

Hepatitis A vaccine versus immunoglobulin for post-exposure prophylaxis

Victor JC, Monto AS, Surdina TY, Suleimenova SZ, Vaughan G, Nainan OV, Favorov MO, Margolis HS, Bell BP. (University of Michigan, Ann Arbor, USA; Kazakhstan Ministry of Health, Almaty, Kazakhstan; Centers for Disease Control and Prevention, Atlanta, USA.) Hepatitis A vaccine versus immune globulin for postexposure prophylaxis. *N Engl J Med* 2007;**357**:1685–94.

SUMMARY

Until now, immunoglobulin (IG) and hepatitis A (HA) vaccine have been recommended for prophylaxis of HA in post-exposure and pre-exposure settings, respectively. This randomized, double-blind, active-control, non-inferiority trial compared the efficacy of HA vaccine and IG in preventing HA when given within 2 weeks after exposure. It was carried out in Almaty, Kazakhstan, an area of intermediate HA endemicity, with day 1 of exposure being defined as the day of onset of first symptom in the index patient.

Household and daycare contacts of confirmed index patients with HA were enrolled if they were between 2 and 40 years of age, and had no history of HA or vaccination, or of liver disease. All contacts had a blood specimen drawn at baseline to test for susceptibility to HA (negative for total antibody against hepatitis A virus [HAV]) and simultaneously randomized to receive either IG (0.02 ml/kg) or vaccine (single dose; VAQTA, Merck) intramuscularly. Analysis was done only for susceptible individuals. Separate randomization was done for household and daycare contacts. All contacts were interviewed every week to check for symptoms of hepatitis, and blood specimens were tested for IgM anti-HAV and alanine aminotransferase (ALT) routinely at 4 and 8 weeks after exposure and whenever symptoms occurred. The primary endpoint was laboratory-confirmed symptomatic HA (IgM anti-HAV positive, ALT >2 fold the upper limit of normal and suggestive clinical features) occurring at 15–56 days after exposure. Blood and stool of those who were IgM anti-HAV positive were tested for HAV RNA using polymerase chain reaction.

Of the 4524 contacts of 920 index patients enrolled, 1090 contacts of 474 index patients were eligible for the per protocol analysis. A large number of contacts were excluded after receiving vaccine ($n=1532$) or IG ($n=1578$) as they were found to be either immune to HA or positive for IgM anti-HAV in the blood specimen collected at enrolment.

Of the 474 index patients, 95% were icteric. Of the 1090 contacts analysed, a majority (83%) were household contacts. Those who received the vaccine ($n=568$) and IG ($n=522$) were similar in age (11.4 [8.1] v. 13.1 [9.4] years) and time from exposure to immunization (10.1 [2.4] v. 10.0 [2.4] days). No adverse reactions were seen in either group. The primary endpoint was reached in 25 (4.4%) vaccine and 17 (3.3%) IG recipients (RR=1.35, 95% confidence interval [CI] 0.70–2.67). The vaccine recipients with HA were younger (11.2 [8.7] v. 16.8 [11.5] years; $p=0.07$) and had higher ALT (1001 [397] v. 725 [461] U/L; $p=0.04$) than the IG recipients with HA, although jaundice and other symptoms were equally frequent. In addition, 20 (3.5%) vaccine recipients and 16 (3.1%) IG recipients had subclinical illness (defined as IgM HAV positive and elevated ALT or presence of HAV RNA) (RR 1.15; 95% CI 0.57–2.37).

Transient vaccine-induced IgM anti-HAV positivity occurred in 102 asymptomatic vaccine recipients with normal ALT at 4 weeks; of these, 72% (73/102) became IgM negative at 8 weeks, much before that in typical HA; this could be related either to vaccine-induced seroconversion or abortive HAV infection. If these cases were

considered as HAV infection, then the efficacy of the vaccine was lower than that of IG ([102+49]/568 v. 35/522).

This comparative trial shows that the rate of HA infection was <5% among contacts receiving prophylaxis with either HA vaccine or IG. Though there was no significant difference in efficacy of the HA vaccine and IG, the rate of HA was somewhat lower in the IG group. Thus, the use of IG may still be preferred in HA-naïve subjects who are at risk for severe disease (such as the elderly, and those with chronic liver disease or immunodeficiency) and those who cannot receive HA vaccine (age <12 months or allergy to a vaccine component). However, the HA vaccine has the advantages of providing active, long-term protection, no interference with other childhood immunizations, no risk of acquiring blood-borne infections and easier availability.

COMMENT

HAV is a hepatotropic virus with faecal–oral transmission and a spectrum of illness varying from asymptomatic transaminase elevation to acute liver failure. It has an incubation period of 15–50 days. Excretion of the virus in the faeces in large amounts and its physical stability contribute to the high potential for household transmission of this infection and occurrence of common source outbreaks of hepatitis A (HA). The infection is milder and less often symptomatic in children than in adults (~30% v. 70%).

This study showed that HA vaccine is as effective as IG in preventing HA in household and daycare contacts of patients with HA, when administered within 2 weeks after exposure to HAV. This report has led the US Advisory Committee on Immunization Practices to change its recommendation for post-exposure prophylaxis of HA; it now favours HA vaccine over IG.^{1,2}

Though this study showed the HA vaccine to be as effective as IG, it lacked a placebo group. However, in another study, HA vaccination within 1 week of exposure was shown to reduce the rate of HA infection among household contacts from 5.8% in the untreated group to 1% with a protective efficacy of 79% (95% CI: 7%–95%).³

In the study under consideration, all patients with HA infection were admitted to hospital. This may have limited the duration of exposure of family contacts, reducing the rate of disease in both the vaccine and the IG groups. However, in many parts of the world, most patients with acute viral hepatitis are not admitted to a hospital. The results of the current study may not be fully applicable in such a setting.

The applicability of this study's data and the utility of HA vaccine for post-exposure prophylaxis in the Indian setting may need consideration. It has been suggested that the epidemiology of HA infection in India is in the transition phase. This implies that improving standards of hygiene, especially in people of a higher socioeconomic group, have led to a reduced exposure to HAV infection in recent years. In population-based serological surveys conducted in urban and rural areas of Pune, during 1982, 1992 and 1998, it was shown that 69% (6–10 years), 53% (11–15 years) and 15% (16–25 years) of the population belonging to the higher socioeconomic group was anti-HAV negative in 1998. In contrast, 94%, 97% and 100%, respectively, of people with a lower socioeconomic group in these age groups had been exposed to HAV.⁴ Similar figures were reported in a study from Delhi, with HAV positivity rates of only 57% in subjects <35 years and 92% in those >35 years of age.⁵ In another multicentric study from India, the anti-HAV positivity rate ranged from 26% to 85%, with almost 50% of children in the age group of 1–5 years being susceptible.⁶ Thus, in recent years, a substantial pool of susceptible people has been generated. Because of a continuing circulation of HAV in our population, these people are at risk for HA outbreaks.⁷

Both daycare outbreaks⁸ and a large common source outbreak⁹ involving nearly 1100 subjects have recently been reported from Kottayam, Kerala. This suggests that the results of this study will find frequent application in India.

However, notwithstanding the above evidence favouring transition in HA epidemiology, a vast majority of our population still belongs to the lower socioeconomic group. In a recent cross-sectional, community-based study from Delhi, only 26.2% of 2095 randomly selected families belonged to the high or upper middle socioeconomic groups.¹⁰ This limits the applicability of any post-exposure prophylaxis to a small percentage of our total population. In fact, in a larger study of anti-HAV seroprevalence done among 500 schoolchildren (age 10–17 years) from two government schools in Delhi, 97.2% of all children were anti-HAV positive with similar exposure rates of 98.6%, 94.8% and 98.3% in the age groups of 10–12, 13–14 and 15–17 years, respectively.¹¹ In another study, these workers found high anti-HAV positivity rates in even younger schoolchildren, i.e. 86.4% and 91% in the age groups of 4–7 and 8–11 years, respectively.¹²

Another group in which prevention of HA infection may be of importance is patients with chronic liver disease, in whom this infection is associated with a poor outcome. However, in India, adults with chronic liver disease are usually already immune to HA, with anti-HAV rates of 93%–97% in several studies.^{12,13}

Even if the HA vaccine is useful in the post-exposure setting, is its use practical in India? We must bear in mind that neither HA vaccine nor IG has been shown to be efficacious if given more than 2 weeks after exposure. Further, both these interventions are costly and thus should be used only if there is a reasonable expectation of benefit. In the current study, nearly 70% of contacts were either already immune or had evidence of co-primary infection by the time HA was identified in the index patient. The prophylactic measure was thus wasted in this large subpopulation of contacts. This wastage may be even higher in the Indian setting. Furthermore, with most HAV infections in India occurring in children, the index patients are likely to be either asymptomatic or to have anicteric disease,¹⁴ precluding their detection and thus the use of prophylactic vaccination of contacts. Even when index patients are icteric, a vast majority of them either do not reach medical services or undergo specific tests to differentiate HA from other causes of hepatitis such as hepatitis B or hepatitis E virus infection. Most often than not, by the time all these steps are completed, more than 2 weeks have passed since the onset of symptoms, rendering both IG and vaccine ineffective.

In routine clinical practice in India, the source of infection in children with HA is infrequently identified. It is rare to encounter children with HA who give a history of another family member or school contact having recently been diagnosed as having HA. Thus, it is unlikely that many of these HA cases would have been prevented by the administration of HA vaccine for post-exposure prophylaxis, even if such a policy were in place and fully implemented. In fact, even in the West, a source of HA can be determined in only 43% of patients, with household contacts and daycare exposures accounting for only 12% and 2% of patients with HA, respectively.¹⁵ In most of these 'unknown exposure' cases, the infection is acquired from unrecognized HA infection among young children in the family. Post-exposure vaccination cannot be expected to be useful in this situation.

The other situation where post-exposure prophylaxis using HA vaccine may be useful is during outbreaks of HA, especially in urban areas. Even there, the applicability in India may be limited since a

specific diagnosis of the agent causing the outbreak is often delayed.

It is likely that, in India, this study will be used by pharmaceutical interest groups to promote the use of HA vaccine among all family members, and school and neighbourhood contacts of patients with any form of viral hepatitis. Any attempts to do so must be thwarted by the medical profession. We must insist on ensuring that the vaccine is used for post-exposure prophylaxis only when the illness in an index patient has been proven to be due to HA, is of <2 weeks' duration and when the contact has been shown to be non-immune to HAV. Otherwise, in the Indian setting of relatively unregulated medical practice, we will waste a lot of scarce resources.

The greater role of HA vaccine will continue to be for pre-exposure prophylaxis in certain populations which may be at a higher risk of HA. Till now, the HA vaccine has been used on an individual basis. There is a need for studies on cost-benefit analysis in Indian population groups to better understand the effects of a universal HA vaccination policy. Also, urgent steps are needed to improve sanitation and provide clean water supplies, which are the most effective strategies known to reduce the transmission of several faeco-oral transmitted diseases including HA.

REFERENCES

- 1 Update: Prevention of hepatitis A after exposure to hepatitis A virus and in international travelers: Updated recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morb Mortal Wkly Rep* 2007;**56**:1080–4.
- 2 Baker CJ. Another success for hepatitis A vaccine. *N Engl J Med* 2007;**357**:1757–9.
- 3 Saggiocca L, Amoroso P, Stroffolini T, Adamo B, Tosti ME, Lettieri G, et al. Efficacy of hepatitis A vaccine in prevention of secondary hepatitis A infection: A randomised trial. *Lancet* 1999; **353**:1136–9.
- 4 Arankalle VA, Chadha MS, Chitambar SD, Walimbe AM, Chobe LP, Gandhi SS. Changing epidemiology of hepatitis A and hepatitis E in urban and rural India (1982–98). *J Viral Hepat* 2001;**8**:293–303.
- 5 Das K, Jain A, Gupta S, Kapoor S, Gupta RK, Chakravorty A, et al. The changing epidemiological pattern of hepatitis A in an urban population of India: Emergence of a trend similar to the European countries. *Eur J Epidemiol* 2000;**16**:507–10.
- 6 Mall ML, Rai RR, Philip M, Naik G, Parekh P, Bhawnani SC, et al. Seroprevalence of hepatitis A infection in India: Changing pattern. *Indian J Gastroenterol* 2001;**20**:132–5.
- 7 Arankalle VA. Hepatitis A vaccine strategies and relevance in the present scenario. *Indian J Med Res* 2004;**119**:3–6.
- 8 Chitambar SD, Chadha MS, Yeolekar LR, Arankalle VA. Hepatitis A in day care centre. *Indian J Pediatr* 1996;**63**:781–3.
- 9 Arankalle VA, Sarada-Devi KL, Lole KS, Shenoy KT, Verma V, Haneephabi M. Molecular characterization of hepatitis A virus from a large outbreak from Kerala, India. *Indian J Med Res* 2006;**123**:760–9.
- 10 Aggarwal OP, Bhasin SK, Sharma AK, Chhabra P, Aggarwal K, Rajoura OP. A new instrument (scale) for measuring the socio-economic status of a family: Preliminary study. *Indian J Commun Med* 2005;**30**:111–14.
- 11 Batra Y, Bhatkal B, Ojha B, Kaur K, Saraya A, Panda SK, et al. Vaccination against hepatitis A virus may not be required for school children in northern India: Results of a seroepidemiological survey. *Bull World Health Organ* 2002;**80**:728–31.
- 12 Acharya SK, Batra Y, Bhatkal B, Ojha B, Kaur K, Hazari S, et al. Seroepidemiology of hepatitis A virus infection among school children in Delhi and north Indian patients with chronic liver disease: Implications for HAV vaccination. *J Gastroenterol Hepatol* 2003;**18**:822–7.
- 13 Joshi N, Rao S, Kumar A, Patil S, Rani S. Hepatitis A vaccination in chronic liver disease: Is it really required in a tropical country like India? *Indian J Med Microbiol* 2007;**25**:137–9.
- 14 Fiore AE, Wasley A, Bell BP. Prevention of hepatitis A through active or passive immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2006;**55** (RR 07):1–23.
- 15 Centers for Disease Control and Prevention. *Hepatitis Surveillance Report No. 59*. Atlanta, GA:US Department of Health and Human Services, Centers for Disease Control and Prevention; 2004.

ANSHU SRIVASTAVA

Department of Paediatric Gastroenterology

RAKESH AGGARWAL

Department of Gastroenterology

Sanjay Gandhi Postgraduate Institute of Medical Sciences

Lucknow

Uttar Pradesh