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Safety of the ChAdOx1 nCoV-19 and the BBV152 vaccines in 724 patients with rheumatic diseases: a post-vaccination cross-sectional survey

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Abstract

Patients with rheumatic and musculoskeletal (RMD) diseases may be at higher risks for COVID-19 infection. Data on the safety of the adenoviral vector-borne ChAdOx1 nCoV-19 and the heat-inactivated BBV152 Vaccines in this group are limited. 724 patients with RMD who had received at least one dose of either the ChAdOx1 or the BBV152 were audited to find out post-vaccination adverse effect (AE) or disease flares. The AE rates in patients with autoimmune rheumatic disease (AIRD) were compared with those with non-AIRD RMDs. The mean age of the cohort was 59.9 (± 10.43) years with a female ($n = 581$; 80.24%) majority. 523 (70.8%) had AIRD. The ChAdOx1 and the BBV152 vaccines were received by 624 (86.18%) and 77 (10.63%), respectively. 23 (3.17%) were unaware of which vaccine they had received. 238 (32.87%) of patients had at least one comorbidity. 436 (60.22%) participants [306 (59.64%) of those with AIRD and 130 (61.61%) with other RMDs] had at least one adverse effect (AE). Four patients reported flare of arthritis that resolved within 5 days. No patient had any severe AE or required hospitalization. All AEs were self-limiting. Both the ChAdOx1 and the BBV152 vaccines appear safe in RMDs. AEs do not differ between patients with AIRD or non-AIRD. This information can help negate vaccine hesitancy amongst all stakeholders.

Keywords Rheumatic diseases · Vaccination · Adenoviral vector · Adjuvant · Immunosuppressants · Adverse effects · Vaccine safety

Introduction

The underlying immune dysregulation in various autoimmune rheumatic diseases (AIRD) is a potential risk for prolonged viremia and severe novel coronavirus disease 2019 (COVID-19) [1]. Thus, they may be at higher risk of COVID-19 [2]. Higher rheumatic disease activity can be a risk for severe disease [3, 4]. Also, patients with RMDs have higher comorbidities or multi-morbidity that puts them at higher risk for COVID-19 [5]. Preliminary guidelines from the American College of Rheumatology (ACR) state that patients with rheumatic and musculoskeletal diseases (RMD) should be prioritized for COVID-19 vaccination as compared to the general population of similar age and sex [6].

In contrast to the western hemisphere where the mRNA-based vaccines (Moderna and Pfizer-BioNTech) have been used, India had started vaccination with the Oxford/AstraZeneca ChAdOx1 nCoV-19 vaccine (COVISHIELD), and the Indian indigenous heat-killed BBV152 vaccine (COVAXIN). The ChAdOx1 nCoV-19 vaccine (AZD1222) is a non-replicating chimpanzee adenoviral vector ChAdOx1, carrying the SARS-CoV-2 structural surface glycoprotein antigen (spike protein) gene [7]. BBV152 is an inactivated whole-virion adsorbed to alum with a toll-like receptor 7/8 agonist molecule (IMDG) as adjuvant [8]. In India, more than 135 million doses of two vaccines have been administered [9].

Patients with autoimmune rheumatic diseases (AIRD) on immunosuppressants have been excluded from

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COVID-19 vaccine trials including those for the ChAdOx1 nCoV-19 vaccine, and the heat-inactivated BBV152 vaccine [7, 8]. Now, preliminary data on the safety of the mRNA vaccines in patients with RMD are available [10, 11]. However, safety data regarding the use of the ChAdOx1 nCoV-19 vaccine and the BBV152 vaccine in patients with RMD are very limited. The presence of adjuvants in both can theoretically flare rheumatic diseases. Also, the viral proteins themselves may have a risk of flaring AIRD. There are also reports of thrombosis associated with the ChAdOx1 vaccine [12] that may be increased in patients with AIRDs due to various.

Thus, we surveyed patients with RMD who had received either of these vaccines for safety issues in terms of vaccine reactivity or disease flare.

Methods

We collated data from RMD patients who had received the first dose of either the ChAdOx1 nCoV-19 vaccine or the BBV152 vaccine up to the 10th of May, 2021. Data were collected on the seventh day after vaccination and included demographic, RMD diagnosis with known comorbidities, current treatment and peri-vaccination status (whether there was flare). Flare was defined as requiring (1) addition of non-steroidal anti-inflammatory drug, (2) addition of or a hike in corticosteroids or any other immunosuppressant in any patient who had been on a stable dose in the preceding 2 months before vaccination.

Ethics clearance was obtained from the Institutional Ethics Committee of Sree Sudheendra Medical Mission Hospital [No IEC/2021/35] on 15/03/2021.

As per the requirement of the Indian Council of Medical Research Ethics for biomedical research during the COVID-19 pandemic, verbal informed consent was taken from patients since this was an audit of safety [13]. The cohort included both patients on regular follow-up at our center and who were consulted via telemedicine as per our previous methodology [14].

Since patients with AIRD have immune dysregulation and were more likely to have an altered response to the vaccines, they were analyzed as a separate group. The patients with non-AIRD RMDs helped to serve as controls.

All analyses were done on SPSS version 23. The normality of the data was confirmed by the Shapiro–Wilk test. Fischer's Exact test was used to compare between proportions. For continuous data, the independent *t* test was used after confirmation of data normality.

Results

We recruited 724 patients, 513 (70.8%) of whom had AIRD while the remaining 211 patients had non-autoimmune RMD. These patients were on regular follow-up at our center and were contacted in person ($n=607$, 83.83%) or via telemedicine ($n=117$, 16.16%). The mean (SD) age was 59.9 (10.43) years and the majority ($n=581$; 80.24%) were females. 624 (86.18%) had received the ChAdOx1 nCoV-19 vaccine while 77 (10.63%) had received the BBV152 vaccine. 23 (3.17%) were unaware of which vaccine they had received. There was no difference between the AIRD and the non-inflammatory RMDs except for drug usage (Table 1).

238 (32.87%) had at least one comorbidity while 140 (19.23%) had more than one comorbidity. After the first dose, 436 (60.22%) participants [306 (70.17%) AIRD and 130 (61.61%) other RMDs] had at least one adverse effect (AE), none of which was severe enough to require hospitalization (Table 2). 592 (81.76%) patients had reported using at least one adult dose of acetaminophen after receiving the vaccine. As per government policy, two acetaminophen tablets were dispensed per patient in all designated vaccine centers and they were advised to take one dose of acetaminophen 3 h after vaccination and another tablet the next day if they develop any adverse events.

All the reported AEs lasted less than 48 h except for four patients who developed increased joint pains post vaccination requiring non-steroidal anti-inflammatory drugs (NSAIDs) for a couple of days more. None of the patients who developed a flare of arthritis required a change in immunomodulatory therapy. There was no statistical difference in adverse effects between the ChAdOx1 nCoV-19 and the BBV152 vaccines (Supplementary Table 1).

Discussion

The data in our cohort were assuring with no increase in adverse effects in patients with AIRD as compared to non-AIRD RMDs. The reported adverse effects are less than those reported in previous cohorts [7, 15], possibly due to the universal dispensing of two acetaminophen tablets to each vaccinee. The lower rates of local or systemic AE compared to other cohorts might be due to the prophylactic use of acetaminophen in a large number of patients.

The lack of difference of AE between patients having AIRD and non-AIRD RMDs reiterates that patients with rheumatological diseases are no more likely to develop an AE after vaccination than the general population. The

Table 1 Basic characteristics of the cohort

Demographics	AIRD ($n=513$)	Non-AIRD ($n=211$)
Age (mean ± SD)	58.46 ± 10.28	59.47 ± 10.64
Gender		
Female	424 (82.65%)	157 (74.40%)
Male	89 (17.34%)	54 (25.59%)
Disease	Rheumatoid arthritis 225 (43.85%)	Osteoarthritis 84 (39.81%)
	SLE 52 (10.13%)	FMS 57 (27.01%)
	Spondyloarthropathies 68 (13.25%)	Neurogenic pain disorders 42 (19.90%)
	Scleroderma 16 (3.11%)	
	Vasculitis 32 (6.23%)	Regional pain syndromes 28 (13.27%)
	Myositis 18 (3.50%)	
	Other connective tissue disorders 22 (4.28%)	
	Inflammatory polyarthritis 80 (15.59%)	
At least one comorbidity	176 (34.30%)	62 (29.38%)
More than one comorbidity	85 (16.56%)	55 (26.06%)
Steroids	97 (18.90%)	Nil
csDMARDS	468 (91.22%)	Nil
Bio-DMARDS	27 (5.26%)	Nil
Vaccines		
ChAdOx1	447 (87.13%)	177 (83.88%)
BBV152	51 (9.94%)	26 (12.32%)
Unknown	15 (2.92%)	8 (3.79%)

AIRD autoimmune rheumatic disease, *SLE* systemic lupus erythematosus, *FM* fibromyalgia, *csDMARD* conventional synthetic disease modifying anti-rheumatic drug, *Bio-DMARD* biological disease modifying anti-rheumatic drug

Table 2 Post-vaccination adverse events in patients group

ADR	AIRD ($n=513$)	Non-AIRD ($n=211$)	*P* value (exact test)
Fatigue	92 (17.93%)	36 (17.06%)	0.831
Fever	94 (18.32%)	42 (19.90%)	0.675
Myalgia	49 (9.55%)	26 (12.32%)	0.284
Headache	71 (13.84%)	24 (11.37%)	0.399
New/increased joint pains	14 (2.72%)	4 (1.89%)	0.609
Diarrhea	12 (2.33%)	3 (1.42%)	0.572
Chills	14 (2.72%)	4 (1.89%)	0.609
Pain in injection site	128 (24.95%)	51 (24.17%)	0.850
No ADR	207 (40.35%)	81 (38.38%)	0.676

ADR adverse drug reaction, *AIRD* autoimmune rheumatic disease

mean age of patients in our cohort was much older than in the healthy cohorts previously reported [7, 15, 16]. The older age reflects the national policy to start vaccination in the elderly first. The lack of any serious AE despite the relatively older age is reassuring.

The few patients who had a flare of joint pain post vaccination suggest that closer follow-up may be required for these patients. This may be attributable to the adjuvants present or may simply be a nocebo effect. However, this lasted in less than 5 days in all four patients and, thus, is less likely to herald any significant danger.

Vaccination is an important part of the care of AIRD patients. Standard practice guidelines are recommending the routine use of various vaccines in such patients [17]. Still, the level of evidence is comparatively less and patients with AIRD are anticipated to have unique issues regarding vaccination [18]. One issue is regarding the immunogenicity of vaccines in the wake of immunosuppressants. The other is

regarding the safety of vaccines, especially live-attenuated vaccines or vaccines using newer strategies. The ChAdOx1 vaccine is the first non-replicating viral vector vaccine that has such widespread use under emergency authorization. No other viral vector vaccines had been approved for use outside clinical trials to date. Thus, demonstration of safety is an important consideration of this vaccine in the pool of AIRD patients.

Regarding immunogenicity, effectiveness and long-term safety of COVID-19 vaccines, the data are emerging. Various groups around the world, including us, are following up with our cohorts for more data.

The ideal time for vaccination in AIRD may be when disease activity is low, patients are on minimal immunosuppression, and before the initiation of any biological DMARD (Disease-modifying anti-rheumatic drug) especially rituximab [19]. These ideal conditions might not be possible in the wake of a gigantic second wave of COVID-19 engulfing our country. Thus, it will be as important to find out whether vaccination at different times, such as in patients with high disease activity or those who have received rituximab previously, induces protective immunity or not. Also, the question will arise which vaccine would be most suited to AIRD patients in terms of effectiveness and safety. Different vaccines are expected to behave differently in different populations, especially in patients with RMDs [20]. These are pertinent questions, and both patients and rheumatologists around the world are anxious for answers [21]. The current consensus does not prefer any one vaccine over any other [22]. Our study has provided the initial information regarding safety and we plan to follow it up with data on immune response, especially after the completion of two doses of the vaccines as per recommended schedules. Future strategies for susceptible populations may include a booster dose with a second vaccine [23].

Vaccine hesitancy may be a major factor in reducing vaccination coverage in this at-risk group. Groups more susceptible to COVID-19 may be more prone to vaccine hesitancy [24]. However, one study has shown that since the onset of the pandemic, patients with AIRD have been more diligent in getting their influenza vaccines [25]. Such behavior is encouraging and we hope that the encouraging results from our study help patients overcome any hesitancy and get themselves protected at the earliest.

Limitations of our study include a convenient sample and dependence on patients' recall. However, the strength is a large number of patients included across a wide variety of AIRD. The heterogeneity of the cohort is less important than the quick dissemination of the safety signals. Furthermore, all such studies for mRNA vaccines have similar heterogeneous population and lesser numbers. And to the best of our knowledge, no other study of the safety of the ChAdOx1 nCoV-19 and the BBV152 vaccines in AIRD or RMD patients is available to date. The number of patients receiving BBV152 is lesser but in proportion to vaccination rates as compared to the ChAdOx1 nCoV-19 in the country.

To summarize, adverse effects were no more in AIRD as compared to non-AIRD rheumatic and musculoskeletal conditions and no serious adverse effects were seen overall. There is an urgent need to disseminate this information to the vulnerable group of patients with AIRD to minimize vaccine hesitancy and eliminate its refusal.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00296-021-04917-0.

Declarations

I declare that no part of this work has been published or submitted for publication. It is entirely original work and all authors fulfill ICMJE criteria for authorship.

Conflict of interest Sakir Ahmed has received honorarium as a speaker from Pfizer (not related to the current work) and has no other potential conflicts of interest.

References

1. Tariq S, Van Eeden C, Tervaert JWC, Osman MS (2021) COVID-19, rheumatic diseases and immune dysregulation-a perspective. Clin Rheumatol 40:433–442. https://doi.org/10.1007/s10067-020-05529-y
2. Williamson EJ, Walker AJ, Bhaskaran K et al (2020) Factors associated with COVID-19-related death using OpenSAFELY. Nature 584:430–436. https://doi.org/10.1038/s41586-020-2521-4
3. Santos CS, Morales CM, Álvarez ED et al (2020) Determinants of COVID-19 disease severity in patients with underlying rheumatic disease. Clin Rheumatol 39:2789–2796. https://doi.org/10.1007/s10067-020-05301-2
4. Wang Q, Liu J, Shao R et al (2021) Risk and clinical outcomes of COVID-19 in patients with rheumatic diseases compared with the general population: a systematic review and meta-analysis. Rheumatol Int 41:851–861. https://doi.org/10.1007/s00296-021-04803-9
5. Ahmed S, Gasparyan AY, Zimba O (2021) Comorbidities in rheumatic diseases need special consideration during the COVID-19 pandemic. Rheumatol Int 41:243–256. https://doi.org/10.1007/s00296-020-04764-5
6. Curtis JR, Johnson SR, Anthony DD et al (2017) American College of Rheumatology guidance for COVID-19 vaccination in patients with rheumatic and musculoskeletal diseases—version 1. Arthritis Rheumatol. https://doi.org/10.1002/art.41734 (**ahead of print**)
7. Voysey M, Clemens SAC, Madhi SA et al (2021) Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet 397:99–111. https://doi.org/10.1016/S0140-6736(20)32661-1
8. Ella R, Reddy S, Jogdand H et al (2021) Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: interim results from a double-blind, randomised, multicentre, phase 2 trial, and 3-month follow-up of a double-blind, randomised phase 1 trial. Lancet Infect Dis. https://doi.org/10.1016/S1473-3099(21)00070-0 (**ahead of print**)

9. Information regarding COVID-19 vaccine. https://www.mohfw.gov.in/covid_vaccination/vaccination/index.html. Accessed 13 May 2021
10. Connolly CM, Ruddy JA, Boyarsky BJ et al (2021) Safety of the first dose of mRNA SARS-CoV-2 vaccines in patients with rheumatic and musculoskeletal diseases. Ann Rheum Dis. https://doi.org/10.1136/annrheumdis-2021-220231
11. Geisen UM, Berner DK, Tran F et al (2021) 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. https://doi.org/10.1136/annrheumdis-2021-220272
12. Østergaard SD, Schmidt M, Horváth-Puhó E et al (2021) Thromboembolism and the Oxford–AstraZeneca COVID-19 vaccine: side-effect or coincidence? Lancet 397:1441–1443. https://doi.org/10.1016/S0140-6736(21)00762-5
13. ICMR ethical guidelines. https://ethics.ncdirindia.org/ICMR_Ethical_Guidelines.aspx. Accessed 13 May 2021
14. Shenoy P, Ahmed S, Paul A et al (2020) Switching to teleconsultation for rheumatology in the wake of the COVID-19 pandemic: feasibility and patient response in India. Clin Rheumatol 39:2757–2762. https://doi.org/10.1007/s10067-020-05200-6
15. Singh AK, Phatak SR, Singh NK et al (2021) Antibody response after first-dose of ChAdOx1-nCOV (Covishield™®) and BBV-152 (Covaxin™®) amongst health care workers in India: preliminary results of cross-sectional coronavirus vaccine-induced antibody titre (COVAT) study. medRxiv. https://doi.org/10.1101/2021.04.07.21255078
16. Kim SH, Wi YM, Yun SY et al (2021) Adverse events in healthcare workers after the first dose of ChAdOx1 nCoV-19 or BNT162b2 mRNA COVID-19 vaccination: a single center experience. J Korean Med Sci 36:e107. https://doi.org/10.3346/jkms.2021.36.e107
17. Furer V, Rondaan C, Heijstek MW et al (2020) 2019 update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Ann Rheum Dis 79:39–52. https://doi.org/10.1136/annrheumdis-2019-215882
18. Wong PKK, Hanrahan P (2018) Management of vaccination in rheumatic disease. Best Pract Res Clin Rheumatol 32:720–734. https://doi.org/10.1016/j.berh.2019.03.006
19. Soy M, Keser G, Atagunduz P et al (2021) A practical approach for vaccinations including COVID-19 in autoimmune/autoinflammatory rheumatic diseases: a non-systematic review. Clin Rheumatol. https://doi.org/10.1007/s10067-021-05700-z (**ahead of print**)
20. Velikova T, Georgiev T (2021) SARS-CoV-2 vaccines and autoimmune diseases amidst the COVID-19 crisis. Rheumatol Int 41:509–518. https://doi.org/10.1007/s00296-021-04792-9
21. Schulze-Koops H, Specker C, Skapenko A (2021) Vaccination of patients with inflammatory rheumatic diseases against SARS-CoV-2: considerations before widespread availability of the vaccines. RMD Open 7:e001553. https://doi.org/10.1136/rmdopen-2020-001553
22. Park JK, Lee EB, Shin K et al (2021) COVID-19 vaccination in patients with autoimmune inflammatory rheumatic diseases: clinical guidance of the Korean college of rheumatology. J Korean Med Sci 36:e95. https://doi.org/10.3346/jkms.2021.36.e95
23. Jung J (2021) Preparing for the coronavirus disease (COVID-19) vaccination: evidence, plans, and implications. J Korean Med Sci 36:e59. https://doi.org/10.3346/jkms.2021.36.e59
24. Velikova T (2021) Infection-acquired versus vaccine-induced immunity against COVID-19. Cent Asian J Med Hypotheses Ethics 2(1):29–35. https://doi.org/10.47316/cajmhe.2021.2.1.05
25. Fragoulis GE, Grigoropoulos I, Mavrea E et al (2021) Increased influenza vaccination rates in patients with autoimmune rheumatic diseases during the Covid-19 pandemic: a cross-sectional study. Rheumatol Int 41:895–902. https://doi.org/10.1007/s00296-021-04817-3