SARS-CoV-2 infection after vaccination in patients with inflammatory rheumatic and musculoskeletal diseases

Patients with inflammatory rheumatic and musculoskeletal diseases (iRMDs) are often treated with immunomodulatory or immunosuppressive medications; consequently, they have been excluded alongside other immunocompromised patients from late stages of SARS-CoV-2 vaccine trials. SARS-CoV-2 vaccine efficacy in this population is unclear, though initial data are reassuring overall.

Table 1 Summary of 38 cases of SARS-CoV-2 infection ≥14 days after the first/single SARS-CoV-2 vaccine dose in the European Alliance of Associations for Rheumatology COVID-19 and COVAX registries, and breakdown by vaccination status

	All patients (N=38, N (%))	Fully vaccinated (n=10, N (%))	Partially vaccinated (n=28, N (%))
Sex			
Female	29 (76)	7 (70)	22 (79)
Male	9 (24)	3 (30)	6 (21)
Age, median (IQR)	58 (49–65)	62.5 (49–72)	57 (49–64)
Country			
Belgium	1 (3)	1 (10)	
Croatia	2 (5)	1 (10)	1 (4)
France	17 (45)	5 (50)	12 (43)
Greece	2 (5)		2 (7)
Hungary	1 (3)		1 (4)
Italy	1 (3)		1 (4)
Netherlands	1 (3)		1 (4)
Portugal	2 (5)		2 (8)
Slovakia	3 (8)	1 (10)	2 (8)
Spain	1 (3)		1 (4)
Turkey	3 (8)	2 (20)	1 (4)
UK	4 (11)		4 (14)
Comorbidities Only collected in COVID-19 registry (n=8 cases), shown as N (%) of 8			
Obstructive lung disease	1 (13)	1 (10)	
Hypertension	3 (38)	1 (10)	2 (7)
Cardiovascular disease	2 (25)		2 (7)
Cerebrovascular disease	1 (13)		1 (4)
Other	1 (13)		1 (4)
Rheumatic disease diagnoses			
ANCA-associated vasculitis (eg, GPA, EGPA)	2 (5)	1 (10)	1 (4)
Axial spondyloarthritis	9 (24)	1 (10)	8 (29)
Giant cell arteritis	1 (3)		1 (4)
Inflammatory myopathy	1 (3)		1 (4)
Polymyalgia rheumatica	1 (3)		1 (4)
Rheumatoid arthritis	17 (45)	5 (50)	12 (43)
Sjogren's syndrome	2 (5)	1 (10)	1 (4)
Systemic lupus erythematosus	3 (8)		3 (11)
Systemic sclerosis	3 (8)	1 (10)	2 (7)
Undifferentiated connective tissue disease	1 (3)	1 (10)	
Other	1 (3)		1 (4)
Inflammatory rheumatic disease activity			
Remission	18 (47)	8 (80)	10 (36)
Low	13 (34)	2 (20)	11 (39)
Moderate	5 (13)		5 (18)
Missing	2 (5)		2 (7)
Rheumatic disease medication and medication changes as a result of COVID-19 vaccination			
None	5 (13)	1 (10)	4 (14)
Abatacept	1 (3)		1 (4)
Antimalarials (including hydroxychloroquine, chloroquine and mepacrine/quinacrine)	5 (13)	2 (20)	3 (11)
Cyclosporine	1 (3)		1 (4)
Denosumab	1 (3)		1 (4)
Glucocorticoids	12 (32)	3 (30)	9 (32)
IL-6 inhibitors (including tocilizumab and sarilumab)	3 (8)		3 (11)
Stopped/held before COVID-19 vaccination	1		1
Stopped/held after COVID-19 vaccination	1		1
IVIG	1 (3)	1 (10)	
JAK inhibitors (including tofacitinib, baricitinib and upadacitinib)	2 (5)	1 (10)	1 (4)

Continued

Table 1 Continued

	All patients (N=38, N (%))	Fully vaccinated (n=10, N (%))	Partially vaccinated (n=28, N (%))
Methotrexate	10 (26)	3 (30)	7 (25)
Stopped/held after COVID-19 vaccination	2		2
Mycophenolate mofetil/mycophenolic acid	3 (8)	1 (10)	2 (7)
Rituximab	1 (3)	1 (10)	
Stopped/held before COVID-19 vaccination	1	1	
Stopped/held after COVID-19 vaccination	1	1	
Sulfasalazine	2 (5)		2 (7)
TNF inhibitors (including infliximab, etanercept, adalimumab, golimumab, certolizumab and biosimilars)	10 (26)	2 (20)	8 (29)
Other	4 (11)		4 (14)
COVID-19 vaccine type			
Pfizer-BioNTech	30 (79)	8 (80)	22 (79)
Moderna	1 (3)		1 (4)
AstraZeneca/Oxford	4 (11)		4 (14)
CoronaVac/Sinovac	3 (8)	2 (20)	1 (4)
COVID-19 vaccine type: N of reinfections/total N of vaccine in registries (% of reinfection per vaccine)			
Pfizer-BioNTech	30/3038 (1)	8/1919 (<1)	22/1119 (2)
Moderna	1/375 (<1)	0/204 (0)	1/171 (1)
AstraZeneca/Oxford	4/730 (1)	0/181 (0)	3/549 (1)
Janssen/Johnson & Johnson	0/40 (0)	0/1 (0)	0/39 (0)
Sputnik V	0/4 (0)	0/4 (0)	
CoronaVac/Sinovac	3/49 (6)	2/41 (5)	1/8 (13)
Other	0/2 (0)	0/2 (0)	
Unknown	0/120 (0)	0/60 (0)	0/60 (0)
COVID-19 outcome			
Deceased due to COVID-19	3 (8)	2 (20)	1 (4)
Vital status not known at this time	1 (3)		1 (4)
Full recovery	28 (74)	8 (80)	20 (71)
Resolved, with sequelae	3 (8)		3 (11)
Missing	3 (8)		3 (11)
Number of days from COVID-19 vaccine to infection, median (IQR)			
COVID-19 registry, most recent dose	23 (17–30)	22 (22–22)	24 (17–30)
COVAX registry, first dose	26.5 (20–52)	76 (52–97)	23 (18–27)
COVAX registry, second dose	24 (13–55)	45 (24–58)	7.5 (3.5–11.5)
COVAX registry, third dose	26.5 (23–30)	26.5 (23–30)	
Number of vaccine doses administered before COVID-19 diagnosis			
One dose	23 (61)		23 (82)
Two doses	13 (34)	8 (80)	5 (18)
Three doses	2 (5)	2 (20)	

All data are N (%) of the column unless stated otherwise.
ANCA-associated vasculitis, anti-neutrophil cytoplasmic antibody-associated vasculitis; COVID-19, Coronavirus disease 2019; EGPA, eosinophilic granulomatosis with polyangiitis; GPA, granulomatosis with polyangiitis; IL-6 inhibitors, interleukin-6 inhibitors; IVIG, Intravenous immunoglobulin; JAK inhibitors, Janus kinase inhibitors; TNF inhibitors, tumour necrosis factor inhibitors.

However, a slightly lower SARS-CoV-2 immunogenicity of vaccines has been documented in some patients with iRMD.[1 2] Some common rheumatic and musculoskeletal disease (RMD) medications have been highlighted as possible influential factors on immunogenicity, particularly rituximab (RTX), mycophenolate mofetil (MMF), methotrexate (MTX), abatacept and glucocorticoids.[3–7]

The European Alliance of Associations for Rheumatology (EULAR) launched a COVID-19 registry in March 2020, capturing COVID-19 outcomes in the European RMD population. Questions on reinfection and vaccination were added in January 2021. A further EULAR registry (COVAX) was launched in February 2021 to collect data on COVID-19 vaccination and related adverse events among patients with RMD. Here we describe a series of patients who contracted SARS-CoV-2 infection after COVID-19 vaccination between 19 January 2021 and 27 July 2021.

The series consists of 38 adults with iRMDs, 8 from the COVID-19 registry (<1%, out of 9118 patients with iRMD diagnosed with COVID-19) and 30 from the COVAX registry (<1%, out of 4393). Cases were deemed eligible if they were 'partially vaccinated' (≥14 days after dose 1 to <14 days after dose 2) or 'fully vaccinated' (≥14 days after dose 2/single dose), as per Centers for Disease Control and Prevention definitions[8] (17 cases were excluded for this reason). A quarter (26%) were fully vaccinated and 28 cases (74%) were partially vaccinated.

As shown in table 1, 76% of the series is female, with a median age of 58 (IQR 49–65) from 12 countries. The most frequent

Table 2 Summary of 34 cases of SARS-CoV-2 infection ≥14 days after the first/single SARS-CoV-2 vaccine dose in the European Alliance of Associations for Rheumatology COVID-19 and COVAX registries, stratified by COVID-19 outcome (excluding cases with missing/unknown COVID-19 outcome, N=4)

	Deceased, n=3 (N)	Full recovery, n=28 (N)	Resolved, with sequelae, n=3 (N)
Sex			
Female	1 (RA+SjS)	21	3
Male	2 (RA, SSc)	7	
Age, median (IQR)	>80 (SSc) >70 (RA, RA+SjS)	58 (49.5–65.0)	50 (49–61)
Rheumatic disease diagnoses			
ANCA-associated vasculitis		2	
Axial spondyloarthritis		7	1
Giant cell arteritis		1	
Inflammatory myopathy		1	
Polymyalgia rheumatica		1	
RA	1	11	2
Sjogren's syndrome		1	
RA+Sjogren's syndrome	1		
Systemic lupus erythematosus		2	
SSc	1	2	
Undifferentiated connective tissue disease		1	
Other		1	
Rheumatic disease activity			
Remission		16	
Low	2 (RA, RA+SjS)	9	1
Moderate	1 (SSc)	3	
Unknown			2
COVID-19 vaccine type			
Pfizer/BioNTech	3	22	2
Moderna		1	
AstraZeneca/Oxford		3	
CoronaVac/Sinovac		2	1
Other			1
COVID-19 vaccination status			
Partially vaccinated	1 (SSc)	20	3
Fully vaccinated	2 (RA, RA+SjS)	8	
Rheumatic disease medication			
None		4	
Abatacept			1
Antimalarials		4	
Cyclosporine		1	
Denosumab		1	
Glucocorticoids	1 (RA)	8	
IL-6 inhibitors		1	1
IVIG		1	
JAK inhibitors		2	
Methotrexate		9	
MMF		2	
MMF+glucocorticoids	1 (SSc)		
Rituximab	1 (RA+SjS)		
Sulfasalazine		1	1
TNF inhibitors		8	1
Other		4	
Number of days from COVID-19 vaccine to infection, median (IQR)			
COVID-19 registry (most recent vaccine dose)		23 (17–30)	
COVAX, first dose	18 (SSc)	29 (21.5–72.0)	26 (18–31)

Continued

Table 2 Continued

	Deceased, n=3 (N)	Full recovery, n=28 (N)	Resolved, with sequelae, n=3 (N)
COVAX, second dose	22 (RA) 32 (RA+SjS)	45 (19–58)	10 (10–10)
COVAX, third dose		26.5 (23–30)	

All data are N (%) of the column unless stated otherwise.
ANCA-associated vasculitis, anti-neutrophil cytoplasmic antibody-associated vasculitis; COVID-19, Coronavirus disease 2019; IL-6, Interleukin-6; IVIG, intravenous immunoglobulin; JAK, janus-kinase; MMF, mycophenolate mofetil; RA, rheumatoid arthritis ; SjS, Sjogren's syndrome; SSc, systemic sclerosis; TNF, tumour necrosis factor.

iRMD diagnoses were rheumatoid arthritis (RA, 45%), axial spondyloarthritis (axSpA, 24%), systemic sclerosis (SSc, 8%) and systemic lupus erythematosus (8%). Most were in remission (47%) or had low disease activity (34%). The top iRMD medications were glucocorticoids (32%), MTX (26%) and tumour necrosis factor inhibitors (TNFi, 26%). The median glucocorticoid dose in users was 5 mg/day (IQR 5–10).

The most common comorbidities among COVID-19 registry cases were hypertension (38%) and cardiovascular disease (25%). Comorbidities are not reported in the COVAX registry. Out of the 30 COVAX cases, 29 had no SARS-CoV-2 infection prior to vaccination, and this was unknown in one case. These data are not collected in the COVID-19 registry.

Seventy-nine per cent received the Pfizer/BioNTech vaccine; 11% received AstraZeneca; 8% received CoronaVac/Sinovac; and 3% received Moderna. Sixty-one per cent had one vaccine dose before COVID-19; 34% had two; and 5% had three. Median times from vaccination to infection are shown in table 1.

Most patients (74%) fully recovered from the SARS-CoV-2 infection; however, several patients recovered with ongoing sequelae (8%) and three patients died (8%).

Two of the deceased patients were male: one >80-year-old man with SSc, treated with glucocorticoids (10 mg/day) and MMF, who received one Pfizer vaccine 18 days prior to SARS-CoV-2 infection (therefore this patient was not fully vaccinated); one >70-year-old man with RA, treated with glucocorticoids (5 mg/day) who received two Pfizer doses (44 and 22 days before SARS-CoV-2 infection). The other patient was female: a >70-year-old woman with RA and Sjogren's syndrome, treated with RTX (the most recent RTX infusion was 195 days before the first vaccine), who received two Pfizer vaccines (60 and 32 days prior to infection) (table 2).

The three patients who recovered with ongoing sequelae had axSpA and RA, and were treated with abatacept, interleukin-6 inhibitors, sulfasalazine and TNFi (table 2).

Overall, the low numbers of SARS-CoV-2 infection post-vaccination in both registries are encouraging. Some observations described here have already been highlighted in existing research; for example, all three deceased patients were treated with medications that are potential negative influences on post-vaccination SARS-CoV-2 immunogenicity in the RMD population.[3 7] However, no vaccine has perfect efficacy; thus, a small number of postvaccination diagnoses of SARS-CoV-2 infections were expected, similarly to existing clinical trial observations; the influence of RMD medications on immunity after vaccination is still unclear.

There are significant limitations to this case series. The sample size is not sufficiently powered to evaluate associations between iRMD population-specific factors and SARS-CoV-2 infection after COVID-19 vaccination or to calculate a vaccine failure rate. Both the EULAR COVID-19 and COVAX registries rely on voluntary case submission, leading to selection bias in the data. No information is provided concerning the presence or the titre of postvaccine antibodies at the time of the infection. No causal conclusions can be drawn from this dataset, and the observations highlighted here cannot be extrapolated onto the wider iRMD population. Further research is needed to more deeply examine possible links between iRMD and medication-specific factors and SARS-CoV-2 infection after vaccination.

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data capture, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for data integration and interoperability with external sources.

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REFERENCES

1 Simon D, Tascilar K, Fagni F, *et al*. SARS-CoV-2 vaccination responses in untreated, conventionally treated and anticytokine-treated patients with immune-mediated inflammatory diseases. *Ann Rheum Dis* 2021;80:1312–6.
2 Geisen UM, Berner DK, Tran F, *et al*. Immunogenicity and safety of anti-SARS-CoV-2 mRNA vaccines in patients with chronic inflammatory conditions and immunosuppressive therapy in a monocentric cohort. *Ann Rheum Dis* 2021;80:1306–11.
3 Spiera R, Jinich S, Jannat-Khah D. Rituximab, but not other antirheumatic therapies, is associated with impaired serological response to SARS- CoV-2 vaccination in patients with rheumatic diseases. *Ann Rheum Dis* 2021;80:1357–9.
4 Haberman RH, Herati R, Simon D, *et al*. Methotrexate hampers immunogenicity to BNT162b2 mRNA COVID-19 vaccine in immune-mediated inflammatory disease. *Ann Rheum Dis* 2021;80:1339–44.
5 Boyarsky BJ, Ruddy JA, Connolly CM, *et al*. Antibody response to a single dose of SARS-CoV-2 mRNA vaccine in patients with rheumatic and musculoskeletal diseases. *Ann Rheum Dis* 2021;80:1098–9.
6 Bugatti S, De Stefano L, Balduzzi S, *et al*. Methotrexate and glucocorticoids, but not anticytokine therapy, impair the immunogenicity of a single dose of the BNT162b2 mRNA COVID-19 vaccine in patients with chronic inflammatory arthritis. *Ann Rheum Dis* 2021;80:1635–8.
7 Furer V, Eviatar T, Zisman D, *et al*. Immunogenicity and safety of the BNT162b2 mRNA COVID-19 vaccine in adult patients with autoimmune inflammatory rheumatic diseases and in the general population: a multicentre study. *Ann Rheum Dis* 2021;80:1330–8.
8 CDC. CDC COVID-19 study shows mRNA vaccines reduce risk of infection by 91 percent for fully vaccinated people. Available: https://www.cdc.gov/media/releases/2021/p0607-mrna-reduce-risks.html [Accessed 16 Aug 2021].