Rheumatoid arthritis disease activity assessed by patient-reported outcomes and flow cytometry before and after an additional dose of COVID-19 vaccine

The Centers for Disease Control and Prevention has recommended that moderately/severely immunosuppressed individuals receive an additional dose (AddDose) of COVID-19 vaccine at least 28 days after an initial mRNA vaccine series, or at least 2 months after a single adenovirus vector vaccine.¹ Rheumatoid arthritis (RA) is frequently treated with immunosuppressive disease-modifying antirheumatic drugs (DMARDs), meaning that most patients with RA are eligible for an AddDose. The American College of Rheumatology suggests patients interrupt use of ('hold') certain DMARDs around the time of COVID-19 vaccination in attempt to boost immunogenicity.² A small number of reports have noted no significant change in RA disease activity pre vaccination versus post vaccination against COVID-19, but they assessed RA disease activity infrequently and did not compare results for patients who held versus continued DMARDs. Furthermore, data are lacking on the assessment of immune cellular populations possibly correlated with RA disease activity around the time of COVID-19 vaccination.

We conducted a prospective observational study of patients with RA treated at Brigham and Women's Hospital who were previously vaccinated against COVID-19 (two doses of mRNA vaccine or one dose of adenovirus vector vaccine). Subjects enrolled between July and November 2021, prior to receiving an AddDose. RA disease activity was assessed weekly using the validated patient-reported RA Disease Activity Index—5 (RADAI-5) from enrolment through 4 weeks post-AddDose via online data entry.³ Subjects completed an additional online survey 2 days after the AddDose regarding vaccine reactogenicity and whether they held or continued DMARDs. We compared mean RADAI-5 in the 4 weeks pre-AddDose versus the 4 weeks post-AddDose using the generalised estimating equation in SAS (V.9.4) to account for correlated data among individual subjects. We aimed to enrol 60 subjects to achieve 91% power to detect a 15% non-inferiority margin in RADAI-5 post-AddDose versus pre-AddDose.

Among 71 subjects, mean age was 62 years (SD 12) and 85% were women. Methotrexate (42%) and tumour necrosis factor inhibitors (38%) were the most common DMARDs; 49% held at least one DMARD (see table 1 for additional characteristics). Symptoms after the AddDose most often included injection site pain/swelling (72%) and fatigue (52%) (see online supplemental file 1). RADAI-5 was normally distributed pre-AddDose and post-AddDose. The mean RADAI-5 was 3.20 (SD 0.23) pre-AddDose compared with 3.25 (SD 0.23) post-AddDose (difference of 1.6%, $p=0.51$) (see online supplemental file 2). Figure 1 displays mean RADAI-5 in 35 (49%) subjects who held DMARDs and 36 (51%) subjects who continued all DMARDs. Mean RADAI-5 did not significantly differ pre-AddDose versus post-AddDose among subjects who held DMARDs, nor in subjects who continued all DMARDs. Mean change in RADAI-5 between pre-AddDose and post-AddDose did not significantly differ based on whether subjects held versus continued DMARDs (p for interaction=0.16).

For a subset of 27 patients with seropositive RA, flow cytometry quantified percentages of 4 lymphocyte populations associated with immune activation in RA—T peripheral helper cells,

Table 1 Characteristics of study subjects

	All subjects (N=71)	Subset of subjects analysed by flow cytometry (N=27)*
Age, mean (SD)	62.2 (11.8)	62.8 (13.3)
Female, n (%)	60 (84.5)	20 (74.1)
White, n (%)	67 (95.7)†	25 (92.6)
Seropositive rheumatoid arthritis, n (%)	62 (87.3)	27 (100.0)
Brand of initial vaccine series, n (%)		
Pfizer	36 (50.7)	11 (40.7)
Moderna	30 (42.3)	12 (44.4)
Johnson & Johnson	5 (7.0)	4 (14.8)
Self-reported RA flare after initial COVID-19 vaccine series, n (%)	13 (18.3)	7 (25.9)
COVID-19 infection prior to additional dose, n (%)	1 (1.4)	0 (0)
Mean (SD) days from completion of initial vaccine series to additional dose	177.8 (48.1)	184.6 (50.5)
DMARDs at the time of additional dose, n (%)‡		
Methotrexate	30 (42.3)	16 (59.3)
TNFi	27 (38.0)	13 (48.1)
Prednisone	15 (21.1)	3 (11.1)
JAKi	11 (15.5)	4 (14.8)
Abatacept	5 (7.0)	0 (0)
Tocilizumab	5 (7.0)	1 (3.7)
Rituximab	3 (4.2)	2 (7.4)
Other	13 (18.3)	2 (7.4)
None	3 (4.2)	0 (0)
Held DMARD(s) around the time of additional dose, n (%)§	35 (49.3)	16 (59.3)

*One subject provided pre-AddDose and post-AddDose blood samples but did not complete post-AddDose rheumatoid arthritis disease activity assessments. This subject only contributed flow cytometry data and was not included among the 71 subjects in the primary analysis.

†Among 70 subjects with data on race.

‡DMARD groups are not mutually exclusive.

§Among 35 subjects who held DMARDs, 21 held all DMARDs and 14 held at least 1 but not all DMARDs.

DMARDs, disease-modifying antirheumatic drugs; JAKi, Janus kinase inhibitor; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor.

T follicular helper cells, age-associated B cells and plasmablasts—in blood samples obtained pre-AddDose and week 4 post-AddDose.^{4–6} Subject characteristics are shown in table 1. Frequencies of these lymphocyte populations did not significantly differ between the pre-AddDose and post-AddDose time-points in either subjects who held at least one DMARD ($n=16$) or subjects who continued all DMARD ($n=11$) (figure 1).

Limitations of this study include a relatively small number of participants, though the study was adequately powered to detect a difference of 15% in RA disease activity pre-AddDose versus post-AddDose. The number of participants providing blood for flow cytometry analyses was low, particularly in subgroups by holding versus continuing DMARDs, and results should be interpreted cautiously.

These results suggest that RA disease activity, measured weekly with a validated patient-reported outcome, is stable around the time of an AddDose of COVID-19 vaccine. Lymphocyte subsets of interest in RA were also similar before and after the AddDose, supporting the observation of stable patient-reported RA disease activity. Holding DMARDs was not associated with greater RA disease activity following the AddDose.

Figure 1 Rheumatoid arthritis (RA) disease activity and lymphocyte subsets among subjects who held at least one disease-modifying antirheumatic drug (DMARD) (top panels) and those who continued all DMARDs (bottom panels) around the time of the additional dose of COVID-19 vaccine. (A) Box-and-whisker plots for Rheumatoid Arthritis Disease Activity Index—5 (RADAI-5) indicate the median (line), mean (diamond), 25th percentile (bottom of box), 75th percentile (top of box), and minimum and maximum values (whiskers). (B) Lymphocyte populations were gated as follows: T peripheral helper (Tph; CD4⁺ PD-1^{hi} CXCR5⁻), T follicular helper (Tfh; CD4⁺ PD-1^{hi} CXCR5⁻), age-associated B cells (ABCs; CD19⁺ CD21⁻ CD11C⁺) and plasmablasts (CD19⁺ CD27^{hi} CD38^{hi}). Patients treated with rituximab (n=3) were included in T-cell analyses, but excluded from B-cell analyses. Summary data on each panel include median (IQR) % lymphocyte population pre and post additional dose. Significance testing of flow cytometry data used Wilcoxon paired tests with Bonferroni correction for multiple testing. All comparisons of pre versus post were non-significant (p>0.0125).

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