SARS-CoV-2 Infection after Vaccination in Patients with Inflammatory Rheumatic and Musculoskeletal Diseases

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Patients with inflammatory rheumatic and musculoskeletal diseases (iRMDs) are often treated with immunomodulatory or immunosuppressive medications; consequently they were 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.

However, a slightly lower SARS-CoV-2 immunogenicity of vaccines has been documented in some iRMD patients.[1,2] Some common RMD medications have been highlighted as possible influential factors on immunogenicity, particularly rituximab (RTX), mycophenolate mofetil (MMF), methotrexate (MTX), abatacept and glucocorticoids.[3,4,5,6,7]

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 re-infection 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 RMD patients. Here we describe a series of patients who contracted SARS-CoV-2 infection after COVID-19 vaccination between 19/Jan/2021 and 27/Jul/2021.

The series consists of 38 adults with iRMDs; 8 from the COVID-19 registry (<1%; out of 9118 iRMD patients 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 one to <14 days after dose two) or "fully vaccinated" (≥14 days after dose two/single dose), as per Center for Disease Control and Prevention (CDC) 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 to 65) from 12 countries. The most frequent 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 5mg/day (IQR, 5 to 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. This data is not collected in the COVID-19 registry.

Seventy-nine percent received the Pfizer/BioNTech vaccine, 11% AstraZeneca, 8% Coronavac/Sinovac and 3% Moderna. Sixty-one percent had one vaccine dose before COVID-19, 34% had two, and 5% had three. Median times from vaccination to infection are shown in Table 2.

Most patients (74%) fully recovered from the SARS-CoV-2 infection; however, several patients recovered with ongoing sequelae (8%) and 3 patients died (8%).

Two of the deceased patients were male: one >80 year-old 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 with RA, treated with glucocorticoids (5mg/day) who received 2 Pfizer doses (44 and 22 days before SARS-CoV-2 infection). The other patient was female: a >70 year-old 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 3 patients who recovered with ongoing sequelae had axSpA and RA, and were treated with abatacept, IL-6 inhibitors, sulfasalazine and TNFi (Table 2).

Overall, the low numbers of SARS-CoV-2 infection post-vaccination in both registries is 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 post-vaccination diagnoses of SARS-CoV-2 infections was 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 post-vaccine 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.

Table 1: Summary of 38 cases of SARS-CoV-2 infection ≥14 days after the first/single SARS-CoV-2 vaccine dose in the EULAR 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)
	United Kingdom	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 (e.g. 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 (60)	10 (36)
	Low	13 (34)	2 (20)	11 (39)
	Moderate	5 (13)		5 (18)
	Missing	2 (5)		2 (7)
Rheumatic disease medication & 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, 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, 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, upadacitinib)	2 (5)	1 (10)	1 (4)
	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)
	Astra Zeneca/Oxford	4 (11)		4 (14)
	CoronaVac/Sinovac	3 (8)	2 (20)	1 (4)
COVID-19 vaccine type: N of re-infections/total N of vaccine in registries (% of re-infection 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 (72)
	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)	
	One dose	23 (61)		23 (82)
	Two doses	13 (34)	8 (80)	5 (18)

Number of vaccine doses administered before COVID-19 diagnosis	Three doses	2 (5)	2 (20)	
All data are N (%) of the column unless stated otherwise. COVID-19, Coronavirus disease 2019; ANCA-associated vasculitis, Anti-neutrophil cytoplasmic antibody-associated vasculitis; GPA, Granulomatosis with polyangiitis; EGPA, Eosinophilic granulomatosis with polyangiitis; IL-6 inhibitors, Interleukin-6 inhibitors; IVIG, Intravenous immunoglobulin; JAK inhibitors, Janus kinase inhibitors; TNF inhibitors, tumour necrosis factor inhibitors.				

Table 2: Summary of 34 cases of SARS-CoV-2 infection ≥14 days after the first/single SARS-CoV-2 vaccine dose in the EULAR 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)	50 (49, 61)
Rheumatic disease diagnoses	ANCA-associated vasculitis		2	
	Axial spondyloarthritis		7	1
	Giant cell arteritis		1	
	Inflammatory myopathy		1	
	Polymyalgia rheumatica		1	
	Rheumatoid arthritis	1	11	2
	Sjogren's syndrome		1	
	Rheumatoid arthritis + Sjogren's syndrome	1		
	Systemic lupus erythematosus		2	
	Systemic sclerosis	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	
	Astra Zeneca/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	
	Mycophenolate mofetil		2	
	Mycophenolate mofetil + 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)	26 (18, 31)
	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. COVID-19, Coronavirus disease 2019; ANCA-associated vasculitis, Anti-neutrophil cytoplasmic antibody-associated vasculitis; IL-6 inhibitors, Interleukin-6 inhibitors; IVIG, Intravenous immunoglobulin; TNF inhibitors, tumour necrosis factor inhibitors.

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