First report on the safety of the influenza vaccine in patients with paediatric inflammatory rheumatic diseases on JAK inhibitors

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Biological therapies have greatly contributed to treating patients with paediatric inflammatory rheumatic diseases (PiRD). The first JAK inhibitor (JAKi) was licensed for children with PiRD in 2022 (1, 2). Infection remains a leading cause of morbidity and mortality in patients with PiRD. The combined immunosuppressive effects of the disease and treatment make patients susceptible to infections. Vaccination is the most effective measure to control vaccine-preventable diseases like influenza, which causes significant morbidity and mortality worldwide (3). The immunogenicity of the flu vaccine is well established in children with PiRD on immune-modulating treatment (4, 5). No data exist regarding the flu vaccine in patients on JAKi.

This prospective study was conducted at the Second Department of Paediatrics, National and Kapodistrian University of Athens School of Medicine, Greece, from October 2023 to March 2024. The study protocol was approved by the hospital Ethics Committee and was conducted in accordance with the standards of Good Clinical Practice. Written informed consent was obtained from the legal guardians of each enrolled child. The study assessed the safety and tolerability of a standard intramuscular dose of a tetravalent influenza vaccine (vaccine components for the 2023-2024 Northern hemisphere influenza seasons included an A/Victoria/4897/2022 (H1N1), an A/Darwin/9/2021 (H3N2)-like virus, B/Phuket/3073/2013 and B/Austria/1359417/2021) in children under treatment with baricitinib or tofacitinib. Children with comorbidities or history of egg allergy were excluded.

Patients were immunised via injection in the left deltoid. Safety was assessed by collecting data concerning local and systemic reactions from investigators at baseline, in the 30 min following vaccine's administration, thereafter reported from the children's parents/legal guardians for the 14 days after vaccination using a diary card and then at three months' time. Local reactions (erythema, swelling, pain) and systemic reactions (fever, irritability, myalgia/arthralgia, GI symptoms) were monitored. Adverse events were evaluated. Disease activity was monitored by the appropriate tools, or by measuring the ESR and CRP in cases where disease activity criteria did not exist. Data were analysed using SPSS 20.1. Wilcoxon test was used to assess differences between the two groups.

Table I. Patients characteristics, treatment and side effects.

Patients	Age (years)	Diagnosis	Concomitant treatment	JAKi duration of treatment (months)	Localised side effects	Systemic side effects	Serious adverse events
1	17	Poly JIA	MTX baricitinib	9	yes	yes	-
2	11	Ext-oligo JIA	MTX baricitinib	10	yes	no	-
3	13	Poly JIA	baricitinib	11	yes	no	-
4	4	Aircardi-Goutieres	Steroids baricitinib	12	no	no	-
5	6	JDM	MTX baricitinib	9	no	no	-
6	3	DADA 2	tofacitinib	14	yes	no	-
7	12	Poly JIA	MTX baricitinib	12	no	no	-
8	9	Poly JIA	MTX tofacitinib	7	yes		-
9	10	SJIA	Prednisolone tofacitinib	9	yes		-
10	7	Poly JIA	tofacitinib	7	no		-
11	12	Poly JIA	MTX baricitinib	6	no		-

Table II. Summary of solicited local and systemic reactions in the 14 days following vaccination with the adjuvant seasonal influenza vaccine in patients treated with JAK inhibitors.

Reactions, no.	Total	Tofacitinib	Baricitinib	*p*-value
Local reactions:	5/11	3/5	2/6	0.09
• Swelling/induration	1	-	1	
• Pain	2	1	1	
• Erythema	2	2	-	
Systemic reactions	4/11	2/5	2/6	0.4
• Fever ≥38°C	2	-	1	
• Malaise	4	2	2	
• Irritability	-	-	-	
• GI symptoms	-	1	1	
• Arthralgias	-	-	-	
At least one local or systemic event	6/11	3/5	4/6	
Serious adverse events	0	-	-	-
Disease flare at 1 or 3 months	0	-	-	-

PiRD: paediatric inflammatory rheumatic diseases; JAKi: JAK inhibitors; GI: gastrointestinal; sDMARDS: synthetic disease-modifying anti-rheumatic drugs; JIA: juvenile idiopathic arthritis; MTX: methotrexate; JDM: juvenile dermatomyositis; DADA 2: deficiency of adenosine deaminase 2; SJIA: systemic juvenile idiopathic arthritis.

Patients' clinical characteristics are seen in Table I. Six patients on baricitinib and five patients on tofacitinib (mean age 8.4 years) (mean duration of treatment 9 months) received a single dose of the flu vaccine. All participants had been vaccinated in the previous years against flu and they were up to date with their immunisations based on the Greek National Vaccination Program. The incidence of local and systemic reactions during the 14 days following vaccination is shown in Table II. Local reactions occurred in 45% of the subjects, and systemic reactions in about 35%. In most cases, reactions were recorded in the first 2 days after vaccine administration and did not require treatment. There was no correlation between type of treatment (baricitinib *vs.* tofacitinib) or concomitant steroid or sDMARDS use and the risk of developing an adverse reaction. No serious adverse events occurred. At the follow-up visits 4 weeks and 3 months post vaccination, none of the patients showed any clinical or laboratory change in disease activity. One patient was infected with type B influenza within 2 months post vaccination, with no major incidents.

This is the first study to report on the reactogenicity to the seasonal influenza vaccine in patients with PiRD on JAKi treatment. Mild and transient side effects were noted. Although our sample size was small and a limited number of patients were included within each disease type and treatment group, it may be concluded that the vaccine has an adequate safety and tolerability profile. In this report we did not measure antibodies titres as they do not reliably reflect the level of protection, as seen with other vaccines. The efficacy of the influenza vaccine is assessed based on the percentage of vaccinated children who still become infected. Additionally, the antibody measurement is not suggested, given that the serotypes of influenza change annually. Furthermore, we did not use controls, as the efficacy of influenza vaccine is well-established in the healthy population. This short-term safety report may support its routine recommendation for children with PiRD. Further collaborative international studies including a large number of participants, will be needed to assess the immu-

nogenicity and teratogenicity and show the effectiveness of the flu vaccines in patients receiving JAKi.

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