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Safety, long-term effectiveness, and immunogenicity of varicella vaccination in children with juvenile idiopathic arthritis treated with biologic therapy

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ABSTRACT

Objective: To evaluate safety, long-term effectiveness and immunogenicity of varicella vaccination in children with JIA, treated with biologic disease-modifying antirheumatic drugs (bDMARDs).
Methods: This is a prospective case-control study. VZV-naive patients with JIA on selected bDMARDs (TNFi, IL-6 and IL-1 inhibitors), who were at risk for contracting varicella, had stable disease and normal values of immunoglobulins and lymphocyte populations, were vaccinated against varicella. Adverse events (AEs) and disease activity were followed after vaccination. VZV-specific humoral (VZV-IgG) and cell-mediated immunity (VZV-CMI) were measured at predetermined time points after vaccination by Liaison and intracellular cytokine staining, respectively. Two healthy control (HC) groups comprised 52 healthy children after varicella vaccination and 69 healthy children after varicella infection.
Results: 17 patients were vaccinated against varicella (12 on TNFi, 4 on IL-6 inhibitors and 1 on IL-1 inhibitor), of whom 14 patients received both the first and second dose on bDMARDs. No vaccine-strain infections or other serious AEs occurred after vaccination. Disease activity increased in 3/17 (18 %) patients following vaccination. Four out of 17 (24 %) patients developed mild breakthrough varicella (BV) 4 months-4.5 years after vaccination, and none of the HC. Fourteen out of 17 (82 %) patients and 50/52 (96 %) vaccinated HC were seropositive after second vaccination and 8/11 (72 %) patients and 42/43 (98 %) vaccinated HC developed VZV-CMI, which persisted longer compared to VZV-IgG. Patients presented lower antibody levels compared to HC. The rate of VZV-IgG decline was comparable between patients and HC after vaccination or infection. Five patients received the third vaccine dose due to primary or secondary vaccine failure, and none of them developed BV.
Conclusions: Varicella vaccination was safe and largely immunogenic in our cohort of JIA patients treated with bDMARDs. Although the vaccination was not always fully effective, it prevented severe disease in all vaccinated patients.

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1. Introduction

Varicella is a highly contagious disease caused by the varicella zoster virus (VZV) [1]. In countries without universal varicella vaccination, most children are exposed to VZV by their early school years [2].

Patients with rheumatic diseases have an altered immune response due to immunomodulatory therapy and the underlying disease process, making them more susceptible to infections [3–6]. While usually a mild disease in immunocompetent children, varicella can cause severe complications such as secondary infections, pneumonia, hepatitis and encephalitis, particularly in immunocompromised individuals [1,7,8].

The best method of protection against varicella is vaccination. Concerns exist about administering live attenuated vaccines to immunocompromised patients, mainly due to the fear of infection with the vaccine-strain virus and uncertainties about the immune response's quality and duration. In previous studies, varicella vaccination was safe and largely immunogenic in JIA patients treated with immunosuppressive (IS) therapy, but only 18 patients vaccinated during treatment with biologic disease-modifying antirheumatic drugs (bDMARDs) were reported [3,9–13].

Cell-mediated immunity (CMI) is essential for protection against VZV [14]. Two studies have shown that patients with pediatric rheumatic diseases (PRD) develop VZV-specific CMI following varicella vaccination, but no data are available for patients treated with bDMARDs [11,13].

According to the EULAR/PReS recommendations for vaccination of PRD patients, varicella vaccination should be strongly considered in VZV-naive patients on methotrexate (MTX) and can also be considered in VZV-naive patients on low-dose glucocorticosteroids and selected bDMARDs (tumor necrosis factor-alpha inhibitors [TNFi], interleukin-6 [IL-6] and interleukin-1 [IL-1] inhibitors). The level of evidence for this approach is currently low due to the limited prospective data available [3].

To this end, we conducted a prospective case-control study to evaluate the safety, effectiveness, and immunogenicity of varicella vaccination in children with JIA treated with bDMARDs.

To assess humoral immunity, we tested two hypotheses: first, that the median level of VZV-IgG in JIA patients vaccinated against varicella during bDMARD treatment is above the seropositivity level; and second, that VZV-IgG levels decline more rapidly over time in these patients than in the general population. Additionally, we present an exploratory analysis of VZV-specific CMI.

2. Material and methods

A prospective case-control study with long-term follow-up was conducted at the Department of Allergology, Rheumatology and Clinical Immunology of the University Children's Hospital (UCH), University Medical Center (UMC) Ljubljana.

An initial observation of the first 6 patients in our cohort was reported in 2015 [9]. VZV-naive patients with JIA, treated with selected bDMARDs (TNFi, IL-6 and IL-1 inhibitors), who were at risk of contracting varicella (*i.e.*, patients and/or their siblings in school or kindergarten), were invited to participate in the study. The inclusion criteria were a negative history of varicella, negative VZV-specific immunoglobulins (VZV-IgG), normal values of IgM, IgG and IgA and T- and B-lymphocyte populations, and stable disease, defined as no change in disease activity in the three months prior to vaccination. Exclusion criteria included acute febrile illness, exacerbation of JIA, abnormal immunoglobulin levels or lymphocyte populations for age, known hypersensitivity to vaccine components, high dose of IVIG ($\geq$ 2 g/kg) within 11 months, any blood products within 3 months, and treatment with high dose glucocorticoids within 1 month prior to vaccination. Concurrent treatment with standard dose MTX or other conventional synthetic DMARDs was allowed [3]. Patients received no other vaccines one month before and three months after each dose.

The two healthy control (HC) groups consisted of age-matched healthy children who had either previously contracted varicella or received the varicella vaccination. Serologic testing was offered to HC prior to vaccination but was not mandatory for study inclusion.

All vaccinated children received two doses (0.5 ml each) of monovalent live-attenuated varicella vaccine, containing >1000 plaque-forming units of the VZV Oka strain (Varilrix® or Varivax®) subcutaneously at least 4 weeks apart, as recommended by the manufacturer (GlaxoSmithKline, UK or MSD, USA). For patients with primary or secondary vaccine failure after the second dose, we considered a third dose of the same vaccine. There was no preference for the vaccination day in relation to the bDMARD administration.

Parents were instructed to document any adverse events (AEs) occurring within one month following each dose and to seek medical attention in case of significant clinical symptoms. We asked them to report any exposure to varicella or herpes zoster (HZ) after vaccination (only close contacts - household contact and face-to-face indoor contact $\geq$5 min with varicella or uncovered, uncrusted HZ lesions were considered in the analyses) and contacted them by telephone at the end of the study period to verify whether exposure, breakthrough varicella (BV), or HZ had occurred. BV is defined as infection with wild-type VZV occurring more than 42 days after vaccination [1].

Disease activity was assessed by counting joints with effusion before and 4–6 weeks after each dose. Signs of systemic manifestations (fever, rash, lymphadenopathy, hepatosplenomegaly, serositis) were assessed in patients with systemic onset JIA (soJIA).

All patients and HC after vaccination were followed prospectively until the end of August 2024, starting in August 2011 for patients and October 2018 for HC. HC after varicella were included based on the time from infection to blood sampling.

Humoral immunity was assessed by measuring VZV-IgG before vaccination, at 4–6 weeks, 3–6 months, 1 year after the second dose, and then at regular follow-up visits every 6–12 months, using a commercial chemiluminescent immunoassay (CLIA, LIAISON® VZV IgG, DiaSorin). The lower limit of seropositivity was 100 mIU/ml.

VZV-specific T-cell-mediated immunity (VZV-CMI) was measured in each patient at least once after vaccination using flow cytometric intracellular cytokine staining. Peripheral blood mononuclear cells (PBMCs) were isolated from fresh heparinized blood samples (stored at room temperature for a maximum of 15 h before isolation) by density gradient centrifugation using Ficoll-Paque (Amersham Biosciences, Little Chalfont, UK). PBMCs were resuspended in supplemented RPMI 1640 medium containing 2 mmol/l L-glutamine, 10 % heat-inactivated fetal calf serum, and 100 I.U. penicillin. The cell concentration was adjusted to 1.5×10^6 cells/ml and stimulated for 15 h *in vitro* with PepMIX VZV (IE62) Varicella-Zoster virus (strain Oka vaccine HHV-3) from Innovative Peptide Solutions at a final concentration of 1 µg/ml. After the first 2 h, Brefeldin A (BD Golgi Plug™) was added to each tube at 1 µl/ml. Unstimulated cells served as negative controls, while phorbol myristate acetate (PMA) at 50 ng/ml and ionomycin at a final concentration of 1 µg/ml (both from Sigma-Aldrich, Gillingham, UK) were used as positive controls. Following stimulations, cells were stained with monoclonal antibodies against CD8 (APC Cy7), CD3 (BV450), CD4 (PerCP-Cy5.5) and CD69 (PE) and intracellularly with interferon gamma (IFN-γ FITC) (all from BD Biosciences, San Jose, California, USA). Multiparametric analysis of activated (CD69+) T lymphocyte populations (CD3+, CD4+, and CD8+) producing IFN-γ was performed using a BD FACS Canto II flow cytometer (BD Biosciences, San Jose, California, USA), with data analyzed using FACS Diva software (version 8.0.1). Activated subpopulation of T lymphocytes producing at least 0.1 % IFN-γ among total T lymphocytes were considered positive.

The VZV-specific immune response in each HC was measured once within a period from 4–6 weeks after varicella vaccination or infection to 3 years after vaccination or 5 years after infection. Values obtained within 3 months after administration of any blood products were excluded.

HC were enrolled at UCH, UMC Ljubljana and through primary care pediatricians. Immunologic tests were performed at the Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Slovenia.

2.1. Statistical analysis

Statistical analysis was performed using R (version 4.2.3) and Julia (version 1.10.4). Differences in AEs between patients and HC were assessed using Fisher's exact test, and differences in age distribution using Mann-Whitney *U* test. Linear mixed models in conjunction with a Box-Cox transformation and Wilcoxon signed-rank test were used to test our hypotheses and to perform an exploratory analysis of VZV-CMI. The association between VZV-IgG and VZV-CMI was assessed using Kendall's τ test.

The statistical significance level was set at $\alpha = 0.05$. For the comparison between patients and HC, only VZV-IgG and VZV-CMI values from patients who received the second vaccination while being treated with bDMARDs were considered. Values obtained after BV were excluded from the calculations.

The study was approved by the National Medical Ethics Committee of the Republic of Slovenia (147/05/12 and 0120/308–2016-2). Parents and patients, if applicable, signed an informed consent form prior to the study enrollment.

3. Results

3.1. Patients and controls

Seventeen patients were vaccinated against VZV while on bDMARD treatment. Fourteen patients received both the first and second dose during bDMARD treatment (ten on TNFi and four on IL-6 inhibitors). Two patients received the first dose before starting systemic IS treatment and the second dose during treatment with TNFi. One patient received the first two doses during treatment with MTX and the third dose during treatment with an IL-1 inhibitor. The median time interval between the first and second doses was 1.8 months (range 1–21.7). A total of five patients received the third vaccine dose, after a median interval of 1.9 years (range 1.2–5) from the second dose. Four of them received the first two doses while on TNFi treatment, and one while on MTX. Four patients discontinued systemic IS therapy an average of 4.5 years (range 2–6) after the second dose, while the remaining patients continued therapy throughout the follow-up period. Patient characteristics are summarized in Table 1.

The mean pre-vaccination values (range) of immunoglobulins and lymphocyte populations in patients were as follows: IgG 9.04 g/l (6.21–12.6), IgA 0.85 g/l (0.37–1.62), IgM 0.99 g/l (0.66–1.35); CD3 2.1 $\times$ 10^9/l (1–3.35), CD4 1.26 $\times$ 10^9/l (0.57–1.9), CD8 0.67 $\times$ 10^9 (0.27–1.22), CD19 0.65 $\times$ 10^9/l (0.19–1.33) and CD16 + CD36 0.37 $\times$ 10^9/l (0.1–0.92). No patient was excluded based on abnormal immunological test results.

Fifty-two HC after varicella vaccination (24 females, 46 %; median age at first vaccine dose 3.7 years, range 1–13.4) and 69 HC after varicella infection (21 females, 30 %; median age at varicella 4 years, range 0.5–11) were included, with age at vaccination or infection comparable between patients and HC ($p = 0.22$ and $p = 0.29$, respectively).

All vaccinated HC had negative history of varicella, confirmed by their parents and pediatricians. Thirty-three of 52 (64 %) HC, including all HC with possible contact with varicella before vaccination, were serologically tested before vaccination and were seronegative. They received two doses of varicella vaccine, with a median interval of 2.4 months (range 1–47) between doses.

Table 1
Patient characteristics[1]

Number (F/M)	17 (12/5)		
Median age at diagnosis (range) [years]	2.5 (0.8–16)		
Median age at first dose (range) [years]	4.2 (2.3–16.8)		
JIA subtype[1] (n)			
polyarticular	7		
systemic onset	4		
extended oligoarticular	4		
oligoarticular	1		
undifferentiated	1		
Therapy at vaccination (n)	first dose (n = 17)	second dose (n = 17)	third dose (n = 5)
etanercept + MTX[2]	5	7	3
adalimumab + MTX[2]	3	3	1
tocilizumab + MTX[2]	2	2	
tocilizumab + tacrolimus[3]	2	2	
infliximab + MTX[2]	1	1	
etanercept	1	1	
MTX[2]	1	1	
anakinra			1
without systemic IS treatment	2		
Disease activity before first dose[4] (mean, range)			
polyarticular[5]	0.3 (0–1)		
systemic onset[5]	1 (0–4)		
extended oligoarticular[5]	0.5 (0–2)		
oligoarticular	0		
undifferentiated	3		

JIA: juvenile idiopathic arthritis, MTX: methotrexate, IS: immunosuppressive
[1] According to ILAR criteria [15]. [2] The median MTX dose at the time of vaccination was 10 mg/m2/week (range 6.5–15) [3]and tacrolimus 1.8 mg/day (range 1.6–2). [4]Disease activity is measured by number of joints with effusion. No patients with soJIA had systemic signs at the time of vaccination. [5]Mean values are used in categories with more than one patient.

3.2. Safety

3.2.1. Adverse events

There were no disseminated vaccine-strain infection or severe AEs (SAEs). Six (35 %) patients and twelve (23 %) HC reported mild AEs ($p = 0.35$) (Table 2), occurring in ten individuals after the first dose, one patient after the first and second doses, six individuals after the second dose, and one patient after the third dose, which included localized pain and/or induration at the injection site, fever, urticaria, maculopapular rash, and arthralgia. One HC developed 5–10 vesicles one week after the first vaccination with no other signs of systemic involvement.

3.2.2. Disease activity

Disease activity remained stable in 14/17 (82 %) patients within 4–6 weeks following vaccination. Three out of 17 (18 %) patients experienced reactivation or exacerbation of JIA. One patient with extended

Table 2
Adverse events in patients and healthy controls within one month following varicella vaccination.

	Patients ($n = 17$)	Vaccinated controls ($n = 52$)
n (%)	6 (35 %)[1]	12 (23 %)[1]
Pain at injection site[2]	3 (18 %)	6 (12 %)
Induration at injection site	1 (6 %)	3 (6 %)
Vesicular rash	0 (0 %)	1 (2 %)
Other types of rash	1 (6 %)	3 (6 %)
Arthralgia	1 (6 %)	0 (0 %)
Fever	2 (12 %)	2 (4 %)

Some individuals presented more than one adverse event.
[1] Fisher's exact test. $p = 0.35$.
[2] Pain at injection site lasted 1–3 days, one patient experienced it after both the 1st and 2nd doses.

oligoarthritis exhibited an increase in the number of active joints from 0 to 4, and an elevated erythrocyte sedimentation rate one month after the first vaccination, which was administered before the initiation of systemic IS therapy. This patient was subsequently treated with TNFi and MTX, and the disease remained inactive after the second dose. Another patient with soJIA, who had received the first two vaccine doses while on MTX, experienced an increase in the number of active joints, rising from 1 to 5, and signs of systemic inflammation one week after the second dose, and was treated with corticosteroids. Disease remained inactive after the third dose, which was administered on an IL-1 inhibitor. In addition, one patient with polyarthritis developed arthritis in one joint one month after receiving the first dose of the vaccine while on TNFi and MTX.

3.3. Effectiveness

Four out of 17 patients (24 %) developed BV between 4 months and 4.5 years after the second dose (Table 3). All four were vaccinated while treated with TNFi and MTX.

In the first year following the second vaccination, only Patient 1 developed mild varicella while on a TNFi and MTX and was treated with oral acyclovir. The other three patients had varicella at least 2.5 years after vaccination. Patient 2 presented with a typical rash and no fever while on a TNFi and was treated with parenteral acyclovir. Patient 3 presented three pruritic papules and a subfebrile temperature while on a TNFi and MTX, and Patient 4 developed mild varicella while on MTX (neither received antiviral treatment). During the varicella episodes, IS therapy was temporarily discontinued in all except for Patient 3, whose rash was atypical and not classified as varicella by her pediatrician. Given the documented contact and a significant increase in VZV-IgG, we categorized her as possible BV.

A further 8 patients reported at least one contact with varicella or HZ between 1 month and 6 years following the second vaccination and exhibited no signs of infection. Six out of 8 were seropositive before the contact and 6/7 had a positive VZV-CMI. After the reported contact, an increase in VZV-IgG was observed in 7/8 patients and positive VZV-CMI in 3/3 patients. The median follow-up time (FT) of the patients was 9.4 years (range 0.2–13.1).

No patients developed BV after the third dose, while one reported a contact with varicella. No vaccinated HC developed BV, while 24/52 (46 %) reported a contact (median FT 2.3 years, range 0.9–5.9 years). None of the vaccinated children developed HZ.

3.4. Immunogenicity

After the second dose, eight patients presented both positive VZV-IgG and VZV-CMI, two positive VZV-IgG, and one neither. In the remaining six patients, four of whom presented positive VZV-IgG, VZV-CMI was first assessed only after the third dose/BV/contact.

Table 3
Immunogenicity measures in patients who got breakthrough varicella.

Patient	Time from second dose	VZV-IgG before [mIU/mL] (time to contact)	CMI before [%] (time to contact)	VZV-IgG after [mIU/mL] (time from contact)	CMI after [%] (time from contact)
1	4 m	472 (3 m)	ND	2625 (1 m) 529 (3.5 y)	ND 2.7 (3.5 y)
2	2.5 y	<10 (1 y)	0.2 (1 y)	1235 (3 y)	0.1 (3 y)
3	2.75 y	65 (1.5 y)	0.3 (1.5 y)	>4000 (3 m) 879 (3.5 y)	ND 0.7 (3.5 y)
4	4.5 y	<10 (2.5 y)	ND	2863 (3 m)	3 (3 m)

CMI: cell-mediated immunity, m: month, ND: not determined, y: year. Seropositivity level > 100 mIU/mL. CMI is expressed as a percentage of CD69 + IFN-γ + T cells among total T lymphocytes after stimulation with VZV peptides.

3.4.1. Humoral immunity

The null hypothesis that the median VZV-IgG level at the first measurement after the second vaccination in patients on bDMARDs is less than or equal to 100 mIU/ml was tested using the one-sided Wilcoxon test. The *p*-value was 0.004, indicating that, for the population undergoing this therapy, measured at a similar time point, the median is greater than 100 mIU/ml.

Fourteen out of 17 (82 %) patients were seropositive after the second vaccination. All three seronegative patients received both doses while on a TNFi (1 infliximab, 1 etanercept and 1 adalimumab) and MTX. After the third dose, all five patients became seropositive (4/5 only transiently).

The trends of VZV-IgG values in 15 individual patients vaccinated while treated with adalimumab, etanercept, or tocilizumab are shown in Fig. 1. Among the remaining two patients, one was vaccinated on infliximab and remained seronegative until developing BV 4 years after the second dose. The other received the first two doses on MTX and was seropositive for one year after the second dose. This patient then received a third dose 5 years later on anakinra and remained seropositive throughout the 5-year follow-up after the third dose. Six patients were seronegative at the time of the last blood sampling.

Fifty out of 52 (96 %) HC after vaccination and all HC after varicella were seropositive. VZV-IgG levels in patients and HC after the second dose of varicella vaccine are shown in Fig. 2.

To test whether VZV-IgG levels decrease more rapidly over time in patients compared to HC we modeled the trend in VZV-IgG levels over time using the following linear mixed model:

$$IgG^{0.3} \sim 1 + t + Group + Group : t + (1|ID),$$

where t represents time (or measurement) in discrete form, *Group* indicates whether an individual was a patient (baseline), HC after vaccination or HC after infection, ID denotes an individual and $Group : t$ denotes the interaction between *Group* and t. We compared this model to the following (null) model using the likelihood ratio test:

$$IgG^{0.3} \sim 1 + k_t{*}t + patient + (1|ID).$$

Potency 0.3 was chosen using the Box Cox transformation. Based on this model, we cannot conclude that VZV-IgG levels change through time in a different way for patients and HC ($p = 0.142$) (Fig. 3).

We repeated the analysis of the VZV-IgG trend using the previous model on a dataset in which we excluded the 24 values obtained after contact or third vaccine dose in vaccinated individuals (15 values in patients and 9 values in HC) (Fig. A.1 in the Appendix). The advantage of this model is that it focuses more on the effects of vaccination. Upon analyzing the adjusted dataset, we also cannot conclude that VZV-IgG levels change through time in a different way for patients and HC ($p = 0.292$).

3.4.2. Cellular immunity

Thirty-five samples from 17 patients were analyzed. In 11 patients, VZV-CMI was measured after the second vaccination and prior to the third vaccination, BV or contact with varicella/HZ. It was positive in 8 (72 %) of them (median time interval from the second dose 1 month, range 1 month-5 years). At the time of vaccination, two out of 3 patients with negative VZV-CMI were treated with TNFi and MTX, and one with an IL-6 inhibitor and tacrolimus. VZV-CMI was positive in all patients after the third dose (median time interval from the third dose 2 months, range 1–36), and in all patients after BV or contact with varicella/HZ. Once VZV-CMI was positive, it remained positive throughout the follow-up period. The VZV-CMI values of the patients are shown in Fig. 4.

VZV-CMI was positive in 42/43 HC (98 %) for up to 3 years after varicella vaccination, and in 21/21 HC (100 %) for up to 5 years after varicella. We used a linear regression model with the Box Cox

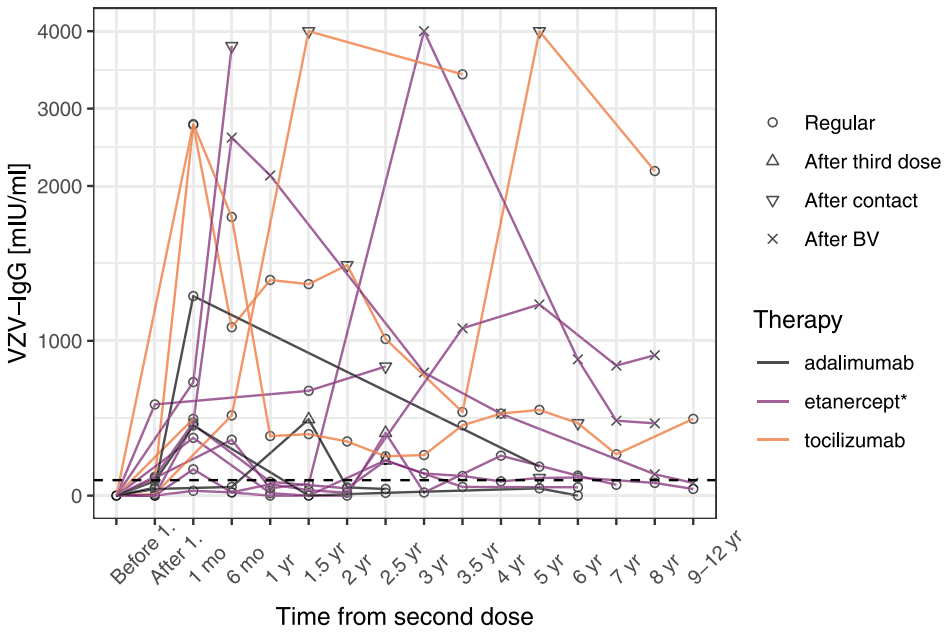

Fig. 1. Humoral response in individual patients after varicella vaccination: *1.: first dose, VZV: Varicella-zoster virus*. The trends og VZV-IgG values of 15 patients are presented. Two patients who were vaccinated on tocilizumab were concurrently treated with tacrolimus and all other patients with methotrexate, except for one patient on etanercept monotherapy. The impact of exposure to wild-type VZV on the VZV-IgG levels was greater than the impact of the third vaccine dose. The dashed line represents the lower limit of seropositivity, which is 100 mIU/ml. *Two of the patients treated with etanercept received the first vaccine dose before starting systemic immunosuppressive treatment.

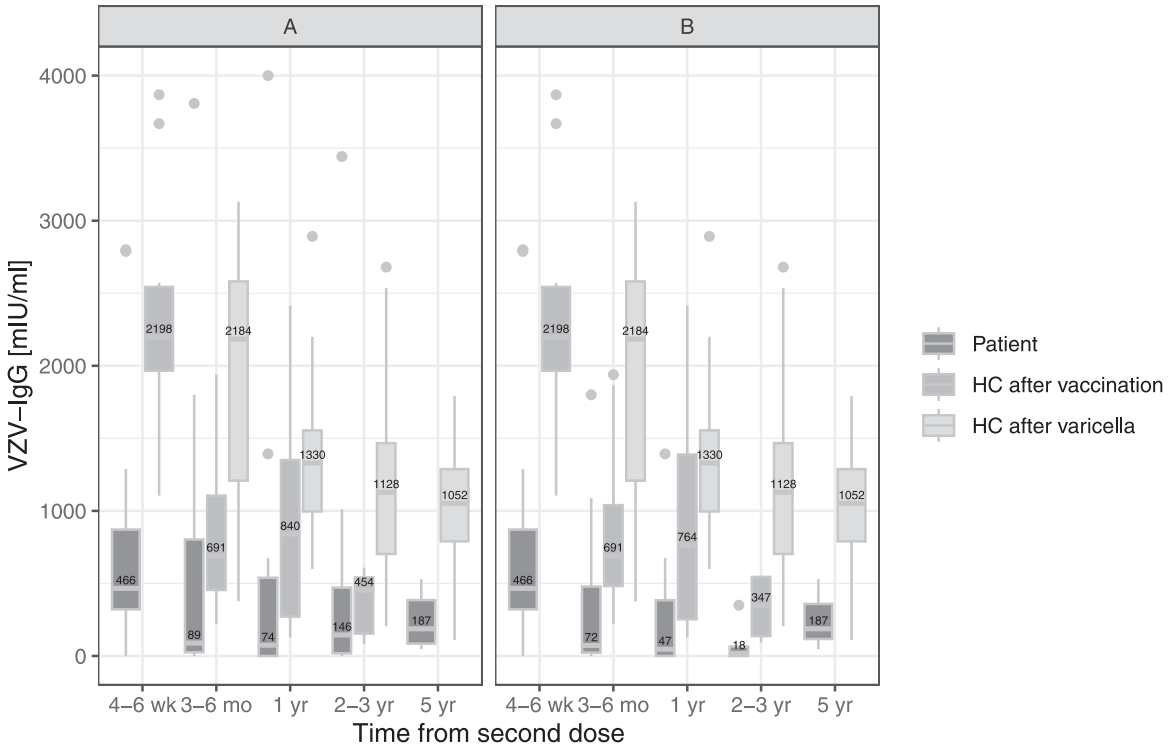

Fig. 2. Humoral response in patients and HC over time: *HC: Healthy control, VZV: Varicella-zoster virus.* VZV-IgG levels in patients ($n = 16$; a total of 54 patient samples were collected over a period of up to 5 years after vaccination) were measured consecutively and in HC after vaccination ($n = 52$) and after varicella ($n = 69$) at a single time point. Values obtained after breakthrough varicella were excluded. A: VZV-IgG levels were higher in vaccinated HC compared to patients and highest in HC after varicella throughout the follow-up period. B: Same dataset, excluding 24 values obtained after close contact with varicella or after the third vaccine dose (15 values in patients and 9 in vaccinated HC). Without exposure to wild-type or vaccine-strain VZV, even lower median VZV-IgG values are observed in vaccinated patients from 3–6 months and in vaccinated HC from 1 year to 3 years after the second vaccination.

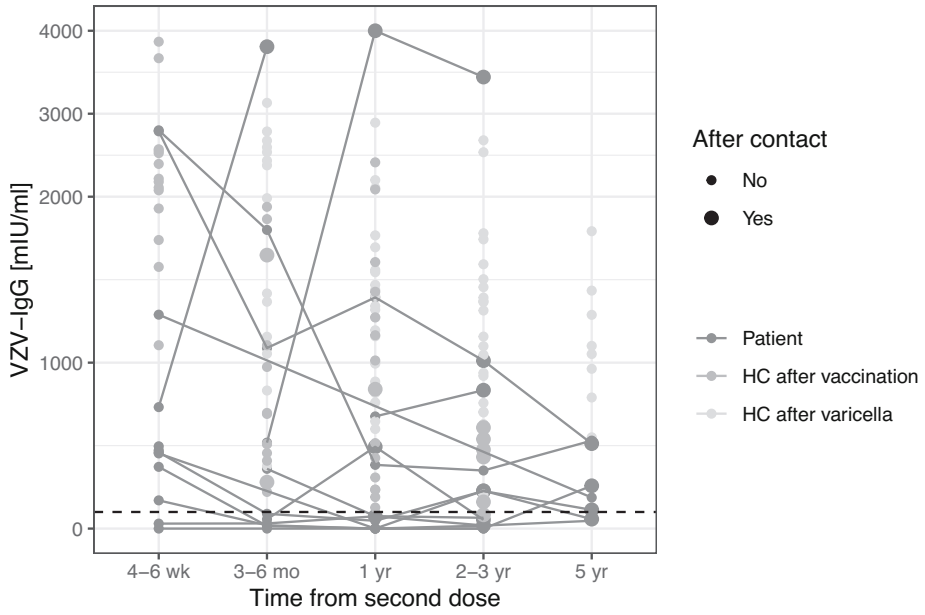

Fig. 3. Trend of VZV-IgG levels over time: *HC: Healthy controls, VZV: Varicella-zoster virus*. VZV-IgG levels in patients ($n = 16$; a total of 54 patient samples were collected over a period of up to 5 years after vaccination) were measured consecutively and in HC after vaccination ($n = 52$) and after varicella ($n = 69$) at a single time point. Values obtained after breakthrough varicella were excluded. Based on our model, VZV-IgG levels do not change through time in a different way for patients and HC ($p = 0.142$).

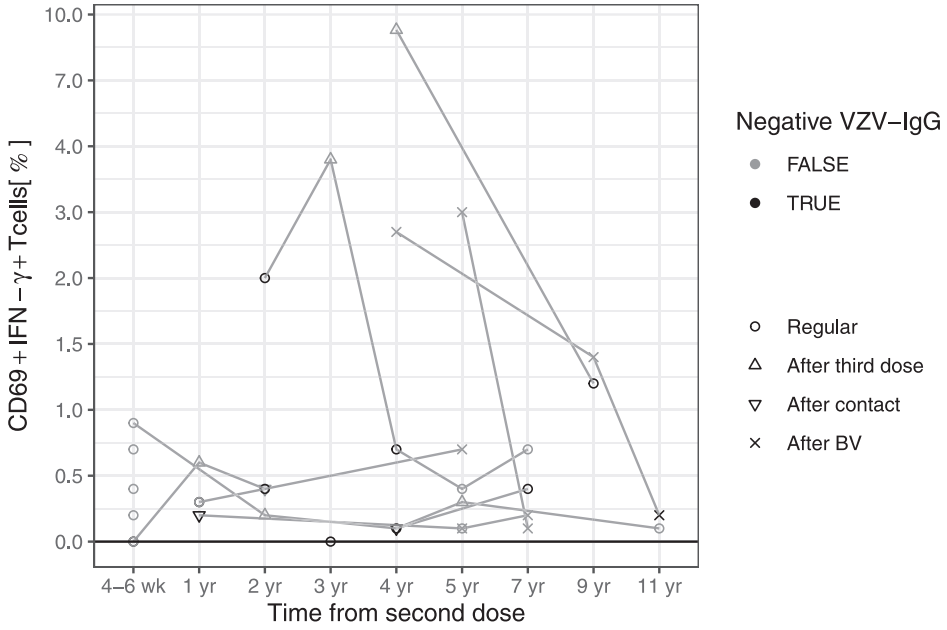

Fig. 4. VZV-specific cellular immunity in patients through time: *VZV: Varicella-zoster virus.* Thirty-five samples from 17 patients were analyzed by flow cytometric intracellular cytokine staining. Activated subpopulation of T lymphocytes (CD69+) that produced at least 0.1 % IFN-γ among total T lymphocytes upon stimulation with VZV peptides were considered positive. VZV-CMI was positive in 8/11 patients whose values were measured before exposure (third vaccine dose, contact with wild-type VZV, or breakthrough varicella) and in all patients after exposure. Compared to humoral immunity, cellular immunity persisted over a longer period of time.

transformation to compare VZV-CMI values between patients and HC after vaccination or infection. Only positive values from vaccinated patients and HC were considered. Values obtained after exposure (third vaccine dose, contact with varicella/HZ, or BV) were excluded.

The model was defined as:

$$(CMI + 1)^{-3/2} \sim 1 + t + Group + Group : t.$$

We tested this model against the null model:

$$(CMI + 1)^{-3/2} \sim 1 + t.$$

In our sample, the difference in the percentage of CD3 + CD69 + IFN-γ + cells among total T-lymphocytes between patients and HC after vaccination or infection during the follow-up period was not significant ($p = 0.449$).

We used the following linear mixed model to assess the difference in CMI-positive control values depending on which treatment individuals

were receiving at the time of blood sampling (bDMARDs and/or MTX, or none):

$$\sqrt{CMI} \sim 1 + Group + biological + mtx + (1|ID),$$

where *Group* indicates whether an individual was a patient (baseline), HC after infection or HC after vaccination, the Boolean term *biological* indicates bDMARDs and the term *mtx* indicates MTX. In our sample the type of treatment had no influence on the value of positive control.

In our sample, we cannot say that the values of VZV-CMI and VZV-IgG are correlated ($p = 0.634$).

4. Discussion

The present study is the first prospective case control study on the safety, effectiveness, and immunogenicity of varicella vaccination in patients with JIA treated with bDMARDs.

In our cohort, varicella vaccination was safe, with no vaccine-strain infections or other SAEs. Reported mild AEs were comparable to those in the healthy population [16].

The main concern with live vaccines in immunocompromised patients is the potential risk of infection with the vaccine-strain virus [3]. After subcutaneous inoculation, host cell defences limit vaccine-strain virus replication in skin. In immunocompetent hosts, VZV-specific T-cell mediated immunity is induced shortly after vaccination, followed by humoral immunity, with both persisting as memory immune responses. If cellular immunity is delayed, the vaccine-strain virus can infect T-cells trafficking through skin, leading to viremia and potential spread to lungs, liver and other organs [17]. Viremic phase was observed in 50 % of healthy vaccinees [18]. Like wild-type VZV, the vaccine-strain can establish latency in sensory nerves [17]. There have been reports of disseminated disease after live vaccination in immunocompromised patients, though none in those with rheumatic diseases [19–21]. In studies of 70 varicella-naive PRD patients, including 18 vaccinated while on TNFi, IL-6 inhibitors, or IL-1 inhibitors, no disseminated varicella infections or other SAEs were reported [9–13]. Varicella vaccination was also safe in pediatric inflammatory bowel disease patients, including 10 on bDMARDs [22,23]. No vaccine-strain infections occurred after MMR booster vaccination in JIA patients on IS therapy, including bDMARDs [24–26].

The exact extent of immunosuppression from rheumatic diseases and their treatments is unclear [19]. We used normal immunoglobulin levels and lymphocyte populations as inclusion criteria [9]. A German group later published a comprehensive pre-vaccination checklist, recommending to consider varicella vaccination based on immunoreactivity, not IS therapy type [10].

One patient experienced arthralgia post-vaccination, which has been reported before [10]. While arthralgia can occur after various vaccinations, wild-type varicella infection can also cause varicella arthritis [27,28]. Thus, arthralgia in some JIA patients post-vaccination may indicate viral replication in a joint due to systemic viremia. Joint fluid could be tested for varicella vaccine virus DNA.

Disease activity remained stable in most patients after vaccination, while three out of 17 (18 %) patients experienced a disease flare. Two of them were vaccinated before starting bDMARDs, and their disease remained inactive after subsequent vaccination on bDMARDs. While some studies reported no flares post-vaccination, two randomized controlled trials on varicella and MMR vaccines found similar flare rates between vaccinated and non-vaccinated patients [10–13,24].

Four out of 17 (24 %) patients developed mild BV, one 4 months and three more than 2.5 years after vaccination. Twice as many patients reported varicella exposure without developing symptoms. While none of the HC developed BV, their FT was shorter than the patients'. Data on varicella vaccine effectiveness in PRD patients are limited. Few cases of BV have been reported, most uncomplicated, similar to the healthy population [3,11,12,29]. One study described severe BV with pneumonia and probable macrophage activation syndrome in a JIA patient on TNFi [12]. Two of our BV patients were treated with acyclovir, standard for patients on bDMARDs. In healthy individuals, two vaccine doses demonstrated 92 % effectiveness against clinical varicella [1]. Our results suggest JIA patients on bDMARDs are three times more likely to develop BV than the healthy population.

We found that two doses of the varicella vaccine are immunogenic in JIA patients treated with TNFi or IL-6 inhibitors. However, patients had a lower response rate and fewer protective antibodies than HC, which may explain the reduced vaccine effectiveness. Consistent with previous studies, post-vaccination antibody levels were higher after natural infection than vaccination [30,31]. Antibody decline dynamics in vaccinated patients were similar to HC, even after excluding values obtained after exposure or a third vaccination. Due to lower initial antibody levels, patients' median VZV-IgG dropped below the seropositivity level within 3–6 months and fluctuated slightly afterward. This may be because all children had similar background VZV exposure, often unrecognized, as varicella is contagious two days before rash onset, and asymptomatic VZV reactivation can enhance the specific immune response [14,32].

Previous studies showed similar humoral responses to varicella vaccination in PRD patients on non-bDMARD IS therapy and HC [11–13]. One study found inadequate response in patients on bDMARDs ($n = 3$), while another showed no difference between PRD patients on low- and high-intensity IS therapy, including bDMARDs ($n = 9$) [10,11]. Since our patients were treated with various bDMARDs and immunomodulators, it is unclear whether treatment, disease activity, or both influenced immunogenicity. Premature immunosenescence in JIA may impact vaccine response [33]. Although other vaccines were generally immunogenic in patients on TNFi and IL-6 inhibitors, several studies reported lower antibody response and persistence compared to HC [3,34–38]. We observed the highest post-vaccination VZV-IgG levels in patients on IL-6 inhibitors, with none developing BV. Larger longitudinal studies are needed to evaluate the impact of different treatments varicella vaccine effectiveness.

Cell-mediated immunity is essential for recovery from varicella and maintenance of VZV latency [14,39,40]. PRD patients treated with non-bDMARD IS therapy have shown a specific cellular immune response to live varicella vaccination, and similar results were seen in patients treated with etanercept for MMR vaccine [11,13,26]. We confirm this for varicella vaccination in patients treated with bDMARDs. While more patients than HC had negative VZV-CMI after vaccination, both the patients and the HC with positive VZV-CMI, as well as HC post-varicella, had similar percentages of activated T lymphocytes producing IFN-γ upon stimulation with VZV peptides. In our sample, IS therapy did not affect IFN-γ production after non-specific stimulation with PMA and ionomycin.

Patients with rheumatic diseases treated with bDMARDs have a higher risk of HZ [41]. The incidence of HZ is lower after varicella vaccination than wild-type varicella infection [13,42]. Inducing a specific cellular response may offer long-term protection against HZ, though the longevity of the immune response after vaccination is unknown [3,11]. In our cohort, VZV-CMI persisted longer than VZV-IgG. In healthy individuals, VZV-CMI lasted up to 20 years post-vaccination and was comparable to natural immunity [40,43]. In rheumatoid arthritis patients, lower levels of VZV-specific and general effector T-cells were found, especially in those treated with IL-6 inhibitors and TNFi [44]. The risk of HZ increases with age, and we will continue to monitor the vaccine effectiveness as our patients transition into adulthood [45].

The correlation between humoral and cellular immunity and protection against VZV infection is uncertain [1,3]. In our cohort, most patients exposed to VZV who did not develop BV had at least one positive marker of immunity, as did three out of four who did develop BV. On the other hand, commercial assays may lack sensitivity to detect vaccine-induced immunity, and laboratory testing of *in vitro* responses to

viral antigens may differ from *in vivo* responses [26,46]. These factors should be considered, as the methods we used are clinically available and can impact decision-making. In our practice, we have not recommended postexposure prophylaxis for vaccinated patients but advised them to seek medical attention if clinical varicella occurs.

Exposure to wild-type VZV poses a significant risk for varicella-naive immunocompromised individuals, including patients on bDMARDs. Post-exposure prophylaxis is indicated, but not always effective [1,7,8,47,48]. Concerns about infection may disrupt social activities and treatment, potentially worsening the rheumatic disease [3]. However, exposure to wild-type VZV may enhance the specific immune response in previously exposed individuals [32,49]. In our cohort, vaccinated patients showed a greater increase in VZV-IgG after exposure to wild-type VZV than after the third vaccination, which mostly induced transient seropositivity. Both induced specific cellular immunity. The current epidemiological situation in a country with high varicella circulation appears favorable for vaccinated patients. With varicella vaccination now recommended and free for all preschool children in Slovenia since January 2025, herd immunity may reduce the burden of varicella, but it could also lessen the beneficial effects of exposure for vaccinated individuals.

None of the five patients developed BV after the third vaccination. Since many JIA patients will need ongoing immunosuppressive treatment, an additional booster vaccination could potentially be considered. Larger studies with longer follow-up are needed to evaluate long-term effectiveness.

Our study has several limitations. JIA is relatively rare, and we included various subtypes and treatment combinations, with individual treatment groups being too small to analyze therapy effects. BV was diagnosed clinically without PCR testing, so HZ from the vaccine-strain could not be ruled out, although all four patients reported prior varicella exposure. Our VZV-CMI analysis only included samples post-vaccination or infection, not before. Because even undetected exposure to wild-type VZV affects the specific immune response, our study can only approximate the long-term immunogenicity of the varicella vaccine. Nonetheless, our findings reflect clinical reality in high varicella burden country and provide insights into vaccine effectiveness.

In conclusion, varicella vaccination was safe and largely immunogenic in JIA patients treated with biologic therapy. Vaccination was not effective in 4/17 (24 %) patients, but none developed severe BV. The response rate and antibody levels were lower in patients compared to HC, while the dynamics of antibody decline were similar. Patients could mount VZV-specific cellular immunity post-vaccination. These findings support the EULAR/PReS recommendation that varicella vaccination can be considered also in varicella-naive patients on TNFi, IL-6, and IL-1 inhibitors [3]. We also suggest that an additional booster dose may be an option for patients requiring ongoing immunosuppressive therapy.

CRediT authorship contribution statement

Maša Bizjak: Writing – original draft, Visualization, Validation, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jakob Peterlin:** Writing – original draft, Visualization, Validation, Methodology, Formal analysis. **Tadej Avčin:** Writing – review & editing, Validation, Supervision, Resources, Methodology, Funding acquisition, Conceptualization. **Miroslav Petrovec:** Writing – review & editing, Validation, Resources, Funding acquisition. **Alojz Ihan:** Writing – review & editing, Validation, Resources, Funding acquisition. **Mojca Zajc Avramovič:** Resources, Investigation. **Gašper Markelj:** Resources, Investigation. **Tina Vesel Tajnšek:** Resources, Investigation. **Veronika Osterman:** Resources, Investigation. **Jerneja Ahčan:** Resources, Investigation. **Helena Mole:** Resources, Investigation. **Katja Dejak Gornik:** Resources, Investigation. **Alenka Biteznik:** Resources, Investigation. **Sara Jevnikar:** Resources, Investigation. **Larisa Janžič:** Writing – review & editing, Resources, Investigation. **Miha Bajc:** Resources, Investigation. **Andreja Nataša Kopitar:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Methodology, Investigation, Formal analysis, Conceptualization. **Nataša Toplak:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvacx.2025.100663.

Data availability

Data will be made available on request.

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