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COVID-19 Vaccination In Autoimmune Diseases (COVAD) Study: Vaccine Safety In Idiopathic Inflammatory Myopathies

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COVID-19 Vaccination In Autoimmune Diseases (COVAD) Study: Vaccine Safety in Idiopathic Inflammatory Myopathies.

Abstract

Introduction/Aims

We studied COVID-19 vaccination-related adverse events (ADEs) 7-days post-vaccination in patients with idiopathic inflammatory myopathies (IIMs) and other systemic autoimmune and inflammatory disorders (SAIDs).

Methods

7-day vaccine ADEs were collected in an international patient self-reported e-survey. Descriptive statistics and multivariable regression were performed.

Results

10,900 respondents [1227 IIMs; 4640 SAIDs; 5033 healthy controls (HCs), median age 42 (IQR 30-55) years, 74% female, 45% Caucasian, 69% completely vaccinated] were analysed. 76.3% IIMs patients reported minor and 4.6% major ADEs. Patients with active IIMs reported more frequent major [OR 2.7 (1.04-7.3)] and minor [OR 1.5 (1.1-2.2)] ADEs than inactive IIMs. Rashes were more frequent in IIMs [OR-2.3(1.2-4.2)] than HCs. ADEs were not impacted by steroid dose, although hydroxychloroquine and intravenous/subcutaneous immunoglobulins were associated with a higher risk of minor ADEs [OR 1.9 (1.1-3.3), OR 2.2 (1.1-4.3)]. Overall, ADEs were less frequent in inclusion body myositis (IBM) and BNT162b2 (Pfizer) vaccine recipients

Discussion

7-day post-vaccination ADEs were comparable in patients with IIMs, SAIDs, and HCs, except for a higher risk of rashes in IIMs. Patients with DM, active disease may be at higher risk, and IBM patients at lower risk of specific ADEs. Overall, the benefit of preventing severe COVID-19 through vaccination likely outweighs the risk of vaccine-related ADEs

Our results may inform future guidelines regarding COVID-19 vaccination in patients with SAIDs, and specifically in IIMs. Studies to evaluate long-term outcomes and disease flares are needed to shed more light on developing future COVID-19 vaccination guidelines.

Keywords: COVID-19, rheumatology, vaccination, myositis, dermatomyositis

INTRODUCTION

The development of vaccines against the novel coronavirus has improved outcomes after COVID-19 infection in the general population. Several reports have demonstrated the safety and efficacy of COVID-19 vaccines in the general population, however there are significant gaps in vaccine safety and efficacy data in vulnerable populations including patients with systemic autoimmune and inflammatory disorders (SAIDs), those on immunosuppressive medications, and pregnancy [1–3]. The exclusion of patients with systemic autoimmune and inflammatory diseases (SAIDs) and those on immunosuppressive medication from the initial vaccine safety trials has inevitably resulted in a paucity of safety and efficacy data of COVID-19 vaccination in this vulnerable patient group. While recent studies have included rheumatic disorders, significant gaps exist in the understanding of safety of COVID-19 vaccination in patients with rare diseases such as idiopathic inflammatory myopathies (IIMs)[4–6]. The study on vaccination related adverse events (ADEs) in dermatomyositis (DM) from the TrinetX (Cambridge, MA) database looks at the overall 1 day, 30 day and 60 day adverse events following 3 vaccines (BNT162b2, mRNA-1273, and Ad26.COV.2.S) used in USA [7]. The study included a total of 6104 vaccinated dermatomyositis patients from US. DM patients experienced a higher rate of ADEs compared to age matched healthy controls. The studies so far available on vaccine ADE in SAIDs or IIM are largely regional and small.[8] Those studies claiming to be global have under-representation of various ethnic groups (Blacks and Asians)[4].

An interplay between underlying autoimmunity and dysregulated immune pathways compounded by the effect of immunosuppressive medications and potentially impacted by comorbid illness may predispose patient with IIM to an increased risk of post vaccination ADEs including allergic reactions, anaphylaxis, and disease flares [9, 10]. Concerns that adjuvants and immune activators in vaccines induce autoimmune disease flares and *de novo* immune thrombotic and demyelinating events have emerged recently [11, 12]. Poor characterization of post vaccination ADEs in patients with IIM due to a lack of vaccine safety and efficacy studies in this group may have contributed to vaccine hesitancy [13, 14]. There is therefore a need for evidence-based vaccine safety data with proper characterization of post vaccination ADEs in order to and potentially improve vaccination rates in patients with IIM, a vulnerable patient group.

In this study, we evaluate the short-term safety of COVID-19 vaccination using a patient self-reported global multi-center electronic survey.

METHODS

Study Design

This is an international, online, cross-sectional, multi-center survey, part of the COVAD study [15]. Informed consent of the participants was obtained via a cover letter. Approval was obtained from the local institutional ethics committee as per local guidelines and the Checklist for Reporting Results of the Internet E-Surveys was adhered to when reporting results [16, 17] .

Data Collection

A comprehensive patient-self reporting electronic survey was developed, consisting of a questionnaire of 36 COVID-19 and SAID-related questions, which included demographic details, SAID diagnosis, treatment details, current symptom status, COVID-19 infection history including symptoms, duration, and complications (hospitalization and need for oxygen therapy), COVID-19 vaccination details, 7-day short term post vaccination ADEs (based on CDC criteria), and patient reported outcome measures as per the Patient Reported Outcomes Measurement Information System (PROMIS) tool [18]. After vetting by international experts, pilot testing, revisions, validation, and translation into 18 languages, the survey was hosted on an online platform - surveymonkey.com - and circulated by the international COVAD study group (over 110 physicians) in health care centres in over 94 countries (Supplementary data), as well as through numerous social media platforms and online patient support groups. Patients with multiple overlapping autoimmune diseases were put into all the corresponding categories. Convenience sampling was used and all participants over the age of 18 years were included. Electronic protocols were used to remove duplicate responses from a single [illegible]lent. Methods have been detailed at length in the published COVAD study protocol [15].

Data Extraction

Data was retrieved on 30th September 2021. Patients who had not received even a single dose of any COVID-19 vaccine at the time of survey completion, and who had not completed the survey in full were excluded from the analysis (Figure 1). Multiple relevant variables were extracted from the survey responses of the included participants, including COVID-19 infection history and 7-day post vaccination ADEs.

Active and inactive disease

Active and inactive disease 4 weeks prior to vaccination were assessed by patients' response to questions about their symptoms prior to vaccination (eg rash, muscle weakness, joint pain and swelling etc) and need to step up immunosuppression (Supplementary methods).

Adverse events post vaccination

Seven-day ADEs were categorized as injection site pain and reaction, minor ADEs, major ADEs, and hospitalizations. Minor ADEs included myalgia, body aches, fever, chills, nausea and vomiting, headache, rashes, fatigue, diarrhoea, abdominal pain, high pulse rate or palpitations, rise in blood pressure, fainting, difficulty in breathing, dizziness, and chest pain. Major ADEs consisted of serious reactions to vaccination, requiring urgent medical attention, including anaphylaxis, a marked difficulty in breathing, throat closure (choking), and severe rashes [19]. Other ADEs that were not listed were reported as "others" via an open-ended question.

Statistical Analysis

The Chi-square and Mann Whitney tests were used for categorical and continuous variables respectively. The variables expected to be independently significant between IIMs, SAIDs and HCs, and between different IIM subtypes, after univariable analysis, underwent binary logistic regression analysis (BLR) with adjustment for factors deemed relevant based on evidence from current literature and clinical judgement, including for age, gender, ethnicity, immunosuppressants, vaccine received and stratified by country of origin. The results for continuous variables were expressed as median (IQR). $P<0.05$ was considered significant. Bonferroni corrected p value for univariate analysis was taken as significant (<0.0125 for 2x2 Chi-square analysis). Since the data was not normally distributed (by Kolmogorov–Smirnov test and Shapiro Wilk test), non-parametric tests were used. Statistical analysis was performed using tSPSS version 20 (IBM, Armonk, NY) and Software R 3.5.3 (R Core Team, 2020).

RESULTS

Population Characteristics

Of the 16,328 total respondents, 2,866 had not received a single dose of any COVID-19 vaccine at the time of survey completion and 2,562 did not complete the survey in full and were thus excluded from further analysis (Figure 1). The 10,900 vaccinated respondents included in the analysis (74% female, median aged 42 (IQR 30-55) years, 46% Caucasian) were primarily from Turkey, Mexico, India, UK and the USA, and consisted of 11.2% with IIMs, 42.6% with other SAIDs, and 46.2% HCs. The most common SAIDs reported in the cohort was rheumatoid arthritis, followed by IIM, and hyper/hypothyroidism. 69% of the respondents had received both primary doses of the COVID-19 vaccine. The largest number of respondents received the BNT162b2 (Pfizer) vaccine (39.8%), followed by the ChadOx1 nCOV-19 (Oxford/AstraZeneca). Of the IIM patients, 34% had dermatomyositis, 17% had polymyositis and 23% had IBM. Other population characteristics of the study cohort are provided in Table 1 and 5, and Supplementary Table 1, 2 and 6.

Post COVID-19 Vaccination associated ADEs in patients with IIM

Any ADE was seen in 76.5%, any minor ADE was seen in 76.3% and any major ADE was seen in 4.6%. All cause hospitalization was seen in 0.6%. Minor ADEs most commonly seen were fatigue, myalgia and fever. Severe rashes were statiystically higher in IIM when compared to HCs (Table 5).

Of the 102 patients with DM who reported a rash in the 4 weeks prior to vaccination, 47 had a heliotrope rash, 66 had Gottron's papules, 17 had a Holster sign, 51 had a malar rash, 63 had a V sign, 42 had a forearm/arm rash, and 60 had mechanic's hands. Of the 22 patients who had a rash following vaccination, 31% had inactive disease prior to vaccination. 27% had a DM rash, 27% had muscle weakness, 22% had joint pain in the hands and 4.5% had joint pain in other regions. The increased rash following vaccination could have represented a flare of the DM rash as 69% had active disease prior to vaccination.

Post COVID-19 Vaccination associated ADEs in patients with Active and Inactive IIM

Among the IIM patients, 855 had active IIM 4 weeks prior to vaccination and 352 had inactive disease. Any ADE following COVID-19 vaccination was more frequent in active IIM. Any minor ADE, myalgia, body ache, headache fatigue, dizziness and overall major ADE were more frequent in patients with active IIM compared to inactive disease prior to vaccination (Table 2).

Post COVID-19 Vaccination associated ADEs in patients with IIM based on the immunosuppression received

Although the wide variety of treatments in IIM results in a low frequency in each one, in adjusted analysis, IIM patients who were on Rituximab (n=40, 3%) had more frequent chills [OR 2.6 (1.2-5.8), p 0.012] and dizziness [OR 3.9 (1.3-11), p 0.010] following vaccination. Among the Iv/sc immunoglobulin recipients (n=117, 9%), any minor ADE was more frequent and muscle pains were less frequent. [OR 2.2 (1.1-4.3), p 0.019; and OR 0.28 (0.1-0.7), p 0.01 respectively]

Post COVID-19 Vaccination associated ADEs in between patients with different IIM subtypes

There was no significant difference in the risk of overall minor ADE between the different IIM subtypes. However, a higher risk of headache was observed in DM patients compared to other IIM subtypes in adjusted analysis, though the absolute risk of rash was very low across IIM subtypes (0-5%). Contrary to their DM counterparts, patients with IBM appeared to be less affected by post vaccination ADEs, with a lower risk of myalgia compared to other IIM subtypes (Table 3, Supplementary Table 3). The risk of major ADEs and hospitalisations remained consistent across

different IIM subtypes with a very small absolute risk (0 to 2%), but the numbers were too small (n=0 to 10) to draw firm conclusions.

Comparison of post COVID-19 vaccination ADE among IIM patients by vaccine type

After adjustment for baseline variables, IIM patients receiving ChAdOx1 nCoV-19 (Covishield Serum Institute India) were at a higher risk of myalgia and fever compared to the rest of vaccine recipients. A significantly overall higher risk of minor ADEs, as well as a higher individual risk of injection site pain, chills, rashes and nausea and vomiting was observed in IIM patients receiving MRNA-1273 (Moderna). Similarly, IIM patients receiving the ChAdOx1 nCOV-19 (Oxford/AstraZeneca) vaccine had a higher risk of myalgia, fever, chills, headache, abdominal pain and tachycardia/palpitations, yet a lower risk of injection site pain compared to other vaccine recipients (Table 4, Supplementary Table 4). Conversely, IIM patients receiving BNT162b2 (Pfizer) had a lower overall risk (Table 4, Supplementary Table 4). The absolute risk in IIMs, SAIDs and HCs, as well as in different IIM subtypes was very small (less than 2% in most cases) across vaccine types (Supplementary Table 5).

Post COVID-19 Vaccination associated ADEs in patients with IIM compared to HCs

The incidence of injection site pain was similar in patients with IIM (63%) and HCs (62%) with a very small absolute risk difference. Among minor ADEs, patients with IIM were at a higher risk of rashes compared to HCs though the absolute risk of rash in both IIMs and HCs was very small (1-2%) (Table 5, Supplementary Table 3). The absolute risk of major ADEs and hospitalisations was small (0-4%), and similar between patients with IIM and HCs (Table 5).

Post COVID-19 Vaccination associated ADEs in patients with IIM compared to other SAIDs

The incidence of injection site pain was similar in patients with IIM (63%) and other SAIDs (65%). While the risk of most minor ADEs was lower in IIM patients than in other SAIDs, the differences observed in uncontrolled univariable analysis did not attain significance after multivariable analysis with baseline adjustment. Regardless, the absolute risk in both IIMs and SAIDs was very small (0.6-1%) (Table 4, Supplementary Table 3). Major ADEs and hospitalisations were rare in patients with IIM and other SAIDs, with a small absolute risk (0-4%) and no significant differences between the two groups. (Table 5).

DISCUSSION

Overall, COVID-19 vaccination is safe in patients with IIMs and other SAIDs, and the majority of minor vaccine ADEs are easily manageable. COVID-19 vaccination in DM may lead to a mild increase in some minor ADEs, mainly rash, without increasing either major ADEs or hospitalization rate. This could be due to flares of cutaneous disease following vaccination. Those with active disease prior to vaccination reported higher minor ADE, major ADE and overall, any ADE. Considering the potentially severe consequences of SARS-CoV-2 infection, this study adds to the growing body of evidence indicating that the benefit of preventing severe COVID-19 through vaccination in SAIDs, especially in IIMs, likely outweighs the risk of post vaccination ADEs, and thus supports guidance statements by the American College of Rheumatology that encourage COVID-19 vaccination in patients with rheumatic diseases [19] . Our results provide insights that may inform future guidelines regarding COVID-19 vaccination in patients with SAIDs, and specifically in IIM.

While large-scale studies regarding COVID-19 vaccination safety in autoimmune diseases are lacking, the safety data gleaned from general population and small studies of immunocompromised patients are reassuring. In a small single-center cohort, Geisen et al. demonstrated the safety and efficacy of SARS-CoV-2 mRNA vaccines, without considerable side effects [20]. Regarding IIM patients, the data thus far is even more limited [21].

Among IIM patients, those with active disease reported higher minor, major, and overall ADEs following vaccination. This is due to the cycle of autoimmunity triggering reactions and vice-versa. Similar results have been demonstrated in other autoimmune diseases [7]. Among IIM subgroups, minor ADEs appear to be increased in DM and less frequent in IBM. However, it is important to note that subset analyses by vaccine type were limited by small numbers, preventing firm conclusions. In particular, few respondents experienced major post vaccine ADEs and hospitalisations. The absolute risk in IIMs, SAIDs and HCs, as well as in different IIM subtypes was very small (less than 2% in most cases) across vaccine types. It is well known that skin rash in DM patients may be exacerbated by environmental insults [22], and hence plausible that COVID-19 vaccination could also induce a flare of pre-existent rashes in these patients. Even though the pathogenesis of IBM remains poorly understood, it has been shown to be an interplay between an autoimmune and degenerative disorder, although antibody against cN-1A (NT5-c1A) has been identified [23]. Whilst autoimmunity is thought to be an important part of IBM pathogenesis, other factors appear to be at play, as manifest by the prominent degenerative features and mitochondrial dysfunction on muscle biopsy analysis. This may provide a possible explanation for the differences found in minor ADEs between IBM and DM. The other possibility is that DM and overlap myositis patients are at an increased risk of rashes inherent to the disease phenotype, accounting for reporting bias in this patient reported e-survey. Patients with active disease normally have rashes, and

these may be misconstrued as ADE of vaccine. Whether this rash worsened was unfortunately not specifically queried by the survey. Notably, 7 had inactive disease, and later developed rashes. Even if it is true that the possibility of a post vaccine flare cannot be substantiated, long term studies analysing patient physical function and other organ involvement may provide further insight into the possibility of disease flares, as data at seven days is insufficient to substantiate these speculations.

With respect to vaccine type, our data suggests that IIM patients have lower ADEs with BNT162b2 (Pfizer), ChadOx1 nCOV-19 (Oxford/AstraZeneca) and MRNA-1273 (Moderna) vaccines, as compared to patients with other autoimmune diseases and healthy controls. Within the IIM cohort, patients receiving the BNT162b2 (Pfizer) vaccine were more protected from most minor ADEs as compared to MRNA-1273 (Moderna), ChadOx1 nCOV-19 (Oxford/AstraZeneca) and ChAdOx1 nCoV-19 (Covishield Serum Institute India) recipients. To explain these differences, several aspects need to be considered: different criteria depending on the country or region for approval of vaccination, different treatment when vaccination took place and different post-manufacturing processes. The type of vaccine and adjuvants present, and their interaction with the underlying immune dysfunction as well as the interplay with the immunosuppressive medications taken by most of these patients may affect the efficacy and safety of these vaccines in patients with IIM and other SAIDs. Further studies are required to ascertain the safety profile of the various vaccines

This study has some limitations. Our data is based on patient self-reported information, which could not be verified by medical records. Our population also represents a convenience sample, where low-income patients without internet access, severely disabled, and deceased are not represented. People of African and African American ethnicity are under-represented in the cohort. Furthermore, we have not looked into the treatment required for the hospitalised patients following vaccination ADEs. Patients receiving immunosuppressive and biological drugs may have impaired humoral responses, although the role of clinical significance of this altered immune response is not yet clearly understood [23]. Furthermore, severe ADEs were rarely observed. Thus, limited events in each subgroup, such as major ADEs and hospitalization, would make it difficult to find any statistically significant correlations. Finally, in this study, the survey has focused on short term ADE, but long-term outcomes and disease flares were not assessed.

Conclusion

This study shows that COVID-19 vaccination has a favourable short-term safety profile in IIM as in healthy individuals and other SAIDs. Marginally higher ADRs such as rashes may be related to patient disease phenotype and did not lead to an increase in hospitalization rate. Those with active disease prior to vaccination had reported higher adverse events. Among IIM patients, the DM subgroup may be predisposed to specific ADEs while the IBM subgroup had fewer reported ADEs. Studies to evaluate long term outcomes and disease flares are needed to shed more light on developing future COVID-19 vaccination guidelines.

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Abbreviations

ADE: Adverse Drug Events

IIM: Idiopathic Inflammatory Myopathies

SAID: Systemic Autoimmune and Inflammatory Disorders

HC: Healthy Controls

BLR: Binary Logistic Regression

OR: Odds Ratio

CI: Confidence Interval

NS: Not Significant

ASSD: Anti-synthetase syndrome

DM: Dermatomyositis

IBM: Inclusion body myositis

JDM: Juvenile dermatomyositis

NAM: Necrotizing myositis, OM Overlap myositis

PM: Polymyositis

OM: Overlap myositis

HCQ: Hydroxychloroquine

CNI: Calcineurin inhibitors

IVIG: Intravenous immunoglobulin

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Figure Legends

Figure 1. Data Extraction

COVID-19 Vaccination in Autoimmune Diseases Study: Vaccine Safety in Idiopathic Inflammatory Myopathies

Objec

To [illegible] COVID-19 vaccination Adverse Events (ADEs) in

- **Idiopathic Inflammatory Myopathies**
- **Other Systemic Autoimmune Inflammatory Diseases**
- **Healthy Individuals**

Methods

COVAD [illegible] patient self-reported [illegible] electronic survey

10,900 vaccinated; complete responses

Other SAIDs **4,640** | IIMs **1,227** | Healthy Controls **5,033**

7- day post COVID-19 vaccination Adverse Events (ADEs)

- Injection Site Pain
- [illegible] ADEs
- Major ADEs
- Hospitalisation

Analysis

- Vaccine Type
- Disease Status
- Immunosuppressants [illegible]ceived
- IIM subtype

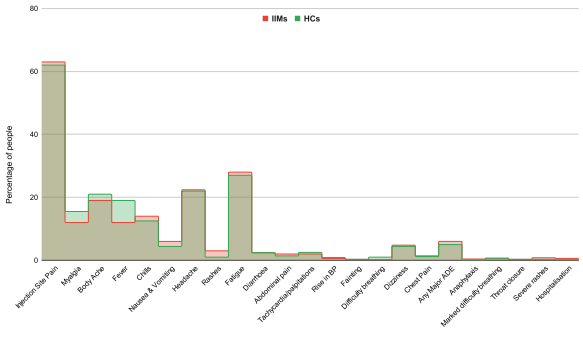
Results

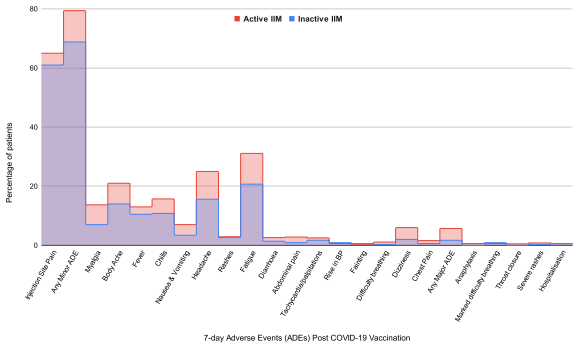
Patients with IIMs

- Older
- Higher Caucasian proportion
- Higher BNT162b2 uptake
- Higher %age on Immunosuppressants

IIMs **vs** HCs

Higher risk in IIMs- Rashes





7-day post COVID-19 vaccination Adverse Events (ADEs) in IIMs vs HCs and in patients with Active vs Inactive IIMs

Active vs Inactive IIM

Active Disease

Higher Risk

- Any Minor ADEs
- Myalgia
- Bodyache
- Headache
- Fatigue
- Dizziness
- Overall Major ADEs

Vaccine Type

IIMs

Lesser ADEs
BNT162b2

Greater ADEs
ChAdOx1 nCoV-19
MRNA-1273

Immunosuppressants

IIMs

Rituximab
- ↑ **Chills**
- ↑ **Dizziness**

Iv/sc immunoglobulin
- ↑ **Any Minor ADE**
- ↓ **Myalgia**

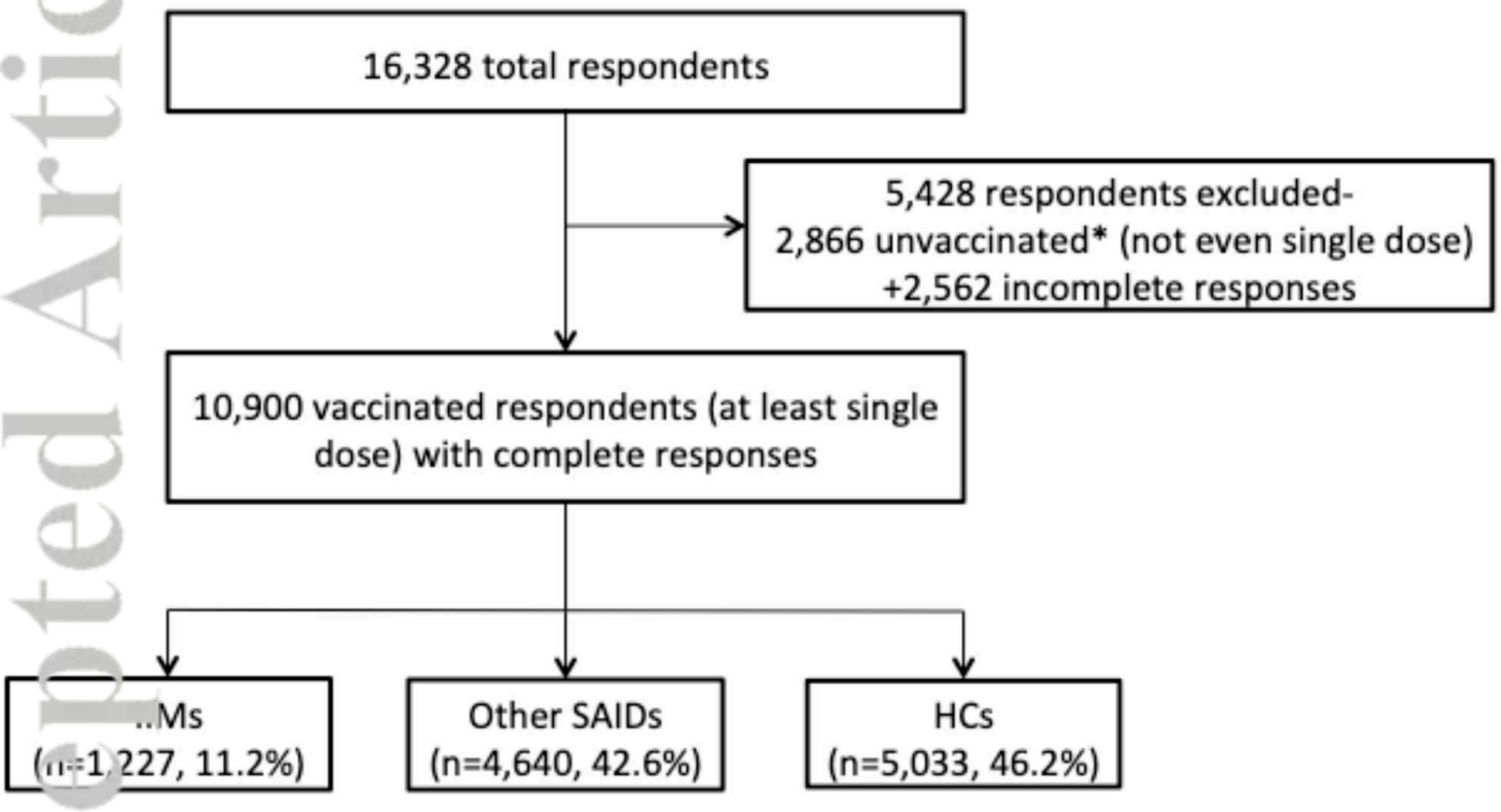
IIM subtype

DM
- ↑ **Headache**

IBM
- ↓ **Myalgia**

Conclusion

- 7 day ADEs- comparable in IIMs, SAIDs, HCs
- Risk of Rashes- Higher in IIMs
- DM, Active IIM- Higher risk of Specific ADEs; IBM- Lower Risk



*An electronic protocol was used that terminated the survey automatically when they responded that they had not received any dose of a COVID-19 vaccine

MUS.png

TABLES

Table 1. Population Characteristics				
Variable	**Total (%) (n=10900)**	**IIMs (%) (n=1227)**	**Other SAIDs (%) (n=4640)**	**HCs (%) (N=5033)**
Age (years)	42 (30-55)	49 (38-61)	47 (36-57)	33 (25-46)
Gender M: F	2432: 8558 (1:2.9)	283:782 (1:2.76)	568:3249 (1:5.7)	1491:2798 (1:1.8)
Ethnicity				
Caucasian	4972 (46)	882 (72)	2303 (49)	1787 (35)
African American or of African origin	83 (0.7)	34 (3)	22 (0.5)	27 (0.5)
Asian	2018 (18)	71 (6)	781 (17)	1166 (23)
Hispanic	1193 (11)	49 (4)	399 (8.5)	745 (15)
Native American/ Indigenous/ Pacific Islander	342 (3)	1 (0)	18 (0.4)	323 (6)
Do not wish to disclose	449 (4)	13 (1)	191 (4)	245 (5)
Other	865 (8)	21 (2)	127 (3)	717 (14)
Vaccine received				
BNT162b2 (Pfizer)-BioNTech	4333 (39)	645 (53)	2042 (44)	1443 (28.7)
ChadOx1 nCOV-19 (Oxford/AstraZeneca)	1456 (13)	124 (10)	845 (18)	487 (9.7)
JNJ-78436735 (JOHNSON AND JOHNSON)	95 (1)	15 (1.2)	42 (1)	38 (0.8)
MRNA-1273 (Moderna)	910 (8)	360 (29)	387 (8)	163 (3.2)
NVX-CoV2373 (Novovax)	14 (0.1)	0 (0)	10 (0.2)	4 (0.1)
ChAdOx1 nCoV-19 (Covishield Serum Institute India)	1194 (11)	43 (3.5)	430 (9)	721 (14)
BBV152 (Covaxin Bharat Biotech)	248 (2)	15 (1.2)	111 (2)	122 (2.4)
Gam-COVID-Vac (Sputnik)	204 (2)	4 (0.3)	64 (1)	136 (2.7)
BBIBP-CorV (Sinopharm)	1821 (17)	4 (0.3)	374 (8)	1443 (28.7)
I am not sure	62 (0.5)	0 (0)	27 (0.5)	35 (0.7)
Others	563 (5)	17 (1.4)	309 (6)	238 (4.7)
Discontinued medicines before vaccination	773 (13)	147 (12)	626 (13)	-
Duration of discontinuing medicines (days)	13 (7-21)	14 (7-21)	12 (7-21)	-
SAIDs: systemic autoimmune and inflammatory diseases, IIM Idiopathic inflammatory myopathies, HC: Healthy controls				

Table 2. Comparison of vaccination related ADE among Active and Inactive IIM						
	Active IIM *(n=855)*	**Inactive IIM *(n=352)***	**Univariate**		**Multivariable**	
			OR *(95%* CI)	p	OR *(95%* CI)	p
Any ADE	681 (79.6)	242 (68.8)	1.7 (1.3-2.3)	<0.001	1.6 (1.1-2.2)	0.006
Injection site pain	557 (65)	216 (61)		0.213		
Minor ADEs						
Any Minor ADE	679 (79.4)	242 (68.8)	1.7 (1.3-2.3)	<0.001	1.5 (1.1-2.2)	0.007
Myalgia	117 (13.7)	25 (7)	2 (1.3-3.2)	0.001	2.2 (1.3-3.8)	0.002
Body ache	178 (21)	49 (14)	1.6 (1.1-2.2)	0.005	1.5 (1.07-2.3)	0.020
Fever	112 (13)	37 (10.5)	-	0.214		
Chills	134 (15.7)	38 (10.8)	1.5 (1.04-2.2)	0.028	1.3 (0.8-2.1)	0.162
Nausea and vomiting	60 (7)	12 (3.4)	2.1 (1.1-4)	0.016	1.7 (0.8-3.6)	0.107
Headache	212 (25)	55 (15.6)	1.7 (1.2-2.4)	<0.001	1.5 (1.04-2.1)	0.028
Pains	25 (2.9)	9 (2.6)	-	0.726		
Fatigue	266 (31.1)	73 (20.7)	1.7 (1.2-2.3)	<0.001	1.5 (1.08-2.1)	0.015
Diarrhoea	22 (2.6)	5 (1.4)	-	0.218		
Abdominal pain	24 (2.8)	3 (0.9)		0.051		
High pulse rate or palpitations	21 (2.5)	6 (1.7)		0.422		
Rise in blood pressure	5 (0.6)	3 (0.9)		0.603		
Fainting	2 (0.2)	2 (0.6)		0.358		
Difficulty in breathing	9 (1.1)	1 (0.3)		0.181		
Dizziness	51 (6)	7 (2)	3.1 (1.4-6.9)	0.003	2.5 (1.08-5.9)	0.031
Chest pain	14 (1.6)	2 (0.6)		0.140		
Major ADEs						
Any major ADE	49 (5.7)	6 (1.7)	3.5 (1.4-8.2)	0.002	2.7 (1.04-7.3)	0.040
Anaphylaxis	5 (0.6)	0 (0)		0.151		
Marked difficulty in breathing	5 (0.6)	3 (0.9)		0.603		
Throat closure	4 (0.5)	0 (0)		0.199		
Severe rashes	7 (0.8)	1 (0.3)		0.298		
Hospitalization	5 (0.6)	2 (0.6)		0.972		

IIMs Idiopathic inflammatory myopathies, ADE Adverse drug event
OR Odd's ratio, CI Confidence interval
Chi square for categorical variables and Mann Whitney test for continuous variables
Factors adjusted in multivariable analysis (binary logistic regression) include age, gender, ethnicity, vaccine received, number of vaccine doses received and Immunosuppressants received

Table 3. COVID infection and COVID-19 vaccination associated ADEs in IIM subtypes

N (%)	DM (n=418)	PM (n=207)	IBM (n=284)	ASSD (n=136)	NAM (n=52)	OM (n=116)	JDM (n=14)
Injection site pain	**298 (71)*****	136 (65)	**145 (51)*****	88 (65)	31 (59)	73 (63)	11 (78)
Minor ADEs							
Myalgia	46 (11)	**35 (17)***	**15 (5)*****#	22 (16)	4 (7)	16 (14)	3 (21)
Body ache	90 (21)	42 (20)	**27 (9)*****	33 (24)	8 (15)	30 (13)	2 (14)
Fever	64 (15)	28 (13)	**19 (7)****	14 (10)	5 (9)	19 (16)	2 (14)
Chills	66 (16)	29 (14)	**23 (8)****	26 (19)	7 (13)	22 (19)	2 (14)
Nausea and vomiting	32 (8)	6 (3)	**7 (2.5)***	9 (7)	4 (7)	**14 (12)****	1 (7)
Headache	**123 (29)*****#	37 (18)	**29 (10)*****	32 (23)	10 (19)	**36 (31)***	2 (14)
Rashes	**21 (5)*****#	2 (1)	**1 (0.4)***	3 (2)	1 (2)	6 (5)	0 (0)
Fatigue	**138 (33)****	63 (30)	**47 (16)*****	40 (29)	19 (36)	34 (29)	6 (43)
Diarrhoea	13 (3)	2 (1)	4 (1.4)	2 (1.5)	1 (2)	**7 (6)***	0 (0)
Abdominal pain	11 (3)	3 (1)	5 (2)	3 (2)	2 (4)	3 (3)	0 (0)
High pulse rate or palpitations	8 (2)	6 (3)	2 (0.7)	4 (3)	1 (2)	5 (4)	1 (7)
Rise in blood pressure							
Fainting	3 (0.7)	1 (0.5)	0 (0)	1 (0.7)	0 (0)	**3 (3)***	0 (0)
Difficulty in breathing	**4 (1)****	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Dizziness	6 (1)	1 (0.5)	1 (0.4)	1 (0.7)	1 (2)	1 (1)	0 (0)
Chest pain	20 (5)	11 (5)	**4 (1.4)****	7 (5)	5 (10)	**11 (9)***	2 (14)
	7 (2)	0 (0)	1 (0.4)	4 (3)	1 (2)	3 (3)	1 (7)
Major ADEs							
Anaphylaxis	5 (0.4)	2 (1)	2 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)
Marked difficulty in breathing	9 (0.7)	0 (0)	1 (0.4)	3 (2)	0 (0)	0 (0)	0 (0)
Throat closure	4 (0.3)	1 (0.5)	1 (0.4)	1 (0.7)	0 (0)	0 (0)	1 (7)
Severe rashes	10 (0.8)	1 (0.5)	0 (0)	0 (0)	1 (2)	1 (1)	0 (0)
Hospitalization	7 (0.6)	2 (1)	1 (0.4)	1 (0.7)	0 (0)	1 (1)	0 (0)

ASSD Anti-synthetase syndrome, DM Dermatomyositis, IBM Inclusion body myositis, IIM Idiopathic inflammatory myopathies, JDM Juvenile dermatomyositis, NAM Necrotizing myositis, OM Overlap myositis, PM Polymyositis
OR Odd's ratio, CI Confidence interval, *P<0.05, ** P<0.005, ***P<0.001
Chi square for categorical variables and Mann Whitney test for Scale variables
Comparisons are between each IIM subtype versus the rest of IIM subtypes
Bold have increased OR when compared to rest, **Bold Underlined** have decreased OR when compared to rest
Significant in BLR (binary logistic regression) adjusted for age, gender, ethnicity, Immunosuppressant dose and stratified by country

Table 4. Vaccine ADEs based on the COVID-19 vaccine received among IIM (In comparison with rest of vaccines)

N (%)	BNT162b2 (Pfizer) (n=634)	ChadOx1 nCOV-19 (Oxford/AstraZeneca) (n=124)	MRNA-1273 (Moderna) (n=360)	ChAdOx1 nCoV-19 (Covishield Serum Institute India) (n=43)
Injection site pain	398 (62)	**69 (55)*#**	**273 (76)***#**	25 (58)
Minor ADEs				
Any minor ADE	**456 (71)***#**	96 (77)	**303 (85)***#**	35 (81)
Myalgia	**55 (8)***#**	**23 (18)*#**	44 (12)	**15 (35)***#**
Body ache	**99 (15)***#**	**35 (28)*#**	76 (21)	12 (28)
Fever	**49 (7)***#**	**26 (21)*#**	54 (15)	**18 (42)***#**
Chills	**72 (11)***#**	**29 (23)*#**	**65 (18)*#**	4 (9)
Nausea and vomiting	**22 (3)***#**	**15 (12)***	**31 (8)*#**	5 (11)
Headache	**120 (18)***#**	**41 (33)**#**	91 (25)	10 (23)
Rashes	**10 (1.5)**#**	5 (4)	**21 (6)***#**	1 (2)
Fatigue	178 (27)	37 (29)	**120 (33)***	**7 (16)***
Diarrhoea	14 (2)	**8 (6)***	8 (2)	1 (2)
Abdominal pain	12 (2)	**9 (7)***#**	7 (2)	2 (4)
High pulse rate or palpitations	12 (2)	**8 (6)**#**	7 (2)	2 (4)
Rise in blood pressure	7 (1)	3 (2)	1 (0.2)	1 (2)
Fainting	5 (0.7)	1 (1)	1 (0.2)	1 (2)
Difficulty in breathing	7 (1)	1 (1)	4 (1)	2 (4)
Dizziness	**21 (3)*#**	9 (7)	**25 (6)***	3 (7)
Chest pain	10 (1.5)	2 (1.6)	4 (1)	2 (4)
Major ADEs				
Any Major ADE	**22 (3.3)***	**11 (8.3)***	17 (4.7)	3 (7)
Anaphylaxis	3 (0.4)	**3 (2)***	1 (0.2)	1 (2)
Marked difficulty in breathing	6 (1)	2 (1.6)	4 (1)	1 (2)
Throat closure	**1 (0.1)***	2 (1.6)	2 (0.5)	1 (2)
Severe rashes	6 (1)	3 (2)	2 (0.5)	1 (2)
Hospitalization	2 (0.2)	1 (1)	3 (0.8)	1 (2)

AID Autoimmune disease, HC Healthy control
*P<0.05, ** P<0.005, ***P<0.001
Chi square for categorical variables and Mann Whitney test for Scale variables
Bold indicates Increased Odd's ratio compared to rest of vaccines, **Bold Underlined** indicates decreased Odd's ratio compared to rest of vaccines
#Significant in BLR adjusted for age, gender, ethnicity, Immunosuppressant dose and stratified by country

Table 5. The effects of the COVID-19 vaccination in IIMs versus other SAIDs, HCs

N (%)	**IIMs (n=1227)**	**Other SAIDs (n=4640)**	**HCs (n=5033)**	**OR 1 (CI)**	**OR 2 (CI)**	**P1**	**P2**
Injection site pain	784 (63)	3036 (65)	3138 (62)			0.316	0.365
Minor ADEs							
Myalgia	**144 (12)**	**777 (17)**	**778 (15.5)**	**0.6 (0.5-0.8)**	**0.7 (0.6-0.8)**	**<0.001**	**<0.001**
Body ache	**233 (19)**	**1067 (23)**	1082 (21)	**0.8 (0.7-0.9)**		**0.003**	0.055
Fever	**151 (12)**	**863 (18)**	**960 (19)**	**0.6 (0.5-0.7)**	**0.6 (0.5-0.7)**	**<0.001**	**<0.001**
Chills	176 (14)	714 (15)	631 (12.5)			0.365	0.104
Nausea and vomiting	**74 (6)**	311 (7)	**222 (4.4)**		**1.3 (1-1.8)**	0.398	**0.021**
Headache	**271 (22)**	**1290 (28)**	1125 (22.4)	**0.7 (0.6-0.8)**		**<0.001**	0.884
Rashes	**34 (3)**	91 (2)	**48 (1)**		**2.9 (1.8-4.5)**	0.081	**<0.001**
Fatigue	**348 (28)**	**1511 (32)**	1359 (27)	**0.8 (0.7-0.9)**		**<0.001**	0.395
Diarrhoea	**29 (2.4)**	**174 (4)**	120 (2.4)	**0.6 (0.4-0.9)**		**0.018**	0.945
Abdominal pain	**27 (2)**	126 (3)	72 (1.4)			0.314	0.059
High pulse rate or palpitations	**27 (2)**	**166 (4)**	125 (2.5)	**0.6 (0.4-0.9)**		**0.016**	0.527
Rise in blood pressure	**8 (0.6)**	**65 (1)**	47 (0.9)	**0.5 (0.2-0.9)**		**0.035**	0.328
Fainting	4 (0.3)	23 (0.5)	16 (0.3)			0.435	0.980

Difficulty in breathing	10 (0.2)	59 (1)	50 (1)			0.187	0.543
Dizziness	**58 (4.8)**	**291 (6)**	**229 (4.4)**	**0.7 (0.5-0.99)**		**0.042**	0.498
Chest pain	17 (1.4)	81 (2)	60 (1.2)			0.381	0.611
Others	77 (6)	431 (9)	270 (5)			0.567	0.247
Major ADEs							
Anaphylaxis	**5 (0.4)**	6 (0.1)	**5 (0.1)**		5 (1.3-19)	0.060	0.070
Marked difficulty in breathing	9 (0.7)	27 (0.6)	27 (0.5)			0.545	0.430
Throat closure	4 (0.3)	23 (0.5)	4 (0.3)			0.435	0.167
Severe rashes	**10 (0.8)**	31 (0.7)	**15 (0.3)**		2.7 (1.2-6)	0.583	**0.011**
Others	**40 (3)**	149 (3)	**56 (1)**		2.9 (1.9-4.4)	0.945	**0.042**
Hospitalization	**7 (0.6)**	20 (0.4)	**11 (0.2)**		2.5 (1-6.7)	0.521	**0.042**

SAIDs systemic autoimmune and inflammatory disorders, IIMs Idiopathic inflammatory myopathies, HC Healthy controls, ADE Adverse drug event

OR Odd's ratio, OR1 OR between IIMs and other SAIDs, OR2 OR between IIMs and HCs, CI Confidence interval, P1 P value between IIMs and other SAIDs, P2 P value between IIMs and HCs, P<0.05 is significant

Chi square for categorical variables and Mann Whitney test for continuous variables