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

5℃

12℃

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Changes of APASL in 9 Years

As the President of APASL 2007, Professor Masao Omata hosted the 17th APASL in Kyoto. He told APASL Daily: "when I hosted APASL 2007 in Kyoto, the number of participants was 3000. But now we are expecting 4500 participants, and of course the main progress at this meeting is the treatment or the complete cure of hepatitis C virus infections. For HBV, we now have more drugs and we have more choices that may produce a very long lasting suppression of the virus without showing resistance. So over the last 9 years, there have been developments and drug discoveries, but we still struggle to treat hepatocellular carcinoma…"

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The Situation of Liver Diseases in Asian-Pacific Countries

Asian-Pacific countries are the major regions where various liver diseases, especially HBV and HCV associated liver diseases, occur and prevail. This area has gathered more than 75% of HBV and HCV carriers all over the world. And with the development of the economy situation in APASL countries, the prevalence of NASH (nonalcoholic steatohepatitis) and alcoholic liver disease may increase further.

See More on Page 4

For HBV/HCV Co-infection Patients in DAA Era, Treat the Viruses both!

Now hepatitis B and hepatitis C are the most important cause of chronic liver diseases in Asia-pacific region, especially China. Due to the similar mode of transmission, co-infection with HBV and HCV is common, especially in high-risk populations and in HBV endemic area. For example, co-infection of HBV in patients with chronic HCV infection has been estimated to be as high as 8.4% in Chinese. To date, no standard-of-care recommendation exists for HBV/HCV co-infection.

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Changes of APASL in 9 Years

Interview with Honor President Masao Omata

Masao Omata

1 APASL Daily: As the President of APASL 2007, you hosted the 17th APASL in Kyoto. What are your comments on the progress in liver disease treatment in that time and how will this conference be different from the 17th, both held in Japan?

Prof. Omata: When I hosted APASL 2007 in Kyoto, the number of participants was 3000. But now we are expecting 4500 participants, and of course the main progress at this meeting is the treatment or the complete cure of HCV infections. For HBV, we now have more drugs and choices which may produce a very long lasting suppression of the virus without resistance. So over the last 9 years, there have been developments and drug discoveries, but we are still struggling to treat hepatocellular carcinoma. There are some advances, but in the area of hepatocellular carcinoma, there are a couple of features that have not necessarily changed. We look forward to developments in immune modulatory cancer therapy which we can expect to come very soon. So I think there are some differences between 2007 in Kyoto and 2016 in Tokyo.

2 APASL Daily: Many studies have shown that treating patients with interferon-free direct-acting antivirals is cost-effective. However, all of those studies were performed in developed countries. What is the cost-effectiveness of interferon-free regimens compared with interferon-based regimen in low- or middle-income countries?

Prof. Omata: Regarding the cost-effectiveness studies of interferon-free direct-acting antivirals, it is true that these were mainly done in developed countries. However, because of the generic license, some of the underdeveloped countries can have very discounted or cheap drugs. So the very expensive drugs that costs $6000/year in Japan compares to only a few (20 to 30) dollars in other countries like Egypt or India. The cost-effectiveness calculation is very complex. There are some studies indicate that despite the high price, because it is a very efficacious treatment with nearly 100% cure of HCV infection, it has been concluded that it is cost-effective compared to the standards of developing countries.

3 APASL Daily: With highly potent oral antivirals available, could we expect an opportunity for the eradication of HCV worldwide?

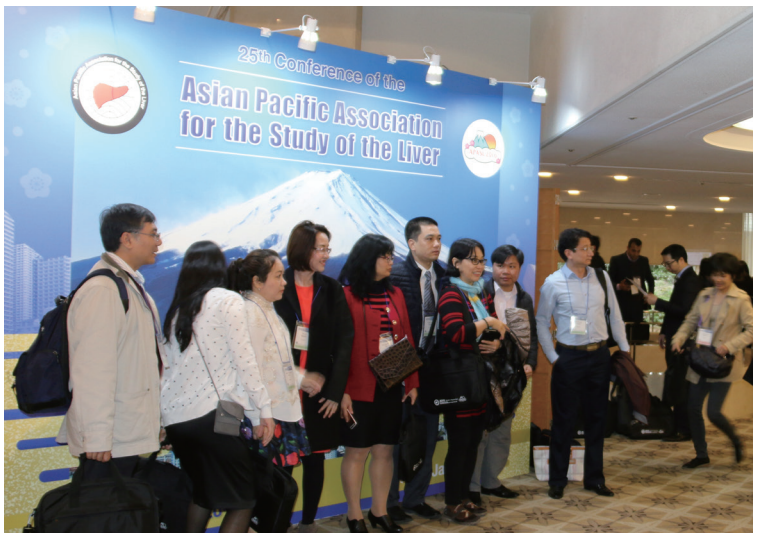
Prof. Omata: Yes, of course. The company Gilead already has generic licenses in 91 countries which could not afford these expensive drugs. In countries like the United States, European countries and Japan, we are treating patients and getting very successful eradication rates. In other countries like China, the drugs are very expensive and beyond the average income of Chinese patients. So maybe there are two extremes: one is the Western countries and Japan which can afford to buy these expensive drugs; and on the other hand, the countries like India, Indonesia or Egypt, where they are supplied with heavily discounted prices. So for China, I understand that it is facing a problem in terms of the cost of the drugs.

4 APASL Daily: What's the most significant barrier of HCV treatment in the Asia-Pacific area? How can we improve the accessibility of direct-acting antivirals in low- or middle-income countries?

Prof. Omata: Of course, the cost can be the barrier for the Asia-Pacific regions. But more importantly, the HCV infection is insidious, or it is a silent killer. In that context, many patients came to the clinics in the late stage with obvious symptoms, such as jaundice, bleeding or hepatic cirrhosis. So the screening of patients can be a barrier for the Asian-Pacific regions. In addition, education about the natural causes and transmission of HCV infection is lacking. Therefore, APASLare trying to update the APASL HCV guidelines at this meeting.

5 APASL Daily: What is the biggest highlight in the upcoming revision of the APASL HCC Guideline compared with prior ones?

Prof. Omata: There are several features in many HCC guidelines that do not necessarily fit the Asian patients. Amongst many of the guidelines, especially those from the Western countries, the treatment modalities differ due to economic reasons. Therefore, we are trying to revise guidelines to suit the Asian situation. Also, treatments like TACE are now becoming very popular amongst Asian countries. Therefore, we have more precise or more specific guidelines for treatments like TACE in Asian countries.



New Threat to Developed Countries: NAFLD-related HCC

As a Professor at the Department of Medicine, University of Indonesia, Jakarta, and the President of APASL2005 (15th, Bali), Dr. Laurentius A. Lesmana has made a significant contribution to the development of hepatology in the Asia-Pacific region. At APASL2016, he will share his experience on the treatment of HBV in Indonesia and will show us the emerging relationship between non-alcoholic fatty liver disease (NAFLD) and hepatocellular carcinoma (HCC).

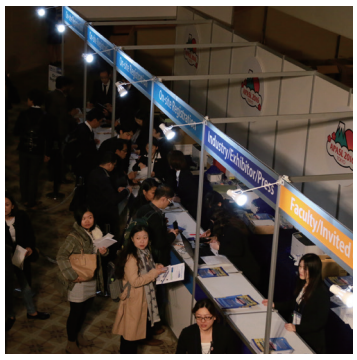
He told APASL Daily that in 2007, the prevalence of hepatitis B in Indonesia was around 9.4%, involved about 230 million people. A significant number of patients with chronic hepatitis B (CHB) received the infection via vertical transmission. HBV infection is also the most common etiology of hepatocellular carcinoma in Indonesia. Most physicians in Indonesia treating patients with CHB follow the guidelines of APASL, EASL or AASLD. The majority of patients with CHB preferred to use nucleos(t)ide analogues (NAs) in Indonesia , because the cost is significantly cheaper (especially the potent NA, tenofovir as a generic drug) compared to pegylated interferon and with far fewer side effects. In private practice, generic tenofovir is the most commonly used drug. Telbivudine is the only NA covered by the government. Combination of NAs and pegylated IFN is rarely used.

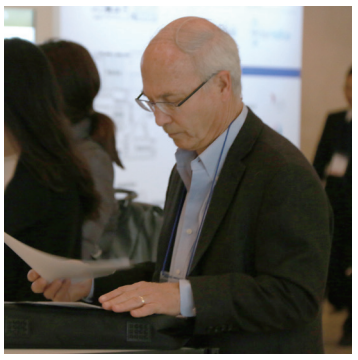
"In our experience, most patients who received pegylated IFN for 48 weeks relapsed at the post-treatment."

On the other hand, worldwide, liver cancer is the fifth most common cancer and the third leading cause of cancer death. Recently, HCC has been correlated to NAFLD. The exact prevalence of HCC in cirrhotic NAFLD remains unknown. According to Prof. Lesmana, about 6-13% of NAFLD cases may progress to cirrhosis and HCC. For NAFLD patients, diabetes and obesity are major risk factors for developing cirrhosis and HCC. NAFLD can develop directly to HCC probably through different pathways compared to cryptogenic cirrhosis. Studies by Prof. Lesmana and others collectively showed that in cirrhotic and non-cirrhotic NAFLD patients, the dimensions of HCC were larger in non-cirrhotic livers.

"The association between NAFLD and HCC is alarming due to the globally high prevalence of these conditions and may contribute to the rising incidence of HCC encountered in many developed countries."

Laurentius A. Lesmana





What to Watch out for Today

Presidential Lecture			
Room 1BC	08:45 - 09:00	The Situation of Liver Diseases in APASL Countries/HCV and HBV	Osamu Yokosuka
Lecture			
Room 1BC	10:45 - 11:05	Hepatitis B Treatment	Anna S. Lok
Room 1BC	11:05 - 11:25	Hepatitis B in EU	Patrick Marcellin
Room 1BC	11:25 - 11:45	Serum HBsAg and AFP Levels during Acute Hepatitis Flare of Chronic Hepatitis B: A New Look in the Natural Course and Antiviral Therapy	Yun Fan Liaw
Symposium 6. Novel Therapeutic Strategies for HBV			
Room 1BC	13:50 - 14:10	Curing Chronic Hepatitis B Depends on the Restoration of Integrative Immunity against HBV	Fu-Sheng Wang
Room 1BC	14:10 - 14:30	Innate Immunity in Hepatitis B	Stephen Locarnini
General Session 4. Treatment Towards HBsAg Clearance			
Room 1D	11:05 - 11:25	New Endpoints in HBV Drug Development	Robert G. Gish
Room 1D	11:25 - 11:45	Curing HBV-New Therapeutic Approaches	Alexander Thompson

The Situation of Liver Diseases in Asian-Pacific Countries and the Urgent Tasks for Beating HCV and HBV

Osamu Yokosuka

Asian-Pacific countries are the major regions where various liver diseases, especially HBV- and HCV-associated liver diseases, occur and prevail. This area accounts for more than 75% of HBV and HCV carriers globally. And with the development of the economic situation in APASL countries, the prevalence of NASH (non-alcoholic steatohepatitis) and alcoholic liver disease may increase further.

Major progress has been made in the study of HCV in recent years, and patients receiving those novel improved treatments have shown sustained viral responses. These inspiring results let us believe that HCV infection will be eradicated in the near future. However, contrary to the upbeat progress in HCV study, research in the field of HBV is quite different. Although the application of nucleotide analogues for suppressing HBV replication has exhibited optimistic results, the potential for complete eradication of HBV infection is still unlikely. After infecting the liver cells, the HBV virus can make cccDNA, which are special DNA structures that arise during virus propagation inside the cell nucleus and these may remain there permanently. HBV can also lead to hepatocellular carcinoma through the integration of its own DNA into the human genome. Although we have been able to control the inflammation of the liver cells after HBV infection as well as the replication of HBV, it is still difficult to eradicate the integrated viral DNA and the leftover cccDNA inside the liver cells.

In his presidential lecture, Dr. Osamu Yokosuka, the President of APASL2016 will give his insights on the situation of liver disease in Asian-Pacific countries and the urgent matters we are facing nowadays in the fight against HCV and HBV infection, and related liver diseases.

TOKYO

Presidential Lecture –
"The Situation of Liver Diseases in APASL Countries / HCV and HBV"
Room 1BC
9:30 – 10:30

Hepatitis B Treatment: Yesterday, Today and Tomorrow

Anna Suk-Fong Lok

This morning, Professor Anna Suk-Fong Lok from the University of Michigan, Ann Arbor, USA will give a lecture on the state-of-the-art of hepatitis B treatment.

Currently available therapies with nucleos(t)ide analogues (NAs) are effective in suppressing HBV replication and decreasing hepatic inflammation and over time can result in reversal of fibrosis and reduction in risk of HCC. However, they could not eradicate HBV and completely eliminate the risk of HCC. Thus, most patients need to remain on treatment for years and often for life to prevent virologic relapse and to derive continued benefit.

While the new NAs, entecavir and tenofovir are associated with very low risk of drug resistance, long-term therapy is expensive and associated with risks of adverse events and non-adherence. Given the limitations of NAs therapies, a major challenge in the management of patients with chronic hepatitis B is to determine when to start and when to stop antiviral therapy.

With improved understanding of HBV biology and host immune response, numerous new antiviral and immunomodulatory therapies are being developed and some are in early phase clinical trials. The challenge is to design efficient clinical trials to prove which of these new therapies is safe, efficacious and acceptable for patients with chronic hepatitis B.

TOKYO

Lecture 1 –
"Hepatitis B Treatment"
10:45 – 11:05
Room 1BC

For HBV/HCV Co-infection Patients in DAA Era, Treat Both of the Viruses!

George K. K. Lau

Currently, hepatitis B and hepatitis C are the most important causes of chronic liver disease in the Asia-Pacific region, especially China. Due to the similar mode of transmission, co-infection with HBV and HCV is common, especially in high-risk populations and in HBV endemic areas. For example, co-infection of HBV in patients with chronic HCV infection has been estimated to be as high as 8.4% in Chinese patients. To date, no standard-of-care recommendation exists for HBV/HCV co-infection.

In general, HCV can suppress the replication of HBV, probably via indirect immune mechanisms. Hence, eradication or suppression of HCV could lead to HBV reactivation. This has not been a big issue in the past when IFN was the main therapy for hepatitis C, because IFN can inhibit HCV and HBV simultaneously. However, successful treatment of chronic hepatitis C infection with pegylated interferon-α and ribavirin has been related to HBV reactivation in patients co-infected with both viruses.

"Up to 30% of patients co-infected with HBV/HCV might experience hepatitis flare after their HCV infections are controlled by DAAs."

But now with the use of pan-oral DAAs that solely target HCV (Professor George Lau and his colleagues are among the first and the largest group to make use of the brand name DAAs treatment of hepatitis C in China), HBV reactivation in HBV/HCV co-infected patients after cure of HCV should not be neglected anymore. At APASL2016, Professor George Lau, Humanity & Health Medical Centre, Hong Kong, Hong Kong SAR, China and his colleagues present a breakthrough finding of increased incidence of hepatitis due to HBV reactivation in HBV/HCV co-infected patients treated with pan-oral DAA therapy. Professor Lau told APASL Daily: "We see a phenomenon which has not been observed previously and that is HBV reactivation when the patients who are co-infected with both viruses and treated with DAAs for hepatitis C, the patient can have reactivation of hepatitis B. This is a novel observation and it is important that we notice this phenomenon and manage it appropriately."

They prospectively studied 355 consecutive CHC Chinese patients treated with 8-24 weeks of pan-oral DAAs. Among these patients, 10(2.8%)were HBsAg-positive. Eleven (3.1%) CHC patients suffered from hepatitis during DAA therapy at week 8, with three due to HBV reactivation (one of them developed liver failure). They also identified that not treating HBsAg-positive patients with anti-HBV NAs is the most significant factor associated with hepatitis in CHC patients treated with pan-oral DAAs (*HR*: 12.28, *P*=0.001).

Prof. Lau noted that up to 30% of untreated (by NAs) patients co-infected with HBV/HCV might experience hepatitis flare after their HCV infections are controlled by DAAs. In severe cases, hepatitis flare can even lead to liver failure. He thinks it is reasonable that in high HBV prevalence areas, all patients with hepatitis C get tested for HBV infection before DAA therapy is initiated. For patients with confirmed co-infection, anti-HBV therapy with potent NAs should start at the same time as DAA therapy.

"With HBsAg loss or seroconversion, it means that we are able to restore the host immune control of the virus."

Another thing Professor Lau will discuss in his lectures is how we are going to move forward beyond 2016 in terms of a cure for hepatitis B.

A cure would mean either a functional cure or a complete cure. A functional cure means HBsAg seroconversion or loss but then these patients can still be reactivated. A complete cure means a complete elimination of all viral DNA, even that which has integrated with the normal DNA, so the patient will be completely cured.

The current management for hepatitis B only controls but not cures the disease.

Most patients can get control of the virus with prolonged medication, such as treatment with entecavir and tenofovir, but we cannot take the patients off the drugs.

However, when a functional cure is achieved, the therapy can be stopped safely and the patient will not have the problem any more. In this regard, the only certain indicator to stop a patient's therapy is HBsAg loss or HBsAg seroconversion. The problem is that it is very difficult to achieve HBsAg loss or HBsAg seroconversion using current therapies with the nucleoside analogues or with interferon-based therapy. In order to improve this, many different approaches are under study, such as combinations of interferon plus entecavir or tenofovir and more promising new therapies.

Professor Lau said: " We have small molecules which block the viral replication cycles at different steps, such as the entry site, capsid and assembly, and to prevent the formation of cccDNA. On the other hand, we also have miRNA to interfere with the replication cycle. Also we have immune modulation methods, such as Toll-like receptors and therapeutic vaccinations, and there is also the very exciting TCR engineering of the T-cells because a functional cure can only happen when we restore the immune control of the viral replication gene. This is based on my paper published in *Gastroenterology* in 1994. We were the first group to make the observation that restoration of the host immune control of hepatitis B can result in a functional cure but these patients can still have reactivations because they still have cccDNA and this will be a very difficult task."

Professor Lau believes that in the next 5 to 10 years, we will be able to see new molecules coming into practice. At the same time, they are working on achieving immune control of viral replication.

TOKYO

Symposium 7:
Treatment of HBV for a Cure – "Nucleotide"
15:10 – 15:30
Room 1BC

Discovering Tokyo - Vintage & Natural

Tokyo (東京 , T ō ky ō) is Japan's capital and the world's most populous metropolis. Prior to 1868, Tokyo was known as Edo. A small castle town in the 16th century, Edo became Japan's political center in 1603 when Tokugawa Ieyasu established his feudal government there. A few decades later, Edo had grown into one of the world's most populous cities. With the Meiji Restoration of 1868, the emperor and capital moved from Kyoto to Edo, which was renamed Tokyo ("Eastern Capital"). Large parts of Tokyo were destroyed in the Great Kanto Earthquake of 1923 and in World War II. However, Tokyo was able to achieve a remarkably rapid recovery both times.

Today, Tokyo is one of the most populous cities in the world and a thriving center of economy, culture and industry. The city's history can be appreciated in districts such as Asakusa, and in many excellent museums, historic temples and gardens.

Senso-ji temple(浅草寺)

Sens ō -ji is Tokyo's largest ancient Buddhist temple and a major Tokyo attractions for Japanese and foreigners located in Asakusa.

The temple is dedicated to the Bodhisattva Kannon, also known as Guan Yin or the Goddess of Mercy.

It is Tokyo’ s oldest temple, and one of its most significant. Formerly associated with the Tendai sect, it became independent after World War II.

Meiji Jing ū （ 明治神宮)

Meiji Shrine is the Shinto shrine that is dedicated to the deified spirits of Emperor Meiji and his wife, Empress Sh ō ken.

To pay respect:

At a Torii (shrine archway): Bow once when entering and leaving.

At Temizuya (water well): Rinse your left hand then right hand. Then Rinse your mouth with your left hand before rinse your left hand again. Lastly rinse the dipper (allow the remaining water to run down the handle of the dipper).

At the Main Shrine building: Bow twice. Clap your hands twice. Make a wish if you like & Bow once again.

Nakamise (仲見世)

Located just before Sensoji after Kaminarimon or “Thunder Gate”, a massive paper lantern dramatically painted in vivid red-and-black tones to suggest thunderclouds and lightning, Nakamise is one of the oldest shopping centers in Japan.

Apart from typical Japanese souvenirs such as yukata, keychains and folding fans, various traditional local snacks from the Asakusa area are sold along the Nakamise.

Cherry blossom viewing (花見)

10 minute walk from Shinjuku Station, 200 yen, 9:00 to 16:30

Shinjuku Gyoen (新宿御苑) is one of Tokyo's largest and most popular parks. In spring Shinjuku Gyoen becomes one of the best places in the city to see cherry blossoms. Shinjuku Gyoen features more than one thousand cherry trees of over a dozen varieties.

Nucleos(t)ide or Interferon to Prevent HBV-related HCC?

Deepak Amarapurkar

Hepatitis B virus (HBV) infection is associated with the development of hepatocellular carcinoma (HCC) worldwide, and many studies have shown that the HBV DNA level is one of the most significant risk factors for the development of HCC in patients with chronic HBV infection. Nucleos(t)ide analogues (NAs) and interferons (IFN), the current standard of care for chronic HBV infection, could decrease the risk of HCC. This morning, Professor Deepak Amarapurkar from Bombay Hospital and Medical Research Centre, India will give a lecture entitled "Nucleotide or Interferon for the Treatment of HBV (Prevention of HCC)".

Currently there are 7 approved agents: two formulations of IFN (IFN, PEG-IFN) and five NAs including lamivudine, telbivudine, entecavir, adefovir and tenofovir. Advantages of IFN include a finite treatment duration associated with a higher percentage of HBsAg clearance compared with NA therapy, and it is especially effective in genotype A or B HBV infected patients with low viral load. The main disadvantages of IFN treatment are significant side effects and administration by injection, and it cannot be used in decompensated patients. Compared with IFN treatment, NAs can be administered orally without significant side effects and can be used in decompensated patients. However, the rate of HBsAg clearance with NAs is very low, so long-term treatment is necessary in most patients and the efficacy is significantly reduced with development of viral resistance.

Systemic reviews and meta-analysis have shown approximately 50-60% risk reduction for HCC with IFN or NA antiviral therapy. However, the risk of HCC couldn't be completely eliminated in patients with chronic HBV infection. Therefore, the patients need to be followed up for HCC surveillance lifelong.

TOKYO

General Session 1:
HBV Treatment in Various Countries 1 – "Nucleotide or IFN for the Treatment of HBV (Prevention of HCC)"
09:00 – 09:20
Room 1A

Don't Miss Tomorrow

8:50 - 10:30	Room 1BC
Symposium 9. Current Situation of HCC and ICC in Asian Pacific	
8:50 - 10:30	Room 1A
Symposium 10. Application of Genome Research for HCC Treatment	
8:50 - 10:30	Room 1D
Symposium 11. Update of HCC Treatment	
08:50 - 11:45	Room 2
General Session 7. Update of NASH/ASH Research	
08:50 - 10:30	Room 3
APASL-AASLD Joint meeting	
8:50 - 10:50	Room 3
ICA (International Club of Asscites)	
10:45 - 11:45	Room 1A
Symposium 12. Liver Regeneration	
10:45 - 11:05	Room 1BC
Lecture 4. Future Perspective of Hepatology	
10:45 - 11:45	Room 1D
Symposium 13. Recent Trend in HCC Treatment	
15:15 - 15:35	Room 1BC
Lecture 5. Disorders of Iron and Copper in the Asian Pacific Region	
11:05 - 11:45	Room 1BC
Okuda Oration - Acute on Chronic Liver Failure: APASL ACLF Research Consortium (AARC) - A Proud Asian Initiative	
13:35 - 15:35	Room 1A
General Session 8. Emerging Trends in NASH	
13:35 - 15:15	Room 1D
General Session 9. Mechanism of Liver Fibrosis	
13:35 - 15:15	Room 1BC
Symposium 14. Complication of Cirrhosis and the Treatment	
13:35 - 15:25	Room 7
CEVHAP-Delivering Health Services to Indigenous and Remote Communities	
15:50-17:10	Room 1BC
Critical Care in Hepatology	
15:50 - 17:30	Room 3
APASL-EASL Joint Meeting	
15:50- 17:10	Room 1A
General Session 10. Current Management of NASH	
15:50-17:30	Room 1D
Symposium 15. Cancer Stem Cell	

Innate Immunity in Hepatitis B: Killer and Protector

HBV has evolved a unique life cycle that results in the production of enormous viral loads as well as antigen loads during active replication without actually killing the infected cell directly, and the liver damage in chronic hepatitis B (CHB) is the result of the host's cellular immune response to HBV-infected hepatocytes as part of the "immune clearance" phase of the disease. This afternoon, Professor Stephen Locarnini from the Victorian Infectious Disease Reference Laboratory, North Melbourne, Australia will give a lecture on the topic of innate immunity in hepatitis B.

HBV has developed a number of strategies to ensure its persistence in the infected host, including the production of excess HBsAg and the expression of HBeAg. The HBeAg is a powerful modulator of the innate immune response by downregulation of Toll-like receptors (TLR), allowing viral persistence within the host. The N-terminal 10 amino acids of the HBeAg (precore protein) contains a Toll/interleukin-1 receptor (TIR) motif, blocking not only TLR-2, but also TLR-3, Mal, TRIF and TRAM signaling, thereby inhibiting both NF-κβ and interferon (IFN)-β activation. Likewise, HBsAg inhibits TLR-9 mediated activation and IFN-α production in plasmacytoid dendritic cells. Thus, HBV could effectively suppress type I IFN responses in hepatocytes.

The cccDNA is found only in infected hepatocytes and as a minichromosome. The HBcAg protein is a key structural component and positive regulator of the minichromosome. Both IFN-α and lymphotoxin β-agonists can activate APOBEC 3A/3B and results in selective (APOBEC-HBV core interaction) HBV cccDNA degradation following cytidine deamination.

Because HBV uses reverse transcription to copy its genome, mutant viral genomes emerge frequently. Particular selection pressures, both endogenous (host immune clearance) and exogenous (vaccines and antiviral drugs), readily select out these escape variants. Therefore, further studies are needed to identify the pathogenesis and clinical sequelae arising from the selection of these particular mutants as well as to the "wild-type" HBV infections.

Stephen Locarnini

TOKYO

Symposium 6:
Novel Therapeutic Strategies for HBV – "Innate Immunity in Hepatitis B"
14:10 – 14:30
Room 1BC