

Inflammatory rheumatic diseases developed after COVID-19 vaccination: presentation of a case series and review of the literature

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Abstract. – OBJECTIVE: An increasing number of new on-set autoimmune-inflammatory rheumatic diseases (AIRD) after COVID-19 vaccination has begun to be reported in the literature. In this article, we present our patients with new-onset AIRD after vaccination for COVID-19 and review the literature on the subject.

PATIENTS AND METHODS: We investigated the clinical characteristics and laboratory parameters of previously described “newly developed AIRD in individuals recently vaccinated for COVID-19”, in 22 cases vaccinated with one of the COVID-19 vaccines (BNT162b2 or CoronaVac) approved in our country.

RESULTS: We collected 22 cases (14 female, 63.6%) that developed an AIRD after COVID-19 vaccination. Mean age was 53±14.4 (24-87) years. The interval between the last dose of vaccination and the development of the first complaint was 23.9±19.5 (4-90) days. CoronaVac was administered to four patients, and the BNT162b2 to 18 patients. AIRD-related symptoms developed in 12 patients after the first dose, in 8 patients after the second dose, and in two patients after the third dose. Twelve out of the 22 (54.5%) cases were diagnosed with rheumatoid arthritis, two with SLE, and the remaining eight patients each with leukocytoclastic vasculitis, Sjogren’s syndrome, psoriatic arthritis, ankylosing spondylitis, systemic sclerosis, mixed connective tissue disease, eosinophilic granulomatosis with polyangiitis, and inflammatory myositis, respectively. Six patients had a history of documented antecedent COVID-19 infection.

CONCLUSIONS: Autoimmune/inflammatory rheumatic diseases may develop after COVID-19 vaccinations. In the era of the COVID-19 pandemic, vaccination should be questioned carefully in newly diagnosed AIRD patients.

Key Words:

COVID-19 vaccines, Autoimmune diseases, Adjuvant, mRNA vaccines.

Introduction

Vaccines have been administered to large populations for more than two hundred years, with great success in the prevention of infectious diseases worldwide^{1,2}. The adverse effects of the COVID-19 pandemic on the global economy within the last two years underlined the importance of vaccines in preventive medicine. However, growing evidence for potential adverse events of the COVID-19 vaccines in recent years concerns both the scientific and the general communities and possibly causes significant fluctuations in vaccination rates.

Adverse reactions of vaccines may occur due to the interplay of factors of the vaccinated individual causing susceptibility to the drug and the certain components of the vaccines³⁻⁷. To date, the association of the vaccines for influenza, measles/mumps/rubella, smallpox, hepatitis B, human papillomavirus, tetanus toxoid, polio, and others have already been studied³⁻¹¹ and possible associations between these vaccines and conditions such as Guillain-Barré syndrome (GBS), immune thrombocytopenic purpura (ITP), myopericarditis, multiple sclerosis, type 1 diabetes, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) have been implicated. However, considering the potential burden of these severe diseases and the protective effect of vaccines, many side effects of vaccines are negligible¹².

On the other hand, as of the last months of 2020, many types of vaccines, some of which were developed with new technologies such as mRNA and some with traditional methods, have been widely used against COVID-19 all over the world¹³⁻¹⁶. To date, about 5 billion people have had at least 1 dose of the COVID-19 vaccine¹⁷. This is an extremely rare event in the history of medicine. The widespread vaccination of the population in such a short time and the simultaneous use of different vaccines produced with new technologies that we are not accustomed to is revealing several problems. While some of them seem to be unexpected side effects, some of them are obscure side effects occurring due to their widespread application to the population. Allergic reactions, vaccine-related thrombotic events, relapses, or the first occurrence of autoimmune diseases are the main reported side effects of COVID-19 vaccines¹⁸⁻²⁰. An increasing number of cases of new-onset autoimmune-inflammatory rheumatic diseases (AIRD) or other immune-mediated diseases after COVID-19 vaccination have begun to accumulate in the literature²¹⁻³².

As the observed number of patients with a temporal relationship of new-onset inflammatory rheumatologic diseases to the COVID-19 vaccination is increasing in our outpatient clinics we aimed to present our case series and review the current literature on the subject.

Patients and Methods

We investigated the clinical features and laboratory parameters of the newly developed AIRD after being vaccinated with one of the COVID-19 vaccines (BNT162b2 or CoronaVac) approved in our country. None of the patients included in the study had previously been admitted to the hospital with a complaint suggestive of any inflammatory rheumatic disease. In this study, we retrospectively analyzed the time between the onset of the complaint and vaccination in patients who did not have a previous diagnosis of rheumatic disease or had any complaints suggestive of it and who applied to the hospital for the first time with such a complaint.

Clinical and laboratory data were collected together with the patients' self and familial history for autoimmune diseases. Having a previous COVID-19 infection is one of the factors that may exaggerate the immune response that may occur after vaccination. For this reason, before the onset of rheumatic complaints of the patients, their vaccination information as well as their COVID-19 infection histo-

ry were also questioned. To exclude the effect of a hyperinflammatory reaction that may be developed after COVID-19, such as multisystem inflammatory syndrome in adults (MIS-A), patients with a history of COVID-19 and who developed symptoms of AIRD at least three months after the recovery from COVID-19 were included in the study³⁰. An informed consent was taken from all participants.

We performed also a PubMed search using the key words "Vaccination induced autoimmune diseases", "COVID-19 Vaccination induced autoimmune diseases" and "vaccine-induced rheumatic disease". The search with these key words resulted in 205, 54 and 77 articles, respectively. The titles or abstracts of these articles were read and 30, 23 and 7 of them were selected, respectively. After the exclusion of shared articles, 53 manuscripts were reviewed.

Results

We collected data of 22 cases (14 female, 63.6%) that developed an AIRD after the COVID-19 vaccination. Clinical characteristics and diagnosis of the cases are outlined in **Supplementary Table I**. The mean age was 53±14.4 (24-87) years. The mean interval between the last dose of vaccination and the development of the first complaints was 23.9±19.5 (4-90) days. Inactivated vaccine (CoronaVac) was administered to four patients, and the BNT162b2 to 18 patients. Three patients in the BNT162b2 group received initially two CoronaVac injections and thereafter a single dose of the BNT162b2. The symptoms of the last three patients developed after BNT162b2 shots. AIRD-related symptoms developed in 12 patients after the first dose, in 8 patients after the second dose, and in two patients after the third dose. Twelve out of the 22 (54.5%) cases were diagnosed with rheumatoid arthritis, two with systemic lupus erythematosus (SLE), and the remaining eight patients each with leukocytoclastic vasculitis, Sjogren's syndrome, psoriatic arthritis, ankylosing spondylitis, systemic sclerosis, mixed connective tissue disease, eosinophilic granulomatosis with polyangiitis, and inflammatory myositis, respectively. There was no history of immune-mediated disease in the families of sixteen patients. Six patients had a history of documented antecedent COVID-19 infection that occurred before symptoms with a mean of 197.8±100.5 (105-380) days.

Among the reviewed manuscripts 19 of them were related to AIRD or other immune-mediated systemic disease, they were outlined in Table I.

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Table I. Main articles about the various immune mediated reactions that vaccines can cause.

Authors	Article type	Vaccine type, which dose	Triggered disease, age (years), gender (F: female; M: male)	Vaccine-AIRD Interval
1. Wieske et al ²⁶	Prospective observational multi-arm multicenter cohort study	ChAdOx1 nCoV-19, mRNA	Short-term adverse events	7 days
2. Báez-Negrón and Vilá ²¹	Case report	mRNA, second	SLE, 27 y, F	14 days
3. Gilio and De Stefano ⁵³	Case report	mRNA, first	Giant cell arteritis; 63 y, F	5 days
4. Cole et al ⁴⁵	Case report	ChAdOx1 nCoV-19, first	Diffuse cutaneous systemic sclerosis; 70 y, M	14 days
5. An et al ³⁰	Case report	CoronaVac, first	Reactive arthritis; 23 y; F	14 days
6. Watad et al ³²	Case Series	ChAdOx1 nCoV-19, mRNA	10 new onset immune-mediated diseases	1-25 days
7. Lai et al ²⁵	Review	ChAdOx1 nCoV-19 and Ad26.COVS COVID-19	Thrombosis with thrombocytopenia syndrome	14 days
8. Finsterer et al ²⁷	Review	ChAdOx1 nCoV-19, Ad26.COVS COVID-19, mRNA	Guillain-Barré syndrome	Up to 15 days
9. Greb et al ²⁸	Case report	mRNA, second	Giant cell arteritis, 79 y, M	2 days
10. Román et al ³¹	Case report and comprehensive clinical review of 43 patients	ChAdOx1 nCoV-19,	Acute transverse myelitis 21 to 73 y; 23 M, 20 F	15 hours to 6 weeks
11. McKean and Chircop ⁴³	Case report	ChAdOx1 nCoV-19, first	Guillain-Barré syndrome; 48 y, M	10 days
12. N et al ⁴⁴	Case report	mRNA, first	SLE 22 y, F	7 days
13. Paulsen et al ⁵⁴	Case series	ChAdOx1 nCoV-19, first	Immune thrombocytopenic purpura; 64 to 72 y; 2 F, 2 M	2 to 15 days
14. Ismail and Salama ⁵⁵	Case series	ChAdOx1 nCoV-19, Ad26.COVS COVID-19, AZD1222; CoronaVac, mRNA; First (71.8%) and second doses (28.1%)	CNS demyelination; 24-78 years; 19 F, 10 M	1-30 days
15. Fanni et al ⁵⁶	Case report	ChAdOx1 nCoV-19, first	Severe thrombotic thrombocytopenia; 58 y, M	13 days
16. Erdem et al ⁵⁷	Case report	CoronaVac, first	Acute transverse myelitis; 78 y, F	21 days
17. Ishay et al ⁴⁸	Case series	mRNA (BNT162b2), first	Symmetric polyarthritis oligoarthritis Temporal arteritis like disease; 22-60 y; 7 M, 1 F	A few hours to -21 days
18. Baimukhamedov et al ⁵⁰	Case report	SPUTNIK-V, first	Swelling and pain in both knee and shoulder joints, 38 y, F	20 days
19. Singh et al ⁵¹	Letter	BBV152, COVAXIN, first	Rheumatoid nodules, symmetric polyarthritis of hands; refractory hyper-eosinophilia. Late 50s, F	60 days

SLE: systemic lupus erythematosus; CNS: central nervous system.

Discussion

COVID-19 has been on the world agenda since the beginning of 2020. To date, it has affected nearly 500 million people and caused over than six million deaths. Despite the milder disease course of the Omicron variant COVID-19 continues to be a life-threatening health problem¹⁷. COVID-19 vaccines, developed using several distinct vaccine platforms towards the end of 2020, are proven to be efficacious in preventing hospitalizations and disease-related deaths^{13,14}.

Classically, two major approaches to active immunization have been used: firstly, live (attenuated) infectious agents and inactivated or detoxified agents or their extracts; secondly, newer generation vaccines, including recombinant protein vaccines and vector-based vaccines, with only a specific antigen or antigen from the pathogen rather than the entire pathogen which provide a better safety profile³³⁻³⁶. Inactivated vaccines are relatively safer as live pathogens are not involved, but they can be lower in immunogenicity and often require multiple doses to establish immune memory. Establishing an antigen-specific immune response requires triggering the innate immune system to detect the antigen as foreign pathogens. However, the inactivated virus and recombinant protein antigens are often weakly immunogenic and require an adjuvant, such as Aluminum salts called “alum”, to boost the immunogenicity. Various theories³ have been proposed to explain the adjuvant effect of alum, such as the “depot theory”, the inflammasome hypothesis, increasing uric acid secretion from dead cells, increasing IL-4 production, and involvement of Syk-PI3 kinase pathway. The last generation vaccine platforms are nucleic acid vaccines including mRNA or DNA vaccines that were first used against COVID-19 and which do not contain alum^{13,14,37}.

A major concern among clinicians is whether immunocompromised patients will elicit an adequate immune response to the vaccine. For this reason, we emphasized that our rheumatology patients should continue to take protective measures during the pandemic process. However, we do know that there are vaccines, such as the influenza vaccine, that are recommended for certain vulnerable groups of people, including those who are immunocompromised. The influenza vaccine appears to induce a good immune response and reduce the risk of respiratory morbidity and mortality in the rheumatology population. Based on this, all other vaccines, except for live vaccines,

are currently considered safe for the use in the rheumatology population and produce an adequate response to induce immunity³⁸.

In general, autoimmune diseases develop as a result of the loss of the immune system's ability to distinguish self and non-self, due to an underlying genetic predisposition and the presence of variations in some proteins or receptors. In addition, the genetic predisposition and variations of many environmental factors such as the sun, chemicals, and hormones may play for the development of autoimmunity³⁹.

There have long been concerns that vaccines could trigger autoimmunity. The adjuvant effect, molecular mimicry or other many mechanisms may cause the triggering of innate and/or adaptive immune system to exacerbation or new onset of AIRD^{23,24,40}. The vaccine-induced immune-mediated diseases concerns are recently grown again with the widespread use of mRNA vaccines, which are developed using novel technologies of vaccine production^{14,37,41}.

Adjuvants in vaccines are blamed as one of the most common triggers of autoimmunity. Autoimmune/Inflammatory Syndrome Induced by Adjuvant (ASIA), which was first described by Shoenfeld and Agmon-Levin⁴⁰, describes autoimmune/inflammatory diseases triggered by various adjuvants, including those used in these vaccines, in genetically susceptible individuals⁴². Of course, the development of ASIA is not a condition that develops in everyone who is vaccinated; in contrast, it is a rare complication. Moreover, it can occur for many other reasons other than vaccines.

Messenger RNA molecules have intrinsic immunogenicity that is analogous to RNA virus infection, often referred to as “self-adjuvant” in mRNA vaccines. For mRNA vaccines, proinflammatory responses may be from the mRNA molecules *per se* and the delivery vehicles, such as the lipid nanoparticles. The non-specific adjuvant effects of the mRNA vaccines may trigger the immune system and lead to different inflammatory disorders³². Chemical modifications of the mRNA molecules may alter their proinflammatory activity, but the delivery vehicles and the mRNA condensing lipids can both induce unwanted pro-inflammatory responses^{43,44}. For these reasons, COVID-19 vaccines, developed with these novel technologies, were used with precaution in patients with autoimmune diseases at first, but it is supported with strong evidence now that they do not trigger flares of existing autoimmune-autoinflammatory diseases^{12,22,23,41}. But, *de novo* autoimmune diseases as a complication of vaccines attract the attention of

rheumatologists in the presence of mass vaccinations for COVID-19^{21-32,45-50}.

In the study of Haslak et al⁵¹, which examined COVID-19 vaccine-related early adverse events among adolescents and young adults with rheumatic diseases, including 246 individuals (23 healthy controls), the most common adverse events were fatigue, headache, myalgia, arthralgia and fever. Local reactions were reported⁵¹ in 20 patients and disease exacerbation was reported in 27 patients within one month after vaccinations.

Undifferentiated Connective Tissue Disease (uCTD) was the most frequent autoimmune disease related to the ASIA syndrome reported in the "International ASIA Syndrome Registry"²⁴⁶. The majority (54.5%) of our case series consisted of rheumatoid arthritis patients, with a female predominance (Supplementary Table I). Similarly, many newly developed rheumatoid arthritis (RA) cases have started to be reported^{49,50} in the literature after vaccination for COVID-19. It can be thought that some of the patients we followed-up with the diagnosis of rheumatoid arthritis had reactive arthritis. However, almost all of these patients were rheumatoid factor (RF) and/or anti-citrullinated protein antibody (ACPA) positive, and all of them required at least one of conventional synthetic disease-modifying antirheumatic drugs besides glucocorticoids in their treatment. Eight of our 12 patients who developed RA had received the BNT162b2 vaccine. In addition, 3 of them were smoker. It is known^{23,24,35,40} that adjuvants can induce autoimmunity, and such an objection has always existed for mRNA vaccines. The mRNA molecules acting as a self-adjuvant or the lipid content may have triggered autoimmunity in genetically predisposed individuals^{43,44}.

For instance, previous observations²⁴ of autoimmune diseases such as SLE, autoimmune hepatitis, and GBS diagnosed after COVID-19 vaccination was developed within days after vaccination. Similarly, we observed a short duration with an average of 23 days between the vaccinations and the first complaints attributed to AIRDs which responded well to treatment with the conventional disease-modifying anti-rheumatic drugs. The sole patient diagnosed with ankylosing spondylitis had no history of inflammatory type low back pain before the COVID-19 vaccination, no family history, and was HLAB27 positive. The emergence of symptoms immediately after vaccination and HLAB27 positivity suggested that the vaccine may have triggered the disease in this patient with a genetic predisposition.

A notable characteristic of this patient was that he was resistant to the treatment with non-steroidal anti-inflammatory drugs, sulphasalazine (2 gr/per day, PO), and adalimumab (40 mg Q14 days, SC), but had a good response to the treatment with etanercept (50 mg/per week, SC) injections.

Cole et al⁴⁵ reported a case of diffuse systemic sclerosis after the first dose ChAdOx1 vaccination in a 70-year-old male. Similarly to our case, this patient was tested negative for the anti-Scl-70 and anti-centromere antibodies. Our patient was tested positive for the polymyositis-scleroderma (Pm Scl) antibody and had elevated creatine kinase levels. Although muscle biopsy was not performed in this patient, based on antibody testing and elevated creatine kinase levels, our patient may be considered a case of overlapping systemic sclerosis and myositis.

The case of eosinophilic granulomatosis with polyangiitis (EGPA), who is a 32-year-old male patient with a previous diagnosis of RA due to symmetric polyarthritis and with a follow-up of five years with subsequential methotrexate and leflunomide treatment, was known to be positive for rheumatic factor before the COVID-19 vaccination. Other than this patient, we do not know the antibody status before vaccination, and we do not have enough information about their genetic predisposition, which limits any interpretation about the role of autoantibodies in the development of AIRD. But 22% of our patients had a family history of autoimmune or autoinflammatory diseases implying that genetic predisposition plays a role in AIRD development. A history of smoking was present in 27% of our patients, and it is the only possible environmental factor associated with this complication. But, without a comparator group for which we know the rate of smokers among non-vaccinated patients with newly diagnosed AIRD, it is not possible to draw any conclusion.

Watad et al³² reported a case series of 27 patients with immune-mediated diseases, but only 10 of these patients had a new-onset immune-mediated or autoinflammatory diseases, including polymyalgia rheumatica, myasthenia gravis, multiple sclerosis, and pericarditis. The remaining 17 had exacerbations of the underlying AIRD. Ishay et al⁴⁸ reported a case series of autoimmune phenomena after COVID-19 vaccination, of which only three were similar to new-onset AIRD cases; others included isolated pericarditis, myocarditis, or acute exacerbations of the underlying AIRD. In our series, all of the AIRD patients had a new onset, and it is the largest series reported in the literature up to date.

Generally, vaccine-related adverse effects occur within days, but late adverse events such as measles/MMR-associated thrombocytopenia developing after up to 83 days have been reported⁷ as well. Also, as can be seen in ASIA, it may be possible in very late-term reactions⁴⁰. While the adjuvant-associated ASIA syndrome may evolve even after years, *de novo* autoimmune diseases that are triggered by COVID-19 vaccines appear to occur more swiftly⁴². Since the late-onset immune-mediated reactions may develop even years after vaccination, a follow-up is important, especially for people vaccinated with new-generation vaccines who are carriers of autoantibodies or have a family history of AIRD. Our observations should not be interpreted as a strict recommendation of avoidance of COVID-19 vaccination in predisposed patients for AIRD. On the other side of the coin a proven efficacy of vaccines in preventing this lethal viral infection was shown⁴⁶. Hence, COVID-19 vaccination may prevent AIRD that may develop due to COVID-19 infection itself^{9,47}. It is necessary to follow current recommendations of vaccination with a precautious follow-up in the AIRD predisposed population.

COVID-19 vaccines, particularly mRNA and other next-generation vaccines, may trigger the development of AIRD, particularly RA, in a predisposing setting of genetic and/or environmental factors. Prospective, follow-up studies observing real-life data after vaccination in predisposed populations are of great interest⁵⁰⁻⁵⁶.

Conclusions

Autoimmune/inflammatory rheumatic diseases may develop after COVID-19 vaccines. Vaccination should be carefully questioned in newly diagnosed AIRD patients in the era of the COVID-19 pandemic. Of course, the available data do not establish a causal relationship between vaccines and autoimmune/inflammatory rheumatic diseases. However, we think that such observational studies are valuable in order to provide clearer data on this subject in the future.

Conflict of Interests

The authors have no conflict of interests to declare.

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Availability of Data and Materials

Authors can confirm that all relevant data are included in the article. The data used to support the findings of this study are included within the article.

Ethics Approval

Not applicable.

Informed Consent

In our retrospective study, the data were analyzed retrospectively through the hospital computer automation system. Informed consent was obtained from the patients for the use of data in the study.

Authors' Contributions

Akkuzu G: conceptualization, data curation, formal analysis, investigation, methodology, validation, visualization, writing-original draft. Bes C: conceptualization, data curation, formal analysis, investigation, methodology, validation, visualization, writing-original draft. Özgür D: data curation, formal analysis, investigation, methodology, writing-original draft. Karaalioğlu B: data curation, formal analysis, investigation, methodology, writing-original draft. Mutlu M: data curation, formal analysis, investigation, methodology, writing-original draft. Yıldırım F: data curation, formal analysis, investigation, methodology, writing-original draft. Atagündüz P: data curation, formal analysis, investigation, methodology, writing-original draft. Gündüz A: data curation, investigation. Soy M: conceptualization, formal analysis, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, writing-review and editing.

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