Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

COVID-19 vaccine-induced T-cell responses in patients with rheumatoid arthritis: preferential induction by ChAdOx1

The improved outcomes of SARS-CoV-2 infections in the UK, especially compared with France and Germany, have been suggested to be a consequence of use of the ChAdOx1 nCoV-19 (Oxford–AstraZeneca) vaccine.[1] From April, 2021, those older than 40 years in the UK received the ChAdOx1 nCoV-19 vaccine, whereas in the EU, BNT162b2 (Pfizer–BioNTech) 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,[2] with an enhanced cellular response reported after ChAdOx1 nCoV-19 compared with BNT162b2 vaccination in people aged 80 years or older, potentially related to an adjuvant effect from the adenovirus vector.[3] In this Correspondence, we report results of a prospective study of vaccination responses in a different group of vulnerable individuals known to have a reduced antibody response to vaccines; namely, patients with rheumatoid arthritis on disease modifying antirheumatic drugs (DMARDs).

Consecutive patients (age ≥18 years) with rheumatoid arthritis and receiving treatment with a biological DMARD or targeted synthetic DMARD attending rheumatology clinics between Jan 4, 2021, and April 30, 2021, at the Leeds Teaching Hospitals NHS Trust (Leeds, UK) were considered for this observational study. This study had ethical approval from Leeds West Research Ethics Committee (09/H1307/98) and participants provided written informed consent according to the Declaration of Helsinki. In line with UK Government guidance, patients received their second vaccine dose 12 weeks after their first vaccine dose irrespective of which vaccine was given.

Blood samples were analysed before vaccination and at 4 weeks after the first vaccine dose (n=99). A subgroup of patients who did not seroconvert after the first vaccine dose were also examined 4 weeks after the second vaccination (n=34, after exclusion of 13 samples due to void analysis). LABScreen COVID Plus Assay (One Lambda; Los Angeles, CA, USA) was used to measure SARS-CoV-2 antibodies according to the manufacturer's instruction, locally adapted for performance at half volume.[4] A SARS-CoV-2 antibody response was identified by the detection of antibodies to any of the spike proteins (spike extracellular domain, S1 subunit, S2 subunit, or receptor binding domain) after vaccination. Individuals with detectable antibodies to the spike proteins or the nucleocapsid protein at baseline (ie, pre-vaccine) were assumed to have had prior SARS-CoV-2 infection. T-cell analysis used the T-SPOT Discovery SARS-CoV-2 assay (Oxford Immunotec; Oxford, UK).[5] A positive T-cell response was defined as more than seven spot forming units (appendix). Descriptive statistics were analysed with χ^2 tests for categorical variables and Mann-Whitney *U* tests for continuous variables; odds ratio (OR) with 95% CI was defined with logistic regression.

Among the 99 patients included in the study, 71 received ChAdOx1 nCoV-19 and 28 received BNT162b2. We found no significant differences in the DMARDs that patients were taking between the two vaccine groups (table). Antibody responses were similar between the two vaccine groups after the first dose; however, T-cell responses after a single vaccine dose showed significant variation between the vaccines. ChAdOx1 nCoV-19 induced specific T-cell responses in 44 (71%) of 62 patients with available data, compared with nine (38%) of 24 patients after BNT162b2 (p=0·0072). A strong positive T-cell response (>30 spot forming units) was seen in 27 (43%) of 63 patients for ChAdOx1 nCoV-19 versus two (8%) of 24 for BNT162b2 (p=0·017). After adjusting for age, concomitant medications, and previous SARS-CoV-2 infection, patients receiving ChAdOx1 nCoV-19 were more than 5 times more likely to develop a T-cell response after the first dose than those receiving BNT162b2 (OR 5·6

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See Online for appendix

	ChAdOx1 nCoV-19 (n=71)	BNT162b2 (n=28)	p value
Age, years	62·8 (10·76)	58 (12·24)	0·057
Gender			
Male	17 (24%)	5 (18%)	..
Female	54 (76%)	23 (82%)	0·45
Ethnicity			
White British	67 (94%)	25 (89%)	..
Unknown	1 (1%)	2 (7%)	..
White Other	2 (3%)	1 (4%)	..
Caribbean	1 (1%)	0	0·45
Biological or target synthetic DMARD			
Rituximab	28 (39%)	9 (32%)	..
Anti-TNF	21 (30%)	10 (36%)	..
Anti-interleukin-6	7 (10%)	3 (11%)	..
Janus kinase inhibitor	5 (7%)	5 (18%)	..
Abatacept	10 (14%)	1 (4%)	0·30
Treatment with rituximab <6 months before vaccine	11/28 (39%)	7/9 (78%)	0·13
Steroids	7 (10%)	5 (18%)	0·27
Concomitant conventional synthetic DMARD	40 (56%)	16 (57%)	0·52
Pre-vaccine SARS-CoV-2 exposure*	11 (15%)	5 (18%)	0·77
Seroconversion 4 weeks after first dose	37 (52%)	15 (54%)	0·27
T-cell responses 4 weeks after first dose†	44/62 (71%)	9/24 (38%)	0·0072
Seroconversion 4 weeks after second dose in non-seroconverters‡	9/23 (39%)	9/11 (82%)	0·020
T-cell responses 4 weeks after second dose in non-seroconverters‡	11/23 (48%)	1/6 (17%)	0·17

Data are n (%) or mean (SD). DMARD=disease modifying antirheumatic drug. TNF=tumour necrosis factor. *Pre-vaccine SARS-CoV-2 exposure defined as positive baseline antibodies to the spike proteins (spike extracellular domain, S1 subunit, S2 subunit, or receptor binding domain) or the nucleocapsid protein. †Discrepancies in denominators for results after the first dose are related to void results. ‡Discrepancies in denominators for results after the second dose are due to void results and missing samples (eg, lost to follow-up).

Table: **Baseline characteristics and immune response in patients with rheumatoid arthritis taking DMARDs**

[95% CI 1·71–18·32], p=0·0044). In the subgroup of patients who did not seroconvert after the first vaccine dose, an enhanced T-cell response was seen after the second dose in those who received ChAdOx1 nCoV-19 (11 [48%] of 23 *vs* one [17%] of six with BNT162b2; p=0·17), although the difference was not significant, potentially due to small numbers of patients. Higher rates of seroconversion were observed after the second dose in those who received BNT162b2.

This study highlights the differences in T-cell and antibody responses after a single dose of vaccine between the ChAdOx1 nCoV-19 and BNT162b2 vaccines in patients with rheumatoid arthritis taking DMARDs. Due to our small sample size, the responses to subsequent doses need further evaluation. Furthermore, the use of a delayed dosing schedule in the UK for the BNT162b2 vaccine might have led to bias and limits the generalisability of our study.

Whether these differences translate to variations in SARS-CoV-2 cases and hospital admissions is unknown. However, for patients with rheumatoid arthritis with reduced antibody responses to vaccines, the potential to enhance T-cell responses with the ChAdOx1 nCoV-19 vaccine is a finding that deserves further consideration.

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Severe COVID-19 as a virus-independent immunothrombotic process

We read with interest the Viewpoint[1] by Dennis McGonagle and colleagues in which they question the strategy of universal immunosuppression in patients with moderate-to-severe COVID-19 because of a concern about ongoing alveolar viral replication in these patients. We believe that this concern is unwarranted, as the key pathology driving severe COVID-19 is not active viral replication in the pneumocytes, but rather antibody-dependent inflammation leading to immunothrombosis.

First, in COVID-19, there is evident temporal and spatial dissociation between active viral replication in the respiratory tract and the development of lung injury. Although initial viral loads are higher and duration of viral shedding is longer in patients who develop severe illness (when compared with those who do not), the viral load typically trends downwards from the time of symptom onset, irrespective of eventual illness severity. Culturable virus is typically absent by the second week after symptom onset, when patients progress to severe illness.[1] Pathologically, there is a lack of topological correlation between the location of lung pathology and presence of the virus,[2] suggesting tissue tolerance to viral multiplication and a mechanism of lung injury other than viral cytopathy. Supporting this interpretation, studies in humanised mice have shown that viral infection of alveolar cells is not necessary for severe COVID-19 to occur.

Second, as we have previously argued,[3] the peripheral ground glass changes seen in patients with COVID-19, which typically appear in the later part of the first week of illness, represent pulmonary infarcts due to small-vessel immunothrombosis rather than viral alveolitis. Inhaled thrombolytics seem to resolve these radiological changes, which would be highly uncharacteristic of viral-induced alveolar injury. Consistent with this explanation, the characteristic silent hypoxaemia of COVID-19 indicates a predominant perfusion problem rather than a ventilation problem.[3]

Third, the key determinant of severe illness appears to be antibody-dependent inflammation,[4] a phenomenon that occurs due to abnormal fucosylation of antibodies specific for viral spike protein during the seroconversion phase of COVID-19 in susceptible patients. These aberrant antibodies are pro-inflammatory;