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.

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Letter to the Editor

Resistance mutations in SARS-CoV-2 omicron variant after tixagevimab-cilgavimab treatment

To the Editor,

In their recent article, Yang et al. [1] reported reduced COVID-19 severity after sotrovimab infusion in solid-organ-transplant (SOT) recipients with SARS-CoV-2 infection. Since the emergence of the BA.2 omicron subvariant, this monoclonal antibody (mAb) therapy is no longer used in France due to its low neutralizing activity against BA.2 and its capacity to induce resistance-associated spike mutations [2,3]. A new combination of two mAbs, tixagevimab-cilgavimab, has recently been authorized in France as an emergency treatment of SARS-CoV-2 BA.2 infections in patients at risk of severe COVID-19. While this association has been shown to protect against severe COVID-19 infections [4], little is known of its capacity to provoke spike mutations in the virus due to selective pressure.

We collected nasopharyngeal (NP) samples from 18 ambulatory patients who were given a single intravenous infusion of tixagevimab-cilgavimab (300 mg/300 mg) between March and May 2022 at the Toulouse-University-Hospital, France. NP samples were taken from them before (day 0) and 7 and 14 days after treatment (Supplementary Appendix).

These patients (median age: 63 years; 67% men), included 14 (78%) who were immunocompromised (11 SOT recipients), 3 with pulmonary disease and one who was obese with high blood pressure. All were infected with the omicron BA.2 subvariant. None of these patients required hospitalization. The median SARS-CoV-2 NP virus load decreased from 5.8 (interquartile range (IQR), 5.3–6.5) $\log_{10}$ copies/ml before infusion to 4.5 (IQR, 3.8–5.7) $\log_{10}$ copies/ml 7 days post-infusion ($p = 0.04$). The virus loads of 11 patients were high enough for sequencing analysis before and after infusion [5]. Resistance-associated mutations in the spike protein, positions 444, 346 and 452 were detected in 8/11 (73%) patients, 7 to 14 days post-infusion (Table 1). When the mutation was detected, the NP virus load increased in 3 patients, slowly decreased (<1 $\log_{10}$ copies/ml) in 4 patients, and significantly declined (>1 $\log_{10}$ copies/ml) in only 2 patients.

The decrease of virus load (1.3 $\log_{10}$ copies /ml) observed 7 days after tixagevimab-cilgavimab infusion was smaller than that of a group of 10 untreated immunocompromised SARS-CoV-2 alpha-infected patients (2.5 $\log_{10}$ copies/ml) [5]. This poor response could be due to the omicron lineage mutations S477N and Q493R in the receptor-binding domain of the spike protein, as they are responsible for tixagevimab having no neutralizing activity [6]. Our results highlight the high risk of developing spike-protein mutations that confer resistance to cilgavimab of patients previously given tixagevimab-cilgavimab, as occurred in patients treated with sotrovimab alone [3]. Patients infected with BA.2 or the new omicron subvariants BA.4/5, against which the neutralizing activity of cilgavimab is lower than that against BA.2 [7,8], require close virological monitoring to minimize the risk of transmission of resistant variants in the community. New neutralizing mAbs should be designed to improve anti-SARS-CoV-2 activity and limit the development of mutations that confer resistance.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2022.07.014.

References

1. Yang M, Li A, Wang Y, Tran C, Zhao S, Ao G. Monoclonal antibody therapy improves severity and mortality of COVID-19 in organ transplant recipients: a meta-analysis. *J Infect* 2022. doi:10.1016/j.jinf.2022.06.027.
2. Takashita E, Kinoshita N, Yamayoshi S, Sakai-Tagawa Y, Fujisaki S, Ito M, et al. Efficacy of Antibodies and Antiviral Drugs against Covid-19 Omicron Variant. *N Engl J Med* 2022;**386**(10):995–8. doi:10.1056/NEJMc2119407.
3. Vellas C, Trémeaux P, Del Bello A, Latour J, Jeanne N, Ranger N, et al. Resistance mutations in SARS-CoV-2 omicron variant in patients treated with sotrovimab. *Clin Microbiol Infect* 2022(22) S1198-743X00258-0. doi:10.1016/j.cmi.2022.05.002.
4. Montgomery H, Hobbs FDR, Padilla F, Arbetter D, Templeton A, Seegobin S, et al. Efficacy and safety of intramuscular administration of tixagevimab-cilgavimab for early outpatient treatment of COVID-19 (TACKLE): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2022;**S2213-2600**(22):00180–1. doi:10.1016/S2213-2600(22)00180-1.
5. Vellas C, Del Bello A, Debard A, Steinmeyer Z, Tribaudeau L, Ranger N, et al. Influence of treatment with neutralizing monoclonal antibodies on the SARS-CoV-2 nasopharyngeal load and quasispecies. *Clin Microbiol Infect* 2022;**28**(1) 139.e5-139.e8. doi:10.1016/j.cmi.2021.09.008.
6. Dejnirattisai W, Huo J, Zhou D, Zahradník J, Supasa P, Liu C, et al. SARS-CoV-2 Omicron-B.1.1.529 leads to widespread escape from neutralizing antibody responses. *Cell* 2022;**185**(3):467–84 e15. doi:10.1016/j.cell.2021.12.046.

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Table 1
Clinical characteristics and SARS-CoV-2 evolution of tixagevimab-cilgavimab-treated patients developing resistance-associated mutation.

Patient number	Clinical characteristics	SARS-CoV-2 vaccination status [a]	Days after tixagevimab-cilgavimab infusion [b]	Resistance mutation acquired (% in quasispecies)	Number of haplotypes	Nasopharyngeal virus load
#1	Kidney transplantation	boosted	7	K444R (26%)	6	rebound
#2	Pancreas and kidney transplantation	boosted	14	K444R (64%) K444N (30%)	2	rebound
#3	Kidney transplantation	boosted	14	K444N (100%)	1	rebound
#4	Lung transplantation	boosted	7	K444R (88%)	5	<1 $\log_{10}$ decline
#5	Primary immunodeficiency	boosted	7	R346T (5%) K444N (17%)	10	<1 $\log_{10}$ decline
#6	Carboplatin-Taxol treatment	boosted	14	R346T (25%) K444N (40%)	10	<1 $\log_{10}$ decline
#7	Liver transplantation	boosted	14	L452M (8%)	4	<1 $\log_{10}$ decline
#8	Heart transplantation	boosted	7	K444R (98%)	2	≥ 1 $\log_{10}$ decline
#9	Rituximab treatment	boosted	7	K444N (18%) K444R (22%)	8	≥ 1 $\log_{10}$ decline

[a] Vaccination with SARS-CoV-2 mRNA-based vaccine (boosted: 3 doses of mRNA-based vaccine).
[b] Time after tixagevimab-cilgavimab infusion when the mutation was detected.

7. Yamasoba D, Kosugi Y, Kimura I, Fujita S, Uriu K, Ito J, et al. Neutralisation sensitivity of SARS-CoV-2 omicron subvariants to therapeutic monoclonal antibodies. *Lancet Infect Dis* 2022;**S1473-3099**(22):00365–6. doi:10.1016/S1473-3099(22)00365-6.
8. Tuekprakhon A, Huo J, Nutalai R, Dijokaite-Guraliuc A, Zhou D, Ginn Helen M, et al. Antibody escape of SARS-CoV-2 Omicron BA.4 and BA.5 from vaccine and BA.1 serum. *Cell* 2022. doi:10.1016/j.cell.2022.06.005.

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