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Immunogenicity, safety and tolerability of MF59-adjuvanted seasonal influenza vaccine in children with juvenile idiopathic arthritis

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ABSTRACT

In order to evaluate the immunogenicity, safety, and tolerability of the MF-59 adjuvanted seasonal influenza vaccine in children and adolescents with juvenile idiopathic arthritis (JIA) treated with different anti-rheumatic drugs, 60 pediatric patients with JIA (30 treated with disease-modifying anti-rheumatic drugs [DMARDs] and 30 with etanercept) were compared with 30 healthy controls of similar gender and age. All of the patients received a single dose of the MF59-adjuvanted seasonal influenza vaccine (Fluad, Siena, Italy). Immunogenicity was assessed at baseline, and 1 and 3 months post-vaccination; safety and tolerability were also evaluated during the study period. The JIA patients treated with etanercept showed significantly lower geometric mean titres (GMTs) against the A/H1N1 strain than those treated with DMARDs ($p < 0.05$) and the healthy controls ($p < 0.05$), who had similar GMTs. The etanercept-treated JIA patients also showed a significant reduction in GMTs against the A/H1N1 and A/H3N2 strains from 1 to 3 months after vaccination ($p < 0.05$). Furthermore, their seroconversion and seroprotection rates, and B antigen GMTs, were all significantly lower than those of the subjects in the other two groups ($p < 0.05$). The safety and tolerability of the vaccine were good and similar between the groups. The results of this study indicate a reduced immune response to MF59-adjuvanted seasonal influenza vaccine in JIA children and adolescents treated with etanercept in comparison with those treated with DMARDs and healthy controls. The safety and tolerability of the vaccine appeared to be good in all of the study population.

1. Introduction

Children and adolescents with rheumatic diseases (RDs) are at greater risk of infection than age- and gender-matched subjects without RD because of their aberrant immunity and frequent use of immunosuppressive drugs [1]. Annual vaccinations against influenza are recommended for these patients by health authorities throughout the world, regardless of the therapy they receive [2–4]. However, compliance with this recommendation is very low everywhere [4] because many experts are unconvinced that the vaccines are protective, and afraid that they may trigger a persistent autoimmune response and lead to severe clinical problems including relapsing RD [5,6].

Concerns about the efficacy of influenza vaccine in patients with RDs are due to the fact that these diseases are accompanied by significant changes in immune system function, and many of the drugs used to control them diseases can substantially reduce antibody production. Data collected from adults suggest that the greatest impairment of antibody response occurs when TNFα blockers are used, although a sub-optimal immune response is possible with some of the so-called disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate [7–10]. However, global evaluation of studies of adults with RDs seems to indicate that, with some limited exceptions, influenza vaccinations offer satisfactory protection, and remain the best means of reducing influenza-related risks.

Unfortunately, the very scanty data regarding children do not allow any firm conclusion to be drawn concerning the clinical importance of influenza vaccination. The available information comes from only small groups of children treated with corticosteroids and/or DMARDs, and all of the drugs are frequently considered together [11–14], and there are only marginal data concerning TNFα blockers [14]. Moreover, in most cases, the study group included children with different RDs and no analysis was made of the possible differences between illnesses. Finally, a considerable number of the studies were carried out some years ago [11,12], when RD therapeutic regimens were quite different and when only the conventional trivalent inactivated vaccine (TIV) was available. There is no published study of the more immunogenic adjuvanted influenza vaccines, the administration of which could overcome the problem of the possibly impaired immune system of children with RD.

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The main aim of this study was to evaluate of the immunogenicity, safety and tolerability of the MF59-adjuvanted influenza vaccine in pediatric patients with stable juvenile idiopathic arthritis (JIA) treated with conventional DMARDs or etanercept.

2. Patients and methods

2.1. Study population

The study involved children and adolescents with stable JIA, diagnosed and treated for at least 1 year in accordance with the recommendations of the International League of Associations for Rheumatology [15], who regularly attended the outpatient clinic of the Department of Maternal and Pediatric Sciences of the University of Milan (Italy), gave their assent to participate in the study, and whose parents or legal guardians signed an informed consent form. Healthy subjects of similar age and gender attending our outpatient clinic for minor surgical problems were enrolled as controls. The study protocol was approved by the Ethics Committee of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, and was conducted in accordance with the standards of Good Clinical Practice for trials of medicinal products in humans.

2.2. Study procedures

Before vaccination, the complete history of the children with JIA was reviewed, they underwent a physical examination, and their therapeutic history was recorded. The children were divided into two groups on the basis of the therapy they were receiving: the first included the children treated with DMARDs (all receiving methotrexate or sulfosalazine), and the second the children treated with the TNFα antagonist etanercept alone or in combination with methotrexate. The patients had been receiving the same drug treatment for at least 6 months and none of them had received corticosteroids for at least 1 year.

All of the enrolled subjects received a single dose of the MF59-adjuvanted seasonal influenza vaccine produced by Novartis (Fluad, Siena, Italy). The vaccine was formulated in accordance with the strain recommendations for the 2010-2011 northern hemisphere influenza season (A/California/7/2009 H1N1-like virus; A/Perth/16/2009 H3N2-like virus; B/Brisbane/60/2008-like virus). Each vaccine dose contained 15 μg of hemagglutinin (HA) of each influenza virus strain in a total volume of 0.5 mL, and was administered by means of an injection into the deltoid muscle of the non-dominant arm.

Serum samples for evaluating the immune response to the vaccine and the laboratory assessment of disease activity were collected immediately before the vaccine was administered, and 4 weeks (28 ± 3 days) and 3 months (90 ± 3 days) later.

To assess vaccine safety and tolerability, all of the subjects were observed for 30 min after the injection. Moreover, all of the patients and their parents were given a diary card in which to record the occurrence of solicited and unsolicited local symptoms (erythema, swelling/induration, and pain) or systemic symptoms (an axillary temperature of $\geq 38\,^{\circ}C$, rhinitis, malaise, sleepiness, changes in eating habits, vomiting, diarrhea) for the following 14 days. The symptoms were considered mild if they did not interfere with normal everyday activities, and severe if they prevented them and required medical attention. Adverse reactions were defined as any reaction that lasted for more than 7 days after the vaccination, and serious adverse reactions as any reaction that required medical attention or hospitalisation during the study period.

Disease activity was assessed on the day of vaccination, and 4 weeks and 90 days later, when the blood samples for evaluating the immune response to the vaccination were drawn.

2.3. Laboratory evaluations

2.3.1. Specific anti-influenza antibodies

Hemagglutination-inhibiting (HI) antibodies against each of the three influenza strains contained in the 2010–2011 influenza vaccine formulation were titred as previously described [16,17], and expressed as the reciprocal of the highest dilution inhibiting agglutination. In order to calculate the HI geometric mean titres (GMTs), a titre of 1:5 was arbitrarily assigned to non-responders as previously described [18]. The immunogenicity endpoints were based on the hemagglutination inhibition licensure criteria established by the guideline of the European Agency for the Evaluation of Medical Products (EMEA) [19], and immunogenicity was determined on the basis of the mean fold-increase in GMT (the ratio between the post- and pre-vaccination titre), the seroprotection rate (the percentage of subjects achieving an HI titre of ≥ 40), and the seroconversion rate (the percentage of subjects with a 4-fold increase in antibody titres with a minimum post-vaccination titre of 1:40). As there are no EMEA/EMA-defined criteria for children, immunogenicity was evaluated on the basis of the criteria used for adults aged 18–60 years, which require at least one of the following for each strain [20]: (1) seroconversion, a $\geq$4-fold increase in HI antibody titre, with a titre of $\geq$1:40 being reached in >40% of the subjects; (2) seroprotection, an HI antibody titre of $\geq$1:40 in >70% of the subjects; and (3) a >2.5-fold increase in HI antibody GMT.

2.3.2. Disease activity assessments

In addition to clinical evaluations, disease activity was assessed by evaluating the erythrocyte sedimentation rate, and measuring C-reactive protein and IgM rheumatoid factor (RF) levels by means of an enzyme-linked immunosorbent assay.

2.4. Statistical analysis

The sample size was calculated on the basis of immunogenicity, which was the primary endpoint. With a 5% type 1 error rate and a power of 90%, 30 subjects per group were required to show a difference of 30% in immunogenicity between one of the two JIA groups and the healthy controls. The continuous variables are given as mean values ± standard deviation (*SD*), and the categorical variables as numbers and percentages. The continuous data were analysed using a two-sided Student's *t* test if they were normally distributed (on the basis of the Shapiro–Wilk statistic) or a two-sided Wilcoxon rank-sum test if they were not. The categorical data were analysed using contingency tables and the chi-squared or Fisher's test, as appropriate. A logistic regression analysis was used to evaluate the factors potentially associated with a reduction in seroconversion rates, GMTs and seroprotection rates. All of the analyses were two-tailed, and p values of 0.05 or less were considered significant.

3. Results

Table 1 shows the baseline characteristics of the JIA patients and healthy controls. A total of 60 pediatric patients with JIA were enrolled (30 males; mean age 8.96 ± 5.12 years), of whom 30 were being treated with DMARDs and 30 with etanercept. Only three patients treated with DMARDs (10.0%) and two treated with etanercept (6.7%) had been previously vaccinated against influenza. Disease duration was similar between the groups as was the number of patients treated with methotrexate. The control group consisted of 30 healthy subjects with similar characteristics in terms of gender (15 males), age (9.11 ± 5.01 years) and previous influenza vaccinations.

Table 2 summarises the endpoints of immunogenicity against the A/H1N1, A/H3N2 and B influenza strains in the JIA patients and