Title: Is vaccination against Covid-19 associated with autoimmune rheumatic disease flare? A self-controlled case series analysis.

Authors: Georgina Nakafero[1], Matthew J. Grainge[2], Tim Card[2,3], Christian D. Mallen[4], Jonathan S. Nguyen Van-Tam[2], Hywel C. Williams[2], Abhishek Abhishek[1].

Affiliations: [1]Academic Rheumatology, School of Medicine, University of Nottingham, Nottingham. [2]Lifespan and Population Health, School of Medicine, University of Nottingham, Nottingham. [3]Nottingham Digestive Diseases Centre, Translational Medical Sciences, School of Medicine, University of Nottingham. [4]Primary Care Centre Versus Arthritis, School of Medicine, Keele University, Keele.

Corresponding author: Dr Georgina Nakafero

Address for correspondence:

Dr G Nakafero

The University of Nottingham, Nottingham, UK.

School of Medicine,

A23, Academic Rheumatology,

Clinical Sciences Building,

NG5 1PB

Email: georgina.nakafero@nottingham.ac.uk

Phone: 01158231655

ORCiD iD: https://orcid.org/0000-0002-3859-7354

Abstract:

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

Methods: Patients with AIRDs vaccinated against Covid-19 who consulted for disease flare between 01/12/2020 and 31/12/2021 were ascertained in Clinical Practice Research Datalink (Aurum). AIRD flare was defined as consultation for AIRD with corticosteroid 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% confidence intervals (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 rheumatoid arthritis 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 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 SARS-CoV-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.

Conclusion: 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

Key messages:

- It is unclear whether AIRD flares associate with Covid-19 vaccination.
- Vaccination against Covid-19 was not associated with significantly increased AIRD flares.
- These data should be used to promote Covid-19 vaccination in people with AIRDs.

Introduction

Autoimmune rheumatic diseases (AIRDs) are associated with increased risk of hospitalization and death from COVID-19.[1] Despite this, only 54% patients with AIRDs were willing to get vaccinated against Covid-19 in the 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% to 15% 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 corticosteroid used to treat disease flares[3-6]. The median duration between vaccination against Covid-19 and disease flares 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, prior Covid-19, and between mRNA (bNT1262) and vectored DNA (AZD1222) vaccines.

Methods

Data source

Data were extracted from Clinical Practice Research Datalink (CPRD) Aurum, a longitudinal anonymized electronic database of health records from 19 million patients from 738 general practices that dates to1995[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 NHS Digital. Covid-19 is defined using GP diagnosis, serology, or polymerase chain reaction 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 ≥1 primary-care consultation for AIRD (either rheumatoid arthritis (RA), psoriatic arthritis (PsA), inflammatory bowel disease (IBD) associated arthritis, reactive arthritis, ankylosing spondylitis (AS), systemic lupus erythematosus (SLE), connective tissue disease (CTD), small vessel vasculitis, polymyalgia rheumatica (PMR), or giant cell arteritis (GCA)); and ≥1 prescription for any conventional disease modifying anti-rheumatic drug (DMARD) prior to 1st December 2020 were eligible to be included in the study, provided they

also received ≥1 vaccination against Covid-19 and consulted their GP for ≥1 AIRD flare in the study period.

Study period

1st December 2020 to 31st December 2021. Follow-up was censored if death, emigration from participating general practice, or last collection of data from general practice occurred before 31st 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 corticosteroid 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 (Figure 1). The vaccine-exposed period was 21-days post-vaccination as it takes approximately 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 1st of December 2020, one week before the first COVID-19 vaccine was administered outside of trial setting in the UK to allow each potential vaccinated participant to have 7 days 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% confidence interval (CI) for association between vaccination and AIRD flares. Stratified analysis considered 1st, 2nd or 3rd 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 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 Figure S1, available at *Rheumatology* online). The majority were female (71.8%) and their mean (SD) age was 65 (15) years. 2427 (68.3%) had RA, 557 (15.7%) had PMR/GCA, 273 (7.7%) had SpA (defined as either PsA, AS, reactive arthritis, IBD associated arthritis) and 297 (8.4%) had CTD/small vessel vasculitis. 1,492 (42%), 2057 (57.9%), and 5 (0.1%) participants received BNT162b2, AZD1222 and mRNA-1273 vaccines respectively as their first dose. 90% participants received ≥1 dose of the vaccine against Covid-19 by the 13th of March 2021. 212 (6%) participants had Covid-19 prior to their first vaccine dose. 2,448 (68.9%), 962 (27.1%), and 144 (4.1%) participants received three, two, and one vaccination against Covid-19 respectively in the study period. 3256 (91.6%), 239 (6.7%) and 59 (1.7%) participants had one, two, and more than two AIRD flares. 29.9%, 24.1%, 21.3%, and 24.7% flares occurred in each quartile of the follow-up period. 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%)). 4055 (94.2%) AIRD flares were not preceded by long-term corticosteroid prescription defined as ≥3 corticosteroid 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 analyzed 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), 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 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, 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.

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 possibility of increased risk of AIRD flares[14]. A re-analysis of the COVAX database suggested that SLE, PsA, and PMR associated with disease flare after vaccination against Covid-19 compared 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 dose 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 generalisability 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 does 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 corticosteroid 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 corticosteroid prescription. Finally, patients with PMR/GCA treated with corticosteroids only were not included as the study required ≥1 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.

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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.

Data availability: 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.

References:

1. Clift AK, Coupland CAC, Keogh RH, et al J. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. BMJ. 2020 Oct 20;371:m3731.
2. Felten R, Dubois M, Ugarte-Gil MF, et al. Vaccination against COVID-19: Expectations and concerns of patients with autoimmune and rheumatic diseases. Lancet Rheumatol. 2021 Apr;3(4):e243-e245.
3. Machado PM, Lawson-Tovey S, Strangfeld A, et al Safety of vaccination against SARS-CoV-2 in people with rheumatic and musculoskeletal diseases: results from the EULAR Coronavirus Vaccine (COVAX) physician-reported registry Annals of the Rheumatic Diseases 2022;81:695-709.
4. Barbhaiya M, Levine JM, Bykerk VP, et al Systemic rheumatic disease flares after SARS-CoV-2 vaccination among rheumatology outpatients in New York City Annals of the Rheumatic Diseases 2021;80:1352-1354.
5. Connolly CM, Ruddy JA, Boyarsky BJ, Barbur I, Werbel WA, Geetha D, et al. Disease Flare and Reactogenicity in Patients With Rheumatic and Musculoskeletal Diseases Following Two-Dose SARS-CoV-2 Messenger RNA Vaccination. Arthritis Rheumatol. 2022; 74(1): 28-32.
6. Sattui SE, Liew JW, Kennedy K, Sirotich E, Putman M, Moni TT et al. Early experience of COVID-19 vaccination in adults with systemic rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance Vaccine Survey. RMD Open. 2021 Sep;7(3):e001814. doi: 10.1136/rmdopen-2021-001814.
7. Wolf A, Dedman D, Campbell J, et al. Data resource profile: Clinical Practice Research Datalink (CPRD) Aurum. International journal of epidemiology. 2019;48(6):1740-g.

8. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. BMJ. 2016 Sep 12;354:i4515.
9. Whitaker HJ, Hocine MN, Farrington CP. The methodology of self-controlled case series studies. Stat Methods Med Res. 2009 Feb;18(1):7-26.
10. Mulligan MJ, Lyke KE, Kitchin N, Absalon J, Gurtman A, Lockhart S et al. Nature. 2020 Oct;586(7830):589-593.
11. Folegatti PM, Ewer KJ, Aley PK, Angus B, Becker S, Belij-Rammerstorfer S, et al. Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial. Lancet. 2020 Aug 15;396(10249):467-478.
12. Li X, Tong X, Yeung WWY, Kuan P, Yum SHH, Chui CSL, et al. Two-dose COVID-19 vaccination and possible arthritis flare among patients with rheumatoid arthritis in Hong Kong. Ann Rheum Dis. 2022;81(4):564-568.
13. Tedeschi SK, Stratton J, Ellrodt JE, Whelan MG, Hayashi K, Yoshida K, Chen L, Adejoorin I, Marks KE, Jonsson AH, Rao DA, Solomon DH. Rheumatoid arthritis disease activity assessed by patient-reported outcomes and flow cytometry before and after an additional dose of COVID-19 vaccine. Ann Rheum Dis. 2022 Feb 15:annrheumdis-2022-222232. doi: 10.1136/annrheumdis-2022-222232.
14. Medeiros-Ribeiro, A.C., Aikawa, N.E., Saad, C.G.S., Emily F. N. Yuki, Tatiana Pedrosa, Solange R. G. Fusco, et al. Immunogenicity and safety of the CoronaVac inactivated vaccine in patients with autoimmune rheumatic diseases: a phase 4 trial. Nat Med 2021; 27, 1744–1751.
15. Rider, L.G., Parks, C.G., Wilkerson, J., Schiffenbauer, A.I., Kwok, R.K., Farhadi, P.N., COVID-19 Global Rheumatology Alliance Vaccine Survey Group. Baseline factors associated with self-reported disease flares following COVID-19 vaccination among adults

with systemic rheumatic disease: results from the COVID-19 global rheumatology alliance vaccine survey, *Rheumatology*, 2022; keac249, https://doi.org/10.1093/rheumatology/keac249

16. Connolly, C.M., Frey, S., Chiang, T. P-Y., Teles, M., Alejo, J.L., Albayda, J., et al. Safety of third-dose SARS-CoV-2 vaccination in patients with rheumatic and musculoskeletal disease, *Rheumatology*, 2022;, keac298, https://doi.org/10.1093/rheumatology/keac298
17. Savage EM, McCormick D, McDonald S, Moore O, Stevenson M, Cairns AP. Does rheumatoid arthritis disease activity correlate with weather conditions? Rheumatol Int. 2015;35:887-90.

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

Covid-19 vaccination	Risk period (days)	Events (n)	IRR[1] (95%CI)[2]	Adjusted[3] IRR (95%CI)[2]	p-value[3]
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)	
	15 - 21 days	181	0.92 (0.79-1.07)	0.94 (0.80-1.09)	
1st dose	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)	
	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)	
2nd dose	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
	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				
3rd dose	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)	

[1]Incidence rate ratio, [2]95% confidence interval, [3]adjusted for four seasons.

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

	Risk period (days)	Events (n)	IRR[1] (95%CI)[2]	Adjusted[3] IRR (95%CI)[2]	p-value[3]
Autoimmune rheumatic disease type					
Rheumatoid Arthritis	Baseline	2163	1	1	-/-
	7-day pre-vaccination	121	0.88(0.73-1.05)	0.89 (0.74-1.07)	0.217
	21-day post-vaccination	342	0.84 (0.75-0.95)	0.85 (0.76-0.96)	0.009
Spondyloarthritis	Baseline	241	1	1	-/-
	7-day pre-vaccination	14	0.91 (0.53-1.57)	0.91 (0.53-1.57)	0.733
	21-day post-vaccination	36	0.81 (0.57-1.14)	0.77 (0.53-1.12)	0.171
Connective tissue diseases/ small vessel vasculitis	Baseline	245	1	1	-/-
	7-day pre-vaccination	16	1.03 (0.62-1.72)	1.08 (0.65-1.80)	0.777
	21-day post-vaccination	45	0.99 (0.72-1.36)	1.05 (0.75-1.47)	0.760
Polymyalgia rheumatica/ Giant cell arteritis	Baseline	528	1	1	-/-
	7-day pre-vaccination	44	1.24 (0.91-1.69)	1.21 (0.88-1.65)	0.237
	21-day post-vaccination	104	0.99 (0.81-1.23)	0.97 (0.77-1.20)	0.752
Covid-19 infection[4]					
No	Baseline	1384	1	1	-/-
	7-day pre-vaccination	84	1.10 (0.88-1.37)	0.93 (0.74-1.17)	0.540
	21-day post-vaccination	186	0.81 (0.70-0.95)	0.76 (0.65-0.89)	0.001
Yes	Baseline	115	1	1	
	7-day pre-vaccination	3	0.53 (0.17-1.69)	0.51 (0.16-0.63)	0.259
	21-day post-vaccination	6	0.36 (0.16-0.81)	0.35 (0.15-0.80)	0.013
Vaccine type[4,5]					
Pfizer	Baseline	584	1	1	-/-
	7-day pre-vaccination	45	1.33 (0.98-1.81)	1.10 (0.81-1.51)	0.553
	21-day 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-day pre-vaccination	42	0.87 (0.64-1.19)	0.77 (0.56-1.05)	0.095
	21-day post-vaccination	110	0.76 (0.63-0.93)	0.75 (0.61-0.92)	0.005

[1]Incidence rate ratio, [2]95% confidence interval, [3]adjusted for four seasons, [4] First vaccine analysed. [5]People vaccinated with mRNA-1273 vaccine (n=3) were excluded from this analysis.

Figure 1. Schematic representation of self-controlled case series (SCCS) analysis

The vaccine-exposed (21-days post vaccination), pre-vaccination induction periods (7-days before vaccination) and vaccine-unexposed (the remaining vaccine-unexposed period) are shaded dark grey, light grey, 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 1st December 2020 and was censored on the earliest of 31st December 2021, death date, transfer out date, date of last data collection from the GP surgery.

Figure 1. Schematic representation of self-controlled case series (SCCS) analysis periods. The vaccine-exposed (21-days post vaccination), pre-vaccination induction periods (7-days before vaccination) and vaccine-unexposed (the remaining vaccine-unexposed period) are shaded dark grey, light grey, 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 1st December 2020 and was censored on the earliest of 31st December 2021, death date, transfer out date, date of last data collection from the GP surgery.

54x30mm (600 x 600 DPI)

Jyseleca® ▽ filgotinib

A 2nd generation, JAK1 preferential inhibitor for moderate to severe RA[1-6]

While 1st generation JAK inhibitors are relatively non-selective,[2-6] JYSELECA has over 5x greater potency for JAK1 over JAK2/3 and TYK2[1]*

Balancing sustained efficacy[7-11] with acceptable tolerability[1,12]

Indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti-rheumatic drugs.[1] May be used as monotherapy or in combination with methotrexate.[1]

*From biochemical assays, the clinical relevance of which is uncertain.
JAK, Janus kinase; RA, rheumatoid arthritis; TYK, tyrosine kinase.

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Refer to Summary of Product Characteristics (SmPC) before prescribing, and for full prescribing information.

JYSELECA® ▽ filgotinib 100 mg or 200 mg film-coated tablets. **Indication:** Jyseleca is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease modifying anti rheumatic drugs (DMARDs). Jyseleca may be used as monotherapy or in combination with methotrexate (MTX). **Dosage:** Adults: 200 mg once daily. Taken orally with/without food. It is recommended that tablets are swallowed whole. Laboratory Monitoring: Refer to the SmPC for information regarding laboratory monitoring and dose initiation or interruption. Elderly: A starting dose of 100 mg once daily is recommended for patients aged 75 years and older as clinical experience is limited. Renal impairment: No dose adjustment required in patients with estimated creatinine clearance (CrCl) ≥ 60 mL/min. A dose of 100 mg of filgotinib once daily is recommended for patients with moderate or severe renal impairment (CrCl 15 to < 60 mL/min). Not recommended in patients with CrCl < 15 mL/min. Hepatic impairment: Mild/moderate hepatic impairment: no dose adjustment required. Severe hepatic impairment: not recommended. Children (< 18years): Safety and efficacy not yet established. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Active tuberculosis (TB) or active serious infections. Pregnancy. **Warnings/Precautions:** See SmPC for full information. Immunosuppression: Combination use, with immunosuppressants e.g., ciclosporin, tacrolimus, biologics or other Janus kinase (JAK) inhibitors is not recommended as a risk of additive immunosuppression cannot be excluded. Infections: Infections, including serious infections such as pneumonia and opportunistic infections e.g. tuberculosis (TB), oesophageal candidiasis, and cryptococcosis have been reported. Risk benefit should be assessed prior to initiating in patients with risk factors for infections (see SmPC). Patients should be closely monitored for the development of signs and symptoms of infections during and after filgotinib treatment. Treatment should be interrupted if the patient is not responding to antimicrobial therapy, until infection is controlled. There is a higher incidence of serious infections in the elderly aged 75 years and older, caution should be used when treating this population. Tuberculosis: Patients should be screened for TB before initiating filgotinib, and filgotinib should not be administered to patients with active TB. Viral reactivation: Cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical studies (see SmPC). If a patient develops herpes zoster, filgotinib treatment should be temporarily interrupted until the episode resolves. Screening for viral hepatitis and monitoring for reactivation should be performed. Malignancy: Immunomodulatory medicinal products may increase the risk of malignancies. Malignancies were observed in clinical studies (see SmPC). Fertility: In animal studies, decreased fertility, impaired spermatogenesis, and histopathological effects on male reproductive organs were observed (see SmPC). The potential effect of filgotinib on sperm production and male fertility in humans is currently unknown. Haematological abnormalities: Do not start therapy, or temporarily stop, if Absolute Neutrophil Count (ANC) <1 × 10^9 cells/L, ALC <0.5 × 10^9 cells/L or haemoglobin <8 g/dL. Temporarily stop therapy if these values are observed during routine patient management. Vaccinations: Use of live vaccines during, or immediately prior to, filgotinib treatment is not recommended. Lipids: Treatment with filgotinib was associated with dose dependent increases in lipid parameters, including total cholesterol, and high-density lipoprotein (HDL) levels, while low density lipoprotein (LDL) levels were slightly increased (see SmPC). Cardiovascular risk: Rheumatoid arthritis patients have an increased risk for cardiovascular disorders. Patients should have risk factors (e.g., hypertension, hyperlipidaemia) managed as part of usual standard of care. Venous thromboembolism: Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving JAK inhibitors including filgotinib. Caution should be used in patients with risk factors for DVT/PE, such as older age, obesity, a medical history of DVT/PE, or patients undergoing surgery, and prolonged immobilisation. Lactose content: Contains lactose; patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take filgotinib. **Pregnancy/Lactation:** Filgotinib is contraindicated in pregnancy. Filgotinib should not be used during breast-feeding. Women of childbearing potential must use effective contraception during and for at least 1 week after cessation of treatment. **Driving/Using machinery:** No or negligible influence, however dizziness has been reported. **Side effects:** See SmPC for full information. Common (≥1/100 to <1/10): nausea, upper respiratory tract infection, urinary tract infection and dizziness. Uncommon (≥1/1000 to <1/100): herpes zoster, pneumonia, neutropenia, hypercholesterolaemia and blood creatine phosphokinase increase. Serious side effects: See SmPC for full information **Legal category:** POM **Pack:** 30 film-coated tablets/bottle **Price:** UK Basic NHS cost: £863.10 **Marketing authorisation number(s):** Great Britain Jyseleca 100mg film-coated tablets PLGB 42147/0001 Jyseleca 200mg film-coated tablets PLGB 42147/0002 Northern Ireland Jyseleca 100mg film-coated tablets EU/1/20/1480/001 EU/1/20/1480/002 Jyseleca 200mg film-coated tablets EU/1/20/1480/003 EU/1/20/1480/004 **Further information:** Galapagos UK, Belmont House, 148 Belmont Road, Uxbridge UB8 1QS, United Kingdom 00800 7878 1345 medicalinfo@glpg.com Jyseleca® is a trademark. **Date of Preparation:** January 2022 UK-RA-FIL-202201-00019

▽ Additional monitoring required

Adverse events should be reported.
For Great Britain and Northern Ireland, reporting forms and information can be found at yellowcard.mhra.gov.uk or via the Yellow Card app (download from the Apple App Store or Google Play Store).
Adverse events should also be reported to Galapagos via email to DrugSafety.UK.Ireland@glpg.com or 00800 7878 1345

References: 1. JYSELECA SPC. Available at: www.medicines.org.uk. Last accessed: June 2022. **2.** Angelini J, *et al.* Biomolecules 2020;10(7):E1002. **3.** Banerjee S, *et al.* Drugs 2017;77:521–546. **4.** O'Shea JJ, *et al.* Nat Rev Rheumatol 2013;9(3):173–182. **5.** Traves PG, *et al.* Ann Rheum Dis 2021;0:1–11. **6.** McInnes IB, *et al.* Arthr Res Ther 2019;21:183. **7.** Combe B, *et al.* Ann Rheum Dis 2021;doi:10.1136/annrheumdis-2020-219214. **8.** Genovese MC, *et al.* JAMA 2019;322 (4):315–325. **9.** Westhovens R, *et al.* Ann Rheum Dis 2021;doi:10.1136/annrheumdis-2020-219213. **10.** Combe B, *et al.* Arthritis Rheumatol 2021;73(suppl 10). https://acrabstracts.org/abstract/clinical-outcomes-up-to-week-48-of-filgotinib-treatment-in-an-ongoing-long-term-extension-trial-of-ra-patients-with-inadequate-response-to-mtx-initially-treated-with-filgotinib-or-adalimumab-during-th/. Last accessed: June 2022. **11.** Buch MH, *et al.* Arthritis Rheumatol 2021;73 (suppl 10). https://acrabstracts.org/abstract/clinical-outcomes-up-to-week-48-of-ongoing-filgotinib-ra-long-term-extension-trial-of-biologic-dmard-inadequate-responders-initially-on-filgotinib-or-placebo-in-a-phase-3-trial/. Last accessed: June 2022. **12.** Winthrop K, *et al.* Arthritis Rheumatol 2021;73(suppl 10). Available at: https://acrabstracts.org/abstract/integrated-safety-analysis-update-for-filgotinib-in-patients-with-moderately-to-severely-active-rheumatoid-arthritis-receiving-treatment-over-a-median-of-2-2-years/. Last accessed: June 2022.

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