Ekaterina I. Alexeeva[1,2], Tatiana M. Dvoryakovskaya[1], Rina V. Denisova[1], Ksenia B. Isaeva[1], Margarita A. Soloshenko[1], Anna V. Mamutova[1], Nikolay A. Mayansky[1], Natalia E. Tkachenko[1], Irina V. Zubkova[1], Tatiana A. Kaluzhnaya[1], Firuza Ch. Shakhtakhtinskaya[1], Anna G. Gayvoronskaya[1], Marika I. Broeva[1], Marina V. Fedoseenko[1]

[1] National Medical Research Center for Children's Health, Moscow, Russian Federation
[2] Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russian Federation

Immunization With a Pneumococcal Polysaccharide Vaccine in Children With Juvenile Idiopathic Arthritis Without Systemic Manifestations: a Prospective Study

Corresponding Author:
Margarita A. Soloshenko, doctor of the Department of Rheumatology in the NMRC for Children's Health
Address: 2, Lomonosov Ave., Moscow 119991, **phone**: +7 (499) 134-14-94, **e-mail**: margosoloshenko@mail.ru

Background. Patients with juvenile idiopathic arthritis (JIA) have an increased risk of being infected. Approximately half of all serious infections in children with JIA are associated with airway involvement. Objective. Our aim was to study the efficacy and safety of the pneumococcal 13-valent conjugate vaccine (PCV) in children with JIA. Methods. In a prospective cohort study, 5 groups were formed: children with JIA in the remission phase on methotrexate therapy (group 1) or etanercept (group 2), with JIA in the active phase prior to the appointment of methotrexate (group 3) or etanercept (group 4), control group (conditionally healthy children). 0.5 ml of the 13-valent PCV was administered once subcutaneously during therapy in patients in the remission phase or 3 weeks before the appointment of methotrexate or etanercept in patients in the active phase. The main study outcome was the proportion of patients with a protective (≥40 mg/L) level of specific anti-pneumococcal antibodies (anti-SPP) IgG to Streptococcus pneumoniae 4 weeks after vaccination. In addition, we assessed the incidence of infectious events before and after vaccination as well as changes in the content of a high-sensitivity C-reactive protein, S100 protein, and post-vaccination period. Results. The study included 100 children. Four weeks after vaccination, the protective level of anti-SPP IgG was established in 21 (84%) patients in the 1st, 23 (92%) in the 2nd, 22 (88%) in the 3rd, 24 (96 %) in the 4th and 5th groups (p =1.0). Increase in the concentration of S100 protein and high-sensitivity C-reactive protein after vaccination was not noted. JIA exacerbation episodes were not recorded in any patient. After immunization, the total number of infectious events decreased in all observed groups (p ≤0.001). Serious adverse events were not registered during the study. Conclusion. Vaccination with the 13-valent PCV in children with JIA is highly effective and is not accompanied by the development of serious adverse events.
Key words: children, juvenile idiopathic arthritis, vaccination, pneumococcal 13-valent polysaccharide vaccine, methotrexate, etanercept.

RESULTS

Table 1. Demographic profile of children with JIA included in the study

Parameter Me (25;75) (min; max)	1st group JIA Remission MT n =25	2nd group JIA Remission ETA n =25	3rd group JIA Exacerbation prior to MT n =25	4th group JIA Exacerbation prior to ETA n =25	Control group (conditionally healthy children) n =25	p
Boys, abs. (%)	14 (56)	13 (32)	10 (40)	9 (36)	11 (44)	0.513
Age, years	6 (4;7) (3;12)	6 (5;10) (2;15)	6 (4;9) (1;14)	6 (4;8) (2;11)	8 (4;10)	0.628
Disease onset age, years	4 (3;6) (1;10)	5 (3;8) (1;14)	6 (4;9) (1;14)	6 (4;8) (2;11)	-	0.457
Disease duration, months	14 (10;17) (6;36)	15 (12;18) (8;25)	3 (2;4) (2;7)	4 (3;5) (2;6)	-	0.001
Therapy duration, months	11 (8;14) (6;30)	12 (8;15) (6;23)	-	-	-	0.734

Note. JIA — juvenile idiopathic arthritis, MT — methotrexate, ETA — etanercept.

Table 2. Clinical profile of patients with JIA without systemic manifestations included in the study before immunization with a pneumococcal 13-valent vaccine

Parameter Me (25;75) (min; max)	1st group JIA Remission MT n =25	2nd group JIA Remission ETA n =25	3rd group JIA Exacerbation prior to MT n =25	4th group JIA Exacerbation prior to ETA n =25	p
Oligoarticular JIA, abs. (%) Polyarticular JIA, abs. (%)	12 (48) 13(52)	16 (64) 9 (36)	18 (72) 7 (28)	19 (76) 6 (24)	0.043
Number of painful joints	0 (0;0) (0;0)	0 (0;0) (0;0)	2 (1;5) (1;7)	3 (1;4) (1;7)	0.751
Number of swollen joints	0 (0;0) (0;0)	0 (0;0) (0;0)	2 (1;5) (1;7)	3 (1;4) (1;7)	0.751
Number of joints with active arthritis	0 (0;0) (0;0)	0 (0;0) (0;0)	2 (1;5) (1;7)	3 (1;4) (1;7)	0.751
Number of joints with impaired function	0 (0;3) (0;3)	0 (0;2) (0;2)	3 (2;5) (1;7)	3 (2;4) (1;7)	0.418
Duration of morning stiffness, min	0 (0;0) (0;0)	0 (0;0) (0;0)	15 (10;30) (10;60)	20 (15;30) (10;90)	0.500
ESR, mm/h (norm up to 15)	4 (3;6) (2;15)	7 (4;10) (2;14)	16 (14;21) (10;32)	21 (17;27) (10;36)	0.001
High-sensitivity CRP, mg/L (norm up to 5)	1 (1;2) (0.1;3)	0.13 (0.1;1.0)	3 (1;6)	3 (1.0;6.0)	0.001

Note. JIA — juvenile idiopathic arthritis, MT — methotrexate, ETA — etanercept, ESR — erythrocyte sedimentation rate, CRP — C-reactive protein.

Table 3. The level of serum anti-SPP IgG in the blood serum of children with JIA before and 4 weeks after immunization with the pneumococcal 13-valent conjugate vaccine

Parameter Me (25;75)	Serum anti-SPP IgG level, mg/L				
	1st group	2nd group	3rd group	4th group	Control group

	JIA Remission MT n =25	JIA Remission ETA n =25	JIA Exacerbation MT n =25	JIA Exacerbation ETA n =25	(conditionally healthy children) n =25
Initially	22.0 (14.1; 35.3)	20.1 (16.5;33.6)	15.9 (12.8; 45.5)	14.3 (7.0; 19.7)	19.9 (13.5; 27.6)
After 4 weeks	59.1# (45.5; 84.4)	86.2 (48.6;152.0)	70.4 (53.3; 148.0)	84.1 (65.0; 170.0)	71.5 (53.2; 185.0)
The intra-group comparison results (before-after values for each group), p	0.001	0.001	0.001	0.001	0.001

Note. # — difference between the 1st and 4th group, $p =0.022$.

JIA — juvenile idiopathic arthritis, MT — methotrexate, ETA — etanercept.

Table 4. High-sensitivity C-reactive protein concentration in the blood serum of children with JIA before and 4 weeks after immunization with the pneumococcal 13-valent conjugate vaccine

Parameter Me (25;75), mg/L	High-sensitivity CRP content				
	1st group JIA Remission MT n =25	2nd group JIA Remission ETA n =25	3rd group JIA Exacerbation MT n =25	4th group JIA Exacerbation ETA n =25	Control group (conditionally healthy children) n =25
Initially	1 (1;2)	0.13 (0.1;1.0)	3 (1;6)#Δ	3 (1.0;6.0)&▶	2 (1.0;2.0)
After 4 weeks	1 (0.11;2.0)	0.1 (0.1;1.0)	1 (0.1;2.0)*	1 (0.1;2.0)*	0.1 (0.1;1.0)
The intra-group comparison results (before-after values for each group), p	0.451	0.543	0.001	0.001	0.352

Note. * — the intra-group comparison results (before-after values for each group), $p =0.001$. # — comparison results of the 1st and 3rd groups, $p =0.008$. Δ — comparison results of the 2nd and 3rd groups, $p =0.001$. & — comparison results of the 1st and 4th groups, $p =0.002$. ▶ — comparison results of the 2nd and 4th groups, $p =0.001$.

JIA — juvenile idiopathic arthritis, MT — methotrexate, ETA — etanercept.

Table 5. S100 protein concentration in children with JIA before and after immunization with the pneumococcal 13-valent conjugate vaccine

Parameter Me (25;75), mg/L	S-100 protein content				
	1st group JIA Remission MT n =25	2nd group JIA Remission ETA n =25	3rd group JIA Exacerbation MT n =25	4th group JIA Exacerbation ETA n =25	Control group (conditionally healthy children) n =25
Initially	0.85 (0.41;2.78)	1.19 (0.39;3.51)	5.73#Δ (3.21;8.96)	5.69&▶ (4.72;8.90)	0.63 (0.52;0.96)

After 4 weeks	0.59 (0.42;1.13)	0.78 (0.44;1.86)	1.30* (0.40;3.49)	0.62* (0.40;2.81)	0.42 (0.31;0.60)
The intra-group comparison results (before-after values for each group), p	0.146	0.067	0.001	0.001	0.054

Note. # — comparison results of the 1st and 3rd groups, p =0.001. Δ — comparison results of the 2nd and 3rd groups, p =0.023. & — comparison results of the 1st and 4th groups, p =0.001. ► — comparison results of the 2nd and 4th groups, p =0.031.

JIA — juvenile idiopathic arthritis, MT — methotrexate, ETA — etanercept.

Table 6. Clinical profile of patients with JIA without systemic manifestations included in the study before and after immunization with a pneumococcal 13-valent vaccine

Parameter Me (25;75) (min; max)	1st group JIA Remission MT n =25		2nd group JIA Remission ETA n =25		3rd group JIA Exacerbation prior to MT n =25		4th group JIA Exacerbation prior to ETA n =25	
	Before vaccination	*After vaccination*	*Before vaccination*	*After vaccination*	*Before vaccination*	*After vaccination*	*Before vaccination*	*After vaccination*
Number of painful joints	0 (0;0) (0;0)	0 (0;0) (0;0)	0 (0;0) (0;0)	0 (0;0) (0;0)	2 (1;5) (1;7)	1 (1;2) (1;3)	3 (1;4) (1;7)	1 (0;2) (1;4)
Number of swollen joints	0 (0;0) (0;0)	0 (0;0) (0;0)	0 (0;0) (0;0)	0 (0;0) (0;0)	2 (1;5) (1;7)	1 (1;2) (1;3)	3 (1;4) (1;7)	1 (0;2) (1;4)
Number of joints with active arthritis	0 (0;0) (0;0)	0 (0;0) (0;0)	0 (0;0) (0;0)	0 (0;0) (0;0)	2 (1;5) (1;7)	1 (1;2) (1;3)	3 (1;4) (1;7)	1 (0;2) (1;4)
Number of joints with impaired function	0 (0;3) (0;3)	0 (0;3) (0;3)	0 (0;2) (0;2)	0 (0;2) (0;2)	3 (2;5) (1;7)	1 (1;2) (1;3)	3 (2;4) (1;7)	1 (0;2) (1;4)
Duration of morning stiffness, min	0 (0;0) (0;0)	0 (0;0) (0;0)	0 (0;0) (0;0)	0 (0;0) (0;0)	15 (10,30) (10,60)	15 (10,20)* (10,40)	20 (15;30) (10;90)	15 (15,30) ► (10,45)
ESR, mm/h (norm up to 15)	4 (3;6) (2;15)	4 (2;6) (2;10)	7 (4;10) (2;14)	4 (3;6) (2;8)	16 (14;21) (10;32)	8 (4;12)# (4;20)	21 (17;27) (10;36)	12 (8;16) & (2;26)

Note. * — comparison before and after vaccination, p =0.002. ► — comparison before and after vaccination, p =0.011. # — comparison before and after vaccination, p =0.001. & — comparison before and after vaccination, p =0.001.

JIA — juvenile idiopathic arthritis, MT — methotrexate, ETA — etanercept, ESR — erythrocyte sedimentation rate.

Fig. The vaccine period course in patients with JIA after immunization with the pneumococcal 13-valent conjugate vaccine.

%
100
90
80
70
60
50
40
30
20
10
0

1st group · 2nd group · 3rd group · 4th group · Control group

■ Painfulness   □ Hyperemia
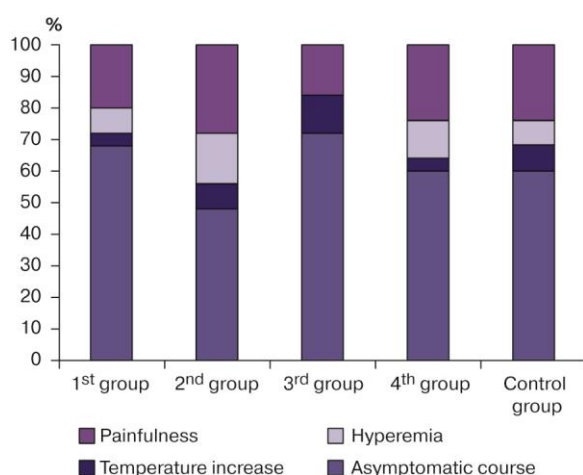■ Temperature increase   ■ Asymptomatic course

Table 7. Dynamics of the number of infectious events in patients with JIA before and after immunization with a 13-valent conjugate vaccine

Incidence		1st group JIA Remission MT *n* =25	2nd group JIA Remission ETA *n* =25	3rd group JIA Exacerbation MT *n* =25	4th group JIA Exacerbation ETA *n* =25
ARI Me (25;75), (min; max)	6 months before vaccination	3 (2;4) (2;5)	3 (2;4) (2,4)	2 (1;3) (1;4)	2 (1;3) (1;4)
	6 months after vaccination	1 (0;1)* 1 (0;2)	1 (0;1)* 1 (0;2)	0 (0;1)* 1 (0;2)	0 (0;1)* 1 (0;1)

Note. * — the intra-group comparison results before vaccination and 6 months after, *p* =0.001.
JIA — juvenile idiopathic arthritis, MT — methotrexate, ETA — etanercept, ARI — acute respiratory infection.

ORCID
Ekaterina I. Alekseeva http://orcid.org/0000-0002-3874-4721
Margarita A. Soloshenko http://orcid.org/0000-0002-6150-0880