Manuscript title: Inactivated SARS-CoV-2 vaccine does not increase the risk of relapse in patients with clinically inactive adult-onset Still's disease

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Abstract

Objective. A succession of cases have reported flares of adult-onset Still's disease (AOSD) after vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), raising concerns. We aimed to investigate the impact of inactivated SARS-CoV-2 vaccines on disease activity in patients with AOSD.

Methods. We prospectively enrolled clinically inactive AOSD patients visiting the outpatient clinics of our department. The patients received SARS-CoV-2 vaccines (BBIBPCorV, Sinopharm, Beijing, China) voluntarily. The occurrence of relapse in the participants was recorded during the follow-up period and a propensity score matching (PSM) method was used to compare the relapse rates between vaccinated and unvaccinated patients. Localized and systemic symptoms were assessed in the vaccinated patients.

Results. A total of 122 patients with inactive AOSD were included, of which 49.2% (n = 60) voluntarily received the inactivated SARS-CoV-2 vaccine. The relapse rate did not increase significantly in vaccinated patients in comparison with unvaccinated patients (after PSM: 6.8% versus 6.8%), and no relapse occurred within one month after vaccination. No obvious adverse reactions were reported in 75.0% of the participants, and none of the patients reported severe reactions.

Conclusion. Increased disease activity or relapse following vaccination with inactivated SARS–CoV-2 were rare in patients with inactive AOSD. Local and systemic adverse reactions were found to be mild and self-limiting. These safety profiles of inactivated SARS–CoV-2 vaccines in patients with AOSD may assist in eliminating vaccine hesitancy and increase the vaccination rate against SARS-CoV-2.

Keywords: Adult-onset Still's disease, SARS-CoV-2 vaccine, relapse.

Rheumatology key messages:

- Inactivated SARS–CoV-2 vaccine did not increase the risk of relapse in patients with inactive AOSD.
- Local and systemic adverse reactions were mild and self-limiting after receiving inactivated SARS–CoV-2 vaccines in patients with inactive AOSD.

Introduction

Adult-onset Still's disease (AOSD) is a rare polygenic systemic autoinflammatory disorder of unknown etiology. The pathogenesis of AOSD is associated with excessive macrophages and neutrophils activation by pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), leading to an overproduction of pro-inflammatory cytokines, including IL-1β, IL-6, IL-18, and TNF-α[1]. It is possible that SARS-CoV-2 vaccines may act as PAMPs and may thus promote inflammation through the activation of Toll-like receptor pathways, leading to cytokine overproduction and immune cell activation, all of which have been associated with AOSD pathogenesis[1].

Given the ongoing coronavirus disease 2019 (COVID-19) pandemic, vaccination against SARS–CoV-2 is a powerful tool for the prevention of infection and the reduction of severe cases in the general population. Although vaccination is strongly recommended in patients with autoimmune inflammatory rheumatic diseases (AIIRDs) [2], there is little available evidence on the safety of SARS-CoV-2 vaccines in patients with AOSD, as the latter have mostly not been included in clinical trials. In addition, there have been several reports in the past two years of new onset or flares of AOSD after SARS–CoV-2 vaccination, with one patient even developing life-threatening macrophage activation syndrome [3-8]. These reports have raised that the issue of whether SARS-CoV-2 vaccines can be safely recommended to patients with inactive AOSD[9]. However, more data are required to understand the impact of the vaccines on AOSD disease activity.

Here, we performed a prospective observational cohort study to evaluate the safety of vaccination with inactivated SARS-CoV-2 vaccines in patients with inactive AOSD.

Patients and Methods

Study design and population

We conducted a prospective observational cohort study in patients with inactive AOSD in the Department of Rheumatology and Immunology, Ruijin Hospital, China. The study was conducted between March 1, 2021, and June 1, 2022. Patients who had been diagnosed with AOSD according to the Yamaguchi criteria[10] or in whom the disease had remained inactive for at least three months off glucocorticoid or on treatment with prednisolone (or equivalent) at a dose of ≤7.5 mg daily were recruited. The exclusion criteria included recent SARS-CoV-2 infection, a medical history of allergic reactions after previous vaccinations, and pregnancy. A total of 122 patients were finally enrolled and provided written informed consent to participate (Supplementary Figure S1, available at *Rheumatology* online). This study was approved by the Institutional Research Ethics Committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, China, and was performed in compliance with the Declaration of Helsinki with written informed consent from the subjects.

Study variables

Patients without disease-related symptoms such as fever, inflammatory arthralgia or arthritis, suggestive skin rash, myalgia, and sore throat were considered clinically inactive. The definition of relapse in this study was as previously described [11], specifically, the presence of at least two AOSD-related symptoms together with elevated levels of inflammatory indicators such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and ferritin,

requiring treatment adjustment. Relapse was confirmed by senior rheumatologists after the exclusion of infection, allergy, or other unrelated conditions. Adverse reactions to the SARS-CoV-2 vaccine were classified into localized or systemic reactions. Localized reactions included pain, redness, itching, swelling, or tenderness at the injection site. Systemic reactions included fever, chills, headache, sore throat, fatigue, nausea, vomiting, diarrhea, joint pain, myalgia, and rash. The severity of the adverse reactions was classified as mild (did not interfere with daily activity), moderate (interfered with daily activity), or severe (required urgent medical attention or medications).

Data collection

Data on demographics, comorbidities, and clinical characteristics were collected at the time of recruitment. Due to the pandemic control policies and difficulties in visiting clinics on schedule, disease activity was primarily assessed by telephone interview or live chat. The participants were asked to contact the investigators promptly if they suffered from disease-related unwellness during the follow-up period and to inform the investigators as soon as they got vaccinated. After SARS–CoV-2 vaccination, the occurrence of localized and systemic adverse reactions within one week of receiving the vaccine was recorded. If individuals reported an adverse reaction to the vaccine, they were asked to rate the severity of the reaction. At the end of the study, all the participants were interviewed to evaluate the occurrence of relapse during the follow-up period.

Statistical analysis

Categorical variables were presented as frequencies (%) and were compared using χ^2 test or Fisher's exact tests. Continuous variables were represented as medians (IQR) and compared using the Mann-Whitney U test or independent t-test as appropriate. A 1:1 propensity score matching (PSM) method was used to compare the relapse rate between vaccinated and unvaccinated patients matched by age, sex, and disease course with a match tolerance of 0.02. A two-sided *p*-value of < 0.05 was considered statistically significant. All analyses were performed using SPSS software (Version 26.0).

Results

Baseline characteristics

A total of 122 patients with AOSD were finally included in the study. Of these, 56.6% (n = 69) of patients volunteered to receive the inactivated SARS-CoV-2 vaccine while 43.4% (n = 53) of patients were hesitant or unwilling to do so. The patients came from different areas in China and could thus receive advice about vaccination from distinct general practitioners. As a result, 7.4% (n = 9) of patients failed to receive the first dose due to the advice of general practitioners related to safety concerns for patients with AOSD. In all, 49.2% (n = 60) of the patients received the inactivated SARS-CoV-2 vaccine (Supplementary Figure S2, available at *Rheumatology* online).

Demographics and medication usage were found to be comparable between vaccinated and unvaccinated participants (Table 1). The common therapeutic regimens included conventional synthetic disease-modifying antirheumatic drugs (DMARDs) (vaccinated: 56.7%;

unvaccinated: 67.7%) and glucocorticoid therapy (vaccinated: 28.3%; unvaccinated: 33.9%) in both groups. However, vaccinated patients exhibited longer disease durations than unvaccinated patients (55.1[37.2,72.3] versus 44.1[32.8,54.3] months, $p = 0.005$). After PSM matching, all the baseline variables were found to be well balanced.

Incidence of relapses and disease characteristics.

Among the vaccinated patients, 13.3% (n = 8) had elevated levels of inflammatory indicators, 6.7% (n = 4) had treatment adjustment due to flares of AOSD and 5% (n = 3) were considered to have relapsed. The most common symptoms observed were inflammatory arthralgia and/or arthritis (13.3%). Among the unvaccinated patients, 6.5% (n = 4) reported relapse, 16.1% had elevated inflammatory indicator levels (n = 10), and 6.5% (n = 4) had treatment adjustment due to disease flares, while the most common symptoms were rash (12.9%) and arthralgia (12.9%). The incidence of relapse and occurrence of AOSD-related symptoms did not increase in vaccinated patients after the matching (Table 2, Supplementary Figure S3, available at *Rheumatology* online).

Of the three patients in the vaccinated group that relapsed, all relapses occurred more than one month after the final vaccine dose, with two relapses occurring approximately six months after the last dose. The patients who relapsed after vaccination mainly presented with arthralgia and rash, both of which were relieved by treatment with low-dose prednisolone and/or conventional DMARDs.

Local and systemic adverse reactions.

The participants were asked to report both localized and systemic adverse reactions within seven days after the first SARS-CoV-2 vaccine dose (D1), the second dose (D2), and the third dose (D3) (Supplementary Table S1, available at *Rheumatology* online).

A total of 25% (n = 15) of patients reported adverse reactions after vaccination. The most frequent local adverse reaction was pain at the injection site (10.0%), while the most common systemic adverse reactions were joint pain (5.0%) and myalgia (3.3%). Adverse reactions that interfered significantly with daily activities were uncommon and no severe reaction was reported.

Discussion

A recent study reported a series of cases of new onset or flares in rheumatic diseases after vaccination against SARS-CoV-2, of which the most common manifestations were related to inflammatory arthritis (n=12, 40.0%), rheumatic polymyalgia (n=10, 33.3%) and adult-onset Still's disease (n=4, 13.3%). These results aroused concern due to a possible relationship between auto-inflammatory conditions and vaccination[12].

In this study, we evaluated the impact of vaccination with inactivated SARS-CoV-2 vaccines on disease activity in patients with inactive AOSD and identified no increased risk of relapse compared with unvaccinated patients. No incidents of severe relapse or hospitalization were reported. Local and systemic reactions were found to be mild and self-limiting. These findings are consistent with those of a previous study on immune-mediated inflammatory diseases (IMID) involving patients with AOSD (n=24) which showed an acceptable safety profile for SARS-CoV-2 vaccination[13]. Overall, severe vaccine-related adverse reactions

were rare, and there was no significantly increased risk of relapse observed after receiving inactivated SARS-CoV-2 vaccines in clinically inactive AOSD patients.

Over 10 cases with new-onset AOSD or flares in AOSD have been reported within the past two years. Indeed, four of these patients had been previously diagnosed with AOSD and found to develop flares less than one month after the last dose of the SARS-CoV-2 vaccine [3-6]. Of these patients with flares, one was mild, while the other three required hospitalization where they were treated with IV corticosteroids and biologic agents. Interestingly, Knabl and colleagues conducted a transcriptomic analysis of a patient who experienced disease flares both before and after vaccination, observing that the vaccination seemingly activated the type I interferon pathway as well as multiple inflammatory mediators [3]. However, we found no relapse within one month after receiving inactivated SARS-CoV-2 vaccines. The risk of relapse after vaccination thus appears to be tolerable. Consistent with these results, it has been reported that post-vaccination disease activity also remained stable in most patients with familial Mediterranean fever, the most common hereditary autoinflammatory disease [14]. It should be noted that, in our study, all the participants were clinically inactive for a long period of time, and some of them were still taking low doses of steroids or DMARDs which might have reduced the risk of relapse even when they were exposed to potential triggers. Besides, the inactivated SARS-CoV-2 vaccines may help to provide the anticipated protective antibodies and regulate T cell response while avoiding triggering disease flares compared to messenger RNA (mRNA) vaccines.

This is the first prospective study evaluating the risk of relapse in patients with AOSD after receiving inactivated SARS-CoV-2 vaccines. However, there are several limitations

associated with this study. First, the vaccination was not randomized in these participants which may have introduced bias, although we performed PSM to reduce bias. In addition, the participants in the study cohort received vaccines containing inactivated SARS-CoV-2, which cannot be generalized to other vaccine types. Specifically, further studies on the safety of mRNA vaccines may be warranted. In addition, long-term follow-up is required to reveal the possible association between SARS-CoV-2 vaccination and the risk of relapse in these patients. Overall, our results demonstrated that vaccination with inactivated SARS-CoV-2 did not lead to an increased risk of relapse in patients with inactive AOSD and serious vaccine-related adverse reactions were rare. These findings may help to overcome vaccine hesitancy and increase vaccine confidence among AOSD patients. Thus, vaccinations should not be withheld because of misguided fears of precipitating AOSD flares and patients should be provided with proper advice about the benefits of vaccination.

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Author contributions:

All authors made substantive intellectual contributions in the study. Dr. Huihui Chi has full access to all the data included in this article and takes responsibility for the integrity of the data and the accuracy of the analyses. All of authors approved the final version of the manuscript.

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Data availability statement: The data underlying this article will be shared on reasonable request to the corresponding author.

References:

1. Feist E, Mitrovic S, Fautrel B. Mechanisms, biomarkers and targets for adult-onset Still's disease. Nat Rev Rheumatol. 2018;14(10):603-18 doi: 10.1038/s41584-018-0081-x.

2. 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 3. Arthritis Rheumatol. 2021;73(10):e60-e75 doi: 10.1002/art.41928.

3. Knabl L, Lee HK, Walter M, Furth PA, Hennighausen L. Immune transcriptome and antibody response in adult-onset Still's disease with mild flare following administration of mRNA vaccine BNT162b2. Rheumatology (Oxford). 2022 doi: 10.1093/rheumatology/keac281.

4. Kim JW, Jung JY, Suh CH, Kim HA. Flare of adult-onset Still's disease following mRNA

COVID-19 vaccination: a case report and review of literature. Clin Rheumatol. 2022;41(5):1583-9 doi: 10.1007/s10067-022-06106-1.

5. Yamamoto S, Nishimura K, Yo K, Waki D, Murabe H, Yokota T. Flare-up of adult-onset Still's disease after receiving a second dose of BNT162b2 COVID-19 mRNA vaccine. Clin Exp Rheumatol. 2021;39 Suppl 132(5):139-40 doi: 10.55563/clinexprheumatol/tvlpnc.

6. Muench F, Krusche M, Sander LE, Rose T, Burmester GR, Schneider U. Macrophage activation syndrome in a patient with adult-onset Still's disease following first COVID-19 vaccination with BNT162b2. BMC Rheumatol. 2021;5(1):60 doi: 10.1186/s41927-021-00237-9.

7. Leone F, Cerasuolo PG, Bosello SL, Verardi L, Fiori E, Cocciolillo F, et al. Adult-onset Still's disease following COVID-19 vaccination. The Lancet Rheumatology. 2021;3(10):e678-e80 doi: 10.1016/s2665-9913(21)00218-6.

8. Magliulo D, Narayan S, Ue F, Boulougoura A, Badlissi F. Adult-onset Still's disease after mRNA COVID-19 vaccine. The Lancet Rheumatology. 2021;3(10):e680-e2 doi: 10.1016/s2665-9913(21)00219-8.

9. Winichakoon P, Chanloung W, Nantsupawat T, Louthrenoo W. Adult-Onset Still's Disease-like Syndrome following COVID-19 Vaccination: A Case Report and Review of the Literature. Vaccines (Basel). 2022;10(7) doi: 10.3390/vaccines10071022.

10. Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H, et al. Preliminary criteria for classification of adult Still's disease. J Rheumatol. 1992;19(3):424-30.

11. Meng J, Chi H, Wang Z, Zhang H, Sun Y, Teng J, et al. Characteristics and risk factors of relapses in patients with adult-onset Still's disease: a long-term cohort study. Rheumatology

(Oxford). 2021;60(10):4520-9 doi: 10.1093/rheumatology/keab023.

12. Gasparotto M, Bindoli S, Padoan R, Cozzi G, Depascale R, Zanatta E, et al. New onset and flare of rheumatic diseases following COVID-19 vaccination are mild and respond well to treatment: 9-month follow-up data from a single centre cohort. Clin Exp Rheumatol. 2022 doi: 10.55563/clinexprheumatol/vx44zn.

13. Tien N, Chang YC, Chen PK, Lin HJ, Chang SH, Lan JL, et al. The Immunogenicity and Safety of Three Types of SARS-CoV-2 Vaccines in Adult Patients with Immune-Mediated Inflammatory Diseases: A Longitudinal Cohort Study. Biomedicines. 2022;10(4) doi: 10.3390/biomedicines10040911.

14. Shechtman L, Lahad K, Livneh A, Grossman C, Druyan A, Giat E, et al. Safety of the BNT162b2 mRNA COVID-19 vaccine in patients with familial Mediterranean fever. Rheumatology (Oxford). 2022;61(SI2):SI129-SI35 doi: 10.1093/rheumatology/keac131.

Table 1. Demographics and clinical characteristics of the participants

	Before propensity score matching			After propensity score matching		
	Vaccinated patients(n=60)	Unvaccinated patients(n=62)	*p* value	Vaccinated patients(n=44)	Unvaccinated patients(n=44)	*p* value
Age, years	39.5(29.3-50.0)	38.0(32.0-52.5)	0.459	40.5(28.5-50.8)	35.0(31.3-46.0)	0.559
Female	45(75.0)	51(82.3)	0.328	34(77.3)	34(77.3)	1.000
Disease course, months	55.1(37.2-72.3)	44.1(32.8-54.3)	0.005	50.8(33.8-62.2)	46.9(35.7-59.4)	0.815
Comorbidities						
Hypertension	4(6.7)	11(17.7)	0.113	3(6.8)	8(18.2)	0.197
Diabetes mellitus	1(1.7)	5(8.1)	0.224	1(2.3)	2(4.5)	1.000
Malignant tumor	0(0.0)	2(3.2)	0.496	0(0.0)	1(2.3)	1.000
Treatments						
Drug withdrawal	24(40.0)	19(30.6)	0.280	19(43.2)	15(34.1)	0.381
Glucocorticoid therapy*	17(28.3)	21(33.9)	0.509	11(25.0)	17(38.6)	0.170
csDMARDs	34(56.7)	42(67.7)	0.207	23(52.3)	28(63.6)	0.280
b/tsDMARDs	4(6.7)	10(16.1)	0.175	3(6.8)	6(13.6)	0.482
csDMARDs only	16(26.7)	19(30.6)	0.627	11(25.0)	11(25.0)	1.000
Combination	18(30.0)	23(37.1)	0.407	12(27.3)	17(38.6)	0.257

Values are presented with median (IQR) or number (%).

*Glucocorticoid therapy: including prednisone and prednisone equivalents.

Abbreviations: IQR, interquartile range; csDMARDs, conventional synthetic disease- modifying antirheumatic drugs; bDMARDs, biological disease-modifying antirheumatic drugs; tsDMARDs, target synthetic disease-modifying antirheumatic drugs.

Table 2. Incidence of relapses and assessment of disease activity in patients with AOSD

	Before propensity score matching			After propensity score matching		
	Vaccinated patients(n=60)	Unvaccinated patients(n=62)	*p* value	Vaccinated patients(n=44)	Unvaccinated patients(n=44)	*p* value
Fever	1(1.7)	4(6.5)	0.381	0	2(4.5)	0.494
Rash	3(5.0)	8(12.9)	0.227	3(6.8)	5(11.4)	0.711
Abnormal liver function tests	0	1(1.6)	1.000	0	1(2.3)	1.000
Lymphadenopathy	0	2(3.2)	0.496	0	1(2.3)	1.000
Leukocytosis	1(1.7)	3(4.8)	0.635	1(2.3)	3(6.8)	0.609
Sore throat	1(1.7)	1(1.6)	1.000	0	1(2.3)	1.000
Myalgia	0	1(1.6)	1.000	0	0	
Inflammatory arthralgia and/or arthritis	8(13.3)	8(12.9)	0.944	8(18.2)	7(15.9)	0.777
Elevated inflammatory indicator*	8(13.3)	10(16.1)	0.663	7(15.9)	7(15.9)	1.000
Treatment adjustment†	4(6.7)	4(6.5)	1.000	4(9.1)	3(6.8)	1.000
Relapse‡	3(5.0)	4(6.5)	1.000	3(6.8)	3(6.8)	1.000

Values are presented with number (%).

*Elevated inflammatory indicator: including ESR, CRP or ferritin.

†Treatment adjustment: an increase in the glucocorticoid dose and/or immunosuppressive agents or a restart of glucocorticoids and/or biologic agents.

‡Relapse: occurrence of at least two AOSD-related symptoms with elevated inflammatory indicators, requiring medication adjustments and confirmed by senior rheumatologists after the exclusion of infection, and allergies.