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Concise report

C-Reactive protein rise in rheumatology patients following COVID-19 vaccination

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Abstract

Objective: The aim was to determine the proportion of patients with inflammatory arthritis who have a flare of their rheumatological disease within 4 weeks of receiving a coronavirus disease 2019 (COVID-19) vaccine, using CRP as a surrogate marker.

Methods: A retrospective review was conducted of notes for patients with inflammatory arthritis within 30 days of their COVID-19 vaccine. An electronic database (DAWN) was used to identify all patients who were currently on a DMARD or biologic therapy. This was then correlated with vaccine data from the National Immunisation and Vaccination System (NIVS) and CRP within 30 days of their vaccination.

Results: From the DAWN database, 1620 adults were identified (mean age 61 years, 64% female). Three types of vaccinations were administered: AstraZeneca (AZ), BioNTech-Pfizer or Moderna. Vaccine uptake was 1542 of 1620 (95.2% for the first dose), 1550 of 1620 (95.7% for the second dose) and 1437 of 1620 (88.7% for the third dose). One hundred and ninety-two of 1542 patients (12.5%) had a CRP rise of >10 mg/l within 30 days of their vaccine, which was higher than the baseline flare rate of 8.6% ($P = 0.0004$).

Conclusion: Patients with inflammatory arthritis and on DMARDs have a high uptake of COVID-19 vaccine (95%), which is greater than the national average. A CRP rise >10 mg/l within 30 days of vaccination was observed in ∼1 in 10 patients in our study population after all three doses. There might be a slight increase in disease flare in patients with inflammatory arthritis after COVID-19 vaccinations, and additional research is required to assess this association further.

Lay Summary

What does this mean for patients?

This study aims to assess the proportion of patients with inflammatory arthritis who had a flare of their rheumatological disease after receiving their coronavirus disease 2019 (COVID-19) vaccination. Patient blood tests were reviewed, and a specific inflammation marker was monitored in a blood test and recorded for each patient. A rise in the inflammation marker post-COVID-19 vaccine was seen in ∼1 in 10 in our patient group. As ongoing booster vaccinations are planned, we recommend that further research is carried out to better inform and counsel inflammatory arthritis patients. Furthermore, this study highlights the need for careful monitoring of inflammatory arthritis patients for disease flares and for swift intervention to prevent loss of disease control.

Keywords: COVID-19, vaccination, disease flare, inflammatory arthritis

Key messages

- There is high uptake of COVID-19 vaccine in patients with inflammatory arthritis.
- Approximately 1 in 10 patients experienced a rise in CRP within 30 days of COVID-19 vaccination that might suggest a disease flare. However, additional research with robust data is required to determine clinical significance.
- Prior to vaccination, patients must be counselled appropriately with regard to disease flare.

Introduction

Since the introduction of coronavirus disease 2019 (COVID-19) vaccination, the landscape of the pandemic has changed completely, with many countries having lifted social restrictions. However, owing to the immunogenic properties of the COVID-19 vaccine, there is concern that it would trigger an immune activation leading to disease flare through mechanisms such as molecular mimicry [1].

In the UK, there are three COVID-19 vaccines that have been approved for use. The BioNTech-Pifzer and Moderna vaccines are mRNA vaccines, and there are currently no data on whether these vaccines can provoke a flare in patients with underlying rheumatic conditions. The original safety trials for these vaccines are limited by not including patients on immunosuppressive agents [2, 3]. Associations with other vaccines (tetanus, influenza and hepatitis B) and disease flares have been reported but causality never proved with large studies [4].

There is low-level evidence that patients with a rheumatological diagnosis often have a flare of disease after COVID-19

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vaccination, with increased joint swelling and pain associated with raised inflammatory markers [5]. This not only has personal health implications, such as pain and reduced mobility, but it also has wider socioeconomic implications resulting from days off work. Furthermore, disease flares can lead to increased requirement for CSs or loss of disease control.

Inflammatory arthritis patients are classified as vulnerable patients requiring booster vaccinations. Therefore, there is a need to ascertain whether there is a risk of disease flare in this group of patients in order to counsel them appropriately to ensure that flares are managed in a timely manner. This is particularly important given the plans for regular booster campaigns to confer continued protection against SARS-CoV-2 infection [6].

Disease flare is defined as 'any worsening of disease activity that would, if persistent, in most cases lead to initiation or change of therapy; and a flare represents a cluster of symptoms of sufficient duration and intensity to require initiation, change, or increase in therapy' [7]. This is often measured using disease activity scores, such as DAS28-CRP [8]. CRP is a marker of inflammation often used as a biochemical marker for disease flare and is incorporated into the DAS28-CRP score.

The aim of this study was to assess the proportion of patients with inflammatory arthritis on DMARD who had a flare of their rheumatological disease within 30 days of receiving a COVID-19 vaccine, using CRP as a surrogate marker.

Methods

This study was reviewed and approved by Health Research Authority (HRA) and Health and Care Research Wales (HCRW) (IRAS reference: 308905) on 8 December 2021. Informed consent was not gained from each patient owing to the use of routinely collected data, and the ethical review panel were satisfied with this.

A retrospective single-centre cross-sectional study was conducted at Great Western Hospital, UK using the DAWN Rheumatology database. The DAWN database is managed prospectively and records blood tests for all patients under the care of the rheumatology department at Great Western Hospital on DMARD or biologic therapy.

Adults with a diagnosis of RA, PsA or undifferentiated inflammatory arthritis were included. The exclusion criteria were patients with other diagnoses in the DAWN database, such as vasculitis, SLE and other autoimmune or autoinflammatory conditions.

The following information was extracted: sex, age, rheumatological diagnosis and current DMARD or biologic therapy. Vaccination details, including type of vaccine and date of vaccination, for each patient identified from the DAWN database were collected using the National Immunisation and Vaccination System (NIVS). For some patients, the first vaccination was not recorded on NIVS, but subsequent vaccines were. Finally, each patient's blood tests were reviewed, and a CRP level within 30 days of the vaccination date was recorded. The baseline incidence of disease flare before the pandemic (January 2019) was also ascertained through the review of notes, and disease flare was presumed if the CRP level was >10 mg/l and/or any calls were made to the rheumatology advice line by patients who were suffering with symptoms. The chi-squared test was performed to assess for a statistically significant increase in disease flare rate.

Table 1. Baseline characteristics

Characteristic	Value
Demographics	
Age, mean (s.d.), years	61 (14.7)
Female, *n* (%)	1041 (64.3)
Male, *n* (%)	579 (35.7)
Total, *n* (%)	1620
Diagnosis, *n* (%)	
RA	978 (60.4)
PsA	403 (24.9)
Undifferentiated inflammatory arthritis	239 (14.8)
Treatment, *n* (%)	
MTX	719 (44)
s.c. MTX	291(17.8)
SSZ	411 (25.1)
HCQ	310 (19)
LEF	291 (17.8)
Others	32 (2)
Biologic	390 (23.9)

Results

One thousand six hundred and twenty adults were identified from the DAWN database in November 2021 (mean age 61 years, 64% female). Baseline demographic data are shown in Table 1. The most frequent rheumatological diagnosis was RA (978 of 1620, 60.4%), followed by PsA (403 of 1620, 24.9%). Seven hundred and nineteen of the 1620 patients were on oral MTX, 291 of 1620 on s.c. MTX and 390 of 1620 on biologic therapy.

Vaccination data were collected in March 2022. Three types of vaccination were used: AstraZeneca (AZ), BioNTech-Pfizer and Moderna. Vaccine uptake was 1542 of 1620 (95.2% for the first dose), 1550 of 1620 (95.7% for the second dose) and 1437 of 1620 (88.7% for the third dose) (Table 2). A blood test result within 30 days of vaccinations was available for 776 of 1542 patients (50.3% for the first dose), 664 of 1550 (42.8% for the second dose) and 614 of 1437 (42.7% for the third dose).

One hundred and ninety-two of 1542 patients (12.5%) had a CRP rise of >10 mg/l within 30 days of their first vaccine. A similar proportion of patients had a CRP rise after second vaccine (167 of 1550 patients, 10.8%) and third vaccine (153 of 1437 patients, 10.6%). The flare rate did not differ between AstraZeneca (88 of 722, 12.2%) and BioNTech-Pfizer (104 of 814, 12.8%) vaccines ($P = 0.73$; Table 2). Only five patients received Moderna vaccine for the first dose.

One hundred and thirty-nine of 1620 patients (8.6%) were identified to have had a disease flare in January 2019, before the pandemic, through either CRP rise and/or calls to the rheumatology helpline. A chi-square test showed that there was a significant increase in disease flare rate with COVID-19 vaccine ($P = 0.0004$) compared with the baseline flare rate in the same population, using CRP as a surrogate marker for disease flare.

Discussion

This study looked at whether COVID-19 vaccinations increase the risk of disease flares in patients with inflammatory arthritis, using CRP as a surrogate marker. Currently, we have limited literature on disease flares in patients with inflammatory arthritis post-vaccination, therefore leaving the medical community and patients with real concerns.

Table 2. Vaccine type and uptake and CRP rise within 30 days of vaccination

Vaccine type	First vaccine [*n* (%)]	Second vaccine [*n* (%)]	Third vaccine [*n* (%)]
Uptake			
AstraZeneca	722 (44.6)	728 (44.9)	1 (0.1)
BioNTech-Pfizer	814 (50.2)	818 (50.5)	1196 (73.8)
Moderna	5 (0.3)	4 (0.2)	240 (14.8)
No vaccine	79 (4.9)	70 (4.3)	183 (11.3)
Total	1620	1620	1620
CRP rise ≥10 mg/l within 30 days of vaccination			
AstraZeneca	88 of 722 (12.2)	78 of 728 (10.7)	0 of 1 (0)
BioNTech-Pfizer	104 of 814 (12.8)	87 of 818 (10.6)	135 of 1196 (11.3)
Moderna	0 of 5 (0)	2 of 4 (50)	18 of 240 (7.5)
Total (%)	192 of 1542 (12.5)	167 of 1550 (10.8)	153 of 1437 (10.6)

In this study, we found that biochemical flares were seen in 10–12% of patients with inflammatory arthritis and on disease-modifying therapy. Owing to severe cases of SARS-CoV-2 infection being attributable to an overactivation of the immune system, there had been considerable anxiety in patients with inflammatory arthritis regarding potential exacerbations of their disease [9]. Trials for COVID-19 vaccinations for both BioNTech-Pfizer and Moderna did not include patients on immunosuppressive agents [2, 3]. Therefore, it was not known whether these vaccines might provoke flares of underlying rheumatological conditions.

This result is in keeping with a recent review conducted by Xie and colleagues [10]. In this review of 20 studies looking at disease flares in patients with rheumatological conditions following a COVID-19 vaccine, the disease flare rate ranged from 0.4 to 20%. Larger studies included in this review did not show a significant association between arthritis flare and COVID-19 vaccinations [11–13]. Xie *et al.* [10] concluded that although the current evidence does not necessarily support an increased risk of disease flare, it might trigger a flare.

Although our results show a statistically significant increase in the rate of disease flare (12.5% compared with a baseline rate of 8.6%), the clinical significance of this increase is uncertain. However, SARS-CoV-2 infection has been shown many times to be an independent risk factor for rheumatic disease flare, ranging from 20–40% [14–16]. Therefore, patients with inflammatory arthritis should still be encouraged to receive COVID-19 vaccination.

This study also showed that there is high uptake of vaccines within our study population compared with the UK baseline average (first dose, 93.1%; second dose, 87.1%; third dose, 69.3%) with >95% of patients having had the first two COVID vaccines and 88.7% having had their third. Given that they are classified as clinically vulnerable, it is imperative to maintain a high level of vaccination within this population, especially given that there is concern over waning immunity in patients on disease-modifying therapy. To maintain high levels of vaccine uptake, it is important to ensure that patients are aware of the risks of vaccinations and are sufficiently safety netted such that flares are managed early.

There are several limitations to this study. Firstly, owing to its retrospective design, nearly half the patients in this study did not have a blood test within 30 days of the COVID-19 vaccine. The denominator for disease flare was calculated as the total number of patients who received the vaccine rather than out of those who had the blood tests, to prevent overestimation of flare rates. Additionally, there was a large variation in when our patient group received a blood test following COVID-19 vaccination (0–30 days). This could mean that there is a large variation in CRP levels depending on when the sample was collected.

Secondly, the retrospective study design means that our results only confer an association between COVID-19 vaccination and disease flare, but not causation. In order to establish causality, a prospective study design will be needed.

Finally, we have used CRP measurements as a surrogate marker for disease flare. However, some patients might experience symptomatic flare without a CRP rise and, conversely, CRP might be raised for other reasons, such as concurrent illnesses. This study was also unable to account for patients with elevated CRP before vaccination because baseline CRP levels were unavailable for all patients. Furthermore, a disease flare is defined as worsening disease activity, and a single CRP level post-vaccination would not provide a full picture. Ideally, a prospective study with a healthy control population in which a formal DAS-28 score was calculated within 30 days of vaccination and where subjective measures (visual analogue scale) and objective measures were considered (CRP and swollen/tender joints) would be more informative. However, the retrospective study does add to the current literature that COVID-19 vaccination can increase the risk of disease flare.

Despite the limitations discussed above, this study showed that there is a rise in CRP following COVID-19 vaccination in patients with inflammatory arthritis, which might suggest that it can trigger a disease flare. As on-going booster vaccinations are planned for rheumatology patients, we recommend further research to better inform and counsel our patients. Furthermore, this study calls for diligence in monitoring patients with inflammatory arthritis for disease flare and for swift intervention to prevent loss of disease control.

Conclusion

Patients with inflammatory arthritis and on DMARDs have high uptake of COVID-19 vaccine (95%), which is greater than the national average. A CRP rise >10 mg/l within 30 days of vaccination was observed in ∼1 in 10 patients in our study population on all three doses, which is consistent with other studies in the literature. This might suggest that COVID-19 vaccinations can trigger a disease flare.

Data availability

Data are available upon reasonable request via corresponding author. All data relevant to the study are included in the article.

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