**Article:**
Saleem, B, Ross, RL, Duquenne, L et al. (2 more authors) (2022) COVID-19 vaccine-induced T-cell responses in patients with rheumatoid arthritis: preferential induction by ChAdOx1. The Lancet Rheumatology, 4 (3). e171-e172. ISSN 2665-9913

https://doi.org/10.1016/s2665-9913(22)00027-3

# T cell vaccine responses in Rheumatoid Arthritis patients on DMARDs: are they preferentially induced by the ChAdOx1 nCoV-19 (Astra Zeneca) vaccine?

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It has been suggested that the improved outcome of SARS-CoV-2 infections in the UK, especially compared to France and Germany, may be as a consequence of use of the ChAdOx1 nCoV-19 vaccine, AZD1222 (A-Z). The elderly population in UK, received the A-Z vaccine, whilst in the EU, the Pfizer-BioNTech COVID-19 (BNT162b2) (PB) was the predominant vaccine used. Supporting this contention, the role of T cells in the response to SARS-CoV-2 infection and vaccination has been highlighted [1] with an enhanced response following A-Z [2], potentially related to an adjuvant effect from the adenovirus vector.

In a prospective study of vaccination responses in a different group of vulnerable individuals with a known reduced antibody response, namely patients with rheumatoid arthritis (RA) on disease modifying antirheumatic drugs, we have found evidence to support this contention. This study had ethical approval from Leeds West ethics committee: 09/H1307/98. Written informed consent was obtained according to the Declaration of Helsinki. All these patients received vaccine 2, 12-week after vaccine 1 irrespective of which vaccine was given in line with UK government guidance.

Ninety-nine patients were studied before, four weeks after first, and a sub-group of non-seroconverters (n=34) four weeks after the second vaccination (71 received the A-Z and 28 PB). LABScreen™ COVID Plus Assay was used to measure SARS-CoV-2 antibody response. Antibody response was defined as the presence of ≥1 antibody to either Spike, S1, S2 or RBD. T cell analysis used the T-Spot-Covid ELISpot assay. A positive T-cell response was >7 spot forming units (SFU).

The patients receiving either A-Z or PB were not significantly different for DMARDs (see table). The antibody responses were reduced equally, however, the T-cell responses after a single vaccine showed significant variation. A-Z induced specific T cell responses in 71 % (43/61) compared to 38% (9/24) following the PB (p=0·007). A strong positive T cell response (> 30 SFU) was seen in 43% for A-Z versus 17% PB (p=0·017). After adjusting for age, concomitant medications and previous SARS-CoV-2 infection, patients receiving A-Z were >5 times more likely to develop a T cell response than those receiving PB (OR 5.6, 95%CI [1.71-18.32] p=0.004). In the sub-group of non-seroconverters after vaccine 1, an enhanced Tcell response remained after vaccine 2 in those who received A-Z; 48% (11/23) vs.17% (1/6) (p=0·168), although with small numbers not significant. For seroconversion, higher rates were observed in those who received PB.

This study highlights the differences in T cell and antibody responses following a single dose of vaccine, between the two vaccines in immunocompromised RA patients. The responses to subsequent doses need further evaluation due to our small sample size. The use of a delayed dosing schedule in the UK for the PB vaccine may have led to bias.

It is not possible to say if these differences translate to variations in SARS-CoV-2 cases and hospital admissions. However, for RA patients with reduced antibody responses to vaccines, the potential to enhance T cell responses with the A-Z vaccine is a finding that deserves further consideration.

References

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2. Parry HM, Bruton R, Tut G, et al. Single vaccination with BNT162b2 or ChAdOx1 in older people induces equivalent antibody generation but enhanced cellular responses after ChAdOx1. SSRN 2021; published online April 13. https://dx.doi.org/10.2139/ssrn.3825573 (preprint).

Table: Comparison of baseline characteristics and response in immune-suppressed RA patients between A-Z and PB vaccines.

| | AZ n=71 | PF n=28 | p VALUE |
|---|---|---|---|
| **Age mean (SD)** | 62·8 (10·76) | 58 (12·24) | 0·057 |
| **Gender**<br>**Male**<br>**Female** | <br>18 (25)<br>54 (75) | <br>5 (18)<br>23 (82) | 0.446 |
| **Ethnicity**<br>**White British**<br>**Unknown**<br>**White Other**<br>**Caribbean** | <br>67 (93)<br>1 (1)<br>3 (4)<br>1 (1) | <br>25 (89)<br>2 (7)<br>1 (4)<br>0 (0) | 0.447 |
| **bDMARD n (%)**<br>**RTX**<br>**Anti-TNF**<br>**Anti-IL-6R**<br>**JAKi**<br>**CTLA-4Ig** | <br>28/71 (40)<br>21/71 (30)<br>7/71 (10)<br>5/71 (7)<br>10/71 (14) | <br>9/28 (32)<br>10/28 (36)<br>3/28 (11)<br>5/28 (18)<br>1/28 (4) | 0·301 |
| **Treatment with Rituximab <6 months before vaccine n (%)** | 11/28 (39) | 7/9 (78) | 0·127 |
| **Steroids n (%)** | 7/71 (10) | 5/28(18) | 0·272 |
| **Concomitant csDMARD n (%)** | 40/71 (56) | 16/28 (57) | 0·521 |
| **Pre-vaccine COVID exposure n (%)** | 11/71 (16) | 5/28 (18) | 0·773 |
| **Seroconversion 4 weeks post vaccine 1: n (%)** | 37/71 (52) | 15/28 (54) | 0·274 |
| **T cell responses 4 weeks post vaccine 1: n (%)** | 44/62 (71) | 9/24 (38) | 0·007 |
| **Seroconversion 4 weeks post vaccine 2 in non-seroconverters: n (%)** | 9/23 (39) | 9/11 (82) | 0·020 |
| **T cell responses 4 weeks post vaccine 2 in non-seroconverters: n (%)** | 11/23 (48) | 1/6 (17) | 0·168 |

csDMARDs=conventional synthetic disease modifying antirheumatic drugs.
RTX=rituximab, Anti-TNF=anti-tumour necrosis factor alpha, Anti-IL-6R=anti interleukin 6 receptor JAKi=janus kinase inhibitor, CTLA-4Ig=abatacept
Pre-vaccine COVID exposure defined as positive baseline antibodies to either Antibodies to Spike, S1, S2, RBD or NP.

## Declaration of interests

Benazir Saleem :Speaker fees for Pfizer and Galapogos

Paul Emery: Grants : AbbVie, BMS, Lilly, Samsung. Consulting fees: BMS, AbbVie, MSD, Pfizer, Novartis, and Roche. Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events:Abbvie, Gilead, Lilly, Novartis

No competing interests for remaining authors.

## Ethical approval information

Leeds West REC: 09/H1307/98; R&I: RR09/9134

## Contributor Statement

All authors have made substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data; were involved in drafting the work or revising it critically for important intellectual content; provided final approval of the version published; and were in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Laurence Duquenne, Benazir Saleem and Paul Emery have directly accessed the raw data and verified the underlying data reported in the manuscript. Benazir Saleem and Paul Emery had final responsibility for the decision to submit for publication.


## Funding, grant/award

NIHR Leeds Musculoskeletal Biomedical Research Centre, Leeds, UK

Leeds hospital charity grant (124664)

Eli Lilly and Company (124893)

## Acknowledgments

The Leeds Rheumatology and Immunology vaccine initiative team


## Appendix

### Method

Consecutive patients with RA and current treatment with a bDMARD or tsDMARD attending rheumatology clinics between January 2021 and April 2021 at the Leeds Teaching Hospitals NHS Trust were considered for this observational study.

### Serological testing

The LABScreen™ COVID Plus Assay (OneLambda, Canoga Park, California) testing was performed according to the manufacturer's instruction locally adapted for performance at half-volume.

A SARS-CoV-2 antibody vaccine response was determined by the detection of antibodies to any of the Spike proteins (Spike extracellular domain, S1 subunit, S2 subunit and receptor binding domain (RBD) as well as the nucleocapsid protein (NP)) following vaccination. Individuals with any baseline antibodies were assumed to have had prior COVID infection.

### T cell analysis

T-Spot-Covid ELISpot assay (Oxford Immunotec; Oxford, UK) was used. PBMC were thawed and viable cells resuspended in AIM-V serum free media onto the ELISpot plate ($2.5x10^5$ viable cells/well) and exposed to negative control, antigen mixtures containing peptides derived from either the Spike protein or NP, or PHA (positive control). Plates were incubated overnight at $37^0$C with 5% CO2. After cell removal, alkaline phosphate conjugated anti IFN gamma antibody incubation, followed by BCIP/NBTplus substrate incubation, the plates were dried and spots (SFU) counted. The reference range was determined by the manufacturer. A significant test was determined by subtracting the SFU in the negative control from the number of SFU in the stimulated wells. A signal of greater than 10 SFU in the negative control invalidated that sample. Results were interpreted according to the manufacturer as: negative 0-4 SFU, borderline 5-7 SFU, weak positive 8-15 SFU, positive 16-30 SFU and strong positive >30 SFU.

Statistical analysis

Descriptive statistics used Chi-square tests for categorical variables and Mann-Whitney U for continuous variables, odds ratio (OR) was defined using logistic regression.