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Then and now: The progress in hepatitis B treatment over the past 20 years

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Abstract
The ultimate goals of treating chronic hepatitis B (CHB) is prevention of hepatocellular carcinoma (HCC) and hepatic decompensation. Since the advent of effective antiviral drugs that appeared during the past two decades, considerable advances have been made not only in controlling hepatitis B virus (HBV) infection, but also in preventing and reducing the incidence of liver cirrhosis and HCC. Furthermore, several recent studies have suggested the possibility of reducing the incidence of recurrent or new HCC in patients even after they have developed HCC. Currently, six medications are available for HBV treatment including, interferon and five nucleoside/nucleotide analogues. In this review, we will examine the antiviral drugs and the progresses that have been made with antiviral treatments in the field of CHB.

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Key words: Chronic hepatitis B; Treatment of hepatitis B; Hepatocellular carcinoma; Nucleoside analogues; Nucleotide analogues

Core tip: Chronic hepatitis B virus (HBV) infection is one of the leading causes of death across the world due to its worldwide distribution and potential sequelae. Advances in knowledge in combination with the development of potent and effective antiviral therapy for chronic hepatitis B have led to decreased complications from the virus. Timely use of nucleotide/nucleosides may improve liver function and increase survival in patients with hepatic decompensation. Maintained suppression of HBV replication with antiviral therapy halts the progression of liver disease, may reverse liver fibrosis, and can reduce the development of cirrhosis and hepatocellular carcinoma.

INTRODUCTION
In the decades after World War II, clinical and epidemiological studies began to differentiate among various types of hepatitis(1). However, it was the discovery of an antigen by Blumberg and his colleagues, now known as hepatitis B surface antigen (HBsAg), in the serum of an Australian Aborigine that reacted with the antibody (now known to be anti-HBs) in serum of a hemophiliac patient that provided the first clue(2). Subsequent development of acute hepatitis in a technician in his laboratory provided the essential link to the illness. For his discovery and subsequent work on the disease progression related to hepatitis B virus (HBV), Blumberg received the Nobel...
Prize in Medicine 1976. In 1970, Dane et al., identified the whole virus particle (Dane particle) using electron microscopy. In 1972, hepatitis B e antigen (HBeAg) was identified by Magnus et al. By the early 1980’s the genome of the virus had been sequenced and the first vaccine (initiated by Millman et al. and developed by Hilleman et al.) were tested. This plasma vaccine became available in 1983 and was rightly designated “The First Cancer Vaccine” by World Health Organization. The close link between HBV and hepatocellular carcinoma (HCC) was lucidly documented by Beasley et al. in their historical prospective study of 22,707 men in Taiwan (Figure 1).

Since the discovery of the virus, our understanding and knowledge about the complexities of HBV have grown tremendously. Chronic HBV infection is one of the leading causes of death across the world due to its worldwide distribution and potential sequelae. People infected with the virus are at risk of developing hepatic decompensation, liver cirrhosis and HCC with 15% to 40% of individuals developing serious sequelae in their lifetime. Despite the implementation of effective universal vaccination programs, over 300 million people are still chronically infected with HBV worldwide with 75% of infected individuals residing in the Asia-Pacific region.

Increased knowledge of the natural history of chronic hepatitis B (CHB) and clinical data demonstrating improved outcomes with medical interventions have led to publication of various treatment guidelines aimed at providing direction regarding initiation/on-treatment management of antiviral therapy and monitoring of outcome measures. These advances in knowledge in combination with the development of potent and effective antiviral therapy for CHB have led to decreased complications from the virus. In this review, we will discuss the advances in the understanding of the natural history of CHB and the progress of anti-HBV treatment over the past two decades.

HEPATITIS B VIRUS

HBV belongs to a group of closely related DNA viruses termed Hepadnaviruses. This family of viruses has a strong preference for infecting liver cells and has a similar life cycle in their hosts. The virus consists of a nucleocapsid and an outer envelope composed mainly of three HBsAgs, which play a central role in the diagnosis of HBV infection. The nucleocapsid contains hepatitis B core antigen (HBeAg), a DNA polymerase-reverse transcriptase, and the viral genome. The genome consists of a partially double-stranded circular DNA molecule of about 3200 base pairs in length. The pre-surface 1/pre-surface 2 and surface genes code for the various HBsAgs.

The protein encoded by the pre-core/core gene undergoes post-translational modification to yield HBeAg, which is a seromarker for high viral replication. The viral DNA polymerase-reverse transcriptase is encoded by the polymerase gene and is of central importance for viral replication. Different from all known mammalian DNA viruses, hepadnaviruses replicate using a reverse transcription of an RNA intermediate. Based on this unique replication cycle of HBV, antiviral therapeutic strategies have been mainly aimed at the reverse transcription of HBV RNA with nucleotide/nucleoside analogues.

The presence of HBV DNA in serum is the best indication of active viral replication. Antibody to HBsAg is produced in exposure to the envelope antigen and confers protective immunity. Antibody to HBeAg is detectable in all patients who have ever been exposed to HBV. However, unlike antibody to HBsAg, this antibody is not protective, but can be helpful in distinguishing acute from chronic infection if IgM antibody (anti-HBc IgM) is present. Antibody to HBeAg appears when the antigen has been cleared and the virus is no longer replicating or has reduced replication.

PATHOGENESIS AND CARCINOGENESIS OF HEPATITIS B

Liver injury in CHB is the result of the host’s immune responses against HBV; an HLA-class 1 antigen-restricted, cytotoxic T lymphocyte-mediated response against HBV antigens expressed on hepatocytes would result in apoptosis and necrosis of the hepatocytes. Accordingly, CHB is a dynamic state of interactions among HBV, the patient’s hepatocytes and the immune system. Based on these interactions, the natural course of CHB can be divided into different changing phases, although not all patients go through all of the phases (Figure 2).

The first phase is the “immune tolerant phase” which consists of HBeAg seropositivity, high viral loads, but with a normal serum alanine aminotransferase (ALT) and near-normal liver histology. Adult-acquired chronic HBV infection usually has a very short “immune tolerant phase”. In contrast, the perinatally or early childhood-acquired chronic HBV infection has a long “immune tolerant phase”. The “immune clearance phase” usually develops during adolescence or adulthood. This phase is characterized by positive HBeAg, high serum HBV levels and increased ALT levels, sometimes complicated by hepatic decompensation. These events may lead to progression to fibrosis or development of cirrhosis in some patients during the HBeAg-positive phase, but may also result in a declining serum HBV DNA level and may eventually lead to HBV DNA seroclearance and HBeAg seroconversion to its antibody (anti-HBe) in most patients. A 3-year clinical study in patients with chronic hepatitis B, or patients in the “immune clearance phase”, showed that cirrhosis developed at an estimated annual incidence of 2.1%, being higher in those seropositive for HBeAg at entry (2.4%/year). The estimated annual incidence of spontaneous HBeAg seroconversion was reported to be 2%-15%, depending on factors such as age, ALT level and HBV genotype. Following HBeAg seroconversion, most of the patients enter an “inactive
phase” with sustained normal serum ALT, low serum HBV DNA and no or minimal necro-inflammatory histological changes, although some of them may have already developed advanced fibrosis or cirrhosis.\textsuperscript{[27-29]} Spontaneous HBsAg seroclearance may occur several years after HBeAg seroconversion at an incidence of \textasciitilde0.7\%-2.4\% per year depending on age at time of infection\textsuperscript{[29]}.

As early as the 1970’s, chronic infection with the HBV was associated with the development of HCC. A powerful substantiation of the association between HBV infection and HCC was the results of a prospective cohort study reported by Beasley \textit{et al} in 1981. These investigators followed more than 22000 male municipal workers in Taiwan and found that those who were seropositive for HBsAg had rates of HCC that were significantly greater than were the rates in uninfected controls. They calculated the relative risk for HCC among those who were HBV-infected to be 63 compared to uninfected controls. More recent cohort studies have confirmed the high risk of HCC in HBsAg-positive individuals as originally identified in the Beasley study. An example is the Haimen City cohort that included about 11000 HBsAg-positive subjects followed over a mean period of 8 years.\textsuperscript{[30]} The mechanism by which HBV infection causes HCC is not completely understood. Evolution to HCC may be the direct effect of the virus itself, or it may be an indirect effect, through the process of the inflammation, regeneration and fibrosis associated with cirrhosis due to the HBV infection.\textsuperscript{[31,32]} HBV DNA has been shown to become integrated within the chromosomes.
Asia, HBV is the leading cause of chronic hepatitis, cirrhosis, and HCC\[37\]. The HBV carrier rates in Asia have been reported to be as high as 20% in the male population of Guangxi Province, China\[38\]. A recent study, conducted in China, showed that HBV carrier rates have fallen to 7.2% in regions where hepatitis B vaccination programs had been implemented\[39\]. In South Korea, the HBV carrier rates ranged from 5.0% to 8.6% in the 1970s and 1980s and have subsequently declined to 3.7%-5.7% as a result of national vaccination programs\[40,41\]. In other parts of Asia, the HBV infection rates remain high, particularly in countries in which vaccine programs have not yet been implemented. Notably, the HBsAg rates among Asians residing in the United States are similar to rates reported in their countries of origin, especially in first-generation immigrants to the United States\[42-45\]. Therefore, the disease burden from HBV, including mortality from liver disease progression and development of HCC, remains a major health problem among Asian Americans with CHB.

### PROGRESSION OF HEPATITIS B TREATMENT

Currently, six treatments are approved for hepatitis B, including interferon (IFN) (two formulations: IFN and PEG-IFN) and five nucleotide/nucleoside analogues (lamivudine, adefovir, entecavir, telbivudine and tenofovir) (Figures 3 and 4)\[46,47\]. The aim of hepatitis B treatment is to achieve sustained viral suppression of HBV replication. With viral suppression, the ultimate goal would be prevention of cirrhosis and HCC. Response to treatment...
is judged based on decrease in serum HBV DNA level, loss of HBeAg with or without seroconversion to anti-HBe, loss of hepatitis B surface antigen (HBsAg) with or without seroconversion to HBs antibody, normalization of serum ALT levels, and a decrease in hepatic inflammation on liver biopsy \[46,47\].

The importance of monitoring individuals with low-serum HBV DNA and normal ALT levels regardless of their HBeAg status has also become recognized in recent years. Serial ALT and HBV DNA monitoring every 3 mo for 1 year after the initial diagnosis and 6-12 mo thereafter is usually recommended to detect intermittent flares of hepatitis B \[37,48\]. This regimen is also useful to differentiate chronic active HBeAg negative hepatitis from inactive carriers in recently diagnosed HBV carriers. Treatment should be initiated regardless of the level
of viremia if active inflammation is also detected on liver biopsy. In the case of HBeAg negative CHB, treatment is continued indefinitely until HBsAg becomes undetectable. Nonetheless, close follow-up is important, and prompt retreatment is necessary if elevation of HBV DNA and ALT levels are observed. Therefore, achieving maximum viral suppression without the development of antiviral drug resistance, reducing progression to cirrhosis and decreasing the risk of developing HCC are the primary treatment endpoints.

**Interferon**

In 1991, conventional IFNα-2a was the first successful treatment approved for CHB with widespread use. Its major mechanism of action is immune modulation, although there is also a weak anti-viral effect. Peg IFNα-2a replaced standard IFN in 2005 due to improved pharmacokinetic properties and a less demanding injection schedule with comparable efficacy. Long-term follow-up of patients treated with conventional IFN therapy showed that responders had a decreased incidence of hepatic decompensation and HCC, and improved overall survival compared with non responders. Forty-eight weeks of therapy with Peg IFN results in a 27% rate of HBeAg seroconversion and 25% rate of loss of HBV DNA. Six months after discontinuation of therapy, the HBeAg seroconversion rates increased to 32%. Loss of HBsAg with the appearance of anti-HBs occurred in 4%-6% of patients after 1 year of treatment and 6 mo of post treatment follow-up. Even after discontinuation of IFN therapy, 12%-65% of patients lost HBsAg within 5 years of HBsAg loss. This results in the highest rate of off-treatment sustained response after 1 year of therapy. Achieving early virological response, defined as > 2 log drop in serum HBV DNA or suppression to < 100 copies/mL in the first 2 wk of therapy, is associated with induction of long-term remission after stopping therapy.

Despite the fixed duration of Peg IFN therapy and the lack of antiviral drug resistance compared with oral agents, the use of Peg IFN only accounts for no more than 10% of all prescriptions for the treatment of CHB in the United States. This low rate can be explained by the drug's substantial side effect profile and the need for administration by injection.

**Lamivudine**

Lamivudine (LAM) was the first nucleoside analogue reverse transcriptase inhibitor that was approved for use by the United States Food and Drug Administration (FDA) in 1998. Although it is not as used as commonly today due to the presence of better oral agents with higher genetic barrier to resistance; it played a major role in the transition CHB treatment and allowed reduction in cirrhosis and risk of HCC to be achieved with some success.

One-year therapy with lamivudine is associated with 16%-18% rate of HBeAg seroconversion; the HBeAg seroconversion rate increases to 50% with 5 years of therapy. Lamivudine therapy also results in 60%-70% HBV DNA suppression in HBeAg-negative CHB after 1 year of therapy. The durability of response is lower than the interferon therapy regardless of the HBeAg status and has been reported to range between 50% and 80% for HBeAg-positive CHB and 20%-25% for HBeAg-negative CHB patients.

Treatment of HBV with LAM has been shown to slow the rate of development of fibrosis, as well as decrease of HCC incidence. Use of LAM is associated with a significant risk of development of resistance with prolonged use. Five years of therapy can lead to 65%-70% rate of resistance. However, thorough review of studies investigating the LAM resistance during CHB treatment revealed a diverse range of methodologies to assess resistance. Studies that use purely genotypic methods report resistance rates at 1 year ranging from 14% to 32%. However, these may overestimate clinically relevant resistance. Studies that use virologic resistance report lower one year resistance rates, ranging from 6.4% to 15.4% and may provide more relevant measure of resistance. When comparing resistance rates with antiviral drugs in CHB, it is important to consider the methodology and definition of resistance used. In addition, baseline HBV DNA was closely related to the resistance rate and HBV DNA level at 6 mo on LAM therapy was an important predictor for LAM resistance at one year and later.

The largest and most compelling study suggesting that antiviral treatment might decrease the risk of HCC was a randomized, controlled trial of LAM vs placebo in patients with advanced chronic hepatitis B and high serum levels of HBV DNA. The primary outcome of the study was progression of liver disease, including an increase in Child-Pugh score, bleeding from esophageal varices and the development of HCC. The study was halted early because of a distinct benefit for the group on LAM treatment compared to the placebo group. Instead of continuing the study for intended 5 years, all received LAM at the end of 3 years on trial. In this study, at year 3, the rate of HCC was 3.9% among LAM recipients vs 7.4% among placebo recipients (P = 0.047). Other retrospective studies observed similar results.

**Adefovir dipivoxil**

Adefovir dipivoxil (ADV) was the first nucleotide analogue approved in United States in 2002 for the treatment of CHB. The arrival of this agent provided new insights into the treatment of CHB. ADV did not only have increased antiviral potency but also had an intrinsic stereochemical structure which was an important factor against the emergence of viral resistance.

One year of therapy with ADV leads to a 12% rate of HBeAg seroconversion and 53% rate of histological improvement in HBeAg-positive patients. Once HBeAg seroconversion occurs, it is sustained in 91% of patients. Like LAM, HBeAg-negative patients require
therapy indefinitely with ADV, and resistance is also a problem with prolonged ADV use. Persistence of viremia after 48 wk of therapy is linked to development of resistance. Resistance rates of 0%, 3%, 18% and 29% have been reported at 1, 2, 4 and 5 years of therapy. These high resistance rates and their potential renal toxicity have lead to declining use of ADV in light of newer therapeutic agents. Furthermore, ADV was highly effective for LAM resistant HBV.\textsuperscript{71,72}

\textbf{Entecavir}

During the period between 1998 and 2004, LAM and ADV for treatment naïve CHB and ADV for LAM-resistant CHB were the main treatment strategies available for CHB. In 2005, entecavir (ETV), a nucleoside analogue, entered the arena when it was approved in United States. It is a potent inhibitor of HBV polymerase at a dose of 0.5 mg daily resulting in 6.98 log\textsubscript{10} copies/mL decrease in HBV DNA levels compared to a 5.4 log\textsubscript{10} copies/mL reduction with LAM.\textsuperscript{73} In clinical studies, patients who received ETV for 52 wk achieved superior virological response, with HBV DNA < 400 copies/mL (67% vs 36%), histological improvement (72% vs 62%) and normalization of ALT (78% vs 70%) compared with those who received LAM.\textsuperscript{73} However, there was no difference between ETV and LAM in achieving HBeAg seroconversion (21% vs 18%). ETV is also superior to LAM in HBeAg-negative patients, but requires indefinite treatment to maintain viral suppression to prevent relapse.\textsuperscript{74-76} ETV demonstrates better virological suppression (91% vs 73%) and improved histology (70% vs 61%). In addition, analysis of two studies of patients who received continuous ETV for up to 5 years revealed that 94% of patients continue to have HBV DNA < 300 copies/mL at 5 years.\textsuperscript{\textsuperscript{81}}

In long term studies, up to 96% of patients (mainly HBeAg-positive CHB) had histological improvement and 88% of the patients had improvement in fibrosis score after 6 years of ETV therapy; this holds true even in patients with cirrhosis.\textsuperscript{77} ETV has also been shown to be superior to ADV in achieving rapid viral suppression within 2 wk of therapy. Even though a 48-wk therapy with ETV compared with ADV was associated with a higher rate of HBV clearance (58% vs 19%) and ALT normalization (76% vs 63%), there was no difference in the rate of HBeAg loss (18% vs 22%) and HBeAg seroconversion (15% vs 22%).\textsuperscript{78}

One of the most important differences from LAM and ADV is that, ETV has a high genetic barrier with a very low incidence of resistance. The cumulative incidence rate of resistance after 6 years of therapy in nucleoside-naïve patients remains low at 1.2%.\textsuperscript{81,82} The low resistance rate is related to both profound viral suppression and the requirement of at least 3 sites of genetic mutations to confer resistance. However, the chance for ETV resistance is much higher in patients who already developed LAM resistance.\textsuperscript{80} ETV therapy has also been associated with HBsAg loss, improvement of liver histology, decreased risk of HCC and very low to undetectable HBV DNA levels.\textsuperscript{81,83} The ability to decrease the incidence of HCC in patients with CHB has been the most exciting attributes of antiviral therapy. Recent report from Hosaka et al.\textsuperscript{80} compared the incidence of HCC in 472 ETV-treated patients and 1143 non-treated HBV patients. The drug mutation resistance was 0.8% (4/472) in the ETV group. The cumulative HCC incidence rates at 5 years were 3.7% and 13.7% for the ETV and control groups, respectively (P < 0.001). The treatment effect was found to be greater in patients at higher risk of HCC.

\textbf{Telbivudine}

While newer treatments for LAM-resistant disease were still under investigation, telbivudine (TLV), another nucleoside analogue was approved by the FDA in 2006 for treatment of chronic CHB. In HBeAg-positive CHB patients, the rate of HBeAg seroconversion with TLV therapy was 22% and 30% at 1 and 2 years respectively. Viral suppression was limited to HBV DNA levels of < 300 copies/mL after 1 and 2 years of therapy in 60% and 56% of HBeAg-positive patients.\textsuperscript{84} In HBeAg-negative CHB patients, HBV suppression was noted in 88% and 82% of patients at 1 and 2 years of therapy, respectively.\textsuperscript{84,85} Resistance to TLV has been reported to be 21.6% in HBeAg-positive patients and 8.6% in HBeAg-negative patients after 1 and 2 years of therapy respectively. Although TLV barrier to antiviral resistance is higher then LAM, is not recommended as a first-line agent.\textsuperscript{87-89} Although this treatment is not used often due to its high rate of resistance it is effective and safe for the prevention of mother-to-child transmission of HBV from chronically infected mothers with a high degree of infectivity late in pregnancy.

Analysis of the baseline characteristics of the patients enrolled in the GLOBE trial revealed important predictive factors of response to therapy. The strongest predictors of achieving a good response to TLV therapy in HBeAg-positive patients were serum HBV DNA < 9 log\textsubscript{10} copies/mL, or ALT $\geq$ 2 times the ULN at baseline with undetectable serum HBV DNA at week 24 of therapy.\textsuperscript{88} Extensive review of TLV for treatment of hepatitis B indicated that there was a specific group of patients who are likely to achieve good therapeutic response with TLV. Patients with low baseline HBV DNA who could achieve negative HBV DNA at week 24 had the best outcome with TLV.\textsuperscript{87} With this data, LAM and TLV can be used in countries where cost is a major concern by selecting patients with favorable baseline HBV DNA and ALT levels. Another important aspect of TLV is its renoprotective effect as recently reported by Gane et al.\textsuperscript{89} In approximately 2500 patients treated with TLV, there was a trend towards in increased GFR in both compensated and decompensated CHB. The mechanism of this renoprotective effect by TLV is unknown.

\textbf{Tenofovir}

Rescue therapy for patients with viral resistance to the nucleoside analogues was the usage of adefovir until 2008 when, tenofovir disoproxil fumarate (TDF), the
second nucleotide analogue was approved for the treatment of CHB. It is structurally related, but more potent than ADV. Forty-eight weeks of TDF compared with ADV therapy in HBeAg-positive CHB resulted in more patients achieving viral suppression defined as < 400 copies/mL (76% vs 13%), normalization of ALT (68% vs 54%), histological improvement (67% vs 12%) and HBsAg loss (3.2% vs 0%) [91]. Data from the TDF trials revealed an excellent durability of response, with a viral suppression (HBV DNA < 400 copies/mL) of 99% and 100% in HBeAg-negative and HBeAg-positive CHB respectively after 4 years of therapy [92,93]. Sub-analysis of the Asian subset of 145 patients revealed similar efficacy (97%) in achieving viral suppression defined as HBV PCR < 400 copies/mL. Four years of TDF therapy has led to HBeAg loss in 41% of patients and HBeAg seroconversion in 29% [94]. TDF is also superior to ADV in achieving increased viral suppression (93% vs 63%), an improved inflammatory score and viral suppression (71% vs 49%) in a phase III study of HBeAg-negative patients [95]. However, besides profound viral suppression, the most impressive characteristic of TDF is that no resistance has been detected to date with 5 years of follow up [96,97]. Due to these excellent features, TDF is recommended as first line agent for treatment-naive CHB patients. Furthermore, treatment with TDF for 5 years showed regression of cirrhosis in 74% of those who showed cirrhosis at baseline [98].

**Emtricitabine**

Emtricitabine is a nucleoside analogue structurally similar to LAM. Emtricitabine was approved by the FDA since 2003 for treatment of HIV infection and is not approved by the FDA for CHB. It is currently being studied as an add-on to TDF therapy in the form of Truvada (tenofovir 300 mg/emtricitabine 200 mg). Like lamivudine, its use as monotherapy for treatment of CHB is limited by its intermediate genetic barrier to resistance. Two years of emtricitabine therapy is associated with 13% risk of development of resistance [99].

A randomized trial in ADV-experienced patients showed equal efficacy in viral suppression to < 400 copies/mL between tenofovir and Truvada at 24 wk of therapy [100]. After 24 wk in the randomized arm, patients were switched to open label Truvada if they had detectable HBV DNA defined as > 400 copies/mL. Eighty one per cent of patients in each treatment arm achieved serum HBV DNA < 400 copies/mL at the end of week 48 according to intention-to-treat analysis [101]. The presence of baseline ADV resistance or LAM resistance did not impact the efficacy of TDF nor Truvada. Both TDF and Truvada were equivalent through week 168 of therapy in achieving viral suppression at a rate of 82%, independent of pre-existing ADV or LAM-resistant mutations [102].

**ROLE OF ANTIVIRALS IN PREVENTION OF HCC RECURRENCE**

With the advent of antiviral therapy, it is now possible to reduce inflammation, regress cirrhosis and reduce the incidence of HCC in patients with CHB. The incidence of HCC recurrence after resection of HBV-related HCC is high. Newer data has shown that there is a role for antiviral therapy for those who have already developed HCC. Since 2005, there have been retrospective studies, small and large in numbers that showed improvement of survival in patients who received concomitant antiviral therapy after curative liver resection and local tumor ablation [103-107]. Treatment with nucleoside/nucleotide analogues may prevent de novo primary tumors and further progression of liver disease, thereby decreasing recurrent HCC. Recent large cohort studies further confirmed the benefit of antiviral therapy in this group of patients with decrease in mortality with the antiviral treatment [108,109]. The longest survivors of those who benefited from antiviral therapy following the existing tumor ablation have reached over 12 years (Hann et al, personal communication). This novel treatment strategy may offer a significant alternative to liver transplantation to relieve the current graft shortage.

**VIROLOGIC BREAKTHROUGH, COMPLIANCE AND SAFETY OF TREATMENT**

As noted above, the development of anti-viral resistance is a barrier in achieving successful therapy in CHB. In large retrospective review of 11000 CHB patients on nucleoside/nucleotide therapy, mean adherence rate to therapy was 87.8% with 1-year persistence of 81%. Although adherence to CHB therapy is high, new and younger age patients tend to be less compliant [100]. In a study of 148 CHB patients on nucleoside/nucleotide therapy with mean follow-up of 3 years, 39 patients had at least one virologic rebound with 38% having no genotypic resistance and 10 patients with further HBV DNA decline while continued on current re-treatment [106]. Medication non-adherence is a common cause of intermittent virologic rebound and should be addressed before changing therapy. In a study of 84 patients treated with LAM, ADV, or ETV who stopped therapy after reaching defined endpoints, 42% of HBeAg-positive and 47% HBeAg negative patients had virologic relapse with HBV DNA more than 1000 copies/mL at a mean of 4.3 mo [107].

Concerns about the possible lose of bone mineral density (BMD) and has been raised from the results of clinical studies on CHB treatment [108,109]. BMD loss has been reported in chronic liver disease. However, accelerated BMD loss has been reported in patients specifically on TDF [108]. This BMD loss has raised concerns regarding the long term safety of TDF. BMD should be monitored in patients on TDF with bone density scans and factors that also contribute to bone loss should be given consideration when selecting a treatment option for CHB [108,109]. Like BMD, renal function is frequently impaired in patients with compensated CHB. These oral antiviral agents
are primarily eliminated unchanged through renal route. Therefore, inpatients with renal insufficiency, dose reduction and/or increased dose intervals are recommended. Renal impairment is frequent after long-term treatment with adefovir\textsuperscript{[10]}. Similarly, a decrease of eGFR has been observed in retrospective cohorts of CHB patients during long-term tenofovir or entecavir-treated\textsuperscript{[11]}.}

**CONCLUSION**

Although a vaccine has been available for hepatitis B since 1982, this chronic infection is still far from eradicated across the world. Timely use of nucleotide/nucleosides may improve liver function and increase survival in patients with hepatic decompensation. Maintained suppression of HBV replication with antiviral therapy halt the progression of liver disease, may reverse liver fibrosis, and can reduce the development of cirrhosis and HCC. Due to the availability of effective and potent treatment options for HBV, there has been a decrease in the proportion of annual liver transplants performed for this indication\textsuperscript{[11,12]}. However, one must remember that this can only achieved with an excellent compliance on the part of patients, early detection of drug resistance and correct choice of medications. Nonetheless, current therapies may not always prevent all adverse sequela. HCC must be monitored using ultrasound and α-fetoprotein assays to improve outcomes by increasing early detection and the chance of curative treatment. Developing safe and affordable agents as well as management strategies to improve sustained HBV suppression should be the ultimate goal in the treatment of chronic HBV infection.

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