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Meeting Report

WHO Informal consultation on WHO recommendations to assure the quality, safety and efficacy of recombinant hepatitis E vaccines

Beijing, People's Republic of China

18-19 April 2018

World Health Organization

Executive summary

Hepatitis E virus (HEV) is a major cause of sporadic and epidemic hepatitis that is found worldwide, the highest sero-prevalence rates being observed in regions with low standards of sanitation. A global burden of disease study estimated that HEV accounts for approximately 20.1 million HEV infections, 3.4 million symptomatic cases, 70000 deaths, and 3000 stillbirths annually. Very recently there were outbreaks in Chad, Niger, Nigeria and Namibia with multiple fatal cases.

To mitigate and prevent the outbreak of hepatitis E, vaccines have been in development. In 2011, a hepatitis E vaccine based on a 239 amino acid recombinant HEV peptide, corresponding to fragment of open reading frame 2 (ORF2) which encodes the capsid protein of HEV was developed and licensed in China. Clinical trial studies demonstrated its efficacy and safety. In response to the request from stakeholders, WHO started the development of Recommendations to ensure the quality, safety and efficacy of hepatitis E vaccines. The first draft of the recommendations was prepared after a working group meeting and followed by a public consultation on the WHO website. An informal consultation was convened with participants of experts from around the world involved in the research, manufacture, regulatory assessment and approval, control-testing and release of hepatitis E vaccines. Participants were drawn from academia, national regulatory authorities (NRAs), national control laboratories (NCLs) and industry. In the meeting the comments and suggestions received were reviewed and discussed. Based on the current situation and experiences in development, manufacture and regulation the suggestions were incorporated into the text as appropriate. Consensuses were reached with the participants on each discussion point. It was agreed that the revised version of the Recommendations will be submitted to the Expert Committee on Biological Standardization (ECBS) for review and adoption in its meeting in October 2018.

Introduction

Hepatitis E virus (HEV) is a major cause of sporadic and epidemic hepatitis and it causes over 3 million symptomatic cases and 70,000 hepatitis E-related deaths every year. A recombinant hepatitis E vaccine was developed and licensed in the China in 2011. In response to the request on the development of recommendations for hepatitis E vaccines to

facilitate the access to the vaccine in outbreak areas, WHO convened a working group meeting in 2017 and reviewed the development and regulation of this vaccine. Following the working group meeting the drafting group developed the recommendations to assure the quality, safety and efficacy of recombinant hepatitis E vaccines which was posted on the WHO website for public consultation. Comments and suggestions were received to improve the document. To finalize it an informal consultation was convened from 18 to 19 April 2018 in Beijing.

Session 1: Welcome and Introduction

The informal consultation was organized by WHO in assistance with the National Institutes for Food and Drug Control in China. The meeting was held from 18-19 April 2018 at National Institutes for Food and Drug Control, Beijing, China. The meeting was attended by representatives from regulators, academia and vaccine developers from Chad, China, Germany, India, Indonesia, Nepal, Pakistan, Thailand, Viet Nam, UK and USA. Dr Li Bo the Director General of NIFDC welcomed the participants to NIFDC. He highlighted the cooperation with WHO, in particular with the Expert Committee on Biological Standardisation (ECBS) in development of international measurement standards and guidelines for biologicals. He expressed the willingness in working together with WHO, NRAs in other countries, academia and industry on the quality, safety and efficacy of vaccines and other biologicals. Mr Li Gang from China National Medical Products Administration (NMPA) of State Administration for Market Regulation (SAMR) welcomed the participants to Beijing. He emphasized the importance of cooperation between NMPA and WHO especially in strengthening regulatory capacity of NMPA on vaccines. He congratulated WHO on the development of WHO Recommendations for HEV vaccines. Mr Yi Tang from WHO China country office welcomed the participants on behalf of the WHO Country office.

After introductions Dr Y. Wang was selected as chair with Dr P. Minor as rapporteur of the meeting.

Session 2:

a. Objectives, expected outcomes and development of the Recommendations

Dr D. Lei gave an introduction to the role of WHO in the development of norms and standards including written standards and reference materials for assuring the quality of

biological products. The process involves the WHO collaborating centres and the ECBS which gives the final approval. Preparation of the current Recommendations was driven by the number of outbreaks and outbreaks of hepatitis E in Asia and Africa and the licensure of a vaccine in China. The virus is a single stranded RNA virus of the Hepeviridae family with at least four different genotypes able to cause disease in humans, but apparently only one serotype based on evidence of cross protection in animal models and human studies. While there are several candidate vaccines in development using bacterial and baculovirus expression systems the licensed vaccine consists of a truncated protein of ORF2 expressed in bacteria. Another vaccine, consisting of a 56 kD protein manufactured by a different producer, was the subject of a successful protective efficacy trial in Nepal but had not been developed further at the time of the meeting. Hecolin, the licensed vaccine, consists of a 239 amino acid fragment expressed from ORF2 of a genotype 1 virus. WHO published a position paper on HEV vaccines in 2015 after a review of the global situation by Strategic Advisory Group Experts on Immunization (SAGE) in 2013.

International reference preparations are available for HEV antibodies from NIBSC, UK and a quantitative reference for nucleic acid detection and a panel for detection of nucleic acid from different genotypes from PEI, Germany. The written standards have been drafted in response to requests from stakeholders and manufacturers and are needed to allow prequalification and purchase of vaccine by UN agencies. A first working group meeting on the HEV Recommendations was held in May 2017 and included regulators, industry and stakeholders from around the world and the resulting document had been sent out for public consultation. The objectives of the current meeting were to review the draft Recommendations to assure the quality safety and efficacy of recombinant hepatitis E vaccines and to discuss pending issues and propose improvement/modifications on the above draft Recommendations. The comments received and proposed of modification on the document where necessary were reviewed with the intention of submitting the finalised document to ECBS in October 2018.

b. Hepatitis E viruses and disease.

Dr E. Gurley gave a summary of the epidemiology of HEV disease. Transmission in most instances is water or food borne, although cases of infection through blood transfusion occur. The disease is normally acute and self-limiting but can be fatal in pregnant women and individuals with existing liver disease. Chronic infections can arise in immunodeficient

individuals and asymptomatic infection is common; overall there are estimated to be about 20 million infections per year with 3.3 million cases and 70000 deaths.

The peak of virus shedding in stools and of viraemia occurs at 8-10 days after the onset of illness, coinciding with peak levels of IgM.

The kits used to assay antibody are not standardized or optimal yet; in one study of seroprevalence the peak prevalence was either 50 % or 80% depending on the kit used. The burden of disease is highest in low income countries in Africa and Asia and Mexico. Genotype 1 causes large and small outbreaks and genotype 3 causes outbreak in high income countries for example in Europe through exposure to contaminated meat. Genotype 4 is common in China.

Session 3: Updates on HEV vaccines development and standardization

Overview of development and production of hepatitis E vaccine in Xiamen University and Innovax. Dr J. Shih (Innovax) described the development of Hecolin. The Hepatitis E virus genome is 7.2 kb in length and contains three open reading frames (ORFs) of which the product of ORF2 contains the target of protective antibodies. The ORF2 protein is 660 amino acids in length and there is broad protection between genotypes indicating a single serotype. All four genotypes significant for human disease classified them into the genus Orthohepevirus A by the International Committee on Taxonomy of Viruses (ICTV) with genotypes 1 and 2 being closely related. Hecolin is based on a 239 amino acid fragment of the ORF2 product of a genotype 1 virus; the other tested vaccine consisted of the intact 56kDa ORF2 protein and while it gave good protection in a trial in Nepal it has not been developed further at the time of writing. Hecolin forms aggregated structures which are not virus like particles in the strict sense. Batch consistency in composition and structure have been demonstrated. It was licensed in China in 2012 and has not yet been licensed elsewhere; the stock available is greater than 100000 doses with an intended capacity of 5 million doses per year. The final vial contains 30 µg of protein adjuvanted with alum and is given at 0, 1 and 6 months to recipients aged 16 or greater. Currently it contains thiomersal as preservative but this will be omitted in the future.

In a clinical trial in China efficacy against clinical disease was 100% (72.1-100%) with persistence for at least five months (9.1-100%). The vaccine is of genotype 1 and the

circulating strain in China was genotype 4 supporting the idea of good cross protection between genotypes. Over 4.5 years the efficacy against disease was 93.3% (71-94%). It is possible that there was boosting of immunity by circulating wild type virus. Efficacy against infection shown by seroconversion or a 4-fold rise in titre was 79.2% (67.7-86.2%). Significant antibody titres persisted for 4.5 years. No safety concerns were detected.

The other vaccine was overseen by GSK and showed a clinical efficacy of 95% against clinical disease in Nepal where the circulating strains are genotype 1 in contrast to China where the circulating strains are genotype 4. There is also experimental data in animal supporting cross protection between genotypes. Further clinical studies are planned including trials in pregnant women and recipients under 16 years of age.

Control of the manufacturing process and product includes characterization of the seed lots for genetic stability and the correctness of the insert, and a variety of assays including ELISA for antigen content and mouse immunogenicity studies. Stability studies are ongoing but a shelf life of 36 months at 2-4^{o}has been approved in China.

Regulatory evaluation of Hepatitis E vaccine in China.

Dr X. Yao, Center for Drug Evaluation of CFDA described the experience of the regulatory authority. While Hecolin, manufactured by Innovax, is the only licensed product two others have completed phase 1 clinical trials; both involve expression of ORF2. The product from Changchun is expressed in bacteria, the other, from the Beijing Institute, is expressed in baculovirus. The Changchun product was well tolerated and gave 100% seroconversion in the 60 patients enrolled in the phase I trial. Results of pre-clinical studies including challenge studies in mice and monkeys were acceptable.

The definition of an HEV case is critical in defining efficacy. The markers of infection are a rise of 4-fold or greater in IgG level, presence of IgM and detection of nucleic acid by PCR. In China the case definition was that any two markers should be positive while the WHO draft required only one. This was addressed in discussing the clinical section of the guideline below. There was some discussion of the mouse potency assay and the need to include a suitable reference preparation to reduce the variation in results seen.

Session 4: Review of the draft Recommendations and comments received.

The sections of the guideline were summarized and the specific comments received presented together with the drafting group response. The guideline was then considered paragraph by paragraph to allow further comment from the group.

1. Introduction, scope and terminology

Dr D. Lei led the discussion. Three substantive comments had been received. The first concerned the need to stress the cross protection seen between serotypes by introducing a new paragraph in the introduction. This had been raised by two responders. The group considered that as the matter was already well covered in the nonclinical and clinical sections no modification was needed. The second point was that the scope of the document is narrow, being concerned essentially with a single vaccine produced in bacteria, and that other vaccines and expression systems were likely. While this is true it was felt that currently other vaccines are at an early stage of development and the possibility of other systems is adequately covered in the current version. Therefore, no modification was needed at present.

The final point concerned the nature of the vaccine which some have described as a virus-like particles (VLP) (similar to human papilloma virus vaccines) adjuvanted with alum. The text was changed to remove the implication that Hecolin is a VLP vaccine rather than an aggregate of immunogenic protein and the possibility of other adjuvants has been made clearer.

There were some slight changes in the wording of parts of the section on terminology to improve clarity.

2. General considerations

Dr P. Minor led the discussion. Two points had been raised by the consultation. The first concerned the number and significance of genotypes. This is under ongoing consideration by ICTV; for example, genotype 7 has been reported although its significance for human health is not clear. The section on genotypes was slightly reworded to indicate the possibility of further developments although the primary focus remains on the four types known to impact human health. Further references were added.

The second point concerned the statement that the performance of antibody kits is suboptimal, with the comment that there was much developmental work ongoing. However, the statement remains correct, so that additional references relating to ongoing work were included without altering the basic statement.

3. Manufacturing recommendations

Dr P. Minor led the discussion. In the draft for comment it had not been clear that determining the molecular characteristics of the plasmid system was required for validation of the process not on an ongoing batch by bath basis. This was corrected.

The statement on microbial purity when bacterial expression platforms are used led to much discussion. There was agreement that the microbial purity of the seed lots was an essential part of their characterization. However, the document also required that each harvest be tested for bioburden, which given that the harvest consists of live bacteria would be hard. The statement was to be checked against the pharmacopoeias to be sure what they require. Plasmid retention test added to monitor the genetic stability of the seed.

The document is mainly concerned with bacterial expression systems and this led to a comment to make it broader as other vaccine types are in development. This was also mentioned by those commenting on the scope and the conclusion of the group was that although the objection was valid the current level of detail is appropriate.

In the circulated draft it was suggested that the product might be denatured then renatured to improve purity and the quality of the VLPs as is done for human papilloma virus vaccines. This is not the manufacturing practice for the licensed vaccine, nor is it a VLP vaccine; the suggestion was therefore removed.

In the example of HPV vaccines several separate bulks may be blended to give the final formulated product, so that tests on the individual and final bulks are required. For Hecolin there is no such blending so that the section caused confusion. However, it was retained in case blending might be used in future, but with a clear statement that the section was irrelevant if this was not manufacturing practice.

The section on the potency assay was revised and clarified. Currently it uses immunogenicity rather than an in vitro ELISA measurement of antigen. ELISA may be in development but is

not currently used for potency assay. The need for inclusion of a routine used reference material in the assay was stressed. It is not clear if one is used at present.

Slight changes of wording were incorporated during reading the text.

4. Nonclinical evaluation of hepatitis E vaccines

Dr Y. Sun led the discussion on the nonclinical section which had attracted five specific comments. One concerned the choice of species for challenge studies. As all four genotypes significant for human disease will infect non-human primates (NHP) the responder had proposed that NHP should be recommended as the species of choice. However other species are susceptible to genotypes 3 and 4, and the group's view was that the text should remain unchanged; it allows the use of non-human primates but does not restrict the use of other species where possible and where the developer wishes to use them.

A second point concerned the evidence for cross protection between genotypes where it was proposed that the studies should be encouraged rather then mandatory. The group considered that the text did not require change as the recommendation was not obligatory, but the studies were thought advisable.

Two other points concerned addition of references and were accepted.

5. Clinical evaluation of hepatitis E vaccines

Dr P. Minor led the discussion on the points received. One major consideration was the case definition of HEV infection in a clinical trial where the original draft proposed any one of three criteria, namely a 4-fold rise in HEV IgG antibody titre, detectable HEV specific IgM and HEV nucleic acid detected by PCR. It was proposed that this should be changed to two out of three, making the confirmation of HEV infection more stringent. This was accepted by the group.

A second point concerned the assessment of other hepatitis infection in the event of a suspected case of HEV; the original version proposed that patients in clinical trials should be examined for chronic infections with hepatitis B or C by measuring antibody levels and PCR detectable viral genomes; the group chose to restrict investigation to detection of acute infections i.e. for HCV PCR detectable virus RNA in the absence of antibody and IgM for hepatitis B.

Conclusions

In general, the first draft had not attracted many comments requiring change and most were either already taken are of or met by slight modification of wording. The group considered that the revised text was suitable to be submitted to the ECBS for review and adoption as a WHO Recommendations to assure the quality, safety and efficacy of recombinant hepatitis E vaccines.

Authors:

Dr Philip Minor, St Albans, United Kingdom,

Dr Dianliang Lei, World Health Organization, Geneva, Switzerland on behalf of the WHO Informal consultation on WHO Recommendations to assure the quality, safety and efficacy of recombinant hepatitis E vaccines.

Appendix 1. Meeting participants

The informal consultation was participated by Dr E. Gurley, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, USA; Mr D. M. Hung, Drug Administration of Vietnam, Ministry of Health, Viet Nam; Dr D. Lei, World Health Organization, Switzerland; Dr Z. Liang, National Institutes of Food and Drug Control, China; Dr J. Martin, National Institute for Biological Standards and Control, United Kingdom; Dr P. Minor, St Albans, United Kingdom; Dr C. N. Pharmacy, Ministry of Public Health, Chad; Dr S. Phumiamorn, Institute of Biological Products, Ministry of Public Health, Thailand; Dr H. I. Qureshi, Pakistan Health Research Council, Pakistan; Dr J. Shin, World Health Organization, Regional Office for the Western Pacific, Philippines; Mr B. Shrestha, Walter Reed/AFRIMS Research Unit Nepal, Nepal; Dr R. Simalango, National Agency of Drug and Food Control, Indonesia; Dr D. Steele, Bill & Melinda Gates Foundation, USA; Dr Y. Sun, Paul-Ehrlich-Institut, Germany; Dr Y. Tang, WHO China Country Office, World Health Organization, Beijing, China; Dr E. Teshale, Centers for Disease Control and Prevention, United States of America; Dr Y. Wang, National Institutes of Food and Drug Control, China; Drs. H. W. T. Wibowo, National Agency of Drug and Food Control, Indonesia; Dr X. Wu, National Institutes of Food and Drug Control, China; Dr M. Xu, National Institutes of Food and Drug Control, China; Dr X. Yao, Center for Drug Evaluation of China Food and Drug Administration, China; Dr J. Zhang, National Institute of Diagnostics and Vaccine, Xiamen University, China; and Dr Q. Zhao, School of Public Health, Xiamen University, China.

Representatives from Industry: Dr H. Chandra, Cadila Healthcare Limited, Vaccine Technology Center, India; Ms W. Huang, Innovax Biotech Co. Ltd., China; and Dr J. W.K. Shih, Xiamen Innovax Biotech Co. Ltd., China.

Appendix 2. Agenda

Informal consultation on WHO Recommendations to assure the quality, safety and efficacy of recombinant hepatitis E vaccines

National Institutes for Food and Drug Control, Beijing, China

18 -19 April 2018

Agenda

Chairman: Dr Y. Wang

Rapporteur: Dr P. Minor

Day one, 18 April 2018 (Wednesday)

9.00-9.30 Session 1. Opening of the meeting

Opening remarks	WHO/CFDA/NIFDC
Self-introduction	All participants
Objectives and Expected Outcomes of the meeting	Dr D. Lei, WHO

9.30-10.00 Session 2. Background

Development of the Recommendations for Hepatitis E vaccines	Dr D. Lei, WHO
Hepatitis E viruses and Diseases	Dr E. Gurley

10.30-11.00 Session 3. Updates on HEV vaccines development and standardization

Overview of development and production of hepatitis E vaccine in Xiamen University and Innovax	Dr J. Shih, Innovax
Regulatory evaluation of Hepatitis E vaccine in China	Dr M. Li, CFDA, China

11.00-12.00 Session 4. Review of draft WHO recommendations on Hepatitis E vaccines

Comments received from first round public consultation	Drafting group

13.00-17.30

Review the draft Recommendations and comments received.	Drafting group

1.	Introduction	Dr D. Lei
2.	Scope	Dr D. Lei
3.	General considerations	Drs P. Minor and E. Gurley
4.	Terminology	Dr D. Lei
5.		

Day 2, 19 April 2018 (Thursday)

9.00-onward Session 4. Review of draft WHO recommendations on hepatitis E vaccines (cont.)

6.	Manufacturing recommendations	Dr P. Minor
7.	Nonclinical evaluation of Hep E Vaccines	Drs Y. Sun and Q. Zhao
7.	Clinical evaluation of Hep E vaccines	Dr P. Minor
8.	Recommendations for NRAs	Dr D. Lei
9.	Appendices	Dr D. Lei
	Recap the discussion and feedback	Dr Y. Wang

16.00-17.30 Session 5 Conclusion and proposals to WHO (close session, regulators only)

1. Consensus regarding the Recommendations
2. Recommendations and suggestions to WHO
3. Next steps for the development of the Recommendations.

Closure of meeting