



Clinical science

Is vaccination against COVID-19 associated with autoimmune rheumatic disease flare? A self-controlled case series analysis

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Abstract

Objectives: To investigate the association between vaccination against coronavirus disease 2019 (COVID-19) and autoimmune rheumatic disease (AIRD) flare.

Material and methods: Patients with AIRDs vaccinated against COVID-19 who consulted for disease flare between 1 December 2020 and 31 December 2021 were ascertained in Clinical Practice Research Datalink (Aurum). AIRD flare was defined as consultation for AIRD with CS prescription on the same day or the next day. Vaccination was defined using date of vaccination and product code. The observation period was partitioned into vaccine-exposed (21 days after vaccination), pre-vaccination (7 days before vaccination) and remaining vaccine-unexposed periods. Participants contributed data with multiple vaccinations and outcomes. Season adjusted incidence rate ratios (aIRR) and 95% CI were calculated using self-controlled case series analysis.

Results: Data for 3554 AIRD cases, 72% female, mean age 65 years and 68.3% with RA, were included. COVID-19 vaccination was associated with significantly fewer AIRD flares in the 21-day vaccine-exposed period when all vaccinations were considered [aIRR (95% CI) 0.89 (0.80, 0.98)]. Using dose-stratified analyses there was a statistically significant negative association in the 21 days after first COVID-19 vaccination but no association after the second or third COVID-19 vaccinations [aIRR (95% CI) 0.76 (0.66, 0.89), 0.94 (0.79, 1.11) and 1.01 (0.85, 1.20), respectively]. On AIRD-type stratified analyses, vaccination was not associated with disease flares. Vaccination without or after severe acute respiratory syndrome coronavirus 2 infection, and with vectored DNA or mRNA vaccines, associated with comparable reduced risk of AIRD flares in the vaccine-exposed period after first COVID-19 vaccination.

Conclusions: Vaccination against COVID-19 was not associated with increased AIRD flares regardless of prior COVID-19, AIRD type, and whether mRNA or DNA vaccination technology were used.

Keywords: COVID-19, autoimmune rheumatic disease, vaccination, side-effect

Introduction

Autoimmune rheumatic diseases (AIRDs) are associated with increased risk of hospitalization and death from coronavirus disease 2019 (COVID-19) [1]. Despite this, only 54% patients with AIRDs were willing to get vaccinated against COVID-19 in the VAccinations against COVid-19 [VAXICOV] study, with vaccine willingness significantly lower in the younger age groups [2]. In this study, vaccine hesitancy was driven by apprehension about novel mRNA vaccine technology and vaccination-induced disease flare [2]. This is not surprising as 5–15% of patients with AIRDs self-reported disease flare after vaccination against COVID-19, 11% self-reported disease flare that required treatment and 8.3% self-reported CS used to treat disease flares [3–6]. The median duration between vaccination against COVID-19 and disease flare was 6 days in the global COVAX study, further raising a possibility that vaccination against COVID-19 may be associated with AIRD flares [3]. However, in the absence of a control group in these studies, it remained

uncertain whether these flares were incidental or associated with recent prior vaccinations.

There is a paucity of data on the association between COVID-19 vaccination and AIRD flares as patients with these conditions were excluded from initial COVID-19 vaccination trials, potentially due to concerns about low vaccine efficacy. Thus, the objectives of this study were to investigate the association between vaccination against COVID-19 and AIRD flare. Exploratory analyses evaluated whether the association varied for sequential vaccinations, according to types of AIRDs and prior COVID-19, and between mRNA (bNT1262) and vectored DNA (AZD1222) vaccines.

Patients and methods

Data source

Data were extracted from Clinical Practice Research Datalink (CPRD) Aurum, a longitudinal anonymized electronic

Rheumatology key message

- It was previously unclear whether autoimmune rheumatic disease (AIRD) flares associate with coronavirus disease 2019 (COVID-19) vaccination.
- Vaccination against COVID-19 was not associated with significantly increased AIRD flares in this study.
- These data should be used to promote COVID-19 vaccination in people with AIRDs.

database of health records from 19 million patients from 738 general practices that dates to 1995 [7]. It includes information on demographic details, lifestyle factors, diagnoses, results of investigations, primary-care prescription and vaccinations. Diagnostic and prescription data are recorded using medical codes (a combination of Read 2, SNOMED and local EMIS[®] codes) and product codes, respectively. Data for vaccination against COVID-19, including date of vaccination and vaccine brand, are provided by National Health Service (NHS) Digital. COVID-19 is defined using general practitioner (GP) diagnosis, serology or PCR result. This study used anonymized patient health records from the CPRD and did not require individual participant consent.

Approvals

CPRD Research Data Governance (Reference: 21_000670).

Study design

Self-controlled case series analysis. This method assesses the association between exposure and outcome using data from exposed participants that developed an outcome and is extensively used in vaccine safety studies [8, 9].

Population

Adults aged ≥ 18 years with one or more primary-care consultation for AIRD (either RA, PsA, IBD-associated arthritis, reactive arthritis, AS, SLE, CTD, small vessel vasculitis, PMR or GCA); and one or more prescription for any conventional DMARD prior to 1 December 2020 were eligible to be included in the study, provided they also received one or more vaccination against COVID-19 and consulted their GP for one or more AIRD flare in the study period.

Study period

The study period covered 1 December 2020 to 31 December 2021. Follow-up was censored if death, emigration from participating general practice or last collection of data from general practice occurred before 31 December 2021.

Exposure

Vaccination against COVID-19 was the exposure of interest and was defined using product codes for vaccines and vaccination dates. Product codes were used to define the vaccine

type and brand, specifically vectored DNA (AZD1222) and mRNA (mRNA-1273, BNT1262b2).

Outcome

AIRD flare was the outcome of interest. It was defined as primary-care consultation with diagnostic coding for AIRD accompanied with CS prescription on the same date or the next date. Date of primary-care consultation for AIRD flares was used to define the outcome date. Participants contributed data with multiple flares; however, AIRD flares within 14 days were considered part of the same flare.

Exposed and unexposed periods

The study period was divided into 21 days vaccine-exposed, 7 days pre-vaccination and the remaining vaccine-unexposed periods (Fig. 1). The vaccine-exposed period was 21 days post-vaccination, as it takes ~ 2 –3 weeks for primary COVID-19 immunization to induce an immunological response [10, 11]. We hypothesized that this period of immune reconstitution was most likely to be associated with increased disease activity. As patients with disease flare or acute illnesses may delay vaccination, the 7 days preceding vaccination was considered separate from the vaccine-unexposed period to minimize potential confounding. The vaccine-unexposed period comprised of the remaining follow-up time post cohort entry and prior to cohort exit.

The study started on the 1 December 2020, 1 week before the first COVID-19 vaccine was administered outside of trial setting in the UK, to allow each potential vaccinated participant to have a 7-day pre-vaccination period.

Statistical analyses

A Poisson model conditioned on the number of events and adjusted for the four seasons as per the Meteorological Office was fitted to calculate the adjusted incidence rate ratios (aIRR) and 95% CI for association between vaccination and AIRD flares. Stratified analysis considered first, second or third vaccine doses; and AIRD type in the entire dataset. Stratified analysis according to vaccine type (AZD1222 *vs* BNT1262b2) and prior COVID-19 was restricted to the first COVID-19 vaccination. The pre-exposure and vaccine-exposed periods were 7 days before and 21 days after the first vaccination against COVID-19, with the entire vaccine-unexposed



Figure 1. Schematic representation of SCCS analysis. The vaccine-exposed (21 days post-vaccination), pre-vaccination induction periods (7 days pre-vaccination) and vaccine-unexposed (the remaining vaccine-unexposed period) are shaded dark grey, light grey and light blue, respectively. Vaccinations against COVID-19 are represented by dark blue arrows. Green and red arrows indicate the start and end of the study period. Not all participants received all three vaccinations. Follow up began on the latest of current registration date in GP surgery or 1 December 2020 and was censored on the earliest of 31 December 2021, death date, transfer out date or date of last data collection from the GP surgery. SCCS: self-controlled case series; COVID-19: coronavirus disease 2019; GP: general practitioner

Table 1. The association between COVID-19 vaccination and autoimmune rheumatic disease flare

COVID-19 vaccination	Risk period (days)	Events (n)	IRR ^a (95% CI) ^b	Adjusted ^c IRR (95% CI) ^b	P-value ^c
All 3 doses	Baseline	3177	1	1	—/—
	7 days pre-vaccinations	195	0.95 (0.83, 1.10)	0.97 (0.84, 1.12)	0.645
	Post-vaccination intervals				
	0–21 days	527	0.88 (0.80, 0.96)	0.89 (0.80, 0.98)	0.015
	0–7 days	176	0.87 (0.74, 1.01)	0.88 (0.75, 1.02)	
	8–14 days	170	0.85 (0.73, 0.99)	0.87 (0.74, 1.01)	
1st dose	15–21 days	181	0.92 (0.79, 1.07)	0.94 (0.80, 1.09)	
	Baseline	3177	1	1	—/—
	7 days pre-vaccination	87	1.11 (0.90, 1.38)	0.97 (0.78, 1.20)	0.785
	Post-vaccination intervals				
	0–21 days	192	0.82 (0.71, 0.95)	0.76 (0.66, 0.89)	<0.001
	0–7 days	61	0.78 (0.60, 1.00)	0.69 (0.53, 0.89)	
2nd dose	8–14 days	69	0.88 (0.70, 1.12)	0.79 (0.62, 1.00)	
	15–21 days	62	0.79 (0.62, 1.02)	0.75 (0.58, 0.96)	
	Baseline	3177	1	1	—/—
	7 days pre-vaccination	49	0.66 (0.50, 0.88)	0.75 (0.56, 1.00)	0.051
	Post-vaccination intervals				
	0–21 days	188	0.85 (0.74, 0.99)	0.94 (0.79, 1.11)	0.441
3rd dose	0–7 days	63	0.86 (0.67, 1.10)	0.95 (0.73, 1.24)	
	8–14 days	59	0.80 (0.62, 1.04)	0.91 (0.70, 1.19)	
	15–21 days	66	0.90 (0.71, 1.15)	0.99 (0.76, 1.28)	
	Baseline	3177	1	1	—/—
	7 days pre-vaccination	59	1.13 (0.87, 1.46)	1.23 (0.95, 1.60)	0.121
	Post-vaccination intervals				
	0–21 days	147	1.02 (0.86, 1.20)	1.01 (0.85, 1.20)	0.903
	0–7 days	52	1.02 (0.77, 1.34)	1.09 (0.83, 1.44)	
	8–14 days	42	0.87 (0.64, 1.17)	0.93 (0.69, 1.27)	
	15–21 days	53	1.18 (0.90, 1.55)	1.19 (0.90, 1.58)	

^a Incidence rate ratio.^b 95% CI.^c Adjusted for four seasons. COVID-19: coronavirus disease 2019.

period as the baseline period. $P < 0.05$ (two sided) were considered as statistically significant. Data analyses were carried out using Stata v.16. The code used was published at GitHub (https://github.com/NGeorgina/study_code).

Results

Data for 3554 AIRD cases were included (supplementary Fig. S1, available at *Rheumatology* online). The majority were female (71.8%) and their mean (s.d.) age was 65 (15) years. A total of 2427 (68.3%) had RA, 557 (15.7%) had PMR/GCA, 273 (7.7%) had SpA (defined as either PsA, AS, reactive arthritis or IBD-associated arthritis) and 297 (8.4%) had CTD/small vessel vasculitis. Overall, 1492 (42%), 2057 (57.9%) and 5 (0.1%) participants received BNT162b2, AZD1222 and mRNA-1273 vaccines, respectively, as their first dose. Ninety percent of participants received one or more dose of the vaccine against COVID-19 by 13 March 2021. Some 212 (6%) participants had COVID-19 prior to their first vaccine dose. A total of 2448 (68.9%), 962 (27.1%) and 144 (4.1%) participants received three, two and one vaccination against COVID-19, respectively, in the study period. A total of 3256 (91.6%), 239 (6.7%) and 59 (1.7%) participants had one, two and more than two AIRD flares, respectively. Some 29.9%, 24.1%, 21.3% and 24.7% of flares occurred in each quartile of the follow-up period. Overall, 151 participants (4.3%) did not contribute data for the entire follow-up period due to death [$n = 84$ (2.4%)] or transfer out of GP practice [$n = 67$ (1.9%)]. In addition, 4055 (94.2%) AIRD flares were not preceded by long-term CS prescription defined as three or more CS prescriptions for ≥ 28 days in the preceding 90 days.

Vaccination against COVID-19 was associated with significantly fewer AIRD flares in the vaccine-exposed period when all vaccinations were analysed together (Table 1). When vaccine doses were considered separately, there was a statistically significant negative association between first vaccination against COVID-19 and AIRD flares in the 21-day post-vaccination period, but no significant association with AIRD flares in the 21-day post-vaccination period after subsequent COVID-19 vaccinations (Table 1). The aIRR (95% CI) for AIRD flare in the vaccination-exposed period in those with RA, SpA, CTD/small vessel vasculitis and PMR/GCA were 0.85 (0.76, 0.96), 0.77 (0.53, 1.12), 1.05 (0.75, 1.47) and 0.97 (0.77, 1.20), respectively (Table 2). After the first COVID-19 vaccination, the aIRRs for AIRD flare in the vaccination-exposed periods were comparable in those with or without prior COVID-19 and vaccinated with mRNA-BNT162b2 and vectored DNA vaccines (Table 2).

Discussion

This study examined the association between AIRD flares and recent prior COVID-19 vaccination. It found no evidence for an association between COVID-19 vaccination and increased AIRD flares overall, and when the data were stratified by AIRD type. There was no obvious difference in the association with either mRNA-BNT162b2 and vectored DNA vaccines. The statistically significant negative association between first COVID-19 vaccination and AIRD flare, particularly in RA, in the subsequent 21-day vaccine-exposed period is difficult to explain. We considered lack of access to NHS services in the first few months of the pandemic as a potential

Table 2. The association between COVID-19 vaccination and AIRD flare: stratified analysis

	Risk period (days)	Events (<i>n</i>)	IRR ^a (95% CI) ^b	Adjusted ^c IRR (95% CI) ^b	<i>P</i> -value ^c
Autoimmune rheumatic disease type					
RA	Baseline	2163	1	1	–/–
	7 days pre-vaccination	121	0.88 (0.73, 1.05)	0.89 (0.74, 1.07)	0.217
	21 days post-vaccination	342	0.84 (0.75, 0.95)	0.85 (0.76, 0.96)	0.009
SpA	Baseline	241	1	1	–/–
	7 days pre-vaccination	14	0.91 (0.53, 1.57)	0.91 (0.53, 1.57)	0.733
	21 days post-vaccination	36	0.81 (0.57, 1.14)	0.77 (0.53, 1.12)	0.171
CTD/small vessel vasculitis	Baseline	245	1	1	–/–
	7 days pre-vaccination	16	1.03 (0.62, 1.72)	1.08 (0.65, 1.80)	0.777
	21 days post-vaccination	45	0.99 (0.72, 1.36)	1.05 (0.75, 1.47)	0.760
PMR/GCA	Baseline	528	1	1	–/–
	7 days pre-vaccination	44	1.24 (0.91, 1.69)	1.21 (0.88, 1.65)	0.237
	21 days post-vaccination	104	0.99 (0.81, 1.23)	0.97 (0.77, 1.20)	0.752
COVID-19 infection ^d					
No	Baseline	1384	1	1	–/–
	7 days pre-vaccination	84	1.10 (0.88, 1.37)	0.93 (0.74, 1.17)	0.540
	21 days post-vaccination	186	0.81 (0.70, 0.95)	0.76 (0.65, 0.89)	0.001
Yes	Baseline	115	1	1	–/–
	7 days pre-vaccination	3	0.53 (0.17, 1.69)	0.51 (0.16, 0.63)	0.259
	21 days post-vaccination	6	0.36 (0.16, 0.81)	0.35 (0.15, 0.80)	0.013
Vaccine type ^{d,e}					
Pfizer	Baseline	584	1	1	–/–
	7 days pre-vaccination	45	1.33 (0.98, 1.81)	1.10 (0.81, 1.51)	0.553
	21 days post-vaccination	81	0.80 (0.63, 1.01)	0.72 (0.56, 0.91)	0.006
Vectored DNA vaccine	Baseline	913	1	1	–/–
	7 days pre-vaccination	42	0.87 (0.64, 1.19)	0.77 (0.56, 1.05)	0.095
	21 days post-vaccination	110	0.76 (0.63, 0.93)	0.75 (0.61, 0.92)	0.005

^a Incidence rate ratio.^b 95% CI.^c Adjusted for four seasons.^d First vaccine analysed.^e People vaccinated with mRNA-1273 vaccine (*n* = 3) were excluded from this analysis. AIRD: autoimmune rheumatic disease; COVID-19: coronavirus disease 2019.

explanation as our flare definition required a primary-care consultation and a drug prescription on the same or next date. However, as the number of flares in each quartile of the study period were comparable, this association was not related to a general lack of access to healthcare services. It could be due to reluctance on the part of the GP to prescribe steroids soon after the first vaccine dose was administered, in order to not inhibit vaccine response. Subsequent vaccinations against COVID-19, and vaccination in the context of prior COVID-19 infection did not associate with AIRD flares in the 21-day vaccine-exposed periods. A higher absolute rate of disease flare was reported after second COVID-19 vaccine dose than after the first COVID-19 vaccine dose in a study from New York [4], and prior COVID-19 infection associated with flares after vaccination in another study [5]. However, our study did not find any such differences, providing reassurance on the safety of booster vaccinations with respect to AIRD flares.

Our findings are consistent with previous study that reported comparable self-reported disease activity in RA patients before and after COVID-19 vaccination [12]. A study from Hong Kong reported no association between vaccination against COVID-19 and any hospital consultation for RA or hospitalization for any reason in patients with RA [13]. However, the outcomes in this study were not specific. Hospital consultation for RA could have included planned pre-arranged routine follow-up appointments and hospitalization was not restricted to admission for RA flare regardless of prior COVID-19.

We did not know if patients in this study suspended their treatment around the time of COVID-19 vaccination as treatment compliance is not recorded in the CPRD. At the time of primary and booster vaccination against COVID-19 there was no recommendation in the UK to hold treatment peri-vaccination. Nevertheless, some patients may have chosen to interrupt their treatment and this may have resulted in flares. Despite this possibility, our study provides reassurance that vaccination against COVID-19 does not associate with AIRD flare.

People with AIRDs had significantly higher reactogenicity to COVID-19 vaccination than healthy controls in a study from Brazil, raising the possibility of increased risk of AIRD flares [14]. A re-analysis of the COVAX database suggested that there was a stronger association between SLE, PsA and PMR and disease flare after vaccination against COVID-19 than for RA [15], while another study from the USA reported overlap CTD as a risk factor for disease flare after vaccination against COVID-19 [16]. The differential association between vaccination against COVID-19 and disease flare-up according to AIRD type could reflect the fact that some AIRDs are less well controlled due to lack of therapeutic options and tend to flare up periodically. Our study used within-person comparisons, was free of these potential confounding issues, and did not report any disease specific association between vaccination against COVID-19 and AIRD flare. The reanalysis of COVAX database demonstrated that vectored DNA vaccination carried a higher risk of AIRD flares, and this was not confirmed in our study [15]. The association between vaccine

technology used and AIRD flares only considered the first vaccination because there was a strong negative association between first COVID-19 vaccination and AIRD flares but not with second or third COVID-19 vaccination. This strong negative association between first vaccination dose against COVID-19 and AIRD flares alongside a difference in vaccine technology preferentially used in first two (57.9% and 55.3% vectored DNA) and third (94.1% mRNA) vaccine doses could potentially confound the association, resulting in a spurious negative association between vectored DNA technology and AIRD flares if all doses were included in the analysis. Given the inconsistency in association between the study utilizing COVAX database [15] and the present study, further research in this field is warranted, potentially using a prospective cohort or nested case-control study design.

Strengths of this study included the use of a nationwide database, inclusion of a broad range of AIRDs, and data analyses stratified by disease type. This increased the generalizability of the findings. This study used self-controlled case series analysis that accounted for within-person confounding and met the assumptions required to conduct this analysis. Analyses were adjusted for meteorological season as AIRD flares exhibit circum-annual variation and self-controlled case series do not account for time-varying covariates [17]. Data on the vaccination date and vaccine brand are reliable as they are collected at source and provided by NHS Digital. This allowed for accurate definition of the observation period. AIRD cases were required to have consultation for AIRD and DMARD prescription prior to cohort entry, increasing confidence in case definition. Outcomes were defined using consultation and prescription dates thereby increasing validity of outcome definition. This also minimized the potential for confounding due to biased self-report of AIRD flares that was used in previous studies [4–6, 15, 16].

However, this study had several limitations. Data on disease activity is not recorded in the CPRD—a substantial limitation. Additionally, consultations would have occurred a few days after flare onset, and mild self-managed flares and those that were managed by a rheumatologist were excluded. However, there is no reason to suspect that the time between flare onset and GP consultation would vary across vaccine-exposed and vaccine-unexposed periods. It is possible that some of the AIRD flares in this study were scheduled appointments at which CS prescriptions were reissued. However, long-term repeat prescriptions are issued without a GP consultation in the UK and not surprisingly, only 5.8% AIRD flares were in the context of long-term CS prescription. Finally, patients with PMR/GCA treated with CS only were not included as the study required one or more prescription of DMARD prior to cohort entry.

In conclusion, vaccination against COVID-19 was not associated with AIRD flare, and vaccination with or without prior COVID-19, and with either mRNA or vectored DNA vaccines, were not associated with AIRD flares. These data should address the apprehension of disease-specific adverse effects from COVID-19 vaccination, an important reason for vaccine hesitancy in AIRDs, that may become even more significant as a barrier against vaccination as the perceived benefit from booster vaccination reduces.

Supplementary data

Supplementary data are available at *Rheumatology* online.

Data availability statement

This study used data from the Clinical Practice Research Datalink (CPRD). Due to the CPRD data sharing policy, we unable to share this study's data. However, access to CPRD data can be directly requested from the CPRD.

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Patient and public involvement (PPI): This study was motivated by immune-suppressed patients with inflammatory conditions as they enquired about the safety of COVID-19 vaccines. The modes of dissemination of study findings were also discussed and agreed with them. One PPI member from the Nottingham-NIHR-BRC-MSK-PPI group is on the study team as a steering committee member.

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