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Neutralisation of ZF2001-elicited antisera to SARS-CoV-2 variants

SARS-CoV-2 variants, particularly the recently emerged delta (B.1.617.2) variant, have caused another wave of infection worldwide.[1,2] Whether these variants are sensitive to the thus far approved vaccines is a global concern.[2]

ZF2001 is a protein subunit vaccine, using tandem-repeat SARS-CoV-2 spike receptor-binding domain (RBD) dimer as the antigen, currently in phase 3 clinical trials.[3,4] ZF2001 has received emergency use authorisation in both China and Uzbekistan since March, 2021, and is rolling out with a three-dose vaccination regimen. Here, we used the pseudotyped virus expressing SARS-CoV-2 spike to test the neutralisation activity of ZF2001 to a panel of variants (appendix p 4), including all four variants of concern (alpha [B.1.1.7], beta [B.1.351], gamma [P.1], and delta [B.1.617.2]) and other three variants of interest (epsilon [B.1.427], eta [B.1.525], and kappa [B.1.617.1]).

We found that all 28 serum samples (appendix p 8) efficiently neutralised pseudovirus expressing wild-type spike (Wuhan-1 reference strain), with the 50% pseudovirus neutralisation titre higher than 1:20. Variants with a single mutation at Leu452Arg (epsilon [B.1.429] spike) or double mutations at both Leu452Arg and Thr478Lys (delta spike) in the RBD showed roughly equivalent sensitivity to ZF2001-elicited antisera compared with pseudovirus expressing wild-type spike (–1·1 for epsilon to wild type and –1·2 fold for delta to wild type; p>0·05). Therefore, ZF2001 preserved the neutralising activity against the newly emerging delta variant. By contrast, the variants with Glu484Lys or Glu484Gln substitution showed more pronounced reduction in sensitivity (beta spike –1·8 fold, p=0·0071; gamma spike –1·5 fold, p=0·0505; eta spike –2·0 fold, p=0·0021; and kappa spike –2·1 fold, p<0·0001), which is consistent with the neutralisation of ZF2001-elicited antisera against authentic beta variant (B.1.351 or 501Y.V2; appendix pp 5–7).[1,5]

Furthermore, the participants with an extended interval between the second and third doses (doses at 0, 1, and 4–6 months) showed higher neutralising activity and resilience to variants than those with shorter interval (doses at 0, 1, and 2 months; appendix pp 5–6), which is consistent with previous study of neutralisation of the SARS-CoV-2 beta variant by ZF2001-elicited antisera.[5] The better performance of the extended interval regimen is probably because of the longer antibody maturation in the recipients than in those with the shorter interval regimen.[1] Our data are consistent with common practice of using the 0, 1, and 6 months regimen for subunit vaccines against diseases such as hepatitis B, and provide guidance to further optimise the vaccination regimen.

Hence, here we provide preliminary evidence of the approved RBD-based protein subunit vaccine for its neutralisation profile to SARS-CoV-2 variants. The high susceptibility of these new variants to the ZF2001 vaccine supports the method of mass immunisation to build herd immunity. However, the vaccine effectiveness against these variants must be validated by phase 3 clinical trials and real-world data.

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See **Online** for appendix