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

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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-vector 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-1273), 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 adenviral-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.

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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.

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