

Inactivated vaccines may not provide adequate protection in immunosuppressed patients with rheumatic diseases

Patients with autoimmune rheumatic diseases (AIRDs) are vulnerable to COVID-19 due to the presence of multiple comorbidities.¹ Moreover, patients on immunosuppressants have blunted responses to vaccination as compared with healthy people.^{2,3} Persistence of the virus in such people may lead to the selection of more virulent mutants of SARS-CoV-2.⁴ It is crucial that they are prioritised for the best possible vaccine. India has crossed 650 million vaccinations with predominantly two vaccines: the adenoviral vector-borne AZD1222 (ChAdOx1 nCoV-19) and the indigenous whole-virion β -propiolactone-inactivated BBV152. In our cohort of around 1500 patients with AIRD who are being followed up to assess the immunogenicity of COVID-19 vaccines, we identified 475 patients who have completed two doses of either vaccine. Serum was collected on median 30th (range 28–35) day after the second dose of vaccine with informed consent after ethics clearance. Titres of IgG antibodies to spike protein were estimated with the Elecsys kit (Roche, Switzerland). To check the neutralisation potential of the sera, age, sex and disease matched 80 BBV152 and 85 AZD1222 recipients were selected. Neutralisation potential of the sera was assessed using the SARS-CoV-2 sVNT Kit (GenScript). Analysis was done in R V.4.0.3. Shapiro-Wilk confirmed normality; antibody titres were compared with unpaired t-test after log transformation, while proportions were compared with Fisher's exact test.

Age was more in the AZD1222 group, but other baseline characteristics were the same as compared with the BBV152 group (online supplemental table 1). Seroconversion had occurred in 342 (93.9%) of the AZD1222 group and 45 (40.5%) of the BBV152 group ($p < 0.001$). Similarly seroconversion of neutralising antibody, defined as a neutralisation activity of more than 30%, was seen in a higher proportion of AZD1222 group (48/80) than of the BBV152 group (25/85) (60% vs 29%, respectively; $p < 0.001$). The antibody levels in

the AZD1222 group were 10–100 \times higher than those in the BBV152 group (figure 1A), while the percentage of neutralisation activity of sera was also higher in the AZD1222 group (figure 1B). There was high correlation between antibody titres and neutralisation potential (Pearson's $R = 0.755$) (figure 1C).

Our data show the poor immunogenicity of the whole-virion β -propiolactone-inactivated vaccine in immunosuppressed patients. This has been validated by estimating neutralisation activity after matching recipients of BBV152 with those of AZD1222. Inactivated vaccines have reduced immunogenicity as compared with other vaccines in healthy individuals.⁵ However, in our patients on immunosuppressants, more than half of the BBV152 recipients failed to generate a humoral immune response, exposing them to higher risk of COVID-19 and its complications.

The limitations of this study include a non-random sample and the lack of T-cell immunogenicity data. However, these are pragmatic data, and statistical differences between the inactivated and vector-borne vaccine have been very clearly demonstrated. Peak titre neutralisation antibodies and anti-spike antibodies have been shown to correlate well with protection from symptomatic COVID-19 infection.⁶ So lack of antibody response at 1 month when the peak response is expected is likely to translate to lack of protection in this high-risk population.

Thus, the humoral responses to the BBV152 vaccine is inferior to that of the AZD1222 (ChAdOx1) vaccine in immunosuppressed patients. This is mirrored in neutralisation assays that are a surrogate for real-world protection. This implies a pressing need to update vaccine policies so that such patients on immunosuppressants receive vaccines other than inactivated ones.

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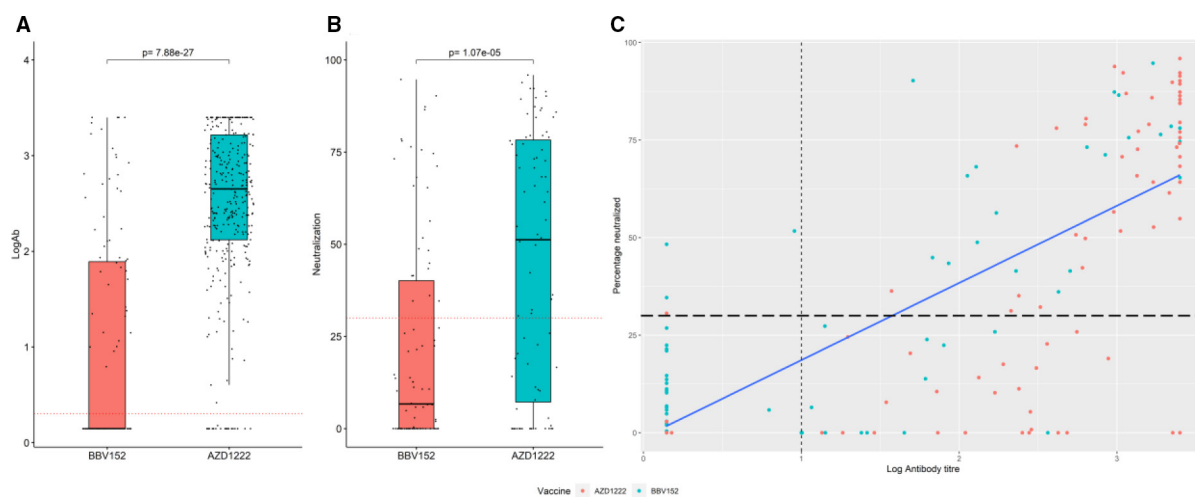


Figure 1 (A) Antibody levels in the AZD1222 group (n=364) versus those in the BBV152 group (n=111) in log₁₀ scale. (B) Neutralisation activity of the sera of matched patients from the AZD1222 group (n=80) versus those in the BBV152 group (n=85). (C) Scatterplot showing the correlation between antibody levels and neutralisation activity. The linear regression line is coloured blue. The vertical line with smaller dashes is the cut-off for antibody positivity, while the horizontal line with the larger dashes represents the 30% cut-off for minimum neutralisation activity.

Handling editor Josef S Smolen

Contributors PS and SA conceptualised and drafted the paper. All authors approved the final version.

Funding This study was funded by the Indian Rheumatology Association.

Competing interests None declared.

Patient consent for publication Consent obtained directly from patient(s)

Ethics approval Ethics approval for the study was obtained from SreeSudheendra Medical mission (IEC/2021/35).

Provenance and peer review Not commissioned; externally peer reviewed.

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► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/annrheumdis-2021-221496>).



To cite Shenoy P, Ahmed S, Paul A, *et al.* *Ann Rheum Dis* Epub ahead of print: [please include Day Month Year]. doi:10.1136/annrheumdis-2021-221496

Received 11 September 2021

Accepted 1 October 2021

Ann Rheum Dis 2021;**0**:1–2. doi:10.1136/annrheumdis-2021-221496

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Supplementary Table 1: Baseline characteristics of the 475 patients of AIRD

Demographics	AZD1222 (n=364)	BVV152 (n=111)	P value
Age (Mean \pm SD)	57.23 \pm 11.28	51.17 \pm 10.37	>0.001
Females (%)	303(83.24%)	91(81.98%)	0.43
Comorbidity present	219(60.16%)	72(64.86%)	0.22
Disease			
Rheumatoid arthritis	261(71.70%)	77(69.36%)	0.36
Spondyloarthropathy	44(12.08%)	11(9.90%)	0.33
Systemic Lupus Erythematosus	8(2.19%)	1(0.90%)	0.34
Others	51(14.01%)	22(19.81%)	0.09
Drugs			
Methotrexate	219(60.16%)	65(58.55%)	0.26
Hydroxychloroquine	236(64.83%)	72(64.86%)	0.54
Sulfasalazine	75(20.60%)	19(17.11%)	0.25
Leflunomide	31(8.51%)	5(4.50%)	0.11
Tofacitinib	38(10.43%)	7(6.36%)	0.13
Mycophenolate Mofetil	18(4.94%)	10(9.09%)	0.09
Tacrolimus	5(13.73%)	2(1.80%)	0.51
Azathioprine	2(0.54%)	3(2.70%)	0.33
Rituximab	31(8.51%)	10(9.09%)	0.50

Anti-Tumor Necrosis Factor	3(0.82%)	3(2.70%)	0.41
Glucocorticoids	37(10.16%)	11(9.90%)	0.49