Hepatitis B and C
Public Policy Association

NEWSLETTER

Prof. Massimo Colombo M.D. Editor-in-Chief

OCTOBER 2015 ISSUE

EASL recommendations on treatment of hepatitis C 2015

Prof. Jean-Michel Pawlotsky, M.D., PhD
National Reference Center for Viral Hepatitis B, C and delta
Department of Virology and INSERM U955
Hôpital Henri Mondor, Université Paris-Est, Créteil, France

The approval of new hepatitis C virus (HCV) direct acting antiviral (DAA) drugs in Europe and other parts of the world in 2014, including sofosbuvir, simeprevir and daclatasvir, created the need for straightforward clinical practice guidelines issued by national or international scientific organizations. The American Association for the Study of the Liver (AASLD) decided to publish online recommendations that would be regularly updated. However, the AASLD guidelines essentially target the US market and its medical insurance environment. The World Health Organization (WHO) also generated guidelines that essentially target low- and middle-income areas. The need for clinical practice guidelines that can be used all over Europe and more broadly by any prescribers interested in evidence-based recommendations independent of local reimbursement strategies was obvious. The European Association for the Study of the Liver (EASL) is in an ideal position to generate such guidelines. The decision was thus made to publish the "EASL Recommendations for Treatment of Hepatitis C 2014" in the Journal of Hepatology and present them at the International Liver Congress (ILC) 2014 in London.

However, things are moving very fast in the field of HCV treatment. Two new combinations were approved in 2015 in Europe, including the fixed-dose combination of sofosbuvir and ledipasvir in one single pill, and the combination of ombitasvir-paritaprevir-ritonavir in one single pill with or without dasabuvir, while a large number of new clinical data was released, in particular in special populations that had not been explored previously. This justified the release of the new "EASL Recommendations for Treatment of Hepatitis C 2015" during the ILC meeting in Vienna in April 2015. The Recommendations were entirely rewritten to provide extensive information and greater clarity, together with comprehensive tables, in particular for drug-drug interactions and the indications for therapy.

Among the key recommendations, the goal of therapy is now to cure HCV infection in order to prevent not only the hepatic complications, but also clinically meaningful extra-hepatic manifestations of HCV infection. All treatment-naïve and treatment-experienced patients with compensated or decompensated liver disease related to HCV should be considered for therapy. However, because of the cost of the drugs and the number of patients to be treated, not everybody can be treated in the short-term. Thus, treatment should be prioritized in patients with F3 or F4 fibrosis with compensated or decompensated disease, patients with HIV or HBV coinfection, patients with an indication for liver transplantation and those with post-transplant HCV recurrence, patients with clinically significant extra-hepatic manifestations or debilitating fatigue, and individuals at risk of transmitting HCV. Treatment is also justified in patients with F2 fibrosis. Importantly, indications for HCV treatment in HIV-coinfected persons are identical to those in patients with HCV monoinfection; however, interactions with antiretroviral drugs must be taken into account carefully.

The EASL Recommendations 2015 are based on evidence from existing publications and presentations or, when no evidence is available, the panel members' experience and opinion. For each group of patients, options are provided: these options are considered equally valuable, and their numbering does not indicate any prioritization. When subgroup delineation was felt difficult in clinical practice, the panel opted for the most efficacious treatment regimen, in order to offer patients the best chance to achieve a cure. Notwithstanding the respective costs of these options, IFN-free regimens are the best options when available because of their virological efficacy, ease of use and tolerability.

Characteristics that should inform treatment option selection include the HCV

Continued on page 2...

Newsletter Contents

(continued from page 1)

genotype/subtype, severity of liver disease, comorbidities, the pharmacokinetic profile of the drugs, drug-drug interactions and prior treatment experience. Available interferon-free treatment options in 2015 include : sofosbuvir plus ribavirin (genotypes 2 and 3) ; sofosbuvir-ledipasvir, with or without ribavirin (genotypes 1, 4, 5 or 6) ; ombitasvir-paritaprevir-ritonavir plus dasabuvir, with or without ribavirin (genotype 1); sofosbuvir plus simeprevir, with or without ribavirin (genotypes 1 and 4); sofosbuvir plus daclatasvir, with or without ribavirin (all genotypes); ombitasvir-paritaprevir-ritonavir, with or without ribavirin (genotype 4). The combination of sofosbuvir plus pegylated interferon alpha and ribavirin can be used to rescue patients with genotype 2 or 3 infection who failed on a DAA-based regimen.

In patients with decompensated cirrhosis (Child-Pugh B or C), simeprevir- and paritaprevir-based regimens are contra-indicated, pending ongoing studies in patients with Child-Pugh B cirrhosis. Thus, only sofosbuvir can be used, in combination with ribavirin (genotypes 2 or 3), ledipasvir with ribavirin (genotypes 1, 4, 5 or 6) or daclatasvir with ribavirin (all genotypes). Antiviral therapy is indicated in patients awaiting liver transplantation because it prevents graft infection. Treatment should be initiated as soon as possible in order to complete a full treatment course before transplantation. However, the optimal timing of treatment to maximize survival (i.e. before transplantation or post-transplantation) is still debatable and requires individual assessment. In the post-transplant setting, sofosbuvir-based regimens are preferred because they do not require immunosuppressant drug dose adjustment. Uncertainty remains as to the optimal treatment strategy in patients with chronic kidney disease.

Retreatment of patients, who failed an interferon-free, DAA-based regimen, is challenging, because of the post-failure persistence of resistance-associated variants, especially in patients exposed to NS5A inhibitors. The EASL Recommendations are based on indirect evidence and subject to change when more data become available. The utility of HCV resistance testing prior to retreatment is unknown. The retreatment regimen should contain sofosbuvir (because of the high barrier to resistance), plus one or two other DAAs (if possible with no cross-resistance with the DAA already administered), plus ribavirin, for 12 to 24 weeks (24 weeks is recommended in F3-F4 patients).

The EASL Recommendations for Treatment of Hepatitis C 2015 have a major impact on real-life treatment strategies, because they are evidence-based and unrelated to local availability and/or reimbursement strategies. The EASL Recommendations have been used to inspire national guidelines and drive discussions between local stakeholders and their governments, in order to provide better access to care and orientate reimbursement decisions. They will serve as a backbone for hepatitis C therapy worldwide until they are updated when new drugs are approved and more data becomes available, probably in early 2016.

Prof. Jean-Michel PAWLOTSKY, M.D., PhD
Director, French National Reference Center for Viral Hepatitis B, C and delta,
Chief, Department of Biology

Head, Department of Virology, Bacteriology-Hygiene, and Mycology-Parasitology

Head, Research Team “Pathophysiology and Therapy of Chronic Viral Hepatitis” (INSERM U955)
Hopital Henri Mondor
Universite Paris Est
51 avenue du Marechal de Lattre de Tassigny
94010 CRETEIL, FRANCE

E-mail: jean-michel.pawlotsky@hmn.aphp.fr

EASL launches joint guidelines with ALEH on the use of non-invasive tests for evaluation of liver disease severity and prognosis

Laurent Castera, M.D., PhD
Secretary General, EASL

2015 has been a very special year for the European Association for the Study of the Liver (EASL). Not only is EASL celebrating its 50th anniversary, but also the 30th anniversary of its flagship journal, the Journal of Hepatology, that for the first time has reached an impact factor above 11. In the July issue of the Journal of Hepatology*, EASL published together with the Latin American Association for the Study of the Liver (ALEH), the first guidelines on the use of non-invasive tests for evaluation of liver disease severity and prognosis. These guidelines were launched in April this year during the International Liver Congress, (ILC) EASL’s annual meeting in Vienna where more than 10 000 liver specialists attended.

EASL Clinical Practice Guidelines assist physicians and other healthcare providers as well as patients and those interested in the clinical decision-making process by describing a range of generally accepted approaches for the diagnosis, treatment and prevention of specific liver diseases. Over the past decade, the development of non-invasive methods to assess liver fibrosis, the major determinant of the prognosis and management of liver diseases, has advanced the practice of Hepatology. These methods are already widely available and used in clinical practice, especially in patients with viral hepatitis. The Clinical Practice Guidelines Panel has considered the following questions:

Q. What are the non-invasive tests currently available and how should they be used in practice?

Non-invasive methods rely on two different approaches: a “biological” approach based on the quantification of biomarkers in serum samples or a “physical” approach based

Continued on page 3...

on the measurement of liver stiffness using ultrasound-based elastography. Transient elastography (FibroScan®), FibroTest® (a patented serum biomarker) and APRI (AST to Platelet Ratio Index, a non-patented serum biomarker) have been the most extensively studied and validated in patients with chronic viral hepatitis. The practical advantages of analyzing serum biomarkers include their high applicability (>95%) and their potential widespread availability (non-patented). However, none is liver specific. Advantages of transient elastography include a short procedure time (<5 minutes), short learning curve, immediate results, and the ability to perform the test at the bedside or in an outpatient clinic. However, its applicability (80%) is not as good as that of serum biomarkers, particularly in case of obesity or limited operator experience. Thus, non-invasive tests should always be interpreted by specialists in liver disease, according to the clinical context, considering the results of other tests (biochemical, radiological and endoscopic) and taking into account the recommended quality criteria for each test and its possible pitfalls. For instance, transient elastography should be performed by an experienced operator (>100 examinations) following a standardized protocol with the patient fasting for at least 2 hours, taking into account several confounding factors such as transaminases levels, body mass index, and alcohol intake.

Q. What are the indications for non-invasive tests for staging liver disease in chronic hepatitis C?

Non-invasive tests perform better for diagnosing cirrhosis (AUROCs 0.87–0.98 and 0.77-0.86 for transient elastography and biomarkers, respectively) than significant fibrosis (AUROCs 0.75–0.93 and 0.72-0.78) although transient elastography appears to be more accurate for detection of cirrhosis. Thus, all HCV patients should be screened to exclude cirrhosis by transient elastography if available. Serum biomarkers can be used in the absence of transient elastography. HCV patients who were diagnosed with cirrhosis based on non-invasive diagnosis should undergo screening for hepatocellular carcinoma and portal hypertension and do not need a confirmatory liver biopsy.

Q. How should non-invasive tests be used when deciding for treatment in in chronic hepatitis C?

Non-invasive tests, using either transient elastography or serum biomarkers, are adequate for diagnosis of severe fibrosis/ cirrhosis in HCV patients and can be used to prioritize patients for treatment with novel direct antiviral agents according to disease stage.

Q. Is there a use for non-invasive tests when monitoring treatment response in chronic hepatitis C?

A major advantage of non-invasive tests, compared with liver biopsy, is that they can be repeated easily over time in patients receiving antiviral therapy and that they could be used to monitor response to treatment and to evaluate fibrosis regression. However, routine use of non-invasive tests after viral eradication in patients with HCV cirrhosis has a high false negative rate and cannot be used to determine which patients no longer need HCC screening or for the diagnosis of cirrhosis reversal.

Finally, there is increasing evidence for the prognostic value of non-invasive tests in the context of cirrhosis. However, routine use of non-invasive tests after viral eradication has not yet established thresholds that predict low risk of liver related events.

** EASL-ALEH Clinical Practice Guidelines. Non-invasive Tests for Evaluation of Liver Disease Severity and Prognosis. J Hepatol 2015; 63: 237-64.*

Laurent Castera M.D., PhD

Service d'Hépatologie, Hôpital Beaujon, AP-HP,
Université Denis Diderot Paris-VII, Clichy, France

Email: laurent.castera@bjn.aphp.fr

An interview on PITER: An ongoing nationwide study on the real-life impact of direct acting antiviral based treatment for chronic hepatitis C in Italy.

Stefano Vella M.D. and Loreta Kondili M.D., PhD
Istituto Superiore di Sanita', Rome, Italy

Q. The advent of direct-acting antiviral agents (DAAs) has dramatically changed the treatment paradigms of chronic hepatitis C (HCV). How rapidly is this medical innovation expected to change the landscape of HCV healthcare?

The development of second-generation DAAs represents a historical breakthrough in that they are capable of eradicating HCV in more than 95% of patients. Considering that chronic HCV infection affects an estimated 130-150 million people worldwide

Continued on page 4...

(about 3% of the world's population), the potential impact of the wide-scale use of these drugs could be enormous, in terms of reducing morbidity and mortality and illness-associated costs. However, to date, the prices of these drugs are exorbitant. Considering the high number of persons in need, there might be unsurmountable financial challenges for national health systems which are currently forced to prioritize whom to treat based on the balance between the benefits of therapy and its affordability, despite the fact that early treatment of HCV infection appears to be, in the mid-long term, the real cost-effective strategy. Access to interferon-free therapy for all those in need shall progressively bring about strategies for drug price reductions, in addition to existing plans for price-discounting in low-middle income developing countries already put in place by some pharmaceutical companies, may also include pharmaceutical industry competition, risk-sharing arrangements, volume taxation, voluntary licenses, and compulsory licenses.

Q. There is great potential for overall harm reduction through these effective therapies. How could research help a better approach to treatment?

Preventing the onset of severe liver disease is today the critical focus of treatment of HCV infection. The current approach to treatment with the available DAAs consists of selecting eligible individuals based on disease severity. However, due to the complex array of variables influencing disease progression it is difficult to define prognosis at an individual level and the overall impact of treatment at various stages and patterns of disease. Therefore, it is necessary to move from the urgency to treat selected patients (including those undergoing liver-transplantation) to evidence-based escalating strategies in other patients with earlier disease to add, to the clinical benefit, an important harm reduction effect. In many ways, the development of DAAs for HCV should be guided by the therapeutic experience with HIV and, accordingly, shall move quickly to more effective paradigms, like treating all infected persons, for both individual and public health benefit by also decreasing the incidence of new infections at a population level. In the case of HCV infection, patients can be cured successfully with DAAs, and in the absence of a specific vaccine, the cure could be part of the disease control, but, again, the cost of providing early treatment to all patients is still currently prohibitive. Hence, it is important that "real-life" clinical research is undertaken to determine the best timing and what the appropriate treatment should be, with cost-effectiveness being a fundamental part of this decision.

Q. How is it possible to reach this last goal?

Reaching this goal would require accurate epidemiological and clinical data, robust enough to inform policy on the magnitude of the disease and the long-term effects of DAAs therapy. To this end, several cohorts of patients with chronic HCV infection have been built in Europe and, in Italy, a longitudinal prospective HCV cohort study known as "PITER" (Italian Platform for the Study of Viral Hepatitis Therapies) is ongoing. PITER is a structured network that benefits from an integrated endeavour involving Italy's National Institute of Public Health (Istituto Superiore di Sanità), the Italian Society for the Study of the Liver (AISF) and the Italian Society for Infectious Diseases (SIMIT), and their affiliated clinical centres.

Q. What are the challenges that will be addressed in the PITER study?

The main goal of PITER is to evaluate in a real-life setting the expected impact of DAAs on the natural course of infection and on long-term morbidity and mortality. The overall treatment effectiveness will be determined assessing the residual risk, after viral eradication has been achieved, of life-threatening complications such as liver failure, portal hypertension, hepatocellular carcinoma and the need for liver transplantation.

The study will address such unresolved questions as: Will early treatment be able to modify long-term outcome in terms of the progression of liver disease ? Will antiviral treatment have an impact on extrahepatic HCV-related diseases or the natural history of other viral coinfections?

Will alternative approaches be needed in patients with coexisting conditions such as kidney failure, hepatic decompensation, in patients waiting for liver transplantation or those who have undergone a liver transplant, in the elderly, in those with previous failure with a DAA combination?

The PITER Study will be the backbone for further specific research studies and is expected to provide much needed guidance in evidence-based health policy for the better management of chronic HCV infection and for prudent resource allocation in order to guarantee equity in access to treatment.

Q. What is the research design and the state of the art of PITER study?

The cohort will consist of a representative sample of approximately 10,000 consecutive patients with chronic HCV liver disease who are undergoing clinical care in more than 100 public general hospitals and university medical centers in various regions of Italy. The follow-up of these patients is expected to last at least 10 years. The bespoke electronic data-collection system covers all clinical and therapeutic aspects of chronic HCV infection. The first round of enrolment began in May 2014 and continued for 6 months. Enrolment will be re-opened regularly for three-month periods during the spring and fall of subsequent years in order to keep up with the changing epidemiological situation and with the introduction of new DAAs and new combinations. To date, 80% of the participating clinical centers have begun enrolment, and they have enrolled about 7500 patients.

Q. Is it worth implementing this study design in low-income countries in Europe?

The burden of disease due to chronic viral hepatitis constitutes a global threat. Unlike most West European countries, in many East European countries particularly in Balkan countries, the burden of chronic liver disease due to hepatitis B and C is increasing due to ageing of unvaccinated populations and migration, and a probable increase in drug injecting. However, in many of these countries the disease burden due to viral hepatitis remains largely unrecognized due to a lack of reliable epidemiological data. Addressing the burden of viral hepatitis in low-income countries will require national commitments in the form of strategic plans and further actions at European and international levels. Research in this field should be used as an instrument and should be oriented to guiding health policy appropriateness for identifying issues and prioritize them through scientific evidence. Research platforms like PITER could be successfully implemented in these countries in order to address the fundamental epidemiological information needed to support further hepatitis actions plans not only at national but also at European level.

Stefano Vella M.D.

Director: Department of Pharmacological Research and Medicines Evaluation

Chair, HIV, Hepatitis & Global Health Group

Istituto Superiore di Sanità (ISS),
Viale Regina Elena 299 - 00161 Rome - Italy

Email: stefano.vella@iss.it

Extrahepatic manifestations of hepatitis E virus (HEV)

Harry R Dalton M.D.
Royal Cornwall Hospital and University of Exeter, Truro, UK

Q. Dr Dalton what is the burden of HEV worldwide?

Hepatitis E is the commonest cause of acute viral hepatitis worldwide. It is a significant health issue in developed countries, particularly Africa and Asia, where it is estimated there are 20 million infections and 70,000 deaths per annum. In these geographical contexts, hepatitis E is caused by HEV genotypes 1 and 2, which are obligate human pathogens spread oro-faecally by infected water.

Q. Is HEV a concern in Europe and how is it transmitted ?

Over the last 10 years, locally-acquired hepatitis E has been found to be common in developed countries, including Europe. Here hepatitis E is a porcine zoonosis caused by HEV genotypes 3 (and 4), spread mostly by consumption of infected pork meat products present in the human food chain and occasionally from human to human by infected blood products. Hepatitis E usually causes an acute self-limiting hepatitis mainly in older males, but patients with underlying chronic liver disease have a mortality of 27%. In the immunocompromised, including transplant recipients, hepatitis E can develop into a chronic infection which untreated leads to rapidly progressive cirrhosis.

In developed countries, recent data suggests that locally-acquired hepatitis E is a very common infection. For instance, the incidence of hepatitis E in England has been calculated at 100,000 infections per annum. This very high figure suggests that most (>90%) infections are asymptomatic. However, some patients with hepatitis E present in unusual ways, including a range of extra-hepatic manifestations, which would not necessarily prompt a clinician to consider HEV as a diagnostic possibility

Q. Is the liver the only target of HEV?

There are a range of reported extra-hepatic manifestations of hepatitis E reported in the literature, mostly as case reports/ small case series. In the vast majority of these, although there is a temporal relationship between the extra-hepatic syndromes described and the onset of hepatitis E infection, causality remains to be established. The best documented extra-hepatic association of hepatitis E is with a range of acute neurological injury (table).

To date, there have been over 80 cases of neurological injury described in the literature in association with hepatitis E infection. This includes meningo-encephalitis (n=12), neuralgic amyotrophy (brachial neuritis, n=20) and Guillain-Barré syndrome (n=36). Most (n=74) occurred in association with acute infection, and have been documented in both developed countries in association with HEV genotype 3, and developing countries where HEV genotype 1 is hyperendemic.

Q. Is there any special feature of HEV-related neuropathy ?

In developed countries patients with hepatitis E and associated neurological injury appear to be younger (median age 40 years) compared to patients without neurological involvement (median age 63 years). Of the 12 cases of HEV-associated encephalitis/ meningo-encephalitis/transverse myelitis, 7 were documented in Europe, 4 in Asia and 1 in the USA. The median age was 42 years and seven of the patients were male. Five of the cases were in immunocompromised patients with chronic infection: such patients appeared to be more likely to demonstrate a prominent ataxic component to their neurological symptoms, and had a poorer outcome. Two of these patients died. Patients generally had a modest hepatitis. HEV RNA was documented in the CSF in six cases, and in one there was significant divergence in sequence homology of HEV RNA found in the serum and CSF. This 'compartmentalisation' of HEV suggests that certain quasispecies of HEV might be neurotropic.

The 20 cases of HEV-associated brachial neuritis have all been documented from Europe in association with HEV genotype 3. The median age of the cases was 43 years, and all but one were male. Most cases were not jaundiced with an ALT <600iu/l. In contrast to non-HEV associated brachial neuritis where the neurological symptoms and signs are predominantly unilateral, it seems that patients who develop this syndrome in association with HEV have bilateral shoulder involvement, and may be more likely to have long term neurological disability. In addition, phrenic nerve involvement is common in HEV-associated cases. Brachial neuritis is thought to be an uncommon condition, with an incidence of 2-3/100,000. However, recent data from General Practice in the Netherlands suggests the incidence is much higher: 1 in 1,000, and that most cases are misdiagnosed as musculoskeletal injury.

Q. Is HEV involved in Guillain Barre syndrome?

Guillain-Barré syndrome is a post infectious immune mediated polyradiculopathy. Campylobacter jejuni is the infective trigger in about a third of patients. In 50% the infectious trigger is uncertain. Approximately 30% of patients with Guillain-Barré syndrome have abnormal liver function tests at the start of their illness, for unknown reasons. Cases of HEV-associated Guillain-Barré syndrome have been described in Europe and Asia, and all but one was immunocompetent. Seventy two percent were males with an age range of 2 -72 years. A Dutch case control study of 201 patients showed that patients with Guillain-Barré syndrome were significantly more likely to HEV infection at the start of their illness (n=10) compared to controls (borderline positive result, n=1). The patients with HEV-associated Guillain-Barré syndrome were not jaundiced and in some cases the ALT was normal. Their clinical course was indistinguishable from cases not associated with HEV.

The above data show that HEV-associated neurological injury is an easy diagnosis to miss. In most cases the neurological injury dominates the clinical picture, patients are usually not jaundiced and may have only a mildly raised or normal ALT. Clinicians should therefore have a low threshold for HEV testing in patients presenting with any acute non-traumatic neurological injury and abnormal LFTS. In my view, all cases of brachial neuritis and Guillain-Barré syndrome should be tested for HEV, irrespective of their LFT results.

Continued on page 6...

Q. Is the relationship between HEV and the associated neurological syndromes causative?

The answer is my view is: 'case not completely proven, but almost certainly yes'. The best evidence for this is the Dutch case-control study outlined above. Other evidence supporting causality includes: the temporal relationship between HEV infection and the onset of neurological injury; recovery of HEV RNA from the CSF, with quasispecies compartmentalisation in some cases; a temporal relationship between HEV clearance (from serum and CSF) and neurological recovery in a patient with chronic HEV and peripheral neuropathy. The neuropathological mechanisms are currently uncertain. Our neurological colleagues favour a post-infectious immune-mediated hypothesis which fits with the existing paradigm in Guillain-Barré syndrome. However, this is not quite congruent with the fact the HEV has been recovered from the CSF in some cases, nor the very recent data from colleagues in Hannover (presented in abstract form at ISHVLD in Berlin in June) which shows that HEV grows very well on neurological cell lines. Only a very small number of patients with HEV-associated neurological injury have been treated with early-intervention anti-viral therapy. The efficacy of such treatment remains to be established.

During the course of my studies on HEV-associated neurological injury, it has been a pleasure and privilege to get to know and collaborate with a number of neurologists from across the globe. One such is Bart Jacobs, who is a very eminent neurologist from the Netherlands, the world's leading expert on Guillain-Barré syndrome and one of the smartest guys I have ever met. Three years ago I visited him in Rotterdam to write up a couple of papers which subsequently appeared as back-to-back papers in the journal Neurology. When we finished our work, we sat down to dinner. Over dinner, Bart asked me the following question: 'Harry, has HEV been misnamed? These patients have a profound neurological injury, but not much of a hepatitis'. My response was: 'Bart. That's a very provocative, but interesting question'.

Harry R. Dalton M.D.

Cornwall Gastrointestinal Unit,
Royal Cornwall Hospital Trust,
TR1 3LJ Truro, UK.

E-mail: harry.dalton@rcht.cornwall.nhs.uk

Report on launch of a hepatitis E vaccine in China

Ting Wu PhD and Jun Zhang M.Sc,
State Key Laboratory of Molecular Vaccinology and Molecular Diagnostics,
National Institute of Diagnostics and Vaccine Development in infectious diseases,
School of Public Health, Xiamen University, Xiamen, Fujian Province, 361102 China

Along with the improved sensitivity and specificity of Hepatitis E diagnostics, awareness of hepatitis E has increased a lot all over the world. Hepatitis E virus (HEV) is now the leading cause of acute viral hepatitis. In China, the annually reported number of new acute hepatitis E cases gradually increased from 16,444 in 2003 to 29,202 in 2011, and similarly the sales of anti-HEV IgM rose from 378,000 tests in 2003 to 6,096,000 tests in 2011. Although more clinical sites started to consider HEV infection as a diagnosis of hepatitis-like symptoms, the fact that the sales of anti-HEV IgM tests are much lower than those of anti-HAV IgM tests in China and that there is still no commercialized hepatitis E diagnostic reagents on the United States' market, would suggest that the disease burden of hepatitis E is most likely still underestimated.

The clinical spectrum caused by HEV infection ranges from asymptomatic infection, acute hepatitis to fulminant liver failure. For immunocompetent adults, the disease is usually self-limited, while HEV infection is more threatening and may be a cause of severe disease in some special populations. The mortality after HEV infection in pregnant women, especially in the third trimester of pregnancy, is as high as 20%. And for patients with underlying liver disease, superinfection with HEV could cause fulminant liver failure. Chronic hepatitis E infection has been reported in immunocompromised patients, such as solid organ transplant patients or HIV carriers. Recent studies in Europe show that HEV is also associated with neurological syndromes including Guillain-Barré syndrome and neuralgic amyotrophy.

There are four genotypes of HEV which can infect human beings and fortunately they belong to the same serotype, which means a hepatitis E vaccine originating from one genotype can protect from infection in all of the 4 HEV genotypes. Although many efforts were made to develop an effective hepatitis E vaccine and two vaccines were tested in clinical trials, only one hepatitis E vaccine (HEV 239 with trade name Hecolin®, Xiamen Innovax Biotech, China) was licensed in 2011 for use in people aged >16 years and has been available in China since 2012.

HEV 239 is an E.coli expressed recombinant vaccine containing HEV capsid antigen of 239 aa originated from ORF2 aa 368 – 606 of HEV genotype 1. The efficacy and safety of HEV 239 was mainly evaluated in a large-scale phase 3 clinical trial in China, which enrolled 112,604 participants aged between 16-65. The participants were randomly assigned to receive 3 doses of 30 μg of

Continued on page 7...

HEV 239 vaccine or the control hepatitis B vaccine at 0, 1, and 6 months. Acute hepatitis patients were identified through an active surveillance system comprising 205 sentinel sites, including almost all the local community, private clinics, and hospitals in the city.

Acute hepatitis E patients were diagnosed by fulfillment of three criteria: 1) hepatitis-like symptoms such as fatigue or loss of appetite lasting for at least 3 days; 2) abnormal ALT levels of 2·5-times ULN (the upper limit of normal range) or greater; 3) at least two of the three virological markers (anti-HEV IgM, RNA, ≥4-times increase in anti-HEV IgG level) were positive. In the per-protocol analysis (of participants who received 3 doses of vaccine and had no important violation of the protocol), 15 participants were diagnosed with hepatitis E during the 12 months started one month after the full vaccination course, all of them were in the control group and reflecting vaccine efficacy of 100% (95% CI: 72.1–100). Another 33 cases (30 in the control group and 3 in the vaccine group) were diagnosed in the subsequent 3 years of follow up, so the long-term vaccine efficacy was 93.3% (95% CI: 78.6–97.9) in the 4 years after the 3 doses. In the intention-to-treat analysis (of participants who received at least one dose), the vaccine efficacy was 86.8% (95% CI: 71.0–94.0) during the 4.5 years following the first dose.

Two or three doses of HEV 239 vaccine can also effectively decrease the risk of asymptomatic HEV infection, while one dose does not seem to. The efficacy against HEV infection, which was revealed by anti-HEV IgG seroconversion or ≥4-times increase of anti-HEV IgG level in paired serum collected at one year interval, was 77% (95%CI, 65.3–84.7) in 2 years in the ITT analysis.

The HEV 239 vaccine was well tolerated in all the pre-licensing clinical trials, most of the reported adverse events were mild and recovered quickly. No vaccine-related serious adverse events were reported. In the phase 3 clinical trial, 2645 subjects were included in the reactogenicity subset and were actively monitored by the investigators at 6 h, 24 h, 48 h, 72 h, 7 days, 14 days, and 28 days after each dose, the rate of solicited local adverse reactions reported in 72 h after each dose was 13.5% (HEV 239 group) vs 7.1% (control group) ($p<0.0001$), mainly attributed to pain, swelling and itching. The recorded systemic adverse events were similar for both groups (20·3% vs 19·8%). Rates of reported serious adverse events were similar in the two groups during the 4.5 years of follow up after the first vaccination.

Limited data relating to the safety of HEV 239 vaccine for pregnant women was carefully reviewed. In the phase 3 clinical trial, 68 pregnant women inadvertently received the HEV 239 vaccine (37 women) or the control vaccine (31 women). Reported adverse events were very rare in these people after vaccination. The weights, lengths and gestational ages of the born babies to the mothers in the two groups were comparable. Immunogenicity and safety of HEV 239 vaccine in hepatitis B virus (HBV) carriers were retrospectively analyzed in the phase 3 clinical trial, and there were no statistical difference between the HBsAg positive and negative cohorts.

Hecolin has been licensed in China for use in people aged >16 years. Those who are at greater risk for severe disease following HEV infection should be the primary target population of this vaccine, including women of childbearing age, patients with pre-existing liver disease, immunosuppressed persons and travelers to HEV endemic areas. Although, more data relating the immunogenicity and safety of HEV 239 vaccine in people older than 65 years, pregnant women, in patients with pre-existing liver disease, the cross protection of HEV 239 vaccine against HEV genotype 2 and 3, remains to be collected, hepatitis E is now a vaccine-preventable disease. Efforts should be made to expedite the availability of the vaccine in other HEV endemic countries outside China.

Prof. Jun Zhang M.Sc

Deputy Director: National Institute of Diagnostics and Vaccine Development in infectious diseases

Xiamen University,
Xiamen, Fujian Province, 361102
China

E-mail:zhangj@xmu.edu.cn