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**Efficacy of Pneumococcal Polysaccharide Conjugate Vaccine (13-valent, Adsorbed) in Patients with Systemic Juvenile Idiopathic Arthritis Treated with Genetically Engineered Biologic Drugs (Tocilizumab or Canakinumab): Prospective Cohort Study**

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***Background****. Immunological potency of 13-valent pneumococcal vaccine (PCV-13) in children with systemic juvenile idiopathic arthritis (SJIA) is still unstudied. Estimates of the genetically engineered biologic drugs (GEBD) effects on pneumococcal vaccination results also remain controversial.* ***Objective****. The aim of the study was to explore the PCV-13 efficacy in patients with SJIA and who is on treatment with monoclonal antibodies against interleukin 6 receptor (tocilizumab) and interleukin 8 receptor beta (canakinumab).* ***Methods****. The study included patients under the age of 18 with SJIA in remission or active form of disease vaccinated with PCV-13. The vaccine was administered in single dose of 0.5 ml intramuscularly in patients on treatment with GEBD or 3 weeks before GEBD administration for the first time (for patients with active disease). Vaccination was considered effective at achievement of the minimum protective level of antibodies to capsular polysaccharide of pneumococcus (anti-SPP IgG; ≥7U/ml) or increase of anti-SPP IgG level ≥2 times in 4 weeks after vaccination. The anti-SPP IgG levels were measured with enzyme immunoassay.* ***Results****. The study included 53 patients (27 girls) in remission of SJIA and 25 (16 girls) in active disease. Median age was 13.3 and 10.8 years respectively. Tocilizumab/canakinumab was administrated in 43/10 and 18/7 patients respectively. Minimum significant anti-SPP IgG level and two-fold increase in anti-SPP IgG level were recorded in 49/53 (92%) and 32/53 (60%) patients with SJIA in remission, as well as in 22/25 (88%) and 18/25 (72%) patients in active disease respectively. PCV-13 immunological potency in patients with SJIA in remission and in active disease (in those who were initially administrated and who did not receive GEBD) did not differ.* ***Conclusion****. PCV-13 vaccination allows to achieve protective antibodies level in most of the patients with SJIA in children population regardless of the disease stage and the history of GEBD administration.*

***Key words****: pneumococcal vaccine, systemic juvenile idiopathic arthritis, genetically engineered biologic drugs, tocilizumab, canakinumab, immunological potency, anti-SPP IgG.*

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**RESULTS**

**Table 1.** Characteristics of patients with SJIA included in the study

|  |  |  |
| --- | --- | --- |
| **Indicators** | **SJIA, remission (*n* = 53)** | **SJIA, active (*n* = 25)** |
| Gender (female), abs. (%) | 27 (51) | 16 (64) |
| Age, years | 13,3 (8,3; 15,0) | 10,8 (6,3; 14,9) |
| SJIA onset age, years | 4,0 (1,9; 8,6) | 5,3 (2,3; 8,9) |
| Duration of disease, months | 65 (27; 108) | 23 (8; 64) |
| Remission duration, months | 27 (6; 53) | – |
| Chronic ENT diseases\*, abs. (%) | 22 (42) | 10 (40) |
| Pathogenic flora of nasopharynx \*\*, abs. (%) | 8 (15) | 7 (28) |
| Therapy before vaccination, abs. (%)   * GCs *per os* * GCs intravenously * GCs intra-articular introduction * methotrexate * cyclosporine | 20 (38)  36 (68)  10 (19)  34 (64)  25 (47) | 10 (40)  15 (60)  6 (24)  15 (60)  8 (32) |
| Therapy at vaccination\*\*\*, abs. (%)   * methotrexate * cyclosporine * GCs per os * tocilizumab * canakinumab | 15 (28)  6 (11)  7 (13)  43 (81)  10 (19) | 8 (32)  6 (24)  8 (32)  18 (72)  7 (28) |
| Lab test values at vaccination   * ESR, mm/h * leucocytes, × 109/l * thrombocytes, × 109/l * ferritin, ng/ml (*n* = 29/17) * CRP, mg/l (*n* = 9/16)\*\*\*\* * hemoglobin, g/l | 2 (2; 4)  6,8 (5,7; 8,2)  285 (236; 323)  18 (12; 27)  3,2 (2,3; 6,6)  133 (124; 146) | 5 (2; 23)  7,3 (6,2; 11,2)  319 (265; 430)  129 (62; 266)  7,0 (1,9; 39,2)  117 (110; 136) |

*Note*. SJIA — systemic juvenile idiopathic arthritis, GCs — glucocorticosteroids, ESR — erythrocyte sedimentation rate, CRP — C-reactive protein. \* Chronic adenoiditis, otitis, rhinosinusitis and/or tonsillitis (according to the results of the parents survey and the study of medical documentation). \*\* *Acinetobacter junii, Klebsiella pneumoniae, Staphylococcus (Staphylococcus aureus, Staphylococcus haemolyticus, Staphylococcus spp.), Enterococcus faecium, Streptococcus pyogenes, Candida*. \*\*\* In patients with active SJIA who received GEBD for the first time (*n* = 8), therapy with tocilizumab or canakinumab was started in 3 weeks after vaccination. \*\*\*\* The CRP level was 0.5 mg/l in 44 (83%) and 9 (36%) patients; these data were not taken into account when calculating quantity values.

**Table 2**. Dynamics of anti-SPP IgG level in patients with SJIA and at achievement of the minimum protective level and two-fold increase of anti-SPP IgG level 4 weeks after PCV-13 vaccination

|  |  |  |
| --- | --- | --- |
| **Indicators** | **SJIA, remission (*n* = 53)** | **SJIA, active (*n* = 25)\*** |
| Anti-SPP IgG, U/l   * initially * in 4 weeks * ratio (95% CI) | 13,7 (3,5)  45,9 (2,8)  3,4 (2,6–4,3) | 11,2 (3,4)  48,9 (3,4)  4,5 (2,9–7,2) |
| ***р*** | < 0,001 | < 0,001 |
| **Major indicators of the study** | | |
| Anti-SPP IgG≥ 7 U/ml, abs. (%)   * initially * in 4 weeks * difference (95% CI) | 32 (60)  49 (92)  32,1 (19,5–44,6) | 16 (64)  22 (88)  24,0 (7,3–40,7) |
| ***р*** | 0,001 | 0,031 |
| Anti-SPP IgG≥ 2 times (in 4 weeks), abs. (%)   * 95% CI | 32 (60)  47–72 | 18 (72)  52–86 |

*Note*. The quantitative indicators were described with mean geometric value and (for anti-SPP IgG concentration) standard deviation (in brackets). \* In one case the initial anti-SPP IgG concentration was below the sensitivity threshold of the set for enzyme immunoassay (half of the sensitivity threshold value was indicated in the analysis).

**Table 3**. ARI, complications of ARI, antibacterial therapy and cessation of GEBD in patients with SJIA for 6 months before and after PCV-13 vaccination

|  |  |  |
| --- | --- | --- |
| **Indicators** | **SJIA, remission (*n* = 53)** | **SJIA, active (*n* = 25)** |
| ***Acute respiratory infection, abs. (%)*** | | |
| 6 months before vaccination | 53 (100) | 24 (96) |
| 6 months after vaccination | 38 (72) | 14 (56) |
| *Difference (95% CI)* | 28,3 (16,2–40,4) | 40,0 (20,8–59,2) |
| *р* | – | 0,002 |
| ***Complications of acute respiratory infection, abs. (%)*** | | |
| 6 months before vaccination | 25 (47) | 7 (28) |
| 6 months after vaccination | 10 (19) | 2 (8) |
| *Difference (95% CI)* | 28,3 (13,2–43,4) | 20,0 (0,8–39,2) |
| *р* | 0,001 | 0,125 |
| **Antibacterial therapy, abs. (%)** | | |
| 6 months before vaccination | 37 (70) | 17 (68) |
| 6 months after vaccination | 16 (30) | 4 (16) |
| *Difference (95% CI)* | 39,6 (24,5–54,7) | 52,0 (26,9–77,1) |
| *р* | 0,001 | 0,002 |
| **Duration of antibacterial therapy, days\*** | | |
| 6 months before vaccination | 10 (7; 14) | 7 (7; 14) |
| 6 months after vaccination | 0 (0; 7) | 0 (0; 0) |
| *Difference (95% CI)* | 7 (7–10) | 7 (6–14) |
| *р* | 0,001 | 0,004 |
| **Cessation of GEBD, abs. (%)\*\*** | | |
| 6 months before vaccination | 50 (94) | 13/17 (76) |
| 6 months after vaccination | 39 (74) | 9/17 (53) |
| Difference (95% CI) | 20,7 (7,6–33,9) | 23,5 (−7,1…54,2) |
| *p* | 0,007 | 0,289 |

*Note.* GEBD — genetically engineered biologic drugs. \* Calculated for persons who received antibacterial drugs (at least one episode) for 6 months before vaccination. \*\* In the group of patients with SJIA the indicator was calculated for 17 patients who previously received GEBD. GEBD withdrawal (at least one episode) was reported in 6 out of 8 cases in the group of «naive» GEBD patients within 6 months after vaccination (the drug was administrated in 3 weeks after vaccination).

**Table 4**. Frequency of adverse effects registered within 4 weeks after PCV-13 vaccination

|  |  |  |
| --- | --- | --- |
| **Indicators** | **SJIA, remission (*n* = 53), % (95% CI)** | **SJIA, active (*n* = 25), % (95% CI)** |
| Mild AE   * edema/soreness in injection site * hyperaemia in injection site * fever (≥ 37 °С) | 42 (29–55)  36 (24–49)  11 (5–23)  21 (12–33) | 28 (14–35)  36 (20–55) |
| Severe AE | 2 (0,3–10) | 0 |

*Note.* AE — adverse effects (all medical events, local (edema/soreness, injection site hyperaemia) and general (fever) occurring within 4 weeks after PCV-13 vaccination; see Methods for more information). In all cases the event rate value and 95% CI are given, the number of events is given in the text.

**Table 5**. Anti-SPP IgG level in serum of patients with SJIA initially and 4 weeks after PCV-13 vaccination

|  |  |  |  |
| --- | --- | --- | --- |
| **Indicators** | **SJIA, active** | | ***p*** |
| ***Initially on GEBD therapy (n = 17)*** | ***Initially without GEBD therapy (n = 8)*** |
| Anti-SPP IgG, U/l   * initially * in 4 weeks * ratio (95% CI) | 7,4 (3,1)  31,5 (3,3)  4,5 (2,4–8,3) | 27,2 (2,5)  124,2 (1,7)  4,6 (2,1–10,3) | 0,013  0,001  0,967 |
| Anti-SPP IgG ≥ 7 U/ml, abs. (%)   * initially * in 4 weeks | 8 (47)  14 (82) | 8 (100)  8 (100) | 0,022  0,527 |
| Anti-SPP IgG ≥ 2 times (in 4 weeks), abs. (%) | 12 (71) | 6 (75) | 1,000 |

*Note*. The quantitative indicators were described with mean geometric value and (for anti-SPP IgG concentration) standard deviation (in brackets).

**STUDY LIMITATIONS**

It is not possible to clearly estimate the comparability of the sample in the present study with the general population of SJIA patients receiving GEBD and, accordingly, the generalizability of the PCV-13 vaccination results. Although, there is the register of patients with SJIA [20] in Russia, any special analysis (description) of the patients subgroup receiving GEBD has not been performed previously.

There were two parameters of the immune protection in this study: the minimum protective anti-SPP IgG level and its two-fold increase in 4 weeks after vaccination. Both outcomes can be used as endpoints for vaccine’s immunological potency studies [21]. However, it is still unknown whether these outcomes can lead to decrease in the risk of developing of pneumococcal infection in patients with SJIA, although there is no doubt using the example of pneumococcal vaccination of children in the general population [22]. It should be noted that we did not examine vaccine’s immunological potency against specific *Streptococcus pneumoniae* serotypes in the present study.

The reduction of frequency of post-vaccination ARI (and, accordingly, frequency of ARI complications and prescribing antibacterial therapy) may have the following explanations. The efficacy of pneumococcal vaccination was estimated, including ARI cases (with complications), without further investigation of *S. pneumoniae*-induced disease cases. For this reason, it is not possible to clearly correlate the fact of vaccination with the decrease in the number of children who underwent ARI within 6 months after vaccination. It should also be noted that for children vaccinated between February and June two or three months (out of previous six) were coincide with winter months that are unfortunate epidemiologically. Accordingly, the morbidity in such children during previous 6 months should be higher, and in vaccinated in August–December period should be lower than in the next 6 months. In the first case this may be the reason for overestimating the effect of pneumococcal vaccination on the ARI frequency due to the natural negative morbidity dynamics, in the second case the reason is underestimation. 51 (65%) out of 78 patients with SJIA in this study were vaccinated during the period between February and June, thus, the effect of vaccination on the ARI frequency and related events could be overestimated in the majority of patients included in the study.

It is impossible to estimate the frequency of relatively rare (< 1/100) or very rare AEs (< 1/1000) according to the data from study. This should be taken into account at results extrapolation on safety of PCV-13 for the entire population of patients with SJIA.

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PCV-13 was purchased out of the funds of regional public organization «The League of Clinical Research» (Moscow). The organization was not involved in the planning and conducting of the present study, nor in the preparation and publication of the article.

**CONFLICT OF INTERESTS**

**Ekaterina I. Alexeeva** — receiving research grants from pharmaceutical companies Roche, Pfizer, Centocor, Novartis.

**Tatyana M. Dvoryakovskaya** — receiving research grants from pharmaceutical companies Roche, Pfizer.

**Rina V. Denisova** — receiving research grants from pharmaceutical companies Roche, Centocor, Novartis.

Other authors confirmed the absence of a reportable conflict of interests.