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.

European Journal of Internal Medicine 100 (2022) 140–142

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Letter to the Editor

Impact of therapeutic plasma exchange on acquired vaccinal anti-SARS-CoV-2 antibodies

ARTICLE INFO

Keywords
Therapeutic plasma exchange
Sars-cov-2
Vaccine
Humoral response

Dear Editor,

As of December 2021, more than 276 million affected cases and 5 million deaths were reported by the World Health Organization, due to the COVID-19 pandemic [1]. Following the outbreak's beginning, patients receiving treatments impairing their immunity (*e.g.,* chemotherapy; immunosuppressive drugs for solid organ transplantation or inflammatory diseases) were soon recognized as being at increased risk of developing severe forms of COVID-19 [2,[3]]. Although anti-SARS-CoV-2 vaccines have proven to be efficacious in reducing the risk of both severe disease and mortality in the general population [4], emerging evidence has revealed that immunocompromized patients actually display a reduction in vaccine-induced humoral responses [5, 6]. To our best knowledge, the impact of therapeutic plasma exchange (TPE) on anti-SARS-CoV-2 vaccines responses has not yet been investigated so far.

Yet, TPE has been widely used for decades in various indications including systemic auto-immune disorders, hematological diseases, and transplantation.

We conducted a monocentric prospective study over a 3-month period from July 2021 to September 2021, involving all consecutive non-critically ill patients from our apheresis unit on regular TPE therapy, who were vaccinated against SARS-CoV-2 (any vaccine type; two doses administered) with detectable vaccine-induced antibodies. Anti-receptor binding domain (RBD) antibody titers were assessed at three time points, namely just before (T0) and immediately after (T1) a TPE procedure, and just prior to the subsequent TPE (T2). The study was performed in accordance with the Helsinki Declaration principles. The protocol was approved by the Institutional Review Board (*Comité Ethique Hospitalo-Facultaire of the Cliniques universitaires Saint-Luc, Brussels, Belgium - B4032021000093*) and registered on ClinicalTrials.gov (NCT05191394). Written consent was obtained from all the participants.

During the study period, the 16 consecutive non-critically ill adult patients from our center on regular TPE therapy were screened, with 14 actually enrolled. The reasons for screening failure were: one patient died owing to his Waldenstrom macroglobulinemia's progression and another kidney transplant recipient had not developped any anti-SARS-CoV-2 antibodies 31 days following the second Oxford/AstraZeneca ChAdOx1 vaccine dose. All participants were already on regular TPE treatment at the time of the vaccination program, and this for more than a year in 11 cases (78.6%). Demographic characteristics of the study population are summarized in Table 1. All the TPE procedures were performed with the Spectra Optia® device, using peripheral venous access and Albumine 5% (Alburex®) as replacement fluid. The volume of plasma processed ranged from 0.8 to 1.2 x the total plasma volume.

Most (92.9%) participants received two mRNA anti-SARS CoV-2 vaccine doses, excepting one who was injected with Oxford/AstraZeneca ChAdOx1 vaccine. No patient displayed a history of clinically documented SARS-CoV-2 infection and all, but one, displayed negative anti-N antibody testing at inclusion. No adverse events related to either TPE procedures or SARS-CoV-2 infection were documented during the study.

At inclusion (T0), the median [range] anti-RBD antibody titer was 339.2 [22–9132.7] BAU/mL. The median [range] time interval between the second vaccine dose and first anti-RBD level determination (T0) was 71 [26–135] days. The median [range] time interval between last TPE and study inclusion was 25.5 [2–62] days. The median [range] schedule of TPE procedures was one session every 3.5 [0.5–8] weeks. The median [range] number of TPE between the second vaccine dose and inclusion was two [1-14]. No statistically significant correlation was found between anti-RBD levels at T0 and either frequency of TPE treatments ($p=0.073$) or number of TPE sessions carried out from the second vaccine dose to inclusion ($p=0.659$). Moreover, neither the age of participants ($p=0.108$) nor concurrent immunosuppressive treatments ($p=0.298$) exerted a significant impact on baseline anti-RBD antibody levels.

Data regarding the evolution of antibody titers between two TPE sessions were available for 13 participants (because of analytical issue for one T2 specimen in one patient). The median [range] time interval between T0 and T2 was 21 [4–50] days. Median [range] anti-RBD antibody titers for the 13 patients at T0, T1, and T2 were 267.8 [22–9132.7] BAU/mL, 125.5 [8.6–3630.7] BAU/mL, and 180.3 [11.1–5452.7] BAU/mL, respectively. Compared to T0, the T1 and T2 anti-RBD antibody titers were decreased by 60.7% ($p<0.001$) and 32.7% ($p=0.155$), respectively. At T2, four (30.8%) patients had returned within baseline values (±20% compared to T0 values). We assessed the

https://doi.org/10.1016/j.ejim.2022.02.014
Received 3 February 2022; Received in revised form 9 February 2022; Accepted 11 February 2022
Available online 14 February 2022

Table 1
Demographics of the population (n=14).

Median [range] age	57 [31–83] years
Female/male	64.3%(n=9)/35.7% *(n=5)*
Indication for TPE	Myasthenia Gravis: 42.9% *(n=6)* Waldenstrom macroglobulinemia: 28.6% *(n=4)* Other: 28.6% *(n=4)* *Cold agglutinin disease (n=1)* *Auto-immune encephalitis (n=1)* *Familial hypertriglyceridemia (n=1)* *MGRS*+cryoglobulinemic nephritis (n=1)*
Active immunosuppressive therapy	64.3% *(n=9)* *Corticosteroids (n=6)* *Azathioprine (n=2)* *Mycophenolate mofetil (n=2)* *Ciclosporine (n=1)* *Ibrutinib (n=1)* *Lenalidomide (n=1)*
Anti-SARS-CoV2 vaccine types	Pfizer/BioNtech: 78.6% *(n=11)* mRNA-1273 Moderna: 14.3% *(n=2)* Oxford/AstraZeneca ChAdOx1: 7.1% *(n=1)*
Median [range] interval between the two mRNA vaccine doses	28 [21–35] days

*MGRS: monoclonal gammopathy of renal significance.

relative impact of different variables on antibody titer kinetics between two plasma exchange sessions. Concurrent immunosuppressive treatments (p=0.504), age (p=0.945), time elapsed between last vaccine dose injection and study inclusion (T0) (p=0.445), TPE number between last vaccine dose injection and study inclusion (T0) (p=0.231), as well as time between the two studied TPE sessions (T0-T2) (p=0.199) exerted no impact on antibody titer decreases.

We have herein provided reassuring data on the anti-SARS-CoV-2 antibody titer distribution in patients undergoing regular TPE therapy. Indeed, 64.3% of participants exhibited anti-RBD titers >143 BAU/mL at inclusion, despite a median time since second vaccine dose exceeding 2 months with several (median: 2) consecutive TPE procedures during this period. Of note is that this threshold of 143 BAU/mL has been proven to correlate with the presence of neutralizing antibodies, being to date the most widely accepted marker of disease protection [7]). This observation even applied to patients on immunosuppressive therapy.

Additionally, our study showed that, although the maximum decrease in antibody titers of about 60% was achieved just after the TPE session, a vast proportion of antibodies were still recovered prior to the following TPE session, with 69.2% of participants displaying antibody titers >143 BAU/mL at T2. This was observed independently of the time interval between both procedures, though total antibody levels were 32.7% lower than at baseline.

Based on our study results, TPE is most unlikely to jeopardize the humoral anti-SARS-CoV-2 immunity acquired post-vaccination. These results are in line with those of other studies that determined TPE's effects on antibodies elicited by vaccination. Guptill et al. demonstrated in a study involving 10 patients with Myasthenia gravis that antibody levels for Varicella zoster, Epstein-Barr virus, diphteria toxin, and tetanus oxoid reached a nadir on the final day of TPE, then gradually returning to baseline values around the day scheduled for the next session [8].

While these preliminary data are ordinarily reassuring for patients undergoing TPE, it must be stressed that these findings' clinical impact deserves further investigations. Whereas no patient from the current study actually developed SARS-CoV-2 infection during the study period, the sample size was too small and follow-up time too short to provide strong evidence, and there was no control group either. Moreover, the exact correlation between the minimum antibody titer thresfold and adequate immune protection against severe SARS-CoV-2 infection is still a matter of debate, which has been further complexified through the emergence of new SARS-CoV-2 variants [9].

Some other study limitations must be acknowledged. First, we did not assess TPE's impact on cellular immunity responses. Second, we did not measure neutralizing antibody levels. Third, we only included patients on chronic TPE, meaning that our results cannot necessarily be extrapolated to other clinical situations, such as TPE delivered in the setting of critical conditions requiring daily procedures as seen in thrombotic microangiopathies, *peri* transplantation in hyperimmunized patients, and those with acute graft rejection.

In conclusion, though validation on a larger scale is still requested, our study has provided encouraging results concerning TPE's safety and impact on the humoral responses induced by anti-SARS-CoV-2 vaccines.

Funding

None.

Authors' contributions

CL, AS and AD designed and initiated the study, and drafted the manuscript. CL coordinated the study. AS perfomed to the statistical analysis. All authors read and approved the final manuscript.

Data availability statement

Data are available on request from the authors.

Declaration of Competing Interest

The authors declare that they have no interests which might be perceived as posing a conflict of interest or bias.

Acknowledgments

All the participants are thanked for their active contribution to the study.

References

[1] WHO Coronavirus (COVID-19) Dashboard (Retrieved 2021, December 15). https://covid19.who.int.
[2] Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584:430–6.
[3] Goffin E, Candellier A, Vart P, et al. COVID-19-related mortality in kidney transplant and haemodialysis patients–A comparative, prospective registry-based study. Nephrol Dial Transplant 2021 Nov 9;36(11):2094–105.
[4] McDonald I, Murray SM, Reynolds C, et al. Comparative systematic review and meta-analysis of reactogenicity, immunogenicity and efficacy of vaccines against SARS-CoV-2. NPJ Vaccines 2021;6:74.
[5] Caillard S, Thaunat O. COVID-19 vaccination in kidney transplant recipients. Nat Rev Nephrol 2021;17:785–7.
[6] Gong I, Vijenthira A, Betschel S, et al. COVID-19 Vaccine response in patients with hematologic malignancy–A systematic review and meta-analysis. Blood 2021;138 (S1):4113.
[7] Caillard S, Thaunat O, Benotmane I, Masset C, Blancho G. Antibody response to a fourth messenger RNA COVID-19 vaccine dose in kidney transplant recipients–A case series. Ann Intern Med 2022 Jan 11:L21–0598.
[8] Guptill JT, Juel VC, Massey JM, et al. Effect of therapeutic plasma exchange on immunoglobulins in myasthenia gravis. Autoimmunity 2016 Nov; 49;(7):472–9.
[9] Christie B. Covid-19–Early studies give hope omicron is milder than other variants. BMJ 2021;375:n314.

Catherine Lambert[a,*,#], Anais Scohy[b,#], Jean Cyr Yombi[c], Eric Goffin[d], Arnaud Devresse[d]

[a] *Department of Hematology, Cliniques Universitaires Saint-Luc, Brussels, Belgium*

[b] *Department of Microbiology, Cliniques Universitaires Saint-Luc, Brussels, Belgium*

[c] *Department of Internal Medicine and Infectious Disease, Cliniques Universitaires Saint-Luc, Brussels, Belgium*

European Journal of Internal Medicine 100 (2022) 140–142

[d] *Department of Nephrology, Cliniques Universitaires Saint-Luc, Brussels, Belgium*

[*] Corresponding author.
E-mail address: catherine.lambert@uclouvain.be (C. Lambert).

[#] These authors participated equally