Vaccine Hesitancy in Patients with Autoimmune Diseases: Data from the Coronavirus Disease-2019 Vaccination in Autoimmune Diseases Study

Dear Editor,

The ongoing COVID-19 pandemic continues to be a cause of unprecedented morbidity and mortality. Vaccination provides a ray of hope as a powerful tool for reducing the poor clinical outcomes of COVID-19. Current evidence indicates that patients with systemic autoimmune rheumatic diseases (AIRD) are at an increased risk of severe COVID-19 clinical outcomes. This emphasizes the importance of COVID-19 vaccination in this patient group.[1-3] However, a high degree of vaccine hesitancy continues to be an obstacle against vaccination in patients with autoimmune diseases.

The exclusion of patients with AIRD from COVID-19 vaccine trials inevitably resulted in gaps in the evidence about the long-term safety and efficacy of COVID-19 vaccination. This, unsurprisingly gave rise to fears of disease flares and adverse effects associated with vaccination in an already vulnerable patient group, as well as health-care professionals, increasing vaccine hesitancy.[4,5]

The COVID-19 Vaccination in Autoimmune Diseases (COVAD) study is a long-term ongoing global patient self-report electronic survey study to assess the safety of the COVID-19 vaccine in idiopathic inflammatory myopathies and other AIRDs and nonautoimmune controls.[6] The survey questions were designed to evaluate previous COVID-19 infection, and current vaccination status including reasons for not getting vaccinated. Informed consent was obtained at the beginning of the survey, and no incentives were offered for survey completion. Ethical approval was obtained from the Institutional Ethics Committee of Sanjay Gandhi Postgraduate Institute of Medical Sciences, as per the local guidelines.[7] We report the data from the baseline survey until August 2021. We adhered to the Checklist for Reporting Results of Internet e-surveys to report the data.[8,9]

In the initial results of the ongoing study, we observed a high degree of vaccine hesitancy in the total of 16,327 respondents. Out of the 2426 (14.86%) respondents who had not received any doses of the COVID-19 vaccine, 411 (16.94%) reported that they would not take the vaccine due to long-term safety concern or fear and 666 (27.45%) said that they were planning to wait for more data on the safety of the vaccine before taking it. This indicates an unwillingness to take the vaccine despite its availability and in the absence of any medical advice against vaccination. These results were comparable across patients with AIRD and non-autoimmune controls.

As of August 2021, the COVAD study has accrued over 16,327 responses with complete responses from 5868 patients with AIRD and 5034 individuals without AIRD, from 29 countries. This makes it one of the largest international databases of information regarding the effects of COVID-19 vaccination in this patient group, with a wide representation of individuals across a spectrum of different regions and ethnicities.

The other reasons respondents gave for not receiving the vaccine was its lack of availability in some parts of the world (32.0%), being scheduled for vaccination at a later date (11.67%), and vaccination not being recommended due to recent COVID-19 infection (7.3%). Some patients also reported not taking the vaccine after being advised against vaccination by their treating physician (5.4%). The proportion of respondents selecting each reason for not receiving the vaccine remained consistent across two different points of data retrieval between July and August 2021 and among patients with AIRD and nonautoimmune controls.

Approximately half the respondents who had not received any dose of the COVID-19 vaccine, reported unwillingness to take the COVID-19 vaccine due to concerns about the lack of data on its long term safety, and fears of delayed adverse effects.

Similar patterns of COVID-19 vaccine hesitancy have emerged in other studies. In a recent international cluster analysis study of 1258 patients with AIRD published in May 2021, over 40% of patients reported that they would decline the vaccine. Interestingly, the predominant differences between the clusters of patients who would take the vaccine and those who would not, were not related to the fear of COVID-19 infection or any state of frailty, but to specific concerns about vaccination. These included the use of the new mRNA vaccine technology, lack of long-term safety data, and potential financial risks with pharmaceutical companies.[10] In the Vaccinations Against COVID-19 study which included 1266 patients with AIRDs and 265 health-care professionals from 56 countries, concerns regarding the adverse effect profile of the SARS-CoV-2 mRNA vaccines were identified as the primary concern resulting in patients' vaccine hesitancy. Over half of the patients with rheumatic and musculoskeletal diseases (RMD) were uncertain or unwilling to take the COVID-19 mRNA vaccines due to the paucity of data.[11] Similar results were obtained from a recent interview based study involving 280 patients with AIRD, 46% of whom were unwilling to get vaccinated, primarily due to fear related to vaccine adverse effects and disease worsening. However, only 35% of the vaccinated subjects had mild adverse effects (fever/headache/myalgia). AIRD

patients, interestingly, had fewer adverse effects than the controls, with a flare up observed in only one patient.[12]

The results from recent international studies indicate that the risk of severe adverse reactions or disease flares postvaccination is negligible.[13] Postvaccination disease flares were reported in only 5%, and severe disease flares in 1.2% of patients with RMDs from the data from the European League Against Rheumatism (EULAR) COVID-19 Vaccination Registry.[14] In the Vaccination Against COVID-19 in Lupus survey, a flare was observed in only 3% of the patients with systemic lupus erythematosus. Similarly, in the Global Rheumatology Alliance COVID-19 Vaccination survey, a flare lasting at least 2 days was reported only in 13.4% patients with RMD, and a new or increased dose of medication after a flare only in 4.6% of the patients.[15] A recent study on the postvaccination adverse effects in 325 adults with RMDs (38% inflammatory arthritis, 28% systemic lupus erythematosus, and 19% overlap connective tissue disease) who had received the first dose of a SARS-CoV-2 mRNA vaccine (51% Pfizer/BioNTech and 49% Moderna) at Johns Hopkins University in the USA reported only local symptoms including pain, swelling, and erythema in 89% of the patients. Systemic symptoms were reported in 69% of the patients. None of the patients experienced allergic reactions requiring epinephrine, and only 3% reported new infections requiring treatment. These results were consistent with the local and systemic adverse effects reported in the vaccine trials.[16,17] These reassuring results may ameliorate some of the concerns regarding postvaccination adverse effects in patients with AIRDs.

What is important to consider is that the potential risk of COVID-19 vaccination-related disease flares and adverse effects is far outweighed by the well-documented risks of severe COVID-19 clinical outcomes and hospitalization from COVID-19 infection, which vaccination can help offset. Therefore, both the American College of Rheumatology (ACR) and EULAR strongly recommend COVID-19 vaccination in patients with AIRD.[18,19] The most recent ACR Guidance statements on COVID-19 vaccination in patients with RMD showed consensus that patients with RMD were at a higher risk of COVID-19 infection, hospitalization and worse outcomes compared to the general population, and strong consensus that patients with RMD should be offered COVID-19 vaccination.

There is certainly an unmet need for further research into the long-term safety and efficacy of COVID-19 vaccination in patients with AIRD. We hope that further analysis of the large sample population of the COVAD study database paves the way for better understanding and further insights into this aspect of the pandemic.[20] However, the current evidence strongly suggests that vaccination offers the potential to directly protect patients with AIRD from morbidity and mortality. Thus, there is a clear need for effective and consistent communication with patients with AID, emphasizing that the benefit of COVID-19 vaccination far outweighs the potential risk of disease flares and adverse effects, the majority of which are mild and manageable.[21,22] The need for effective communication of credible, evidence-based information on vaccine safety and efficacy is becoming increasingly important to counter a wave of rising anti-vaccination movements. Despite being based on erroneous hypotheses and misinformation, these movements are becoming dangerously popular.[22] Communication and education through social media can play a pivotal role in effectively combating this spread of misinformation.[22,23]

Further contributing to vaccine hesitancy in AIRD patients is the hesitancy among treating doctors and vaccination center staff, whose expressions of uncertainty regarding vaccination safety reinforces their patients' concerns. Thus, there is an urgent need to educate health-care professionals in all countries about vaccination safety in patients with autoimmune diseases, encouraging those providers to promote this message among the patients under their care.[24] This is especially important, because treating physicians are often the most trusted people by the patients under their care.[10]

Acknowledgments

The authors thank all respondents for filling the questionnaire. The authors thank The Myositis Association, Myositis India, Myositis UK, the Myositis Global Network, Cure JM, Cure IBM, Sjögren's India Foundation, EULAR PARE, and various other patient support groups and organizations for their invaluable contribution in the dissemination of this survey among patients which made the data collection possible. The authors also thank all members of the COVAD study group.

Financial support and sponsorship

HC is supported by the National Institution for Health Research Manchester Biomedical Research Center Funding Scheme. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

Conflicts of interest

OD has/had consultancy relationship with and/or has received research funding from or has served as a speaker for the following companies in the area of potential treatments for systemic sclerosis and its complications in the last 3 years: Abbvie, Acceleron, Alcimed, Amgen, AnaMar, Arxx, Baecon, Blade, Bayer, Boehringer Ingelheim, ChemomAb, Corbus, CSL Behring, Galapagos, Glenmark, GSK, Horizon (Curzion), Inventiva, iQvia, Kymera, Lupin, Medac, Medscape, Mitsubishi Tanabe, Novartis, Roche, Roivant, Sanofi, Serodapharm, Topadur and UCB.

Patent issued "mir-29 for the treatment of systemic sclerosis" (US8247389, EP2331143).

Parikshit Sen, James B. Lilleker[1,2], Vishwesh Agarwal[3], Sinan Kardes[4], Marcin Milchert[5], Tamer Gheita[6], Babur Salim[7], Tsvetelina Velikova[8], Abraham Edgar Gracia-Ramos[9], Ioannis Parodis[10,11], Albert Selva O'Callaghan[12], Elena Nikiphorou[13,14], Ai Lyn Tan[15,16], Lorenzo Cavagna[17], Miguel A Saavedra[18], Samuel Katsuyuki Shinjo[19], Nelly Ziade[20,21], Johannes Knitza[22], Masataka Kuwana[23], Giovanni Cagnotto[24,25], Arvind Nune[26], Oliver Distler[27], Hector Chinoy[28,29,30], Rohit Aggarwal[31], Latika Gupta[32]

Maulana Azad Medical College, New Delhi, [3]Mahatma Gandhi Mission Medical College, Navi Mumbai, Maharashtra, [32]Department of Clinical Immunology and Rheumatology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, Uttar Pradesh, India, [1]Centre for Musculoskeletal Research, Division of Musculoskeletal and Dermatological Sciences, School of Biological Sciences, Faculty of Biology, Medicine and Health, Manchester Academic Health Science Centre, The University of Manchester, Manchester, [2]Manchester Centre for Clinical Neurosciences, Salford Royal NHS Foundation Trust, [30]Department of Rheumatology, Manchester Academic Health Science Centre, Salford Royal NHS Foundation Trust, Salford, [13]Centre for Rheumatic Diseases, King's College London, [14]Department of Rheumatology, King's College Hospital, London, [15]NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals Trust, [16]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, [26]Southport and Ormskirk NHS Trust, Southport, PR8 6PN, [28]Division of Musculoskeletal and Dermatological Sciences, Centre for Musculoskeletal Research, School of Biological Sciences, The University of Manchester, [29]National Institute for Health Research Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, The University of Manchester, Manchester, UK, [4]Department of Medical Ecology and Hydroclimatology, Istanbul Faculty of Medicine, Istanbul University, Capa-Fatih, Istanbul, Turkey, [5]Department of Rheumatology, Internal Medicine, Geriatrics and Clinical Immunology, Pomeranian Medical University, Szczecin, Poland, [6]Department of Rheumatology, Kasr Al Ainy School of Medicine, Cairo University, Cairo, Egypt, [7]Department of Rheumatology, Fauji Foundation Hospital, Rawalpindi, Pakistan, [8]Department of Clinical Immunology, Medical Faculty, University Hospital "Lozenetz," Sofia University St. Kliment Ohridski, Sofia, Bulgaria, [9]Department of Internal Medicine, General Hospital, National Medical Center "La Raza", IMSS, Mexico City, Mexico, [18]Department of Rheumatology, Dr Antonio Fraga Mouret Speciality Hospital, National Medical Center "La Raza", IMSS, Mexico City, Mexico, [10]Department of Medicine, Division of Rheumatology, Karolinska Institutet, Karolinska University Hospital, Solna, Stockholm, [11]Department of Rheumatology, Faculty of Medicine and Health, Örebro University, Örebro, [24]Rheumatology, Department of Clinical Sciences, Lund University, Malmö, [25]Department of Rheumatology, Skåne University Hospital, Lund, Sweden, [12]Department of Internal Medicine, Vall D'hebron General Hospital, Autonomous University of Barcelona. Barcelona, Spain, [17]Department of Internal Medicine and Therapy, Rheumatology Unit, The University of Pavia, Pavia, Lombardy, Italy, [19]Division of Rheumatology, Faculty of Medicine FMUSP, University of Sao Paulo, Sao Paulo, SP, Brazil, [20]Department of Rheumatology, Saint-Joseph University, [21]Department of Rheumatology, Hotel-Dieu de France Hospital, Beirut, Lebanon, [22]Medical Clinic 3- Rheumatology and Immunology, University Hospital Erlangen, Friedrich-Alexander University, Erlangen, Nuremberg, Germany, [23]Department of Allergy and Rheumatology, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan, [27]Department of Rheumatology, University Hospital Zurich, University of Zurich, Zurich, Switzerland, [31]Division of Rheumatology and Clinical Immunology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

Address for correspondence: *Dr. Latika Gupta, Department of Clinical Immunology and Rheumatology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Rae Bareilley Road, Lucknow - 226 014, Uttar Pradesh, India. E-mail: drlatikagupta@gmail.com*

Received: 26-Sep-2021
Revised: 01-Nov-2021
Accepted: 07-Nov-2021
Published: 04-Mar-2022

References

1. Anderson RM, Vegvari C, Truscott J, Collyer BS. Challenges in creating herd immunity to SARS-CoV-2 infection by mass vaccination. Lancet 2020;396:1614-6.
2. Velikova T, Georgiev T. SARS-CoV-2 vaccines and autoimmune diseases amidst the COVID-19 crisis. Rheumatol Int 2021;41:509-18.
3. Gianfrancesco M, Hyrich KL, Al-Adely S, Carmona L, Danila MI, Gossec L, *et al.* Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: Data from the COVID-19 global rheumatology alliance physician-reported registry. Ann Rheum Dis 2020;79:859-66.
4. Gupta L, Lilleker JB, Agarwal V, Chinoy H, Aggarwal R. COVID-19 and myositis – Unique challenges for patients. Rheumatology (Oxford) 2021;60:907-10.
5. Gupta L, Kharbanda R, Agarwal V, Misra DP, Agarwal V. Patient perspectives on the effect of the SARS-CoV-2 pandemic on patients with systemic sclerosis: An international patient survey. J Clin Rheumatol 2021;27:31-3.
6. Sen P, Gupta L, Lilleker JB, Agarwal V, Kardes S, Milchert M. COVID-19 vaccination in autoimmune disease (COVAD) study protocol. Rheumatol Int Published online November 15, 2021. doi: 10.1007/s00296-021-05046-4.
7. Available from: https://main.icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf. [Last accessed on 2021 Aug 16].
8. Eysenbach G. Improving the quality of web surveys: The checklist for reporting results of internet E-surveys (CHERRIES). J Med Internet Res 2004;6:e34.
9. Gaur PS, Zimba O, Agarwal V, Gupta L. Reporting survey based studies – A primer for authors. J Korean Med Sci 2020;35:e398.
10. Felten R, Dubois M, Ugarte-Gil MF, Chaudier A, Kawka L, Bergier H, *et al.* Cluster analysis reveals three main patterns of beliefs and intention with respect to SARS-CoV-2 vaccination in patients with autoimmune and inflammatory diseases. Rheumatology (Oxford) 2021;60:I68-76.
11. Felten R, Dubois M, Ugarte-Gil MF, Chaudier A, Kawka L, Bergier H, *et al.* Vaccination against COVID-19: Expectations and concerns of patients with autoimmune and rheumatic diseases. Lancet Rheumatol 2021;3:e243-5.
12. Gaur P, Agrawat H, Shukla A. COVID-19 vaccine hesitancy in patients with systemic autoimmune rheumatic disease: An interview-based survey. Rheumatol Int 2021;41:1601-5.
13. Tariq J, Gupta L. Safety and efficacy of COVID-19 vaccines in pregnant women with rheumatic diseases: An immunologic perspective. Rheumatol Int 2021;41:1545-7.
14. Machado PM, Lawson-Tovey S, Hyrich K, Carmona L, Gossec L, Mateus E, *et al.* Lb0002 COVID-19 vaccine safety in patients with rheumatic and musculoskeletal disease. Ann Rheum Dis 2021;80 Suppl 1:199-200.
15. Felten R, Kawka L, Dubois M, Ugarte-Gil MF, Fuentes-Silva Y,

Piga M, *et al.* Tolerance of COVID-19 vaccination in patients with systemic lupus erythematosus: The international VACOLUP study. Lancet Rheumatol 2021;3:e613-5.
16. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, *et al.* Safety and efficacy of the BNT162b2 mRNA COVID-19 vaccine. N Engl J Med 2020;383:2603-15.
17. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, *et al.* Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med 2021;384:403-16.
18. EULAR | EULAR Sars Cov 2 Vaccination RMD Patients. Available from: https://www.eular.org/eular_sars_cov_2_vaccination_rmd_patients.cfm. [Last accessed on 2021 Aug 10].
19. Curtis JR, Johnson SR, Anthony DD, Arasaratnam RJ, Baden LR, Bass AR, *et al.* American college of rheumatology guidance for COVID-19 vaccination in patients with rheumatic and musculoskeletal diseases: Version 1. Arthritis Rheumatol 2021;73:1093-107.
20. Sonani B, Aslam F, Goyal A, Patel J, Bansal P. COVID-19 vaccination in immunocompromised patients. Clin Rheumatol 2021;40:797-8.
21. Soy M, Keser G, Atagunduz P, Mutlu MY, Gunduz A, Koybaşi G, *et al.* A practical approach for vaccinations including COVID-19 in autoimmune/autoinflammatory rheumatic diseases: A non-systematic review. Clin Rheumatol 2021;40:3533-45.
22. Khan H, Gasparyan AY, Gupta L. Lessons learned from publicizing and retracting an erroneous hypothesis on the mumps, measles, rubella (MMR) vaccination with unethical implications. J Korean Med Sci 2021;36:e126.
23. Goel A, Gupta L. Social media in the times of COVID-19. J Clin Rheumatol 2020;26:220-3.
24. Morales-Torres J, Aceves-Ávila FJ. Rheumatologists in the COVID-19 era: Will there be a new role for the rheumatologist in the care of rheumatic patients? Clin Rheumatol 2020;39:3177-83.

Access this article online

Website: www.indianjrheumatol.com

Quick Response Code

DOI: 10.4103/injr.injr_221_21

How to cite this article: Sen P, Lilleker JB, Agarwal V, Kardes S, Milchert M, Gheita T, *et al.* Vaccine hesitancy in patients with autoimmune diseases: Data from the coronavirus disease-2019 vaccination in autoimmune diseases study. Indian J Rheumatol 2022;17:188-91.