RMD Open
Rheumatic & Musculoskeletal Diseases

LETTER

Does an adjustment to the dosing and timing of immunomodulatory drugs alter the immunogenicity of the COVID-19 vaccines in patients with autoimmune and inflammatory rheumatic disease (AIIRD)?

Andrew J Laster ,[1] Gordon K Lam,[1] Heather S Gladue,[1] Ahmad A Kashif,[1] Erin P Siceloff,[1] Virginia D Lackey,[1] Cheryl R Robertson,[1] Ashley L Toci,[1] Leonard H Calabrese [2]

To cite: Laster AJ, Lam GK, Gladue HS, *et al*. Does an adjustment to the dosing and timing of immunomodulatory drugs alter the immunogenicity of the COVID-19 vaccines in patients with autoimmune and inflammatory rheumatic disease (AIIRD)?. *RMD Open* 2022;**8**:e002203. doi:10.1136/rmdopen-2022-002203

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2022-002203).

Accepted 13 April 2022

Check for updates

© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

[1]Arthritis & Osteoporosis Consultants of the Carolinas, Charlotte, North Carolina, USA
[2]Rheumatology/Immunology, Cleveland Clinic, Cleveland, Ohio, USA

Correspondence to
Dr Andrew J Laster;
ajlaster@aocc.md

Clinical trials leading to approval of the COVID-19 vaccines did not include immunocompromised individuals. Concerns have been raised that immunogenicity of the vaccines may be impaired in patients with autoimmune and inflammatory rheumatic disease (AIIRD) on immunomodulatory drugs. In December of 2020, our clinic recommended adjustments to the dosing/timing of select drugs to attempt to optimise vaccine response. The ACR COVID-19 Vaccine Clinical Guidance Task Force first provided recommendations in February 2021.[1] Our recommendations were similar but differed in some key aspects (online supplemental table 1). In contrast, EULAR guidance states that 'pausing or reducing immunosuppression may increase the risk of flare, and therefore it is generally advised not to, or only temporarily, interrupt or decrease your medication for this purpose…'[2] As there is limited published data on the effects of adjustments to dosing and/or timing of immunomodulatory drugs in patients with AIIRD,[3] we sought to characterise antibody responses to the SARS-CoV-2 spike protein in those who adjusted and did not make adjustments to their drug therapy in a community based rheumatology practice in Charlotte, North Carolina.

We measured SARS-CoV-2 IgG antibody levels to the receptor-binding domain of the S1 spike antigen using a semiquantitative assay (Siemens Atellica; QUEST) in which a negative result is <1.00 and a positive result is reported as 1.00–20 or >20.[4] This assay had a Pearson correlation coefficient of 0.8 when compared with viral neutralisation titers.[5] All tests were performed by day 14 or later following completion of the two vaccine series using BNT162b2, mRNA-1273 or single dose Ad26COV2.S vaccine. Patients were excluded if they self-reported a prior clinical history of COVID-19 infection or if labs were drawn more than 6 months after their vaccine course was completed. We compared the number of antibody positive (Ab+) versus antibody negative(Ab−) and mean Ab levels in Ab+ patients for those who did or did not make adjustments to dosing/timing of methotrexate (MTX), JAK inhibitors (JAKi), rituximab (RTX) and/or abatacept (ABA). Continuous variables were analysed using a non-parametric Wilcoxon rank-sum test and categorical variables using either χ^2 or Fisher's exact test for association. Patients were not selected systematically but came to our attention during the course of routine clinical care. Patients with internet capability had been notified regarding vaccine dosing adjustments or when seen by their provider.

We studied 198 patients with AIIRD between 17 March and 14 May 2021. The mean age was 69 years and 77% were female. About 97% received the two dose mRNA vaccine series. About 77% of patients had RA. Additional baseline characteristics are provided in online supplemental table 2. There were no significant differences in age, gender, vaccine type or underlying disease for those who did or did not adjust their medication.

Table 1 Effect of adjustments to dose/timing of immunomodulatory drugs on serologic response to the COVID-19 vaccine

Drug	N	Total without antibody response (%)	Total with antibody response (%)	No adjust (% of subgroup)		Adjust (% of subgroup)		No adjust mean Ab* (SD)	Adjust mean Ab* (SD)	P value
				Ab–	Ab+	Ab–	Ab+			
Methotrexate (all)	110	27 (25%)	83 (75%)	16 (27%)	44 (73%)	11 (22%)	39 (78%)	12.08 (7.83)	10.76 (7.41)	0.340
Methotrexate (no biologic or JAKi)	51	10 (20%)	41 (80%)	6 (20%)	24 (80%)	4 (19%)	17 (81%)	12.92 (8.21)	8.79 (6.09)	0.087
JAK inhibitor	23	2 (9%)	21 (91%)	1 (8%)	11 (92%)	1 (9%)	10 (91%)	12.62 (7.85)	17.07 (4.73)	0.240
Rituximab	38	33 (87%)	5 (13%)	24 (89%)	3 (11%)	9 (82%)	2 (18%)	5.07 (2.55)	11.28 (12.33)	1.00
Abatacept	27	13 (48%)	14 (52%)	5 (45%)	6 (55%)	8 (50%)	8 (50%)	10.14 (5.29)	13.65 (8.81)	0.340
Abatacept intravenous	20	11 (55%)	9 (45%)	4 (67%)	2 (33%)	7 (50%)	7 (50%)	5.40 (2.95)	12.74 (9.11)	0.467
Abatacept subcutaneous	7	2 (29%)	5 (71%)	1 (25%)	4 (75%)	1 (50%)	1 (50%)	12.51 (4.61)	20.00 (-)	

* refers only to those patients who were antibody positive

Findings related to percentage of total patients on MTX, JAKi, RTX and ABA with absent antibody response and comparison of antibody response with or without adjustment in dosing and/or timing are presented in table 1.

The mean time from completion of the vaccine series to measurement of antibodies was 50 days. Only 13% of all patients on RTX and 52% of all patients on ABA were Ab+. In contrast, fully 91% of patients on JAKi were Ab+ whereas 80% of patients on methotrexate alone were Ab+. Adjustments to the dose of MTX or JAKi did not significantly alter the immunogenicity as measured by IgG antibodies to the S1 spike antigen. Adjustments to the timing of vaccine in relationship to last RTX dose and last vaccine injection in relation to next RTX infusion failed to increase the likelihood of an antibody response. Adjustments to the timing of ABA (either intravenous or subcutaneous) did not significantly increase antibody response. These findings were not influenced by age of the patient, time from last vaccine dose to measurement of antibody levels, percentage of patients on steroids or the mean steroid dose (table 2).

Only 62% (123/198) of the patients reported in this cohort were seropositive for SARS-CoV-2 spike protein. This is significantly lower than the 90%–95% range of seroconversion seen in other studies[6 7] Our patient population was also much older and had a significantly greater number of patients on rituximab and abatacept. We have previously shown that vaccine response is age dependent and in a multiple regression analysis declines by 5% with every advancing decade.[8] Low rates of seropositivity are by now well recognised for patients on rituximab.[7 9 10] Our patients on rituximab had a mean age of 68. The mean time from last rituximab infusion to first vaccine dose was 146 days (range: 106–211 days; SD: 35.34) in the 11 patients who adjusted rituximab and 53 days (range: 10–96 days; SD: 23.83) in the 27 patients who did not adjust. It is now apparent that holding vaccine dose until peripheral B cells repopulate (at least 9 months and often up to 12 months)[11 12] is often required before seroconversion occurs. Information is more limited for abatacept.[11] We did see a lower rate of seroconversion for intravenous abatacept (45%) versus subcutaneous abatacept (71%) which may in part be due to the older age in the intravenous group(69 vs 56, respectively).

Our initial recommendation to reduce the dose of methotrexate to 7.5 mg per week for 2 weeks following each vaccine dose differs from the ACR recommendation that methotrexate should be held for 1 week after each vaccine dose. This is based on our reading of the Park study which indicated that a dose of ≤7.5 mg methotrexate per week for 2 weeks following the influenza vaccine resulted in comparable vaccine response to the four influenza antigens studied as did holding methotrexate for 2 weeks (see Park *et al*, figure 3).[13] As the COVID-19 mRNA vaccines required two doses, we also reasoned that the lower dose of methotrexate versus stopping methotrexate for 2 weeks would be less likely to result in disease flare.

This study has a number of limitations. We did not measure antibodies to the nucleocapsid protein but relied on the patients' self-reported history of COVID-19 infection. The study was not randomised as to who adjusted and did not make adjustments to

Table 2 Potential confounders

Drug	N	Mean age			Mean time from vaccine to antibody testing in days (range; SD)			N on prednisone (% of total on prednisone)			Mean prednisone dose in mg of those on prednisone		
	Total	No adjust	Adjust	P value	No adjust	Adjust	P value	No adjust	Adjust	P value	No adjust	Adjust	P value
Methotrexate (all)	110	67	66	0.52	46	58	0.02	11	9	0.96	5.6	4.7	0.60
		(13)	(13)		(14–95; 23)	(19–113; 26)		(**18**)	(**18**)				
Methotrexate	51	68	68	0.96	45	56	0.11	5	3	1.00	7	5	0.36
(no biologic or JAK inhibitor)		(12)	(12)		(16–95; 23)	(20–104; 26)		(17)	(14)				
JAK inhibitor	23	58	60	0.95	41	34	0.32	0	1	0.48	N/A	7	–
		(16)	(14)		(14–83; 18)	(15–63; 15)			(8)				
Rituximab	38	67	69	0.91	53	44	0.36	8	6	0.27	7.2	3.7	0.11
		(11)	(7)		(17–109; 26)	(17–86; 23)		(30)	(55)				
Abatacept	27	68	64	0.64	56	48	0.70	2	4	1.00	5.5	4.4	0.32
		(13)	(17)		(26–96; 24)	(14–79; 22)		(18)	(25)				
Abatacept intravenous	20	72	68	0.60	62	54	0.60	1	3	1.00	6	4.2	0.42
		(4)	(15)		(26–96; 27)	(14–79; 21)		(17)	(21)				
Abatacept subcutaneous	7	62	41	0.22	48	27	0.28	1	1	1.00	5	5	–
		(14)	(18)		(32–86; 22)	(19–35; 11)		(20)	(50)				

their medication although this did not appear to affect outcomes. We did not control for patients on RTX and ABA who were on additional immunosuppressive therapies aside from prednisone and sample size was relatively small for several of the drugs studied. Finally, we do not provide any data on cellular immune responses.

This study suggests that holding JAKi, lowering the dose of MTX or altering the timing of the vaccine in relation to RTX or ABA administration did not alter immunogenicity as measured by SARS-CoV-2 Abs to the S1 spike antigen. Although these findings may assist in future recommendations for dosing and timing of immunomodulatory therapies in the setting of COVID-19 vaccinations including boosters in patients with AIIRD, conclusive evidence for this question can only be provided by well controlled prospective randomised clinical trials.

Acknowledgements Maggie S.J. McCarter MSPH for statistical analysis; Clifton O. Bingham III MD for early guidance regarding adjustment to dosing and timing of immunomodulatory drugs.

Contributors Substantial contributions to the conception and design of the study or the acquisition, analysis or interpretation of data for the work were done by AJL, GKL and LHC. Substantial contribution of patient cases for inclusion in the study was given by AJL, GKL, HSG, AAK, EPS, VDL, CRR and ALT. Drafting the work or revising it critically for important intellectual content was performed by AJL, GKL and LHC. Final approval of the version to be published was given by all the authors (AJL, GKL, HSG, AAK, EPS, VDL, CRR, ALT, LHC).

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests AJL has the following relevant financial disclosures: consulting and speaking honoraria from Amgen, Lilly, Novartis, Pfizer, Roche/Genentech, Sanofi. GKL has the following relevant financial disclosures: consulting and speaking honoraria from Abbvie, Astra Zeneca, BMS, GSK, Horizon, Janssen, Pfizer, UCB. HSG has the following relevant financial disclosures: consulting and speaking honoraria from Astra Zeneca, GSK. LHC has the following relevant financial disclosures: consulting and speaking honoraria from Astra Zeneca, BMS, GSK, Janssen, Regeneron, Sanofi.

Patient consent for publication Not applicable.

Ethics approval This study was exempt from IRB approval because it was merely a descriptive case series that was deemed to be not greater than minimal risk to the participants as defined by US federal regulations as the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives or in the routine medical, dental or psychological examination of patients. Furthermore, this study did not involve the administration or use of drugs or devices. Lastly, all data were recorded in a manner such that all participants could not be readily identified (directly or indirectly), and the investigators did not contact the subjects and will not reidentify the subjects. Formal informed consent was not obtained because this study was exempt from IRB approval under qualifications as outlined above. However, all participants agreed to having their SARS-CoV-2 spike antibody checked as part of routine medical care. Doing so represented no more than minimal risk and did not adversely affect the rights and welfare of the patients. All participants were offered additional pertinent information after participation.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Andrew J Laster http://orcid.org/0000-0002-5035-5032
Leonard H Calabrese http://orcid.org/0000-0002-1789-4923

REFERENCES

1 COVID-19 vaccine clinical guidance summary for patients with rheumatic and musculoskeletal diseases. Available: https://www.rheumatology.org/Portals/0/Files/COVID-19-Vaccine-Clinical-Guidance-Rheumatic-Diseases-Summary.pdf
2 EULAR View-points on SARS-CoV-2 vaccination in patients with RMDs. Available: https://www.eular.org/eular_sars_cov_2_vaccination_rmd_patients.cfm [Accessed 20 Feb 2022].
3 Connolly CM, Chiang TP-Y, Boyarsky BJ. Temporary hold of mycophenylate augments humeral response to SARS-CoV-2 vaccination in patients with rheumatic and musculoskeletal diseases: a case series. *Ann Rheum Dis* 2021. doi:10.1136/annrheumdus-2021-221252
4 SARS-CoV-2 IgG assays. Available: https://www.siemens-healthineers.com/en-us/laboratory-diagnostics/assays-by-diseases-conditions/infectious-disease-assays/sars-cov-2-igg-assay
5 Evaluation of the enhanced SARS-CoV-2 IgG (sCOVG) Assay* on the Atellica Im analyzer. Available: https://cdn0.scrvt.com/39b415fb07de4d9656c7b516d8e2d907/8574c66edc7a2af7/d4c3e7ac8d63/Evaluation-of-Enhanced-sCOVG-Assay-on-Atellica-IM-Analyzer.pdf
6 Ruddy JA, Connolly CM, Boyarsky BJ, *et al*. High antibody response to two-dose SARS-CoV-2 messenger RNA vaccination in patients with rheumatic and musculoskeletal diseases. *Ann Rheum Dis* 2021;80:1351–2.
7 Deepak P, Kim W, Paley M. Glucocorticoids and B cell depleting agents substantially impair immunogenicity of mRNA vaccines to SARS –CoV-2. *Ann Intern Med*.
8 Lam G, Laster A, McCarter S. Immunogenicity of COVID-19 vaccines in patients with autoimmune and inflammatory rheumatic diseases (AIIRDs) [abstract]. *Arthritis Rheumatol* 2021;73 https://acrabstracts.org.abstract/immunogenicity-of-covid-19-vaccines-in-patients-with-autoimmune-and-inflammatory-rheumatic-diseases-aiirds
9 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.
10 Bitoun S, Henry J, Desjardins D, *et al*. Rituximab impairs B cell response but not T cell response to COVID-19 vaccine in autoimmune diseases. *Arthritis Rheumatol* 2021. doi:10.1002/art.42058. [Epub ahead of print: 28 Dec 2021].
11 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.
12 Jyssum I, Kared H, Tran TT, *et al*. Humoral and cellular immune responses to two and three doses of SARS-CoV-2 vaccines in rituximab-treated patients with rheumatoid arthritis: a prospective, cohort study. *Lancet Rheumatol* 2022;4:e177–87.
13 Park JK, Lee YJ, Shin K, *et al*. Impact of temporary methotrexate discontinuation for 2 weeks on immunogenicity of seasonal influenza vaccination in patients with rheumatoid arthritis: a randomised clinical trial. *Ann Rheum Dis* 2018;77:898–904.