) |

BAU, binding antibody unit; COVID-19, coronavirus disease 2019; mTOR, mammalian target of rapamycin.

Data are given as mean ± SD or n (%).

^aNonresponder: level of anti-spike antibody was <7 BAU/ml (threshold of detection); weak responder: level of anti-spike antibody was between 7 and 264 BAU/ml.

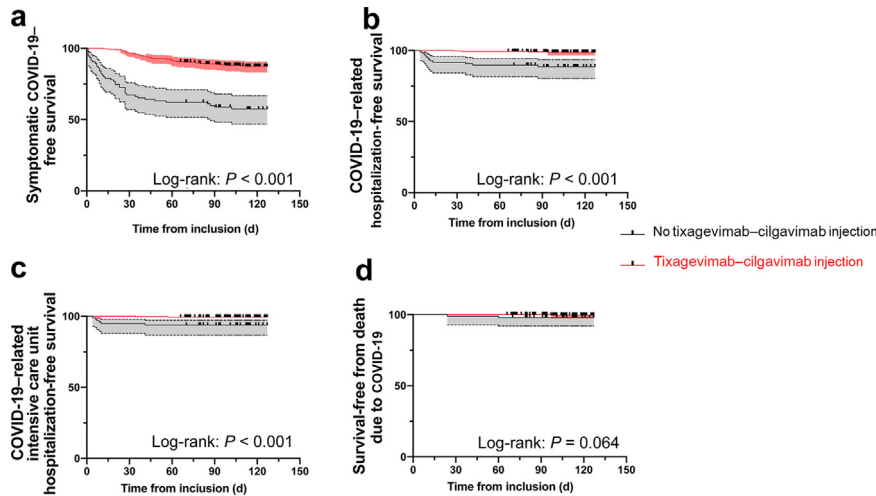


Figure 1 | Survival-free from Omicron infection. (a) Symptomatic coronavirus disease 2019 (COVID-19)-free survival. (b) COVID-19-related hospitalization-free survival. (c) COVID-19-related intensive care unit hospitalization-free survival. (d) Survival-free from death due to COVID-19. Log-rank test was used to compare the 2 groups and was considered as significant when $P < 0.05$.

among those who did not (hazard ratio [HR], 0.011; 95% confidence interval [CI], 0.063–0.198; $P < 0.001$; Figure 1a). SARS-CoV-2 sequencing was performed in 5 KTRs receiving tixagevimab–cilgavimab (BA.1, $n = 3$; BA.1.1, $n = 1$; and BA.2, $n = 1$). Hospitalization was required for 1.2% tixagevimab–cilgavimab KTRs in comparison with 11.3% KTRs without tixagevimab–cilgavimab (HR, 0.046; 95% CI, 0.013–0.158; $P < 0.001$; Figure 1b). Intensive care unit hospitalizations were required for 0.6% of KTRs with tixagevimab–cilgavimab and 6.2% without (HR, 0.045; 95% CI, 0.008–0.240; $P < 0.001$; Figure 1c). One KTR (0.3%) with tixagevimab–cilgavimab and 2 KTRs (2%) without died from COVID-19 acute respiratory distress syndrome (HR, 0.076; 95% CI, 0.005–1.161; $P = 0.066$; Figure 1d). Tixagevimab–cilgavimab viral neutralization activity was not conducted in this study.

The first conclusion of this real-life study is that tixagevimab–cilgavimab use was associated with (i) a significantly lower risk of symptomatic COVID-19 and (ii) fewer COVID-19-related hospitalizations (including intensive care unit), compared with patients who did not receive this prophylactic treatment. Although this study is inherently retrospective and not randomized, it reports an effectiveness of the preexposure prophylaxis by tixagevimab–cilgavimab in KTRs, during an Omicron wave dominated by the BA.1 and BA.2 variants. However, symptomatic COVID-19 occurred in 12.3% of KTRs despite tixagevimab–cilgavimab injection, with 2 cases of serious infection and 1 death in a recent ABO-incompatible KTR treated for antibody-mediated rejection with antithymocyte globulins and plasma exchanges. These data suggest that 150 mg tixagevimab and 150 mg cilgavimab offers an incomplete protection. Consequently, the US Food and Drug Administration now recommends increasing the dose of tixagevimab–cilgavimab (<https://www.fda.gov>). The second lesson learned from this study is that COVID-19 preexposure prophylaxis in our center has not been implemented fast enough (11.9% of our KTRs did not obtain a

tixagevimab–cilgavimab injection appointment during the incidence peak). The rate at which infection has spread has outstripped our limited human and organizational resources.

In conclusion, this retrospective real-life study supports (i) the relative effectiveness of tixagevimab–cilgavimab on COVID-19 infection caused by Omicron and (ii) the need to implement this type of prophylaxis to SARS-CoV-2 vaccination unresponsive patients more quickly.

DISCLOSURE

All the authors declared no competing interests.

DATA STATEMENT

All relevant data are within the article.

ACKNOWLEDGMENTS

The authors wish to thank the health care professionals of the University Hospital of Bordeaux who were involved in the care of the patients, and particularly Brigitte Bonpunt, Aurélie Seniuta, Laurence Pina, Véronique Bessac, and Charlotte Porredon. We also thank Audrey Macary, Audrey Montero, and Guillaume Rebillon for their help.

1. Caillard MPS, Anglicheau MPD, Matignon MDM, et al. An initial report from the French SOT COVID Registry suggests high mortality due to Covid-19 in recipients of kidney transplants. *Kidney Int.* 2020;98:1549–1558.
2. Bertrand D, Hamzaoui M, Lemée V, et al. Antibody and T cell response to SARS-CoV-2 messenger RNA BNT162b2 vaccine in kidney transplant recipients and hemodialysis patients. *J Am Soc Nephrol.* 2021;32:2147–2152.
3. Levin MJ, Ustianowski A, Wit SD, et al. Intramuscular AZD7442 (tixagevimab–cilgavimab) for prevention of Covid-19. *N Engl J Med.* 2022;386:2188–2200.
4. Iketani S, Liu L, Guo Y, et al. Antibody evasion properties of SARS-CoV-2 Omicron sublineages. *Nature.* 2022;604:553–556.
5. Takashita E, Kinoshita N, Yamayoshi S, et al. Efficacy of antiviral agents against the SARS-CoV-2 Omicron subvariant BA.2. *N Engl J Med.* 2022;386:1475–1477.
6. Bertrand D, Laurent C, Lemée V, et al. Efficacy of anti-SARS-CoV-2 monoclonal antibody prophylaxis and vaccination on the Omicron variant of COVID-19 in kidney transplant recipients. *Kidney Int.* 2022;102:440–442.
7. Benotmane I, Velay A, Vargas GG, et al. Pre-exposure prophylaxis with 300 mg Evusheld elicits limited neutralizing activity against the Omicron variant. *Kidney Int.* 2022;102:442–444.

Hannah Kaminski¹, Mickael Gigan², Agathe Vermorel¹, Manon Charrier¹, Laura Guirle², Frederic Jambon¹, Arthur Lacapère¹, Coline Ménard¹, Karine Moreau¹, Martine Neau-Cransac¹, Marine Novion¹, Frederique Pribat², Benjamin Taton¹, Sébastien Borde³, Laure Burguet⁴, Charlie Martinez⁵, Magali Jasiak⁶, Pauline D'Halluin⁷, Marie-Edith Lafon⁸, Pierre Merville¹ and Lionel Couzi¹

¹Department of Nephrology, Transplantation, Dialysis and Apheresis, Bordeaux University Hospital, Bordeaux, France; ²Department of Pharmacy, Bordeaux University Hospital, Bordeaux, France; ³Department of Nephrology, Centre Hospitalier de Saintes, Saintes, France; ⁴Department of Nephrology, Centre Hospitalier de Pau, Pau, France; ⁵Clinique Saint-Augustin Centre de Traitement des Maladies Rénales (CTMR), Bordeaux, France; ⁶Department of Nephrology, Centre Hospitalier de Mont de Marsan, Mont de Marsan, France; ⁷Department of Nephrology, Centre Hospitalier de Bayonne, Bayonne, France; and ⁸Department of Virology, Bordeaux University Hospital, Bordeaux, France

Correspondence: Lionel Couzi, Department of Nephrology, Transplantation, Dialysis and Apheresis, Pellegrin University Hospital, Place Amélie Raba Léon, 33076 Bordeaux, France. E-mail: lionel.couzi@chu-bordeaux.fr

Kidney International (2022) **102**, 936–938; <https://doi.org/10.1016/j.kint.2022.07.008>

Copyright © 2022, International Society of Nephrology. Published by Elsevier Inc. All rights reserved.

Response to the commentary “Modeling pulse wave velocity trajectories—challenges, opportunities, and pitfalls”



To the editor: We thank Heinze *et al.*¹ for their commentary on our publication² highlighting the virtue of linear mixed regression modeling. We would like to address some potential misunderstandings.

Reverse causation was excluded by 2 additional models for the pre-kidney replacement therapy course of pulse-wave velocity z-score (PWVz). Ensuring that the interaction between sex and underlying disease was adequately considered (Supplementary Figure S5²), we could safely conclude that sex differences in PWVz were not due to underlying disease. We did not demonstrate a faster chronic kidney disease progression in girls, and girls were not more likely to receive transplantation, as incorrectly stated.¹ We also reiterate that our objective was characterizing the PWVz evolution in girls and boys with progressing CKD and subsequent transplantation. Thus, we respectfully disagree with the claim that the key conclusion (i.e., differences in PWVz in girls and boys that develop during the time before transplantation) is not supported by our analysis.

The post-transplantation analyses showed only in girls that a longer time—not a shorter time as incorrectly

stated¹—to transplantation (Table 3²) was associated with a higher PWVz. Importantly, models using interaction terms with sex yielded similar findings: post-transplantation PWVz differed by sex but not their slope. Joint models are preferable in cases of nonrandom missingness with the availability of an auxiliary variable,³ which was not the case. Finally, we also highlight that sex is often deemed not important but should be included as a central consideration in medical research.

DISCLOSURE

All the authors declared no competing interests.

ACKNOWLEDGMENT

This study was made possible by grants from the German Federal Ministry of Education and Research (no. 01EO0802), the European Renal Association–European Dialysis and Transplant Association, and Roche Organ Transplant Research Foundation (no. 365520785). Several co-authors are members of the European Reference Network for Rare Kidney Diseases.

1. Heinze G, Christensen J, Haller MC. Modeling pulse wave velocity trajectories—challenges, opportunities, and pitfalls. *Kidney Int.* 2022;101:459–462.
2. Sugianto RI, Memaran N, Schmidt BMW, et al. Findings from 4C-T Study demonstrate an increased cardiovascular burden in girls with end stage kidney disease and kidney transplantation. *Kidney Int.* 2022;101:585–596.
3. Wang C, Hall CB. Correction of bias from non-random missing longitudinal data using auxiliary information. *Stat Med.* 2010;29:671–679.

Rizky I. Sugianto¹, Nima Memaran¹, Bernhard M.W. Schmidt², Anke Doyon³, Daniela Thurn-Valsassina^{1,4}, Harika Alpay⁵, Ali Anarat⁶, Klaus Arbeiter⁷, Karolis Azukaitis⁸, Aysun K. Bayazit⁶, Ipek K. Bulut⁹, Salim Caliskan¹⁰, Nur Canpolat¹⁰, Ali Duzova¹¹, Jutta Gellerman¹², Jerome Harambat¹³, Denise Homeyer¹⁴, Mieczyslaw Litwin¹⁵, Francesca Mencarelli¹⁶, Lukasz Obyrcki¹⁵, Dusan Paripovic¹⁷, Bruno Ranchin¹⁸, Rukshana Shroff¹⁹, Uwe Tegtbur¹⁴, Jeannine von der Born¹, Ebru Yilmaz²⁰, Uwe Querfeld¹², Elke Wühl³, Franz Schaefer³ and Anette Melk¹

¹Department of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany; ²Department of Nephrology, Hannover Medical School, Hannover, Germany; ³Center for Pediatrics and Adolescent Medicine, University Hospital Heidelberg, Heidelberg, Germany; ⁴Department of Pediatrics and Adolescent Medicine, Medical University of Vienna, Vienna, Austria; ⁵Medical Faculty, Marmara University, Istanbul, Turkey; ⁶Department of Pediatrics, Faculty of Medicine, Adana, Turkey; ⁷Department of Pediatric Nephrology and Gastroenterology, Medical University of Vienna, Vienna, Austria; ⁸Clinic of Pediatrics, Faculty of Medicine, Vilnius University, Vilnius, Lithuania; ⁹Department of Pediatrics, Faculty of Medicine, Ege University, Izmir, Turkey; ¹⁰Department of Pediatric Nephrology, Faculty of Medicine, Istanbul University-Cerrahpasa, Istanbul, Turkey; ¹¹Division of Pediatric Nephrology, Hacettepe University Faculty of Medicine, Ankara, Turkey; ¹²Charité Children's Hospital, Berlin, Germany; ¹³Pediatrics Department, Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France; ¹⁴Institute of Sports Medicine, Hannover Medical School, Hannover, Germany;