Ensuring the Safety of COVID-19 Vaccines among Rheumatic and Musculoskeletal Disease (RMD) Patients in Seremban: A Cross-Sectional Study Investigating Adverse Reactions

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Introduction: Coronavirus disease 2019 (COVID-19) has severely influenced all aspects of life since its emergence and one of the strategies to end this pandemic rests on the vaccination to achieve herd immunity. While vaccinations are usually a safe and effective tool, the abbreviated development process of the available COVID-19 vaccines has increased uncertainties about the safety among the general population especially among patients with rheumatic and musculoskeletal diseases (RMD).

Methods: A cross-sectional analysis was performed on rheumatic disease (RMD) patients from the rheumatology clinic at Hospital Tuanku Ja'afar Seremban (HTJS), investigating adverse events occurring within one month of receiving COVID-19 vaccines administered from 1st May 2021 to 30th September 2021.

Results: 549 RMD patients were recruited in this study. Pfizer/BioNTech was the predominant vaccine (n = 257, 64.3%), followed by Sinovac (n = 60, 47.2%), Oxford/AstraZeneca (n = 7, 1.3%) and Moderna (n = 1, 0.2%). 330 (60.1%) patients experienced at least one adverse event, none of which required hospitalisation. Common side effects included pain at the site of injection (n = 169, 30.8%), generalised muscle pain (n = 91, 16.4%), fever (n = 90, 16.4%), arthralgia (n = 55, 10.0%), and lethargy (n = 43, 7.7%). Female patients (OR = 0.88, CI 0.79-0.97, p = 0.012), Sinovac recipients (OR = 0.51, CI 0.34-0.76, p = 0.001) and age >50 years (OR = 0.62, CI 0.44-0.89, p = 0.009) had significantly lower risks of experiencing adverse events. Among patients with autoimmune rheumatic disease (AIRD), 28 (6.4%) experienced disease flare. Patients with spondyloarthropathy (SpA) and overlap syndrome were more likely to experience disease flare following COVID-19 vaccination compared to rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) patients (OR = 2.87, CI 1.23 - 6.69, p = 0.014). The use of combination conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) was associated with a tendency toward increased risk of disease flare (OR = 2.34, CI: 0.97–5.64, p = 0.056). However, the use of glucocorticoids (OR = 2.02, CI 0.72–5.61, p = 0.17) and an active disease state (OR = 1.94, CI 0.75–5.02, p = 0.171) did not show a statistically significant impact on the frequency of disease flares.

Conclusions: The study affirms the overall safety of COVID-19 vaccines in rheumatic musculoskeletal disease patients, supporting efforts to address vaccine hesitancy in this population.

Keywords: *Adverse events; COVID-19; Rheumatic and musculoskeletal disease; SARS-CoV-2; Vaccination*

Background

Coronavirus disease 2019 (COVID-19) is a global threat to humanity and has severely influenced all aspects of life since its emergence. Immune dysregulation in various autoimmune rheumatic diseases (AIRD) poses a risk for prolonged viremia and severe COVID-19 due to a few factors such as high comorbidities and high disease activity.[1] One of the strategies to tackle this rests on vaccination to achieve herd immunity. While vaccinations are usually a safe and effective tool, the accelerated development process of the available COVID-19 vaccines has increased uncertainties about safety among the general population, especially among

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patients with AIRD.[2] Furthermore, these individuals were largely excluded from the initial vaccine trials and the evidence of vaccine safety in patients with AIRD is limited.

Connolly *et al*, published the first available data on the safety and reactogenicity of mRNA COVID-19 vaccine among rheumatic and musculoskeletal diseases (RMD) patients. In this study, local and systemic adverse events were consistent with expected vaccine reactogenicity, mainly mild and similar in frequency to those reported in the vaccine trials.[3] Studies on COVID-19 vaccine hesitancy among patients with RMD showed that the main reasons for vaccine refusal were fear of disease worsening and occurrence of adverse events related or regardless to disease.[4]

Our objectives are to explore the safety of COVID-19 vaccination among RMD patients and to identify precipitating factors for the occurrence of adverse events post-vaccination.

Methods

Patient recruitment

Patients with rheumatic and musculoskeletal diseases (RMDs) aged 18 years and older, who were being monitored in the rheumatology clinic at Hospital Tuanku Ja'afar Seremban and had received at least one dose of the COVID-19 vaccine between 1st May 2021 and 30th September 2021, were invited to participate in this cross-sectional study. All participants were informed of the purpose of the survey and verbal consent was obtained before their inclusion. Participant information sheets in two languages (English and Bahasa Malaysia) were also made available at the rheumatology clinic.

Data collection

The survey included demographic data (age, sex and ethnicity), RMD condition (diagnosis, disease activity and treatment), underlying medical illness, and SARS-CoV-2 infection and vaccination history. Information on demographic data and RMD conditions were obtained from the out-patient case notes while SARS-CoV-2 infection and vaccination history were obtained through interviewing the participant, either face-to-face or via telephone calls. Questions on SARS-CoV-2 vaccination included date, type and number of vaccines received, presence of adverse event within a month following the injection and the nature of the adverse event. No identifiable data were recorded.

Statistical analysis

Data collected were entered into IBM SPSS Software version for statistical analysis. Frequency distributions of the demographic variables were summarised using counts (n) and percentages (%). The relationships between categorical variables were analysed using the Pearson chi-square test. To assess the association of demographic and clinical characteristics with the occurrence of adverse events and disease flare-ups, we employed the chi-square test to determine unadjusted odds ratios (ORs) with 95% confidence intervals. A p-value of 0.05 or lower was considered statistically significant.

Operational definition

Disease flare among the AIRD patients was defined as requiring increment or introduction of corticosteroid or addition of immunosuppressants in any patient who had been on a stable dose in the preceding three months before vaccination.

Ethics statement

This study was granted approval by the Joint Committee on Research & Ethics, International Medical University (CSc/Sem6(25)2021) and Medical Review & Ethics Committee (MREC) (22-00880-DMT).

Results

We studied 549 patients with RMD. More than half of the patients (n = 306, 55.7%) were older than 50 years and majority were female (n = 417, 76.0%). Among the participants, 277 (50.5%) were Malay, 149 (27.1%) were Chinese, and 105 (19.1%) were Indian. Four hundreds and fourteen (75.4%) patients received Pfizer-BioNTech, 127 (23.1%) received Sinovac, 7 (1.3%) received Oxford-AstraZeneca and 1 (0.2%) received Moderna. Four hundreds and forty (80.0%) patients were diagnosed with AIRD and 109 (19.9%) with non-AIRD.

A comparison of demographic and clinical characteristics between patients with and without adverse events within a month following the COVID-19 vaccination were included in Table I. Female patients (OR = 0.88, CI 0.797-0.977, p = 0.012), Sinovac recipients (OR = 0.51, CI 0.34-0.76, p = 0.001) and age >50 years (OR = 0.63, CI 0.44-0.89, p = 0.009) had significantly lower risks of experiencing adverse events. No significant differences were observed in adverse event occurring between AIRD and non-AIRD groups (p = 0.447).

Table I: Demographic and clinical characteristics of all RMD patients with and without adverse events within a month following the COVID-19 vaccination.

CHARACTERISTICS *n* (%)	ALL (n = 549)	WITH ADVERSE EVENTS (n = 330)	WITHOUT ADVERSE EVENTS (n = 219)	P VALUE
AGE				**0.031**
< 30	65 (11.8%)	42 (64.6%)	23 (35.8%)	
31-50	178 (32.4%)	119 (66.9%)	59 (33.1%)	
>50	306 (55.7%)	169 (55.2%)	137 (44.8%)	
GENDER				**0.012**
Female	417 (76.0%)	263 (63.0%)	154 (37.0%)	
Male	132 (24.0%)	67 (50.1%)	65 (49.9%)	
ETHNICITY				**0.144**
Malay	277 (50.5%)	165 (59.6%)	112 (40.4%)	
Chinese	149 (27.1%)	99 (66.4%)	50 (33.6%)	
Indian	105 (19.1%)	58 (55.2%)	47 (44.8%)	
Others	18 (3.3%)	8 (44.4%)	10 (53.7%)	

VACCINES				**0.001**
Pfizer-BioNTech	414 (75.4%)	263 (63.5%)	151 (36.5%)	
Sinovac	127 (23.1%)	60 (47.2%)	67 (52.8%)	
CO-MORBIDITIES				**0.606**
none	222 (40.4%)	138 (41.8%)	84 (43.0%)	
1-2	244 (44.4%)	141 (43.0%)	103 (47.0%)	
>2	83 (15.1%)	51 (15.4%)	32 (14.6%)	
AUTOIMMUNE RHEUMATIC DISEASE (AIRD)	440 (80.1%)	268 (60.9%)	172 (29.1%)	**0.447**
RA	219 (49.7%)	125 (57.0%)	21 (43.0%)	
SLE	122 (27.9%)	83 (68.0%)	39 (32.0%)	
SpA	44 (10.0%)	23 (52.3%)	21 (47.7%)	
Overlap syndrome	18 (4.1%)	14 (77.8%)	4 (22.2%)	
Dermatomyositis	11 (2.5%)	9 (81.8%)	2 (18.2%)	
Systemic sclerosis	8 (1.8%)	3 (37.5%)	5 (62.5%)	
Vasculitis	9 (2.1%)	3 (66.7%)	6 (33.3%)	
Others	9 (2.1%)	8 (88.9%)	1 (11.1%)	
NON-AUTOIMMUNE RHEUMATIC DISEASE (NON-AIRD)	109 (19.9%)	62 (56.9%)	47 (43.1%)	
Gout	65 (59.6%)	32 (49.2%)	33 (50.8%)	
Osteoarthritis	16 (14.7%)	9 (56.3%)	7 (43.8%)	
Osteoporosis	10 (9.2%)	8 (80.0%)	2 (20.0%)	

Data are shown as n (%). RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, SpA: spondyloarthropathy

At least one adverse event was recorded in 330 (60.1%) RMD patients, none of which required hospitalisation. The most common symptoms reported were pain at the site of injection (n = 169, 30.8%), generalised muscle pain (n = 91, 16.4%), fever (n = 90, 16.4%), arthralgia (n = 55, 10.0%), and lethargy (n = 43, 7.7%).

The association between COVID-19 vaccination and AIRD flare

In this study, 440 participants (80.1%) had an autoimmune rheumatic disease (AIRD). Among them, 219 patients (49.7%) had rheumatoid arthritis (RA), 122 patients (27.9%) had systemic lupus erythematosus

(SLE), 44 patients (10.0%) had spondyloarthritis (SpA), 18 patients (4.1%) had overlap syndrome, and 11 patients (2.5%) had dermatomyositis. Disease flare was recorded in 28 (6.4%) patients. Fourteen RA patients who experienced disease flare were solely arthritis-related. Six SpA patients experienced flares, with 4 exhibited only arthritis-related symptoms and 2 observed arthritis along with psoriasis flare. Among the 5 SLE patients who flared, 3 were renal-related, 1 had arthritis, and 1 had mucocutaneous flare. Additionally, 3 patients with overlap syndrome experienced arthritis flares.

Among the AIRD, patients with SpA and overlap syndrome were significantly more likely to experience disease flare-ups following COVID-19 vaccination compared to those with RA and SLE (OR = 2.87, CI 1.23–6.69, p = 0.014). The use of combination conventional synthetic disease-modifying anti-rheumatic drug (csDMARDs) was associated with a tendency toward increased risk of disease flare (OR = 2.34, CI 0.97–5.64, p = 0.056). However, the use of glucocorticoids (OR = 2.02, CI 0.72–5.61, p = 0.17) and an active disease state (OR = 1.94, CI 0.75–5.02, p = 0.171) did not show a statistically significant impact on the frequency of disease flares. No case of disease flare was noted among patients who received biologic/targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs) (Table II).

Table II: Clinical characteristics of AIRD patients with and without disease flare within a month following the COVID-19 vaccination.

PARAMETERS	ALL N = 440 (100%)	WITH DISEASE FLARE N = 28 (6.4%)	WITHOUT DISEASE FLARE N = 412 (93.6%)	P VALUE
AGE				**0.123**
< 30	60 (13.6%)	2 (3.3%)	58 (96.7%)	
31-50	145 (33.0%)	14 (9.7%)	131 (90.3%)	
>50	235 (53.4%)	12 (5.1%)	223 (94.9%)	
GENDER				**0.325**
Female	374 (85.0%)	22 (5.9%)	352 (94.1%)	
Male	66 (15.0%)	6 (9.0%)	60 (91.0%)	
ETHNICITY				**0.144**
Malay	210 (47.8%)	10 (4.7%)	200 (95.3%)	
Chinese	119 (27.0%)	6 (5.0%)	113 (95%)	
Indian	95 (21.6%)	9 (9.5%)	86 (90.5%)	
Others	16 (3.6%)	3 (18.8%)	13 (81.2%)	

TYPES OF AIRD				**0.0436**
Rheumatoid arthritis	219 (49.7%)	14 (6.4%)	205 (93.6%)	
SLE	122 (27.9%)	5 (4.1%)	117 (95.9%)	
Spondyloarthropathy	44 (10.0%)	6 (13.6%)	38 (86.4%)	
Overlap syndrome	18 (4.1%)	3 (16.7%)	15 (83.3%)	
Dermatomyositis	11 (2.5%)	0	11	
Systemic sclerosis	8 (1.8%)	0	8	
Vasculitis	9 (2.1%)	0	9	
Others	9 (2.1%)	0	9	
VACCINES				**0.274**
Pfizer-BioNTech	336 (76.4%)	23 (6.8%)	313 (93.2%)	
Sinovac	99 (22.5%)	4 (4%)	95 (96%)	
DISEASE ACTIVITY				**0.654**
Remission/inactive	380 (86%)	22 (5.8%)	356 (93.7%)	
Low	12 (3.1%)	1 (8.3%)	11 (91.7%)	
Moderate	34 (8.6%)	4 (11.8%)	30 (88.2%)	
High	10 (2.3%)	1 (10%)	9 (90%)	
GLUCOCORTICOSTEROID USE				**0.037**
None	395 (90%)	23 (5.8%)	372 (94.2%)	
Low dose (≤ 7.5mg / day)	33 (6%)	2 (6%)	31 (94%)	
Medium (7.5mg – 30mg / day)	12 (2.2%)	3 (25%)	9 (75%)	
TREATMENT				
Cs-DMARDs	338 (76.8%)	24 (7.1%)	314 (92.9%)	
1 cs-DMARDs	178 (52.5%)	8 (4.5%)	170 (95.5%)	**0.063**
≥2 cs-DMARDs	160 (47.5%)	16 (10.0%)	144 (90.0%)	
b/ts-DMARDs	32 (7.3%)	32 (100%)	0 (0%)	
Anti-TNF alpha	16 (2.9%)	16 (100%)	0 (0%)	
Anti-IL6	9 (1.6%)	9 (100%)	0 (0%)	
JAK-i	7 (1.3%)	7 (100%)	0 (0%)	
not on any DMARDs	70 (15.9%)	1 (3.4%)	28 (96.6%)	

Data are shown as n (%). b/ts-DMARDs: biologic/target synthetic-Disease Modifying Antirheumatic Drugs; Cs-DMARDs: conventional synthetic-Disease Modifying Antirheumatic Drugs; IL-6: intermeulin-6; JAK-i: Janus kinase inhibitor; TNF: tumor necrosis factor. ^Chi-Square test was conducted exclusively for the categories of RA, SLE, Spondyloarthritis (SpA), and Overlap Syndrome.

Discussion

Our study provides valuable insights into the adverse effects of COVID-19 vaccination among patients with RMD, shedding light on vaccine safety, tolerability and the occurrence of disease flares post-vaccination.

The predominance of Pfizer-BioNTech recipients in our cohort aligns with global trends given its early availability and widespread distribution. Notably, 60.1% of patients experienced at least one adverse effect within a month post-vaccination, with pain at the site of injection, generalised muscle pain and fever being commonest. All of them were mild and did not warrant hospitalisation.

Our analysis indicated notable differences in adverse events based on gender and vaccine type. Additionally, there was a weak inverse correlation between age and adverse events suggesting that older individuals experienced slightly fewer adverse events. These were similar to previous studies.[5,6,7] mRNA vaccines like Pfizer-BioNTech were often associated with a higher rate of reactogenicity compared to other vaccine platforms. Conversely, the Sinovac vaccine, being an inactivated virus vaccine, tended to have a different safety profile, which aligns with our finding that Sinovac recipients had fewer adverse events.[5] Older adults generally experience fewer adverse events following vaccination and this might be due to age-related differences in immune response and reactogenicity.[6]

There was no significant difference in the occurrence of adverse events between patients with AIRD and those with non-AIRD. This observation aligns with findings from other studies suggesting that COVID-19 vaccines were generally well-tolerated among autoimmune patients.[8,9,10] It is possible that the immune dysregulation seen in autoimmune diseases does not predispose individuals to a higher incidence of common vaccine side effects, although they seem to exhibit increasing susceptibility to develop severe forms of COVID19 infection with higher mortality rates.

Although the overall adverse event rate was similar between AIRD and non-AIRD patients, the study revealed that specific subtypes of AIRD, such as SpA and overlap syndrome, were associated with a higher likelihood of experiencing disease flares following vaccination. This suggests that while the general adverse event rate may be comparable, certain autoimmune conditions might interact differently with the vaccine, leading to a higher incidence of disease flare-ups. This observation is supported by other studies highlighting that patients with certain autoimmune conditions may experience transient exacerbations post-vaccination.[11] Among the patients who had psoriatic arthritis flare also encountered worsening of psoriasis. All of them received Pfizer vaccine. This resonates with findings by Wu *et al*, where most of the patients with psoriasis flare received mRNA vaccines with the onset of flare ranging from 1 day to 90 days.[12]

In this study, glucocorticoid use did not demonstrate a significant association with the frequency of disease flares. This aligns with the findings of a systematic review by Shaun *et al*, which examined disease flare patterns among SLE patients following COVID-19 vaccination. However, the authors did note that a high SLE disease activity score was associated with an increased risk of flares, a finding that contrasts with our results among AIR patients.[13]

It is known that some immunosuppressive or immunomodulatory drugs reduce seroconversion rates, rendering the vaccine less immunogenic and potentially impacting flare rates.[14]

Limitation

This study was cross-sectional, which introduces limitations related to temporal relationships and increases the risk of recall bias. Additionally, majority of the study's participants received Pfizer-BioNTech vaccine. This limited diversity in vaccine types may affect the generalisability of the findings to other vaccines or newer vaccine formulations. This study also did not investigate the impact of vaccine dose on adverse events and disease flares. Examining dose-dependent effects could provide insights into whether higher or lower doses of the vaccine have varying safety profiles for RMD patients.

Conclusion

Our data confirm good tolerability and low frequency of disease flare following COVID-19 vaccination. While most adverse effects were mild and self-limiting, close monitoring and individualised management strategies are essential, especially for patients at higher risk of adverse events or disease flares.

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