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Breakthrough omicron COVID-19 infections in patients receiving the REGEN-Cov antibody combination

To the editor: Coronavirus disease 2019 (COVID-19) vaccines are efficient to prevent severe COVID-19 infections. Immunocompromised patients are at increased risk of both severe COVID-19 and poor immunologic response to anti–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines.

Preexposure prophylaxis using anti-spike neutralizing monoclonal antibodies to prevent COVID-19 infection has been proposed as an alternative in patients with no immunologic response after 3 doses of COVID-19 vaccines.[1,2] We herein provide the first report, to our knowledge, of breakthrough COVID-19 infections in immunocompromised patients treated preventively with REGEN-Cov (Regeneron; casirivimab + imdevimab).

Between September 24, 2021 and December 23, 2021, 80 patients who had received at least 3 doses of a COVID-19 vaccine and had a negative anti–SARS-CoV-2 spike protein antibody response received at least 1 injection of 600 mg of casirivimab and imdevimab for preexposure prophylaxis in our center (Figure 1). Causes of poor immunologic response to vaccination were kidney transplantation (n = 57 [71%]), treatment with rituximab (n = 9 [11%]), end-stage kidney disease (n = 7 [9%]), and other (n = 7 [9%]). All patients were asked to report COVID-19 infection.

Among this cohort, we received 12 reports of COVID-19 infection between December 25, 2021, and January 18, 2022 (Figure 1). SARS-CoV-2 infection was diagnosed using an antigenic test in 1 case and by polymerase chain reaction test in the remaining 11 cases. The Omicron variant (the lack of the L452R mutation) was detected in 8 cases, whereas screening for Omicron was unavailable in the remaining 3 polymerase chain reaction–proven cases. Two patients were hospitalized because of severe symptoms but did not require a transfer to the intensive care unit. These breakthrough COVID-19 infections due to the Omicron variant are consistent with *in vitro* evidence of a complete escape of SARS-CoV-2 variant Omicron to casirivimab and imdevimab.[3,4]

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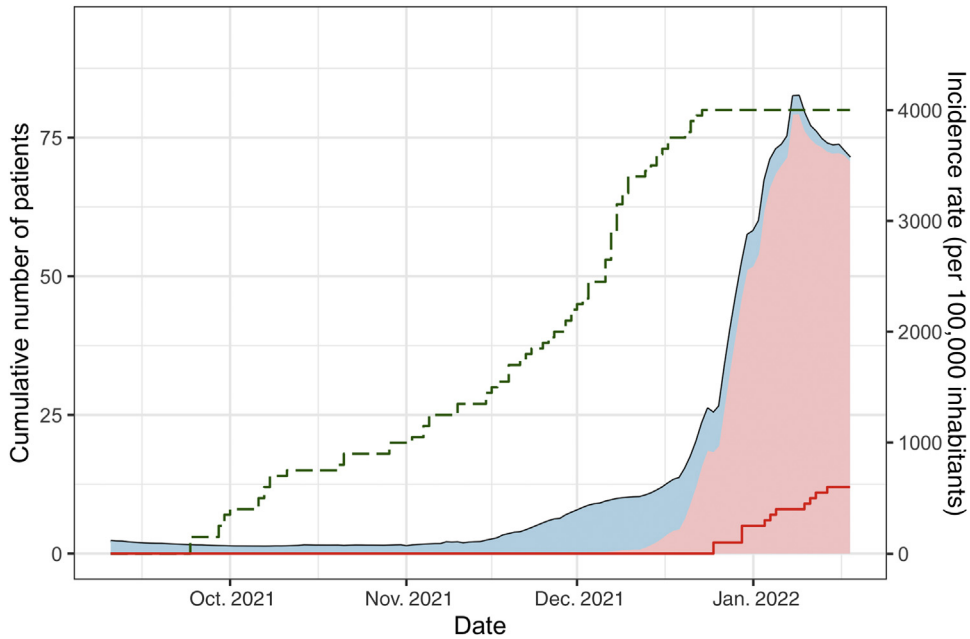

Figure 1 | Occurrence of coronavirus disease 2019 (COVID-19) breakthrough infections is associated with the occurrence of the Omicron variant in Ile-de-France, France. Green dashed line: cumulative number of REGEN-Cov administrations. Red line: cumulative number of COVID-19 infections among patients treated with REGEN-Cov in our cohort. Black curve: COVID-19 incidence rate in Ile de France, France, per 100,000 inhabitants. Blue area: proportion of COVID-19 cases with the suspected Delta variant (the presence of the L452R mutation) in Ile-de-France, France. Pink area: proportion of COVID-19 cases with suspected Omicron variant (the lack of the L452R mutation) in Ile-de-France, France. Data for Ile de France were obtained from Santé Publique France (https://geodes.santepubliquefrance.fr) on January 22, 2022.

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A fourth SARS-CoV-2 mRNA vaccine in strictly seronegative kidney transplant recipients

To the editor: Solid organ transplant recipients have demonstrated a lower humoral immune response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccination, leading transplant physicians to perform a third vaccine injection.[1] However, despite this early booster, about 35% of patients remained seronegative and, thus, inadequately protected against coronavirus disease 2019 (COVID-19).[2] Recently, a fourth mRNA injection has become available in France, as well as the possibility of monthly preventive preexposure monoclonal antibody therapy in low-responder or nonresponder patients.[3,4] On the basis of physicians' expertise and patients' choice, kidney transplant recipients from 2 French university hospitals with a strictly negative serologic assessment (i.e., binding antibody unit [BAU] <1/ml) 1 month after the third injection were proposed to receive a fourth mRNA vaccine as an alternative to preexposure monoclonal antibody prophylaxis.

We retrospectively evaluated 49 nonresponder kidney transplant recipients with a serologic assessment following a fourth mRNA vaccine (Table 1). The mean age was 63 years, and 47% were men. None of them had a history of COVID-19 infection nor anti-nucleocapsid IgG.

Table 1 | Characteristics of kidney transplant recipients strictly negative after 3 mRNA vaccines having received a fourth mRNA vaccine

	Negative (n = 28)			Positive (n = 21)			
Characteristic	NA	No.	%	NA	No.	%	*P* value
Male recipient	0	15	53.6	0	8	38.1	0.38
Transplant rank ≥2	0	4	14.3	0	2	9.5	0.68
Calcineurin inhibitor treatment	0	20	71.4	0	18	85.7	0.31
mTOR inhibitor treatment	0	0	0	0	1	4.7	0.43
Antimetabolite treatment	0	23	82.1	0	18	85.7	1
Steroid treatment	0	18	64.2	0	10	47.6	0.26
Belatacept treatment	0	0	0	0	1	4.7	0.43
BNT162b (Pfizer) mRNA vaccine	0	19	67.8	0	18	85.7	0.19
Lymphocytes <1500/mm^3	0	21	75.0	0	13	61.9	0.36
CMV seropositive status	0	17	60.7	1	8	40.0	0.15
Presence of donor-specific antibody	0	5	17.8	0	3	14.3	0.77
History of biopsy-proven acute rejection	0	6	21.4	0	1	4.8	0.21
	NA	Mean	SD	NA	Mean	SD	*P* value
Age, yr	0	63.4	11.1	0	62.4	12.8	0.87
Time from transplantation, yr	0	8.0	7.2	0	7.1	6.5	0.76
Time between third and fourth vaccine, d	0	82.6	25.7	0	93.4	31.7	0.30
Anti-spike IgG titer, BAU/ml	0	0.3	1.0	0	81.4	93.7	< 0.001
Allograft function by MDRD, ml/min	0	43.2	18.8	0	40.1	13.5	0.73

BAU, binding antibody unit; CMV, cytomegalovirus; MDRD, Modification of Diet in Renal Disease; NA, not available.

Maintenance therapy consisted of calcineurin inhibitors in 77%, antiproliferative drugs in 83%, and steroids in 57%. All of them had a strictly negative serology after the third injection (BAU, <1/ml, evaluated in different laboratories by ECLIA Roche, Architect Abbott, or Diasorin). Serologic screening was assessed in a median of 35 days following the fourth injection, and anti-spike IgG titers were expressed in BAU/ml after conversion, depending on the laboratory test. A total of 21 of 49 patients (42.8%) seroconverted (i.e., positive serology considered by laboratory thresholds) following the fourth injection, with a mean BAU titer of 82/ml (Figure 1). Of note, 4 of them had a high BAU titer (>264/ml), which can be considered as neutralizing,[5] and 3 patients without seroconversion had a slight increase in anti-spike IgG. SARS-CoV-2 infection occurred in 1 patient, who previously developed a low humoral response following 4 injections (BAU, 14.2/ml), presenting with mild symptoms and not requiring oxygen supportive care. Although no statistical differences were found between responders and nonresponders because of the small analyzed cohort, we noted lower steroid use (47% vs. 64%), less lymphopenia (62% vs. 75%), longer time between the third and fourth dose (93 vs. 82 days), and a larger utilization of the BNT162b vaccine (86% vs. 68%) in patients who developed a humoral response