Influenza vaccination in children with chronic rheumatic diseases and long-term immunosuppressive therapy

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Abstract

Objective

To study the immunogenicity, safety and efficacy of influenza vaccine in children with chronic rheumatic diseases (CRD) receiving long-term immunosuppressive therapy.

Methods

Seventy children (F:M 51:19) with CRD (JIA = 49, SLE = 11, other = 10) aged 4-17 yrs and 5 healthy siblings of the patients (aged < 11 yrs) received a "split type" influenza vaccine (Fluarix® SB) licensed for the 1999-2000 winter season. Clinical and laboratory evaluation were performed at study entry and at 1, 3 and 6 months after vaccination. Blood samples were collected before and one month after vaccination and antibody titers to A/Beijing, A/Sydney and B/Beijing influenza antigens were measured using a standardized hemagglutination inhibition assay.

Results

Patients were assigned to groups according to the therapeutic regimen [prednisone (PDN), PDN plus 1 disease modifying antirheumatic drug (DMARD), PDN plus 2 DMARDs and 1 or 2 DMARDs without PDN]. 5/70 patients reported local (3) or systemic (2) reactions and 1/5 siblings local reaction. Nine more patients reported mild upper respiratory tract symptoms 1-4 weeks post-vaccination. No patient was found to fulfill criteria for deterioration or flare of the underlying disease. At completion of vaccination 97.14% of patients developed protective HI titers to A/Beijing, 100% to A/Sydney and 80% to B/Beijing. No significant difference in the mean geometric titers was found between patients with different therapeutic regimens or age or between those with JIA or SLE. Disease activity was not related with response or non-response to B/Beijing. No patient reported "flu-like" symptoms during the 6-month period of follow-up.

Conclusion

The results of our study indicate that children with CRD receiving long-term immunosuppressive therapy at conventional doses respond to influenza vaccination similarly to healthy children without serious adverse reactions or disease flares regardless of their age, type of CRD or therapeutic regimen.

Key words

Influenza vaccine, chronic rheumatic diseases, immunosuppressive therapy.

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Introduction

Influenza vaccine is specifically recommended for elderly people and all age groups at high risk of developing serious complications due to influenza virus infection. Among these high-risk groups are children with chronic conditions who are being treated with immunosuppressive drugs (1, 2).

Protection against influenza in vaccinated healthy children is usually 70 to 80% (range 50-95%) depending on the closeness of the vaccine strain match to the circulating strain (1,2). However, there is limited data regarding the antibody responsiveness and efficacy of this vaccine in children with chronic rheumatic diseases receiving long-term immunosuppressive therapy (3).

In September 1999, the Regional Influenza Reference Center informed us about an expected influenza epidemic caused by strains of influenza virus closely related antigenically to those of the available vaccine. This information prompted us to immunize all children with chronic rheumatic diseases who were being followed up in our clinic and were receiving long-term immunosuppressive treatment. Up until then, such patients were not immunized routinely every year. Before starting immunization, we decided to prospectively study the seroconvertion rate and efficacy of the vaccine in these children, as well as the relapse or flare rate of their underlying disease following vaccination.

Subjects and methods

Subjects studied

Seventy children with chronic rheumatic diseases attending the Pediatric Clinic for Rheumatic Diseases of Childhood, 1st Department of Pediatrics, Aristotle University, Thessaloniki, were enrolled in the study after obtaining informed consent. Fifty-one of the children were females and 19 were males aged 4-17 years (mean 11.6 ± 4.5). The majority of patients (60/70) were suffering from juvenile idiopathic arthritis (JIA, 49) and systemic lupus erythematosus (SLE, 11); 10/70 had other rheumatic diseases (Table I).

All patients were receiving immunosuppressive treatment consisting of one or more of the following drugs: prednisone (≤ 0.5 mg/kg/d or on alternate days), methotrexate (15-20 mg/m^2/w), cyclosporine (2.5-3.5 mg/kg/d), azathioprine (2-2.5 mg/kg/d). In all cases the duration of any type immunosuppressive treatment was more than 6 months. At the time of immunization 17/70 patients had active disease and 53 were in remission. The distribution of the patients according to diagnosis, disease activity and duration of immunosuppressive treatment are shown in Table I. For evaluation of disease activity the following criteria were used: for JIA patients, the physician's global assessment for disease activity, the parent/patient assessment of overall well-being, functional ability, the number of joints with active arthritis or limited range of motion and the erythrocyte sedimentation rate (4); for SLE patients, the SLEDAI score (5); and for JDM patients the core set of variables proposed by Rider *et al.* (6). For the remaining patients, the physician's global assessment and the parent/patient assessment of overall well-being were used.

All patients were assessed by one of the investigators (MT) at the study entry and the main clinical and laboratory indices of disease activity at that time were recorded. They were then assigned to 4 groups depending on their therapeutic regimen; group 1: prednisone only; group 2: prednisone plus one disease-modifying antirheumatic drug (DMARD) (methotrexate, cyclosporine or azathioprine); group 3: prednisone plus two DMARDs; and group 4: one or more DMARDs without prednisone (Table II).

In addition, 5 healthy young children (F/M 4/1, aged 4-9 years) who were siblings of the patients were immunized in order to help protect their brothers or sisters from the intra-familial spread of influenza infection according to the WHO recommendations.

Immunization against influenza

None of the children studied had ever been vaccinated against influenza. All patients and healthy siblings received a "split type" influenza vaccine (Fluarix®, SB) prepared for the 1999 - 2000

Table I. Clinical characteristics of patients with chronic rheumatic diseases before immunization against influenza.

Diagnosis / Disease type	No. of pts./ No. of pts. with active disease at immunization (70/17)	Duration of immunosuppressive treatment (Range in years)	No. of non-responders to B/Beijing (n = 15)
Juvenile idiopathic arthritis (JIA)	49/15	2 - 6	13
JIA/Systemic progressing to polyarticular	10/4	3 - 6	3
JIA/Oligoarticular persistent	8/2	2 - 2.5	5*
JIA/Oligoarticular extended	11/4	2 - 5	2
JIA/Polyarticular RF (-)	13/3	2 - 5	2
JIA/Polyarticular RF (+)	2/2	2 - 6	0
JIA/Psoriatic	2/0	2 - 3	0
JIA/Non classified	3/0	2 - 2.5	1
Systemic lupus erythematosus	11/0	2 - 5	1
Juvenile dermatomyositis	3/0	2 - 3.5	
Systemic vasculitis	3/0	2 - 4.5	1
Mixed connective tissue disease	2/1	2 - 6	
Behçet's syndrome	1/1	2	
Idiopathic recurrent pericarditis	1/0	2.5	

* 2/5 non-responders were patients with active persistent oligoarticular JIA.

Table II. Patients' distribution according to their immunosuppressive therapeutic regimen.

Treatment groups	No. of pts. (main goups)	No. of pts. (subgroups)
Group 1: Prednisone	16	
Group 2	33	
2a. Prednisone + MTX		16
2b. Prednisone + Cyclosporin A		11
2c. Prednisone + Azathioprine		6
Group 3 Prednisone + Methotrexate + Cyclosporin A	8	
Group 4	13	
4a. Methotrexate		5
4b. Cyclosporin A		4
4c. Methotrexate + Cyclosporin A		4

winter season following the WHO guidelines. Children aged 4-8 years were scheduled to receive 1 or 2 doses, one month apart, according to their pre-immunization antibody titer and children ≥9 years to receive only one dose (1). All vaccinations were administered by two of the investigators (MT, ET). Parents were then provided with a pre-formatted diary to report any local or systemic reaction related to the vaccine for the 10 post-vaccination days. They were also requested to report in the same diary any findings indicating worsening of their child's underlying disease or any change in their child's health status for at least one month post-vaccination. In addition,they were asked to report in the diary any flu-like symptoms occurring within 6 months following completion of the vaccination. All diaries were collected at 1, 3 and 6-8 months after vaccination and at the same time re-evaluation of patients regarding the disease activity (1-3 months) or influenza morbidity (1-6 months) was done by the same investigator (MT) according to the predefined criteria (4-6). Any exacerbation or development of new signs and symptoms that in the opinion of the attending physician (FKT) required a change in therapy was defined as a disease flare (7).

Antibody titer assessment

Blood samples were drawn prior to vaccination (1st sample), 30-38 days later (mean 34 days) and just before the second dose (2nd sample), and one month after the 2nd dose (3rd sample) in those patients who received two vaccine doses. The samples were sent to the Regional Influenza Reference Center where they were stored at -20°C until tested for assessment of the antibody levels.

Antibody titers to the influenza antigens contained in the vaccine licensed for the 1999 - 2000 season [A/Beijing/262/95(H1N1)-like virus, A/Sydney/5/97(H3N2)-like virus and B/Beijing/184/93-like virus] were measured by a standardized hemagglutination inhibition (HI) assay using human red cells group 0, Rh negative.

HI titers ≥40 were considered as protective ones. A ≥4-fold increase in titer post vaccination (including a change from <20 to 40) was considered as a satisfactory response to vaccine antigens.

Statistical analysis

The response rates to the 3 vaccine antigens were compared between patient groups with different therapeutic regimens, between different age-groups (4-8 yrs and ≥9 yrs) and between groups with diagnosis of JIA and SLE using the Fisher exact test. The same test was used to compare the percentage of patients with active disease between

Table III. Serologic response of the 70 patients to influenza vaccination, expressed as number of patients (%).

HI titers (10^{-1})	A / Beijing Pre-vaccination	A / Beijing After 1st dose	A / Beijing After 2nd dose	A / Sydney Pre-vaccination	A / Sydney After 1st dose	A / Sydney After 2nd dose	B / Beijing Pre-vaccination	B / Beijing After 1st dose	B / Beijing After 2nd dose
≤ 20	49(70)			1 (1.5)			34 (49.5)		
≥ 40	21 (30)	60 (86)	68 (97.14)	69 (98.5)	70 (100)	70 (100)	36 (51.5)	52 (74.3)	56 (80)
Geometric mean titer	27.73	414	492	452	1449	1449	39.21	108.9	112
Significant rise*		30/ 49# (61)	13/19 (68.4)		1/1 (100)			12/34 (35.3)	1/22 (4.5)

*At least a 4-fold rise; #number of patients with a significant rise (≥ 4-fold rise in titer) after current vaccine dose / number of patients with a non-protective titer prior to this dose (< 40).

responders and non-responders. For non-parametric data regarding geometric means of HI titers, calculations were performed on log-transformed values using the Kruscal-Wallis test (8).

Results

Vaccine reactogenicity and safety

Of the 70 patients 5 reported local (3) or systemic (2) reactions after the 1st or 2nd vaccine dose. More specifically, one patient reported pain and redness at injection site and two more patients reported only local pain. Two other patients reported fever ≥ 39°C plus convulsions (1) and sore throat plus mild cough (1). The child with convulsions had epilepsy and was receiving anti-epileptic treatment. Convulsions were self-limited after a few minutes duration according to the mother's report. Nine other patients reported upper respiratory tract symptoms (sore throat with or without cough accompanied by low grade fever < 38°C of 1-2 days duration) 1-4 weeks after the 2nd vaccine dose.

Deterioration of disease activity or flare

None of the subjects fullfilled the predefined criteria for a deterioration of disease activity (4-6) or flare (7) at any of the reassessments (1, 3 and 6-8 months). In addition, no increase in the ANA, anti-DNA, ENA, RF or other autoantibody titers (SS-A, SS-B, Sm etc) was demonstrated.

Serologic response

The serologic responses of the patients are summarized in Tables III-V. Before vaccination 30% of patients were found to have a protective HI titer (≥ 40) to strain A/Beijing, all but one (98.5%) to A/Sydney, and 51.5% to B/Beijing. At the completion of vaccination the majority of patients developed protective HI titers to all 3 strains, namely 97.14% to A/Beijing, 100% to A/Sydney and 80% to B/Beijing. The percentage of patients with a non-protective titer prior to the 2nd vaccine dose who then developed a 4-fold rise in titer, was significantly higher for antigen A/Beijing (68.4%) than for antigen B/Beijing (4.5%, $p < 0.001$, Table III). Comparison of the geometric mean titers before and one month following vaccination showed no difference for any of the various strains between the different therapeutic groups. Similarly there was no difference between patients with JIA and patients with SLE (Tables IV-V). Fifteen patients did not develop protective HI titers mainly to strain B/Beijing despite the 2-doses of vaccination; 13 were patients with JIA (one did not develop protective titers to either A/Beijing or B/Beijing) one had SLE, and another had a systemic vasculitis. Of these 15 non-responders 13 were in remission and 2 had active disease at the time of immunization. There was no significant difference in the mean age, the type of rheumatic disease or the drug combination between the groups of responders and non-responders ($p = 0.24$, $p = 0.7$ and $p = 0.33$, respectively). Furthermore there was no significant difference in the percentage of patients with active disease between responders and non responders ($p = 0$, Table I). All 5 vaccinated siblings developed satisfactory response (> 40) to the 3 vaccine strains.

Table IV. Geometric mean titers pre- and post vaccination in the 4 groups of patients receiving different therapeutic regimens.

HI Titers (10^{-1})	Group 1	Group 2	Group 3	Group 4	p*
A / Beijing					
Pre-vaccination	25.93	29.18	25.94	27.54	0.95
Post-vaccination	339.38	438.51	1722.75	545	0.34
A/ Sydney					
Pre-vaccination	472.58	429.39	525.01	396.07	0.83
Post-vaccination	2560	1152	1159.93	465.05	0.08
B/Beijing					
Pre-vaccination	61.68	34.53	59.44	26.11	0.25
Post-vaccination	390.08	93.002	390.08	52.22	0.06

*Wilcoxon/Kruskal-Wallis test on log transformed values of the geometric mean titers.

Efficacy of vaccination

No patient or healthy sibling reported "flu-like" symptoms during the 6-month period following completion of vaccination, a period which coincided with the seasonal influenza outbreak (January to June 2000).

Discussion

There is no definite consensus for the

Table V. Geometric mean titers and range of titers in patients with juvenile idiopathic arthritis (49) and systemic lupus erythematosus (11) pre- and post vaccination.

	A / Beijing			A / Sydney			B/ Beijing		
	JIA	SLE	P	JIA	SLE	P	JIA	SLE	P
Pre-vaccination	25.08 (10-320)*	33.11 (10-160)	0.48	510.37 (20-5120)	600.91 (160-1280)	0.74	25.8 (10-320)	90.75 ** (10-640)	0.01
Post-vaccination	414.95 (20-5160)	362.98 (40-5120)	0.88	1373.81 (160-5120)	1989.64 (640-5120)	0.31	83.67 (10-5120)	248.71 ** (10-5120)	0.05

* Numbers in parentheses indicate the range of titers.

** Although the GMT to B/Beijing in SLE patients was significantly higher (p = 0.01) compared with that in JIA patients before vaccination,no significant difference (p = 0.05) was observed at completion of vaccination.

influenza immunization of children or adults with rheumatic diseases who are receiving immunosuppressive treatment although it has been reported that patients with chronic conditions receiving immunosuppressive drugs are at increased risk to develop severe complications of influenza, especially severe respiratory disease (1,2). This discrepancy is due mainly to the conflicting results of previous studies regarding the post-vaccination flare of the patients' underlying disease and their ability to mount a protective antibody response to vaccine strains (9-14). However, recent studies in children with JIA and adults with rheumatoid arthritis (RA) have shown that these patients are capable of responding adequately to influenza vaccination without significant reactions or arthritis flares (3,15,16). Furthermore, reports from the CDC and other relevant centers published in the year 2000 recommend this vaccine for children with long-term immunosuppressive therapy (1, 17-19).

Our study showed that children with various rheumatic diseases and long-term immunosuppressive therapy mounted a satisfactory antibody response to all vaccine strains regardless of their age, therapeutic regimen, and type of rheumatic disease. In fact, at completion of vaccination (one month after the 1st or 2nd dose) a protective HI titer was demonstrated in 97% of patients to the strain A/Beijing, 100% to A/Sydney, and 80% to B/Beijing. This response was similar to that reported for healthy children (55 - 95%) (1, 19). There was no control group of healthy children in this study as only 5 healthy siblings were vaccinated. However, similar or lower response rates (82% to influenza A and 60% to influenza B) were previously reported in healthy siblings of pediatric solid organ transplant recipients who were immunized against influenza (20). The lower response rate to influenza B in this and other relevant studies (3, 20) may be attributed to the less frequent circulation of this antigenic type of influenza virus not only in our area but worldwide, as well as to the lower immunogenicity of this antigen in the vaccine that was prepared for the season the studies were performed.

The influenza vaccine used in our study was found to have very low reactogenicity and proved to be safe since no serious illness or worsening of the underlying disease was reported. The only child who manifested a serious systemic reaction (high fever and convulsions) was one who had epilepsy in addition to persistent JIA.

The efficacy of vaccination was demonstrated by the absence of any "flu-like illness" during the 6-month period of parents' observation following vaccination.

The findings of our study are in agreement with those of Malleson *et al.* (3) and Chalmers *et al.* (15) regarding vaccine reactogenicity, safety and immunogenicity. Malleson *et al.* (3) immunized 34 children with JIA and 13 healthy children. Of the 34 children, 12 were receiving prednisone and/or slow-acting antirheumatic drugs (SAARD). However, antibody responsiveness did not appear to be affected by concomitant treatment with prednisone and/or a SAARD. Chalmers *et al.* (15) immunized 126 adult patients with rheumatoid arthritis (RA) and 61 age-matched healthy subjects. Fifty-two of the 126 patients were receiving immunosuppressive treatment similar with that of our pediatric patients and the remaining 74 were receiving NSAID and SAARDS. The response to vaccination in all the patient groups was not significantly different from those of vaccinated control subjects. In both of the above mentioned studies, some flares of arthritis were reported within a month after vaccination that according to the authors cannot be absolutely attributed to the influenza vaccine since flares also happened in the controls (15). In our study, which included a wider spectrum of CRD, no deterioration in disease activity or flares of the underlying disease were observed during a longer period of observation (3 months following vaccination).

As no published data on the impact of influenza vaccination on children with SLE could be found, we followed the recommendation for adult SLE patients who should be vaccinated when the disease is under control to avoid post-vaccination flare of renal disease (16). Therefore, only patients with SLE in a remission phase were selected to be vaccinated and no relapse or exacerbation of the disease activity was demonstrated during the 3-month period following vaccination.

The results of our study indicate that children with chronic rheumatic diseases receiving long-term immunosuppressive therapy at conventional doses respond to influenza vaccination similarly to healthy children and without serious adverse reactions or disease

exacerbations. These results do not justify the reluctance of some authors to vaccinate children with CRD merely due to the risk of a flare when an influenza epidemic is expected (21).

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