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Editorial Open Access

Hepatitis E Virus: A Renewed Hope with Hecolin

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Abstract

After the availability and wide spread administration of the Hepatitis A and Hepatitis B Virus vaccines, Hepatitis E Virus (HEV) has recently emerged globally as the leading cause of acute hepatitis with jaundice. Although the recombinant vaccines were initiated for HEV about two decades back the results could not be concluded due to various constraints. A pioneer recombinant vaccine (Hecolin) developed and tried over the last couple of years in China has not only shown promising results but has also given impetus for global development of such vaccines for the HEV. It is hoped that recombinant vaccines if combined with other public health measures will play a significant role in not only controlling the HEV epidemics in the developing countries but also help in reducing the sporadic infections in the developed world.

Keywords: Hepatitis E Virus; Hecolin

Editorial

Consequent upon the availability and wide spread administration of Hepatitis A and Hepatitis B Virus vaccines before the conclusion of 20th century, the Hepatitis E Virus (HEV) emerged globally as the leading cause of acute hepatitis with jaundice in the recent years. The HEV remained largely underappreciated for years but more recently with the renewed interest in the development of recombinant vaccines, the global control of the HEV disease could be a reality in the offing. HEV was discovered in 1983 [1]. It is a non enveloped single stranded positive sense 7.5kb RNA virus about 30nm in diameter under the genus *Hepevirus* in the *Hepeviridae* family. The genome has 3 Open Reading Frames (ORFs) ORF1, ORF2 and ORF3 with their specific roles in virus replication, activation of immune system and pathogenesis. The virus not only infects humans but is also universally distributed in both domestic and wild animals including pigs, deers, rodents, birds and a host of other species. While there is only one serotype, the HEV strains fall under the two main genotype groups, the avian and the mammalian. The avian strains have three genotypes and exhibit 50% genomic homology with the mammalian strains. Since the avian strains have failed to infect monkeys experimentally, they are unlikely to have any potential risk of infecting humans. However, the mammalian strains which are more relevant to us are grouped into four genotypes each with multiple subtypes demonstrating 80% homology among them. Whereas genotypes 1 and 2 are confined to humans, the genotypes 3 and 4 are prevalent in both humans and animals. HEV genotypes 1, 2 and 4 have been responsible for causing large outbreaks and epidemics in developing countries in Asia, Africa and Central America over the last six decades ever since the first retrospectively reported large outbreak involving 29,300 people following the flooding of Yamuna river in Delhi in 1955-1956 [2-7]. In the developed world, usually the HEV infections are sporadic and are caused by genotype 3 which is known to be least virulent. Although sporadic infections can be attributed to the consumption of raw/undercooked pig meat or shellfish or to the direct contact with infected animals/persons in some cases, in others both the source and the mode of infection can not be ascertained. The source of infection in the developing countries is invariably the contaminated water and the infection is acquired through the feco-oral route. Transfusion associated HEV infections have also been reported occasionally particularly with genotypes 1 and 3. After an incubation period of 15-60 days (average 40 days), the patient develops jaundice, malaise, anorexia, fever, hepatomegaly and pruritus like other hepatotropic acute virus infections with the rise of serum bilirubin and sharp increase in liver enzymes. The jaundice appears in 90 to 100% of infections acquired during epidemics. But fortunately, the infections mostly resolve spontaneously and the fatality rate is usually less than 1%. However, in pregnant women especially during the third trimester the case fatality may be 10-25% [8]. High mortality rates have also been recently reported among children less than 2 years age [9,10]. Chronic infections or chronic carrier stage may be present in HIV/AIDS, organ transplant, immunosuppressed patients and others with preexisting hepatic disease. After a variable period, neurological complications may be seen in some susceptible patients following acute or chronic HEV infections both in the endemic and nonendemic countries. They are thought to be due to autoimmune phenomenon. These patients usually present with Gullain-Barre syndrome, brachial neuritis, cranial nerve palsies, transverse myelitis, seizures, ataxia, acute encephalitis, polyradiculoneuropathy, intra cranial hypertension (pseudotumor cerebri) or some other manifestations pertaining to the nervous system. In the industrialized nations, usually the HEV infections were recognized in people with a travel history to an endemic country but recently a substantial number of autochthonous cases have also been realized [11]. Given the wide global distribution of the virus in the animals and animal products and varied cooking and eating habits of people and multiple modes of transmission, it is quite likely that small outbreaks might be occurring in the developed countries as well but they are either underreported or they may go largely unrecognized. Effective immunity is known to develop following HEV infections and second attacks seldom occur. After an acute infection, anti-IgM and anti-IgG immunoglobulins are detectable up to 4-6 months and 12 years respectively. The prevalence of anti HEV antibodies may be 20-40% in countries with low sanitary standards, but in the western world it is between 1-3%, but in certain

risk groups it could even be up to 21% there. Most of the available serodiagnostic kits have their own limitations because of high percentage of false positive and false negative results. All seropositive results should be confirmed by RT-PCR. Unfortunately, no commercial antibody assays are currently approved by the FDA. However, using enzyme immune assays, HEV RNA can be demonstrated in blood samples in early stages of infection from about 2 weeks before to 1 week after onset of jaundice. HEV RNA can also be detected in the stool after a few days of its appearance in and for about 2 weeks of its disappearance from the blood. Testing samples for anti-HEV with epidemiological purposes is limited by the lack of genotype specific tests. The treatment of acute HEV infections is essentially supportive. Interferon-ribavirin combination has been beneficial in a few chronic and complicated cases.

Though, HEV recombinant vaccine developments were initiated between 1995 and 2004 by DynCorp and GlaxoSmithKline with promising results, further progress could not be possible due to various constraints. Recently, Xiamen Innovax Biotech Co, Ltd, China has produced the recombinant HEV 239 vaccine (expressed in *Escherichia coli*) under the trade name of Hecolin which was approved in December 2011 by the China's State Food and Drug Administration (SFDA) renamed as China Food and Drug Administration (CFDA). The vaccine hit Chinese market by the end of 2012. Hecolin is a 26 kDa polypeptide derived from genotype 1 HEV strain. It is administered parenterally in three doses of 30ug each at 0, 1 and 6 months. The vaccine gives almost 100% protection without any significant side effects. It is too early to mention how long does the immunity last or how often are the boosters required. In limited trials the vaccine is also quoted to be safe in pregnancy. The vaccine requires WHO preauthorization before being available outside China. It is interesting to note that the HEV 239 vaccine has also been tried in rabbits with excellent immunogenicity [12].

While approximately 2 billion people (about one third of world population) are positive for anti HEV-IgG antibodies, nearly 20 million new HEV infections including 3 million acute hepatitis cases and about 70,000 deaths occur every year. Despite all these observations, it is deplorable that HEV has largely remained underappreciated. The poor appreciation can be attributed to the difficulties encountered in virus culture, non availability of reliable serodiagnostic tests, presence of mild/asymptomatic cases and the wide variation in clinical presentation in the developing and developed world. The occurrence of epidemics only in the developing countries with limited resources may also be responsible for relatively a few epidemiological studies on HEV. In fact, the developing countries had earlier been occupied struggling with the prevention, control and treatment of other infections diseases with the funds and the resources diverted.

With the recombinant vaccines becoming available globally at an affordable price particularly in Asia and Africa, it will be possible to at least control the HEV infection, though the elimination may not be a feasible preposition as the virus is widely distributed in various animal species. Where ever cost effective, the domestic animals especially the pigs should be vaccinated to minimize the incidence of the HEV infection in human population. There is urgent need for the development of reliable genotype specific serodiagnostic kits with high degree of specificity and sensitivity so that they could be approved by the FDA. Besides, improvement in the sanitary and hygienic standards, the provision of safe drinking water and avoidance of eating raw/undercooked meat are the other issues to be readdressed. If the results of the phase 4 human clinical trials (likely to start in near future) are favorable, Hecolin or other recombinant vaccines may prove to be highly useful in limiting both the epidemics and the sporadic HEV infections globally.

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