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Immunomodulatory and immunosuppressive medication modification among patients with rheumatic diseases at the time of COVID-19 vaccination

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Due to concerns about underlying immune dysregulation and immunosuppression, patients with systemic rheumatic diseases might modify their medications at the time of COVID-19 vaccination to optimise their immune response and mitigate vaccine side-effects. Immunosuppressed patients in New York state were approved for vaccination on Feb 15,2021,[1] soon after the American College of Rheumatology COVID-19 Vaccine Clinical Guidance Task Force issued its first management guidelines on Feb 8, 2021.[2] Whether real-world behaviour was aligned with these guidelines is unknown. Therefore, our study evaluated medication modifications at the time of COVID-19 vaccination by patients with rheumatic diseases at a single centre in New York City.

We emailed a secure web-based survey between March 5 and March 25, 2021, to 7505 patients aged 18 years or older who were evaluated at least once by a rheumatologist between April 1, 2018 and April 21, 2020, at a large rheumatology centre in New York City. We collected data on immunomodulatory and immunosuppressive medications at the time of COVID-19 vaccination, including whether doses were taken earlier than scheduled, delayed, or skipped. We also identified the individual responsible for the medication modification—ie, rheumatologist, other physician, or the patient themselves. This study was approved by the Hospital for Special Surgery, New York, institutional review board and patient consent was obtained via the survey.

As of March 2021, out of 2753 respondents to our COVID-19 vaccine questionnaire (36·7% response rate), 1852 respondents (67·3%) who reported receiving at least one vaccine dose and completed the medication modification questions were included in the current analysis. The mean age of patients receiving at least one vaccine dose was 63·0 (SD 14·2). 1474 (79·6%) of 1852 patients were female, 1619 (87·4%) were White, 58 (3·1%) were Black, and 88 (4·8%) were Hispanic or Latinx. The characteristics of survey recipients and respondents are reported in the appendix (p 5). Out of 1852 patients who received at least one vaccine dose, 998 (53·9%) received the Pfizer vaccine, 821 (44·3%) received the Moderna vaccine, 26 (1·4%) received the Janssen vaccine, and seven (0·4%) received other (six AstraZeneca and one Sinovac). 1173 (64·2%) of 1826 patients who were eligible to receive two vaccine doses reported that they had received both.

See **Online** for appendix

There were 1373 individual reports of using immunomodulatory or corticosteroid medications at the time of the first vaccine dose. Before the first vaccine dose, 215 (15·7%) of 1373 medication schedules were modified; of these, 41 (19·1%) medications were taken earlier than scheduled, and 174 (80·9%) medications were delayed or skipped (table; appendix p 1). Medications accounting for these modifications included: biologics (43·7%), conventional synthetic disease-modifying antirheumatic drugs (DMARDs; 35.3%), hydroxychloroquine (11·2%), corticosteroids (5·1%), and small molecules (4·7%; table).

	First vaccine dose (N=1852)				Second vaccine dose (N=1173)				
	Overall medication uses (N=1373)	Any medication modification before vaccine (N=215)	Medication taken early before vaccine (N=41)	Medication delayed or skipped before vaccine (N=174)	Overall medication uses (N=899)	Any medication modification before or after vaccine (N=251)	Medication delayed or skipped between first and second dose (N=105)	Medication taken early before vaccine (N=41)	Medication delayed or skipped after vaccine (N=105)
Any Immunomodulatory or immunosuppressive medication (excluding corticosteroids)	1203 (87·6%)	204 (94·9%)	37 (90·2%)	167 (96·0%)	796 (88·5%)	241 (96·0%)	102 (97·1%)	36 (87·8%)	103 (98·1%)
Hydroxychloroquine	381 (27·7%)	24 (11·2%)	11 (26·8%)	13 (7·5%)	219 (24·4%)	20 (8·0%)	5 (4·8%)	13 (31·7%)	2 (1·9%)
Biologics	364 (26·5%)	94 (43·7%)	13 (31·7%)	81 (46·6%)	245 (27·3%)	104 (41·4%)	46 (43·8%)	10 (24·4%)	48 (45·7%)
TNF inhibitors*	205 (14·9%)	49 (22·8%)	7 (17·1%)	42 (24·1%)	125 (13·9%)	41 (16·3%)	19 (18·1%)	5 (12·2%)	17 (16·2%)
IL-1 inhibitors†	4 (0·3%)	1 (0·5%)	0	1 (0·6%)	3 (0·3%)	1 (0·4%)	0	1 (2·4%)	0
IL-6 inhibitors‡	33 (2·4%)	6 (2·8%)	1 (2·4%)	5 (2·9%)	27 (3·0%)	11 (4·4%)	5 (4·8%)	1 (2·4%)	5 (4·8%)
IL-17 or IL-23 inhibitors§	51 (3·7%)	8 (3·7%)	0	8 (4·6%)	40 (4·4%)	19 (7·6%)	8 (7·6%)	1 (2·4%)	10 (9·5%)
Abatacept	31 (2·3%)	16 (7·4%)	3 (7·3%)	13 (7·5%)	19 (2·1%)	13 (5·2%)	5 (4·8%)	2 (4·9%)	6 (5·7%)
Rituximab	21 (1·5%)	8 (3·7%)	1 (2·4%)	7 (4·0%)	17 (1·9%)	9 (3·6%)	4 (3·8%)	0	5 (4·8%)
Belimumab	19 (1·4%)	6 (2·8%)	1 (2·4%)	5 (2·9%)	14 (1·6%)	10 (4·0%)	5 (4·8%)	0	5 (4·8%)
Conventional synthetic DMARDs	381 (27·7%)	76 (35·3%)	12 (29·3%)	64 (36·8%)	275 (30·6%)	106 (42·2%)	48 (45·7%)	11 (26·8%)	47 (44·8%)
Methotrexate	234 (17·0%)	57 (26·5%)	5 (12·2%)	52 (29·9%)	180 (20·0%)	84 (33·5%)	38 (36·2%)	7 (17·1%)	39 (37·1%)
Other conventional synthetic DMARDs¶	147 (10·7%)	19 (8·8%)	7 (17·1%)	12 (6·9%)	95 (10·6%)	22 (8·8%)	10 (9·5%)	4 (9·8%)	8 (7·6%)
Other DMARDs	13 (0·9%)	0	0	0	8 (0·9%)	0	0	0	0
Ciclosporin	2 (0·1%)	0	0	0	1 (0·1%)	0	0	0	0
Tacrolimus	11 (0·8%)	0	0	0	7 (0·8%)	0	0	0	0
Small molecules	64 (4·7%)	10 (4·7%)	1 (2·4%)	9 (5·2%)	49 (5·5%)	11 (4·4%)	3 (2·9%)	2 (4·9%)	6 (5·7%)
Apremilast	16 (1·2%)	2 (0·9%)	1 (2·4%)	1 (0·6%)	14 (1·6%)	2 (0·8%)	0	2 (4·9%)	0
JAK inhibitors‖	48 (3·5%)	8 (3·7%)	0	8 (4·6%)	35 (3·9%)	9 (3·6%)	3 (2·9%)	0	6 (5·7%)
Corticosteroids	170 (12·4%)	11 (5·1%)	4 (9·8%)	7 (4·0%)	103 (11·5%)	10 (4·0%)	3 (2·9%)	5 (12·2%)	2 (1·9%)
Prednisone	128 (9·3%)	8 (3·7%)	2 (4·9%)	6 (3·4%)	80 (8·9%)	7 (2·8%)	2 (1·9%)	4 (9·8%)	1 (1·0%)
Methylprednisolone	34 (2·5%)	3 (1·4%)	2 (4·9%)	1 (0·6%)	21 (2·3%)	3 (1·2%)	1 (1·0%)	1 (2·4%)	1 (1·0%)
Steroid injection	8 (0·6%)	0	0	0	2 (0·2%)	0	0	0	0

Data are n (%). Rows not mutually exclusive (ie, patients were able to select ≥1 option). DMARDs=disease-modifying antirheumatic drugs. IL=interleukin. JAK=Janus kinase. TNF=tumour necrosis factor. *Infliximab, etanercept, adalimumab, golimumab, certolizumab pego. †Anakinra, canakinumab, rilonacept. ‡Tocilizumab, sarilumab. §Secukinumab, ixekizumab, ustekinumab, guselkumab. ¶Azathioprine or mercaptopurine, leflunomide, mycophenolate mofetil or mycophenolic acid, sulfasalazine. ‖Baricitinib, tofacitinib, upadacitinib.

Table: **Immunomodulatory and immunosuppressive medication modifications among 1852 rheumatology patients at each COVID-19 vaccination**

Within these categories, tumour necrosis factor (TNF) inhibitors (22·8%) and methotrexate (26·5%) were the medications most commonly modified at the time of the first vaccine; and were more likely to be delayed or skipped before or after either vaccine dose rather than taken early (table). Patients and physicians were responsible for similar proportions of medication modifications at the first vaccine dose (appendix pp 1–2).

At the second vaccine dose, 251 (27·9%) of 899 medication schedules were modified. Medication categories accounting for modifications at the second vaccine dose included: conventional DMARDs (42·2%), biologics (41·4%), hydroxychloroquine (8·0%), small molecules (4·4%), corticosteroids (4·0%). 105 (41·8%) medications were delayed or skipped between the first and second dose, 41 (16·3%) medications were taken earlier than scheduled and 105 (41·8%) were delayed or skipped after the second vaccine dose (table). TNF inhibitors accounted for 16·3% of modifications and methotrexate accounted for 33·5% around the second vaccine dose (table). Modifications to other medications such as hydroxychloroquine, small molecules, other

biologics, and other conventional synthetic DMARDs also occurred (table). Patients were responsible for 49·4% of modifications at the second dose, 46·2% of modifications were advised by rheumatologists, and 4·4% by other physicians. Among immunosuppressive or immunomodulatory medications taken early before the second vaccine dose, 73·2% were initiated by patients. Rheumatologists were responsible for over half (52·4%) of medications that were delayed or skipped after the second vaccine dose (appendix pp 1–2).

In summary, up to 27·9% of immunomodulatory or immunosuppressive medications were modified around the time of COVID-19 vaccination, and patients were responsible for most of the overall modifications. A higher percentage of any immunosuppressive or immunomodulatory medications were modified around the second vaccine dose (27·9%) than the first dose (15·7%), perhaps suggesting that more adverse events were anticipated at the second vaccine dose,[3] or patients had enough time to make medication adjustments prior to a scheduled second dose. Modifications such as delaying or skipping methotrexate prior to either vaccine dose, or any modifications of TNF inhibitors or hydroxychloroquine, were not consistent with best practices as advised by the American College of Rheumatology task force. It is unknown how medication modification, much of which was done without physician oversight, might affect systemic rheumatic disease activity post-vaccination. Although our study assessed the timing of medication schedules and not changes in dosage, these data provide insight into patient behaviour and underscore the need for increased dissemination of evidence-based guidelines to inform patients and physicians of vaccine management decision-making. With the recent approval of a third vaccine booster dose in the USA for patients on immunosuppressive medications,[4] it is important to anticipate that patients with rheumatic disease might modify medications without physician oversight. Future studies are needed to assess the effect of medication modifications on systemic rheumatic disease activity post-vaccination.

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