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SHORT REPORT

Effectiveness of SARS-CoV-2 vaccination in patients with rheumatoid arthritis (RA) on DMARDs: as determined by antibody and T cell responses

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ABSTRACT

Objectives To assess antibody and T cell responses to SARS-CoV-2 vaccination in patients with rheumatoid arthritis (RA) on disease-modifying antirheumatic drugs (DMARDs).

Methods This prospective study recruited 100 patients with RA on a variety of DMARDs for antibody and T cell analysis, pre-vaccination and 4 weeks post-vaccination. Positive antibody response was defined as sera IgG binding to ≥1 antigen. Those that remained seronegative after first vaccination were retested 4 weeks after second vaccination; and if still seronegative after vaccination three. A T cell response was defined an ELISpot count of ≥7 interferon (IFN) γ-positive cells when exposed to spike antigens. Type I IFN activity was determined using the luminex multiplex assay IFN score.

Results After vaccine one, in patients without prior SARS-CoV-2 exposure, 37/83 (45%) developed vaccine-specific antibody responses, 44/83 (53%) vaccine-specific T cell responses and 64/83 (77%) developed either antibody or T cell responses. Reduced seroconversion was seen with abatacept, rituximab (RTX) and those on concomitant methotrexate (MTX) compared to 100% for healthy controls (p<0.001). Better seroconversion occurred with anti-tumour necrosis factor (TNF) versus RTX (p=0.012) and with age ≤50 (p=0.012). Pre-vaccine SARS-CoV-2 exposure was associated with higher quantitative seroconversion (≥3 antibodies) (p<0.001). In the subgroup of non-seroconverters, a second vaccination produced seroconversion in 54% (19/35), and after a third in 20% (2/10). IFN score analysis showed no change post-vaccine.

Conclusion Patients with RA on DMARDs have reduced vaccine responses, particularly on certain DMARDs, with improvement on subsequent vaccinations but with approximately 10% still seronegative after three doses.

Key messages

What is already known about this subject?

- Patients treated with disease-modifying antirheumatic drugs (DMARDs) have been reported to have variably reduced antibody and T cell responses to SARS-CoV-2 vaccination; however, knowledge of the impact of individual drugs is limited particularly in patients with rheumatoid arthritis (RA).
- Data on the immune response of patients with RA, either exposed to SARS-CoV-2 or naïve for infection, treated with DMARDs are also limited.

What does this study add?

- The lowest seroconversion rates were seen in patients with RA treated with abatacept, rituximab (<6 months from infusion) and those on concomitant MTX. The strongest antibody responses were seen in patients with evidence of previous SARS-CoV-2 infection, regardless of DMARD therapy.
- T cell responses were less affected by individual drugs, apart from a potential effect of corticosteroids.

INTRODUCTION

SARS-CoV-2 vaccination has produced reductions in infection rates and hospital admissions. However, the populations evaluated have generally been healthy volunteers; whereas patients with chronic diseases have suboptimal vaccine responses,[1] impaired by immunomodulatory therapy and possibly the disease itself.

There is evidence that within the spectrum of autoimmune rheumatic disease, there is a difference both in the morbidity and mortality from SARS-CoV-2 infection[2–4] and

Key messages

How might this impact on clinical practice?

- RA patients ideally should be vaccinated off abatacept, >6 months after rituximab, and off MTX, taking the minimal dose of corticosteroids.
- RA patients can be reassured that post-vaccination disease activity remained stable, and that the majority of immunosuppressed patients had either an antibody or T cell response to the vaccine. In those failing to seroconvert after first vaccine dose, 54% seroconverted after second.
- These data suggest that vaccine responses are reduced but can be improved by sufficient vaccine /virus exposure.The data support the use of a third dose of the vaccination with cessation of specific drugs to optimise response.

the response to the SARS-CoV-2 vaccine.[5] The impact of concomitant disease-modifying antirheumatic drugs (DMARDs) and corticosteroids on vaccine responses is uncertain.

Vaccine antibody and T cell responses, together with interferon (IFN) activity, were measured in patients with rheumatoid arthritis (RA) on various DMARDs, comparing pre-SARS-CoV-2 to 4 weeks post-SARS-CoV-2 vaccination. Then the effectiveness of a second vaccination on patients with absent seroconversion to the first was measured and subsequently in those with absent seroconversion to the second vaccine to a third vaccination.

METHODS

Study participants

Patients were recruited prospectively from Leeds Rheumatology clinic and written informed consent was obtained according to the Declaration of Helsinki. Baseline samples were collected from 116 patients with RA starting from January 2021. Patients received either Pfizer-BioNTech COVID-19 (BNT162b2) or ChAdOx1 nCoV-19 vaccine, AZD1222. The UK vaccine schedule provided vaccine two, 12 weeks after vaccine one (regardless of specific vaccine) and third doses for immunosuppressed patients at least 8 weeks after second dose. Samples were taken at baseline and 4 weeks after their first dose of the vaccine. The subgroup of patients who did not seroconvert after the first vaccine were re-tested after vaccine two, likewise for vaccine three. IFN score analysis was performed on 107 patients. Nine healthy controls were recruited.

Serological testing

LABScreen COVID Plus Assay (OneLambda, Canoga Park, California, USA) was used to detect the presence of antibodies to the SARS-CoV-2 antigens comprising the Spike extracellular domain, S1 subunit, S2 subunit and receptor binding domain as well as the nucleocapsid protein. Individuals with any baseline antibodies were assumed to have had prior COVID-19 infection. A positive antibody response was defined as IgG present to ≥1 antigens.

T cell analysis

T cell analysis used the T-Spot-Covid ELISpot assay (Oxford Immunotec; Oxford, UK), according to manufacturer's instructions, using frozen peripheral blood mononuclear cells. The cut-off for a positive T cell response was >7 spot forming units.

See online supplemental material for detailed methods.

IFN score analysis

Paired sera samples (pre-vaccine vs post-vaccine) were tested using a Human Magnetic Luminex xMAP custom made multiplex assay to measure the concentration of IFN-inducible chemokines (Bio-techne, Oxford, UK).[6 7]

Statistical analysis

All analysis were performed without imputation using IBM SPSS statistics V.25. Variables were compared using Fisher test for ordinal values and one way analysis of variance (ANOVA) for continuous values (age). Logistic regression was used to define respective OR in univariable and multivariable analysis on every variable. Area under the curve of the receiving operator curve was used to define cut-offs.

RESULTS

All patients were anti-cyclic citrullinated peptide (CCP) positive. Clinical characteristics and DMARD therapies are summarised in table 1. Seventeen patients with RA and three healthy controls had detectable SARS-CoV-2 antibody responses before vaccination indicating prior SARS-CoV-2 infection. None of these patients were aware of the exposure.

Response after vaccine one in patients without previous SARS-CoV-2 exposure

In patients without SARS-CoV-2 exposure pre-vaccine, 37/83 (45%) developed SARS-CoV-2 antibody responses, 44/83 (53%) SARS-CoV-2 T cell responses; 64/83 (77%) developed either antibody or T cell responses after a single dose of the vaccine.

Seroconversion in patients taking abatacept was 0/11 (0%); RTX 10/29 (35%); anti-TNF 17/26 (65%); Janus Kinase inhibitor (JAKi)5/9 (56%) and anti-interleukin 6 (IL-6) 5/8 (63%) while antibody responses were found in all the healthy controls (p<0.001). For patients treated with RTX >6 months from time of first SARS-CoV-2 vaccination, 8/14 (57%) had detectable SARS-CoV-2 antibody responses compared with 2/15 (13%) (p=0.012, OR: 2) treated at <6 months. Table 2 demonstrates the reduced seroconversion rates observed with concomitant MTX. There were no differences in SARS-CoV-2 T cell responses rates between DMARDs (see table 3) or with the use of concomitant MTX. In patients with absent antibody

responses, T cell responses were found in 32/43 (74%) patients post-vaccine one.

Responses after vaccine one in patients with previous SARS-CoV-2 exposure

Table 1 describes vaccine responses. Patients with antibody reactivity to 1–2 SARS-CoV-2 antigens pre-vaccine were 17 times more likely to develop reactivity to ≥3 antigens after a single dose of the vaccine when compared with patients with absent pre vaccine antibodies (p<0.001).

Multivariable analysis

The following factors were associated with seroconversion after single vaccine dose: age ≤50 years old (p=0.012, OR: 18, 95% CI: 1.87 to 179.09), >6 months from RTX therapy (p=0.029, OR: 10, 95% CI: 1.26 to 76.24), anti-TNF compared with RTX (p=0.012, OR: 12, 95% CI: 1.71 to

Table 1 Demographics of all patients and by previous SARS-CoV-2 exposure

	All (n=100), n (%)	Without pre-vaccine SARS-CoV-2 exposure (n=83), n (%)	With pre-vaccine SARS-CoV-2 exposure (n=17), n (%)
Age mean (SD)	61.5 (11.3)	61.6 (11.2)	61.1 (11.8)
bDMARD group			
RTX	38 (38)	29 (34.9)	9 (52.9)
Anti-TNFs	31 (31)	26 (31.3)	5 (29.4)
Anti-IL-6	10 (10)	8 (9.6)	2 (11.8)
JAKi	10 (10)	9 (10.8)	1 (5.9)
Abatacept	11 (11)	11 (13.3)	0
bMARD plus MTX	45 (45)	34 (40.9)	11 (64.9)
Anti-TNF plus MTX	17 (17)	14 (16.9)	3 (17.6)
RTX plus MTX	19 (19)	12 (14.5)	7 (41.1)
Systemic steroid in last 3 months	12 (12)	9 (10.8)	3 (17.6)
Time from last RTX			
≤6 Months	18 (18)	15 (18.1)	3 (17.6)
>6 Months	20 (20)	14 (16.9)	6 (35.3)
Spike extracellular domain			
No	53 (53)	48 (57.8)	5 (29.4)
Yes	47 (47)	35 (42.2)	12 (70.6)
S1 subunit			
No	58 (58)	57 (68.7)	1 (5.9)
Yes	42 (42)	26 (31.3)	16 (94.1)
S2 subunit			
No	75 (75)	72 (86.7)	3 (17.7)
Yes	25 (25)	11 (13.3)	14 (82.3)
RBD			
No	64 (64)	62 (74.7)	2 (11.8)
Yes	36 (36)	21 (25.3)	15 (88.2)
>3 spike antigens			
No	66 (66)	64 (77.1)	2 (11.8)
Yes	34 (34)	19 (22.9)	15 (88.2)
Overall seroconversion			
No	46 (46)	46 (55.4)	0
Yes	54 (54)	37 (44.6)	17 (100)
Overall T cell responses			
No	33 (33)	29 (34.9)	4 (23.6)
Yes	55 (55)	44 (53.0)	11 (64.7)
T cell or seroconversion			
Yes	81 (81)	64 (77.1)	17 (100)

Anti-IL-6, Anti interleukin -6 ; Anti-TNF, Anti tumour necrosis factor; bDMARDS, biological disease modifying anti rheumatic drug; JAKi, Janus Kinase inhibitor; MTX, methotrexate; RBD, receptor binding domain; RTX, rituximab.

Table 2 Effect of concomitant methotrexate on seroconversion by treatment groups in patients without pre-vaccine SARS-CoV-2 exposure (n=83)

	Seroconversion		
	No, n (%)	Yes, n (%)	P value*
MTX (n=34)	23 (67.7)	11 (32.4)	0.06
No MTX (49)	23 (46.9)	26 (53.1)	
Anti-TNF plus MTX (14)	7 (50)	7 (50)	0.07
Anti-TNF (12)	2 (16.7)	10 (83.3)	
RTX plus MTX (12)	10 (83.3)	2 (16.7)	0.09
RTX (17)	9 (52.9)	8 (47.1)	

Anti TNF, Anti-tumour necrosis factor ; MTX, methotrexate; RTX, rituximab.

85.24). Factors associated with a failure to develop antibody responses include absent previous SARS-CoV-2 exposure (p=<0.001, OR: 0.01, 95% CI: 0.00 to 0.008) and concomitant MTX usage (p=0.01, OR: 8, 95% CI: 1.63 to 37.98).

There was a trend for better development of T cell responses in patients treated with JAKi (p=0.079, OR: 0.24, 95% CI: 0.05 to 1.18) and abatacept (p=0.098, OR: 0.26, 95% CI: 0.05 to 1.28) when compared with RTX, and those who had not received recent corticosteroids (p=0.083, OR: 0.28, 95% CI: 0.07 1.18).

The impact of subsequent vaccines in patients with absent antibody responses to the first SARS-CoV-2 vaccine

Of those with absent antibody responses to vaccine one (n=46), a further 19/35 (54%) seroconverted after a second dose of the vaccine. See online supplemental material for individual drug data. However, of the 16 who did not, 10 have to date received a third dose, with only 2 patients seroconverting (20%). After a total of three SARS-CoV-2 vaccines, and accounting for missing data, 11% (8/74) patients failed to seroconvert.

Type I IFN activity post-vaccination

The serum IFN scores of each patient were determined pre-vaccine and post-vaccine (n=107) and showed strong correlation (R=0.8554, p<0.0001), with no statistical difference between visits.

Table 3 Seroconversion rates in patients without pre vaccine SARS-CoV-2 exposure

Immunosuppressive drug	Seroconversion, n (%)	T cell responses, n (%)
Abatacept	0/11 (0)	4/10 (40)
RTX	10/29 (35)	17/24 (71)
Anti-TNF	17/26 (65)	15/24 (63)
JAKi	5/9 (56)	4/8 (50)
Anti-IL-6	5/8 (63)	4/7 (57)

Anti-IL-6, Anti-interleukin -6; Anti TNF, Anti - tumour necrosis factor; JAKi, Janus Kinase inhibitor; RTX, rituximab.

Efficacy post vaccine

There were eight SARS-CoV-2 infections confirmed (PCR and patient notes) symptomatic cases during the study follow-up. See online supplemental material.

DISCUSSION

This study provides real-world data from a single centre on the immune response to the SARS-CoV-2 vaccines in patients with RA on DMARDs. The novel aspects were the prospective analysis with pre-vaccine data, the variety of DMARDs assessed, the combined antibody and T cell data with IFN responses, together with follow-up. Although patient numbers are small, it highlights the reduced antibody immunity seen with abatacept, <6 months post RTX, as well as a negative impact of MTX.

In virally unexposed patients with RA, the seroconversion rate after vaccination one was 45% and the T cell response rate 53%; 23% of patients had neither antibodies nor T cell responses, compared with 100% seroconversion in patients with pre-vaccine SARS-CoV-2 exposure. Following doses two and three of the vaccine; a further 54% and 11% seroconverted.

The seroconversion and T cell response rates, following a single SARS-CoV-2 vaccine, were higher than those reported with connective tissue diseases, although for RTX treated <6 months the data were comparable; (22% vs 28% seroconversion). This is consistent with previous data for RTX therapy with impaired antibody responses to both the influenzae and pneumococcal vaccines.[8] The impact of abatacept on vaccine response is conflicting[8] and no abatacept patient in this study seroconverted after the first dose (but 50% did so post second vaccine). This is consistent with abatacept's action on both T and B cells, and its known ability to inhibit antibodies. One hundred per cent of our healthy controls seroconverted consistent with the previous data.[9] Almost half of our patients with RA used concomitant MTX in combination with other DMARDs and had reduced seroconversion rates but no significant differences in T cell response rates, consistent with other publications.[10]

Patients with antibodies pre-vaccination (presumably following SARS-CoV-2 infection) all had strong vaccine responses. Our data, however, suggest that there are some patients who are unable to mount an antibody response despite three vaccinations. On-going follow-up of this cohort will determine whether the serological and T cell responses correlate with clinical protection from COVID-19 infection and if sustainability of response matches healthy individuals. Currently, eight patients have tested positive for COVID-19 infection since the second dose of the vaccine and all but one (void sample) had either antibody or T cell responses following the first dose of the vaccine.

There was no evidence of post -vaccination immunological or clinical flares, with stable levels of sera type I IFN-inducible chemokines although on continued therapy.[11 12]

A limitation of this study is the small numbers, particularly of healthy controls, with the numbers limited by requirement for baseline samples. Although the 100% seroconversion rate validates our antibody analysis, as do publications that also demonstrate reduced seroconversion in patients treated with rituximab, abatacept and concomitant methotrexate.[13]

These data confirm reduced immune responses to SARS-CoV-2 vaccine in patients with RA particularly on certain DMARDs. The impact of a booster dose in patients with absent antibody responses to a three dose vaccination schedule will need to be determined.

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Patient and public involvement statement The participant information sheet and consent form used for the study were taken from an existing study where public contributors had already approved them, saying that they explained the research well and what was expected of them. As well as this, they were already familiar with the study schedule and the site. The main difference to this was that they were visiting the site during the pandemic. Through the 'Restarting Research' public contributor group, barriers to accessing the site and solutions were discussed and considered in the study schedule. This included making reception staff aware of the participants who were coming in for the study, providing clarity around the claiming of travel expenses and ensuring this was discussed during the consenting process. For participants, having an awareness of their response to the vaccine was of clear benefit to them and involvement with public contributors needs to continue to ensure this information is disseminated appropriately.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Leeds West REC: 09/H1307/98; R&I: RR09/9134. Leeds East REC: 16/YH/0290 (Healthy controls). Participants gave informed consent to participate in the study before taking part.

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