Immunogenicity and safety of the inactivated hepatitis A vaccine in children with juvenile idiopathic arthritis on methotrexate treatment: a matched case-control study

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Abstract

Objective

To describe the immunogenicity and side effects of immunisation against hepatitis A virus (HAV) in JIA patients on methotrexate treatment, who have not been previously exposed to HAV.

Methods

Case-control study performed in JIA patients and healthy controls matched on age and gender. The subjects received two doses of inactivated anti-HAV vaccine (720 mIU/ml) intramuscularly at 0 and 6 months. Seroconversion, seroprotection rates and anti-HAV-IgG titres were measured at 1, 7 and 18 months. Children were monitored for adverse events.

Results

83 JIA patients and 76 controls were enrolled in the study. At one month, seroprotection rates were lower in children with, as compared to those without JIA (48.2% vs. 65%; p=0.05). At 7 and 18 months, rates of seroprotection rose significantly and were similar in both groups. The titre of anti-HAV-IgG was lower in children with JIA than healthy children at all time points (p<0.001). Vaccines were well tolerated.

Conclusion

Two doses of inactivated HAV vaccine were well tolerated and immunogenic in most immunosuppressed children with JIA; however, a single dose of HAV vaccine was insufficient to induce seroprotection in half of the patients. Further studies are required to analyse the long-term immunity against HAV in this population and optimal HAV immunisation regimen.

Key words

inactivated hepatitis A vaccine, juvenile arthritis, methotrexate, immunogenicity, safety

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Introduction

As children with juvenile idiopathic arthritis (JIA) are at increased risk of infection (1), immunisation against vaccine-preventable diseases remains a critical component of their long-term care. Recently published recommendations for vaccinations by EULAR include a recommendation that children with JIA receive hepatitis A virus (HAV) vaccine (2), although there are limited data on the efficacy of this vaccine in this patient population (3). Additionally, vaccination of patients with rheumatic diseases has been an area of debate as it has been postulated that vaccines may trigger an autoimmune response and a clinical flare of their disease (4-5). Although there is strong evidence of vaccine safety in immunocompromised patients, including children with JIA, some physicians remain skeptical (6). The objective of this study was to describe the immunogenicity and side effects of the inactivated HAV vaccine in JIA patients on a single immunosuppressive drug (methotrexate-MTX) and to investigate the factors associated with induction of a protective antibody response.

Patients and methods

Patients and study setting

The study was conducted between November 2011 and November 2014 at the Second Department of Paediatrics, P. & A. Kyriakou Children's Hospital, University of Athens, Greece. All patients between 2 and 16 years of age diagnosed with clinically inactive JIA (7) (according to the criteria of the International League of Associations for Rheumatology) were eligible to participate if they were in clinical remission for at least six months (8) while receiving MTX. We excluded patients with acute febrile illness at the time of immunisation, history of malnutrition, other immunodeficiency, blood transfusion or treatment with immunoglobulin or systemic steroids during the preceding 3 months, and patients with serological evidence of previous HAV infection or immunisation. We collected demographic data and disease characteristics such as disease duration, presence of uveitis and antinuclear antibody (ANA), rheumatoid factor (RF) and HLA-B27 status. Healthy children were recruited from the Paediatric Outpatients Department when they presented for routine checks.

Hepatitis A vaccination

We used a 2-dose immunisation schema with a minimum of 6 months between the first and second dose of the inactivated HAV vaccine (Havrix, 720IU/ml; GlaxoSmithKline Biologicals, Rixensart, Belgium). Immunisations were administered intramuscularly.

Analysis of vaccine-induced humoral immunity

Blood samples were obtained for serology at enrolment, a month after the first and second dose of the vaccine and 12 months after the last dose (0, 1, 7 and 18 months). Anti-HAV-IgG antibodies were assessed by ELISA (Enzygnost-Anti-HAV; Dade-Behring-Marburg-GmbH, Germany), according to the manufacturer's instructions. We defined seroconversion and seroprotection by measurement of an anti-HAV-IgG concentration of >10 mIU/ml and >20 mIU/ml respectively, based on results from previous studies (9).

Analysis of the vaccine-induced reactogenicity and tolerability

Adverse events were defined as any parental report of an adverse change from the child's baseline condition. The families of all patients were requested to report to the researchers any local (pain, erythema, swelling, and induration) or systemic symptoms (fever, malaise, nausea, vomiting and headache) for 7 days after each vaccination. Subjects with JIA were actively monitored for disease flare and/or novel autoimmune disease within 3 months of vaccination (based on prior reports suggesting that most autoimmune reactions occurred within 3 months following vaccination (10)). Moreover, we collected data on number of JIA flares and disease activity (Juvenile Arthritis Disease Activity Score – JADAS) for 18 months immediately prior to the study as well as data on number of flares and JADAS occurring during the 18-month study period.

Table I. Demographics, clinical characteristics and rates of the JIA and control group.

Parameters	JIA group	Control group	*p*-value
Study sample	83	76	0.87*
Age (years) (mean +/-SD)	6.3 ±2.3	5.3±2.7	0.8*
Gender	56 (66%) females	54 (45%) females	0.96+
Greek	54 (65.1%)	41 (53.9%)	0.36+
Albanian	17 (20.5%)	20 (26.9%)	0.45+
Other	12 (14.5%)	15 (19.7%)	0.45+
Time between doses (months), mean (SD)	6.3 (0.5)	6.5 (0.5)	0.7*
Medications	Methotrexate (15 mg/m^2)	None	–
Mean dose	12.5 mg/week		
Mean duration of MTX	27 months		
Oligoarticular JIA	42 (51%)	Not applicable (NA)	
Polyarticular JIA	21 (25%)		
Enthesitis-related arthritis	13 (16%)		
Psoriatic JIA	7 (8%)		
Uveitis	23 (28%)	NA	–
ANA	38 (45.8%)	-	
RF	3 (3.6%)		
HLA-B27	5 (6%)	NA	
Seroconversion rates			
Month 1	60 (72.3%)	62 (81.6%)	0.07+
Month 7	82 (98.8%)	75 (98.7%)	0.82+
Month 18	82 (98.8%)	75 (98.7%)	0.82+
Seroprotection rates			
Month 1	40 (48.2%)	49 (65%)	0.05+
Month 7	78 (94%)	75 (98.7%)	0.21+
Month 18	76 (91.6%)	74 (96.1%)	0.33+
Adverse events	9 (10.9%)	6 (8.4%)	0.65+
Injection site reaction	5	4	
Malaise	3	2	
Fever	3	2	
JADAS score			
Oligoarticular JIA	1		
Polyarticular JIA	2	NA	–
Psoriatic JIA	1.8		
Enthesitis-related arthtirits	2.0		
JADAS score (at 18 months)			
Oligoarticular JIA	1		–
Polyarticular JIA	1	NA	
Psoriatic JIA	1		
Enthesitis-related arthtirits	1.5		

*Student's t-test; +Pearson's chi-square test.

Definition of study end points

Seroconversion and seroprotection rates and anti-HAV-IgG antibodies at months 1, 7 and 18 were the primary study end points. Secondary end points included vaccine adverse events, including local and systemic side effects, 1 month after the first and the second dose of vaccine.

Statistical methods

Quantitative variables were expressed as mean values with standard deviation (SD), while categorical variables were expressed as absolute and relative frequencies. Anti-HAV-IgG titres were expressed as geometric means (GMT). Proportions were compared using chi-square and Fisher's exact tests. Repeated measurements analysis of variance (ANOVA) was performed to compare anti-HAV-IgG antibody titres among the different study groups. All reported *p*-values are two-tailed. Statistical significance was set at $p<0.05$ and analyses were conducted using SPSS statistical software (v. 19.0).

This study was approved by the Hospital's Research and Ethics Committee and conducted in accordance with the principles of the Declaration of Helsinki and the standards of good clinical practice. Written informed consent was obtained.

Results

Study demographics

Eighty-three patients and 76 controls completed the study; demographic characteristics and time interval between the two vaccine doses were similar in both groups (Table I). JIA disease type and characteristics are shown in Table IIA. Patients remained on the same dose of methotrexate during the study period. None of them received systemic steroids in between the two vaccine doses.

Immunogenicity

Immune responses were evident after each dose of HAV vaccine, as assessed by IgG levels in all groups. The seroconversion rates were similar at all time points for both groups. After primary immunisation, the seroprotection rate was significantly lower in the JIA group ($p=0.050$). The rates of seroprotection were similar in both groups at 7 and 18 months. The seroconversion and seroprotection rates were similar at all measured time points when compared according to JIA type, presence of uveitis and ANA positivity (Table IIA). The GMT of anti-HAV-IgG titres were significantly lower in the JIA group at all time points ($p<0.001$); there was no difference in the anti-HAV-IgG titre among JIA patients with different clinical presentation (Table IIB). Anti-HAV-IgG antibody titres increased significantly from 1 to 7 months and from 1 to 18 months for both groups ($p<0.01$). From 7 to 18 months the anti-HAV-IgG antibody levels increased significantly for the control ($p=0.04$) but not for the JIA group ($p>0.05$). During the follow-up period the control group had a greater increase in antibody levels as indicated from the significant interaction effect of analysis.

Safety and tolerability

The inactivated anti-HAV vaccine was associated with reactogenicity in a significant proportion of both healthy and JIA participants; reactions were in 10.5% of the JIA patients and 8.4% of the healthy children ($p=0.65$). Systemic reactions were more frequent than injection site reactions. No serious adverse event or death was report-

Table IIA. Seroconversion and seroprotection rates according to clinical characteristics in the JIA group.

	Seroconversion			Seroprotection		
	1 month n (%)	7 months n (%)	18 months n (%)	1 month n (%)	7 months n (%)	18 months n (%)
Diagnosis						
ERA	12 (75)	15 (93.8)	15 (93.8)	8 (50.0)	14 (87.5)	14 (87.5)
oligoJIA	28 (71.8)	39 (100.0)	39 (100.0)	18 (46.2)	39 (100.0)	37 (94.9)
polyJIA	16 (76.2)	21 (100.0)	21 (100.0)	12 (57.1)	18 (85.7)	18 (85.7)
psJIA	4 (57.1)	7 (100.0)	7 (100.0)	2 (28.6)	7 (100.0)	7 (100.0)
p-value*	0.783+	0.277+	0.277+	0.623+	0.055+	0.508+
Uveitis						
No	40 (66.7)	59 (98.3)	59 (98.3)	26 (43.3)	56 (93.3)	55 (91.7)
Yes	20 (87)	23 (100.0)	23 (100.0)	14 (60.9)	22 (95.7)	21 (91.3)
p-value*	0.065	1.000+	1.000+	0.152	1.000+	1.000+
ANA						
Negative(<1/160)	30 (66.7)	44 (97.8)	44 (97.8)	20 (44.4)	42 (93.3)	42 (93.3)
Positive (>1/160)	30 (78.9)	38 (100.0)	38 (100.0)	20 (52.6)	36 (94.7)	34 (89.5)
p-value*	0.213	1.000+	1.000+	0.457	1.000+	0.697+

**p*-value for comparison between groups (Pearson's chi square test); + Fisher's exact test.

Table IIB. Geometric means of Anti-HAV antibody titres and changes during the follow-up period.

	Anti-HAV antibody titres						
	1 month	7 months	18 months	*p*** 1 month *vs.* 7 months	*p*** 1 month *vs.* 18 months	*p*** 7 month *vs.* 18 months	*p*‡
Group							
Control	47.92	162.52	200.32	<0.001	<0.001	0.004	0.001
JIA cohort	0.00	94.03	98.19	<0.001	<0.001	1.000	
p-value*	0.001	<0.001	<0.001				
Diagnosis							
ERA	31.86	103.69	102.52	<0.001	<0.001	1.000	0.151
oligoJIA	23.99	95.42	104.54	<0.001	<0.001	0.835	
polyJIA	29.89	85.82	86.12	<0.001	<0.001	1.000	
psJIA	0.00	91.18	92.91	<0.001	<0.001	1.000	
p-value*	0.229	0.889	0.851				
Uveitis							
No	0.00	89.52	90.24	<0.001	<0.001	1.000	0.646
Yes	34.60	106.91	122.34	<0.001	<0.001	0.638	
p-value*	0.105	0.322	0.137				
ANA							
Negative	0.00	89.29	93.98	<0.001	<0.001	1.000	0.585
Positive	28.64	99.98	103.40	<0.001	<0.001	1.000	
p-value*	0.346	0.484	0.606				

p*-value for group effect.*p*-value for time effect. ‡Repeated measurements ANOVA. Effects reported include differences between the groups in the degree of change over the follow-up period.

ed. None of the subjects developed a new autoimmune disease. There were 18 episodes of flare recorded in the JIA group during an 18-month period preceding the study period. We observed 15 JIA disease flares during the total follow-up period. Two patients developed a flare after the first dose (mean time 4.3 months) and 13 after the second dose (mean time 8 months). These flares were not considered to relate to vaccinations. No JIA flare was reported during the three-month monitoring period after each vaccine. JADAS scores at enrolment and at the end of the study are shown in Table I.

Discussion

This is a novel study concerning immunogenicity and safety of the inactivated anti-HAV vaccine in patients with established JIA on immunomodulating treatment. Our primary finding was that two doses of the vaccine given six months apart were effective in inducing seroconversion and seroprotection in the majority of patients with JIA on MTX treatment. The antibody response was low after the first dose but it reached satisfactory levels following the second dose. Antibody levels remained high 12 months after the second dose. Similarly seroprotection rates were lower for JIA patients after the 1st dose but increased considerably following the completion of the vaccination schedule. The vaccine was well tolerated by the majority of subjects.

In general, our results are in line with studies that assessed the immunogenicity and safety of HAV vaccine performed in healthy children (12) as well

as in children with JIA (13) and other immunosuppressed patients with autoimmune diseases (14). Similarly, two studies performed in adult cohorts with rheumatoid arthritis (15) and inflammatory bowel disease also found comparable safety and immunogenicity. However, in these studies the mean antibody concentration and seroprotection rates were markedly lower compared to our JIA cohort. The aforementioned studies lacked a control group. Clinical studies performed in JIA patients on disease-modifying anti-rheumatic drugs showed an overall satisfactory response to other inactivated vaccines, such as the influenza (16), the conjugated 7-valent pneumococcal (17), and the human papilloma virus vaccines (18).

Further analysis of the disease duration, presence of uveitis, ANA positivity, RF status and type of JIA did not identify any associations with immune response. We further assessed immunity status a year after completion of the vaccination schedule, and identified persistently raised antibody titres in JIA patients (although lower than their healthy counterparts). Prior studies demonstrated that a two-dose schedule of the inactivated HAV vaccine conferred ten to twenty years of immunity in healthy children (19); nonetheless data on immunocompromised populations remain unknown. Studies of children with JIA who were immunised with the hepatitis B or tetravalent meningococcal vaccine noted that the rate of antibody loss was accelerated in children with JIA as compared to healthy controls (20-21). Thus, further studies are needed to evaluate the persistence of seroprotection after HAV vaccination of children with JIA.

To date, we have lacked data regarding vaccine safety and the risk of disease flare in children with JIA on immunosuppressive treatment. In our study, we directly assessed these parameters and noted similar percentages of minor side effects in JIA patients and controls and no serious adverse events. We carefully monitored our cohort for JIA flares for up to three months after each dose and none were noted.

Our study has certain drawbacks. Firstly, we were unable to perform elaborate studies on B and T cell repertoire function as well as to assess the early post immunisation response by measuring IgM concentrations. Due to the relatively small number of participants in our JIA cohort we were underpowered to detect differences in immune responses amongst the various JIA subtypes or related to other clinical features. Finally, our group was preselected in terms of JIA disease activity and steroid use; hence we were unable to comment on the immunogenicity and safety of HAV in this population of JIA patients.

Conclusion

Immunisation against HAV with two doses of the inactivated vaccine is safe and immunogenic in the vast majority of children with JIA on MTX treatment. Immunity persists at least 12 months following completion of the scheme. A single dose of the vaccine is insufficient in half of the patients. Vaccination against HAV should be considered in countries where hepatitis A is endemic. Further studies are required to analyse the long-term immunity against HAV in this group of patients.

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