Neutralising antibodies against the Omicron variant after COVID-19 vaccination in UK haemodialysis patients

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The SARS-CoV-2 variant-of-concern (VOC) Omicron is now the predominant VOC in the UK [1]. Whilst early estimates suggest the severity of disease with Omicron infection is less than Delta, of the >50,000 confirmed Omicron cases within the UK, less than 5% are in the over 60s, and over a 25% of admissions are in individuals aged 70 years or older [1]. This raises the possibility of unchanged disease severity in the elderly, and other clinically vulnerable groups. The burden of >30 mutations in spike suggests at least a degree of vaccine evasion [2], and UKHSA estimates of vaccine efficacy against infection are reduced compared to Delta [1]. Therefore, we sought to establish the neutralising antibody (nAb) titres in in-centre haemodialysis (IC-HD) patients, a cohort we have previously shown to have attenuated nAb responses to Delta[3] and have ongoing excess risk of hospitalisation and death during the Delta wave [4]. The increased transmissibility of Omicron is likely to prove challenging in HD units, where in-unit transmission with prior VOCs has occurred [5].

In the UK, a small subset of patient groups have been declared eligible for a three dose primary course, and are therefore eligible for 4th doses [6]. This excluded most IC-HD patients, although a fraction qualify on the basis of immunosuppression use (either for failed renal transplants, or ongoing treatment of their primary renal disease). Currently, therefore, IC-HD are considered 'fully vaccinated' after two doses, and 'boosted' after three.

To assess the induction, maintenance and diversity of nAbs we convened UK-wide consortium study assessing **n**eutralising **a**ntibody after C**O**VID vaccination in hae**m**od**i**alysis patients (NAOMI) [3]. This is an observational multi-centre meta-cohort study to compare neutralising antibody responses between different vaccine regimens, and in pre-specified patient subgroups. Previously, we compared neutralising antibody responses after two doses of the adenoviral vector Oxford/AstraZeneca vaccine (ChAdOx-1, AZD1222) or the Pfizer-BioNTech mRNA vaccine (BNT162b2). mRNA vaccine neutralising responses against wildtype virus and variants of concern (VOCs) were similar to those seen in healthcare or laboratory workers [3,7,8].

Here we report the first nAb titres (nAbT) against Omicron in the at-risk IC-HD population (n=98) at 158 days [146-163] after dose 2, and at 27 days [21-35] after

dose 3 (median, [interquartile range]; appendix p3). We report Delta as a comparator VOC, and full demographics are listed in the appendix (appendix p4). Doses 1 and 2 were either AZD1222 (n=30) or BNT162b2 (n=68). All third doses were BNT162b2 (at full dose). Earlier timepoints from one HD centre have already been reported [3]. Given the urgency of these data, we locked this first set once n>=50 sera after dose 3 were available for testing. These patients were vaccinated in September - November 2021 and are from two UK HD centres (appendix p3), reflecting the local variation in the deployment of third 'booster' doses.

Firstly, we assessed the nAbT against Omicron and Delta at a median of 158 days after two doses of either AZD1222 or BNT162b2 (appendix p4). After two doses of AZD1222 in IC-HD patients, the median nAbT against either VOC was less than the lower limit of detection of our assay (<1:40), in keeping with our previous report of Delta nAbT at 1 month after the second dose [3]. At 158 days after two doses of BNT162b2, median nAbT against Delta were 112 and median Omicron nAbT were below the range of the assay (appendix p4).

Next, we considered the effect of an additional full dose of BNT162b2 (n=51, appendix p4). For AZD1222-AZD1222-BNT162b2 (AZD-AZD-BNT, n=21) recipients, Delta titres rose after a third dose to a median nAbT of 282. However, the median titres against Omicron remained below the quantitative range. Recipients of BNT162b2-BNT162b2-BNT162b2 (BNT-BNT-BNT, n=30) had boosted nAbTs against Delta from 112 to 461 [4.1x fold change], and developed detectable nAbTs against Omicron at a median nAbT of 236 after their third dose.

For both AZD-AZD-BNT and BNT-BNT-BNT recipients there are a proportion of IC-HD patients that do not mount nAbT responses to either VOC (AZD-AZD-BNT IC_{50}<40 after dose 3: 33% and 52% of patients against Delta or Omicron respectively; BNT-BNT-BNT 3.4% and 27.6% respectively). We hypothesised that these may be patients taking immunosuppressants or with immunosuppressive comorbidities – beyond the immunosuppression associated with end-stage renal disease and haemodialysis itself – and therefore stratified our analysis by the presence of or absence of an immunosuppressed state (appendix p 3). The immunosuppressed AZD-AZD-BNT patients had a median nAbT against Omicron

below the lower limit of the assay and immunosuppressed AZD-AZD-BNT patients had a median nAbT against Omicron of 135 (~50% of the response of the rest of the cohort). In the un-immunosuppressed recipients, the median Omicron nAbT after dose 3 was 107 for AZD-AZD-BNT recipients (n=16) and 236 for BNT-BNT-BNT recipients (n=23).

The main limitation of our study is its observational nature. Given there is no randomisation, we risk unbalanced groups for comparisons. For example, the AZD-AZD-BNT and BNT-BNT-BNT cohorts are matched imperfectly, with AZD1222 recipients being older (mean age: 68.8 vs 60.3 respectively, *P*=0.001, appendix p3). Therefore, we have reported responses within these vaccine cohorts, not between. Age may be a particularly important factor in the UK's Omicron wave, in which to-date whilst the majority of infections, have been in younger individuals, risk of admission remains age-associated.

In summary, we report the first nAbT against Omicron in IC-HD, a vulnerable population to COVID-19, frequently requiring hospitalisation and with an excess risk of death. BNT-BNT-BNT generates nAbT that are likely above the correlate of protection from severe disease from Delta or Omicron in the majority of IC-HD patients. AZD-AZD-BNT in IC-HD patients, provides median nAbT against Delta that are likely protective from severe disease with Delta infection, but not against Omicron. Whilst sotrovimab is the only monoclonal therapeutic that binds and neutralises Omicron *in vitro*, its UK license is only in the out-patient setting (those not receiving supplementary oxygen) [9]. As many IC-HD patients require admission with COVID-19 disease, they may be denied this treatment, despite being likely to have non-neutralising Omicron antibody responses.

There are several implications of these data. Firstly, the deployment of third doses took ~ 8 weeks between eligibility announcements for third/booster doses and their receipt in this highly vulnerable patient group. This contrasts with their very rapid access to first doses. Secondly, 'non-response' after two doses does not predict on-going 'non-response' to third doses. We suggest that each further dose reduces this fraction further. Some of these 'non-responders' are already eligible for four doses in the UK, as their 'primary course' has already been deemed 3 doses due to

immunosuppression use, or co-morbidities [6]. Thirdly, that adequate nAbT titres against Delta in IC-HD required three doses of vaccine, and this is reflected in the epidemiological data from the Delta wave in IC-HD [4]. Finally, Omicron neutralisation will require at least three vaccine doses, perhaps four doses, in UK IC-HD patients, particularly as the kinetics of waning of Omicron nAb are unknown. Together our data shows that the current generation vaccines still have utility in CEV patient groups, and that the number of doses that constitute an appropriate primary course differs between VOCs: for Omicron, three doses in IC-HD may be insufficient.

References

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