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Short and long-term immunogenicity and safety following the 23-valent polysaccharide pneumococcal vaccine in juvenile idiopathic arthritis patients under conventional DMARDs with or without anti-TNF therapy

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ABSTRACT

Objectives: To assess immunogenicity and safety of the 23-valent polysaccharide pneumococcal vaccine (PPV23) in juvenile idiopathic arthritis (JIA) patients under conventional DMARDs with or without anti-TNF therapy. The influences of demographic data, disease activity and treatment on immune response and the potential deleterious effects of vaccine on disease itself were also evaluated.
Methods: 17 JIA patients immediately pre-etanercept (Group 1) and 10 JIA patients on stable dose of methotrexate (Group 2) received one dose of PPV23. All patients were evaluated pre-vaccination, 2 months and 12 months post-vaccination for seven pneumoccocal serotypes. Serology was performed by enzyme immunoassay and the immunogenicity endpoints included seroprotection (SP), seroconversion (SP) and geometric mean concentration of antibodies(GMC). Clinical and laboratorial parameters of JIA were evaluated before and after vaccination.
Results: Groups 1 and 2 were comparable regarding age, gender, disease duration and other DMARDs use ($p > 0.05$). Pre-immunization SP and GMC were alike in patients with and without anti-TNF therapy ($p > 0.05$). The frequencies of patients achieving adequate vaccine response (seroconversion in $\geq$50% of all serotypes) at 2 months (53 vs. 30%, $p = 0.424$) and 12 months (36 vs. 40%, $p = 1.0$) were similar in JIA patients with and without anti-TNF therapy. Further comparison of patients with and without adequate response at 2 months revealed no influence of demographic, clinical and laboratorial JIA parameters ($p > 0.05$). Serious adverse events were not observed.
Conclusions: Anti-TNF therapy in JIA patients does not seem to have an additional deleterious effect on short/long-term PPV23 immunogenicity compared to MTX alone and no influence on disease parameters was observed with this vaccine.

1. Introduction

Anti-tumor necrosis factor (TNF) therapy significantly improved health related quality of life in juvenile idiopathic arthritis (JIA) population [1]. However, infections, especially of upper respiratory tract, remain an important cause of morbidity in these patients, as they may contribute to JIA flares [2]. Pneumococcal vaccination is therefore recommended for all patients under immunosuppressive therapy, particularly, with anti-TNF blockage indication [3,4].

There are no studies evaluating the 23-valent polysaccharide pneumococcal vaccine (PPV23) in JIA patients and the only available report in this disease with 7-valent conjugate pneumococcal vaccine in patients receiving anti-TNF blockage therapy revealed a low humoral response against some serotypes in a short-term assessment [5]. Likewise, a previous study of adult population with rheumatic or gastrointestinal chronic diseases under anti-TNF agents, mainly rheumatoid arthritis (RA), demonstrated lower

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responses against 23-valent polysaccharide pneumococcal vaccine (PPV23) in patients using the combination of anti-TNF and methotrexate [6].

It is still unclear whether anti-TNF agents may affect pneumococcal polysaccharide vaccination response in juvenile population with rheumatic diseases.

In addition, there is no study evaluating short and long-term immunogenicity and safety assessments of PPV23 in patients with JIA under biologic therapy.

Therefore, the objectives of this study were to assess the humoral response of the PPV23 in patients with JIA under methotrexate with and without anti-TNF therapy. The possible influence of demographic data, disease activity and treatment on immunogenicity and the potential deleterious effects of the vaccine on the disease itself were also evaluated.

2. Material and methods

Seventeen JIA patients with polyarticular course (International League Against Rheumatism criteria) [7] followed at the Pediatric Rheumatology Unit of Children's Institute of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo and who were refractory to high doses of methotrexate [median dose 0.9 mg/kg/week (0.7–1)] were included immediately before the start of anti-TNF (etanercept 0.8 mg/kg/week, Group 1) in association with the previous therapy. Group 2 consisted of 10 JIA patients on stable dose of methotrexate [median dose 0.8 mg/kg/week (0.3–1.0)]. One intramuscular dose of PPV23 (Sanofi Pasteur), lot B0381-3, at the immunization center of the same hospital was given to each study subject. In Group 1, etanercept was started two weeks after vaccination.

Participants were ≥5 and ≤18 years old and patients with history of previous vaccination against *S. pneumoniae* were excluded. This study was approved by the Local Ethical Committee of our University Hospital and an informed consent was obtained from all participants or their legal guardians.

This study was registered in ClinicalTrials.gov with the number NCT02196480.

3. Vaccine immunogenicity

Blood samples were collected pre-vaccination, 2 months and 12 months post vaccination for the detection of antibodies against seven pneumoccocal serotypes (4, 6B, 9V, 14, 18C, 19F, 23F). Samples were centrifuged and serum was frozen and stored at −70 °C until tested. In order to eliminate non-specific antibodies that could exhibit cross-reactivity, the samples were pre-absorbed with the C-polysaccharide and with the heterologous serotype 22F.

Serology for each serotype was performed by enzyme immunoassay and immunogenicity endpoints included seroprotection rate (SP) (percentage of subjects achieving antibodies titers ≥1.3 mcg/mL), seroconversion rate (SC) (percentage of subjects with a minimum of 2-fold increase in post-vaccination antibodies titers) and the geometric mean concentration of antibodies (GMC). Adequate vaccine response was considered when SC (at least a 2-fold increase) pre- to post-vaccination antibody levels occurred for at least 50% (four of the seven serotypes) of all vaccine serotypes.

During the period of 1 year after PPV23 vaccination, all upper and lower respiratory tract infections were weekly recorded during clinical appointments.

4. Safety

Vaccine adverse reactions were recorded by patients and parents in a weekly diary. Local reactions were considered to be related to the PPV23, while systemic adverse events were analyzed individually to determine their causality. Severe adverse events were defined as those requiring hospitalization or leading to death.

5. Clinical, laboratorial and therapy assessment

All patients were evaluated on the day of vaccination, 2 months and 12 months after immunization for clinical and laboratorial parameters: number of active joints (swelling within a joint, or limitation in the range of joint movement with joint pain or tenderness), number of limited joints, morning stiffness, physician global assessment of arthritis activity measured in cm on a 10 cm horizontal visual analogy scale (VAS), parent/patient global assessment of well-being measured on a 10 cm VAS and validated Brazilian version of Childhood Health Assessment Questionnaire (CHAQ) [8]. Erythrocyte sedimentation rate (ESR) was evaluated by Westergreen method and C-reactive protein (CRP) by nephelometry. The Juvenile Arthritis Disease Activity Score with 27-joint reduced count (JADAS-27), defined as the linear sum of the scores of four components [physician global assessment of disease activity (measured on a 10-cm VAS), parent/patient global assessment of well-being (measured on a 10-cm VAS); number of active joints (0–27 joints); and ESR] (range: 0–57 points), was calculated in all JIA patients [9]. Current concomitant treatment with non-steroidal anti-inflammatory drug, prednisone, methotrexate, leflunomide and cyclosporine were assessed.

6. Statistical analysis

Immunogenicity and safety analyses were descriptive and data were presented as number (%) or median (range). The GMCs were compared between JIA patients with and without anti-TNF therapy using a two-sided Student's *t*-test or Mann–Whitney *U*-test on the $\log_{10}$-transformed titers. The prospective analysis of GMCs for each of the seven pneumococcal serotypes was performed by Friedman Repeated Measures ANOVA on Ranks. Categorical variables (rates of seroprotection and seroconversion, prednisone and immunosuppressive drugs use) were compared using Fisher's exact test. The prospective analysis of seroprotection and seroconversion rates for each of the seven pneumococcal serotypes was performed by McNemar's Test. The effects of the vaccination on disease activity were analyzed with the Wilcoxon signed ranks test. The statistical significance was set at p value < 0.05.

7. Results

On the day of vaccination, Group 1 and Group 2 were comparable regarding current age (11.6 vs. 9.2 years, $p = 0.15$), female gender (47 vs. 40%, $p = 1.0$), age at diagnosis (7.6 vs. 7.1 years, $p = 0.9$) and disease duration (3.7 vs. 2 years, $p = 0.1$).

At baseline (immunization day), patients in Group 1 had significantly higher number of active joints (4 vs. 0, $p = 0.02$), limited joints (6 vs. 2, $p = 0.01$) and ESR (31 vs. 15 mm/1st hour, $p = 0.03$) compared to Group 2. Moreover, JADAS-27 score was higher in Group 1 (10.5 vs. 1, $p = 0.005$). The frequencies of glucocorticoids [5 (29.4%) vs. 0, $p = 0.12$] and non-biological drugs (methotrexate, leflunomide and cyclosporine) were similar in both groups ($p > 0.05$). The median dose of glucocorticoids was 7.5 (7.5–50 mg) in Group 1.

At 2 and 12 months, there was a significant decrease in disease activity parameters, including JADAS-27 in Group 1 (10.5 vs. 5.4 vs. 3.7, $p < 0.001$) and remained unchanged in Group 2 (1.0 vs. 1.5 vs. 3.0, $p = 0.92$) (Table 1).