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Long-term safety and efficacy of varicella vaccination in children with juvenile idiopathic arthritis treated with biologic therapy

N. Toplak[a,b,*], T. Avčin[a,b]

[a] Department of Allergology, Rheumatology and Clinical Immunology, University Children's Hospital, University Medical Centre Ljubljana, Ljubljana, Slovenia
[b] Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

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ABSTRACT

Objective: To evaluate the long-term safety and efficacy of varicella vaccination in children with juvenile idiopathic arthritis (JIA) treated with biologics.
Methods: We performed a prospective study with long term follow up. Six patients with JIA treated with biologics, received 2 doses of varicella vaccine. Before vaccination, JIA was stable on therapy and peripheral blood lymphocyte populations were within normal limits. After vaccination, children were followed for disease activity, infections and production of protective antibodies.
Results: There were no serious side effects after vaccination and no varicella infection. Disease activity remained stable. Five patients (83%) produced protective antibodies against varicella virus 6 weeks after the second vaccination. One patient with low level of protective antibodies got mild varicella infection 4 months after the second vaccination.
Conclusion: Varicella vaccination appears to be safe in our group of six JIA patients treated with biologics. Vaccination does not always protect against varicella infection.

1. Introduction

Varicella infection is a highly contagious disease which can have a complicated course especially in immunocompromised patients. Serious complications include encephalitis, pneumonia, sepsis, hemorrhagic varicella and death [1]. Vaccination against varicella virus is the most effective method for achieving protection against infection. However, varicella vaccine is a live attenuated vaccine and as such it is not recommended in immunocompromised patients [2]. Since data on vaccination with live attenuated vaccines in patients treated with biologic disease modifying anti-rheumatic drugs (biologics) are scarce, the EULAR recommendations for vaccination in pediatric patients with rheumatic diseases suggested withholding live vaccines in these patients [3]. However, in a real-life pediatric clinical practice vaccinations with live vaccines are frequently considered on a case-to-case basis weighing the risks of infection versus the hypothetical risks of vaccination [3].

In children with rheumatic diseases only one study investigated the safety and efficacy of varicella vaccination [4]. To the best of our knowledge, no study has addressed the safety and efficacy of varicella vaccination in children with JIA receiving biologic therapy.

The aim of our study was to assess the long-term safety and efficacy of varicella vaccination in children with JIA treated with biologic therapy.

2. Methods

The study design was a prospective cohort study with a long term follow up. Six patients with stable JIA (median age 4.7, range 2.5–7 years), treated with biologic therapy (3 etanercept, 2 tocilizumab, 1 infliximab), received 2 doses of varicella vaccine (varicella–zoster (Oka strain) virus $10^{3.3}$ plaque forming units propagated in MRC5 human diploid cells) as recommended by the manufacturer (GlaxoSmithKline, UK). The study was performed between August 2011 and March 2015, and median follow-up duration after varicella vaccination was 17 months (range 2 months–2.7 years).

Four patients received both doses of varicella vaccine during treatment with biologics and two patients received the first dose of varicella vaccine 3 weeks before starting methotrexate and the second dose while treated with etanercept for 9 and 11 months

* Corresponding author at: Department of Allergology, Rheumatology and Clinical Immunology, University Children's Hospital, University Medical Centre Ljubljana, Bohoričeva 20, 1000 Ljubljana, Slovenia. Tel.: +386 15229277; fax: +386 15229357.
E-mail address: natasa.toplak@kclj.si (N. Toplak).

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respectively. Children treated with tocilizumab and infliximab received varicella vaccine on the same day as biologic drug infusion. There was no preference for the vaccination day in patients treated with etanercept.

Inclusion criteria for performing the varicella vaccination were as follows:

1. High risk of acquiring varicella infection (patient or sibling in a day-care or kindergarten)
2. Stable disease in the last 3 months
3. Negative history for varicella infection and negative prevaccinal serology to varicella virus
4. Normal results of peripheral blood lymphocytic populations and serum immunoglobulins

After vaccination children were followed for disease activity, infections and production of protective antibodies (pAb) against varicella virus for a median period of 17 months. Disease activity was measured by number of joints with effusion. Stable disease before vaccination was defined as no change in disease activity in the last three months before vaccination [5].

All children included in the study were followed for adverse events and infections at least 3 months after the second varicella vaccination (median time to second dose 1.8 months, range 1.5–21 months). Parents were instructed to write a diary about any adverse events and infections after the vaccination.

JIA disease activity was assessed before the first and second varicella vaccinations and then every 3 months at an outpatient clinic.

The presence of pAb was assessed before the first vaccination, 6 weeks after the first dose, before the second vaccination and 3 months after the second dose. After that pAb were checked during the regular check-up visits every 6–12 months. The method for determination of pAb was ELISA test performed by commercially available kit Enzygnost anti-VZV/IgG (Siemens). Lower limit of pAb was 106 mIU/ml.

The parents of all patients included in the study were informed about the aim of the study and asked for written informed consent for vaccination and drawing blood before and after vaccinations. The study was approved by the Ethics' Committee of the Slovenian Ministry of Health, and was conducted according to the principles of the Helsinki Declaration.

3. Results

Study population consisted of 6 patients with stable JIA. Main characteristics of the study group are presented in Table 1. One patient treated with tocilizumab was also treated with tacrolimus, the other 5 patients were receiving concomitant treatment with methotrexate.

Disease activity remained stable in all patients treated with biologic drug in a period of three months after the second dose of varicella vaccine. In both children who received the first dose of varicella vaccine before therapy with methotrexate was started, increased number of active joints and ESR one month after the first varicella vaccination was observed. Both received the second dose of varicella vaccine while they were already treated with etanercept, 15 and 22 months after the first vaccination, respectively. The disease remained inactive after the second vaccination.

There were no serious side effects after vaccination and no clinical varicella infection within 3 months after vaccination. One patient had mild local reaction after the first dose. One patient treated with etanercept got adenovirus infection 3 days after the second dose of varicella vaccine.

Table 1
General characteristics of the study group.

	Children with JIA vaccinated against varicella
Number (M/F)	6 (2/4)
Mean age ± SD (range)	4.7 ± 1.6 y (2.5–7)
Mean disease duration ± SD (range)	2 ± 1.7 y (4 m–4.5 y)
Disease subtype[*]	
POA[**]	2
EOA	1
PA	1
SJIA	2
Disease activity before vaccination[˙]	
POA[**]	0.5[¨]
EOA	0
PA	3
SJIA	1[¨]

JIA—juvenile idiopathic arthritis, M—male, F—female, SD—standard deviation, m—month, y—year. Mean number of joints with effusion is used were 2 patients are included.

[*] POA—persistent oligoarthritis, EOA—extended oligoarthritis, PA—polyarthritis (RF negative), SJIA—systemic JIA, PsA—psoriatic arthritis, ERA—enthesitis-related arthritis.

[**] One child had cervical spine involvement at the beginning of the disease, inactive at the time of vaccination.

[˙] Disease activity measured by number of joints with effusion.

[¨] Mean number of joints with effusion is used were 2 patients are included.

The efficacy of varicella vaccination was evaluated by determination of specific antibody production after vaccination (Fig. 1, 2). Five patients (83%) had pAb against varicella virus 6 weeks after the second dose. One patient treated with infliximab and methotrexate did not develop pAb after the second dose. Two patients treated with tocilizumab developed low levels of pAb after the first dose (220 and 150 mIU/ml respectively) and very high levels of pAb after the second dose (1800 and 2500 mIU/ml, respectively). Two patients treated with etanercept developed low protective levels of pAb after the second dose (460 and 170 mIU/ml respectively). One patient treated with methotrexate developed low level of pAb after the first dose of vaccine (190 mIU/ml). Six months after the first vaccination the patient was started on etanercept and before the second dose of vaccine (15 months after the first vaccination) he had negative pAb. This patient got mild varicella infection 4 months after the second vaccination and was found to have low protective level of pAb in spite of two varicella vaccinations previously (360 mIU/ml) (Fig. 2).

During the long term follow up, one patient treated with etanercept lost his pAb 22 months after the second dose (Fig. 1). One patient treated with tocilizumab had low pAb 27 months after the second dose and one patient treated with tocilizumab had very high pAb 3 months after the second dose but after 11 months the level of pAb significantly declined (Fig. 1).

4. Discussion

Vaccinations with live attenuated vaccines in patients treated with biologics are still controversial and there are no evidence based recommendations available. In general, live attenuated vaccines are advised to be postponed, but can be considered on a case to case basis weighting the risk of infection versus the hypothetical risks of vaccination [3].

Varicella vaccination in our series of patients was safe and was not associated with varicella infection 3 months after vaccination. Moreover, no child treated with biologic therapy at the time of vaccination had a disease flare after the vaccination.

All children received two doses of vaccine based on the manufacturer's recommendations and according to the current data showing that 2 doses schedule is far more successful in preventing breakthrough than a one dose schedule [6]. There were no