SAFETY AND IMMUNOGENICITY OF A COMBINED VACCINE AGAINST HEPATITIS A AND B IN PATIENTS WITH AUTOIMMUNE HEPATITIS

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SUMMARY

Patients with autoimmune hepatitis (AIH) are a group at risk of disease exacerbation or relapse of the underlying disease should they fall ill with infectious hepatitis A (HAV) or B (HBV). Therefore, it seems appropriate to protect this group of persons against HAV and HBV disease by vaccination. An open study evaluated the safety, reactogenicity and immunogenicity of a combined HAV and HBV vaccine in 10 patients with AIH (6 patients aged 1-15 years and four patients aged 16+ years). The vaccine was administered using a three-dose vaccination schedule (0, 1 and 6 months). The vaccine course was well tolerated, safe and did not aggravate the clinical course of the underlying disease. Patients responded with 100% seroconversion for antibody to the HAV vaccine component and geometric mean antibody concentration (GIVIC) comparable to healthy cohorts. Response to the HBV component antigen was comparable to previous reports of HBV vaccination in immune compromised individuals with lower GMC than observed in healthy populations. One month after the third vaccine dose (month 7), all six vaccinees in the 1-15 years age group developed protective levels of anti-HBs as compared to two of the four vaccinees in the 16+ years age group.

Key words: vaccination, autoimmune hepatitis, combined vaccine, anti-HAV seroconversion, anti-HBs seroprotection

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INTRODUCTION

The immunization of persons with immunopathological status can provide a dual benefit comprised of prevention of both infectious disease and possible subsequent aggravation of the underlying disease. One such group consists of patients with autoimmune hepatitis (AIH), a serious inflammatory disease of the liver of incompletely defined etiology. Its etiopathogenesis is being explained by genetic predisposition, immunoreactivity to autoantigens, and certain trigger factors which may AIH start or worsen. Those trigger factors are not fully understood and are still being researched (1–5). The disease is a multisystem disorder characterised by hypergammaglobulinaemia, high levels of serum transaminases and the presence of organ-specific and nonspecific autoantibodies. Standard treatment for AIH is immunosuppression either with prednisone alone or with a combination therapy of prednisone and azathioprine. According to Norwegian scientists and their study performed in the 10 year period (1986–1995), the AIH incidence equals 1.9/100 000 and prevalence is 16.9/100 000 (6). About 70% of those with AIH are women, most between the ages of 15 and 40 years (7). The prevalence in children ranges from 1 to 10 per million (8).

Viral hepatitis could result in aggravation or relapse of the AIH with a threat of transition to hepatic cirrhosis and even death from hepatic failure (9–10). Furthermore, AIH development after suffering from hepatitis A (HAV) and (HBV) has been described (11–12). These factors imply sufficient risk to support the need for HAV and HBV vaccination in this group of patients. Nevertheless, the question remains as to whether the immune reaction induced by vaccination can exacerbate the AIH.

A study was undertaken to assess the safety, reactogenicity and immunogenicity of the combined vaccine against HAV and HBV administered in a three-dose schedule to patients affected with AIH. An additional aim was to ascertain any AIH disease course change elicited by vaccination.

MATERIALS AND METHODS

This open, prospective study was conducted at one centre in the Czech Republic during 2000–2001. The study was conducted according to the requirements of the Helsinki Declaration and its amendments and Good Clinical Practice guidelines in operation at the time of the initiation of the study.

Ten patients in two age cohorts (six patients aged 1–15 years and four patients aged 16 years and over) were enrolled after written informed consent was obtained from all parents/guardians, and from the patients, if required with respect to age.

Inclusion in the study required a diagnosis of AIH or variant syndrome of AIH including overlap syndrome between AIH

Table 1. *Patient characteristics*

Characteristics	Aged 1–15 years (N=6)	Aged 16+ years	Total (N=10)
Mean age (years)	12.8	19.8	15.6
Male n (%)	2 (33)	1 (25)	3 (30)
Female n (%)	4 (67)	3 (75)	7 (70)
AIH n (%)	4 (67)	4 (100)	8 (80)
AIH-PBC n (%)	1 (17)	0	1 (10)
AIH-PSC n (%)	1 (17)	0	1 (10)

AIH = autoimmune hepatitis, AIH-PBC = overlapping syndrome of AIH and primary biliary sclerosis, AIH-PSC = overlapping syndrome of AIH and primary sclerosing cholangitis

and primary biliary cirrhosis (AIH-PBC), or AIH and primary sclerosing cholangitis (AIH-PSC). Comprehensive clinical histories, complete physical examination and laboratory assessments confirmed patient eligibility.

Exclusion criteria included acute illness on the day of vaccination, axiliary body temperature ≥ 37.0 °C, allergy to any vaccine component, history of HAV or HBV infection or previous vaccination against HAV or HBV, pregnancy or breast-feeding, simultaneous administration of another vaccine, at screening visit serum sample positive for hepatitis B surface antigen (HBsAg) or antibody to either HAV (anti-HAV) or HBsAg (anti-HBs) or HBcAg (anti-HBc).

The vaccines used in this study were commercially available combined HAV and HBV vaccines manufactured by GlaxoSmith-Kline Biologicals (Rixensart, Belgium). Patients aged 1–15 years received TWINRIX™ Junior containing 360 ELISA units (EL.U) of inactivated HAV and 10 μg of recombinant HBsAg in a volume of 0.5 ml (production batch: HAB 164D9A). Patients aged 16 years and over (16+ years) received TWINRIX™ Adult containing 720 EL.U of inactivated HAV and 20 μg of recombinant HBsAg in a volume of 1 ml (production batch: HAB 144B6A). The vaccines were administered intramuscularly in the deltoid muscle of the non-dominant arm according to a three-dose vaccination schedule at months 0, 1 and 6.

Solicited local (injection site pain, redness, swelling) and general symptoms (fever defined as axillary temperature above 37.4 °C, headache, fatigue, gastrointestinal symptoms) were recorded on a diary card by the vaccinee or his/her parent or guardian for 3 days after each vaccination. Any other unsolicited general or local symptoms observed or reported by the patient or parent or guardian within 30 days after each vaccine dose were recorded, including any medicament used to treat any symptom after vaccination.

Blood samples were obtained at screening visit and then at months 2, 6 and 7 and assayed for the presence of anti-HAV and anti-HBs. Screening samples were also examined for the presence of HBsAg and anti-HBc, in order to determine eligibility to enter into the study.

The commercially available quantitative EIA "Access Beckman Coulter" was used for "total" anti-HAV measurement. "Total" anti-HBs, anti-HBc were also measured by quantitative EIA Abbott Murex in "Minilyser SLT". The same equipment was used for qualitative EIA Abbott Murex for detection of HBsAg.

Seropositivity during the study for both antigens was defined as antibody titres above the assay cut-off (≥33 mlU/ml for anti-HAV and ≥10 mlU/ml for anti-HBs). For hepatitis A, seropositivity after vaccination in previously seronegative subjects was termed seroconversion. For hepatitis B, seroprotection is defined as anti-HBs antibody titers ≥10 mlU/ml.

Geometric mean concentration (GMC) of anti-HAV and anti-HBs were calculated by age group at all blood sampling timepoints using the log-transformation of titres and taking the anti-log of the mean of these transformed values.

The clinical picture of the underlying AIH was monitored over the course of the study and for one year following the first vaccine dose. Laboratory indices included measurements of total bilirubin, alanine aminotransferase (ALT), aspartate aminostransferase (AST), γ-flutamyltranspeptidase (GMT) activity, alkaline phosphatase, immunoglobuin G (IgG) and γ-globulin concentrations.

RESULTS

Table 1 details the demographic and baseline disease characteristics of the 10 patients enrolled in the two age groups of patients. Three diagnostic subgroups were represented by 10 patients: eight patients with AIH, one patient with AIH-PBC, and one patient with AIH-PSC. All patients aged to 15 years were on maintenance prednisone therapy at an average total daily dose of 8 mg. In the 16+ years cohort only one patient was being treated with prednisone total daily dose of 5 mg.

The vaccines were well-tolerated. Injection site pain was the most frequently reported symptom after vaccination (reported by 4/10 patients overall). Local swelling and redness were each reported by 1/10 patients. Fatigue was the most common general symptom (reported by 3/10 patients) and gastrointestinal symptoms were reported by 1 patient. No fever or headache was reported over the vaccination course. All symptoms were described as easily tolerated and did not interfere with usual daily activity. All symptoms resolved spontaneously after an average duration of two days. No serious adverse event, as defined by the International Congress for Harmonization, occurred during the course of the study.

No clinically significant change in any laboratory indices of the underlying AIH was noted in any vaccinee at any time point over the course of the study. A few mild, asymptomatic, and transient increases in liver transaminases, bilirubin, IgG and γ-globulin occurred and alkaline phosphatase increased by a ratio of 1.2 in one patient. These changes did not generally correlate

Table 2. *Antibody response elicited by a three dose vaccination course with a combined hepatitis A and B vaccine in AIH patients*

Subject number	Study vaccine anti-HAV (mIU/ml)			Study vaccine anti-HBs (mIU/ml)		
	month 2	month 6	month 7	month 2	month 6	month 7
Age of subjects 1–15						
1	12,000	1,000	17,000	245	1,084	1,132
2	140	neg.	700	9,3	50	1,071
3	neg.	neg.	190	neg.	neg.	16
4	90	46	1,400	neg.	neg.	759
5	400	110	2,800	neg.	29	818
6	610	360	4,400	33	102	699
Age of subjects 16+						
7	100	130	5,100	neg.	neg.	neg.
8	13,000	1,700	55,000	257	860	1,291
9	1,400	610	29,000	neg.	420	1,213
10	460	250	3,000	neg.	neg.	neg.

At time of the screening all enrolled subjects were negative for anti-HAV, anti-HBs, HBsAg and anti-HBc

Table 3. *Antibody response elicited by a three dose vaccination course with a combined hepatitis A and B vaccine*

Cohort	Month	anti-HAV Response		anti-HBs Response	
		Seroconversion n (%)	GMC (mIU/ml)	Seroprotection n (%)	GMC (mIU/ml)
1–15 years (N = 6)	2	5 (83)	182	3 (50)	6
	6	4 (67)	35	4 (67)	23
	7	6 (100)	1,842	6 (100)	451
16+ years (N = 4)	2	4 (100)	957	1 (25)	4
	6	4 (100)	428	2 (50)	25
	7	4 (100)	12,499	2 (50)	35

N = total number of vaccinees, Seroconversion = appearance of antibody in previously seronegative subject, Seroprotection = anti-HBs titre ≥10 mIU/ml, N (%) = number (percentage) of vaccinees within a given parameter

with administration of vaccine and none were considered vaccine related. Comparison of pre and post-vaccination laboratory values did not reveal any marked fluctuation in any vaccinee regardless of health history. The clinical status remained unchanged after completion of the vaccination course in all except one female patient. In this patient, for whom liver transplantation had been planned prior to vaccination, the AIH status deteriorated over the duration of the study and resulted in liver transplantation 124 days after the third vaccine dose. One year after receiving the first vaccine dose, the clinical status in none of the patients had been adversely affected by the vaccines.

Table 2 and 3 details the antibody response to the three doses of combined vaccine in terms of seroconversion rates for anti-HAV, seroprotection rates for anti-HBs and GMC of antibodies. All 10 vaccinees responded to the hepatitis A component antigen; notably all four vaccinees in the 16+ years age group seroconverted after the first vaccine dose. At each blood sampling time point, anti-HAV concentration ranged from five to 12-fold higher in the 16+ years age group as compared to 1–15 years age group. Conversely, response to the hepatitis B component antigen was more robust in the 1–15 years age group. One month after the third vaccine dose (month 7), all six vaccinees in the 1–15 years age group developed protective levels of anti-HBs as compared to two of the four vaccinees in the 16+ years age group. In addition, GMC of anti-HBs was 12-fold higher in 1–15 years age group as compared to the 16+ years age group. Both patients who failed to respond to the hepatitis B component antigen were female aged 19 and 21 years. Serum ALT, AST and GMT activities and IgG level in the 19-year-old and increased level of γ-globulin in the 21-year-old indicated active disease in these two patients but the overt clinical status of both patients remained unchanged.

DISCUSSION

The combined hepatitis A and B vaccine was safe when administered to this small cohort of young patients with AIH. The low incidence of post-vaccination symptoms and the absence of adverse effect on hepatocellular status as indicated by the stability of serum liver enzyme activity, total bilirubin, alkaline phosphatase and other laboratory indices confirmed vaccine tolerability.

Patients with AIH present a particular challenge to effective immunization for the effective treatment of their chronic condition is comprised of immunosuppressive drugs. The immune system is an extraordinarily complex system that relies on an elaborate and dynamic communications network that exists among the many different kinds of immune system cells that patrol the body. At the heart of the system is the ability to recognize and respond to antigens whether they are infectious agents, vaccine antigens or part of the body (self antigens). Maintenance immunosuppressive therapy further impedes the body‘s response to vaccination.

The immunogenicity of vaccination is generally evaluated according to two parameters: the induction of antibodies to the vaccine antigen and the level of antibody concentration after the full vaccination course. In this study the HAV component antigen elicited a satisfactory immune response in these patients with chronic liver disease as indicated by 100% seroconversion after the third dose. There was expected decrease of anti-HAV antibodies between second and third vaccine dose. This phenomenon is observed also among healthy immunised subjects (13). Furthermore, geometric mean anti-HAV concentrations in the two age groups were higher than reported levels attained by a two dose HAV vaccination regimen in adult patients with chronic liver disease (13) and actually within the same range as has been reported in healthy subjects (14). All 6 patients in the 1–15 year age responded to the HBV component antigen with protective anti-HBs titres while only two of the four patients aged 16 and over were seroprotected at month 7. Many studies have shown that individual immune responses to hepatitis B vaccination vary and are compounded in immune compromised patients (15). The two patients in the 16+ age groups who failed to respond to the HBV vaccine component antigen were female. The first one has been treated for autoimmune hepatitis type II, mental anorexia, compensated hepatic cirrhosis, portal hypertension but she didn’t have an overlap syndrome. She was treated by prednisone 5 mg once per day. The second patient has been followed up for autoimmune hepatitis type I (asymptomatic course), and she didn’t have an overlap syndrome and she wasn’t treated by prednisone.

Although a small sample size, the results in this study indicate the feasibility of use of the combined hepatitis A and B vaccine in patients with AIH. In view of the obvious risks posed by infection with either of these hepatitis viruses in patients with chronic liver disease, these results indicate that this group could benefit from immunization with the combined vaccine.

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The Ethical Review Committee reviewed the study protocol and the study was conducted in accordance with the provisions of the Helsinki Declaration and its amendments. The study design took into consideration the Good Clinical Practise guidelines in operation at the time of the initiation of the study. Informed consent from subjects and their parents was obtained before start of any procedure.

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REFERENCES

1. Czaja AJ: Autoimmune hepatitis – evolving concepts and treatment strategies. Dig Dis Sci, 1995; 40:435–456.
2. Krawitt EL: Autoimmune hepatitis. N Eng J Med, 1996; 334:897–903.
3. Manns MP: Recent developments in autoimmune liver diseases. J Gastroenterol Hepatol, 1997; 12:256–271.
4. Meyer zum Büschenfelde KH, Lohse AW, Manns M, et al: Autoimmunity and liver disease. Hepatology, 1990; 12:354–363.
5. Trivedi P, Mowat AP: Chronic hepatitis. In: Suchy FJ. Liver disease in children. St. Louis: Mosby-Year Book; 1994;510–522.
6. Boberg KM, Aadland E, Jahnsen J et al: Incidence and prevalence of primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis in a Norwegian population. Scand J Gastroenterol, 1998; 33:99–103.
7. Anon. http://www.niddk.nih.gov/health/digest/pubs/autoimmune/autohep.htm
8. Wirth S, Koletzko S: Autoimmunhepatitis im Kindesalter. Monatsschr Kinderheilkd, 1994; 142:908–916.
9. Czaja AJ: Diagnosis and therapy of autoimmune liver disease. Med Clin N Amer, 1996; 80:973–994.
10. Czaja AJ: Autoimmune hepatitis – evolving concepts and treatment strategies. Dig Dis Sci, 1995; 40:435–456.
11. Huppertz HI, Treichel U, Gassel AM, et al: Autoimmune hepatitis following hepatitis A virus infection. J Hepatol, 1995; 23:204–208.
12. Manns MP, Obermayer-Straub P: Viral induction of autoimmunity: mechanisms and examples in hepatology. J Viral Hepatol, 1997; 4(Suppl. 2):42–47.
13. Keefe E, Iwarson S, McMahon BJ et al: Safety and immunogenicity of hepatitis A vaccine in patients with chronic liver disease. Hepatology, 1998; 27 (3): 881–886.
14. Clemens R, Safary A, Hepburn A, Roche C, Stanbury WJ, Andre FE: Clinical experience with an inactivated hepatitis A vaccine. J Infect Dis, 1995;171 (Suppl 1):S44–49.
15. Safary A, André F: Over a decade of experience with a yeast recombinant hepatitis B vaccine. Vaccine, 2000; 18: 57–67.

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