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Effect of a 2-week interruption in methotrexate treatment on COVID-19 vaccine response in people with immune-mediated inflammatory diseases (VROOM study): a randomised, open label, superiority trial

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Summary

Background Methotrexate is the first-line treatment for immune-mediated inflammatory diseases and reduces vaccine-induced immunity. We evaluated if a 2-week interruption of methotrexate treatment immediately after COVID-19 booster vaccination improved antibody response against the S1 receptor binding domain (S1-RBD) of the SARS-CoV-2 spike protein and live SARS-CoV-2 neutralisation compared with uninterrupted treatment in patients with immune-mediated inflammatory diseases.

Method We did a multicentre, open-label, parallel-group, randomised, superiority trial in secondary-care rheumatology and dermatology clinics in 26 hospitals in the UK. Adults (aged ≥18 years) with immune-mediated inflammatory diseases taking methotrexate (≤25 mg per week) for at least 3 months, who had received two primary vaccine doses from the UK COVID-19 vaccination programme were eligible. Participants were randomly assigned (1:1) using a centralised validated computer program, to temporarily suspend methotrexate treatment for 2 weeks immediately after COVID-19 booster vaccination or continue treatment as usual. The primary outcome was S1-RBD antibody titres 4 weeks after COVID-19 booster vaccination and was assessed masked to group assignment. All randomly assigned patients were included in primary and safety analyses. This trial is registered with ISRCTN, ISRCTN11442263; following a pre-planned interim analysis, recruitment was stopped early.

Finding Between Sept 30, 2021, and March 7, 2022, we screened 685 individuals, of whom 383 were randomly assigned: to either suspend methotrexate (n=191; mean age 58·8 years [SD 12·5], 118 [62%] women and 73 [38%] men) or to continue methotrexate (n=192; mean age 59·3 years [11·9], 117 [61%] women and 75 [39%] men). At 4 weeks, the geometric mean S1-RBD antibody titre was 25 413 U/mL (95% CI 22 227–29 056) in the suspend methotrexate group and 12 326 U/mL (10 538–14 418) in the continue methotrexate group with a geometric mean ratio (GMR) of 2·08 (95% CI 1·59–2·70; p<0·0001). No intervention-related serious adverse events occurred.

Interpretation 2-week interruption of methotrexate treatment in people with immune-mediated inflammatory diseases enhanced antibody responses after COVID-19 booster vaccination that were sustained at 12 weeks and 26 weeks. There was a temporary increase in inflammatory disease flares, mostly self-managed. The choice to suspend methotrexate should be individualised based on disease status and vulnerability to severe outcomes from COVID-19.

Funding National Institute for Health and Care Research.

Introduction

Methotrexate is the first-line treatment for rheumatic diseases such as rheumatoid arthritis, psoriatic arthritis, and is often the first-line systemic therapy for skin diseases such as psoriasis.[1,2] It is combined with biologics to optimise their efficacy and to minimise antidrug antibody formation.[3,4] Methotrexates has broad immune-suppressive effects that attenuate immune response to COVID-19 vaccines.[5–7] Interrupting methotrexate treatment for 2 weeks immediately after vaccination against seasonal influenza enhanced the immunity from vaccination, with no effect on vaccination-induced humoral immunity of interrupting treatment for either 2 or 4 weeks before vaccination.[8,9]

We hypothesised that a 2-week interruption in methotrexate treatment immediately after a COVID-19 booster vaccination would enhance immunity following vaccination without substantial deterioration of inflammatory disease activity. Understanding the effectiveness and safety of this intervention would facilitate durable immunity following COVID-19 vaccine boosters in this vulnerable population including against emergent

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See Online for appendix

Research in context

Evidence before this study

Methotrexate is used first-line for the treatment of many immune-mediated inflammatory diseases. However, it inhibits vaccine-induced immunity, which was a major concern during the COVID-19 pandemic. We searched PubMed for randomised controlled trials published between database inception and Aug 31, 2023, using the terms (methotrexate AND vaccin*) AND (influenza OR COVID-19 OR SARS-CoV-2) AND (clinical trial[filter]), with no language restrictions, to identify trials that evaluated the effect of interrupting methotrexate treatment peri-vaccination on vaccine immunogenicity. We also searched reference lists of these studies. We identified two reports of clinical trials conducted in South Korea before the COVID-19 pandemic. These trials showed that interrupting methotrexate treatment for 2 weeks immediately after vaccination against seasonal influenza improved vaccine-induced immunity. There was no effect of interrupting treatment before vaccination and a longer 4-week treatment interruption after vaccination did not improve vaccine induced immunity more than a 2-week interruption. A 2023 trial from South Korea reported that a 1-week break from methotrexate treatment immediately after influenza vaccination was non-inferior to a 2-week interruption in treatment on vaccine induced immunity at 4 weeks. We also identified two small single-centre, tertiary hospital-based trials conducted in Brazil and India, limited to patients with well controlled inflammatory arthritis without previous SARS-CoV-2 infection. They reported that a 2-week methotrexate interruption after primary vaccination against COVID-19 improved the S1 receptor binding domain (S1-RBD) antibody response. However, these studies were at high risk of bias due to exclusion of participants after randomisation for previous SARS-CoV-2 infection, had a short follow-up period, excluded patients due to disease flares and had a high dropout rate.

In September 2021, we set out to find the effect of a 2-week interruption in methotrexate treatment immediately after COVID-19 booster vaccination on vaccine induced immunogenicity and inflammatory disease control.

Added value of this study

In this randomised clinical trial that included 383 adults, the S1-RBD antibody titres in the suspend treatment group were higher at weeks 4, 12, and 26 than in the continue treatment group. Treatment interruption improved neutralisation of Wuhan-Hu-1 up to 26 weeks and Omicron BA.1 at 4 weeks. Self-reported inflammatory disease activity deteriorated at 4 weeks and 12 weeks in the suspend methotrexate group. More patients in the suspend methotrexate group self-reported at least one inflammatory disease flare over 12 weeks. However, comparable numbers of people in both groups of the study required clinical input to manage flares. The self-reported disease activity was similar in both groups at week 26 and the number of people self-reporting at least one disease flare over the 26-week study period were comparable in both study groups. 2-week interruption of methotrexate treatment enhanced boosting of antibody responses after COVID-19 vaccination that were sustained at 26 weeks.

Implications of all the available evidence

With the emergence of new variants, and vaccine hesitancy among patients, it is important to optimise durable protection in those who are susceptible to COVID-19. Evidence from this study will help patients and clinicians make informed choices about the risks and benefits of interrupting methotrexate treatment around the time of vaccination against COVID-19. It will be useful for policy makers, national immunisation advisory committees, and specialist societies formulating recommendations on the timing of vaccination in those treated with or starting immunosuppression.

variants of concern that might have lower cross-protection. The aim of this study was to analyse the effect of a 2-week interruption in methotrexate treatment immediately after COVID-19 booster vaccination on antibody responses against the S1 receptor binding domain (S1-RBD) of the SARS-CoV-2 spike protein and SARS-CoV-2 neutralisation (ancestral Wuhan-Hu-1 and omicron BA.1) in adults with immune-mediated inflammatory diseases. We did a pre-planned interim analysis once week 4 S1-RBD antibody titres were available for at least 250 participants. Based on these findings, the independent Data Monitoring and Trial Steering Committees recommended to stop recruitment of new participants, publish the interim results due to their public health importance,[10] and complete follow-up of randomly assigned participants. Here we present results from the full trial cohort and include data on the S1-RBD antibody titres, live virus neutralisation, and inflammatory disease activity from the 26-week study period.

For the **study protocol** see https://vroom.octru.ox.ac.uk

Methods

Study design and participants

The Vaccine Response On/Off Methotrexate (VROOM) study was an open-label, two-arm parallel-group, multicentre, randomised, controlled, superiority trial. The dominant circulating SARS-CoV-2 variants in the UK at the time of recruitment to the study were the delta (June 12 to Dec 19, 2021), omicron BA.1 (Dec 20, 2021, to March 1, 2022) and omicron BA.2 (March 2 to June 15, 2022) as per the Office for National Statistics. The detailed methods are published elsewhere.[11] The study protocol is available online.

Participants were recruited from rheumatology and dermatology clinics in 26 National Health Service hospitals in the UK. This study was approved by Leeds West Research Ethics Committee and Health Research Authority (REC Reference: 21/YH/0209, HRA COVID-19 fast-track reference: 21/HRA/3483, IRAS: 303827). Independent oversight was provided by separate

independent trial steering committee and data monitoring committee. The trial is registered with ISRCTN, ISRCTN-11442263.

To be eligible, participants were required to be at least 18 years old, diagnosed with an immune-mediated inflammatory diseases (eg, rheumatoid arthritis, psoriasis, etc) prescribed methotrexate (≤25 mg per week) for at least 3 months with or without hydroxychloroquine, be able to temporarily suspend methotrexate treatment for 2 weeks in the opinion of their clinical team, have received at least two vaccine doses from the UK COVID-19 Vaccination Programme and be eligible for an additional vaccine dose.[12]

Key exclusion criteria were immune-mediated inflammatory diseases for which treatment cannot be interrupted safely; recent or planned rituximab infusion as it is a strong inhibitor of vaccine-induced immunity with lasting effects; use of other glucocorticoid-sparing drugs in previous 2 months; use of prednisolone dose of more than 7·5 mg per day within previous 1 month; radiotherapy or chemotherapy for cancer in previous 6 months; and visceral cancer. Sex was self-reported as either male or female. Participants were approached by their usual care team and gave written informed consent before taking part in the study.

Patients with inflammatory conditions were involved in prioritising the research question. They advised on the study design and selected self-reported disease activity as the key secondary outcome measure over objective face-to-face disease activity assessment as the latter meant more face-to-face contact with another health professional. A key concern for the vulnerable patients during the COVID-19 pandemic was to minimise their risk of infection. Our dissemination strategy was developed in partnership with the patient and public involvement members.

Randomisation and masking

Randomisation was done using a centralised validated computer randomisation program accessed through a secure (encrypted) web-based service provided by the Oxford Clinical Trials Research Unit (OCTRU). A minimisation algorithm including a random element ensured balanced allocation across treatment groups, and a 1:1 ratio to allocate to either suspend methotrexate use for 2 weeks immediately after COVID-19 booster vaccination or continue as usual. The trial used immune-mediated inflammatory disease type (rheumatic disease with or without skin disease, or skin disease alone); age (<40 years, 40–64 years, ≥65 years); and primary vaccination technology (mRNA, vector, or combination) as minimisation factors. The minimisation factors were chosen to balance immune-mediated inflammatory diseases and key prognostic factors that effect COVID-19 vaccine response between trial groups.[13–16] Self-reported previous SARS-CoV-2 infection was not controlled for despite it being a strong modifier of serological response to COVID-19 vaccination[14–16] due to inconsistent access to diagnostic PCR testing in the UK. Previous SARS-CoV-2 infection status was established by measuring N-serology at baseline and used in the statistical analysis. The study participants were not masked (ie, it was not possible to mask participants in this study without a matching placebo, which was deemed unfeasible). The primary outcome and serological secondary outcomes were accessed masked to treatment allocation.

Procedures

The VROOM study evaluated temporarily interrupting versus continuing methotrexate treatment immediately after the COVID-19 vaccine boosters (predominantly full dose BNT162b2 [Pfizer–BioNTech], half dose [50 µg] or full dose [100 µg] mRNA-1273 [Moderna]; and full dose AZD1222 [Oxford–AstraZeneca]) delivered through the UK COVID-19 Vaccination Programme.[12] For the suspend group, methotrexate dosing was interrupted for 2 weeks immediately after receiving the COVID-19 vaccine. Participants vaccinated on the day on which they usually took methotrexate were asked to miss the methotrexate on the day of vaccination and another dose 1 week later. For others the advice was to suspend the weekly methotrexate doses for 2 weeks immediately after vaccination. For the continue group, methotrexate was continued at the same dose on the same day. In both groups, any concomitant medicine including folic acid and hydroxychloroquine was continued and disease flares treated as per standard care. Participants could also stop or take methotrexate against trial allocation if clinically indicated, for example, if there was an intercurrent infection or disease flare.

The VROOM study was initially designed with visits at 4 weeks and 12 weeks. In view of the results of the interim analysis,[10] a 26-week visit was added in March 2022, to evaluate the durability of the improvement in immune response.

Outcomes

The primary outcome was fully quantitative Roche-Elecsys S1-RBD antibody[17] titre 4 weeks after COVID-19 booster vaccination. It was measured centrally at the UK Health Security Agency masked to group allocation. This assay was selected to allow for comparability between studies.

Secondary outcomes were S1-RBD antibody titre 12 and 26 weeks after COVID-19 vaccine dose blinded to group allocation; live virus neutralisation (ancestral Wuhan Hu-1, Omicron BA·1)[18] at weeks 4, 12, and 26 (assessed in 100 participants) blinded to group allocation; self-reported inflammatory disease activity at weeks 2, 4, 12, and 26 with a 1-week recall on an 11-point (0–10) numeric rating scale with higher scores reflecting better general health; self-reported disease flare, actions taken to manage flares, quality of life (using EQ-5D-5L), self-reported five-point ordinal patient global assessment of disease activity ranging from none or

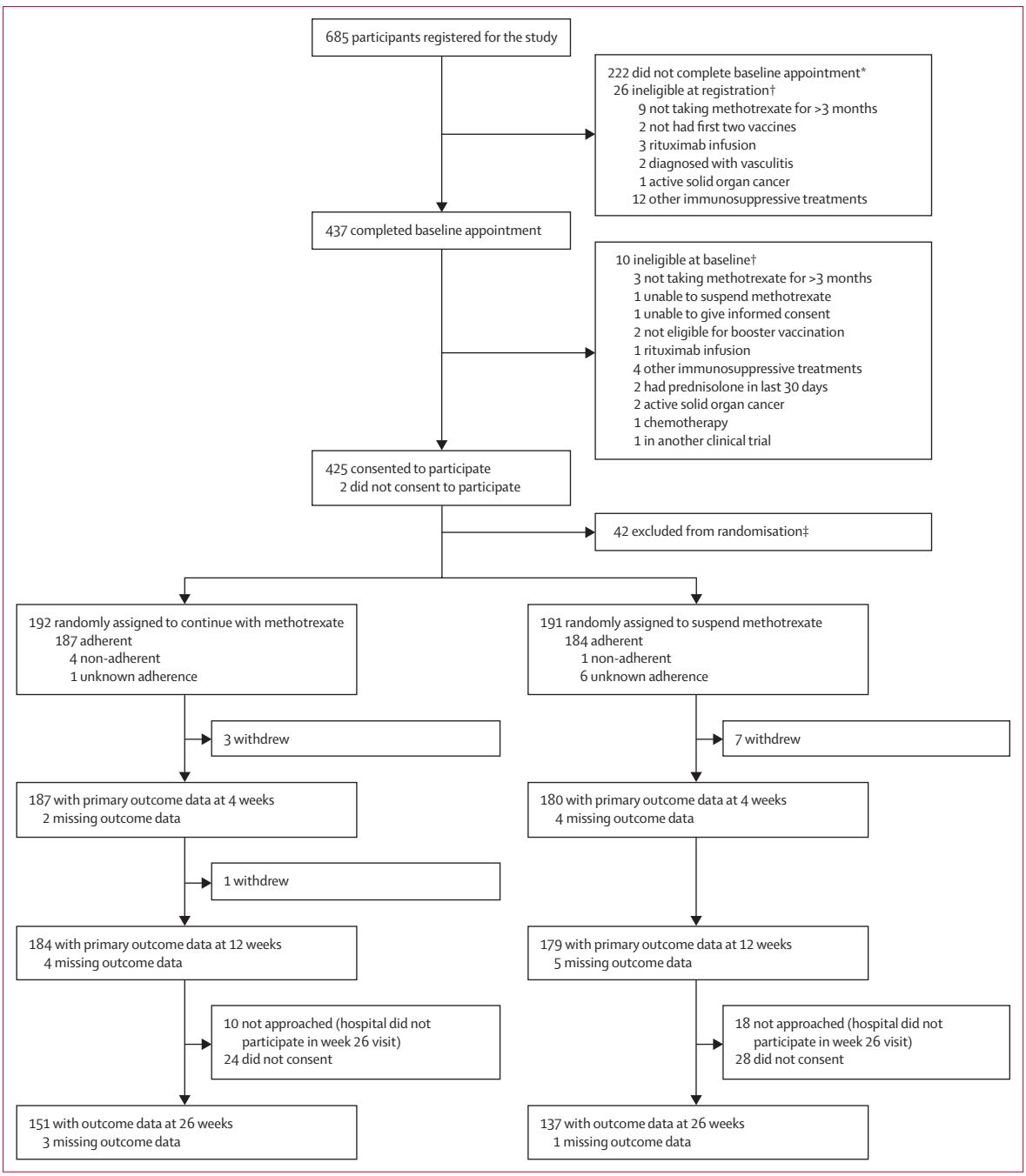


Figure 1: **Consort diagram**
*This occurred primarily due to recruitment being stopped early. †Some patients had more than one stated reason for ineligibility. ‡Due to recruitment being stopped early.

inactive to very severe activity with a 1-week recall at weeks 4, 12, and 26, and inflammatory disease control since vaccination using a five-point ordinal scale ranging from much better to much worse at weeks 4 and 12; self-reported adherence with trial allocation and serious adverse events. See appendix (p 3–5) for details of live virus neutralisation assay. Biochemical adherence to oral methotrexate was measured using a validated assay masked to group allocation.[19] Ancestral S1-RBD antibody titre was chosen as the primary outcome as it is correlated with ancestral SARS-CoV-2 neutralisation antibody titre, a correlate of protection from COVID-19 during the first wave;[20–23] which is feasible to be measured rapidly in many samples.

Statistical analysis

Statistical analyses were based on the as randomised (intention to treat) population. The study was powered to detect at least 25% lower antibody response in the methotrexate continue group (Cohen's d effect of 0·29) with 90% statistical power at two-sided 5% significance level. Using S1-RBD antibody response elicited by the booster dose of COVID-19 vaccine,[11] this effect size translates to a target difference in S1-RBD antibody titre of approximately 5000 U/mL (appendix p 2).

Antibody data were log-transformed (base 10) to normalise distribution before analysis. The difference in S1-RBD titres at weeks 4, 12, and 26 between study groups was estimated using a multi-level mixed effects model, allowing for repeated measures clustered within participants. The model was adjusted for minimisation factors, previous SARS-CoV-2 infection assessed using N-serology and COVID-19 vaccine platform received as booster dose as fixed effects. A treatment by time point interaction was also included along with treatment and time point as fixed effects. Adjusted geometric mean ratios (GMR) between the groups are presented, together with 95% CI and p value for the primary outcome measure.

Consistency of treatment effect for prognostic subgroups (age, rheumatic and skin disease, methotrexate dose and route, primary vaccination platform, and previous SARS-CoV-2 infection) were explored at weeks 4, 12, and 26 using treatment by subgroup interactions. Other secondary outcomes were analysed using generalised linear models for binary and continuous data, as appropriate, with model adjustment as described above. The widths of the 95% CI have not been adjusted for multiplicity and these should not be interpreted as formal hypothesis tests. The number and details of serious adverse events are presented by treatment group. Data analyses were done using STATA (version 18.0). OCTRU was responsible for trial operations including data analysis.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Sept 30, 2021, and March 7, 2022, we screened 685 individuals, 425 of whom were recruited into the study. The trial stopped recruiting early upon the recommendations of the independent Data Monitoring and Trial Steering Committees given the findings of the interim analysis.[10] By recruitment stop, 383 eligible participants had been randomly assigned: 191 participants were randomly assigned to suspend methotrexate use for 2 weeks immediately after COVID-19 booster vaccination and 192 to continue methotrexate (figure 1). Seven participants in the suspend methotrexate group and four

	Continue methotrexate (n=192)	Suspend methotrexate (n=191)	Total (n=383)
Age, years	59·3 (11·9)	58·8 (12·5)	59·0 (12·2)
Sex			
Male	75 (39%)	73 (38%)	148 (39%)
Female	117 (61%)	118 (62%)	235 (61%)
Ethnicity			
White	182 (95%)	177 (93%)	359 (94%)
Other	10 (5%)	12 (6%)	22 (6%)
Missing data	0	2 (1%)	2 (1%)
BMI, kg/m²	28·7 (6·0)	29·6 (5·7)	29·2 (5·9)
Serum creatinine, µmol/L	73·1 (14·0)	75·9 (14·5)	74·5 (14·3)
Missing data	15 (8%)	15 (8%)	30 (8%)
Serum albumin, g/L	41·2 (3·5)	41·6 (4·0)	41·4 (3·7)
Missing data	18 (9%)	19 (10%)	37 (10%)
Smoking status			
Never smoked	95 (49%)	104 (54%)	199 (52%)
Ex-smoker	80 (42%)	71 (37%)	151 (39%)
Current smoker	17 (9%)	16 (8%)	33 (9%)
Residence			
Own home	178 (93%)	183 (96%)	361 (94%)
Residential care	1 (1%)	1 (1%)	2 (1%)
Living with family or friends	12 (6%)	7 (4%)	19 (5%)
Missing data	1 (1%)	0	1 (<1%)
Type of immune-mediated inflammatory disease			
Inflammatory rheumatic disease (with or without skin disease)	160 (83%)	155 (81%)	315 (82%)
Skin disease only	32 (17%)	36 (19%)	68 (18%)
Immune-mediated inflammatory disease*			
Rheumatoid arthritis	111 (58%)	97 (51%)	208 (54%)
Psoriasis with arthritis	37 (19%)	38 (20%)	75 (20%)
Psoriasis without arthritis	22 (11%)	25 (13%)	47 (12%)
Seronegative (axial) spondyloarthritis	3 (2%)	2 (1%)	5 (1%)
Atopic eczema	9 (5%)	9 (5%)	18 (5%)
Polymyalgia rheumatica	3 (2%)	3 (2%)	6 (2%)
Systemic lupus erythematosus	3 (2%)	2 (1%)	5 (1%)
Other rheumatic disease	8 (4%)	14 (7%)	22 (6%)
Other skin disease	5 (3%)	7 (4%)	12 (3%)
Patient global assessment of disease activity			
Mean (SD)	7·8 (2·0)	7·4 (2·0)	7·6 (2·0)
0–3	7 (4%)	7 (4%)	14 (4%)
4–6	34 (18%)	43 (23%)	77 (20%)
≥7	151 (79%)	141 (74%)	292 (76%)
Comorbidities*			
Diabetes	23 (12%)	20 (10%)	43 (11%)
Hypertension	49 (26%)	44 (23%)	93 (24%)
Ischaemic heart disease	6 (3%)	8 (4%)	14 (4%)
Congestive cardiac failure	0	1 (1%)	1 (<1%)
Asthma	25 (13%)	28 (15%)	53 (14%)
Chronic obstructive pulmonary disease	5 (3%)	8 (4%)	13 (3%)
High cholesterol	25 (13%)	25 (13%)	50 (13%)
Stroke (including transient ischaemic attack)	4 (2%)	4 (2%)	8 (2%)
None of the above	105 (55%)	105 (55%)	210 (55%)

(Table 1 continues on next page)

	Continue methotrexate (n=192)	Suspend methotrexate (n=191)	Total (n=383)
(Continued from previous page)			
Dose of methotrexate, mg/week	20·0 (15·0–25·0)	20·0 (15·0–22·5)	20·0 (15·0–22·5)
Route of methotrexate administration			
Oral	106 (55%)	106 (55%)	212 (55%)
Subcutaneous	86 (45%)	85 (45%)	171 (45%)
Concomitant systemic medications*			
Folic acid	188 (98%)	188 (98%)	376 (98%)
NSAIDs	30 (16%)	29 (15%)	59 (15%)
Hydroxychloroquine	38 (20%)	38 (20%)	76 (20%)
Median dose, mg/day	200 (200–400; n=37)	200 (200–200; n=37)	200 (200–400; n=74)
Insulin	4 (2%)	1 (1%)	5 (1%)
Oral glucocorticoids	3 (2%)	7 (4%)	10 (3%)
None	3 (2%)	2 (1%)	5 (1%)
Current use of topical glucocorticoid cream			
Yes	28 (15%)	29 (15%)	57 (15%)
No	164 (85%)	162 (85%)	326 (85%)
Parenteral glucocorticoids in the past 3 months			
Intra-articular glucocorticoids	2 (1%)	7 (4%)	9 (2%)
Intramuscular glucocorticoids	3 (2%)	5 (3%)	8 (2%)
Intravenous glucocorticoids	0	0	0
COVID-19 disease history*			
COVID-19 hospitalisation	1 (1%)	3 (2%)	4 (1%)
COVID-19 not requiring hospitalisation	22 (11%)	27 (14%)	49 (13%)
SARS-CoV-2 positive PCR test	15 (8%)	24 (13%)	39 (10%)
No COVID-19 event	163 (85%)	155 (81%)	318 (83%)
Randomisation to booster, days	6·3 (7·1)	6·1 (7·2)	6·2 (7·1)
Baseline assessment to booster, days	11·8 (12·0)	11·7 (11·4)	11·8 (11·6)
Previous vaccination to booster, days	174·2 (43·8)	180·8 (42·2)	177·5 (43·1)
Primary COVID-19 vaccine type			
mRNA (BNT162b2, mRNA-1273)	73 (38%)	70 (37%)	143 (37%)
Vector (AZD1222)	118 (61%)	119 (62%)	237 (62%)
Combination	1 (1%)	2 (1%)	3 (1%)
Third and fourth booster vaccination			
Third vaccination	149 (78%)	154 (81%)	303 (79%)
Fourth vaccination	43 (22%)	37 (19%)	80 (21%)
COVID-19 booster vaccine type			
BNT162b2	147 (77%)	143 (75%)	290 (76%)
AZD1222	8 (4%)	4 (2%)	12 (3%)
mRNA-1273	35 (18%)	37 (19%)	72 (19%)
Unknown	0	2 (1%)	2 (1%)
Did not have booster	2 (1%)	5 (3%)	7 (2%)

Data are n (%), mean (SD), or median IQR. Data for time between latest previous vaccination before entering the trial to booster vaccination received in the VROOM study, baseline visit to booster vaccination received in the VROOM study, and randomisation to booster vaccination received in the VROOM study were missing for two participants in the continue methotrexate arm, and for three participants in the suspend methotrexate arm. Patient global assessment of disease activity was assessed on a 0–10 numeric rating scale with 0 being poor and 10 being excellent and a 1 week recall using the question: "In all the ways that your condition affects you, over the last 7 days, how would you rate the way you felt?". *Participants can have more than one category. NSAIDs=non-steroidal anti-inflammatory drugs.

Table 1: **Baseline characteristics**

in the continue methotrexate group withdrew before their 12 week visit, among them seven and three did so before their 4 week visit (appendix p 8). The baseline characteristics of participants were well balanced between the groups (table 1). The mean age was 59·0 years (SD 12·2) and BMI was 29·2 kg/m² (5·9). Of 383 participants, 235 (61%) were women and 148 (39%) were men. 208 (54%) had rheumatoid arthritis, 122 (32%) had psoriasis with or without arthritis, and 68 (18%) had an inflammatory skin condition alone. The median methotrexate dose was 20·0 mg (IQR 15·0–22·5) per week. 362 (95%) of 383 participants received a mRNA vaccine booster. The mean time between the latest COVID-19 vaccination received before entering the VROOM study and the vaccine booster received after randomisation was 177·5 days (SD 43·1).

Adherence to the intervention was high, with self-reported adherence 184 (96%) in the suspend group and 187 (97%) in the continue methotrexate group (appendix p 9). One participant in suspend group and four participants in the continue group were partially compliant with trial allocation taking one weekly dose. Compliance data were missing for seven participants. Participants were not excluded for non-compliance. Participants in both groups had high levels of adherence to oral methotrexate in a validated biochemical assay (appendix p 10). This could only be assessed for oral methotrexate as the assay is not validated for subcutaneously administered methotrexate.

The S1-RBD antibody response was significantly higher in the methotrexate suspend group compared with the continue treatment group at 4 weeks (geometric mean 25 413 U/mL [95% CI 22 227–29 056] *vs* 12 326 U/mL [10 538–14 418]). In an adjusted mixed-effect model, the GMR of S1-RBD antibody on suspending methotrexate for 2 weeks was 2·08 (95% CI 1·59–2·70; p<0·0001; table 2). The results were unchanged on post-hoc sensitivity analyses that also included the methotrexate dose as a covariate (appendix p 11). Planned exploratory subgroup analyses (figure 2, appendix p 12) suggested a greater treatment effect at higher methotrexate dose (interaction GMR effect 1·48 [95% CI 1·04–2·12]). The treatment effects were consistent across methotrexate administration route, rheumatic and skin disease, age, primary vaccination platform, and prior SARS-CoV-2 infection status.

The S1-RBD antibody titre was higher in the methotrexate suspend group compared with the continue treatment group at 12 weeks and 26 weeks (table 2). In an adjusted mixed-effect model, the GMR for S1-RBD antibody on suspending methotrexate for 2 weeks was 1·88 (95% CI 1·44–2·46) at 12-weeks, and 1·50 (1·12–2·01) at 26 weeks. At 12 weeks, results were similar across subgroups except for methotrexate dose which indicated a greater treatment effect at higher doses (interaction GMR effect 1·56 [95% CI 1·03–2·37]; figure 2, appendix p 13). The results were unchanged on

	Continue methotrexate		Suspend methotrexate		Geometric mean ratio (95% CI)*	p value
	N	Geometric mean (95% CIs)	N	Geometric mean (95% CIs)		
S1-RBD antibody						
Baseline	191	948 (711–1263)	190	890 (677–1169)	..	..
4 weeks	187	12 326 (10 538–14 418)	180	25 413 (22 227–29 056)	2·08 (1·59–2·70)	<0·0001
12 weeks	184	8972 (7500–10 733)	179	17 131 (14 882–19 721)	1·88 (1·44–2·46)	<0·0001
26 weeks	151	9971 (8050–12 350)	137	15 318 (12 430–18 878)	1·50 (1·12–2·01)	0·0063
Neutralisation of live SARS-CoV-2 virus						
Baseline						
Wuhan Hu-1 IC_{50}	50	2229 (1096–4531)	50	1524 (736–3155)	..	..
Omicron BA.1 IC_{50}	50	157 (103–239)	50	122 (80–185)	..	..
4 weeks						
Wuhan Hu-1 IC_{50}	50	18 342 (9059–37 139)	50	35 919 (17628–73191)	2·56 (1·21–5·44)	..
Omicron BA.1 IC_{50}	50	339 (220–522)	50	724 (426–1230)	2·42 (1·45–4·05)	..
12 weeks						
Wuhan Hu-1 IC_{50}	50	21 879 (11 084–43 187)	50	22 150 (10 874–45 119)	1·32 (0·62–2·81)	..
Omicron BA.1 IC_{50}	50	280 (172–454)	50	274 (170–443)	1·11 (0·67–1·86)	..
26 weeks						
Wuhan Hu-1 IC_{50}	29	11 161 (4517–27 578)	28	25 613 (9865–66 500)	3·50 (1·34–9·18)	..
Omicron BA·1 IC_{50} †	29	881 (399–1946)	28	1001 (370–2703)	1·50 (0·69–3·29)	..

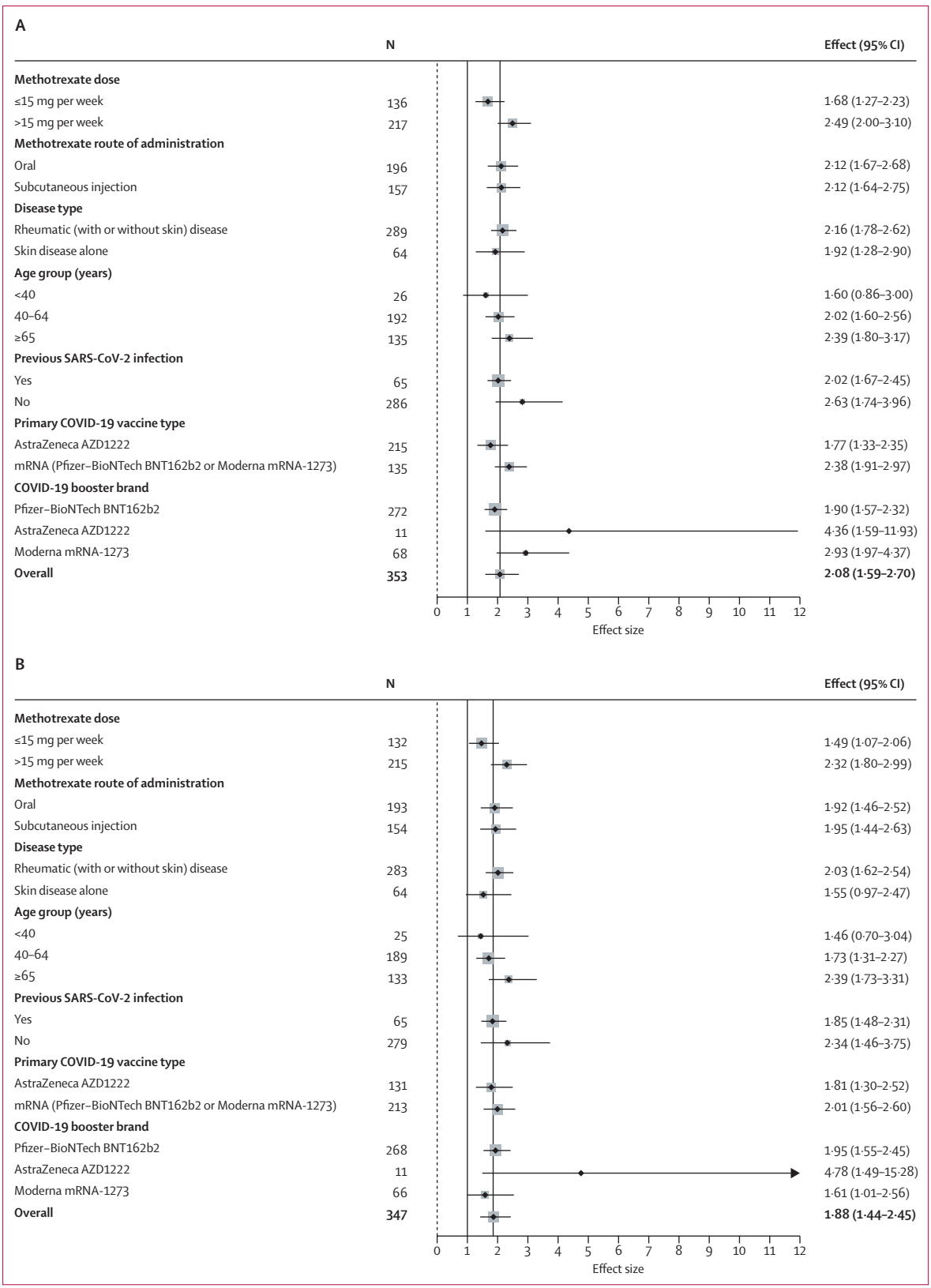
S1-RDB=S1 receptor binding domain. IC_{50}=in vitro concentration required to neutralise 50% of the virus. *Mixed effects model, adjusted by baseline value, randomisation factors (age, inflammatory condition, and vaccine platform), previous infection, booster vaccine platform, and included time by treatment interaction. †Participants got vaccinated against COVID-19 in this period using a bivalent vaccine including Omicron and this explains a higher neutralisation titre at week 26 than at week 12.

Table 2: **Serological outcomes at primary and secondary endpoints**

post-hoc sensitivity analyses that also included the methotrexate dose as a covariate (appendix p 11). At 26 weeks, the subgroup results were similar across all prognostic factors (figure 2, appendix p 15). A post-hoc sensitivity analysis that excluded participants in receipt of an additional booster vaccination before their week-26 visit yielded similar results (appendix p 11). This sensitivity analysis was needed as the UK COVID-19 vaccination program offered patients taking methotrexate 6-monthly vaccine boosters against COVID-19 and for some participants in the VROOM study their week-26 visit could not be completed before they received this additional vaccine dose.

The IC_{50} neutralising antibody titre for Wuhan-Hu-1 was higher in the methotrexate suspend group compared with the continue treatment group at 4 weeks and 26 weeks (table 2). In a mixed-effect model, the GMR for Wuhan-Hu-1 IC_{50} neutralising antibody titre on suspending methotrexate for 2 weeks was 2·56 (95% CI 1·21–5·44) at 4 weeks, and 3·50 (1·34–9·18) at 26 weeks. The omicron BA.1 IC_{50} cross neutralising antibody titre was higher in the methotrexate suspend group compared with the continue treatment group at 4 weeks with a GMR of 2·42 (95% CI 1·45–4·05). The omicron BA.1 IC_{50} neutralising antibody titre was comparable between the two groups at other time-points.

Self-reported general health due to inflammatory disease and EQ-5D-5L utility values were comparable between the two groups at all timepoints (table 3). Self-reported inflammatory disease activity was worse at 4 weeks and 12 weeks in the suspend methotrexate group but was comparable in the two groups at 26 weeks (appendix pp 17–18). Self-reported inflammatory disease control since vaccination was worse at 4 weeks in the suspend methotrexate group but was comparable between the two groups by week 12. This was not assessed at week 26 to minimise potential biased recall. More participants self-reported at least one disease flare in the methotrexate suspend group than in the continue treatment group at week 4 (102 [53%] *vs* 63 [33%], OR 2·28 [95% CI 1·72–3·66]) and week 12 (124 [65%] *vs* 89 [46%], 1·98 [1·33–2·90]). However, there was no difference at week 26 (132 [69%] *vs* 117 [61%], 1·37 [0·72–2·17]). Most disease flares were self-managed with a similar proportion of participants seeking medical or specialist-nurse help for flares in both groups (ie, 12 [6%] *vs* 8 [4%] in weeks 0–4, 25 [13%] *vs* 25 [13%] in weeks 0–12, and 32 [17%] *vs* 39 [20%] in weeks 0–26 in the suspend and continue methotrexate groups; table 4). More participants who suspended methotrexate self-reported using non-steroidal anti-inflammatory drugs or analgesics, glucocorticoids, and topical treatments for managing disease flares up to week 12. At baseline comparable number of participants had SARS-CoV-2 infections in both groups of the study when assessed using the N-serology (appendix p 19). In weeks 0–4, 5–12, and 13–26, eight (4%), 16 (9%), and 24 (16%) participants in the continue methotrexate group and ten (6%), 18 (10%), and 30 (22%) participants in the



(Figure 2 continues on next page)

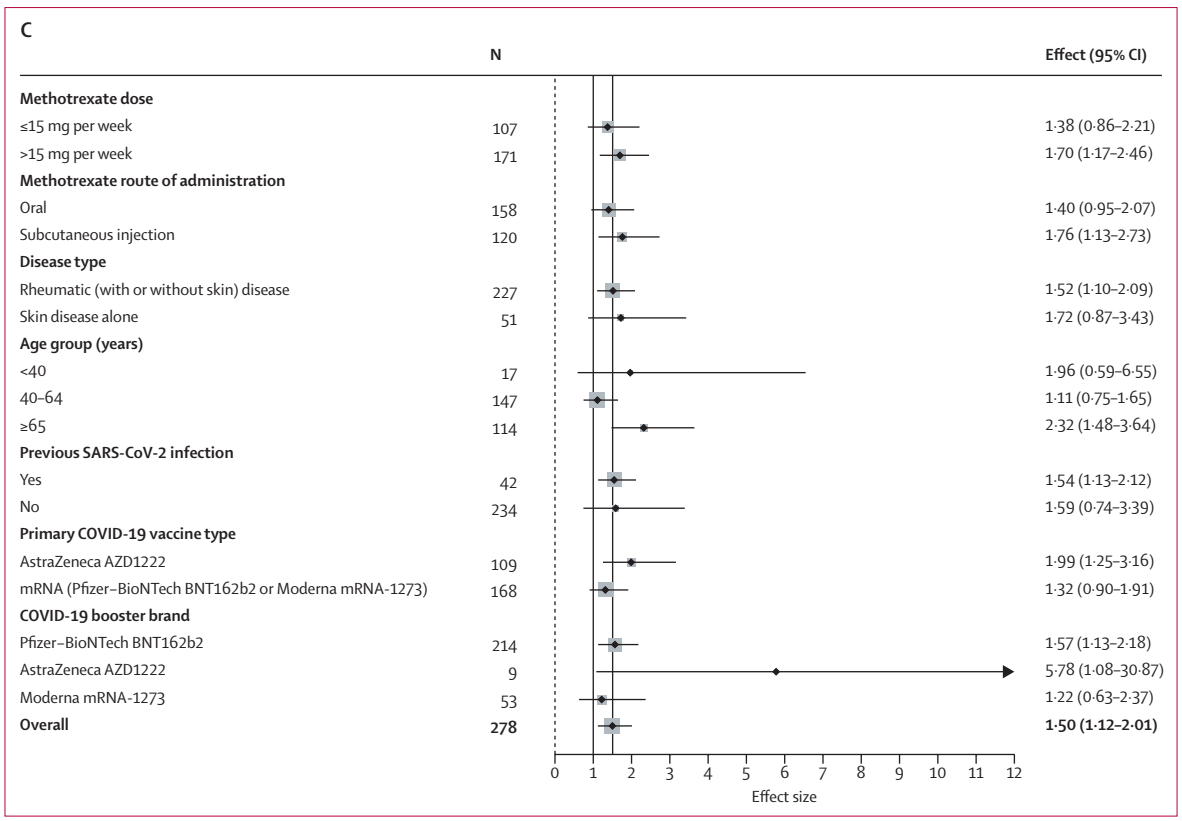


Figure 2: **Subgroup analysis at week 4 (A), week 12 (B) and week 26 (C)**
X-axis is geometric mean ratio (95% CI).

suspend methotrexate group tested positive for anti-N antibodies for the first time (appendix p 19). There were no hospitalisations or deaths due to COVID-19 in the study. There were three serious adverse events (two in the intervention group and one in the control group) unrelated to the intervention; no intervention related serious adverse events occurred.

Discussion

Immunosuppression attenuates immunity following vaccination against COVID-19 and antibody waning results in reduced vaccine efficacy, particularly against SARS-CoV-2 variants.[24–27] A 2-week interruption of methotrexate treatment immediately after COVID-19 booster vaccination enhanced the S1-RBD antibody response that was maintained at 26 weeks. The effect was present across a range of prognostic factors including previous SARS-CoV-2 infection, an exclusion criterion in previous studies, thereby increasing the generalisability of these findings.[28–29] There was a greater effect on S1-RBD antibody response from interrupting treatment in those on higher doses of methotrexate. The S1-RBD antibody titre in the suspend methotrexate group at 26 weeks was greater than that in the continue methotrexate group at 4 weeks. The neutralising capacity was higher for the ancestral Wuhan-Hu-1 strain at week 4

	Continue methotrexate (n=192)	Suspend methotrexate (n=191)	Treatment effect (95% CI)*
EQ-5D utility scores, mean (SD)			
4 weeks	0·769 (0·181; n=186)	0·743 (0·213; n=181)	−0·024 (−0·063 to 0·015)
12 weeks	0·763 (0·191; n=188)	0·745 (0·220; n=182)	−0·014 (−0·052 to 0·025)
26 weeks	0·787 (0·183; n=153)	0·756 (0·201; n=142)	−0·033 (−0·104 to 0·037)
EQ VAS, mean (SD)			
4 weeks	77·0 (16·5; n=186)	73·6 (19·4; n=181)	−3·090 (−6·687 to 0·508)
12 weeks	75·3 (17·9; n=188)	72·0 (20·2; n=181)	−2·787 (−6·382 to 0·810)
26 weeks	77·9 (16·7; n=153)	75·1 (19·4; n=142)	−2·301 (−6·075 to 1·562)
Patient assessment of inflammatory disease, mean (SD)			
2 weeks	7·3 (1·7; n=184)	6·8 (2·2; n=184)	−0·437 (−1·226 to 0·353)
4 weeks	7·4 (1·9; n=182)	6·9 (2·2; n=176)	−0·462 (−1·254 to 0·331)
12 weeks	7·2 (2·0; n=187)	7·0 (2·1; n=181)	−0·177 (−0·966 to 0·612)
26 weeks	7·5 (1·9; n=154)	7·0 (2·1; n=142)	−0·475 (−1·292 to 0·342)
Participants with at least one flare†			
0–4 weeks	63 (33%)	102 (53%)	2·28 (1·72 to 3·66)
0–12 weeks	89 (46%)	124 (65%)	1·98 (1·33 to 2·90)
0–26 weeks	117 (61%)	132 (69%)	1·37 (0·72 to 2·17)

*Mixed effects model for EQ-5D, patient assessment of inflammatory disease outcomes, and flares adjusted by baseline value, randomisation factors (age, inflammatory condition, vaccine platform), prior infection, booster platform, and included time by treatment interaction· †OR for participants with at least one flare.

Table 3: **Self-reported clinical outcomes at primary and secondary endpoints**

	Continue methotrexate (n=192)	Suspend methotrexate (n=191)	Total (n=383)
Participants with at least one serious adverse event and disease flare			
Serious adverse events related to intervention	0	0	0
Serious adverse events unrelated to intervention	1 (1%)	2 (1%)	3 (1%)
Self-reported disease flares			
Any self-reported disease flare by 4 weeks	63 (33%)	102 (53%)	165 (43%)
Any self-reported disease flare by 12 weeks	89 (46%)	124 (65%)	213 (56%)
Any self-reported disease flare by 26 weeks	117 (61%)	132 (69%)	249 (65%)
0–4 weeks			
Number of separate self-reported disease flares			
0	129 (67%)	89 (47%)	218 (57%)
1	30 (16%)	46 (24%)	76 (20%)
2	18 (9%)	24 (13%)	42 (11%)
3	10 (5%)	13 (7%)	23 (6%)
4	2 (1%)	5 (3%)	7 (2%)
5	0	4 (2%)	4 (1%)
>6	3 (2%)	10 (5%)	13 (3%)
Medical or nursing help sought to treat disease flares*			
Total	8 (4%)	12 (6%)	20 (5%)
Hospital helpline	0	3 (2%)	3 (1%)
GP or practice nurse	4 (2%)	6 (3%)	10 (3%)
Hospital outpatient (telephone or in person)	4 (2%)	3 (2%)	7 (2%)
Hospital A&E	1 (1%)	0	1 (<1%)
Other	1 (1%)	0	1 (<1%)
Pain killers or NSAIDs used to treat disease flares			
Yes	60 (31%)	76 (40%)	136 (36%)
No	92 (48%)	78 (41%)	170 (44%)
Unknown†	32 (17%)	30 (16%)	62 (16%)
Glucocorticoid used to treat disease flares			
Yes	12 (6%)	21 (11%)	33 (9%)
No	148 (77%)	140 (73%)	288 (75%)
Unknown†	32 (17%)	30 (16%)	62 (16%)
Cream used to treat flare of skin condition			
Yes	30 (16%)	36 (19%)	66 (17%)
No	99 (52%)	97 (51%)	196 (51%)
Unknown†	32 (17%)	30 (16%)	62 (16%)

(Table 4 continues in next column)

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	Continue methotrexate (n=192)	Suspend methotrexate (n=191)	Total (n=383)
0–12 weeks			
Number of separate self-reported disease flares			
0	103 (54%)	67 (35%)	170 (44%)
1	29 (15%)	27 (14%)	56 (15%)
2	19 (10%)	31 (16%)	50 (13%)
3	11 (6%)	12 (6%)	23 (6%)
4	6 (3%)	14 (7%)	20 (5%)
5	6 (3%)	12 (6%)	18 (5%)
>6	18 (9%)	28 (15%)	46 (12%)
Medical or nursing help sought to treat disease flares*			
Total	25 (13%)	25 (13%)	50 (13%)
Hospital helpline	8 (4%)	7 (4%)	15 (4%)
GP or practice nurse	6 (3%)	10 (5%)	16 (4%)
Hospital outpatient (telephone or in person)	11 (6%)	12 (6%)	23 (6%)
Hospitalisation	0	1 (1%)	1 (<1%)
Hospital A&E	1 (1%)	0	1 (<1%)
Other	2 (1%)	2 (1%)	4 (1%)
Pain killers or NSAIDs used to treat disease flares			
Yes	81 (42%)	88 (46%)	169 (44%)
Glucocorticoid used to treat disease flares			
Yes	22 (11%)	34 (18%)	56 (15%)
Cream used to treat flare of skin condition			
Yes	38 (20%)	54 (28%)	92 (24%)
0–26 weeks‡			
Medical or nursing help sought to treat disease flares*			
Total	39 (20%)	32 (17%)	71 (19%)
Hospital helpline	13 (7%)	11 (6%)	24 (6%)
GP or practice nurse	12 (6%)	12 (6%)	24 (6%)
Hospital outpatient (telephone or in person)	17 (9%)	15 (8%)	32 (8%)
Hospitalisation	0	1 (1%)	1 (<1%)
Hospital A&E	1 (1%)	0	1 (<1%)
Other	5 (3%)	4 (2%)	9 (2%)

NSAIDs=non-steroidal anti-inflammatory drugs. A&E=accident and emergency. *Participants can seek help from more than one source. †Participants did not provide answer for this question. ‡Participants were not asked to self-report the number of separate disease flares they experienced between weeks 13 and 26 at the week 26 visit due to potential for recall bias; data on pain killer, glucocorticoid, and cream use for flares were also not collected to avoid recall bias.

Table 4: **Safety, flare outcomes, and their treatment by study group**

and week 26, and for the omicron BA.1 variant of concern at week 4, an important finding as neutralising antibody IC_{50} titres are associated with protection against COVID-19 including severe disease.[20–27]

High compliance with the intervention indicated patient acceptability. Interrupting methotrexate for 2 weeks did not effect quality of life, general health, or patient assessment of inflammatory disease on a 10-point numeric rating scale. A temporary deterioration of inflammatory disease control and an associated increase in self-reported disease flares were apparent in the initial 12 weeks of the study. However, there was no excess risk of self-reported flares, inflammatory disease activity, and inflammatory disease control when longer follow-up periods were considered. The majority of flares were self-managed with no appreciable differences in seeking health-care input across the two groups. Interrupting treatment seemed to be associated with worsening self-reported inflammatory disease control in the next few

weeks. Although the differences were absent when longer follow-up periods were considered there will need to be a balancing of possible risk of a flare versus enhanced protection against COVID-19 to be considered together by patients and their physician. The choice to suspend methotrexate should be individualised based on disease status and vulnerability to severe outcomes from COVID-19.

Strategies to boost vaccine response will facilitate optimal benefit from vaccination in terms of longevity of protection and protection against variants of concern. A 2-week break in methotrexate treatment immediately after vaccination provided a simple, low-cost, and easy to implement intervention. The break could potentially translate into greater vaccine efficacy and longer duration of protection for immunosuppressed vulnerable groups.[20–24, 27]

This finding is supported by the fact that higher S1-RBD binding antibodies and neutralisation are associated with protection against COVID-19. Early data from a cohort study and five trials showed increasing neutralising titres to be a correlate of protection against COVID-19.[20,23] Subsequently, a neutralising and binding antibody titre threshold for protection against COVID-19 was identified using data from a trial of the ChAdOx1 nCoV-19 (AZD1222) vaccine.[21] A more recent systematic review and meta-analysis reported a non-linear dose–response relationship between both binding and neutralising antibody titre and efficacy against symptomatic and severe infections but there remained large unexplained variations in the relationship.[27] Higher antibody titres do not necessarily mean greater protection at an individual level. Similarly, in a cohort of patients with inflammatory bowel disease treated with either vedolizumab or infliximab with or without immunomodulators, lower S1-RBD titres after two doses of COVID-19 vaccine were associated with breakthrough SARS-CoV-2 infection.[22] In a large prospective cohort, there was significantly lower neutralising antibody titres 6 months after COVID-19 booster vaccination in those that were immunosuppressed compared with the general population suggesting that interventions to optimise immune response in this population are needed and relevant.[24]

We did not detect differences in the number of SARS-CoV-2 infections between the two groups and none of the participants experienced severe COVID-19 defined as either hospitalisation or death due to COVID-19. This study was not designed to detect a difference in clinical outcomes, and this finding should be interpreted with caution. We did not collect patient reported data on COVID-19 symptom duration or severity and are unable to comment on whether patients with greater immunity also experienced milder symptoms.

Previously, other small single-centre trials limited to patients with well controlled rheumatoid arthritis or psoriatic arthritis without prior SARS-CoV-2 infection reported that 2-week methotrexate interruption improved the S1-RBD antibody response at 4 weeks and 6 weeks after the second vaccine dose.[28,29] These studies were limited by exclusion of participants with prior SARS-CoV-2 infection, exclusion after randomisation for SARS-CoV-2 infection or inflammatory disease flares, or both, that contributed to high attrition, per-protocol analysis, and short-follow-up.[28,29] A clinical trial from South Korea reported that either a 1-week or a 2-week interruption in methotrexate treatment immediately after quadrivalent influenza vaccination in patients with rheumatoid arthritis resulted in comparable humoral immunity against seasonal influenza, and similar disease activity scores in the two groups at 4 weeks follow-up.[30] Whether a 1-week interruption in methotrexate treatment would result in durable improvement in vaccine induced immunity—eg, over 26 weeks—is not known. Nevertheless, further research is required to ascertain if a 1-week interruption in methotrexate treatment immediately after vaccination against COVID-19 would improve vaccine induced immunity.

Patients in our study entered the trial with their third or fourth vaccine dose against COVID-19. Presently, many patients are receiving their fifth to seventh COVID-19 vaccine doses and the applicability of our findings can be called into question. We are reasonably confident that our findings will hold true in future vaccination cycles as an improvement in influenza vaccine induced immunity was observed with an interruption in methotrexate treatment immediately after vaccination against influenza in middle-aged and older patients with long-standing rheumatoid arthritis from South Korea who would have received multiple previous vaccinations against influenza.[8,9,30]

Strengths of our study included broad eligibility criteria with a range of immune-mediated inflammatory diseases and recruitment regardless of prior SARS-CoV-2 infection status making the results generalisable, excellent adherence to intervention, and minimal attrition at the primary endpoint. Neutralisation assays used live viruses and included cross neutralisation, derived from Wuhan-Hu-1 spike exposure that was tested against an Omicron variant. Limitations included absence of participant masking which could result in potential bias of self-reported inflammatory disease activity, quality of life, and flare outcomes. It was not possible to mask participants in this study without a matching placebo, which would have made this time-critical study unfeasible. Nevertheless, the pragmatic trial design reflected real-world practice and patient experience making the results useful to clinicians and patients. In addition, this study mostly recruited people with well controlled inflammatory diseases and patients using biologics were ineligible. Thus, the findings about the risk of flares and increased disease activity associated with temporary interruption in methotrexate treatment are not generalisable to those with poorly controlled inflammatory diseases or to those with disease requiring biologics. Furthermore, some hospitals declined to

participate in the 26-week follow-up visit which was added to the study in March 2022 after the interim analysis was conducted, due to lack of capacity. This contributed to increased attrition at week 26. Condition-specific inflammatory disease activity measures were not used as we recruited participants with a range of diseases, many without validated outcome measures to assess flare. Another limitation was the absence of data for memory B cell and T cell responses. However, S1-RBD antibody and neutralising antibody titres are associated with increased protection.

In conclusion, we identified a sustained increase in binding S1-RBD antibodies on interruption of methotrexate treatment for 2 weeks immediately after vaccination against COVID-19 with a short-term increase in risk of inflammatory disease flares that were mostly self-managed.

Contributors

AA, RJB, ÁMK, LCC, JB, VB, AMV, IR, TB, AS, DMA, JSNV-T, HW, and JAC were involved in study conception, and, AA, RJB, ÁMK, LCC, JB, VB, LC, AF, DA, LE, PJ, NP, TB, AS, AMV, IR, DMA, JSNV-T, HW, and JC were involved in trial design. ÁMK, JMG, and CP did neutralisation studies. AO led on S1-RBD antibody analysis supervised by TB and AS. AA, JAC, NP, AMK, and RJB drafted the Article. AA, RJB, ÁMK, LCC, JB, VB, LC, AF, JAEW, DA, LE, PJ, JMG, CP, NP, AO, AMV, IR, DMA, JSNV-T, HW, JAC critically revised the article for intellectual content. All the authors read and approved the Article. NP, IR, and JC provided statistical expertise. NP and JAC have directly accessed and verified the underlying data reported in this manuscript. All authors had full access to all the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. AA and JAC assume full responsibility for the veracity and completeness of the reported data. All authors contributed to protocol development, data collection and acquisition, database development, discussion and interpretation of the results, and manuscript writing.

Declaration of interests

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Data sharing

The authors will make available relevant anonymised patient level data to bona fide researchers upon reasonable request. Data requests should be directed to the corresponding author at abhishek.abhishek@nottingham.ac.uk.

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