

**Herpes zoster following BNT162b2 mRNA Covid-19 vaccination in patients with autoimmune inflammatory rheumatic diseases: a case series**

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## Abstract

### Objectives:

As global vaccination campaigns against COVID-19 disease commence, vaccine safety needs to be closely assessed. The safety profile of mRNA-based vaccines in patients with autoimmune inflammatory rheumatic diseases (AIIRD) is unknown. The objective of this report is to raise awareness to reactivation of herpes zoster (HZ) following the BNT162b2 mRNA vaccination in patients with AIIRD.

### Methods:

The safety of the BNT162b2 mRNA vaccination was assessed in an observational study monitoring post-vaccination adverse effects in patients with AIIRD (n=491) and controls (n=99), conducted in two Rheumatology Departments in Israel.

### Results:

The prevalence of HZ was 1.2% (n=6) in patients with AIIRD compared to none in controls. Six female patients aged 49±11 years with stable AIIRD: rheumatoid arthritis (n=4), Sjogren's syndrome (n=1), and undifferentiated connective disease (n=1), developed the first in a lifetime event of HZ within a short time after the first vaccine dose in 5 cases and after the second vaccine dose in one case. In the majority of cases, HZ infection was mild, except a case of HZ ophthalmicus, without corneal involvement, in RA patient treated with tofacitinib. There were no cases of disseminated HZ disease or postherpetic neuralgia. All but one patient received antiviral treatment with a resolution of HZ-related symptoms up to 6 weeks. Five patients completed the second vaccine dose without other adverse effects.

**Conclusion:** Epidemiologic studies on the safety of the mRNA-based COVID-19 vaccines in patients with AIIRD are needed to clarify the association between the BNT162b2 mRNA vaccination and reactivation of zoster.

### Key words

herpes zoster, reactivation, COVID-19 BNT162b2 mRNA vaccine, vaccination, rheumatic diseases/AIIRD

### Key messages

- Herpes zoster reactivation following COVID-19 vaccination is reported in 6 patients with stable AIIRD.
- COVID-19 BNT162b2 mRNA vaccine might provoke reactivation of herpes zoster in patients with AIIRD.
- Epidemiologic studies on the safety of COVID-19 vaccines in patients with AIIRD are warranted.

## Introduction

Since the emergence of coronavirus disease 2019 (COVID-19) pandemic, the prevention of the rapidly spreading infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become of paramount importance. Two mRNA-based vaccines, BNT162b2 and mRNA-1273, have demonstrated a high efficacy rate with an acceptable safety profile(1,2), leading to their expedited authorization by the regulatory authorities. A nationwide mass BNT162b2 vaccination campaign has been launched in Israel with an exceptionally rapid pace and high uptake of vaccination, with 53% (n=4,745,665) and 38% (n=3,399,367) of the population vaccinated with the 1<sup>st</sup> and 2<sup>nd</sup> vaccine dose, respectively, updated to March 1st, 2021. Immunosuppressed patients, including patients with autoimmune inflammatory rheumatic diseases (AIIRD), have been prioritized for urgent vaccination, consistent with the ACR COVID-19 Vaccine Clinical Guidance Task Force recommending vaccination in most patients with AIIRD.(3)

To date, there is no data available on the safety of mRNA COVID-19 vaccination in AIIRD patients, as immunosuppressed patients were excluded from the vaccines' clinical trials. Therefore, safety monitoring and surveillance of vaccinated patients is especially warranted in this population. In this report, we present a series of six patients with AIIRD who developed a first episode of herpes zoster (HZ) closely after vaccination with the BNT162b2 mRNA vaccine. We further discuss potential mechanisms for this clinical observation and a potential causal link between the vaccination and reactivation of zoster infection.

## Methods

The safety of the BNT162b2 mRNA vaccination was assessed in a two-center observational study **4,745,665** monitoring post-vaccination adverse effects in patients with AIIRD (n=491) and controls (n=99). The study has been conducted since December 2020 and is presently ongoing at the Rheumatology Departments of the Tel Aviv Medical Center, Tel Aviv and Carmel Medical Center, Haifa, Israel. Consecutive patients with AIIRD, including rheumatoid arthritis (RA), spondyloarthropathies, connective tissue diseases (CTD), vasculitis and myositis) followed at both departments were offered to enroll into the observational study monitoring potential adverse effects following the BNT162b2 mRNA vaccination provided as a standard of care. The study has been approved by the Institutional Board Review of both institutions, TLV-1055-20 and CMC-0238-20, respectively. All participants signed a written informed consent to be participate in the study. The present case series is based on the interim analysis of the safety results collected within the initial 6-week post-vaccination period.

## Case summaries

Demographic, clinical and treatment-related characteristics of each of the six patients are reported in Table 1.

**Case 1.**

A 44-year-old woman, with a history of Sjogren's syndrome treated with hydroxychloroquine (HCQ) presented with the first episode of HZ after COVID-19 vaccination. She had a history of varicella and was not vaccinated against HZ. She received the first dose of the BNT162b2 mRNA vaccine on December 27, 2020 and three days later developed headache, low back pain, vesicular skin rash and pruritus, consistent with HZ affecting the dermatome L5. She did not receive any treatment for HZ with a spontaneous resolution of symptoms within 3 weeks. She received the second vaccine dose 4 weeks apart from the first one, without other adverse effects. No flare of rheumatic disease was reported during that period.

**Case 2.**

A 56-year-old woman, with a history of a longstanding seropositive RA presented with the first episode of HZ ophthalmicus (HZO) following COVID-19 vaccination. The patient was treated with multiple biologics and achieved a low disease activity under tofacitinib initiated in 2014. She had a history of varicella and was not vaccinated against HZ. She received the first dose of BNT162b2 mRNA vaccine on January 4th, 2021, followed by development of malaise, intense headache, and sensation of cold at the left hemicranium. She had no fever. Four days after vaccination, left-sided severe pain of the left eye and forehead appeared, accompanied by a typical rash of HZ at the distribution of the ophthalmic division (V1) of the V cranial nerve. On the eye examination, she had hyperemic conjunctivitis, without corneal involvement. She was treated with acyclovir for 14 days, lubricant eye drops, and analgesics with a gradual resolution of symptoms within 6 weeks. The treatment with tofacitinib was temporarily discontinued for two weeks. During that time, she did not experience any flare of arthritis. Due to concern of further complications, she declined the second dose of the vaccine.

**Case 3.**

A 59-year-old woman, with seropositive RA presented with the first episode of HZ following COVID-19 vaccination. The patient was resistant to multiple biologics and baricitinib. Since June 2020, she has been treated with upadacitinib and prednisone 5 mg/day with a partial response. She had a history of varicella and received a live-attenuated zoster vaccine (Zostavax ®) prior to initiation of baricitinib in February 2019. She uneventfully received the first dose of the BNT162b2 mRNA vaccine on December 28, 2020 followed by the second dose on January 18<sup>th</sup>, 2021. Two days later, she presented with pain and typical HZ vesicular skin rash at the low abdomen, inguinal area, upper thigh, and buttock, without systemic symptoms. She was treated with valacyclovir for three days that was discontinued due to side effects. Upadacitinib was discontinued with a subsequent severe polyarticular flare of RA. The disease course was characterized by a slow healing of skin lesions within 6 weeks. Her anti-rheumatic therapy was switched to etanercept.

**Case 4.**

A 36-year-old woman, with a history of a longstanding seropositive RA complicated by interstitial lung disease, presented with the first episode of HZ following COVID-19 vaccination. Her anti-rheumatic treatment was stable for the last 2 years and included mycophenolate mofetil 2 grams/day, rituximab provided in July 2020, and prednisone 7 mg/day. She had a history of varicella and was not vaccinated for HZ. She received the first dose of the BNT162b2 mRNA vaccine on December 28, 2020. Ten days later, she developed pain and typical vesicular skin rash at the abdomen and back at the distribution of T10 dermatome. She was treated with acyclovir for one week with a resolution of symptoms within 6 weeks. She received the second dose of vaccine 4 weeks apart from the first vaccine dose, without other adverse effects. No flare of rheumatic disease was reported during that period.

#### **Case 5.**

A 38-year-old woman with a longstanding history of undifferentiated CTD and anti-phospholipid syndrome (APS), treated with HCQ and aspirin, presented with the first episode of HZ following COVID-19 vaccination. She had a history of varicella and was not vaccinated against HZ. The patient received the first dose of the BNT162b2 mRNA vaccine on December 28, 2020 and two weeks later developed tingling, itching followed by vesicular skin rash typical for HZ at the right breast, without systemic symptoms. She was prescribed acyclovir for one week with a consequent resolution of symptoms in 3 weeks. She received the second dose of the vaccine 4 weeks apart from the first vaccine dose, without other adverse effects. She did not experience any flare of her baseline disease during that period.

#### **Case 6.**

A 61-year-old woman with a longstanding seropositive RA treated with tocilizumab and prednisone 5 mg/day presented with the first episode of HZ following COVID-19 vaccination. She had a history of varicella in childhood and was not vaccinated for HZ. She received the first of the BNT162b2 mRNA vaccine on January 11, 2021. Two weeks later, a typical HZ rash appeared at the distribution of T6 dermatome, without systemic symptoms. She was treated with valacyclovir for one week with a complete recovery within 10 days. In addition, she experienced a mild flare of arthritis and increased the dose of prednisone to 7.5 mg/day. She received the second vaccine dose three weeks apart from the first one as scheduled, without other adverse effects.

#### **Discussion:**

We present a case series of six patients with AIIRD who developed the first episode of HZ closely following the BNT162b2 mRNA vaccination against COVID-19. In our study, the prevalence of HZ corresponded to 1.2% in patients with AIIRD compared to none in controls. All but one patient presented with HZ after the first dose of the vaccine. HZ reactivation was reported following trivalent influenza, hepatitis A, and rabies vaccines, suggesting vaccine-modulated immunomodulation.(4) To our knowledge, there were no reports of varicella-like skin rash or HZ in the mRNA-based vaccines

COVID-19 clinical trials(1,2) and our case series is the first one to report this observation in patients with AIIRD. Our study sample included female patients within a relatively young age range: 36 to 61, average age  $49 \pm 11$  years. In all cases, the baseline rheumatic disease was either mild (cases 1, 5) or stable under medical treatment (cases 2-4, 6), three patients were currently treated with low dose (<10 mg) prednisone, two with biologic DMARDS and two with JAK inhibitors. The severity of HZ was mild with the involvement of one or two dermatomes in all but one patient (case 2) who developed HZO, without corneal involvement. None of the patients developed disseminated disease or post-herpetic neuralgia. Notably, one patient developed HZ despite being vaccinated for HZ two years prior to the reported event. Five patients received an oral anti-viral therapy with a good clinical result. The close temporal association between COVID-19 vaccination and the first reactivation of the latent zoster infection poses a question of a potential causality between both events versus a pure coincidence.

Cell-mediated immunity plays an important role in the prevention of VZV reactivation. Declining cell-mediated immunity with age or disease is associated with a reduction in VZV-specific T cells, disrupting immune surveillance and increasing the risk of reactivation, with age being the major risk factor for 90% of cases of HZ.(5)

The risk of HZ infection in the AIIRD population is increased compared to the general population(6–8), with a pooled incidence rate ratio of 2.9, 95% confidence interval 2.4-3.3.(9) Among patients with RA, the risk of HZ infection is estimated to be 2-fold compared to the healthy population within the same age range.(6) Risk factors for HZ infection in RA include old age, high disease activity, and dose-related use of glucocorticoids(10) which were absent in RA patients with HZ in our case series. Treatment with JAK inhibitors doubles the risk of HZ in RA compared to other biologics.(11,12) Indeed, in our report, two RA patients were treated with JAK inhibitors but for a substantial amount of time, with one of the patients previously vaccinated for HZ, suggesting vaccination as a potential trigger for HZ. Another RA patient (case 4) was significantly immunosuppressed which indeed may explain HZ reactivation at any time point.

Since the emergence of the COVID-19 pandemic, varicella-like exanthem(13) and HZ(14–21) have been globally reported in the context of COVID-19 infection. The suggested pathogenetic mechanism relates to an observation that SARS-CoV-2 infection can damage the function of CD4+ T cells and promote excessive activation and possibly subsequent exhaustion of CD8+ T cells.(22) Together, these perturbations of T cell subsets may eventually diminish host antiviral immunity.(23)

Potential mechanisms that might explain the pathogenetic link between mRNA-COVID19 vaccination and HZ reactivation are related to stimulation of innate immunity through toll-like receptors (TLRs) 3,7 by mRNA-based vaccines.(24) TLR signaling has been implicated during reactivation of herpesviruses, a process essential for these viruses to maintain themselves in the host.(25) Defects in TLR expression in patients suffering from diseases caused directly by herpesvirus infection highlight the importance of these signaling pathways during infection and eventual disease progression.(25)

The vaccine stimulates induction of type I INFs and potent inflammatory cytokines, which instigate T and B immune responses but may negatively affect antigen expression potentially contributing to HZ reactivation.

Our report has a number of limitations. First, the study design is not structured to determine a causal relationship between vaccination and HZ, as non-vaccinated patients with AIIRD were not included in the study. Second, HZ diagnosis was based solely on clinical grounds, without histologic or molecular confirmation. We also acknowledge that the real number of HZ cases following COVID-19 vaccination may be under reported in both general and AIIRD populations.

In summary, the presented cases raise awareness to a potential causal link between COVID-19 vaccination as a trigger of HZ reactivation in relatively young patients with stable AIIRD. While the causality between both events cannot be proved based on a small number of cases, further vigilance and safety monitoring of COVID-19 vaccination side effects is warranted. Clinical registry of safety of COVID19 vaccination among patients with AIIRD will provide further insight into this open question.

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#### Conflicts of interest

The authors declare no conflicts of interest.

#### Data statement

Not applicable

#### Ethics

The study complies with the Declaration of Helsinki approved by the Tel Aviv Medical Center and Carmel Medical Center committees: TLV-1055-20 and CMC-0238-20, respectively. Informed consent has been obtained from all the participants.

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Table 1. Clinical summary.

Case #	Gender/ Age (yr)	RMD	RMD treatment	History of varicella (Y/N)	HZ vaccinated (Y/N)	Time interval between COVID-19 vaccination and HZ onset	HZ localization/ dermatome	HZ severity & symptoms	HZ treat ment	HZ course	Completed two doses of COVID-19 vaccine (Y/N)
1.	F, 44	Sjogren's syndrome	HCQ	Y	N	3 days after the 1 <sup>st</sup> dose	L5	<b>Mild</b> skin rash, pruritus, pain, inguinal lymphadenopathy	None	Resolution within 3 weeks	Y
2.	F, 56	RA	tofacitinib	Y	N	4 days after the 1 <sup>st</sup> dose	V1 of V cranial nerve	<b>Moderate/HZO</b> headache, tingling & burning, facial skin rash, eyelids swelling, conjunctivitis	Acyclovir 14-day course	Resolution within 6 weeks	N
3.	F, 59	RA	upadacitinib, low dose prednisone	Y	Y	2 days after the 2 <sup>nd</sup> dose	L1-L2	<b>Mild</b> Skin rash, pain, inguinal lymphadenopathy, slow healing of skin lesions	Valacyclovir 3-day course	Resolution within 6 weeks	Y
4.	F, 36	RA, ILD	mycophenolate mofetil,	Y	N	10 days after the 1 <sup>st</sup> dose	T10	<b>Mild</b> skin rash,	Acyclovir one-week	Resolution within 6	Y

			prednisone, rituximab - 07/2020					pruritus, pain	course	weeks	
5.	F, 38	Undifferentiated CTD, APLA	HCQ, aspirin	N	N	2 weeks after the 1 <sup>st</sup> dose	T4	<b>Mild</b> skin rash, pruritus, pain	Acyclovir one-week course	Resolution within 3 weeks	Y
6.	F, 61	RA	Tocilizumab, prednisone 5 mg/day	Y	N	2 weeks after the 1 <sup>st</sup> dose	T6	<b>Mild</b> skin rash	Valacyclovir one-week course	Resolution within 10 days	Y

Legend: APLA – anti-phospholipid antibody syndrome, CTD – connective tissue disease, HCQ -hydroxychloroquine, HZ – herpes zoster, HZO – herpes zoster ophthalmicus, ILD – interstitial lung disease, N – no, RA – rheumatoid arthritis, RMD - rheumatic disease, Y - yes