

Hepatitis B vaccination in juvenile systemic lupus erythematosus

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Abstract

Objective

In this study, we examined the antibody responses after recombinant hepatitis B vaccine in juvenile SLE patients and whether antibody levels were affected by immunosuppressive therapy.

Methods

This study consisted of 64 juvenile SLE patients and 24 healthy controls. We evaluated HBsAg, Anti-HBs and Anti-HbcIgG titers in SLE patients. 24 patients (37%) were non-immunised, 39 patients were immunised (61%) and 1 patient (1.5%) was chronic hepatitis B carrier. Of the 24 non-immunised patients, 3 had active disease (SLEDAI>10) and 1 was being treated for tuberculosis infection so they were not included in the vaccination program. Twenty non-immunised SLE patients were given 3 dose recombinant hepatitis B vaccine doses at 0,1,6 months. AntiHBs antibody titer >10 IU/ml one month after the last dose of vaccine was accepted as seroconversion.

Results

After 3 doses of vaccination, 16 (80%) of SLE patients and all of the healthy controls had seroconversion. Since two patients had SLEDAI score >10 after the first 2 doses of vaccine and one patient had SLEDAI score >10 after the first dose, these patients were given only two doses of hepatitis B vaccine. These patients had already seroconverted. One patient had exacerbation of the disease one month after the third dose of the vaccine. Protective antibody responses were statistically insignificant between the two groups ($p=0.49$). Geometric mean antibody titers of SLE patients were lower than those of the healthy controls. Adequate antibody response was not affected by immunosuppressive treatment as prednisone, azathioprine, and hydroxychloroquine.

Conclusion

Juvenile SLE patients could reach an adequate antibody response after recombinant hepatitis B vaccination and this response is not affected by immunosuppressive treatment.

Key words

juvenile systemic lupus erythematosus, hepatitis B vaccination

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Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystemic autoimmune inflammatory disease that can affect every organ system in the human body. Although the specific cause is unknown, auto antibodies against host's self antigens play an important role in the pathogenesis of the disease. Due to the inflammation mediated by auto antibodies, end organ damage ensues (1, 2).

Children represent up to 15–17% of SLE patients worldwide. SLE often waxes and wanes with flares and quiescent periods in effected individuals throughout life (1, 2). Many factors such as genetics, hormones, race and environment are responsible in the etiology of the disease. Infections possess an important role as an environmental trigger (1-3). It has been shown that infections could lead to development of autoimmune disease with different mechanisms. However, infections would not lead to autoimmunity in genetically nonsusceptible individuals (3-7).

Infection remains a major cause of morbidity and mortality in SLE patients (20–55%) (4-8). Immunosuppressive agents used in the treatment of the disease make these patients susceptible to many infectious agents (1, 5, 7, 9).

The priority in juvenile onset SLE is to prevent end organ damage mediated by the disease itself (10). However, serious precautions against infections should be taken as well. Immunisation is the primary tool to combat against infections (11-15).

Despite the increased risk of infections, efficacy and reliability of vaccination in this group of patients has been a subject of debate for many years (12, 14, 15). Trials concerning vaccination in rheumatologic patients haven't been given the deserved attention due to the possibility that vaccines could trigger autoimmunity with different mechanisms as infectious agents (12, 16-18). There are reports describing subjects with new onset SLE or with exacerbation of the pre-existing disease following immunisation (12, 16-18).

It has been shown that influenza and polysaccharide pneumococcal vaccines are both safe and effective in SLE

patients (19, 20). However, the benefit of immunisation of SLE patients has still been a subject of controversy due to inadequate immune responses after vaccination (12, 14).

The presence of some case reports postulating that recombinant hepatitis B vaccine could trigger immune mechanisms precluded the widespread studies investigating the efficacy of hepatitis B vaccine in patients with chronic rheumatologic diseases (16-18). The study by Kuruma *et al.* (21) demonstrated the efficacy and safety of hepatitis B vaccine in adult SLE patients. To our knowledge, there has been no study investigating the efficacy and reliability of hepatitis B vaccine, the amount of immune response and the effects of immunosuppressive agents on immune response to vaccines in juvenile SLE patients. The aim of our study was to determine whether or not an adequate immune response would occur after recombinant hepatitis B vaccine in juvenile SLE patients and to investigate the effect of treatment on antibody response and the risk of exacerbation following HBV vaccination in this group of juvenile SLE patients.

Materials-methods

Study design and patients

Sixty four subjects (56 female, 8 male) with all age groups who were followed-up with the diagnosis of SLE in Istanbul University, Cerrahpasa Medical Faculty, Paediatric Rheumatology Outpatient Clinic were included in the study. Diagnosis of SLE was made according to the classification criteria of American College of Rheumatology which was revised in 1997 (22). All patients were under 16 years of age at the time of diagnosis. The ages of the subjects during study enrolment ranged between 9.1–19.8 years.

HBsAg, anti-HBsAg and total anti-HBc antibody titers were evaluated in the study group. HBsAg, anti-HBs and total anti-HBc titers were negative in 24 (37.5%) of the patients (non-immunised) while in 39 (60.9%) patients, HBsAg was negative, anti-HBs was positive and total anti-HBc was negative (immunised). In only one patient (1.5%), HBsAg was positive, anti-HBs

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titer was negative and total anti-HBc was positive (chronic hepatitis). Hepatitis B vaccine has been included in the national immunisation schedule since 1999 in Turkey. However, none of the study subjects had been immunised against hepatitis B in the national immunisation programme.

The patients whose HBsAg, anti-HBsAg and total anti-HBc titers were negative had never been immunised with Hepatitis B vaccine before.

Of the 24 non-immunised subjects, those (3 patients) with a SLEDAI (Systemic lupus erythematosus disease activity index) score ≥ 10 and one who was on antituberculosis treatment were excluded from the study.

No hepatic disease or any clinical sign related to hepatic disease was present in any of the non-immunised patients (20 subjects) who would be given hepatitis B vaccine. Control group consisted of 24 healthy subjects (12 female, 12 male) who had never been vaccinated with hepatitis B vaccine before.

This study was approved by local ethics committee (34257/25 November 2008). Informed consent was obtained at the time of the first visit.

Medications

During the study period, 17 patients were using prednisone. Mean prednisone dose was 6.25 mg (range 2.5–15 mg/day). Prednisone dosage was changed only in patients with flares during the study period. Eleven patients were on azathioprine (AZA) (mean dose 100 mg/day), 3 were on mycophenolate mofetil (mean dose 1000 mg/day) and 2 were on hydroxychloroquine (mean dose 200 mg/day). Three patients were not taking any medications. None of the study subjects had been given rituximab in the year before vaccination or any time before that.

Vaccination

Non-immunised patients with SLEDAI score < 10 and healthy controls with weights < 20 kg were vaccinated with 0.5 ml (10 μ g) and those > 20 kg were vaccinated with 1 ml (20 μ g) recombinant hepatitis B vaccine (Engerix-B, Glaxo, Smith-Kline) intramuscularly

applied in the deltoid region. Three doses were given. The first dose was applied at entry, the second and third doses were given one and six months after the first dose, respectively. Efficacy of this vaccination schedule was demonstrated in our previous study (21). All the vaccination doses were applied by a trained paediatric resident (MBA). Disease activity index (SLEDAI) was evaluated one month after each vaccine dose (first, second and seventh months of study enrolment).

Clinical evaluation

Vaccinated patients were clinically evaluated at the entry and one month after each vaccine dose (first, second and seventh months of study enrolment) regarding the presence of probable vaccine side effects (local oedema, redness and tenderness). Patients were followed up for occurrence of malar rash, oral ulcers, photosensitivity, arthritis, psychosis, seizures and serositis. In every follow-up, SLEDAI score of patients was re-evaluated and those with a score over 10 were excluded from the study.

Laboratory evaluation

Complete blood count, erythrocyte sedimentation rate, C-reactive protein, urinalysis, C3, C4 and anti-dsDNA levels were evaluated after one month of each vaccine dose. All changes concerning these laboratory results were noted. Amount of proteinuria in 24 hour urine sample was evaluated when necessary.

Evaluation of immune response

One month after the last dose of the vaccine, venous samples were obtained from juvenile SLE patients and controls. HBsAg, Anti-HBc total and Anti-HBsAg antibody were deter-

mined by enzyme immunoassay using commercial test kits SURASE B-96 (TMB), GBC (General Biologicals Corporation), Taiwan, ANTICORASE B-96 (TMB), GBC (General Biologicals Corporation), Taiwan and DIA-PRO, Italy; respectively.

Antibody titers were defined as IU/ml. Anti-HBs antibody titer ≥ 10 IU/ml after vaccination was considered protective.

Statistical analysis

Anti-HBs titers were log-transformed to calculate the geometric mean titers (GMT) and groups were compared by Kruskal-Wallis one-way ANOVA. All statistical analyses were carried out with the SPSS version 11.5. *P*-values of less than 0.05 were considered significant.

Results

Demographic features of the enrolled subjects are summarised in Table I.

Seroconversion rate and vaccine safety

One month after the third vaccination, 16 of the SLE patients (80%) and all of the healthy controls developed positive antibody response. Geometric mean titer of anti-HBsAg antibody of SLE patients with a positive antibody response was lower than that of healthy control group. However, there was no statistical difference between SLE patients and controls with regard to development of positive antibody response ($p=0.49$) (Table II).

Clinical assessment

During the study period, SLEDAI score > 10 was observed in 2 patients after the second dose of the vaccine and in 1 patient after the first dose of the vaccine. So, no further vaccinations

Table I. Demographic and clinical characteristics of study subjects with juvenile systemic and healthy controls.

	n.	Female/Male	Mean age at investigation	Mean disease duration
Juvenile systemic lupus erythematosus	20	16/4	13.2 \pm 2.58 years (range 9.1–19.8 years)	4.44 \pm 2.83 years (range 1.6–5.6 years)
Healthy controls	24	12/12	8.83 \pm 2.72 years (range 5–14 years)	

Table II. Vaccination results in the study groups.

Study groups	Seroprotection status	Anti-HBs level (GMT)
Juvenile systemic lupus erythematosus	16/20 (80%)	310.38 IU/ml (range 0–500 IU/ml)
Healthy controls	24/24 (100%)	618.46 IU/ml (range 70–900 IU/ml)

Table III. The variations of the SLEDAI scores in this study period.

	SLEDAI. (pre-vaccination)	SLEDAI-I (After the first dose Hepatitis B vaccine)	SLEDAI-II (After the second dose Hepatitis B vaccine)	SLEDAI-III (After the third dose Hepatitis B vaccine)
Mean SLEDAI score	3.20±3.01 (range 0–8)	3.20±4.02 (range 0–12)	3.80±4.15 (range 0–12)	4.60±4.52 (range 0–12)

were given to these patients. One more patient also had a SLEDAI score >10 after the third dose of the vaccine. These 3 patients (15%) were considered to have a flare and their treatment protocol was revised by increasing the prednisone dose. Only one of these three patients had developed a positive antibody response (anti-HBs level=70 U/ml) while the other two had not developed any antibody response. The 15% flare rate of our study patients was not different than the 18% flare rate of other juvenile SLE patients on follow-up. No significant change was observed in SLEDAI score after vaccination doses in the rest of the study subjects (Table III).

Effect of medication

The vaccine responsiveness was not influenced either from prednisone or AZA treatment. The GMT of patients who were under medication with prednisone and/or AZA and of patients who were without treatment did not show any statistical significance [prednisone using GMT: 282.6 IU/ml (n=17), prednisone not using GMT: 411.7 IU/ml (n=3), AZA using GMT: 282.8 IU/ml (n=11), AZA not using GMT: 316.2 IU/ml (n=9)]. However, there was an insignificant negative correlation between prednisone dosage and anti-HBs titer ($r=-0.08$, $p=0.81$).

Vaccine side effects

No side effects related to vaccination were observed in any of the SLE patients and controls.

Discussion

The mostly accused vaccine has been the recombinant hepatitis B vaccine (15–17). There are some case reports postulating the induction of autoimmune disease and SLE after recombinant hepatitis B vaccination despite the fact that there are millions of people being vaccinated without any sequela (17). The presence of a causal relationship between recombinant hepatitis B vaccine and chronic rheumatologic diseases is not clear yet due to the limited number of studies (11, 16–18).

We evaluated the safety and efficacy of recombinant hepatitis B vaccine in non-immunised SLE patients and healthy controls. To our knowledge, this is the first study conducted in childhood SLE patients. Eighty per cent of our SLE patients and all of the healthy controls developed a positive immune response after 3 doses of the vaccine. There was no statistical difference between groups with regard to protective antibody response. Antibody response after recombinant hepatitis B vaccination was as adequate as that of healthy controls in our SLE patients. Although statistically insignificant, geometric mean titers of AntiHBs antibody of SLE patients after vaccination was lower than that of the healthy controls. We hypothesized that this could be due to underlying disease itself and to the immunosuppressive therapy. However, some previous studies involving influenza (19) and pneumococcal (20) vaccines reported that the inadequate antibody response might not be due to the

medications or disease activity itself but rather to the dysregulation of the immune system. However, it is known that SLE patients who are on >20mg/day prednisone and immunosuppressive medication develop an inadequate immune response (19).

The immunosuppressive medications used during the study period could be one of the reasons of the lower antibody titers after recombinant hepatitis B vaccine in our SLE patients. This finding was in accordance to our previous study conducted in children with juvenile idiopathic arthritis (23). In that study, antibody response was found to be adequate but was lower than the control group.

In the study of Kuruma *et al.* (21), 26 (93%) out of 28 adult SLE patients developed a protective antibody response after HBV vaccination. Only 3 patients (11%) showed a flare in that study and this flare percentage was found to be similar to that observed in the previous year. No significant change was observed in SLEDAI score at baseline compared to one month after each dose of the vaccine and immunosuppressive therapy use during the study period was not significantly different. The authors concluded that hepatitis B vaccination was safe in inactive SLE patients with an adequate vaccine response rate.

In our study, an increase in SLEDAI scores was observed in 3 patients and one patient flared one month after the third dose of the vaccine. The safety and reliability of recombinant hepatitis B vaccine demonstrated in adult inactive SLE patients by recent studies was also supported by our study which was conducted in childhood SLE patients.

One of the main limitations of our study was the small sample size of the non-immunised SLE patients. The rate of juvenile SLE is lower than that in adults. Due to the routine national immunisation programmed of hepatitis B vaccination in infancy, the number of non-immunised subjects is limited. These might have contributed to our small sample size. Although we postulated that the immunosuppressive medication did not affect the antibody response, it would have been better if larger sample size of patients using

different immunosuppressive agents could be compared in this study. Another limitation of our study was that none of the patients had received newer biologic agents such as anti CD20 antibodies. So, further vaccination studies involving patients using these biologic agents are needed.

In conclusion, we found that children with SLE developed an adequate antibody response after recombinant hepatitis B vaccine which was, however, lower than the healthy control group. It can be postulated that antibody response after vaccination might not be affected by the immunosuppressive treatment. If possible juvenile SLE patients should be vaccinated in a stable phase of their disease prior to such treatments. However, further studies with larger sample sizes are needed to determine the efficacy and reliability of hepatitis B vaccine in paediatric SLE patients.

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