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An open study of inactivated hepatitis A vaccine (VAQTA) in Taiwanese healthy adult volunteers: safety, tolerability, and immunogenicity

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The safety, tolerability and immunogenicity of inactivated hepatitis A vaccine (VAQTA, Merck and Co. Inc., West Point, PA, USA) were investigated in 28 seronegative healthy adult volunteers. The age range was 25-35 years, and the mean age was 29 years. Two doses of the vaccine, each containing 50 U of hepatitis A virus antigen, were administered into the deltoid region 24 weeks apart. No serious vaccine-related adverse reactions were reported. Four weeks after the first dose, the geometric mean titer (GMT) was 150 mIU/mL, and the seroconversion rate was 100%. Twenty eight weeks after the first dose (4 weeks following the second dose), the GMT was 4576 mIU/mL. This study demonstrated that VAQTA is safe and highly immunogenic in healthy young adults in Taiwan.

Key words: Hepatitis A, hepatitis A antibodies, inactivated vaccine, toxicity

Acute hepatitis A is the most common form of acute viral hepatitis throughout the world. In young children, acute hepatitis A virus (HAV) infection is often asymptomatic. In contrast, older children and adults develop a range of clinical manifestations, from mild and anicteric infection to fulminant hepatic failure, with substantial morbidity and economic consequences. In the 1970s, more than 90% of Taiwanese adults had anti-HAV antibody, and most of them contracted HAV infection during childhood [1,2]. With improvements in socioeconomic conditions and environmental sanitation, seroepidemiological studies in Taipei city in 1984, 1989 and 1999 demonstrated decreased seropositivity to HAV in children aged 1 to 12 years [3-5]. With a growing number of susceptible populations, endemic outbreaks have become a serious public health concern.

Human immune globulin was shown to prevent hepatitis A in the 1940s [6], but it offered protection for only 3 to 6 months [7]. In previous studies, HAV vaccine prepared from any human HAV genotype provided protection against infection of all strains [8]. VAQTA (Merck and Co. Inc., West Point, PA, USA), an inactivated whole HAV vaccine, was licensed in the United States by the Food and Drug Administration in March, 1996. It is supplied in both syringes and vials. In December 2001, Merck and Co. Inc. and its subsidiaries voluntarily recalled batches of VAQTA packaged in syringes from certain markets in Europe, the Asia Pacific region and parts of the Americas. The voluntary recall was the result of an investigation in which some syringes were found with an antigen content below the product's specification limit. This recall raised some concerns on the effectiveness of VAQTA in Taiwan. We conducted the following study to investigate the safety, tolerability, and immunogenicity of the vial form of VAQTA in healthy, young Taiwanese adults.

Subjects and Methods

Recruitment of subjects started in July of 2002. Staff members of a company and a medical laboratory who were aged 18 years or more, who had no evidence of liver disease or other systemic disease, and who had a normal physical examination were asked to participate in the study. Written consent was obtained from all volunteers upon entry into the study. Subjects were excluded if they had any of the following conditions: abnormal liver function 7 days prior to vaccination, allergic to any vaccine component (including alum formaldehyde or neomycin), having signs of acute illness, having received any blood-derived product within the previous 6 months, having taken immunosuppresants, or having coagulation or immunodeficiency disorders.

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The vaccine was prepared at Merck Research Laboratories (VAQTA, Hepatitis A Vaccine, inactivated, Merck and Co. Inc., West Point, PA, USA). The vaccine is an inactivated whole virus preparation produced by growth of the live attenuated HAV strain (CR326F) in cell culture of human MRC-5 diploid fibroblasts. The virus is grown, harvested, and purified by a combination of physical and high performance liquid chromatographic techniques, formalin inactivated, and then adsorbed onto amorphous aluminum hydroxyphosphate sulfate. One mL of the vaccine contains approximately 50 U of HAV antigen, which is purified and formulated without a preservative. Within the limits of current assay variability, the 50-U dose of VAQTA contains less than 0.1 μg of non-viral protein, less than 4×10^{-6} μg of DNA, less than 10^{-4} μg of bovine albumin, and less than 0.8 μg of formaldehyde. Other process chemical residuals are less than 10 parts per billion (ppb). The vial form of the product was used in this study.

Two doses of VAQTA, each having approximately 50 U of HAV antigen, were administered into the deltoid muscle at 0 and 6 months. Serum levels of anti-HAV were measured 7 days in advance, on the day of first inoculation and at 1 and 7 months after the first inoculation. Activities of aspartate aminotransferase and alanine aminotransferase were measured 7 days before the first dose. The vaccinees were asked to record on a diary card any adverse reaction occurring within 7 days postvaccination.

Quantitative determination of anti-HAV was done by use of an enzyme immunoassay method (Mediagnost anti-HAV; Germany). Serum samples were diluted to 1:10 and then added to the wells of a microtiter plate, coated with an inactivated HAV antigen, and incubated for 2 hours at 37°C. Then the conjugate (peroxidase labeled anti-HAV immunoglobulin G) was added and incubated for 1 hour at 37°C. After washing, the substrate was added and incubated for 30 minutes at room temperature. The reaction was terminated by adding a stop solution. A microtiter plate reader was used to detect the color reaction. Screening of seropositivity was determined by fast semiquantitative evaluation, according to the manufacturer's instructions. After the screening test, serum titers of enrolled seronegative individuals were determined by simple linear regression using curve fitted to the standard curve and expressed in milli-International Units (mIU)/mL, in accordance with the standard reference serum of the World Health Organization, and titers ≥20 mIU/mL were considered to show seropositivity.

Results

Thirty five subjects were recruited for pre-vaccination screening. Seven individuals were excluded (20%) due to seropositivity for anti-HAV. Twenty eight healthy adult volunteers (aged 25-35 years; mean age, 29 years; 20 females, 8 males) were enrolled and received the 2-dose regimen of VAQTA adminstered 24 weeks apart.

Safety and tolerability

The most common side effect was transient pain and mild soreness at the site of inoculation (Table 1). This side effect was reported in 39% and 28.5% after the first and second inoculation, respectively. No serious systemic reactions were reported. Fatigue, with an incidence of 3.6% after each inoculation, was the most common general symptom. The vaccine was well tolerated, and the vaccinees continued their routine activity without interruption.

Immunogenicity

Before inoculation, the geometric mean titer (GMT) was 14 mIU/mL. Four weeks after the first dose, the GMT was 150 mIU/mL with a seropositivity rate of

Table 1. Symptoms following VAQTA vaccination

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Local pain								
Dose 1	11/28 (39%)	3/28 (10.7%)	1/28 (3.6%)	0%	0%	0%	1/28 (3.6%)	1/28 (3.6%)
Dose 2	8/28 (28.5%)	4/28 (14%)	1/28 (3.6%)	0%	0%	0%	0%	0%
Local erythema								
Dose 1	1/28 (3.6%)	0%	0%	0%	0%	0%	0%	0%
Dose 2	1/28 (3.6%)	0%	0%	0%	0%	0%	0%	0%
Fatigue								
Dose 1	1/28 (3.6%)	0%	0%	1/28 (3.6%)	0%	1/28 (3.6%)	1/28 (3.6%)	0%
Dose 2	0%	0%	1/28 (3.6%)	0%	0%	0%	0%	0%

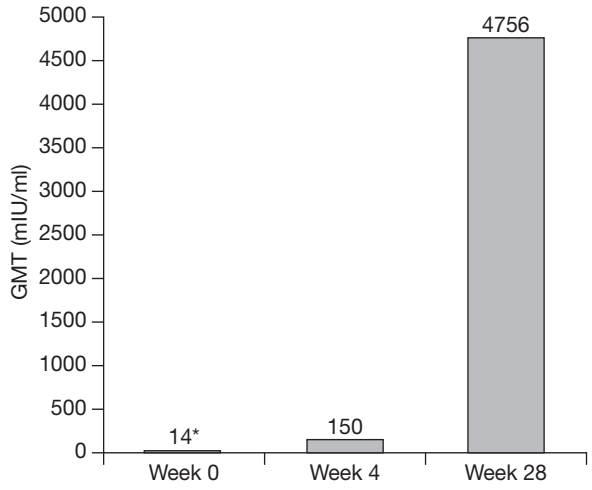

Fig. 1. Immunogenicity of inactivated hepatitis A vaccine at week 4 and 28 after the first dose. Seroconversion rate was 100% at weeks 4 and 28. GMT = geometric mean anti-hepatitis A titer.

100%. One month after the second dose, the anamnestic response was remarkable with a GMT value of 4756 mIU/mL (Fig. 1).

Discussion

The results in this study confirm that the vial form of VAQTA is well tolerated. Only one-third of the vaccinees experienced transient mild local reactions. No severe adverse reactions were observed. The vaccine is highly immunogenic. Four weeks after the first dose, the GMT was 150 mIU/mL. A 100% seroconversion rate was achieved after the first inoculation, a phenomenon supported by previous studies [9,10]. The great effectiveness of the single-dose hepatitis A vaccine carries strong public health implications, as it is capable of improving vaccination compliance and reducing cost. It may also be applied as a postexposure prophylaxis. A booster dose given 6 months later induced an anamnestic response, about 32 times the GMT after the first dose, indicating intact immune memory produced by the priming dose. The response to the booster was similar to the response of naturally immune-protected individuals who are re-exposed to hepatitis A. This suggests that vaccine-induced protection from clinical disease is long-lasting.

The seropositivity rate was about 20% (7/35) in this small study population, which was similar to that reported by Tseng in 1999 [5]. In their anti-HAV seroprevalence study in Taipei, the seropositive rate was 18.2% in the age group of 21 to 25 years. Considering the large population of young adults susceptible to HAV infection, an effective hepatitis A vaccine is a useful tool to control HAV infection and to achieve better herd immunity against HAV. In summary, this study demonstrated that the vial form of VAQTA is safe, well tolerated and highly immunogenic in healthy Taiwanese adults.

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References

1. Sung JI, Chen DS, Yu JY, Wang TH, Lai MY, Wang CY, et al. Hepatitis A virus infection in Taiwan. A hospital based study. Trop Geogr Med 1980;32:324-8.
2. Wu JS, Chen CH, Chiang YH, Lee MH, Ko YC, Hu HT. Hepatitis A infection in Taiwan. J Formos Med Assoc 1980; 79:694-9.
3. Hsu HY, Chang MH, Chen DS, Lee CY, Sung JL. Changing seroepidemiology of hepatitis A virus infection in Taiwan. J Med Virol 1986:17:297-301.
4. Tzen KT, Chang MH, Tsen YJ, Lee CY, Chen DS. Hepatitis A infection in Taipei city in 1989. J Formos Med Assoc 1991;90: 138-40.
5. Tseng HY, Lu CY, Lee CY, Yeh CC, Lin SC, Shih WY, et al. Hepatitis A virus infection in Taipei in 1999. J Formos Med Assoc 2001;100:604-7.
6. Krugman S, Overby RL, Mushawar IL, Frosner CMG, Deinhardt F. Viral hepatitis, Type B. Studies on natural history and prevention re-examined. N Engl J Med 1979;300: 101-6.
7. Conrad ME, Lemon SM. Prevention of endemic icteric viral hepatitis by administration of immune serum gamma globulin. J Infect Dis 1987;156:56-63.
8. Koff RS. Hepatitis A. Lancet 1998;351:1643-9.
9. Shouval D, Ashur Y, Adler R, Lewis JA, Armstrong ME, Davide JP, et al. Single and booster dose response to an inactivated hepatitis A virus vaccine: comparison with immune serum globulin prophylaxis. Vaccine 1993;11(Suppl. 1):S9-14.
10. Lo YC, Lee SS, Wong KH, Lim WL. Inactivated hepatitis A vaccine in healthy Chinese adults. J. Int Med 1996;239: 173-6.