Nephrol Dial Transplant (2022) 37: 1384–1386
https://doi.org/10.1093/ndt/gfac033
Advance Access publication date 9 February 2022

RESEARCH LETTER

Heterologous versus homologous triple anti-COVID-19 vaccine regimens in patients on maintenance haemodialysis

Björn Meijers[1,2], Annelien Goedgezelschap[3], Domien Peeters[4], Annelien Van Der Veen[1], Margo Verbinnen[1,3], Pieter Vermeersch[5], Koen Stas[3] and Dirk Kuypers[1,2]

[1]Nephrology and Transplantation Unit, University Hospitals Leuven, Leuven, Belgium, [2]Laboratory of Nephrology, KU Leuven, Leuven, Belgium, [3]Nephrology Unit, Jessa Ziekenhuis, Hasselt, Belgium, [4]Nephrology Unit, Sint Trudo Ziekenhuis, Sint-Truiden, Belgium and [5]Department of Laboratory Medicine, University Hospitals Leuven, Leuven, Belgium

Correspondence to: Björn Meijers; E-mail: bjorn.meijers@uzleuven.be; Twitter handle: @bkimeijers

Patients on maintenance haemodialysis are prone to severe coronavirus disease 2019 (COVID-19) and have a high case fatality rate. Vaccination is a promising strategy to reduce mortality and morbidity. Most published data are available for the adenovirus-vector ChAdOx1 nCoV-19/AZD1222 (AstraZeneca) and the mRNA-based vaccines [BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna)] [1, 2].

Despite widespread deployment of vaccination, dialysis patients remain a vulnerable population. Patients receiving dialysis have a poorer antibody response rate as compared with individuals not receiving dialysis [1]. Factors determining response include past infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and comorbidities, e.g. diabetes. The prevalence of absent or diminished antibody response to COVID-19 vaccination also seems to vary by vaccine type [3], with a lesser humoral response to AZD1222 as compared with the mRNA-based vaccines (BNT162b2 and mRNA-1273) [3, 4]. Triple vaccination in vulnerable populations such as patients on maintenance dialysis may be of benefit, especially in those patients having a poor initial response [5].

We investigated whether there are differences in the humoral response to the vector-based AZD1222 vaccine versus two mRNA-based vaccines (BNT162b2 and mRNA-1273) using samples collected as part of a prospective longitudinal study in three dialysis units (Sint Trudo, Jessa Hospital and University Hospitals Leuven) in the Flanders region, Belgium (NCT04378686). We measured IgG anti-S (spike) SARS-CoV-2 antibody levels using the SARS-CoV-2 IgG II Quant assay (Abbott). As longitudinal sampling demonstrated response maturation with a gradual increase in seroconversion rates and antibody titres over several weeks following the first and especially following the second vaccine dose [6], we analysed antibody response at 53 (SD 17) days after vaccination. IgG titres in response to the different vaccine regimens were compared using Kruskal–Wallis test. The fraction of patients below/above the cut-off was compared using Fisher's exact test.

Using the manufacturer's cut-off value of 50 AU/mL, 88.3% (83/94), 96.6% (137/149) and 100% (59/59) of patients seroconverted after dual vaccination with AZD1222, BNT162b2 and mRNA-1273, respectively. The anti-S antibody titre, however, significantly differed ($P < 0.001$ for trend) between vaccines (Figure 1A) with the lowest response to the adenoviral-vectored AZD1222. As a surrogate measure of neutralizing antibodies, we evaluated for the presence of IgG levels at or above 4160 AU/mL, reported to correspond to a 0.95 probability of obtaining a plaque reduction neutralization test ID50 at a 1:250 dilution [7]. After two vaccine doses, only 16.0% (15/94) of patients had an anti-S antibody titre exceeding this threshold after vaccination with AZD1222, versus 22.8% (34/149) and 62.7% (37/59) in response to BNT162b2 and mRNA-1273, respectively ($P < 0.0001$ for mRNA-1273 versus both).

The humoral response significantly ($P < 0.0001$) increased for triple dosing regimens as compared to double dosing regimens (Figure 1A). A detectable anti-S titre (>50 AU/mL) was reached in 95.8% (90/94) with the heterologous double AZD1222 plus BNT162b2 and in 98.0% (146/149) and 100% (59/59) after triple vaccination with BNT162B2 and mRNA-1273, respectively (P = NS). As compared with the response after two vaccines, a significantly larger fraction of patients reached the surrogate neutralizing antibody threshold ($P < 0.01$, Figure 1). After the heterologous AZD1222/BNT162b2 regimen, anti-S titres exceeded this threshold in 56.4 (53/94) versus 75.2% (112/149) and 88.1% (52/59) after triple vaccination with BNT162B2 and mRNA-1273, respectively [$P < 0.01$, heterologous AZD1222/BNT162b2 versus the homologous triple mRNA regimens (BNT162B2 or mRNA-1273)].

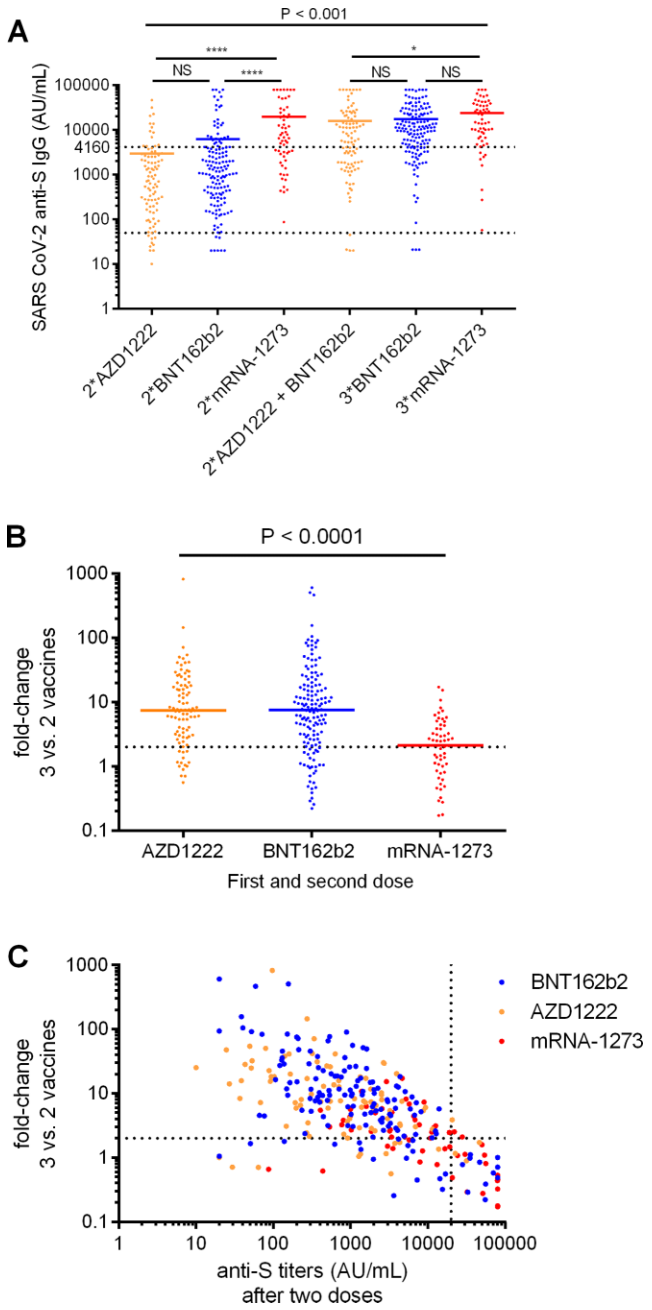

FIGURE 1: The humoral response to different COVID-19 vaccine regimens, consisting of either homologous prime-boost vaccination (AZD1221, BNT162b2, or mRNA-1272), homologous triple vaccination (BNT162b2, mRNA-1272) or heterologous triple vaccination (twice AZD1221 plus BNT162b2 booster). (**A**) Anti-S IgG titres measured using the SARS-CoV-2 IgG II Quant assay (Abbott), in response to the different regimens. Two cut-offs are given, at 50 AU/mL (based on assay manufacturer) and at 4160 AU/mL as proxy for 95% of obtaining a plaque reduction neutralization test ID50 at a 1:250 dilution [7]. (**B**) Fold-change of anti-S IgG following a third vaccine, as a function of the different homologous prime-boost vaccine regimens. Bars represent median values. A 2-fold cut-off is given as relevant change. (**C**) Fold-change of anti-S IgG following a third vaccine, as a function of the anti-S IgG titres following conventional prime-boost vaccination. A 2-fold cut-off is given as relevant change. *P < 0.05; ****P < 0.001; NS, not significant.

When comparing all six groups, there is a clear difference between vaccination strategies. Double vaccination with AZD1222 and BNT162b2 results in lower anti-S titres, as compared with the other vaccination strategies (P < 0.0001, Kruskal–Wallis test) or the fraction of patients exceeding the threshold (P < 0.01). Of note, anti-S titres after homologous double mRNA-1273 are not significantly different from those after triple vaccination by BNT162b2 and not significantly different from after heterologous triple vaccination (two times AZD1222 plus BNT162b2 booster). However, a third mRNA-1273 vaccination was accompanied by a further significant (P < 0.01) increase in the number of patients reaching the surrogate threshold of neutralizing antibodies (>4160 AU/mL).

We analysed the fold-change between humoral response after second versus after third vaccination (Figure 1B and C). This significantly (P < 0.0001) differed and is clearly less after initial double vaccination using mRNA-1273. A greater than 2-fold increase was found in 85% (two times AZD1222 plus BNT162b2 booster), 79% (triple BNT162b2) and 55% (triple mRNA-1273).

These differences may be explained by the differential response to the initial prime-boost vaccination. To analyse this, we plotted the fold-changes as a function of the humoral response after the second vaccine dose (Figure 1C). There is a clear negative slope and above a threshold of 20000 AU/mL, none of the patients had a more than 2-fold increase.

We analysed the contribution of clinical factors to the humoral response after homologous versus heterologous vaccination using multivariate linear regression. In this cohort, age, gender, diabetes and past history of cardiovascular disease were not independent predictors of serological response. A past episode of COVID-19 infection confirmed by nasopharyngeal swab polymerase chain reaction ($N = 39$, 12.9%) was a highly significant (P < 0.0001) predictor of a stronger serologic response. When analysing the effects of the three different triple vaccine regimens, only the heterologous regimen with two times AZD1222 plus BNT162b2 booster remained significantly associated (P = 0.03) with a lower humoral response.

In conclusion, triple vaccination against SARS-CoV-2 results in significantly higher levels of anti-S IgG antibodies. Our data are in line with data in the general population [8] and in patients after solid organ transplantation [9]. The yield of a third dose of mRNA-1273 is substantially less than a third dose of BNT162b2. This, however, mainly reflects the superior humoral response to conventional prime-boost vaccination with mRNA-1273. Heterologous vaccination with a combination of the adenoviral-vectored prime-boost of AZD1222 followed by a second booster consisting of the mRNA-based BNT162b2 leads to a strong increase in anti-S IgG antibodies. While antibody titres after this regimen are more comparable to the homologous triple mRNA-based regimens, in multivariate analysis this strategy still is significantly less efficacious to elicit a humoral response.

A limitation of our data is that we only evaluated the humoral response to triple vaccination. The cellular response against SARS-CoV-2 in response to homologous versus heterologous regimens might be different and this requires

Table 1. Patient characteristics and vaccine regimen

	Group 1	Group 2	Group 3
Patients, *n*	94	149	59
Regimen	Heterologous	Homologous	Homologous
Vaccine 1	AZD1222	BNT162b2	mRNA-1273
Vaccine 2	AZD1222	BNT162b2	mRNA-1273
Vaccine 3	BNT162b2	BNT162b2	mRNA-1273
COVID episode, Yes	10	17	12
Age, years	73.6 (10.9)	71.5 (13.5)	68.6 (13.4)
Gender, male/female	55/39	81/68	40/19
Height, cm	166 (9)	166 (10)	170 (9)
Weight, kg	72 (17)	74 (19)	76 (18)
Dialysis vintage	28.5 (10–64)	36 (16–69)	42 (22–82)
Access, AVF/AVG/TC	58/1/35	82/2/65	34/0/25
Cause of ESKD, *N* (%)			
Diabetes	14 (15)	38 (26)	5 (8)
ADPKD	5 (5)	10 (7)	9 (15)
Glomerulonephritis	28 (30)	21 (14)	11 (19)
Tubulo-interstitial	8 (9)	12 (8)	2 (3)
Vascular	21 (22)	44 (29)	9 (15)
Other/unknown	18 (19)	24 (16)	23 (38)
Comorbidities			
Diabetes, yes (%)	21 (22)	56 (37)	17 (29)
CVD, yes (%)	56 (60)	77 (52)	30 (51)
CVA, yes (%)	12 (13)	22 (15)	17 (29)
Hypertension, yes (%)	25 (27)	93 (62)	20 (34)

Patient characteristics, including vaccine regimen. Heterologous vaccination consisted of a combination of the adenoviral-vector AZD1222, followed by the mRNA-based BNT162b2. Homologous regimes consisted of triple vaccination with either three times BNT162b2, or three times mRNA-1273.

cm, centimetre; kg, kilogram; AVF, arteriovenous fistula; AVG, arteriovenous graft; TC, tunnelled catheter; ESKD, end-stage kidney disease; ADPKD, autosomal dominant polycystic kidney disease; CVD, cardiovascular disease; CVA, cerebrovascular accident.

additional analyses. Neutralizing antibodies were not probed directly using cellular assays. Given the good correlation between anti-S IgG titres and neutralizing antibodies in previous studies, the S-Ab titre cut-off (4160 AU/mL) is considered a valid proxy given the 0.95 probability of obtaining a plaque reduction neutralization test ID50 at a 1:250 dilution. Of note, the emergence of new variants of concern will impact neutralization by the humoral response. More research is required to investigate how our findings correlate to patient outcome. With the available evidence, as the pandemic unfolds and new variants emerge, it seems prudent to prioritize vaccination of dialysis patients using mRNA-based vaccines when available.

ACKNOWLEDGEMENTS

We thank all patients for their participation in this study and for providing informed consent. We thank the nursing staff for their dedication to safeguarding the patients as best they can. B.M. is supported by the research foundation Flanders (Senior clinical investigator 1800820N). We acknowledge the valuable contributions of H. Wielandt, A. Herelixka, H. De Loor, S. Dejongh, A. Louwagie and K. Vanhees.

AUTHORS' CONTRIBUTIONS

B.M. conceived the study, developed the protocol, contributed to data collection, contributed to data analysis and drafted the manuscript. A.G., D.P., Av.D.V. and M.V. all contributed to data collection and drafted the manuscript. P.V. conceived the study, developed the protocol, contributed to data analysis and drafted the manuscript. K.S. conceived the study, developed the protocol and contributed to data collection. D.K. conceived the study, contributed to data analysis and drafted the manuscript.

CONFLICT OF INTEREST STATEMENT

The results presented in this paper have not been published previously in whole or part.

REFERENCES

1. Chen JJ, Lee TH, Tian YC *et al.* Immunogenicity rates after SARS-CoV-2 vaccination in people with end-stage kidney disease: a systematic review and meta-analysis. *JAMA Netw Open* 2021; 4: e2131749
2. Sibbel S, McKeon K, Luo J *et al.* Real-world effectiveness and immunogenicity of BNT162b2 and mRNA-1273 SARS-CoV2 vaccines in patients on hemodialysis. *J Am Soc Nephrol* 2021; 33: 49–57
3. Garcia P, Anand S, Han J *et al.* COVID-19 vaccine type and humoral immune response in patients receiving dialysis. *J Am Soc Nephrol* 2022; 33(1): 33–37
4. Carr EJ, Wu M, Harvey R *et al.* Neutralising antibodies after COVID-19 vaccination in UK haemodialysis patients. *Lancet* 2021; 398: 1038–1041
5. Espi M, Charmetant X, Barba T *et al.* A prospective observational study for justification, safety, and efficacy of a third dose of mRNA vaccine in patients receiving maintenance hemodialysis. *Kidney Int* 2021; 101: 390–402
6. Attias P, Sakhi H, Rieu P *et al.* Antibody response to the BNT162b2 vaccine in maintenance hemodialysis patients. *Kidney Int* 2021; 99: 1490–1492
7. Ebinger JE, Fert-Bober J, Printsev I *et al.* Antibody responses to the BNT162b2 mRNA vaccine in individuals previously infected with SARS-CoV-2. *Nat Med* 2021; 27: 981–984
8. Atmar RL, Lyke KE, Deming ME *et al.* Homologous and heterologous covid-19 booster vaccinations. *N Engl J Med* 2022; 386(11): 1046–1057
9. Schrezenmeier E, Rincon-Arevalo H, Stefanski AL *et al.* B and T cell responses after a third dose of SARS-CoV-2 vaccine in kidney transplant recipients. *J Am Soc Nephrol* 2021; 32: 3027–3033

Received: 6.1.2022; Editorial decision: 4.2.2022