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.

SUPPLEMENTARY MATERIAL

Supplementary File (PowerPoint)

Table S1. Baseline characteristics of the patients and occurrence of Omicron infection in the 3 groups. The χ^2 test (nominal variables) and the *t* test (continuous variables) were used to compare the 3 groups; results were considered significant when $P < 0.05$. *P: comparison between groups 1 and 2. **P: comparison between groups 2 and 3. ***P: comparison between groups 1 and 3. AZA, azathioprine; eGFR, estimated glomerular filtration rate, estimated by Modification of Diet in Renal Disease (MDRD) formula; F, female; ICU, intensive care unit; M, male; MMF, mycophenolate mofetil.

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Kidney International (2022) **102,** 440–442; https://doi.org/10.1016/j.kint.2022.05.007

Pre-exposure prophylaxis with 300 mg Evusheld elicits limited neutralizing activity against the Omicron variant

To the editor: Immunocompromised patients show an impaired vaccine-induced immune response, resulting in an increased risk of severe coronavirus disease 2019 (COVID-19).[1] In an effort to address this issue, health authorities in the US and various European countries have subsequently authorized the use of anti–severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) monoclonal antibodies for pre-exposure prophylaxis. Although the combination of casirivimab–imdevimab (Ronapreve, Roche Regeneron) has been shown to confer satisfactory protection against the Delta variant, it has limited neutralizing activity against Omicron.[2] In March 2022, the combination of cilgavimab–tixagevimab (Evusheld, AstraZeneca) was approved in the UK for protecting transplant recipients with poor response to vaccination against the Omicron variant.[3] In France also, Evusheld was granted approval as of December, 2021. Although the Phase III Double-blind, Placebo-controlled Study of AZD7442 for Pre-exposure Prophylaxis of COVID-19 in Adult (PROVENT) study showed good efficacy for 300 mg Evusheld in the context of Delta-variant circulation, the question of whether this dosage is sufficient to prevent Omicron infection remains unanswered. Previous data indicated that the serum-neutralizing capacity against SARS-CoV-2 is positively associated with protection against severe forms of COVID-19.[4] Here, we analyzed the neutralizing capacity of Evusheld against Omicron in a cohort of kidney transplant recipients who received the drug for pre-exposure prophylaxis.

Both anti–receptor binding domain (RBD) IgG titers and neutralizing antibody titers against the Omicron BA.1 variant were measured in serum samples collected from 63 adult kidney transplant recipients who received gluteal i.m. prophylactic injections of Evusheld (150 mg tixagevimab and 150 mg cilgavimab) in the Lyon and Strasbourg University Hospitals. Recipients with a history of COVID-19 or positive anti-nucleocapsid IgG were excluded. Patients who received prophylactic Ronapreve (600 mg casirivimab and 600 mg imdevimab, $n = 39$) and those who were infected with SARS-CoV-2 during the fifth wave of the pandemic ($n = 14$) were used as the negative and positive control groups, respectively. The study protocol was approved by the local ethics committees (identifier: DC-2013–1990 and DC-2021-4460), and written informed consent was obtained from all participants.

After a median interval from injection of 29 days (interquartile range: 29–33 days), patients who received Evusheld had a low level of neutralizing activity (Figure 1a), and only 9.5% of them (6 of 63) were able to neutralize the Omicron variant, compared with 71% of patients (10 of 14) who were infected with SARS-CoV-2, and 2.6% (1 of 39) of those who received Ronapreve. Interestingly, convalescent patients displayed higher levels of neutralizing antibodies than those who received Evusheld (median: 2.3 log IC50, interquartile range: 1.5−2.7 vs. 0.00 log IC50, interquartile range: 0−0.05; $P < 0.001$). Although anti-RBD IgG titers were generally low after Evusheld injection (median: 2583 binding antibody units (BAU)/ml, interquartile range: 1906−3611 BAU/ml), a high interindividual variability was observed (range: 262−7032 BAU/ml; Figure 1b). This variability was explained largely by the patients' body mass index, which showed an inverse

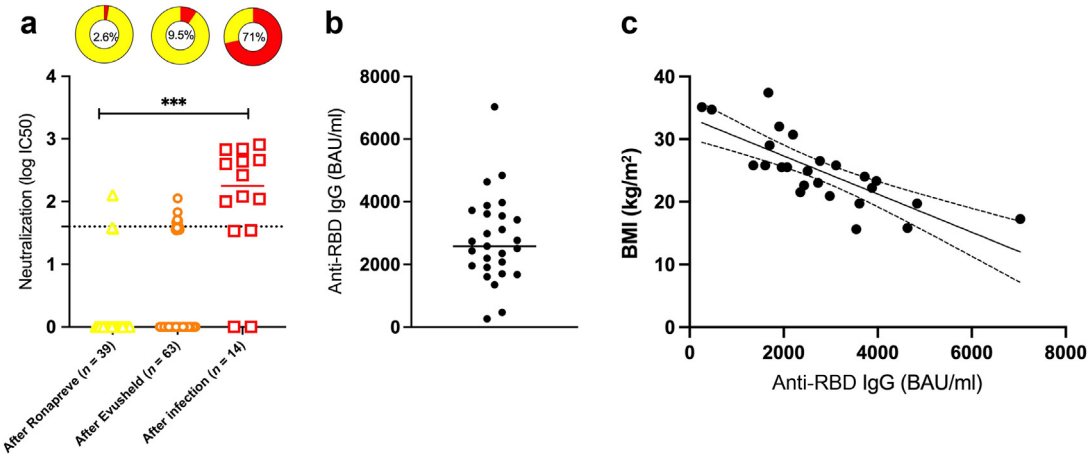

Figure 1 | (a) Serum-neutralizing IgG titers (log IC50) measured with a previously described in-house viral pseudoparticle-based assay[4] in 3 groups of kidney transplant recipients. Orange circles denote titers measured at 28 days post-injection in patients ($n = 63$) who received Evusheld (300 mg; AstraZeneca), whereas yellow triangles indicate titers quantified at 31 days post-injection in patients ($n = 39$) who received Ronapreve (1200 mg; Roche Regeneron). Red squares denote titers measured at 27 days post-infection in patients ($n = 14$) infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Dotted line represents the neutralizing positivity threshold (1.6 log IC50). Groups were compared with the Kruskal-Wallis test. The contingency graphs at the bottom of the figure indicate the percentages of patients with neutralizing activity in each group (with positive in red and negative in yellow; the percentage is reported in the middle). (**b**) Anti–receptor binding domain (RBD) IgG titers (binding antibody units [BAU]/ml, Abbott Architect) 28 days after Evusheld injection (300 mg) in 27 patients who did not receive Ronapreve™ before Evusheld. (**c**) Correlation between body mass index (kg/m^2) and anti-RBD IgG titers (BAU/ml, Abbott Architect) 28 days after Evusheld injection (300 mg) in 27 patients who did not receive Ronapreve before Evusheld; $r^2 = 0.595$. BMI, body mass index.

correlation with anti-RBD IgG titers (Figure 1c). Further analysis revealed that participants with anti-RBD titers <2500 BAU/ml after Evusheld injection had no neutralizing activity (Figure 2). Furthermore, 7 patients of this cohort developed symptomatic COVID-19, including 2 who required hospitalization. All had negative neutralizing activity at the time of infection diagnosis.

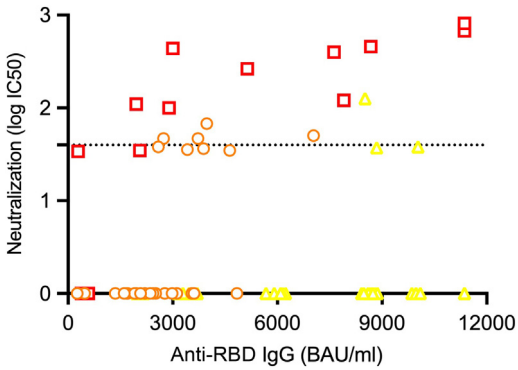

Figure 2 | Correlation between anti–receptor binding domain (RBD) IgG (Abbott Architect) and neutralizing antibody titers[3] in 3 groups of kidney transplant recipients. Orange circles denote titers measured at 28 days post-injection in patients ($n = 63$) who received Evusheld (300 mg; AstraZeneca), and yellow triangles indicate titers quantified at 31 days post-injection in patients ($n = 39$) who received Ronapreve (300 mg; Roche Regeneron). Red squares denote titers measured at 27 days post-infection in patients ($n = 14$) who were infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). BAU, binding antibody units.

Taken together, these data indicate that less than 10% of patients who received Evusheld were able to neutralize the Omicron BA.1 variant at 29 days post-injection. Therefore, the dose of 300 mg Evusheld is likely insufficient to achieve the required neutralization activity *in vivo*. These findings corroborate those of a recent study conducted in transplant recipients who received 3 vaccine doses[5]; specifically, the authors reported that anti-RBD levels associated with serum neutralizing activity against Omicron in this population were approximately 8500 BAU/ml.[5] Finally, our study also supports recent FDA recommendations,[6] derived from *in vitro* models, regarding the need to increase the dose of Evusheld. To our knowledge, data on the effectiveness of tixagevimab−cilgavimab in the prevention of Omicron BA.2 infection have not yet been published. Research aimed at assessing the correlation between anti-RBD titers after Evusheld administration and the *in vivo* neutralizing capacity against the BA.2 Omicron variant is currently ongoing.

DISCLOSURE

SC and OT have received consultant fees from AstraZeneca. All the other authors declared no competing interests.

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Kidney International (2022) **102,** 442–444; https://doi.org/10.1016/j.kint.2022.05.008

Do the benefits of subcutaneous immunoglobulin therapy for secondary hypogammaglobulinemia in ANCA vasculitis extend beyond infection prevention?

To the editor: Antineutrophil cytoplasmic autoantibody–associated vasculitides (AAV) are necrotizing small-vessel vasculitides characterized by a relapsing course. Rituximab is recommended for both remission induction and maintenance in AAV.[1] Hypogammaglobulinemia is being increasingly recognized with over 50% of patients developing moderate-to-severe hypogammaglobulinemia, and infection risk remains a key concern in these patients.[2] Infection is not only a serious complication in immunosuppressed patients but has also been theorized to play a role in triggering AAV such as through pathways of molecular mimicry or lymphocyte activation.[3] In patients with serum IgG less than 300 mg/dl, it is recommended to use alternatives for rituximab. S.c. Ig therapy (SCIG) has been used to treat antibody deficiency in AAV.[4] I.v. Ig dosed at 2 g/kg given over 5 days has been shown to improve disease activity in active AAV,[5] but their role in modulating maintenance immunosuppression is unknown. We report a potential benefit of SCIG in modulating maintenance

Table 1 | Patient characteristics, immunosuppression regimen, details of infections, and s.c. Ig administration

ID	Age (yr)	Sex	Race	ANCA type	Induction treatment	Maintenance treatment		Number and type of infections		SIgG (mg/dl)		Number of AAV relapses		Follow-up from last RTX use (mo)
						Before SCIG	After SCIG	Before SCIG	After SCIG	Before SCIG	After SCIG	Before SCIG	After SCIG	
1	68	F	C	PR3	MTX+RTX+GC	RTX every 6 mo and then every 4 mo	RTX stopped P 7.5 mg	5 Sinusitis, pneumonia, urosepsis	1 Dental	300	987	2	None	33
2	79	F	C	NEG	RTX+GC	None	None	4 UTIs	None	367	879	None	None	29
3	69	F	C	PR3	PLEX, CYC, RTX+GC	AZA, P	P 3 mg	5 Pulmonary candidiasis, PCP, influenza, C. diff	None	209	953	None	None	128
4	16	M	C	PR3	RTX, GC	AZA, LEF, P, RTX 1000 mg every 6 mo	RTX dose and duration decreased initially and then stopped	None	None	474	1202	6	None	53
5	50	M	C	NEG	MTX, CYC, RTX+GC	RTX every 6 mo	RTX duration decreased initially and then stopped	3 Streptococcus pharyngitis	None	289	850	1	None	47

ANCA, antineutrophil cytoplasmic antibody; AAV, ANCA-associated vasculitis; AZA, azathioprine; C, Caucasian; C. Diff, clostridioides difficile; CYC, cyclophosphamide; F, female; GC, glucocorticosteroids; LEF, leflunomide; M, male; MTX, methotrexate; NEG, negative; P, prednisone, PCP, pneumocystis pneumonia; PLEX, plasma exchange; PR3, proteinase-3; RTX, rituximab; SCIG, s.c. Igs; SIgG, serum IgG; UTIs, urinary tract infections; Y, yes.