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REVIEW

Hepatitis A vaccination

Li Zhang[a,b]

[a]Academy of Preventive Medicine, Shandong University, Jinan, China; [b]Shandong Provincial Key Laboratory of Infectious Disease Control and Prevention, Shandong Center for Disease Control and Prevention, Jinan, China

ABSTRACT

Hepatitis A is an important public health issue worldwide. Hepatitis A vaccine (HepA) was first licensed in 1992. Both inactivated HepA (HepA-I) and live attenuated HepA (HepA-L) are highly immunogenic and well tolerated, and immune protection postvaccination can persist for at least 20 y. HepA is effective for both preexposure and postexposure prophylaxis, especially among children and young adults. The strategy of HepA vaccination varies in different countries and mainly includes vaccination among high-risk populations, regional childhood vaccination and universal childhood vaccination. The incidence of hepatitis A has decreased greatly in many countries in the last 30 y, but hepatitis A outbreaks frequently occur among high-risk populations and those who have not been covered by universal child vaccination programs in recent years. Disease surveillance and serosurveys are suggested to clarify the shift in the epidemiology of hepatitis A. The long-term persistence of immune protection after one dose of HepA should be further studied, as well as the cost-effective evaluation of different strategies of HepA vaccination. Based on this evidence, the recommendation on HepA vaccination should be put forward scientifically and updated in a timely and well-implemented manner.

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Introduction

Hepatitis A, caused by the hepatitis A virus (HAV), is primarily transmitted by the fecal-oral route. In 1973, HAV was first detected in an infected person in the United States.[1] The largest hepatitis A outbreak in the world happened in Shanghai, China in 1988, where more than 310,000 cases occurred and over 8000 patients were hospitalized.[2] Hepatitis A vaccine (HepA) was first used worldwide in 1992 and its role in hepatitis A control has been proven in many countries.[3–6] However, more than 7000 persons died from hepatitis A worldwide in 2016.[7] The goal of eliminating viral hepatitis by 2030 was put forward by the World Health Organization (WHO) in 2016,[8] and more efforts should be made to achieve this goal. This review provides an outline of HepA vaccination throughout the world, trying to find ways to accomplish the goals as scheduled.

Development of HepA

HepA was developed following the success of HAV cultivation in cell lines suitable for vaccine production during the twentieth century.[9–11] Currently, both inactivated hepatitis A vaccine (HepA-I) and attenuated live hepatitis A vaccine (HepA-L) are available worldwide, which contain HAV propagated in different human and nonhuman mammalian cells.

The world's first licensed HepA-I [Havrix™, GlaxoSmithKline (GSK) Biologicals, Rixensart, Belgium] was developed in early 1992,[12] followed by Merck, Sharp & Dohme Corp (Vaqta®,1993),[13] Sanofi Pasteur S.A. (Avaxim®, 1996)[14] and Crucell Switzerland AG (Epaxal®,1997).[15,16] Next, two types of HepA-I, Healive® and Weisarulan® were licensed in China in 2002 and 2006, respectively.[17]

The first HepA-L strain in the world was licensed in China in 1992, and the HAV H_2 strain was used to produce it.[18] Next, HepA (H_2 strain) was licensed in India (2005), Guatemala (2006), the Philippines (2008), and Thailand (2010).[17] In 1997, the Chinese Food and Drug Administration (FDA) licensed another HepA-L (AL-1 strain).[18] HepA-L was initially produced in liquid form, but was instead available as a freeze-dried vaccine in the year of 2000, the latter is more stable and easier for storage and transportation. According to the data from the official websites of the Chinese FDA, 16.7 million doses of HepA-L (H2 strain) and 4.57 million doses of HepA-L (LA-1 strain) were released in 2017.

A combined hepatitis A and hepatitis B vaccine (HepAB) provides the possibility of preventing both hepatitis A and B simultaneously, and is highly immunogenic and well tolerated,[19] potentially saving cost and logistic resource. To date, there are two kinds of combined vaccines containing HepA distributed worldwide: combined hepatitis A and B vaccines (Bilive™, Twinrix™) and combined hepatitis A and typhoid vaccines (Viatim®).[20] To our knowledge, no new monovalent or combined HepA has been newly licensed or developed in the last decade.

Administration of hepatitis A vaccine

HepA-I is licensed for intramuscular administration in a 2-dose schedule with a flexible interval between the first dose and the second dose (from 6 months up to 4–5 y, usually

CONTACT Li Zhang ZL9127@163.com Jingshi Road 16992, Jinan City, Shandong Privince, China, 250014

6–18 months).[21] The timing of the second dose is not critical and a similar anti-HAV titer could be achieved after a two-dose HepA interval schedules of 6 months, 12 months or 18 months.[22] High immunogenicity could be detected even if the interval between the two doses of HepA-I was up to 2 y.[23] For consideration of cost, a single-dose HepA-I schedule has been integrated in the routine universal vaccination of children in Argentina, Brazil, Chile, Paraguay, Colombia and Tunisia.[7] Compared with HepA-I, which is used widely throughout, HepA-L is mainly used in China and India and is administered as a single subcutaneous dose.[17] Although a high seroconversion rate could be elicited after single-dose HepA-I or HepA-L, the immunity duration after one-dose HepA might be shorter compared with the two-dose schedule.

The targeted population of HepA-I is at the age of 1 y or older, while the initial age for HepA-L vaccination is 18 months. Because many adults gain protective antibodies against HAV during childhoods through HAV infection, HepA is usually administered to children for routine vaccination, but it is often used as postexposure prophylaxis (PEP) for adults. According to the updated guidelines, HepA is recommended for infants aged 6–11 months before traveling to HAV-endemic countries from the US and Canada.[25] Although receipt of two doses of HA-containing vaccines was safe and immunogenic for infants 6 to 12 months of age, its effectiveness and efficacy are still unknown.[25] Given that infants are usually asymptomatic or present with mild disease after HAV infection, it might be unnecessary to inject HepA into infants less than 12 months of age for routine vaccination. Clinical trials show that HepA does not affect the tolerability or immunogenicity of the following vaccines: Japanese encephalitis, typhoid fever, yellow fever, rabies, tetanus, diphtheria and hepatitis B.[18,26] This immunological compatibility makes it fit well for travelers who are often required to complete several vaccines in the short term. HepA is permitted to be injected simultaneously with other routine pediatric vaccines.[21] It is feasible to complete a two-dose schedule of HepA-I using HepA-I from different manufacturers.[27–29]

Immunogenicity following HepA vaccination

Antibody response following HepA vaccination

HepA vaccination induces immune protection by both cellular and humoral pathways. Geometric mean concentration (GMC) and seroconversion rate of anti-HAV is the most widely used indicators to evaluate the immunogenicity of HepA. Anti-HAV could be detected by enzyme-linked immunosorbent assays (ELISA) and microparticle enzyme immunoassay (MEIA), and the sensitivity differs by the detection method.[30,31] The minimal protective level of anti-HAV IgG was unknown until now.[32] Serological cutoffs for seroconversion rate differed widely between studies (from 10 mIU/ml to 40 mIU/ml).[33–37] Seroconversion of anti-HAV could be achieved after two doses of HepA-I among almost all children regardless of the manufacture of the vaccine.[5,22,28,29,37-43] The anti-HAV seroconversion rate could reach approximately 95% at 14–30 d after the first dose of HepA-I,[22,29,41,44,45] and the second-dose could greatly elevate the anti-HAV level postvaccination.[22,37,43] A similar seroconversion rate after one-dose vaccination was reported between HepA-I and HepA-L among children and adults,[39,42,43] and GMC was much higher after two doses of HepA-I compared with one-dose of HepA-I or HepA-L.[42] The nature of the prompt immune response after HepA vaccination is important for its use for PEP.

Immunosuppressed individuals, such as HIV-positive patients, user of immunosuppressive drugs, etc., are more susceptible to catching HAV, and more severe results will occur after HAV infection. The seroconversion rate following two doses of HepA-I is lower among immunosuppressed individuals than among healthy individuals.[46–50] A booster dose sandwiched between the first dose and the 6-mon dose (4 weeks after the first dose) might help increase the antibody response following HepA among immunosuppressed individuals.[51,52] Although immune protection is weak after primary vaccination of HepA among immunosuppressed individuals,[46,51,53] one-dose of HepA-I was reported to lead to high seroconversion of anti-HAV among HIV-positive individuals who lost anti-HAV after primary vaccination, indicating good immune memory after HepA vaccination.[54] Increasing attention has been paid to HepA vaccination among immunosuppressed individuals. Clinical trials are needed to find an optimal schedule for HepA vaccination among them.

It has been nearly 30 y since HepA began to be used and long-term immunity following HepA vaccination has become an important issue. It has been proved that the protective level of anti-HAV (□20 mIU/mL) could persist for more than 20 y following two or three doses of HepA-I among both children and adults.[55–57] According to a mathematical model, the immunity following two-dose HepA-I could last for at least 33 y among 95% vaccinated participants.[56] The peak antibody level is associated with the duration of anti-HAV postvaccination.[57]

Studies concerning the long-term duration of anti-HAV following single-dose of HepA are rare for both HepA-I and HepA-L. A study found that a single dose of HepA resulted in sustained immunologic protection for up to 9 y among 1-y-old children in Argentina.[58] A Chinese study found that at 15 y postvaccination with a single dose of HepA-L, the seropositive rate of anti-HAV was still very high (81.3%) among children.[59] In another Chinese study, a similar persistence of anti-HAV postvaccination was detected between one-dose of HepA-L and one-dose of HepA-I among children, but the follow-up time was only 5 y postvaccination.[60] These studies indicate that immune protection after one dose of HepA might last for more than 10 y. Further studies should be conducted to clarify this hypothesis.

Factors associated with immunogenicity of HepA

Several factors could influence the antibody response post-HepA. First, the dosage of HepA plays an important role in the immunogenicity of HepA. In the early day of HepA-L manufacturing, the dose of HepA-L was $10^{5.0–5.5}$ $TCID_{50}$ and the seroconversion proportion postvaccination was 30–40%;[61,62] when the dose was increased to $10^{6.52}$ $TCID_{50,}$ $10^{6.83}$ $TCID_{50}$ and $10^{7.0}$

$TCID_{50}$, the seroconversion increased to 90.4%, 94.8% and 97.5%, respectively.[63–65] Now the dose of HepA-L is required to be above $10^{6.5}$ $TCID_{50}$ according to the Chinese Pharmacopoeia. A similar trend could be found for HepA-I.[66] Second, the immunogenicity of HepA is found to decrease with age.[67,68] Anti-HAV following HepA vaccination is much lower among vaccinees aged >40 y when compared with younger adults,[69,70] which is the main reason why immunoglobulin (IG) instead of HepA is recommended for elderly persons for PEP during hepatitis A outbreaks in some countries.[69] Third, obesity and smoking are reported to decrease the antibody response to HepA.[20] In addition, maternal anti-HAV is another factor influencing the antibody response post-HepA, which lasts for 12 months in infants and might reduce the immunogenicity of HepA.[71–73] Interference with the antibody response is more obvious among infants whose mothers have immunity after natural infection (versus postvaccination).[74] Finally, according to previous studies, the immunogenicity of HepA is consistent across ethnic groups and races.[75,76]

Safety following HepA vaccination

Excellent safety has been documented for HepA-I and HepA-L in both children and adults. Most of adverse events following HepA vaccination are mild. The incidence of both solicit and unsolicited adverse events was reported to be slightly higher following the first dose of HepA-I than following the second dose.[77] The Chinese National Adverse Events Following Immunization information System (CNAEFIS), which was developed in 2005,[78] suggested that the incidence of adverse events following HepA-L and HepA-I were similar in 2016 (23.00/100,000 dose vs 25.12/100,000 dose). According to the CNAEFIS, the incidence of AEFI (Adverse Event Following Immunization) following HepA was much lower compared with most of other vaccines in childhood routine vaccination (MV: 211.48/100,000 dose; DTaP: 78.36/100,000 dose; DT: 72.52/100,000 dose; MR:81.00/100,000 dose; MMR:35.66/100,000 dose), but was higher compared with hepatitis B vaccine (16.98/100,000 dose).[79] In the US, after reviewing the Vaccine Adverse Event Reporting System (VAERS) data reported in 1996–2013, no concerning pattern of pregnancy-specific outcomes was identified among pregnant women or their infants who received HepA or Hep AB.[80]

The main concern about HepA-L is the transmission of vaccine strain viruses from vaccinees to nonvaccinees. In the primary study of H2-derived HepA-L, attenuated HAV could be detected after culture in the stools of the vaccinees who received HepA 8–30 d prior, indicating that attenuated HAV was excreted in the stools although at a much lower level than the wild type.[81] In a randomized, parallel controlled, phase IV study in China, 12 (25%) of the 48 randomized selected participants who received HepA-L tested positive for HA antigen in stool samples within 28 d after vaccination, and the detection rates of vaccine HAAg in stool samples on d 1, 7, 14, 21 and 28 postvaccination were not significantly different.[43] In another Chinese study, HAV was isolated from 70% (53/75) of tool samples from children whose roommates received HepA-L, but elevated ALT was not detected among these children, suggesting that HepA-L could cause horizon transmission of HAV, but could not induce hepatitis A clinical disease.[82] Further surveillance should be implemented on the possibility of horizon transmission of HepA-L and its implication in hepatitis A elimination in countries using HepA-L.

Efficacy of HepA

HepA is highly effective in preventing hepatitis A clinically apparent disease when used for pre-exposure prophylaxis. A Thai randomized controlled trial (RCT) with 38157 subjects aged 1–16 y suggested that the efficacy of HepA-I was 95% (95% CI: 82–99)[83] and another RCT conducted among 994 subjects aged 2–16 y showed that the efficacy of HepA-I was 100% (95% CI: 87–100).[35] In a Chinese multicenter RCT with 457251 subjects, the efficacy of HepA-L in preventing hepatitis A clinical case was 95%, which is similar between the H2 strain and LA-1 strain, but it seemed to be useless in preventing inapparent HAV infection.[84] However, the efficacy of HepA is not clear when injected into immunosuppressed individuals.

The efficacy of HepA-I for PEP (postexposure prophylaxis) was first reported in a double-blind placebo-controlled trial in 1992 in the US,[35] where a total of 519 and 518 children were injected with HepA-I and placebo (aluminum hydroxide diluent), respectively, at the beginning of a hepatitis A outbreak, and 34 hepatitis A clinically apparent cases occurred in the placebo group while no hepatitis A case occurred in the vaccine-group, indicating an efficacy of 100%.[35] Next, the efficacy of HepA-I used for PEP was reported in many areas throughout the world.[85–88] The efficacy of HepA-L was reported in an observational study published in Chinese. In that study, the incidence of hepatitis A was 94.5% lower among children vaccinated with HepA-L than among unvaccinated children in a hepatitis A outbreak.[89] Mainly because HepA-L is only available in a few countries in the world, studies on the efficacy of HepA-L used for PEP are limited and more evidence is needed.

Hepatitis A vaccination strategy

Universal childhood vaccination program (UCVP) against hepatitis A

Hepatitis A vaccination strategy mainly depends on the endemicity of hepatitis A and economic resources in a region.[21,32] The highest cost-effectiveness of universal childhood vaccination program (UCVP) against hepatitis A could be gained among countries with intermediate endemicity or those in transition from high to intermediate endemicity of hepatitis A infection.[90] The WHO recommends that vaccination against HAV be integrated into the national vaccination schedule for children aged ≧1 y after synthesizing the incidence of acute hepatitis A, epidemiological characteristics of HAV infection and cost-effectiveness.[21]

Israel is the first country to introduce HepA into UCVP, where two doses of HepA-I (at 18 and 24 months of age) was recommended to children for routine vaccination in July 1999.[91] According to the WHO report, as of May 2019,

28 countries had already introduced HepA into routine vaccination of children throughout the country, including 10 countries in the Americas, five countries in the Eastern Mediterranean, eight countries in Europe and five countries in the Western Pacific; two countries were planning to involve HepA in UCVP, including Honduras (in January 2020) and Turkmenistan (in October 2019).[7] In the above 30 countries, HepA-I is recommended for children in 29 countries with the exception of China, and the initial age for routine HepA vaccination is 12 months in all countries. As far as we know, HepA-I is involved in UCVP in four provinces of China, and HepA-L is involved in UCVP in the other 27 provinces until now.

Reducing cost is an important consideration for a single-dose universal mass vaccination strategy, which was conducted in 12 countries throughout the world, mostly in Latin America.[7] Argentina was the first country (in June 2005) to implement vaccination with a one-dose HepA-I schedule, and surveillance data proved the dramatic decrease in hepatitis A incidence in the country.[58] The effectiveness of a one-dose schedule has also been verified in Brazil, where UCVP was conducted since August 2014.[92] In 2012, the WHO position paper on hepatitis A vaccines suggested that national vaccination programs might consider the inclusion of single-dose HepA-I in vaccination schedules.[21]

In the US, universal vaccination was reported to prevent 94,957 infections, 46,179 outpatient visits, 1286 hospitalizations, and 15 deaths annually and had an incremental cost-effectiveness ratio of 21,223 USD/quality-adjusted life-year.[93] In addition to the US, a universal childhood vaccination program against hepatitis A was also reported to be cost-saving in Brazil,[94] Rio de Janeiro[90] and Argentina.[95]

Regional childhood vaccination of hepatitis A

In some countries where the epidemiological pattern of hepatitis A is not homogenous in all regions, regional vaccination of HepA instead of UCVP is conducted among children. According to the WHO, four countries implement regional childhood vaccination of hepatitis A, including Canada, Italy, Romania and the Russian Federation.[7] Due to a relatively high prevalence of hepatitis A in Puglia (a region of Italy), HepA has been offered free to all children aged 15–18 months and preadolescents aged 12 y by the local government in this region since 1998.[96] Between 1998 and 2009, the incidence of acute hepatitis A declined from 14.8 to 0.8 per 100,000 in Puglia.[96] The strategy of regional vaccination of HepA is based on the good operation of the surveillance system of hepatitis A. In countries where hepatitis A infection varies greatly with geographic location, regional vaccination of HepA is more economical than the UCVP.

Hepatitis A vaccination among high-risk population

In countries with very low or very high endemicity of hepatitis A, HepA is usually recommended for high-risk populations.[21] Population at high risk of hepatitis A usually include those who are at increasing risk for HAV infection or those who have increased risk for HAV-associated complications. According to the WHO position paper updated in 2012, the high-risk population of HAV included travelers from areas with HAV low-endemicity to areas with intermediate or high endemicity, patients requiring life-long treatment with blood products, men having sex with men (MSM), workers in contact with nonhuman primates, injection drug users and patients with chronic liver disease.[21] In addition to the list, HepA is recommended to the staff of children care centers and kindergarten and foodborne handlers because of the severities of HAV transmission to others in some countries. In 2018 in the US, HepA was recommended to persons experiencing homelessness mainly due to the HepA outbreak frequently reported among such individuals.[97] Currently, HepA is not routinely recommended for adults infected with HIV in the US; the main reason is the low immunogenicity of HepA among patients with HIV, and the evidence in favor and against the recommendation is under consideration.[98] Although HepA is recommended for patients with viral hepatitis C, a meta-analysis did not support routine vaccination with HepA among hepatitis C patients because of its high cost and low benefit.[99] The targeted high-risk population differed geographically and would be adjusted according to the shift of the status of HepA control. The recommendation should be provided after careful assessment of the HAV prevalence among special groups, hepatitis A-related hospitalization and deaths, and costs of treatment of hepatitis A.

Hepatitis A vaccination for PEP

In the early years, IG instead of HepA was used for PEP after a hepatitis A outbreak. Due to the high immunogenicity and safety of HepA in both children and adults, accompanied by limited supplies of IG and its potential risk for blood-borne infectious disease, HepA began to be used for PEP. Currently, HepA-I is preferentially recommended for PEP over IG in Australia (in 2009),[100] the UK (in 2009),[101] Israel (in 2015),[102] Canada (in 2016)[25] and the US (in 2018)[24] for adults younger than 40 y old. Due to the relatively low immunogenicity among elderly persons, it is recommended to inject IG instead of HepA for PEP in Israel (for persons aged >40 y, in 2014) and to inject both IG and HepA for PEP in Argentina (for persons aged ≧40 y, in 2014), Canada (for persons aged ≧60 y in 2016) and the UK (for persons aged ≧51 y, in 2009).[69] In the US, only IG was recommended for PEP among persons above 40 y of age in 2007.[48] Based on a systematic review,[69] in 2018, the recommendation was changed to HepA being administered to all persons aged ≧12 months for PEP and IG being administered to persons aged >40 y depending on the provider's risk assessment.[24]

Epidemiological shift after hepatitis A vaccination

With the improvement of sanitary conditions and hygienic practices, accompanied with HepA vaccination, the incidence rate of hepatitis A is decreasing and the average age at infection is increasing worldwide.[3] The most obvious decrease was detected in some middle-income countries where the UCVP against HepA was introduced.[4,78,91,95,96,103,104] However, given that younger adults will be much sicker after HAV infection than

children, the increase of HAV infection age might initially cause an increase in the number of clinically apparent cases and hospitalization from hepatitis A. In recent years, hepatitis A outbreaks were reported frequently among populations in age groups not covered by the UCVP in Korea.[105] A catch-up campaign for HepA among older children or adults was recommended to deal with this challenge.[105–109] The other issue is the hepatitis A outbreaks frequently reported in developed countries in recent years. With the development of globalization across economic, political, cultural and other domains, some hepatitis A outbreaks occur through traveling and imported food in developed countries.[110–112] HepA vaccinations should be received before traveling to countries with high or intermediate endemicity of HepA. It is difficult to avoid HAV transmission through frozen foods imported from countries with HAV endemicity unless manufacturing process is improved. Another issue is that hepatitis A outbreaks are frequently reported among some special groups including persons experiencing homelessness and MSMs in developed countries.[112–118] Hepatitis A vaccination has been approved to be effective in controlling these outbreaks.

Comparison between HepA-I and HepA-L

Compared with HepA-I, HepA-L could be vaccinated with lower price and less dose, but it is more sensitive to outside temperature and is more difficult to be kept and transported. Moreover, HepA-L could not be administrated among immunosuppressed individuals. Both HepA-l and HepA-L are proved to be well tolerated, but the transmission of vaccine strain virus postvaccination of HepA-L has not been denied till now. As for the immunogenicity postvaccination, high positive rate of anti-HAV could be achieved after one dose of both HepA-l and HepA-L, but GMC of anti-HAV was reported to be higher after one dose of HepA-I when compared with one-dose HepA-L among young adults,[37] and much higher antibody level and longer immune duration could be obtained after the second dose of HepA-I compared with one dose of HepA-I or HepA-L. In a word, although HepA-L and HepA-I have their own advantages and disadvantages, both of them have showed its important role in hepatitis A control in different countries.

Concluding remarks

Both HepA-I and HepA-L have been proved to be highly immunogenic and well tolerated and immune protection postvaccination of HepA-I could persist for at least 20 y. With the improvement of sanitary condition and implementation of HepA vaccination, the incidence of hepatitis A decreased worldwide, especially in the regions where HepA is introduced into UCVP. However, hepatitis A outbreaks are frequently reported among high-risk population and age-groups not being covered by UCVP in the last few years. In addition, globalization of economic markets makes HAV transmitting from one country to another much easier.

In the near future, to achieve the goal of hepatitis A elimination as scheduled, the following issues should be emphasized. For highly endemic regions of hepatitis A, more efforts are needed to improve the sanitary conditions and hygienic conditions. Clean drinking water and food are critical for decreasing the incidence of foodborne infectious diseases including hepatitis A. UCVP should be taken into consideration for countries that are transferring from highly endemic regions to intermediately endemic regions. For countries with intermediate endemicity, given that the infection age of HAV is increased to youngsters and adults, the long-term immunity protection after HepA and the need for the booster dose should be carefully analyzed to avoid the increase in hospitalization and death due to HAV infection, especially where one-dose HepA is introduced in UCVP. The high-risk population for HAV infection should be focused on in low endemic regions, especially travelers, drug users and homeless persons.

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