Vaccine 37 (2019) 4581–4586

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Safety and immunogenicity of hepatitis E vaccine in elderly people older than 65 years

Xu-ya Yu [a,1], Zhi-ping Chen [b,1], Shen-yu Wang [b], Hui-rong Pan [a], Zhi-fang Wang [b], Qiu-fen Zhang [a], Ling-zhi Shen [b], Xiao-ping Zheng [c], Chuan-fu Yan [c], Mei Lu [c], Bo Chen [c], Ya Zheng [d], Jun Zhang [d], Hua-kun Lv [b,*], Shou-jie Huang [d,*]

[a] Xiamen Innovax Biotech Co.Ltd, Xiamen 361022, China
[b] Zhejiang Provincial Center for Disease Control and Prevention, Hangzhou 310051, China
[c] Kaihua Center for Disease Control and Prevention, Quzhou 324300, China
[d] National Institute of Diagnostics and Vaccine Development in Infectious Diseases, State Key Laboratory of Molecular Vaccinology and Molecular Diagnostics, School of Public Health, Xiamen University, Xiamen 361005, China

ARTICLE INFO

Article history:
Received 9 October 2018
Received in revised form 18 March 2019
Accepted 3 April 2019
Available online 28 June 2019

Keywords:
Hepatitis E vaccine
Clinical trial
Elderly people
Safety
Immunogenicity

ABSTRACT

Background: Hepatitis E virus (HEV) infection is a leading cause of acute hepatitis worldwide, and results in high morbidity and mortality rates among elderly people in China. The hepatitis E vaccine, Hecolin®, has been shown to be safe and highly efficacious among healthy adults aged 16–65 years old. However, there is no data about Hecolin® vaccination in elderly people older than 65 years (y).

Methods: An open-labeled, controlled trial was conducted to evaluate the safety and immunogenicity of Hecolin® among the elderly aged >65 y. A total of 601 eligible participants were enrolled. Among them, 200 elderly people aged >65 y and 201 adults aged 18–65 y were assigned to the Hecolin® groups and vaccinated at day 0, month 1 and month 6. Serum samples were collected for anti-HEV IgG determination at day 0 prior to immunization and at month 7. The remaining 200 elderly people aged >65 y were assigned to the safety control group and received no intervention but were instructed to report any adverse events that occurred during the whole study period in the same way as those in the Hecolin® groups.

Results: After receiving 3 doses of Hecolin® with the standard schedule, most (96.7%) of the vaccinated elderly people aged >65 y seroconverted at one month after the final dose (month 7). At month 7, the geometric mean concentrations of anti-HEV IgG were 5.36 (95% CI, 3.88–7.41) and 19.65 (95% CI, 16.81–22.98) among the baseline seronegative and seropositive elderly, respectively. Of the vaccinated elderly, 97.3% (177/182) had anti-HEV IgG levels higher than 1.0 WU/ml at month 7. Hecolin® was very well tolerated in this population. No vaccine-related SAEs were reported.

Conclusions: Hecolin® is immunogenic and well tolerated in elderly people aged greater than 65 years.

1. Introduction

Hepatitis E virus (HEV) is a leading cause of acute viral hepatitis worldwide that might result in sporadic or epidemic hepatitis E in different areas [1]. Based on data from 2005, there are approximately 20.1 million HEV infections occurring globally, leading to 3.4 million symptomatic cases, 70 000 deaths and 3 000 stillbirths [2].

Most cases are from developing countries, especially countries in East and South Asia and Africa. In China, although outbreaks due to HEV infection are rare in recent years, the incidence of hepatitis E increased from 0.21 cases/100 000 person-years to 1.99 cases/100 000 person-years from 1997 to 2014, affecting mainly middle-aged and elderly people [3,4]. For the elderly, poor physical conditions contribute to high mortality rates, which aggravates the disease burden [3]. Meanwhile, an increasing number of

Abbreviations: HEV, hepatitis E virus; CI, confidence interval; PPS, per-protocol sets; GMC, geometric mean concentration; AE, adverse event; SAE, serious adverse event; ELISA, enzyme-linked immunosorbent assay; WHO, World Health Organization.

* Corresponding authors.
E-mail addresses: hklv@cdc.zj.cn (H.-k. Lv), huangshoujie@xmu.edu.cn (S.-j. Huang).

[1] Co-first authors: Both authors contributed equally to this work.

https://doi.org/10.1016/j.vaccine.2019.04.006
0264-410X/

autochthonous hepatitis E cases in Western developed countries were reported, and the hepatitis E cases were also mainly in elderly people [5].

Hepatitis E vaccine (HEV 239), with the commercial name of Hecolin®, has been approved for use in people aged 16 y and above in China since 2011, supported by a large Phase 3 clinical trial involving adults aged 16 to 65 years [6–9]. However, the direct evaluation of the safety and immunogenicity of Hecolin® among elderly individuals aged >65 y has not been reported.

2. Methods

2.1. Ethics statement

The study was designed by the Zhejiang Provincial Center for Disease Control and Prevention (ZJCDC) and Xiamen University and obtained ethics committee approval from the Ethics Committee of ZJCDC. The trial was conducted in accordance with the standards of Good Clinical Practice and registered with ClinicalTrials.gov, number NCT02417597. Informed consents were signed by all the participants.

2.2. Participants and vaccination

This open-labeled, controlled trial was conducted from April 2015 through December 2015 in Kaihua County, Zhejiang Province, China to evaluate the safety and immunogenicity of Hecolin® among the elderly aged >65 y. Inclusion and exclusion criteria were similar to those in the Phase 3 clinical trial of Hecolin® [9]. In brief, the participants should be aged ≥18 y, not pregnant or lactating, not suffering severe acute or chronic disease, and additionally, the blood pressure of the participants should be not higher than 160/100 mmHg. A total of 200 elderly people aged >65 y and 201 adults aged 18–65 y were eligible for enrollment and assigned to the Hecolin® group. Two hundred healthy elderly people aged >65 y were enrolled and assigned to the safety control group, which was similar to the Hecolin® group in economy, geography, population structure and epidemic condition of disease and received no vaccine or other intervention (Fig. 1). The participants in the safety control group were similarly observed for adverse events or serious adverse events as those in the Hecolin® groups to eliminate the influence of some confounding factors related to the age, such as senile disorders.

For the participants in the Hecolin® groups, Hecolin® (Xiamen Innovax, Xiamen, China), containing 30 μg of recombinant HEV capsid antigen absorbed to 277 μg of aluminum adjuvant suspended in 0.5 ml of buffered solution [9,10], was intramuscularly vaccinated at month 0, month 1 and month 6.

2.3. Follow-up treatments

All participants in the Hecolin® groups were followed-up on day 0, month 1, month 6 and month 7. After each dose, participants were observed for 30 min for immediate adverse reactions and given systematic safety observations within 30 days. Once a participant missed any follow-up visit, she/he dropped out of the study and would not take part in the rest of the visits. The participants in the safety control group were followed-up in the same way as those in the Hecolin® groups to record all the adverse events reported. The solicited adverse events were defined as local adverse events (such as pain, redness, swelling, induration, rash and itching at the inoculation site) and systematic adverse events (such as fever, allergic reaction, headache, fatigue, nausea and vomiting, diarrhea, myalgia and cough) occurring within 7 days after each vaccination. The unsolicited adverse events included any adverse events that occurred during the whole period of observation after each vaccination but did not match the above definition of solicited adverse events. The serious adverse events (SAEs) were events related to death, hospitalization for treatment, extension of hospitalization period, persistent disability, or having no ability to conduct normal daily living activities. All adverse events were graded. The detailed grading criteria for local adverse

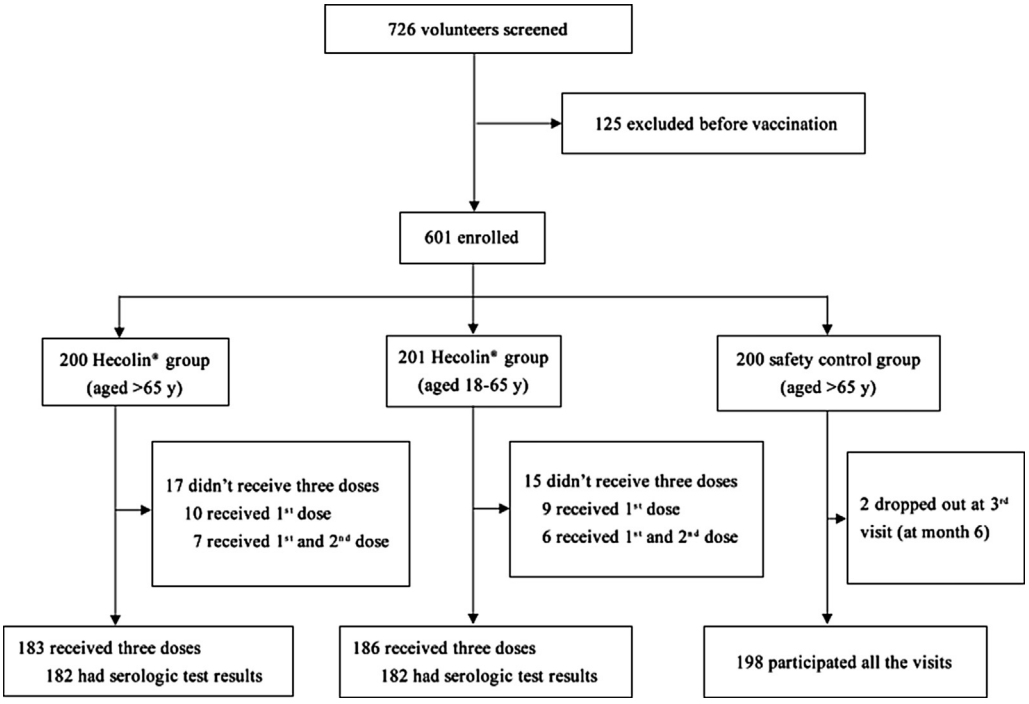

Fig. 1. Flowchart of the study. The enrolled participants were followed-up at day 0, month 1, month 6 and month 7. Once a participant missed any follow-up visit, she/he dropped out of the study and would not take part in the rest of the visits.

events and systematic adverse events are shown in the online Supplementary information.

During the follow-up period, all of the adverse events experienced within 30 days after each vaccination were recorded on a standardized diary card. SAEs occurring during the whole study were reported to the investigator as soon as possible and were investigated in detail by experienced medical workers.

Among the vaccinated groups, serum samples were collected at month 0 prior vaccination and at month 7 for the determination of IgG antibodies against HEV (anti-HEV IgG, HEV-IgG).

2.4. Laboratory test

The specimens were tested for anti-HEV IgG qualitatively and quantitatively by ELISA kits (Beijing Wantai Co., Beijing, China) and performed according to the manufacturer's instructions as previously described [8–9]. Each serum sample was tested in duplicate for qualitative analysis. Samples positive for IgG anti-HEV were further quantified and expressed in World Health Organization (WHO) units per ml (WU/ml). The lower limit of IgG anti-HEV quantification was 0.064 WU/ml.

2.5. Statistical analysis

The safety was assessed according to the rate of adverse events in those who received at least one injection of vaccine in the Hecolin® groups and in all participants in the safety control group. The immunogenicity was assessed according to the rate of seroconversion and the geometric mean concentration (GMC) of anti-HEV IgG in those who received three doses of the vaccine and had available serologic test results at one month after the third dose in the per-protocol sets (PPS). For calculating the GMC, the levels of anti-HEV IgG in negative samples were artificially set as 0.032 WU/ml. Data analysis was performed with SAS software, version 9.4. All reported p values are two-sided with an α value of 0.05.

3. Results

3.1. Study population

A total of 726 participants were recruited, and among them, 601 participants were eligible for enrollment. The main exclusion reasons were hypertension or other chronic diseases. A total of 200 elderly people aged older than 65 y (mean age of 70.9 ± 3.9 y, 49.5% (99/200) were female) and 201 adults aged 18–65 y (mean age of 43.9 ± 13.4 y, 52.2% (105/201) were female) were assigned to the two Hecolin® groups, respectively. Another 200 elderly people aged older than 65 y (mean age of 71.4 ± 4.2 y, 52.5% (105/200) were female) were included in the safety control group. Among the participants in the Hecolin® groups, 90.8% (364/401) received three doses of vaccines and had available serologic test results of day 0 and month 7 (one month after the final dose), and were included in the PPS to evaluate the immunogenicity (Fig. 1). All but 2 of the participants in the safety control group finished all the visits, and the 2 elderly participants were lost to follow-up at the 3rd visit (month 6). All 601 participants were eligible for the evaluation of safety issues.

3.2. Immunogenicity

Immunogenicity was assessed only in the PPS who received 3 doses of Hecolin® and had antibody results at both day 0 and one month after the final dose (month 7). Of the vaccinated elderly aged >65 y, 96.7% (176/182) seroconverted at month 7, the seroconversion rates in the elderly who were baseline seronegative (96.2%, 76/79) and seropositive (97.1%, 100/103) were similar (Table 1). For the vaccinated adults aged 18–65 y, all but 2 (98.9%, 180/182) seroconverted at month 7, and the 2 adults were seropositive at entry (Table 1). Among seronegative participants who received three doses of vaccines, the difference between the seroconversion rates in the elderly group (aged >65 y) was not significant from that in the younger group (aged 18–65 y) ($p > 0.05$).

At baseline, 56.6% (103/182) of the elderly aged >65 y were seropositive for anti-HEV IgG, which was higher than that of the adults aged 18–65 y (36.3%, 66/182), while the baseline GMC levels were similar in the two age groups (Table 1). At month 7, the GMC levels of the elderly aged >65 y and the adults aged 18–65 y in the baseline seronegative were 5.36 WU/ml (95% CI: 3.88–7.41 WU/ml) and 10.84 WU/ml (95% CI: 9.42–12.47 WU/ml), respectively. While the GMC levels of the elderly and the adults in the baseline seropositive were 19.65 WU/ml (95% CI: 16.81–22.98 WU/ml) and 24.52 WU/ml (95% CI: 21.63–27.80 WU/ml), respectively. (Table 1). The reverse cumulative distributions of the anti-HEV IgG levels induced by Hecolin® vaccination in both the elderly and the adult cohorts are shown in Fig. 2. Except for the 3 elderly who remained seronegative at month 7, all but 2 of the elderly (97.3%, 177/182) had anti-HEV IgG levels higher than 1 WU/ml.

3.3. Safety

All 601 enrolled participants were included in the safety analysis, and all the reported adverse reactions or events by the participants during the whole study period were recorded. For the elderly in the safety control group, although no vaccination was given during the 7 months, they were instructed to record any adverse events that occurred during the same periods as those in the Hecolin® groups with the same diary card.

Of the elderly aged >65 y in the Hecolin® group, 40% reported adverse events, which is similar to that of the adults aged 18–65

Table 1
Immunogenicity of Hecolin® in the elderly older than 65 y.

	Anti-HEV IgG seronegative at baseline		Anti-HEV IgG seropositive at baseline	
	Hecolin® group (age > 65 y) n = 79	Hecolin® group (age 18–65 y) n = 116	Hecolin® group (age > 65 y) n = 103	Hecolin® group (age 18–65 y) n = 66
At baseline				
GMC (95% CI) (WU/ml)	<0.064	<0.064	0.48 (0.37–0.63)*	0.49 (0.36–0.68)*
At one month after the final dose (month 7)				
No. of Seropositive n (%)	76 (96.2)	116 (100.0)	103 (100.0)	66 (100.0)
No. of Seroconverted n (%, 95% CI)	76 (96.2, 89.3–99.2)	116 (100.0, 96.9–100.0)	100 (97.1, 91.7–99.4)	64 (97.0, 89.5–99.6)
GMC (95% CI) (WU/ml)	5.36 (3.88–7.41)	10.84 (9.42–12.47)	19.65 (16.81–22.98)	24.52 (21.63–27.80)

GMC: geometric mean concentration; CI: confidence interval; WU/ml: World Health Organization units per ml.
* Only seropositive samples were calculated for baseline GMC.

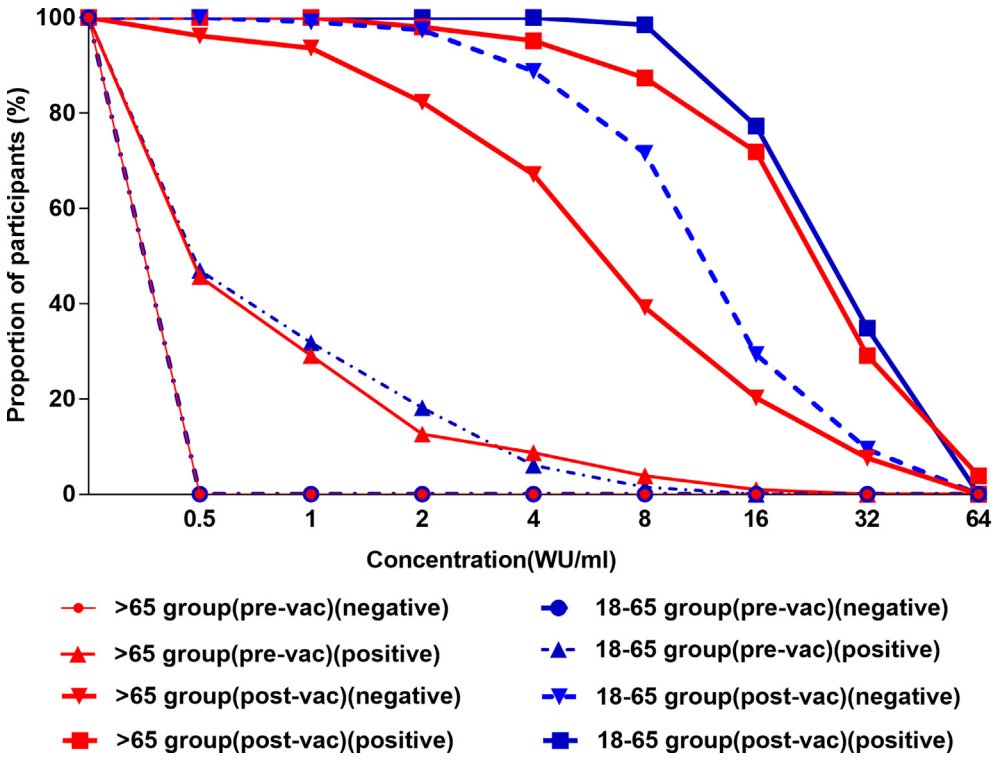

Fig. 2. Reverse cumulative distribution of anti-HEV IgG concentration at day 0 and one month after the final dose (month 7) in per-protocol cohorts in the Hecolin® groups. The red solid line represents the elderly aged >65 y, the blue dashed line represents the adults aged 18–65 y. The thick lines represent data at month 7, and the thin lines represent data at day 0. Pre-vac, before vaccination, at day 0. Post-vac, after vaccination, at month 7. Negative, Anti-HEV IgG was negative at day 0. Positive, Anti-HEV IgG was positive at day 0. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Adverse reactions or events reported during the study.

Adverse reactions/events, n (%)	Hecolin® group (aged >65 y) n = 200	Safety control group (aged >65 y) n = 200	Hecolin® group (aged 18–65 y) n = 201
Any adverse events in 30 days after each vaccination	80 (40.0)	80 (40.0)	85 (42.3)
Solicited adverse events	50 (25.0)	14 (7.0)	62 (30.9)
Local adverse events	28 (14.0)	NA	48 (23.9)
≥ grade 3	0 (0.0)	NA	2 (1.0)
Systemic adverse events	28 (14.0)	14 (7.0)	21 (10.5)
≥ grade 3	0 (0.0)	0 (0.0)	0 (0.0)
Unsolicited adverse events	44 (22.0)	76 (38.0)	45 (22.4)
≥ grade 3	2 (1.0)	12 (6.0)	3 (1.5)
SAEs reported throughout the study period	3 (1.5)	9 (4.5)	2 (1.0)
Vaccine related SAEs	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)

SAEs: serious adverse events; NA: not applicable.

y (42.3%). The occurrence rates of solicited local adverse events in the vaccinated elderly group were lower than that in the adult group, while the occurrence rate of solicited systemic adverse events was slightly higher in the vaccinated elderly group (Table 2). All but 2 of the reported solicited adverse events in the adult group were mild and moderate (grade 1 or grade 2); the only 2 events of grade 3 were swelling reported by relatively young adults (aged 21 y and 46 y). The most often reported vaccine-related events were pain (50/401) and fever (no less than 37.0 °C, 40/401, 8 among 40 fever events were over 37.5 °C), which were the most common adverse reactions due to vaccination. The occurrence rate of total adverse events in the vaccinated elderly group was similar to that in the safety control group who received no vaccination (40.0% vs 40.0%). Compared with the elderly in the safety control group, the occurrence rate of unsolicited adverse events in the vaccinated elderly was lower (22.0% vs 38.0%), which further make the safety data of Hecolin® in the elderly assured.

A total of 14 serious adverse events (SAEs) were reported during the study (see the online Supplementary information), among which 5 were from the Hecolin® groups, and the rest were from the safety control group. All of these SAEs were judged not to be related to the vaccination of Hecolin®. No deaths occurred.

4. Discussion

In 2011, the first recombinant hepatitis E vaccine, Hecolin®, was licensed in China and approved for use in people aged 16 y and

above [11,12]; however, data on the immunogenicity and safety of Hecolin® in the elderly older than 65 y was still lacking until now. Therefore, this is the first study to fulfill this important knowledge gap. Our data suggested that most (96.7%) of the Hecolin® vaccinated elderly aged >65 y seroconverted after the standard vaccination schedule at day 0, month 1 and month 6, the anti-HEV IgG level increased dramatically at one month after the final dose, and Hecolin® was very well tolerated in this population. No vaccine-related SAEs were reported.

No matter based on the China's National Notifiable Disease Report System [3] or a large and sensitive hepatitis surveillance system in Jiangsu province [4], the data indicated that the incidence and mortality from hepatitis E were the highest among adults older than 60 in China. In Western developed countries where HEV genotype 3 is epidemic, the main hepatitis E cases are also elderly people [11]. In this population, the hepatitis E vaccination is important for the prevention and control of hepatitis E.

The data indicated that Hecolin® is well immunogenic in the elderly aged >65 y. After receiving 3 doses of Hecolin® with the standard schedule, most (96.7%) of the elderly seroconverted at month 7. No special factor was noted to be potentially related to nonresponsive individuals. Nonresponse might be related to individual immunity, heredity and other factors. The anti-HEV IgG GMC level in the elderly was lower than that in adults aged 18–65 y, which is consistent with the previous understanding, based on experiences of using other recombinant vaccines, that the immune response to vaccines decreases with age [13,14]. To date, the protective antibody level against symptomatic HEV infection has not been defined. Nevertheless, the antibody level was quantitatively associated with the relative risk of overall infection (mostly asymptomatic infection) previously, which indicated that even marginal levels of anti-HEV IgG (0.077–1.0 WU/ml) were protective for HEV infection and antibody levels of over 1.0 WU/ml significantly lowered the infection risk to 0.09 (95% CI, 0.04–0.17) [15]. The current study showed that 97.3% (177/182) of the vaccinated elderly reached anti-HEV IgG levels higher than 1.0 WU/ml at month 7.

All of the reported solicited adverse events in both the Hecolin® vaccinated elderly group and adult group were mild and moderate, except for 2 adults (aged 21 y and 46 y) who reported swelling of grade 3. The occurrence rates of solicited adverse events and unsolicited adverse events in the elderly were not higher than those in the adults aged 18–65 y (Table 2). A safety control group, which included elderly people with a similar age and gender distribution as the elderly in the vaccine group, but didn't receive an intervention, was observed for safety issues in the same way as the vaccine group. The occurence rates of unsolicited adverse events and SAEs in the vaccinated elderly were not higher than the safety control elderly group, which further made the safety data of Hecolin® in the elderly assuring. It was not unexpected that the solicited adverse events, local or systemic, were more common in the vaccinated group than in the safety control group because the participants in the safety control group had not been injected at all.

One of the limitations of this study is the lack of randomization in the elderly which might make the basic health status of these elderly slightly unbalanced, while all the participants were screened carefully with the same criteria and by the same investigators before enrollment and only relatively healthy participants were enrolled. Another limitation is the lack of a placebo vaccine for the safety control elderly group. The vaccinated elderly might be more inclined to report adverse events after vaccination due to worry, so the data might underestimate the safety of Hecolin®. Furthermore, the serum collection from only the vaccinated groups might affect the adverse events reporting and make it impossible to compare the antibody responses between the vaccinated and unvaccinated groups.

5. Conclusions

The data indicated that three doses of Hecolin® are immunogenic and well tolerated in the elderly older than 65 y. Due to the high incidence and poor prognosis of hepatitis E in elderly people, vaccination strategies in this population should be carefully considered and designed.

Authors' contributions

The study was conceived and designed by Jun Zhang, Zhi-ping Chen, Hua-kun Lv and Shou-jie Huang. Supervision of the long-term monitoring of populations in the region was conducted by Shen-yu Wang, Zhi-fang Wang and Qiu-fen Zhang. Samples were collected in the field by Ling-zhi Shen, Xiao-ping Zheng, Chuan-fu Yan, Mei Lu and Bo Chen. The laboratory work was conducted by Hui-rong Pan. Data analysis was carried out by Xu-ya Yu and Ya Zheng. The manuscript was written by Xu-ya Yu and Zhi-ping Chen in consultation with all coauthors. Jun Zhang, Zhi-ping Chen, Hua-kun Lv and Shou-jie Huang revised the manuscript. All authors accepted the final version of the manuscript.

Acknowledgements

We express heartfelt thanks to all the participants for their great effort in the study. Special thanks to Professor Ting Wu and Professor Wei-guo Shi for their guidance on this article. This study was registered with ClinicalTrials.gov (number NCT02417597).

Conflicts of interest

Xu-ya Yu, Hui-rong Pan and Qiu-fen Zhang are employees of the Xiamen Innovax. The other authors declare that they have no conflicts of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.04.006.

References

[1] WHO. The global prevalence of hepatitis E virus infection and susceptibility: a systematic review. 2010; <http://apps.who.int/iris/bitstream/handle/10665/70513/WHO_IVB_10.14_eng.pdf?sequence=1>.
[2] Rein DB, Stevens GA, Theaker J, Wittenborn JS, Wiersma ST. The global burden of hepatitis E virus genotypes 1 and 2 in 2005. Hepatology 2012;55:988–97. https://doi.org/10.1002/hep.25505.
[3] Ren X, Wu P, Wang L, Geng M, Zeng L, Zhang J, et al. Changing epidemiology of hepatitis A and hepatitis E viruses in China, 1990–2014. Emerg Infect Dis 2017;23:276–9. https://doi.org/10.3201/2302.161095.
[4] Zhu FC, Huang SJ, Wu T, Zhang XF, Wang ZZ, Ai X, et al. Epidemiology of zoonotic hepatitis E: a community-based surveillance study in a rural population in China. Plos One 2014;9:e87154. https://doi.org/10.1371/journal.pone.0087154.
[5] Dalton HR, Kamar N, Izopet J. Hepatitis E in developed countries current status and future perspectives. Future Microbiol 2014;9:1361–72. https://doi.org/10.2217/fmb.14.89.
[6] Li SW, Zhao Q, Wu T, Chen S, Zhang J, Xia NS. The development of a recombinant hepatitis E vaccine HEV 239. Hum Vaccin Immunother 2015;11:908–14. https://doi.org/10.1080/21645515.2015.1008870.
[7] Wu T, Li SW, Zhang J, Ng MH, Xia NS, Zhao Q. Hepatitis E vaccine development: a 14 year odyssey. Hum Vaccin Immunother 2012;8:823–7. https://doi.org/10.4161/hv.20042.
[8] Zhang J, Zhang XF, Huang SJ, Wu T, Hu YM, Wang ZZ, et al. Long-term efficacy of a hepatitis E vaccine. N Engl J Med 2015;372:914–22. https://doi.org/10.1056/NEJMoa1406011.
[9] Zhu FC, Zhang J, Zhang XF, Zhou C, Wang ZZ, Huang SJ, et al. Efficacy and safety of a recombinant hepatitis E vaccine in healthy adults: a large-scale, randomised, double-blind placebo-controlled, phase 3 trial. Lancet 2010;376:895–902. https://doi.org/10.1016/S0140-6736(10)61030-6.

[10] Zhang X, Wei M, Sun G, Wang X, Li M, Lin Z, et al. Real-time stability of a hepatitis E vaccine (Hecolin®) demonstrated with potency assays and multifaceted physicochemical methods. Vaccine 2016;34:5871–7. https://doi.org/10.1016/j.vaccine.2016.10.045.
[11] WHO. Hepatitis E vaccine-WHO position paper. Weekly epidemiological record; 2015. <http://www.who.int/wer/2015/wer9018.pdf>.
[12] Park SB. Hepatitis E vaccine debuts. Nature 2012;49:21–2. https://doi.org/10.1038/491021a.
[13] Dobson SR, McNeil S, Dionne M, Dawar M, Ogilvie G, Krajden M, et al. Immunogenicity of 2 doses of HPV vaccine in younger adolescents vs 3 doses in young women: a randomized clinical trial. JAMA 2013;309:1793–802. https://doi.org/10.1001/jama.2013.1625.
[14] Iversen OE, Miranda MJ, Ulied A, Soerdal T, Lazarus E, Chokephaibulkit K, et al. Immunogenicity of the 9-valent HPV vaccine using 2-dose regimens in girls and boys vs a 3-dose regimen in women. JAMA 2016;316:2411–21. https://doi.org/10.1001/jama.2016.17615.
[15] Zhang J, Zhang XF, Zhou C, Wang ZZ, Huang SJ, Yao X, et al. Protection against hepatitis E virus infection by naturally acquired and vaccine-induced immunity. Clin Microbiol Infect 2014;20:O397–405. https://doi.org/10.1111/1469-0691.12419.