EBioMedicine 71 (2021) 103567

Contents lists available at ScienceDirect

EBioMedicine

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

Commentary

Measuring cellular and humoral immunogenicity of a SARS-CoV-2 mRNA vaccine (BNT126b2) in patients on maintenance haemodialysis

Paul Martin[a,*], Candice Clarke[a,b]

[a] Imperial College Renal and Transplant Centre, Imperial College Healthcare NHS Trust, Hammersmith Hospital, London W12 0HS, United Kingdom
[b] Centre for Inflammatory Disease, Department of Immunology and Inflammation, Imperial College London, Hammersmith Campus, Du Cane Road, London W12 0NN, United Kingdom

ARTICLE INFO

Article History:
Received 17 August 2021
Accepted 17 August 2021
Available online xxx

During the course of the SARS-CoV-2 pandemic, patients established on in-centre maintenance haemodialysis found themselves in a unique and unenviable predicament: deemed to be clinically extremely vulnerable to COVID-19 by virtue of their end stage kidney disease (ESKD), and yet unable to shield due to their need to regularly access a life-sustaining therapy in a healthcare setting.

Renal healthcare providers around the world did their best to adapt in-centre haemodialysis environments to safely deliver the service. Screening protocols and infection prevention measures were established, and infected patients were cohorted at specific dialysis centres where possible. Despite these efforts, both infection and mortality rates in this cohort of patients were high at up to 20% and 32%, respectively [1]. The advent of safe, effective SARS-CoV-2 vaccines was met with both relief and caution as patients with ESKD were excluded from the large phase III SARS-CoV-2 vaccine trials, and attenuated responses to vaccines (hepatitis B, influenza) is well documented in haemodialysis populations [2].

Since December 2020, the body of work detailing the early immunogenicity to SARS-CoV-2 vaccines in haemodialysis patients has been growing steadily. In dialysis populations, the mRNA BNT126b2 vaccine is by far the most studied, with the detection of serum anti-spike IgG being the most commonly evaluated marker of immunogenicity.

Following on from initial studies undertaken after a single dose of vaccine, there are now multiple published studies assessing antibody responses in haemodialysis patients after two doses: reassuringly seroconversion rates are reported to be as high as 96%, in comparison to rates of 99–100% seen in healthy controls, however antibody titres are significantly lower in the dialysis cohorts compared to controls [3–5].

The presence of both neutralising antibodies and vaccine specific T-cell responses have been linked to the prevention of symptomatic SARS-CoV-2 infection in non-renal populations [6]. A recent study in a dialysis cohort reassuringly found titres of neutralising antibodies to be comparable to those seen in healthy controls after two doses of BNT126b2 vaccine [7], however there are still limited published data on cellular responses to vaccination in the dialysis population; reports from three studies show that between 62-100% of patients have a detectable T-cell responses after mRNA vaccination [4,8,9]. As antibody titres are expected to wane over time, longitudinal serological and cellular follow-up will be important in this group of patients, alongside studies evaluating what detectable level of immunogenicity correlates to clinical protection.

Being mindful that the immune response elicited by vaccines is multi-faceted, it is with interest that we read the paper by *Strengert M et al* published in the August issue of *EBioMedicine* [10]. Compared with similar published studies of vaccine immunogenicity undertaken in haemodialysis populations to date, *Strengert M et al* have performed a more comprehensive assessment of the immune responses in their study cohort beyond measurement of anti-spike IgG levels. By including only infection-naïve patients, they have also ensured all reported cellular and humoral responses are vaccine specific. This is the first study which reports salivary IgG and IgA levels in haemodialysis patients after vaccination; relevant, of course, because SARS-CoV-2 is a mucosal-targeted virus. Acknowledging the threat that SARS-CoV-2 "variants of concern" pose to the vaccination programme, this study also analyses antibody binding capability toward four current SARS-CoV-2 variants; including the beta variant which has a high rate of vaccine escape, but notably not including the delta variant which is now the dominant strain internationally. Antibody neutralisation potency is shown to be diminished in the haemodialysis group compared with the control group and variable when tested against variants of concern. Finally, in measuring IFN-gamma levels and an array of other relevant cytokines, vaccine induced T-cell responses are shown to be attenuated in the haemodialysis group.

In keeping with other published studies on the topic, the overall finding is that immune responses to BNT126b2 mRNA vaccine are diminished in haemodialysis patients. Reassuringly, however, only a small minority were deemed to be serologic "non-

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2021.103524.
* Corresponding author.
E-mail address: paul.martin9@nhs.net (P. Martin).

https://doi.org/10.1016/j.ebiom.2021.103567

responders". The authors rightly highlight that the relatively small sample size limited any inferential statistical analysis, particularly when identifying any patient-related factors associated with diminished immune response to vaccination, but they should be commended for undertaking a relatively broad immunological assessment that reiterates that, although blunted, haemodialysis patients are capable of mounting humoral and cellular responses to mRNA platform vaccines.

So, what does this mean for haemodialysis patients? Ultimately, as societies emerge from "lockdown" restrictions, both clinicians and patients wish to know the effectiveness of current vaccination strategies in preventing the development of severe COVID-19 illness. Real world effectiveness studies will be required to assess clinical outcome data with reporting of infection rates, severity of disease, hospitalisations, and mortality among vaccinated haemodialysis patients. Longitudinal studies are required to understand how long we can expect protection to persist after vaccination and whether this cohort of patients will require regular booster doses in view of their relative immunosenescence. Without doubt, multi-centre collaboration will be essential to ensure high quality data is generated to guide future vaccination programmes in this vulnerable group.

Contributors

Dr Paul Martin completed the literature search and wrote the original draft. Dr Candice Clarke reviewed and edited the final draft.

Declaration of Competing Interest

All authors have no conflicts of interest to disclose.

References

[1] Francis A, Baigent C, Ikizler TA, Cockwell P, Jha V. The urgent need to vaccinate dialysis patients against severe acute respiratory syndrome coronavirus 2: a call to action. Kidney Int 2021;99. doi: 10.1016/j.kint.2021.02.003.

[2] Dikow R, Eckerle I, Ksol-Rudek D, Hampel H, Schwenger V, Zeier M, et al. Immunogenicity and efficacy in hemodialysis patients of an AS03(A)-adjuvanted vaccine for 2009 pandemic influenza A(H1N1): a nonrandomized trial. Am J Kidney Dis 2011;57(5):716–23 MayEpub 2011 Feb 23. PMID: 21349617. doi: 10.1053/j.ajkd.2010.11.031.

[3] Grupper A, Sharon N, Finn T, Cohen R, Israel M, Agbaria A, et al. Humoral response to the Pfizer BNT162b2 vaccine in patients undergoing maintenance hemodialysis. Clin J Am Soc Nephrol 2021 Apr 6:CJN.03500321Epub ahead of print. PMID: 33824157. doi: 10.2215/CJN.03500321.

[4] Stumpf J, Siepmann T, Lindner T, Karger C, Schwobel AL, et al. Humoral and cellular immunity to SARS-CoV-2 vaccination in renal transplant versus dialysis patients: a prospective, multicenter observational study using mRNA-1273 or BNT162b2 mRNA vaccine. Lancet 2021 July 22. doi: 10.1016/j.lanepe.2021.100178.

[5] Grupel D, Gazit S, Schreiber L, Nadler V, Wolf T, Lazar R, et al. Kinetics of SARS-CoV-2 anti-S IgG after BNT162b2 vaccination. Vaccine 2021 Aug 11S0264-410X(21)01045-8. doi: 10.1016/j.vaccine.2021.08.025.

[6] Khoury DS, Cromer D, Reynaldi A, Schlub TE, Wheatley AK, Juno JA, et al. Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection. Nat Med 2021;27(7):1205–11 JulEpub 2021 May 17. PMID: 34002089. doi: 10.1038/s41591-021-01377-8.

[7] Carr EJ, Wu M, Harvey R, Wall EC, Kelly G, Hussain S, et al. Neutralising antibodies after COVID-19 vaccination in UK haemodialysis patients. Lancet 2021 Aug 12S0140-6736(21)01854-7Epub ahead of print. PMID: 34391504. doi: 10.1016/S0140-6736(21)01854-7.

[8] Bertrand D, Hamzaoui M, Lemee V, Lamulle J, Hanoy M, Laurent C, 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 Jun 10:ASN.2021040480Epub ahead of print. PMID: 34112706. doi: 10.1681/ASN.2021040480.

[9] Broseta JJ, Rodriquez-Espinosa D, Rodriguez N, Mosquera M, Marcos MA, Egri N, et al. Humoral and cellular responses to mRNA-1273 and BNT162b2 SARS-CoV-2 vaccines administered to hemodialysis patients. Am J Kidney Dis 2021 Jun 23:S0272-6386(21)00689-2Epub ahead of print. PMID: 34174364; PMCID: PMC8223037. doi: 10.1053/j.ajkd.2021.06.002.

[10] Strengert M, Becker M, Ramos GM, Dulovic A, Gruber J, Juengling J, et al. Cellular and humoral immunogenicity of a SARS-CoV-2 mRNA vaccine in patients on haemodialysis. EBioMedicine 2021;70. doi: 10.1016/j.ebiom.2021.103524.