Vaccine: Development and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Immunogenicity and safety of live attenuated hepatitis A vaccine (Biovac-A™) in healthy Indian children

This article was published in the following Dove Press journal:
Vaccine: Development and Therapy
19 December 2013
Number of times this article has been viewed

Sheila Bhave[1]
Apurba Ghosh[2]
Amita Sapru[1]
Monjori Mitra[2]
Suparna Chatterjee[3]
Nisha Bhattacharya[2]
Ganesh Kadhe[4]
Amey Mane[4]
Sucheta Roy[4]

[1]Department of Pediatrics, KEM Hospital Research Centre, Pune, Maharashtra, India; [2]Department of Pediatrics, Institute of Child Health, Kolkata, West Bengal, India; [3]Institute of Post Graduate Medical Education & Research, Kolkata, West Bengal, India; [4]Medical Affairs Department, Wockhardt Ltd, Mumbai, India

Introduction: The World Health Organization (WHO) recommends either inactivated or live attenuated vaccine against the hepatitis A virus (HAV) infection in countries with high incidence. Live attenuated vaccines against HAV infection have been developed and used exclusively in the People's Republic of China and have shown promising results. This is the first study conducted outside the People's Republic of China to evaluate the immunogenicity and safety of live attenuated hepatitis A vaccine (Biovac-A™) in healthy Indian children.

Material and methods: This was an open-labeled, 8-week (July 2012 to October 2012), non-comparative, non-randomized, confirmatory study conducted at two centers (Kolkata and Pune) in India. A total of 140 healthy Indian children aged 12 months to 12 years were administered live attenuated hepatitis A vaccine at the two centers. Overall, 137 subjects (female: 66, mean age: 4.09±2.5 years) completed the study. The subjects were vaccinated (subcutaneous over the deltoid muscle of the upper arm) with 0.5 mL of live attenuated H2 strain hepatitis A vaccine.

Results: Eight weeks after a single dose of the vaccine, 136 subjects from both the centers developed protective immunoglobulin (IgM) G antibodies ≥20 mIU/mL. The overall seroconversion rate was 99% (Kolkata: 100%, Pune: 98%). The hematological and biochemical parameters remained within normal limits. All the adverse events were non-serious and mild in severity.

Conclusion: Live attenuated H2 strain hepatitis A vaccine is immunogenic and safe in Indian children.

Keywords: hepatitis A, children, live attenuated vaccine, seroconversion

Introduction

With the recent change in the epidemiology of hepatitis A virus (HAV) infection, a large proportion of the adult population in developing countries is now susceptible to the disease.[1] Compared to infection in early childhood, the disease in adolescents and adults is known to be more severe and with a higher mortality.[2] The World Health Organization (WHO) and the Indian Academy of Pediatrics Committee on Immunization (IAPCOI) has recommended the inclusion of hepatitis A vaccination in the routine immunization program of our country.[3]

Currently, two types of vaccines: live attenuated and inactivated vaccines, are available for vaccination against HAV infection.[2] According to the WHO, live attenuated vaccines are as safe and effective as inactivated HAV vaccines.[4] The first live attenuated HAV vaccines (H2 and LA-1 strains) were developed and licensed in the People's Republic of China. The only other country where the live vaccine (H2 strain derived) is registered is India, where it was licensed in 2005.[2]

Correspondence: Monjori Mitra
Department of Pediatrics, Institute of Child Health, 11, Dr Biresh Guha Street, Kolkata, West Bengal, India
Tel +91 983 107 5734
Email monjorim@medclinsearch.com

Live attenuated vaccines mimic natural infection up to a limited extent and induce an immune response without causing a severe infection.[5,6] The live attenuated vaccines have a higher intensity of innate response and higher antigen content following replication thereby leading to a more prolonged antigen persistence generally resulting in a higher antibody response. Because of this, they produce lifelong immunity with the primary dose compared to most inactivated vaccines that require a booster dose.[2,7,8]

Previous studies with this live attenuated vaccine conducted in the People's Republic of China and India have shown remarkable long-term immunogenicity with a single dose of the vaccine.[9–11] The present study was a regulatory requirement of the Drugs Controller General of India (DCGI) due to a change in the manufacturing facility (in the People's Republic of China) and the addition of new inactive stabilizers. The Chinese authorities have approved the new facility and five million individuals have already been inoculated with the vaccine manufactured at the new facility with an excellent safety profile (data on file; Wockhardt Ltd [2012-13]). This is the first two-center study conducted outside of the People's Republic of China to evaluate the immunogenicity and safety of the live attenuated hepatitis A vaccine (new Biovac-A™; Wockhardt Ltd, Mumbai, India).

Materials and methods

Study design and patients

This was an open-labeled, non-comparative, non-randomized, 8-week (July 2012 to October 2012), confirmatory study, carried out at two centers (Kolkata and Pune) in India. All the subjects were recruited from the outpatients department of the hospital. These subjects were screened for anti-HAV antibodies. The recruited subjects had anti-HAV levels <20 mIU/mL and provided informed consent/assent for the study. The parents/guardians were given an explanation in their language about the study before they signed an informed consent form (subject >7 years also signed the assent form along with the parents/guardians) as per the guidelines of the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use.[12]

The study consisted of three visits (screening visit, baseline visit, and the end of the study visit). During the screening visit (–7 to 0 days), healthy subjects aged 12 months to 12 years were tested for anti-HAV antibodies (AxSYM® HAVAB® –M 2.0 and AxSYM® HAVAB® 2.0 kits; Abbott Laboratories, Abbott Park, Illinois, USA), biochemical liver profile serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvate transaminase (SGPT), bilirubin, and other hematology parameters. Subjects with negative anti-HAV antibodies (<20 mIU/mL) and normal hematological and biochemical parameters were enrolled. The study was reviewed and approved by the institutional ethics committees of both sites and was conducted in accordance with the good clinical practice guidelines, the Declaration of Helsinki,[13] and other applicable regulatory requirements.

Study vaccine and administration

The enrolled subjects were vaccinated (subcutaneous over the deltoid muscle of the upper arm) with 0.5 mL of new Biovac-A™ (Wockhardt Ltd). The Biovac-A™ (H2 strain, freeze dried, live vaccine) is developed by Zhejiang Pukang Biotechnological Co, Ltd, People's Republic of China, and imported and marketed in India by Wockhardt Ltd.

Assessment of safety

The safety of the vaccine was assessed on the basis of adverse events (AE) observed/reported after the administration of HAV vaccine, until the end of the study. Every vaccinated subject was observed closely at the study site for 1-hour and followed up with a telephone call after 48 hours for local/systemic reactions (local: pain, redness, itching, swelling, ecchymosis; systemic: nausea, vomiting, headache, irritability, restlessness, muscular pain, rash, fever ≥100°F, collapse, convulsion, unusual crying for ≥3 hours).

Assessment of immunogenicity

A repeat blood sample was taken at the end of the study (visit three) after 60±7 days for the measurement of anti-HAV antibodies (total HAV and immunoglobulin [IgM]) and hematology and biochemistry parameters. There is no consensus on the threshold level of anti-HAV seropositivity and different studies have used different cut-offs varying from 10 mIU/mL, 15 mIU/mL, and 20 mIU/mL. Based on the previous studies, we considered ≥20 mIU/mL antibody titer after vaccination as seroprotective.[14,15]

Statistical analysis

Descriptive statistics were used to summarize baseline demographics, hematology, and biochemical data. Differences in means (before and after vaccination) were compared using paired *t*-test. Comparison of the proportions was done using the Fisher's exact test/chi-squared test. Data analysis was done using SPSS version 17 software (IBM Corporation, Armonk, NY, USA).

Results

Subjects

The demographic characteristics of the subjects are tabulated in Table 1. A total of 195 healthy Indian children were screened for the present study. Of these, 53 subjects were excluded from the study (anti-HAV level ≥20 mIU/mL: 48; abnormal hematological values: 4; acute respiratory tract infection: 1). Two subjects were lost to follow-up between screening and baseline (enrollment) visits. The remaining 140 seronegative children were enrolled at the two centers. Three subjects were lost to follow-up between vaccination and the end of the study (shifting to a different location: 1; not willing to come for last visit: 2). Thus, 137 subjects (female: 66; mean age: 4.09±2.5 years) completed the study and were analyzed for immunogenicity and safety. The disposition of subjects is presented in Figure 1.

Safety and reactogenicity

In the 48 hours post vaccination observation period, systemic AEs were seen in six children (mild fever: 4; cough: 2) and local AEs in four (local pain: 3; local swelling: 1). The AEs reported during the remaining study period were respiratory tract infection (5.1%), fever (6.5%), vomiting (0.7%), and gastroenteritis (0.7%). Overall, 36 AEs were recorded in the evaluable subjects and 28 (20%) subjects experienced at least one AE during the study period. No serious adverse event (SAE) was observed during the study (Table 2).

The liver function tests before and after vaccination were normal in all the subjects except in one in whom SGPT levels rose to 110 U/L post vaccination but who had normal SGOT, serum bilirubin, and a negative anti-HAV IgM value. The SGPT returned to normal (11 U/L) on retesting after 1 month.

Table 1 Post vaccination immunogenicity (8 weeks)

	Kolkata (n=67)	Pune (n=70)	Total (n=137)
Age (years; mean ± SD)	2.6±1.5	5.5±2.8	4.1±2.5
Female; n (%)	27 (40.2)	39 (55.7)	66 (48.2)
Immunogenicity; seroprotection (%)	100	98	99
Post vaccination GMT; total Anti-HAV mIU/mL (95%CI)			
Overall	78.4 (64.1, 96.1)	78.9 (64.6, 96.4)	78.8 (68.4, 90.5)
1–2 years (n=38)	–	–	109.3 (82.3, 145.3)
>2 years (n=99)	–	–	67.2 (56.8, 79.4)

Abbreviations: CI, confidence interval; GMT, geometric mean titer; HAV, hepatitis A virus; SD, standard deviation.

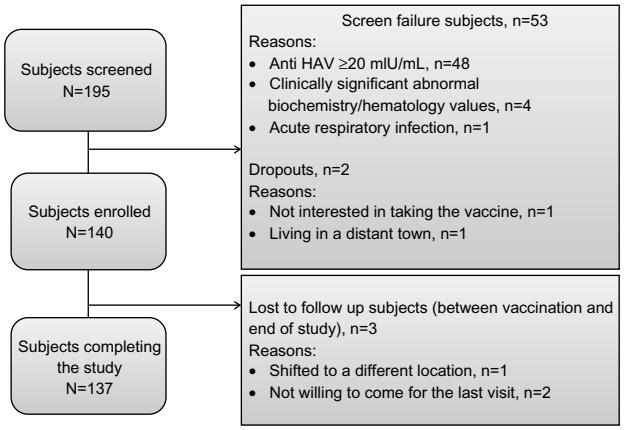

Figure 1 Flow diagram of the study with subject disposition.
Abbreviation: HAV, hepatitis A virus.

Immunogenicity

Out of 137 subjects, 136 attained seroprotection at the end of the 8-week study. The overall seroprotection (≥20 mIU/mL) rate was 99% (Kolkata 100%, Pune 98%). One subject from Pune site, aged 4 years, did not seroconvert (3.01 mIU/mL) after the vaccination. The geometric mean titer (GMT) for total anti-HAV was 78.8 mIU/mL (95% confidence interval [CI]: 68.4, 90.5; Kolkata 78.4 mIU/mL [95%CI: 64.1, 96.1], and Pune 78.9 mIU/mL [95%CI: 64.6, 96.4]) (Table 1). The GMT values for different age groups are presented in Table 1.

Table 2 List of adverse events observed

	Immediate AEs Post-vaccination (48 hours)	AEs in remaining study period	Total
Total AEs	10	26	36
Fever	4	9	13
Dengue fever	0	1	1
Pain at injection site	3	0	3
Swelling at the injection site	1	0	1
Cough/dry cough	2	3	5
Respiratory tract infection	0	4	4
Headache	0	1	1
Coryza	0	1	1
Rhinitis	0	1	1
Apthous ulcer	0	1	1
Acute gastroenteritis	0	1	1
Vomiting	0	1	1
Fall while playing, abrasions over right knee	0	1	1
IgM positive at visit 3	0	1	1
Increased level of SGPT at visit 3	0	1	1

Abbreviations: AE, adverse event; IgM, immunoglobulin; SGPT, serum glutamic pyruvate transaminase.

Anti-HAV IgM levels (post-vaccination) were negative in all except in one subject. This subject was, however, clinically well and had normal liver enzymes and serum bilirubin levels. He also had a seroprotective anti-HAV antibody level of 720 mIU/mL. On follow-up after 4 months, the IgM levels were negative.

Discussion

The results of the present study show that the H2 strain live attenuated hepatitis A vaccine from the new manufacturing facility and with the new additional stabilizers (sorbitol, trehalose, dextran 40, and mannitol) is optimally immunogenic and has a good tolerability profile with minimal reactogenicity in healthy Indian children aged 12 months to 12 years. The seroprotection achieved after a single dose of the vaccine was close to 100% at the end of 8-weeks post-vaccination. The mean titer values of anti-HAV were 78.8 mIU/mL (68.4, 90.5) at the end of the study (8-weeks post-vaccination). The GMT of anti-HAV was higher in subjects >2 years (109.3 mIU/mL [82.3,145.3]) compared to >2–12 years (67.2 mIU/mL [56.8,79.4]). The prevalence of higher GMT in subjects >2 years substantiates the recommendation by the various immunization committees to vaccinate at 12 months of age for a higher antibody response.[16]

The prevalence of HAV infection is strongly associated with the socioeconomic status and the sanitary conditions.[17] With the improvement of these factors in middle-income countries like India over the past two decades, an epidemiological shift in HAV infection has been observed with adults becoming more susceptible to HAV infection compared to children.[18–21] Due to this transition, the incidence of clinically significant hepatitis A infection in these countries is increasing.[17]

Live HAV vaccines have been used in the People's Republic of China for over 20 years and have shown remarkable safety, immunogenicity, and long-term protection to millions of subjects.[5] The incidence of hepatitis A reduced dramatically in the Chinese regions where the vaccine was used in mass and routine public immunization programs.[22] The first study using this vaccine outside of the People's Republic of China was reported from Pune, India in 2006 showing a seroprotection rate of 95.8%, 6 weeks after a single dose of live attenuated hepatitis A vaccine. A multicenter study from India, which followed the Pune study, reported in 2008, showed similar results.[10] Long-term follow up studies of immunogenicity are ongoing at both centers (unpublished data). Both these previous Indian studies were conducted with the vaccine manufactured at the original Chinese facility. The present study, using vaccine from a new manufacturing facility showed similar remarkable immunogenicity of the vaccine.

Though not many equivalence or non-inferiority studies are available that compare the seroconversion rates of the live attenuated and inactivated hepatitis A vaccine, Zheng et al and Wang et al in their studies were not able to identify any difference between both the vaccines in terms of seroconversion.[23,24] However, compared to the inactivated HAV vaccine, live attenuated vaccine has several advantages, such as the requirement of a single dose to produce long-lived immunity and stimulate generation of humoral, as well as memory cellular, response.[9,22,25] However, the major advantage of live attenuated vaccine is that it causes weak infection and closely reproduces the natural stimulus to the immune system.[25]

AEs related to the HAV vaccines (both with live attenuated and inactivated) are reported to be infrequent and mild in severity.[10,26] The most commonly observed AEs are fever, pain, redness, and swelling at the injection site. Most of these AEs resolve within a few hours or days.[26,27] Previous studies from India have not reported any significant AEs with the live attenuated vaccine.[9,10] The post vaccination AEs observed in the present study were also minimal and no SAE was observed. One subject had raised post-vaccination SGPT levels (110 U/L) but had no symptoms suggestive of hepatitis and SGOT and serum bilirubin levels were within the normal range. The anti-HAV IgM levels for this subject were negative. On follow-up, the child remained asymptomatic and SGPT levels repeated after 1 month were within normal limits. Such isolated transaminitis, (raised SGPT and negative anti-HAV IgM antibody) are not indicative of vaccine induced hepatitis.[28] Interestingly, another child had an isolated elevated IgM level, which reverted to negative after 4 months. This could well have been related to the vaccine as reported by others also.[29,30] Overall, the AEs observed in the present study were minimal, but due to the small sample size of the present study, the chance of detecting any rare AE was low.

Conclusion

In conclusion, the present study showed that the live attenuated H2 strain hepatitis A vaccine from the new manufacturing facility and with added stabilizers was highly immunogenic and safe in Indian children and comparable to the previously used live hepatitis A vaccine. In this environment of the changing epidemiology of HAV in India, with a shift in the age leading to more adults susceptible to the HAV

infection, a single dose of live attenuated hepatitis A vaccine in children was found to have an excellent seroconversion. This live attenuated hepatitis A vaccine also had a good tolerability and safety profile in this study population.

Acknowledgments

The authors acknowledge the help provided by Knowledge Isotopes (www.knowledgeisotopes.com) in drafting and editing the paper and the statistical help from Dr Manoranjan Pal and Professor Premanda Bharati of the Indian Statistical Institute, Kolkata.

Disclosure

Wockhardt Ltd provided financial support and was involved in the protocol design, data analysis, and the decision to submit this manuscript. The authors have no other conflicts of interest to declare.

References

1. Franco E, Meleleo C, Serino L, Sorbara D, Zaratti L. Hepatitis A: Epidemiology and prevention in developing countries. *World J Hepatol*. 2012;4(3):68–73.
2. World Health Organization. *Hepatitis A Vaccine*. Geneva: World Health Organization; 2003. Available from: http://www.who.int/vaccines/en/hepatitisa.shtml. Accessed June 3, 2013.
3. Indian Academy of Pediatrics Committee on Immunization (IAPCOI). Consensus recommendations on immunization and IAP immunization timetable 2012. *Indian Pediatr*. 2012;49(7):549–564.
4. Walldius G, Jungner I, Holme I, Aastveit AH, Kolar W, Steiner E. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet*. 2001;358(9298):2026–2033.
5. Mao JS, Chen NL, Huang HY, et al. Development of live attenuated hepatitis A vaccine (H2-strain). *Chin Med J (Engl)*. 1992;105(3):189–193.
6. Remaley AT, Warnick GR. High-density lipoprotein: what is the best way to measure its antiatherogenic potential? *Expert Opin Med Diagn*. 2008;2(7):773–788.
7. Bhave S, Bavdekar A, Sapru A, Bawangade S, Pandit A. Immunogenicity of single dose live attenuated hepatitis a vaccine. *Indian Pediatr*. 2011;48(2):135–137.
8. Plotkin SA, Orenstein WA, Offit PA. *Vaccines*. 6th ed. Philadelphia, PA, USA: Elsevier; 2004.
9. Bhave S, Bavdekar A, Madan Z, et al. Evaluation of immunogenicity and tolerability of a live attenuated hepatitis a vaccine in Indian children. *Indian Pediatr*. 2006;43(11):983–987.
10. Faridi MM, Shah N, Ghosh TK, et al. Immunogenicity and safety of live attenuated hepatitis A vaccine: a multicentric study. *Indian Pediatr*. 2009;46(1):29–34.
11. Zhao YL, Meng ZD, Xu ZY, et al. H2 strain attenuated live hepatitis A vaccines: protective efficacy in a hepatitis A outbreak. *World J Gastroenterol*. 2000;6(6):829–832.
12. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6(R1). 1996. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf. Accessed September 10, 2013.
13. World Medical Association Inc. Declaration of Helsinki. Ethical principles for medical research involving human subjects. *J Indian Med Assoc*. 2009;107(6):403–405.
14. Berger R, Just M, Althaus B. Time course of hepatitis A antibody production after active, passive and active/passive immunisation: the results are highly dependent on the antibody test system used. *J Virol Methods*. 1993;43(3):287–297.
15. Sharapov UM, Bulkow LR, Negus SE, et al. Persistence of hepatitis A vaccine induced seropositivity in infants and young children by maternal antibody status: 10-year follow-up. *Hepatology*. 2012;56(2): 516–522.
16. Fiore AE, Wasley A, Bell BP; Advisory Committee on Immunization Practices (ACIP). Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2006;55(RR-7):1–23.
17. WHO position paper on hepatitis A vaccines: June 2012-recommendations. *Vaccine*. 2013;31(2):285–286.
18. Syed R, Mohammed A, Sindiri P, Athani A, VVR R. Seroepidemiology of hepatitis A virus in Hyderabad, South India. *J Med Allied Sci*. 2012;2:58–61.
19. World Health Organization. The global prevalence of hepatitis A virus infection and susceptibility: A systematic review. Immunization, Vaccines and Biologicals. 2009. Available from: http://whqlibdoc.who.int/hq/2010/WHO_IVB_10.01_eng.pdf. Accessed November 8, 2013.
20. Chitambar SD, Chadha MS, Joshi MS, Arankalle VA. Prevalence of hepatitis a antibodies in western Indian population: changing pattern. *Southeast Asian J Trop Med Public Health*. 1999;30(2):273–276.
21. Murhekar MV, Sehgal SC, Murhekar KM, Padbhidri SP, Chitambar SD, Arankalle VA. Changing scenario of hepatitis A virus and hepatitis E virus exposure among the primitive tribes of Andaman and Nicobar Islands, India over the 10-year period 1989–1999. *J Viral Hepat*. 2002;9(4):315–321.
22. Zhuang FC, Qian W, Mao ZA, et al. Persistent efficacy of live attenuated hepatitis A vaccine (H2-strain) after a mass vaccination program. *Chin Med J (Engl)*. 2005;118(22):1851–1856.
23. Wang XY, Xu Z, Yao X, et al. Immune responses of anti-HAV in children vaccinated with live attenuated and inactivated hepatitis A vaccines. *Vaccine*. 2004;22(15–16):1941–1945.
24. Zheng H, Chen Y, Wang F, et al. Comparing live attenuated and inactivated hepatitis A vaccines: an immunogenicity study after one single dose. *Vaccine*. 2011;29(48):9098–9103.
25. Baxter D. Active and passive immunity, vaccine types, excipients and licensing. *Occup Med (Lond)*. 2007;57(8):552–556.
26. World Health Organization. *Information Sheet: Observed Rate of Vaccine Reactions (Hepatitis A Vaccine)*. Geneva: World Health Organization; 2012. Available from: http://www.who.int/vaccine_safety/initiative/tools/Hep_A_Vaccine_rates_information_sheet.pdf. Accessed February 4, 2013.
27. Wasley A, Samandari T, Bell BP. Incidence of hepatitis A in the United States in the era of vaccination. *JAMA*. 2005;294(2):194–201.
28. Prevention of hepatitis A through active or passive immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 1999;48(RR-12):1–37.
29. Shouval D, Ashur Y, Adler R, et al. Single and booster dose responses to an inactivated hepatitis A virus vaccine: comparison with immune serum globulin prophylaxis. *Vaccine*. 1993;11 Suppl 1:S9–S14.
30. Vidor E, Fritzell B, Plotkin S. Clinical development of a new inactivated hepatitis A vaccine. *Infection*. 1996;24(6):447–458.