Choice of Oral Drug for Hepatitis B: Status 2011

Asokananda Konar

Chronic hepatitis B (CHB) is a global public health challenge with an estimated 350 to 400 million people with chronic HBV infection, despite the availability of an effective vaccine. CHB is particularly prevalent in the Asia Pacific region and sub Saharan Africa, where the infection is acquired predominantly during the perinatal period or early childhood. Perinatal infection leads to chronicity in 90%, compared to 20-40% in early childhood infection and 10% infected in adult life. This large carrier pool worldwide may act as a global liver disease burden, of which 15-40% progresses eventually to cirrhosis and hepatocellular carcinoma (HCC).

THE NATURAL COURSE OF CHB INFECTION (Fig.1)
The natural history is highly variable at the individual level but depends on the age of infection. The classic description of the natural course consists of Immune tolerance phase, Immune clearance phase, Inactive carrier phase and Reactivation phase. Immune tolerance phase signifies peaceful coexistence of the virus and the host, without any liver injury. It occurs following perinatal transmission and is characterised by presence of HBsAg, HBeAg, high level of HBV DNA and normal ALT. Liver histology classically shows minimal hepatitis and does not progress to advanced fibrosis. This phase may last for years and does not occur with adolescent or adult age infection. They are not considered as candidates for therapy. Following the immune tolerance phase the infected persons, in their twenties and thirties, pass on to a stage of immune clearance, when host immune system interacts with the infected hepatocytes with a view to eliminate them. This results in necroinflammation in liver with raised ALT and some reduction in the HBV-DNA level.

The immune clearance phase is highly variable in frequency and duration. Repeated cycles of injury (necroinflammation) and repair (fibrosis) leads to increased risk of progression to cirrhosis and HCC. In most cases there is a natural seroconversion to anti HBe status when liver history becomes rather inactive.

Inactive carrier phase has continued presence of HBsAg, absence of HBeAg but presence of Anti HBe, normal ALT and low HBV DNA. This phase may be durable and lasts for a long time.

However in some patients there is a further phase of reactivation with high ALT, higher HBV DNA, and presence

Fig.1: Natural history of chronic hepatitis B virus infection. HBsAg, hepatitis B surface antigen
of anti HBe. In these patients viral replication persists with further liver injury and presence of mutant viruses (pre-core and basal core promoter mutant) and this stage is designated as HBeAg negative CHB. Progression to cirrhosis in chronic HBV carriers occur at a rate of 2-7% annually and 3% cirrhotic decompensate per year. The 5 yr. Survival rate for compensated cirrhotic is 84% but drops to 14-28% who have decompensated cirrhosis. The estimated life time risk of death from liver cancer in patients with CHB infection is as high as 20-25%. Recently the REVEAL study has shown that the HBV-DNA level across a biologic gradient is very strongly predictive of the risk of disease progression to cirrhosis and HCC.

THE GOALS OF THERAPY IN CHB
The ultimate goal is to prevent development of cirrhosis, its decompensation and development of HCC. However these distant goals are not addressed in clinical trials lasting for 12-24 months. Hence certain surrogate markers are devised for monitoring during therapy, normalisation of ALT, HBV DNA suppression to undetected level, histological improvement has been observed in almost all RTC. HBeAg serconversion to anti HBe has been one end point which is important and has been observed in almost all RCT. On the other hand HBsAg loss and seroconversion to anti HBs would be the target for HBeAg negative disease.

Of all the end points of therapy, HBsAg loss is probably the most robust surrogate marker, however it is difficult to achieve with current therapy with interferons and nucleoside analogs.

The issue of eradication of virus has become unrealistic because of the persistence of ccc DNA within the hepatocytes which acts as a template for further viral replication. Current anti-viral therapy has not shown any decline in intrahepatic ccc DNA, which persists within the nucleus of the hepatocytes till cell death. Hence we are using changes in short term virologic, biochemical and histological parameters to infer the likelihood of long term benefits in CHB therapy.

Which persons with Hepatitis B should be treated
(a) Patients for whom therapy is indicated
i. Patients with acute liver failure due to hepatitis B.
ii. Patients with acute flare of CHB, characterised by very high ALT (>10 N).
iii. Decompensated cirrhosis - cirrhosis with complications like ascites, hepatic encephalopathy or varicial bleeding. No controlled trials have been conducted in these population but therapy with anti viral (nucleoside analogs) has been recommended in recent NIH, consensus statement, because of their life saving effects. Interferon are contraindicated.
iv. Compensated cirrhosis with HBV DNA>2000 IU, even with normal ALT and HBV-DNA <2000 IU but elevated ALT.
v. Patient who are HBsAg(+) and receiving chemotherapy or immune suppression, are at risk of disease reactivation and should receive pre-emptive anti viral therapy with nucleoside analogs.

(b) Patients for whom therapy may be indicated (Fig.2)
i. Patients in the immune-active phase with, HBeAg(+), high ALT (>2N), high DNA (>20000 IU/ml) and active histology may be treated. These groups of patients may be watched for six months for any spontaneous seroconversion before starting therapy.

ii. Patients in the reactivation phase - they are usually HBeAg Negative, with fluctuating ALT and moderately high HBV-DNA (>2000 IU/ml). Histology may show inactive cirrhosis. These groups of patients may need long term treatment with NA.

(c) Patients for whom therapy is not routinely recommended
i. Patients in immune-tolerant phase.
ii. Patients in inactive-carrier phase (low replicative)
iii. Patients with latent HBV infection (HBsAg Negative, HBV DNA positive)

CHOICE OF THERAPY FOR CHB
Oral nucleoside analogs vs. Interferons: Therapy with oral agents (NA) usually longer, often indefinite in duration, when compared to treatment αpeg interferon given for 48 weeks. Peg interferon for a finite duration results in better HBeAg and HBsAg seroconversion rate compared to 1yr of NA therapy. However this small advantage comes
at a significant cost of injection therapy, side effects and medical expenses. In fact extending oral therapy to more than a year achieves the same rate of serological outcomes and HBeAg seroconversion can attain 50% with 5 yrs of NA therapy. HBsAg loss and seroconversion to anti HBs continues to occur with both peg interferons and nucleoside analogs. Though Peg interferon therapy does not encourage viral mutation and therefore avoids resistance, new generation antivirals (Tenofovir & Entecavir) also have a favorable resistance profile.

Nucleoside analogs have demonstrated actively in reversing hepatic fibrosis, cirrhosis and hepatic decompensation. In fact treatment with these agents are life saving since the widespread use of NA therapy for last decade, the number of CHB patients in the US, registered for liver transplantation has fallen by a third.  

Nucleoside Analog  

Oral nucleoside / nucleotide agents have become available for last decade and at present we have 5 agents approved by FDA for use in chronic hep B. Hepatitis Be antigen loss and seroconversion to anti HBe occurs in about 20% patients with HBeAg(+) disease when treated for 1 yr or a range of average HBV DNA suppression from 5 to 7 log10 IU/ml. 

Nucleoside Analog  

Fig.3: Comparisons of the virological and biochemical endpoints achieved during 1 year (48-52 weeks) of animal therapy in patients with HBeAg-positive and HBe-Ag-negative chronic hepatitis B

Durability of HBeAg seroconversion after a consolidation phase of 6-12 months is about 80% in western population (lower in Asian) and uniform across oral agents are a range of HBV-DNA suppression from 4 to 7 log10 IU/ml.

In registration trials clinical endpoints were measured at 1 year, Lamivudine and Adefovir were compared to placebo and were statistically superior to placebo in achieving virological, biochemical, serological and histological endpoints. In the registration trials for entecavir, telbivudine, and tenofovir, these agents were superior to comparator (entecavir and telbivudine vs. lamivudine and tenofovir vs. adefovir), though serological endpoints were similar.

Loss of HBsAg during one year of oral NA therapy is limited but extended therapy can yield HBsAg loss similar to peg interferon therapy.

Most oral agents are approved for 1-2 years of therapy, however, these NA are used indefinitely especially in patients with advanced fibrosis, cirrhosis and decompensated liver disease.

Lamivudine

First introduced in 1999, is an L-nucleoside analog that interferes with HBV DNA polymerase activity by chain termination. At a daily dose of 100mg, treatment for 52 weeks results in HBV DNA suppression of 5.5 log10 copies/ml
in HBeAg (+) patient, 4.7 log10 copies/ml in HBeAg negative patients. 1 yr HBeAg seroconversion rate is approximately 20% and improves hepatic histology in 50-65% patients. Its current use is limited by high frequency of resistance (upto 30% in 1yr and upto 70% in 5 yrs. therapy). Lamivudine resistance results in loss of clinical benefit and may have disastrous effect on patients with advance liver disease.

**Adefovir**

A nucleotide analog that inhibit HBV DNA polymerase by chain termination was the second drug approved for CHB. In registration trials, HBV DNA suppression of 3.5 - 4 log10 copies/ml were achieved over 48 weeks of therapy. HBV DNA suppression was relatively slow and HBeAg seroconversiom of 12% has been reported. Its appeal has been further lessened by primary non response (failure to reduce HBV DNA by 2 log10 over 6 months) affecting 20 to 50% patients. The advantage of adefovir lies in the fact that it has no cross resistance to Lamivudine and was the drug of choice for Lam resistant patients. Resistance rates are slow to appear but become substantial when used for 5 years in HBeAg negative patients. Potential renal toxicity prevents further escalation of its dose of 10mg/day.

**Entecavir**

A cyclopentyl guanosine analog which has profound activity against HBV. In registration trials Entecavir was superior to Lamivudine in degree of suppression of HBV DNA 6.9 vs. 5.5 log10 copies/ml in HBeAg positive patients and 5.0 vs 4.5 log10 copies/ml in HBeAg negative patients. Undetected HBV DNA at the end of 48 weeks was 67% in HBeAg (+) (vs 36% with Lamivudine) and 90% in HBeAg (-) patient (72% with Lam). However HBeAg seroconversion rate was similar (21% vs. 18%). HBsAg loss at the end of 2 yrs was 5% vs 2% in Lam treated patients. It has a very high barrier to resistance and at the end of 5 yrs therapy in NA naive patients a resistance rate of 1.2% has been reported. However in Lam resistant patients entecavir resistance emerged in 7% in 1yr to 43% in 4 yr therapy with 1mg/day dosage.

**Telbivudine**

A potent L-nucleoside that causes chain termination. It was superior to Lamivudine in suppressing HBV DNA (6.4 log vs 5.5 log10 reduction in HBeAg(+) and 5.2 log vs 4.4 log10 reduction in HBeAg(-) patients) HBeAg seroconversion was 23% (vs 22% in Lam) in 1 yr and rises to 30% at the end of 2yrs. Antiviral resistance of 5% at year 1 and 25% at year 2 in HBeAg(+) patients and 2% at year 1 and 11% at year 2 in HBeAg (-) patient has reduced its appeal as an antiviral. However GLOBE trial has shown for the first time that those patients with undetected DNA at 24 weeks will have a very low resistance rate at year 2 (4% in HBeAg (+) and 2% HBeAg (-)patients)12.

**Tenofovir**

Approved in 2008 for use in CHB. It is an oral acycline nucleotide analog similar to Adefovir. In 2 RCT's over 48 weeks oral Tenofovir was compared to adefovir and has been shown to reduce HBV DNA by 6.2 log10 IU/ml and suppressed HBA DNA to undetected Levels in 80% compared to 13% in the adefovir group. HBeAg seroconversion was 27% and HBsAg loss was 6% at the end of 2 yrs of continuous therapy. In HBeAg(-) patients DNA suppression of 4.6 log10 µ/ml was achieved and undetected DNA at the end of 1 yr was 95% (vs 64% in Adefovir). No evidence of resistance was seen over 2 years of therapy. High frequency of primary non response to adefovir has not been observed in Tenofovir treated patients. However Tenofovir has the potential to be nephrotoxic. In view of its superior anti viral effect, lack of primary non response and excellent resistance profile it has replaced adefovir in clinical practice.

**Other oral agents**

Emtricitabine and clevndine are L-nucleoside analogs that has anti viral activity against HBV but are not approved in the USA or Europe. Emtricitabine is similar to Lamivudine in its efficacy and resistance profile. In combination with Tenofovir it has been used in HBV / HIV co-infection. Clevndine, based on animal studies, has been predicted to eradicate HBV ccc DNA and to yield sustained virologic response. However in clinical trials it has not been able to improve upon existing antivirals.

**Durability of Response**

In HBeAg+ patients, consolidation treatment with oral agents for at least 6 months after seroconversion has led to durable response in 80% of western patients but the rate substantially lower in Asian patients. A recent data from Asia13 shows that baseline HBV-DNA can predict durability. HBV DNA <108C/ml has 11% replace (89% durability) vs 44% relapse (56% durability) when HBV-DNA at base line was >108 copies/ml.

In HBeAg negative patients one year therapy has resulted in relapse in virtually all patients who have stopped therapy. Because one year therapy achieves durable response in so few treatment is continued beyond 52 weeks. It works in preventing progression of disease which was shown elegantly from Taiwan in 2004 14.
Long term treatment with NA is safe and can maintain and enhance clinical endpoints, however one has to monitor them for any evidence of resistance.

**CHOICE OF ORAL AGENTS**

Based on superiority in efficacy and resistance profile in RCT entecavir and tenofovir have been recognised as the best agent to use as first line therapy. Measurement of HBV DNA at 24 weeks can predict the likelihood of subsequent sustained virologic response. Same anti virals may be continued if there is full suppression (<60 IU/ml). Partial responders (60-2000 IU/ml) may need another drug if the initial drug has a low genetic barrier. Non responders (>2000 IU/ml) will certainly need another drug of higher potency (The ‘Road Map’ proposal).

Although tenofovir and entecavir are both ideal first line drugs, tenofovir may be preferred in patients who are Lamivudine exposed, and in young women who plan to have family, on the other hand entecavir is preferred in older patients, NA naive and with other medical condition that increase the risk of renal failure.

**REFERENCES**