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Uptake of HBV and HCV treatment in China

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In China, complications related to chronic liver diseases, such as end-stage liver cirrhosis and hepatocellular carcinoma, result in more than half a million deaths every year. The most important causes of chronic liver diseases are chronic hepatitis B infection (CHB) and chronic hepatitis C (CHC) infection. Despite the availability of effective therapy for CHB and CHC to prevent the development of undesirable outcomes, there remains a large proportion of patients left untreated or inadequately treated.[1]

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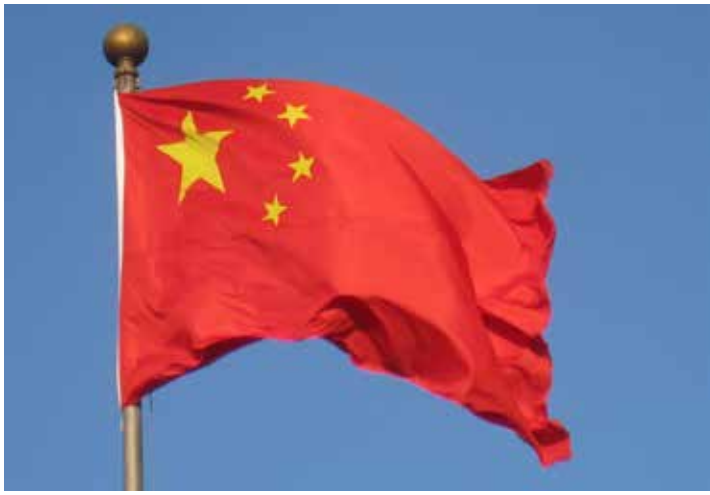
According to a national cross-sectional seroepidemiological survey in 2006, the prevalence of hepatitis B surface antigen (HBsAg) carriers was reduced to less than 8.0% and among children aged 5 years, to less than 1.0%. Based on the National Disease Supervision Information Management System of China, the mean reported incidence of hepatitis B was 84.3 per 100,000 in China between 2005 and 2010.[2]

In China, all FDA and EU-registered effective therapy such as conventional interferon, pegylated interferon, lamivudine, adefovir, entecavir, telbivudine and tenofovir are currently available.
In addition, due to expiry of drug patents, generic interferon, pegylated interferon, nucleos(t)ide analogues such as lamivudine, adefovir and entecavir are also used in many hospitals in China. In most clinical practice, interferon-based therapy is used as first-line therapy unless there are contraindications for its use or the CHB patients developed intolerable adverse events. Generally, around one-third of the CHB patients treated received interferon-based therapy and the remaining two-thirds received nucleos(t)ide analogues. The most commonly used nucleotide analogue is entecavir (up to 60% of cases). However, mainly due to the cost of the medications and lack of public understanding of the relevance of therapy, especially with long-term nucleos(t)ide analogues therapy, compliance problems with premature withdrawal from therapy have been noted in up to 65% of CHB patients. This is further compounded by a lack of awareness of CHB infection by the public. The lack of awareness is more serious in rural (~5-10%) than urban regions (~20-30%) and is one of the major reasons why there remains a high incidence of liver cancer in China, with an age-standardized rate of incidence of 19.48/100,000.[3]



Chronic hepatitis C (CHC) infection is also endemic in China and is grossly undertreated. The estimated prevalence rate is 0.39-3.2%. In the past two decades, there has been an increasing incidence of medical cases for HCV infection, rising from 0.7 to 15.0 cases

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per 100 000 with the largest burden of disease concentrated among individuals over 35 years of age, rural residents and those tested as part of routine screening. Of the six HCV major genotypes (GT), 1b (~70-80%) and 2a (~15-20%) are most common. Other subtypes includes 3a, 6a, 3b, 6n, and 1a, detected at frequencies of 3 %, 2 %, 2 %, 0.4 %, and 0.4 %. To date, there are three HCV treatment regimens in Mainland China - peginterferon alpha plus ribavirin, standard interferon alpha (including interferon alpha-1b, alpha-2a and alpha 2b) plus ribavirin or peginterferon alpha monotherapy. In accordance with the China hepatitis C management guidelines, the recommended treatment duration was 48 weeks. For HCV non-G1-infected patients, peginterferon alpha plus ribavirin was recommended for 48 weeks, standard interferon alpha plus ribavirin for 24–48 weeks, and monotherapy with peginterferon alpha or standard interferon was recommended for patients intolerant to ribavirin.[4]

In Mainland China, there are at least two reimbursement systems: the urban reimbursement system and the new rural cooperative medical system (NRCMS). Social security insurance covers most of the cost, but not all Chinese are covered. The overall sustained viral response (SVR) rate in Chinese CHC patients is around 70% and is higher than that in Western patients. This is mainly related to the higher frequency of IFN-responsive or favorable interleukin- 28B (IL-28B) genotype in Chinese populations than in other ethnic populations. Among patients with HCV GT1, GT2, GT3, and GT6 infections, IL28B genotype CC was around 79%, 89%, 96%, and 92%, respectively. In addition, the introduction of response-guided therapy, where the optimized treatment duration is based on the early viral kinetics during the first 12 weeks of treatment, increases the SVR rate. Recently, a multicenter study supported by the National Science and Technology Major Project for Infectious Disease Control during the 11th Five-Year Plan Period showed that SVR was around 63 % by intention-to-treat (ITT) analysis and 82% by per protocol (PP) for genotype 1 when 48-week treatment was carried out by combining peginterferon-alpha-2a and ribavirin.[5]

Despite the availability of partly reimbursed effective interferon/ribavirin therapy, there remains a large number of CHC patients untreated or inadequately treated due to: (1) under-diagnosis and management (2) intolerance to PR therapy and (3) failure to respond to PR therapy. It is estimated that less than ten percent of CHC patients in China have ever been treated due to lack of awareness, poor public and medical education. In one study, it was shown that less than 1% of the general population knows the route of HCV transmission and less than 5% had been tested for HCV infection. This lack of knowledge on CHC is also common in non-specialist physicians. Indeed, a recent survey showed that testing for HCV was not performed before invasive procedures in nearly half of the cases and less than five percent even in those with accidental injury at the hospital. More than half of them do not know there is effective therapy for CHC.[6,7]

Recently, treatment of CHC has recently entered a new era with the advent of direct-acting antiviral agents (DAAs). DAAs are well-tolerated, safe, orally deliverable, and can cure almost all HCV patients within 8 to 24 weeks of treatment. However, no DAA has been approved in Mainland China to date. Clinical trials with DAAs-containing regimen including (1) peginterferon/ribavirin and simeprevir (2) peginterferon/ribavirin and sofosbuvir (3) daclatasvir and asunaprevir and (4) ABBvie 3D have been conducted. For those CHC who required DAA therapy, they can either obtain the DAAs via consultation abroad such as Hong Kong, Japan, South Korea, USA or EU countries where the DAAs are registered. The cost of such regimens is nonetheless onerous and in the real world, this has adversely affected treatment access, drug compliance and has encouraged drug counterfeiting, which could create substantial public health hazards and cause safety concerns. Alternatively, generic DAAs were shipped to patients in China via mailing (illegal black-channel). This certainly has posed the problem of quality control. A conservative estimate is that the proportion of patients using illegal generics exceeds at least 50-100 times more than those treated with “brand-name” DAAs. Hence, HCV treatment cost reduction, without affecting efficacy is of utmost importance. This objective could be achieved by personalized therapy, based on renewed understanding of virus-host factors which will then allow shortening of treatment duration and early switching from PR therapy to DAAs.[8]

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An Update on HCV Treatment in Egypt - a question and answer session

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Q. Professor Yosry, what is the burden of HCV in Egypt?

The current population of Egypt is around 90 million and the latest demographic health survey in 2014 indicates that the prevalence of HCV viremia in individuals 1-59 years old is 4.4% and in individuals 15-59 years old is 7%. Ninety percent of the infections are genotype 4 and 10% genotype 1 HCV, causing an estimated number of new infections of 150,000 annually, mostly resulting from nosocomial transmission of the virus.

Q. What public health policy is in place to counteract HCV?

A national program for the treatment of patients with chronic hepatitis C was initiated by the ministry of health (MOH) in 2007. Around 50,000 patients were treated annually with free of charge pegylated interferon and ribavirin leading to SVR rates of approximately 50% following a 48 week course of treatment. The introduction of directly acting antivirals (DAAs) heralded a new era in the management of HCV infection in Egypt. Though newer generations of DAAs offer high cure rates (SVR>90%), and are safe, well-tolerated and of wider access and shorter duration, however they are exceedingly expensive and thus unaffordable. The MOH was able to negotiate discounted prices with the pharmaceutical companies, as low as 1% of their world market price, making DAAs affordable.

Q. When did DAA therapy become available to treat HCV in your country?

Sofosbuvir was introduced into the national program in October 2014 whereby Interferon eligible patients were given triple therapy (sofosbuvir + pegylated interferon + ribavirin) for 12 weeks whereas Interferon ineligible patients were given dual therapy (sofosbuvir + ribavirin) for 24 weeks. Patients with advanced liver disease, i.e. Metavir F3 and F4 at liver biopsy, were prioritized to receive treatment. The SVR 12 for triple therapy and dual therapy was 92% and 72% respectively; the difference in outcome being imputable to excess patients with advanced fibrosis receiving the dual therapy group, in the face of 50% pegylated interferon and ribavirin failures, and this explains the relatively low SVR in the latter group.

Q. Were other DAAs introduced in 2015?

Simeprevir was introduced to the national program in May 2015, and the treatment protocol was modified in order to have Interferon eligible patients given triple therapy (sofosbuvir + pegylated interferon + ribavirin) for 12 weeks whereas Interferon ineligible patients received sofosbuvir + simeprevir for 12 weeks. Prioritization by disease severity was abolished so that all chronic HCV patients received treatment irrespective of their fibrosis stage. However, compensated cirrhotic patients could be treated only when Child-Pugh score was ≤ 6. In a cohort of 665 chronic HCV patients (F0-F4) treated with sofosbuvir and simeprevir for 12 weeks, the SVR 12 was as high as 98%. In December 2015, daclatasvir, paritaprevir/r, ombitasvir were approved by the MOH and the treatment protocol starting January 2016 will therefore include sofosbuvir + daclatasvir for most patients except those with renal impairment who will be switched to paritaprevir/r + ombitasvir + ribavirin.

Q. Does the current capacity of liver centers meet the therapeutic needs in Egypt?

The national program now runs 50 treatment centers distributed all over the country and this number will be doubled in the next couple of years. All centers are equipped to screen individuals for HCV, assess the severity of disease and dispense DAAs free of charge to HCV infected persons under the supervision of liver specialists. Over one million individuals have already registered for treatment with DAAs, and 150,000 have started treatment.

Q. Have generic DAAs been endorsed by MOH to fight against HCV?

Yes. The availability of highly developed with the goal to provide a sufficient patient pool to match the projected increase in treatment.

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Pros & cons to treating hepatitis C infection before or after liver transplantation

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The approval of direct antiviral agents (DAAs), combined together and all-oral interferon free regimen, has dramatically changed the landscape of HCV therapy, especially for the most severe patients with decompensated cirrhosis, awaiting transplantation or liver transplant recipients. In the era of interferon, treatments were ineffective and poorly tolerated, due to a high risk of infection and/or rejection. At present, clinicians have to face a dilemma to prevent HCV recurrence: to treat before or after transplantation. Although both strategies are acceptable, there are subtle differences.

Q. Is there a difference in efficacy?

DAAs have shown remarkable efficacy to treat liver transplant patients in several studies. If the first strategy combining sofosbuvir and ribavirin was suboptimal with sustained virological response (SVR) rates of 70%, combinations of DAAs allow HCV clearance in over 90% of patients, regardless of the chosen combination with one NS5B inhibitor and one NS5A inhibitor and/or one second-generation protease inhibitor.[1-5] This result is particularly remarkable in patients suffering from the most severe form of recurrence, fibrosing cholestatic hepatitis.[6, 7] Although some questions are pending as the optimal duration of treatment or the need for the use of ribavirin, DAAs are extremely effective in liver transplant patients who achieve the same results as non-transplanted patients.

Treating cirrhotic patients is more challenging. Although there is no difference in terms of efficacy for treating compensated cirrhotic patients, some studies show poorer results in patients with decompensated cirrhosis, with overall SVR rates between 72 and 88% in this context.[4, 8-10] Most severe patients obtain poorer results. The ALLY-1 trial, combining sofosbuvir+daclatasvir, shows a difference according to class of Child-Pugh score (CTP) with 92%, 94% and 56% of SVR for CTP A, B and C, respectively.[8] Real-life studies have confirmed these results. In the UK cohort study that included 467 cirrhotic patients with CTP>B7, the combination of sofosbuvir plus one NS5A inhibitor, ledispavir or daclatasvir lasting 12 weeks shows SVR rates between 71 and 80%.[11] Finally, DAAs are also effective in cirrhotic patients but the severity of cirrhosis is still a predictor of SVR. Will the new combinations improve these results? Although the combination of sofosbuvir+velpatasvir for 12 weeks provides SVR in over 90% of patients, SVR rate was 83% (n=90) in patients with decompensated cirrhosis. The addition of ribavirin increases SVR rate of 94% (n=87).[12]

All in all, there are better results in terms of efficacy in treating liver transplant patients than patients with decompensated cirrhosis, particularly Child C.

Q. Is there a difference in terms of tolerance?

DAAs are well tolerated before or after transplantation. All reported studies show a rate of serious adverse events (SAE) of about 20%, expected in regard of the severity of these populations. After transplantation, the main issue is drug-drug interactions (DDI) between immunosuppressive drugs and DAAs. Basically, DDI are not clinically relevant when sofosbuvir combines one NS5A inhibitor. However, the use of protease inhibitors requires dose adjustment and close monitoring.[13] The combination of cyclosporine and simeprevir is contraindicated due to overexposure to simeprevir.

Before transplantation, the main issue is DAAs pharmacokinetic changes in patients with hepatic impairment. With the exception of sofosbuvir that has a renal clearance, other DAAs are metabolized by the liver. In patients with severe hepatic impairment, concentrations of DAAs may be significantly increased. Although these changes are not clinically relevant for NS5A inhibitors, concentrations of protease inhibitors can vary between 5-32 fold when using simeprevir and asunaprevir, for example.[13] Finally, some unexpected SAE may occur in the most serious patients. Recently, 5 cases of cardiac arrhythmias have been reported in cirrhotic patients.[14, 15] Although concomitant use of amiodarone or beta-blockers are incriminating factors, they do not explain everything because at least one patient had no concomitant treatment.

All in all, safety profiles are excellent before and after liver transplantation. Safety issues are mainly DDI and hepatic impairment. Both argue for the use of NS5A inhibitors more than protease inhibitors.

Q. Can we avoid liver transplantation in treating hepatitis C prior to transplantation?

This is the critical point arguing for treatment before transplantation. Treatment is recommended for Child A patients with hepatocellular carcinoma if there is no risk of drop out from the list due to the tumor (LT should not be delayed by the treatment). The discussion concerns mainly patients listed for decompensated cirrhosis without hepatocellular carcinoma. About 2/3 of patients achieve clinical and biological improvement during treatment in studies enrolling decompensated cirrhotic patients.[4, 8, 12, 16] However, we must look with caution at these results. First, 1/3 of patients does not improve or worsen during treatment, regardless of virological response. Then, improvement is often modest with variations of only 1 or 2 points in MELD

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score. In a recent meta-analysis including 533 patients, 28% experienced an improvement of MELD score over 3.[17] Finally, who may be withdrawn from the list? A French cohort study that included 183 patients awaiting transplantation showed that out of 53 patients with decompensated cirrhosis, 36% had a complete clinical and biological response, meaning a CTP A at the end of treatment[16]. The best predictor of improvement was baseline CTP, with an AUC of 0.81, the best threshold being 7.5. Therefore, several questions remain unresolved. Some patients will keep improving over longer follow-up. Comorbidities are likely to be considered in this setting. To date, the point of no return is not established. Although we could expect significant improvement of 1/3 of patients, it probably concerns the less serious patients. For others, we have to be cautious: access to transplantation is conditioned by the severity of the disease. Treating patients to get partial improvement may be deleterious.

Finally, should we treat patients before or after liver transplantation? Both strategies are relevant with excellent efficacy results and good safety profiles. Regarding efficacy, better results are achieved in transplant recipients than in decompensated cirrhotic patients. Regarding safety, DAA and hepatic impairment are still issues and favor the use of NS5A inhibitors. To withdraw patients from the waiting list is feasible and should concern about 30% of patients.

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Question and Answer Session on the role of DAA in Transplant Medicine: USA perspective

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Q. What have been the challenges due to HCV infection in organ transplant?

HCV infection remains the most frequent etiology of decompensated cirrhosis requiring liver transplantation (LT) and is also a major factor in the exponential rise in hepatocellular carcinoma (HCC) in North America and Western Europe. A major challenge has been reinfection of the liver allograft with HCV resulting in diminished patient outcomes after an otherwise successful procedure. Confounding management of HCV infection was the generally poor tolerance of interferon and ribavirin-based regimens in liver transplant recipients due to hematological side effects, and also because of the potential for induction of graft rejection due to the immune modulating effects of interferon.

Importantly, HCV infection has also been an issue in solid organ transplant other than liver. This has been especially true in renal transplantation due to the continued high prevalence of HCV infection in the dialysis population. HCV infection in renal transplant recipients has been implicated in diminished patient and graft survival. As in other solid organ transplant recipients HCV infection also increases the likelihood of post-transplant diabetes mellitus. Antiviral therapy before renal transplant however had been especially difficult due to poor tolerance. The hemolytic anemia induced by ribavirin can be hazardous in patients with chronic kidney disease in whom baseline anemia is typical. Importantly ribavirin is not efficiently dialyzed and thus the associated anemia can be long lasting. Interferon based HCV therapy post-renal transplant was not advised due to a well-founded concern about its use precipitating graft rejection.

In heart and lung transplant candidates infected with HCV there has been reluctance to offer transplantation because of a perception that therapeutic immunosuppression would lead to hepatic decompensation.

Q How will the introduction of DDA therapy alter management of HCV infection in transplant patients?

The availability of all oral regimens has already dramatically expanded treatment options in transplant patients. It is now possible to eradicate HCV infection in most patients in these previously difficult to treat populations including transplant candidates and recipients.

Q. What is the data in cirrhotic patients?

A number of seminal studies have confirmed the efficacy of oral DAA regimens in liver transplant candidates and recipients. Longer follow-up will be required however to determine whether patients with advanced cirrhosis will improve sufficiently to obviate the need for liver transplant.

A number of authors have confirmed the efficacy of all oral antiviral therapy with the nucleotide polymerase inhibitor sofosbuvir. Lawitz and colleagues reported their experience in 103 cirrhotic genotype 1 patients treated with the so-called Cosmos protocol namely simeprevir 150 mgs daily, an NS3/4A inhibitor, and sofosbuvir 400 mgs daily administered for 12 weeks.[1] In treatment-naïve patients, SVR 12 was 88% and in treatment-experienced patients, it was 79% with this regimen generally well tolerated.

Modi and colleagues reported an overall SVR 12 of 74% in 42 patients with decompensated cirrhosis due to HCV genotype genotype 1 with Cosmos. In the 14 patients infected with HCV genotype 1b SVR was 100%. Overall therapy was well tolerated. However, of the seven patients who had received ribavirin as part of this regimen two required blood transfusion.[2] Other groups have also sounded a word of caution about the use of this oral regimen in patients with more advanced cirrhosis. Mitchell et al. treated 103 cirrhotic patients, deemed to be ineligible for interferon-based therapy, with the Cosmos regimen. SVR rates were 87%, 77% and 67% in Child's A, B and C patients respectively. However, 11% of patients had severe adverse events including a fatal septic episode in one patient.[3] Soriano and colleagues observed fatal hepatic decompensation in an elderly patient during therapy with Cosmos.[4] However, given the morbidity of clinically overt cirrhosis it can be difficult to distinguish antiviral therapy-related events from the natural history of disease. Saxena et al. for instance in their analysis of outcomes in cirrhotic patients treated with Cosmos noted that adverse clinical events were not substantially more frequent in treated patients compared to untreated controls.[5] However another report in 35 patients with extensive fibrosis or cirrhosis treated for HCV infection with sofosbuvir and ribavirin implicated this regimen in development of lactic acidosis in five (14%) accompanied by hepatic decompensation.

Sofosbuvir has also been successfully combined with NS5A inhibitors in the treatment of cirrhotic HCV patients. Bourliere and colleagues treated 155 cirrhotic patients infected with HCV genotype 1 who had failed prior antiviral therapy with either 12 weeks of sofosbuvir, ledispavir and ribavirin or 24 weeks of dual therapy with SVR rates of 96% and 97% respectively with overall good tolerance of therapy.[6] More recently, Curry and colleagues described the use of another NS5A inhibitor, velpatasvir, with sofosbuvir with or without ribavirin in Child B cirrhotics with a variety of genotypes.[7] Overall SVR rates were 83% and 86% with 12 weeks and 24 weeks of dual therapy respectively and 94% with 12 weeks of triple therapy. Again, treatment was well tolerated.

The Abbvie regimen which incorporates protease, NS5A and polymerase inhibitors ("PROD") has also been studied in cirrhotic patients. Poordad and colleagues treated 380 Child's

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A cirrhotics for 12 or 24 weeks with ribavirin with SVR rates of 91.8% and 95.9% respectively.[8] Therapy was well tolerated. In another report, Feld and colleagues achieved an SVR of 100% in HCV genotype 1b patients with 12 weeks of PROD without ribavirin.[9] However, use of this regimen in cirrhotics has been restricted by an FDA warning after its use was implicated in hepatic failure in patients with more advanced cirrhosis.

Overall, these results with different regimens indicated treatment of HCV with progression cirrhosis is feasible and highly effective. However, in patients with more advanced cirrhosis toxicity is a concern and has led to avoidance of the PROD regimen in Child's B patients. Ongoing studies will clarify whether achieving SVR will allow frequent delisting of liver transplant candidates as some authors have reported.[10] Curry and colleagues established that successful antiviral therapy with SVR pre-liver transplant prevents recurrent HCV in the graft.[11]

Q. How successful is DAA therapy in liver transplant recipients?

One of the most urgent indications for HCV therapy is severe recurrent HCV. Compassionate use of sofosbuvir in recurrent HCV including fibrosing cholestatic hepatitis allowed salvage of grafts even with this severe manifestation of HCV recurrence with excellent SVR rates.[12] Charlton and colleagues used the combination of sofosbuvir lediprasvir and ribavirin in patients with advanced liver disease including liver transplant recipients with severe HCV recurrence. SVR rates with this regimen administered for 12 weeks resulted in high SVR rates although these fell to less than 75% in recipients with more severe hepatic impairment.[13] Kwo and colleagues reported a 97% SVR in 34 liver transplant recipients infected with HCV genotype 1 using the PROD regimen. Importantly, adjustment of calcineurin dosing is required with this regimen.

Q. What is the role of DAA therapy in the renal transplant population?

Patients with renal failure have been difficult to treat safely with interferon and ribavirin-based therapy due to anemia associated with renal failure. However, DAA therapy has been successively used pre- and post-renal transplant. Initial reports have described a high rate of SVR with good patient tolerance even in the presence of advanced renal failure.[14] Bhamidimarri has reported successful use of reduced dose sofosbuvir with simeprevir in renal transplant candidates.[15] In another report, all 17 patients on chronic hemodialysis infected with HCV genotype 1 treated by Nazario and colleagues achieved with standard dose sofosbuvir and simeprevir.[16]
Other reports also support the use of sofosbuvir-based regimens in this population.[17] Ongoing studies are addressing use of PROD in this population also. Not surprisingly, reports are also starting to appear about use of DAA therapy in renal transplant recipients. Sawinski and colleagues successfully treated 20 renal transplant recipients, predominantly infected with HCV genotype 1, with a sofosbuvir-based regimen achieving 100% SVR without major toxicity and with adjustment of immunosuppression necessary in only half.

Q. What is the optimal timing of antiviral therapy?

It is clearly feasible to cure HCV infection in most solid organ transplant candidates and recipients with acceptable toxicity. However, an important issue that requires further study is the optimal timing of antiviral therapy in a patient awaiting organ transplant. A potential recipient with HCV infection can now safely be offered an organ from an HCV infected donor with the expectation that post-transplant antiviral therapy can cure HCV infection. In contrast, a transplant candidate who has had successful treatment of HCV can no longer be offered an organ from a HCV infected donor because of the risk of HCV reacquisition. In a recent analysis, Reese and colleagues drew attention to the substantially shorter waiting times for renal transplant in the United States for renal transplant candidates prepared to accept an organ from a HCV positive donor which comprises 4% of the US deceased donor pool.[18] Use of HCV positive donor organs could conceivably be extended to HCV naïve patients with pre-transplant antiviral therapy.

Clearly, the management of HCV infection in organ transplant has entered a new phase and will no longer be the threat to graft and patient as it has been.

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New Treatments for HBV – AASLD 2015 Update and Beyond

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Q. How has the standard of care treatment for chronic hepatitis B evolved?

Antiviral treatment of HBV has made such remarkable progress in the least five years that only few challenges remain. Owing to its immunomodulatory and antiviral properties, IFN remains the best antiviral strategy in a subset of young patients with mild to moderate liver disease.[1-4] In approximately 30% of such patients, a 48-week course of IFN provides long-term sustained response, including HBsAg clearance, and reduces long-term complications. For all the patients who cannot tolerate or respond to IFN, such third-generation oral nucleos(t)ide analogues (NUCs), as ETV or TDF, are indicated.[1-4] Long-term administration of these NUCs is indeed the most popular anti-viral strategy worldwide, as they efficiently suppress HBV replication in most patients (>95%) without any major safety issues, resulting in the prevention of most liver complications.

Q. What unmet clinical needs are we still dealing with?

The only challenge of IFN-based therapy is cost-effectiveness. To this end, several strategies have been implemented, i.e. selection of best candidates by baseline prediction scores, tailoring of duration of therapy based upon on-treatment qHBsAg levels, combination with NUC in selected cases.[1-4] For NUC therapy, the only unmet medical need is duration of therapy. HBsAg seroconversion is the best and safest stopping rule but this endpoint is achieved in a significant proportion of HBeAg positive patients with short duration of infection and favorable viral genotype (20% at 5-8 years) but in only few (approximately 1-5%) HBeAg positive Asian carriers or HBeAg negative carriers over 10 years' treatment.[1-4] Recent studies do suggest that NUC therapy

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could be safely discontinued before HBsAg loss in selected patients but the identification of these patients during NUC therapy is still challenging.

Q. What steps forwards are expected in the treatment of HBV and how do reports from AASD meet our expectations?

Several pre-clinical and phase I clinical studies were presented at the AASLD 2015 meeting. Different steps of the HBV life cycle have been targeted by small biotech companies and large big Pharma alike. Though very interesting and promising, these studies are still very preliminary and serve to provide the frame in which the future of HBV therapy will develop.

For clinicians, few new studies were presented. Among the most interesting studies presented at AASLD 2015 was the efficacy and safety of GS-4774 in long-term NUC suppressed CHB patients.[5] There are two reasons why this study is relevant. First, although several previous studies with HBV specific vaccines had failed, this study enrolled only patients long-term suppressed by NUC with the sole aim to foster HBsAg kinetics. Second, this strategy may substitute add-on IFN that is of limited efficacy and prone to side effects. Unfortunately, a 20-week course of GS-9774 did not improve HBsAg kinetics in the overall analysis nor at the individual patient level. Only three patients in the high GS-4774 dose group achieved more than 0.5 log HBsAg decline but none cleared HBsAg at week 48. These results are even more disappointing owing to the fact that most patients had baseline favorable features such as long-term suppression of HBV by TDF and median HBsAg levels of approximately 3 log IU/ml. In a similar population of patients, add-on peg-IFN, the only other immunomodulatory add-on approach currently available for HBV patients, yielded better results, showing a 0.5 log decline of HBsAg and 3-5% of patients clearing HBsAg or achieving very low qHBsAg (<10 IU/ml) in a difficult to cure genotype D patients.[6,7] Another interesting study presented at AASLD 2015 was the phase II study involving RNA interference technology.[8] A single iv injection of ARC-520 produced a 40% or 0.3 log reduction of HBsAg levels in HBeAg negative Chinese patients fully suppressed by ETV for many years. This decline of qHBsAg was maintained for 30-45 days following a single injection setting the stage for multiple dose studies.

In the setting of IFN therapy, the first GWAS study aimed to identify genetic predictors of sustained virological response to IFN was presented.[9] One thousand five hundred HBeAg positive and negative patients, both Asians and Caucasians, treated with IFN in different countries were enrolled. To most clinicians' surprise, only a moderate association between a SNP in a NCOA2 gene region, a nuclear hormone receptor involved in activation of cell cycle genes, on chromosome 8 was demonstrated for Caucasians (P-value of lead SNP in Caucasians is 1.3x10-6; MAF=0.13) while no genetic predisposition could be identified among Asian patients. The role of this genetic association requires further analysis.

Q. What novelties are coming out in 2016?

2016 is going to be an important year for HBV therapy as several new phase II/III studies will be completed and analyzed. Among these, the TAF phase III study, the TLR-7 agonist, the therapeutic vaccine for naïve patients, new immunomodulators for both naïve and suppressed patients, the RNA small interfering products, entry inhibitors, release inhibitors, core inhibitors, and cccDNA inhibitors, just to quote only some of these new approaches. Many of these anti-HBV strategies are likely to fail because of safety issues or limited efficacy but some will proceed to phase II and phase III in 2017 setting the stage for the future of HBV therapy that will address eradication and functional cure.

Only one week ago, a press release published the preliminary results of the phase III RCT of TDF vs TAF which is a modified TDF endowed with similar antiviral efficacy but lower systemic exposure.[10] Indeed, while the 48-week virological responses were similar between the two NUCs (93% vs 94% for HBeAg negative patients, 67% vs 64% for HBeAg positives), patients receiving TAF had smaller mean percentage decreases in BMD in the hip and spine (p<0.001), median eGFR change from baseline to eeek 48 favored TAF (p<0.01) and smaller increases in serum creatinine were observed in HBeAg positive patients on TAF (p=0.02). However, AEs leading to study drug discontinuation were similar between groups (~0.7-1%) as well as comparable were the most commonly reported AEs. The final results of this study will be presented at EASL 2016.

Q. Is there a holy grail for HBV treatment ?

The holy grail for HBV treatment has already been within reach for many years now. Third-generation NUC, i.e. ETV and TDF, improve patients' survival by reducing most complications, although HCC attack rates remain significant, and this comes with a user friendly strategy, simple and efficient monitoring (every 6 months), limited price and excellent safety profile. Many patients affected by other chronic diseases, and their physicians too, would love to have a therapeutic strategy based on the long-term administration of a single pill every day, available to treat their disease as efficiently and safely as is now possible for HBV.

Therefore now is the time for the hepatology scientific community to change the goal of anti-HBV therapy from reduction of the complications aimed to improve survival to improvement of HBsAg decline/loss to stop NUC therapy. Everyone would see how this new endpoint would revolutionize not only therapeutic strategies and study designs but also the measurable endpoints of these new regimens. With the aim to shorten duration of therapy, combination therapy with immunomodulators and/or new antiviral agents targeting different and new steps of the HBV life cycle, are the most likely answers. However, unlike the HCV setting where the new DAAs fill a major therapeutic gap as many patients would die of liver disease if DAAs were not available, it should not be overlooked that in the HBV setting, current oral therapies already provide full viral suppression with no complications and improved survival. Not to mention the cost issues. How much are the payers, the patients, the health systems willing to pay, in terms of both money and side effects, just to stop a very effective oral therapy, given the fact that the costs of ETV and TDF will fall shortly as their patents will soon expire ?

Many public health policy issues remain unsettled though. Awareness of HBV infection in the general population is limited and referral to chronic carriers to secondary and tertiary referral centers for staging and treatment is still suboptimal. Moreover, while HBV is no longer a therapeutic challenge for those countries where ETV and TDF are marketed and fully reimbursed, it must be underlined that this is still not the case for many countries, most of whom belong to high or intermediate endemic areas for HBV. In these countries, due to the fact that these newer NUCs are not available or reimbursed and often virological testing is also unavailable, the management of HBV infection still remains a major challenge.

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