Daily News

Modern Hepatology

25th Conference of the Asian Pacific Association for the Study of the Liver

The Japan Gastroenterological Endoscopy Society · The Japan Society for Portal Hypertension · The Japan Society of Hepatology · The Japanese Liver Transplantation Society · The Japanese Society of Gastroenterological Surgery · The Japanese Society of Gastroenterology · The Liver Cancer Study Group of Japan · The Organization of JDDW

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Inside

Today

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Hepatology Keeps Moving into the Future

APASL has become one of the leading scientific conferences in hepatology. All of us, including the patients, have been contributing to its development. Today, APASL2016 will come to a successful close. As the President of APASL 2016, Dr. Osamu Yokosuka must have been the busiest but the happiest person during the 25th APASL meeting. He told APASL Daily, “the APASL meeting is a very big meeting. The majority of the world’s patients with liver disease live in the Asia-Pacific region, so for us, liver diseases are very important. We have to conquer hepatitis for our own Asian-Pacific population and to benefit everyone in the world.” This is what makes APASL attractive and unique to him.

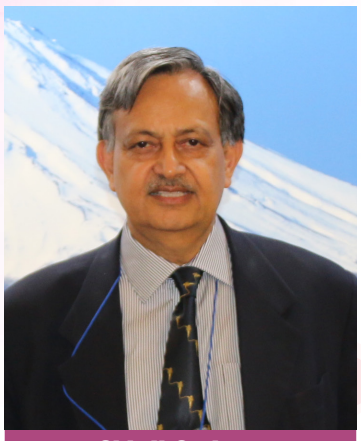
He also explained his reasoning for the theme of APASL2016 - “Modern Hepatology”. Technology and methods of therapy have progressed and there are a lot of new developments. For hepatitis C, the direct-acting antiviral agents have become available and many HCV patients are being cured and many more will be cured. With regard to HBV, we have new agents together with interferon that allow us to control hepatitis B and we can stop the progress of disease. The other area is non-HBV/HCV NASH, which has increased in prevalence due to economic and social changes in the Asia-Pacific region. There are more patients developing NASH than was anticipated and we have to conquer this condition. Lastly, although we have drugs like sorafenib for hepatocellular carcinoma, we have to consider new therapeutics and new approaches to treatment of this cancer. That is why we have used the theme of “Modern Hepatology”.

As a wrap up of APASL2016, Dr. Yokosuka believed that we needed to get the message out to the Asian-Pacific community that hepatitis C is curable. Also, we are accumulating new knowledge about HBV, so spreading the word about new advances there is one of the tasks of APASL2016. Although it will be difficult for us to eradicate HBV due to persistent cccDNA in the liver, it is very important that we continue to work to eliminate the virus entirely from the body. Work in that area is a highlight and important message of this meeting.

At the end of the interview, Dr. Yokosuka expressed his best wishes for APASL2017 in Shanghai. “Dr. Jinlin Hou will be the President of the APASL2017 meeting in Shanghai. There are a lot of HBV infected patients in China, so the treatment of HBV as well as HCV will be a focus of APASL2017. I hope the APASL2017 Annual Meeting will be very successful under the leadership of Dr. Hou.”

Portal Vein Thrombosis in Cirrhotic and Non-cirrhotic Liver

Interview with Dr. Shiv K. Sarin, President of APASL 2004



Shiv K. Sarin

1 APASL Daily: What are the major risk factors for the development of portal vein thrombosis (PVT) in cirrhosis and non-cirrhosis?

Dr. Sarin: PVT in non-cirrhotics is mainly because of hypercoagulable states which are genetically determined, like being procoagulant. Besides genetic factors, local factors and systemic factors like dehydration or pancreatitis can precipitate PVT in non-cirrhotics. But in cirrhotic patients, PVT is a result of cirrhosis causing hepatic frugal flow (blood flowing away from the liver). Sluggish flow and high pressure in the liver leads to thrombosis. Also, tumor thrombi can occur. So the most important cause is hemodynamics in patients with cirrhosis and in non-cirrhotics it is procoagulant factors. Thrombosis can be acute or chronic. Chronic thrombosis is generally because of infections.

2 APASL Daily: What progress has been made in the diagnosis and treatment of PVT in recent years?

Dr. Sarin: The diagnosis of PVT has improved with the use of ultrasound Doppler and contrast-enhanced CT scans. With the Doppler, you can see where there is no or sluggish flow, and with the CT scan you will see causative material in the portal vein. There are also certain blood tests which indicate procoagulant factors. Sometimes myelodysplastic syndrome is present and a bone marrow biopsy is needed to find out if the patient has a hypercoagulable state.

In treatment also, there are many advances. If patients have a procoagulant state (i.e. hypercoagulable), they are given continuous lifelong anticoagulation starting with drugs like enoxaparin and continuing with oral drugs. In those patients with no procoagulant factors, we give them three to six months of therapy and try to recanalize. In acute thrombosis of the portal veins, it may be required to implant a stent. The stent can extend from the portal vein to the hepatic vein. A catheter can also be placed in the portal vein by instilling urokinase. There are new drugs called inhibitors of thrombin, which are very effective and can be used in all liver disease patients, but have not been fully evaluated. If the PVT is recognized early, prognosis is improved.

The most important thing is, in cirrhotics who are on a transplant list, 50% of these patients will have thrombosis of the portal vein. If we dissolve this thrombus, the patient's ascites and jaundice may improve to the point of perhaps not requiring a transplant.

It has been shown that long-term survival improves if you give anticoagulants. Our own group has shown that giving anticoagulants is safe. If a patient has varices and portal vein thrombosis, I would suggest first blocking the varices and eradicate them and then start with enoxaparin and later switch to Acitrom (nicoumalone) or warfarin to resolve the thrombus. These patients need to be monitored every three to six months. At the end of one year, about 50% resolution of thrombosis can be achieved.

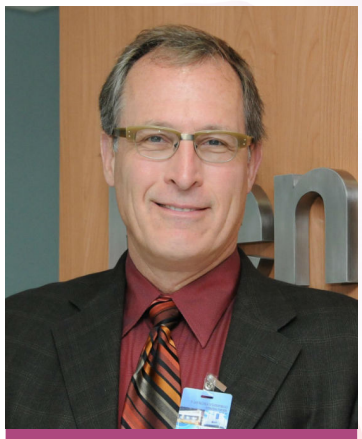
3 APASL Daily: What is the role of growth factors in the treatment of liver failure?

Dr. Sarin: In liver failure, regeneration is slow. Normally in acute liver failure, the hepatocytes can replicate by themselves. But in cirrhosis with liver failure (acute-on-chronic liver failure), the hepatocyte regeneration is very weak, so progenitor or resident stem cells are required. To stimulate them, we give growth factors which work on the bone marrow, like G-CSF or erythropoietin, and they mobilize cells from bone marrow like CD33-positive or CD34-positive cells, and those work in the liver to stimulate regeneration. In two large studies published by our group in 2012, in acute-on-chronic liver failure, patients given G-CSF every day for five days and every alternate day for the rest of the month (a twelve-dose schedule), showed improved survival compared to placebo (69% vs. 30%). A second study used two growth factors, G-CSF plus darbepoetin, in cirrhotics who were on transplant lists. Giving growth factors decreased the chance of infection from about 35% to 5% and also improved survival. This was published last year in Gastroenterology. So growth factors are very important for managing liver failure and improving liver regeneration.

4 APASL Daily: Next year's APASL annual conference will be held in Shanghai, China. What are your hopes for that meeting?

Dr. Sarin: China is the most populated country in the world with a very heavy burden of liver disease and consequently the best liver experts are in China. With Professors Jinlin Hou, Lai Wei and Ji-Dong Jai, you have the best three people in Asia to lead the liver disease field. The 2017 meeting has my fullest support and I am sure attendance in Shanghai will exceed 6000 people and I would predict that it will be a most memorable congress. In 2018, APASL will be in New Delhi and we invite all the Chinese hepatologists to attend our meeting also. My best wishes to Jinlin Hou and to China.

New Endpoints in HBV Drug Development



Robert G. Gish

Chronic hepatitis B (CHB) is the world's most common serious liver infection and is a widespread global health issue that is under-diagnosed and under-treated. Although hepatitis B virus (HBV) infection is not currently curable, it can be effectively controlled using pegylated IFN-α (PegIFN-α) and/or nucleos(t)ide analogue antivirals (NUCs). The next steps in the HBV therapeutic strategy are towards the cure of HBV infection according to Prof. Robert G. Gish, Stanford University, USA.

Right now, the antiviral regimens are limited for the strategy of HBV elimination.

PegIFN-α has the advantage of a fixed duration of therapy with the option of response-guided therapy based on HBsAg levels and can be an ideal option for some patients with high ALT and medium to low HBV DNA, but the rate of HBsAg seroconversion is lower than 20%. Entecavir and tenofovir treatment is indefinite for most patients but maintains extended virologic control over several years resulting in histologic improvement. There is also evidence that hepatic cccDNA levels can be modestly decreased with NUC therapy but without achieving cccDNA clearance.

The success of long-term NUC treatment prompts new questions for future HBV treatment strategies.

We can say "yes" to all these questions, Prof. Robert G. Gish said optimistically. It is possible to permanently eliminate HBV infection with therapies that specifically target the cccDNA pathway and we be aiming to achieve a "functional cure" using HBsAg elimination as an endpoint and thus, the ultimate maker that we are changing outcomes. We will have a new role for HBV RNA and HBcrAg testing and there will be new technologies for FNA and liver sampling for cccDNA and intracellular intermediates of HBV replication, including HBV pregenomic RNA (pgRNA) and mRNA testing.

The next step for antiviral therapy: new technologies and new anti-viral tools.

The new technologies and anti-viral tools include: iRNA, anti-sense, blocking viral entry, inhibiting viral release, using cellular mechanisms of viral replication such as cyclophilins, capsid inhibitors, and immune modulators including PD-L1 antagonists, TLR-7 agonists, Tarmogen-based vaccines, vaccines with adjuvants and extended preS1 epitopes; as well as attacking the virus in the nucleus using CRISPR/Cas9, changing histones, and acylation patterns are all new milestones towards the elimination of HBV infection.

The steps towards eliminating HBV.

"For the strategy of HBV elimination with anti-viral therapy, we are on the path and next need to clear HBsAg, then clear cccDNA, and finally clear all cells with HBV DNA integration and prevent HBV integration from occurring in those patients with early phases of disease", said Prof. Gish.

The new concept of HBV therapy is usage of new combination therapeutic tools in combination and sequence.

The new Guidelines from APASL, AASLD and EASL will guide current therapy, but we need to further suppress the virus, stop the regeneration of cccDNA and awaken the host immune system so it will ultimately have the final "word" in viral control and clearance. The new therapies need to target multiple sites in the HBV genome and/or the immune system. The major concept moving forward with HBV therapeutics is the use of new combination therapies, and/or new therapies in sequence.

Prof. Gish concluded that it will be very exciting that we will have the chance to achieve a cure for HBV infection in our lifetime.

Screening, Novel Treatment Modalities and Multidisciplinary Teams for HCC

Massimo Colombo

Dr. Massimo Colombo is Professor of Gastroenterology at the University of Milan, Italy. Yesterday, he addressed the issue of Treatment of Advanced HCC in BCLC B/C Patients. After that, he shared his opinions on some interesting topics in the management of HCC with APASL Daily.

1 APASL Daily: What are the main difficulties that currently exist in HCC research?

Prof. Colombo: First of all, I think that we need to develop screening methods that can be used in the general community. Currently, we screen patients for the risk of cancer that are represented either in the patient populations or attending hospitals. We need to bring surveillance for liver cancer into the community and to do this we need to develop predictors of liver cancer that can be obtained through urinalysis or blood tests.

2 APASL Daily: When we talk about cancer targeted therapy, we must first be clear about its pathogenesis. In recent years, what important progress has there been in the field of the pathogenesis of HCC?

Prof. Colombo: Currently, we have only one targeted therapy that works in patients with advanced cancer and provides a survival benefit of three months only on average. The next step would be to develop treatment modalities, possibly by looking better at the stratification of our patient populations and, in this respect, I believe the studies in the molecular analysis of tumor compositions and possibly also development of combined treatment modalities might provide us with stronger medical therapies compared to what we have currently.

3 APASL Daily: Several studies found that some types of commonly used prescription drugs have the function of protecting against and preventing HCC, such as statins, metformin, and aspirin. What is your opinion in this regard? What kinds of patients would be likely to obtain benefit from these prescription drugs?

Prof. Colombo: Data indicating that these drugs might reduce the risk of liver cancer to some extent are flawed by many methodological problems. First there are several biases. Patients were recruited based on a diagnosis different from liver cancer or cancer risk. Secondly, treatment was not homogeneously pursued in all patients. And thirdly, most of these patient populations have received multiple drugs that might interact with each other, so the data presented in the literature provides an insight that some of these molecules may have an anticancer effect but there is no robust evidence that these drugs should be entering the therapeutic armamentarium of the hepatologists to prevent liver cancer in patients at risk.

4 APASL Daily: One of your talks is on the topic of treatment of advanced HCC in BCLC B/C patients. In recent years, more and more experts recommend multidisciplinary treatment (MDT), including systemic drug therapy. Can you introduce some important progress in the study of chemotherapy for HCC?

Prof. Colombo: Our own experience tells us that the multidisciplinary teams are essential to improve the management of the patient with liver cancer. They provide a more precise location of the patient populations to these specific treatment modalities and they also speed up the process of treatment allocation and delivery. As far as medical therapy of liver cancer is concerned, currently sorafenib is the only licensed drug and in our own experience, treatment with sorafenib requires expertise. So first of all, doctors should be trained to pursue therapy and to continue therapy even in the presence of adverse events and doctors should be trained to stratify patients according to the pattern of adverse events and reactions that may identify a subpopulation of patients who are refractory to sorafenib and need to consider second-line therapies.

5 APASL Daily: Are there any other experiences in HCC treatment you would share with the Asian-Pacific physicians and researchers?

Prof. Colombo: Frankly, most of what we learn about liver cancer comes from Asia - China and Japan particularly. I think that the multidisciplinary team is what our Asian colleagues should start and build up as a strategy to improve management of patients with liver cancer. Secondly, here in the Asian-Pacific region, there is still a long-standing tradition of hepatic resection to treat patients with liver cancer. By comparison, in Europe we switched to local ablative techniques. Resection of liver cancer is not only a very effective treatment modality, but also allows for the recovery of liver cancer tissue to undergo appropriate investigations, particularly in the area of molecular biology.

What to Watch Out for Today

CEV-HAP Symposium	
8:30-10:00	Room 1BC
Viral Hepatitis Policy Symposium	
-Hepatitis in the UN Sustainable Development Goals: How Can the SDGs Help Clinicians Advance Hepatitis Policy and Core in Asia Pacific?	
WHO Symposium	
10:20-12:20	Room 1BC
Early Release of New Recommendations from Updated Guidelines for the Treatment of Persons with Hepatitis C Infection	
Closing Ceremony	
12:20-12:40	Room 1BC

Achieving a Functional Cure for Chronic Hepatitis B: Challenges and Progress

Around 240 million people worldwide have been persistently infected with hepatitis B virus (HBV) and are at risk of end-stage liver diseases such as liver cirrhosis, liver failure and hepatocellular carcinoma (HCC). Currently available therapeutics for chronic hepatitis B (CHB) are mainly limited to nucleoside analogues (NAs) and interferon-α (IFN-α). These drugs reduce viral load and improve long-term outcomes, but rarely lead to a functional cure of CHB, currently defined as HBsAg seroconversion together with residual cccDNA existence. Failure to achieve such a "functional cure" of chronic HBV infection is linked with an inability to elicit an effective immune response that resembles acute resolved infection. Therefore, a "cure" strategy for chronic HBV infection has been proposed which would be dependent on the full restoration of an efficient immune response against HBV. The list of immunotherapeutic strategies against CHB under active investigation keeps increasing.

Cure of HBV infection is closely associated with HBsAg clearance

Drugs specific to the clearance of viral cccDNA are not yet available and are difficult to assay clinically. Therefore, clearance of HBsAg becomes one of the critical issues for the functional cure of CHB patients. HBsAg, a milestone discovery that was identified around 50 years ago by Nobel laureate, Dr. S Blumberg, is the hallmark of overt HBV infection.

Functional cure of CHB is dependent not only on the cccDNA/HBsAg inhibitors, but also on restoration of host anti-HBV immunity.

Basic and clinical studies have provided evidence to support the notion that the functional cure of chronic HBV infection is mostly dependent on the host immune responses against HBV.

The ideal host anti-HBV immune responses include rapid viral control, HBeAg seroconversion and HBsAg seroconversion. However, functional cure occurs in only 1-3% of patients per year with current NA or IFN antiviral treatment, which implies that efficient cccDNA/HBsAg inhibitors need to be identified or developed in future.

Current immunotherapies for CHB and unmet issues

Based on the most recent understanding of the immune mechanisms of chronic HBV infection, several immunotherapeutic strategies have been under investigation (Table 1). These immunotherapies target various immune components and present promising data for the future. They include as follows: (1) Targeting innate immune responses. GS-9620 working selectively with TLR-7, has the potential to induce prolonged HBV suppression and anti-HBV innate immune responses in chronically infected chimpanzees. Current data demonstrates that short and finite duration treatment with the oral TLR7-agonist GS-9620 can induce a sustained antiviral response in chronic HBV infection. (2) Targeting adaptive immune responses. Optimal immune activation of naive CD8 T-cells requires signal 1 mediated by the T-cell receptor, signal 2 mediated by co-stimulation and signal 3 provided by pro-inflammatory cytokines. On-going studies have indicated that increasing the three signals may rescue HBV-specific T-cell responses and could be clinically beneficial. Although engineering HBV-specific T cells through transfer of HBV-specific T cell receptors or HBV-specific CAR showed encouraging results in vitro and in animal models and might have potential, safety concerns, cost, and ethical issues related to viral vector use need to be addressed. (3) Blockade of co-inhibitory pathway. Some immunotherapeutic approaches, such as the blockade of co-inhibitory PD-1 and CTLA-4 pathways, have been put into clinical trials although their long-term efficacy needs to be confirmed.

Removing the HBV antigens or cccDNA in vivo

Both circulating HBeAg and HBsAg are postulated as possible immune-suppressing agents against host anti-HBV immunity. Therefore, efficient drugs that can clarify the HBsAg or cccDNA urgently need to be identified or developed.

Fusheng Wang

Challenges and prospectives

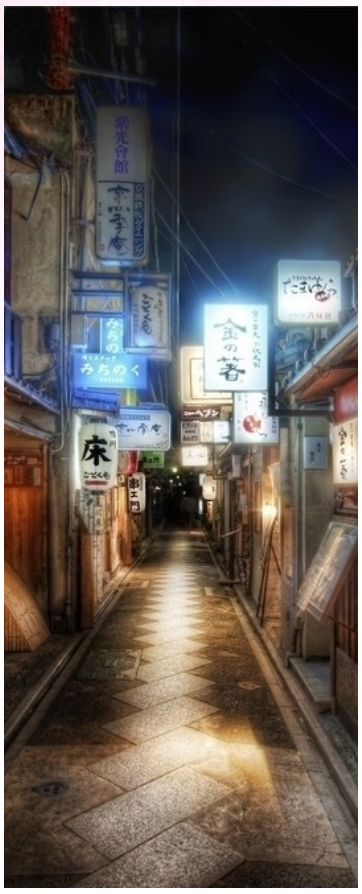
There are still many challenges in the field, even if efficient immune therapeutic approaches were available. For example, the optimal therapeutic approaches (how to combine different antiviral drugs and immunotherapies), the optimal timing and indications (which patient population is optimal for adding-on immunotherapy) and the optimal immunotherapeutic combination (boosting innate and adaptive immune responses particularly, the double-swords of immune responses) remain unknown.

(From: Fu-Sheng Wang, Treatment and Research Center for Infectious Diseases, Beijing 302 Hospital, Beijing, China. Email: fswang302@163.com)

Table 1. The current immunotherapeutic strategies on HBV infection

Immune Targets	Immune strategy	Phase
Innate immune responses	TLR-7 agonist	phase I
	NK cell adoptive transfer	preclinical
	IFN-α	clinical
	IL-12	lab
	GM-CSF	clinical
Adaptive T cell responses	Envelope-specific T cells-expressing chimeric antigen receptor	HBV transgenic mice
	TCR-electroporated T cells	clinical HCC
	TCR-like antibody targeting IFN-α	lab
	HBV-specific CD8 T cell reconstitution: blockade of Bim, modulation of co-inhibitory receptors (PD-1, CTLA-4, Tim-3) and modulation of inhibitory cytokines (TGF-β, IL-10)	lab
	Therapeutic vaccine	clinical
	Cytokine induced killer cells	clinical HCC
	DC vaccine	clinical
Adaptive B cell responses	GM-CSF+HBV Vaccine	clinical
	Antibody (anti-HBs)	clinical

Chronic Hepatitis B "Cure" - Still A Dream



The majority of HBV patients live in a chronic carrier statewith the risk of flaring up to progressive disease and hepatocellular carcinoma. Currently, the available approved treatment drugs are Peg-IFN-α and a few nucleoside/nucleotide analogues.

If the goal is to cure (functionally) chronic hepatitis B, then not only does there need to be normalization of a patient's ALT levels and reduction of serum HBV DNA levels, but also clearance of HBeAg and achievement of HBsAg seroclearance, ideally with anti-HBs antibody production. So can we achieve this "cure" with current drugs?

Fumitaka Suzuki, MD, Toranomon Hospital, Japan, tried to use data from four clinical trials to address that question.

The first clinical trial involved 615 Japanese CHB patients treated with IFN, with a median follow-up period of 8.1 years. The results shown that 11%(69 patients) achieved HBsAg seroclearance, and that status continued after more than 20 years follow up in some of these patients. According to Dr. Suzuki, it seemed that age >30 years, genotype A and male were all independent factors predictiveof achievement of HBsAg seroclearance.

The second trial concerned 22 CHB patients treated with Peg-IFN for either 24 weeks or 48 weeks and followed up for 5 years. In HBeAg-positive patients, 13%, 14% and 21% patients achieved HBeAg seroconversion at the end of 1, 3 and 5 years treatment respectively. In HBeAg-negative patients, the ALT normalization rates were 0%, 20% and 20%, respectively. One patient achieved HBsAg clearance at 3.5 years.

The third trial was 791 patients treated with LAM over a period of 12 years. Later on, 299 patients had ADV added on andpatients could also choose to switch from LAM to ETV. Five percent (38) of patients cleared HBsAg successfully. The overall cumulative rates of HBsAg clearance was 0.2% at 1 year, 1.2% at 2 years, 2.6% at 5 years and 6.4% at 9 years in the HBeAg-positive cohort. According to Dr. Suzuki, patients with previous IFN treatment and HBV genotype A baseline characteristics showed more favorable outcomes.

The last trial was 556 nucleos(t)ide naïve CHB patients treated with entecavir, and the results demonstrated that the cumulative HBsAg clearance rate was 3.4% at 5 years. The independent predictors of HBsAg seroclearance were genotype A patients and HBsAg level<500 IU/ml.

From the above convincing data, Dr. Suzuki has concluded that for majority of patients, clinical cure of chronic hepatitis B is not a reality yet.

Treatment of HCV in Developing Countries, Way to Go!

"Bangladesh is now on its way to becoming an example for other developing countries to overcome the challenge of eradicating HCV infection."

Globally, it is estimated that 130-170 million people are infected with HCV through different modes of transmission. With the population base in Asian-Pacific regions and with prevalence in certain countries ranging from 0.56%-11%, the absolute figures are still strikingly large in many developing countries in this region. The HCV prevalence in Bangladesh is 0.8%.

"HCV increases the risk of developing HCC 25-fold, causes 3-4 times more liver-related death than HBC and no vaccine is available, which makes HCV a silent killer in many developing countries", said Prof. Salimur Rahman, President of the South Asian Association for Study of the Liver and Chairman of the Viral Hepatitis Foundation Bangladesh.

The goal and endpoint of HCV treatment is to eradicate HCV virus, delay disease progression, and prevent complications and recurrence after liver transplant. In Asian-Pacific regions, the main HCV genotypes are 1 and 3, with genotype 3 the most difficult to treat.

In recent years, the treatment choice for HCV has evolved from peg-interferon alfa with ribavirin as the gold standard treatment to direct antiviral agents (DAAs), which has created the potential to cure the majority of HCV patients, even patients with decompensated cirrhosis.

The caveat to the newly established DAA drugs are their high cost; so high that even in developed countries there are accessibility and affordability problems, let alone for patients in developing countries.

Fortunately, from 2015, the generic versions of DAAs became available in some developing countries and Bangladesh is one of these lucky countries. From February of 2015, sofosbuvir, daclatasvir and ledipasvir have been made available in Bangladesh at much lower prices, according to Prof. Rahman.

For treating HCV patients without cirrhosis, there is the choice of sofosbuvir/daclatasvir (all genotypes), or ledipasvir/sofosbuvir (genotypes 1, 4, 5, 6) for 12 weeks without ribavirin. For treating HCV patients with cirrhosis, the choices are sofosbuvir/daclatasvir or ledipasvir/sofosbuvir without ribavirin for 24 weeks; or both regimens with ribavirin just for 12 weeks. For genotype 2, the choice is sofosbuvir/ribavirin for 16-20 weeks in Bangladesh.

For some special subgroups, such as patients co-infected with HBV or HIV, there is no need to change the regimen. And there is no need to change DAA dosages for patients with renal creatinine clearance between 30-80ml/min.

With most of the other developing countries still struggling with access to affordable DAA drugs, "Bangladesh is drawing focus worldwide with the availability of daclatasvir and ledipasvir most recently," stated Prof. Rahman. "Bangladesh is now on its way to becoming an example for other developing countries to overcome the challenge of eradicating HCV infection."

HCC and the Promise of Immune Therapy

Every thirty seconds, one person dies from liver cancer in the world and most people with HCC are not candidates for curative therapy when they are diagnosed. The recent success of immune-based therapies for other solid tumors offers new hope for targeting processes related to immune responses for the treatment of HCC. This was reported by Prof. Tushar Patel, Mayo Clinic, Florida, USA, at a lecture on the application of genome research for HCC treatment at 25th APASL conference on Feb 23rd.

The current treatments for HCC include surgery, local and regional therapies and systemic therapies. However, the available therapeutic options for advanced HCC treatment have limited efficacy. We need more effective treatments.

The immune system and HCC

The incidence of HCC is increased in immunocompromised individuals such as transplant patients or HIV infected patients, indicating the immune system plays a critical role in the carcinogenesis of HCC. However, because of its tolerogenic effects and unique immunobiology, the use of conventional immunotherapy is challenging in the liver. PD-1/PD-L1 interactions maintain the immune tolerance in HCC. Adaptive immune responses can occur during the formation of HCC, including DC, APC, etc. and adoptive immunotherapy can improve outcomes in HCC, Prof. Patel stated.

Future therapeutic strategies for HCC: the immunotherapeutic strategies

The immunotherapeutic strategies for HCC include cancer vaccines, monoclonal antibodies, checkpoint inhibitors, growth factors and cytokines. Immunotherapy trials for HCC conducted so far have had contrasting results. The results for the PD-1 inhibitor, nivolumab, in advanced HCC in promising with 62% overall survival at 12 months.

The potential approaches for HCC therapies could target both tumor cell specific antigens and immune cells. Synergistic anti-tumor activity may be observed when immunotherapy is used in combination with conventional treatment such as immunotherapy plus systemic therapies, or immunotherapy plus local regional therapies.

Prof. Patel concluded that targeting immunity offers new potential therapeutic approaches for HCC, and is very promising as a future treatment strategy for HCC.

Welcome Message

Jinlin Hou

Dear Colleagues,

We are delighted and honored to introduce you to the 26th Conference of the Asian Pacific Association for the Study of the Liver (APASL), which will take place in Shanghai, China. We will bring together a distinguished faculty of renowned specialists from the Asia-Pacific region and from around the world to this conference.

The APASL Annual Meeting has grown as the leading conference focusing on remarkable advances in liver disease, aimed at providing the latest scientific and evidence-based research results that will be applicable to everyday clinical practice. It provides an excellent opportunity to share and exchange experiences especially from the viewpoint of Asian-Pacific countries. These elements are essential to pave the way for the further development of hepatology.

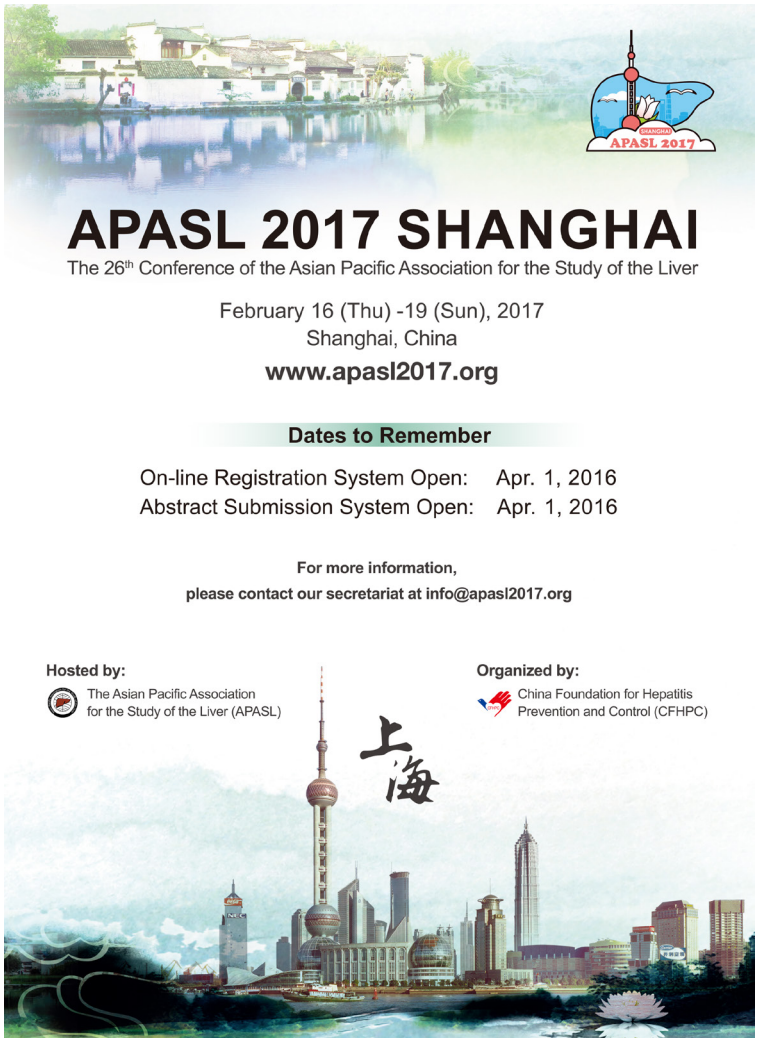
We plan to have a three-day core program to provide an overview of various liver diseases with the State-of-the-Art Lectures on hot-off-the-press issues. Additionally, Postgraduate Courses and Morning Sessions will be designed for the in-depth discussion of particular topics.

Free paper and poster presentations are always the soul of the conference to share research findings and there will be several awards available aimed at supporting young scientists to attend the conference and encourage scientific research.

We thus enthusiastically invite you to submit abstracts and join us at this conference as well as our blooming city, Shanghai.

We look forward to welcoming you in Shanghai!

Jinlin Hou, M.D., PhD
President, APASL 2017



Serial AFP Assay Deserves Attention in Acute Hepatitis Flare

Yun-Fan Liaw

In chronic HBV patients with episodes of acute hepatitis flare (defined as an event with an abrupt rise of ALT >5 times ULN), patients may progress to remission or may experience severe hepatitis or hepatic decompensation. According to APASL guidelines, patients should be monitored with 1-2 weekly measurements of serum ALT, bilirubin and prothrombin time.

So what kind of laboratory tests or prognostic factors could be effectively used to guide the management strategy? According to Prof. Yun-Fan Liaw, Liver Research Unit, Chang Gung Memorial Hospital, Taipei, China, serial AFP (alpha-fetoprotein) assays are the answer.

As early as 1974, Prof. Liaw had pioneeredthe monitoring of AFP levels in "chronic progressive hepatitis" and carried out studies to discover the relationship between AFP levels and what was once called "acute hepatitis-like" episodes, now acute hepatitis flare.

Prof. Liaw and other researchers found that when AFP was above 100 ng/ml with HBV patient flare, it reflected bridging necrotic hepatitis(BNH), which correlated to the extent of hepatolysis. But unlike ALT, AFP>100 ng/ml was significantly superior to ALT to predict HBeAg loss.

When HBV DNA and HBsAg declined before the peak of ALT, it suggested that the patient had effective immune clearance in a flare, and that the patient could just be observed for the next 3-6 months. If HBV DNA and HBsAg was stable or increasing, it suggested that the patient had ineffective immune clearance, and the patient may have liver function decompensation so needed treatment right away.

Recently, regardless of whether Peg-IFN, TDF/ADV, Peg-IFN/TDF or ETV/TDF antiviral regimens were used to treat HBV patients, studies have confirmed that hepatitis flares enhanced HBsAg decline. During a newly published ETV treatment study, it was found that HBsAg decline was dependent on AFP and ALT levels, with a stronger correlation to changes in AFP.

In short, AFP>100 ng/ml may serve as a surrogate marker for BNH, and AFP is superior to ALT as a factor for HBeAg loss, rapid HBsAg decline and possible HBsAg loss, according to Prof. Liaw.

"We used to rely on liver biopsy, an invasive method, to find out what is going on with the patient, but now we can just do an AFP test to see whether the patient has BNH, to find out if AFP>100 ng/ml, and then comes down. Otherwise, we need to be concerned about the patient's HCC risk, as AFP is also a liver cancer marker," said Prof. Liaw.