

Hepatitis E Vaccine: Time to Let the Cat Out...!

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ABSTRACT

HEV is an emerging pathogen responsible for an estimated 20.1 million cases of liver infection, worldwide. Notably, in pregnant women hepatitis E results in fulminant liver failure, spontaneous abortions and stillbirths with an overall fatality rate of 20-30%. Therefore, developing a safe and effective hepatitis E vaccine has been an important issue. Of these, while the first safe and efficacious vaccine failed to reach the market, the second approved vaccine Hecolin® is now commercialized in China only. Very recently, Hecolin® has completed an extended follow up in a small phase IV study in South Asia and Africa that further warrants its most awaited universal access and endorsement.

Key words: HEV; Hepatitis E; Vaccine; HEV239; Hecolin

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INTRODUCTION

Hepatitis E virus (HEV) is an emerging pathogen of acute and chronic hepatitis, worldwide. While waterborne outbreaks in developing countries are associated with poor sanitation, sporadic autochthonous cases of foodborne infection linked to swine and boar meat consumption are increasingly reported in industrialized nations^[1]. According to WHO report, HEV is responsible for an estimated 20.1 million cases of liver infection, including 70,000 deaths every year^[2]. Of the four recognized pathogenic HEV strains (genotypes 1-4), HEV1 and HEV2 infect only humans whereas HEV3 and HEV4 are linked to zoonosis in swine, boar, deer and several other mammals^[3]. HEV1 is responsible for the most endemic and epidemic cases in Central and Southeast Asia, and HEV2 is prevalent in North and West Africa and Mexico^[4]. Notably, in highly endemic areas, HEV1 infection of pregnant women results in fulminant liver failure, spontaneous abortions and stillbirths with an overall fatality rate of 20-30%^[5]. In addition, in Europe and the United States, HEV3 and HEV4 have recently evolved to establish chronic infection that may progress to cirrhosis in clinically immunosuppressed patients^[1,6].

THE HEV VACCINE

Vaccines remain an important cornerstone in the prevention of viral hepatitis associated morbidity and mortality in a cost-effective manner. Akin to hepatitis A and hepatitis B with substantial disease burden, developing a safe and effective hepatitis E vaccine has been an important issue. Due to difficulty and poor yields in culturing HEV, it has not been possible to produce sufficient virus particles for live attenuated or inactivated vaccines. HEV vaccine research therefore, mainly focuses on the expressions of recombinant viral capsid protein (ORF2) that shares over 85% identity among the four genotypes^[7]. Sero-epidemiologic evidence showed that anti-

HEV antibodies persist for 14 years or longer in infected individuals capable of protecting against severe symptomatic hepatitis E and reinfection^[8]. In pre-clinical assessments, protective efficacy of a candidate HEV vaccine is evaluated in HEV infected non-human primates that closely mimic clinical acute hepatitis E with serological, virological, biochemical, and histopathological markers.

The first candidate subunit vaccine, rHEV (HEV1-ORF2; full length) was produced in a recombinant baculovirus-insect cell system^[9]. In the GlaxoSmithKline (GSK, Rixensart, Belgium) sponsored phase II trial in Nepal, rHEV was well-tolerated and showed high immunogenicity with 95% efficacy^[10]. Unfortunately, it was not commercialized because of the non-profitable market. The second vaccine, *E. coli* expressed HEV239 (HEV1-ORF2; aa 368-606) in a large-scale, double-blind randomized phase III clinical trial showed 100% protection in Jiangsu Province, China where endemic circulation of HEV4 predominates over HEV1^[11]. This indicated that in spite of the HEV1 origin, HEV239 could provide cross-protection against HEV4. Notably, for this trial, pregnancy was one of the exclusion criteria where conception was confirmed orally. HEV239 was thus, the first HEV vaccine licensed under the trade name of Hecolin® (Innovax Biotech, Xiamen, China) for commercial distribution in China in 2012. Further, the long term efficacy of Hecolin® for up to 4.5 years was 86.8% in men and women aged 16-65 years^[12]. However, until now Hecolin® is available only in China, and it is unclear whether this vaccine could provide protection outside China irrespective of ethnicity as well as other genotypes, especially HEV3 in Western countries.

CURRENT UPDATES

The WHO Strategic Advisory Group of Experts on Immunization (SAGE) meeting in Geneva has recently reviewed the status of Hecolin® and recommended further immunogenicity and safety studies in South Asia and Sub-Saharan Africa before approval for commercialization^[13]. These included safety studies in pregnant women, children, patients with underlying chronic liver disease, and individuals on immune-suppressive drugs. The SAGE also advised for the evaluation of the immunogenicity and efficacy of a more accelerated vaccine schedule to be used in these high-risk populations or on the general population to prevent HEV infection during a humanitarian emergency. Very recently, an extended follow up of the phase III clinical trials as well as a small phase IV study involving subjects of 65 years of age and over has been completed^[14]. Further clinical trials of Hecolin® and evaluation of a combined HEV/human papilloma virus (HPV) vaccine are also planned.

SUMMARY

Universal access of the available HEV vaccine would be very useful in high risk-groups of severe morbidity and/or mortality, such as those with underlying chronic liver disease, pregnant women, clinically immunosuppressed patients, naïve travelers to highly endemic regions, veterinarians, swine herders, sewage workers etc. Nonetheless, considering the cost-benefit ratio, this is subject to endorsement and approval in other parts of the world. Given the recognition of HEV as a global public health issue, there is an urgent

need to make the vaccine accessible globally.

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