Review Article

Treatment of chronic hepatitis B

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INTRODUCTION:

Chronic hepatitis B is a serious clinical problem with worldwide distribution and has been well documented in Pakistan (1,2). Chronic hepatitis B is important in Asia pacific region because of its perinatal mode of transmission and high prevalence rate in early childhood where the carriage of hepatitis B virus (HBV) ranges from 0.1-20% (1-3). Chronic hepatitis B virus infection generally consist of an early replicative phase which is characterized by presence of hepatitis Be antigen (HBeAg) and high levels of serum HBV DNA and alanine aminotransferase (ALT) may be normal or abnormal (3). A late phase involves immune clearance of HBV and destruction of infected hepatocytes which may be manifested by more marked increases of aminotransferase levels and spontaneous, as well as treatment related, HBeAg sero-conversion is common (3).

It is likely that almost all hepatitis B carriers who are HBeAg positive will eventually, even if untreated, spontaneously seroconvert (4). This event can sometimes take many years to occur, and longer the duration of ongoing hepatitis prior to sero-conversion, the greater is the chance of progression to cirrhosis (3-4). Therefore, antiviral therapy to prevent this progression to cirrhosis is important goal of treatment of hepatitis B virus infection.

DEFINITIONS:

Seroconversion means loss of HBeAg and appearance of anti HBe. *Biochemical response* means normalization of ALT. *Virological response* means loss of HBV DNA. *Histologic response* means reduction of necroinflammation and liver fibrosis by 2 points of Histologic activity index (HAI). *End of treatment response (ETR)* means normal ALT,

loss of HBeAg and HBV DNA at the end of treatment. *Sustained response (SR)* means all of above as ETR measured at least twice at one month apart after the end of treatment. *HBeAg-positive hepatitis B* means elevated ALT and presence of HBeAg. *HBeAg negative hepatitis B* means elevated ALT and absent HBeAg and detectable HBV DNA. This is also called precore mutant strains. *Inactive HBsAg carrier* has normal ALT, absent HBeAg and undetectable HBV DNA. *YMDD mutant strains* appear during lamivudine therapy. This is as opposed to "Wild Type Virus" which is capable of generating HBeAg.

GOALS OF TREATMENT:

The primary goal of treatment in chronic hepatitis B is to eliminate or permanently suppress HBV replication. The short term goal is to ensure the loss of HBeAg (with appearance of anti HBe and /or loss of HBV DNA or significant suppression with ALT normalization at the end of the treatment. The ultimate goal of is to decrease the progression to cirrhosis and /or hepatocellular carcinoma and thus improve survival (3,4).

CURRENT AVAILABLE TREATMENTS:

Alpha Interferon

Alpha Interferon given 5 MU subcutaneously daily or 10 MU subcutaneously every other day for 4-6 months has given a seroconversion rate of 35-40% compared to 10-20% of controls (4). This has been in patients with ALT > 3 times upper limit of normal (ULN). In patient with lower ALT, the conversion rates have been lower. In those patients who achieve HBeAg sero-conversion, more than 80% cases are sustained and it may be followed by loss of hepatitis B surface antigen (HBsAg). However, loss of HBsAg has been rare in Asian patients (5). Seroconversion occurs either during or shortly after the therapy and may occurs upto one year after initiation of treatment (6). A biochemical "flare up" evidenced by a rise in serum aminotransferase levels often coincides with a fall

in HBV DNA and was mostly observed near the end of treatment in responders to INF-a (6). Patients treated with interferon have significant side effects and hepatitis flares may lead to hepatic decompensation in some patients with cirrhosis. Also INF is contraindicated in patients with uncontrolled seizures, autoimmune disease, cardiac arrhythmias and decompensated cirrhosis (6). Patient with high ALT and high HIA score and low HBV DNA level respond better to INF (5,6).

Lamivudine

Lamivudine has extensively been studied and has been shown to the effective in HBV DNA suppression, ALT normalization and improvement of histology in both HBeAg-positive and HBeAg-negative (pre core mutant) patients (5-7). A dose of 100 mg per day produces HBeAg sero-conversion in proportion to pre treatment ALT levels. A response of 65% in patients with ALT >5 x ULN and 25% in patients with ALT 2-5 x ULN and only 5% in those with ALT < twice ULN has been noted (5,6). Lamivudine is a dideoxynucleside that inhibits DNA synthesis by terminating the nascent proviral DNA chain (6). Lamivudine has been found to be effective in Asian patients with chronic hepatitis B when used for extended period of time (8). Its efficacy has been demonstrated in patients with HBeAg-positive and HBeAg-negative chronic hepatitis B (9). Patient with elevated ALT and active histologic disease were most important factor in prediction of HBeAg loss after lamivudine therapy (10). Prolong therapy with lamivudine increases the proportion of HBeAg sero-conversion and those patients who achieve this have more than 80% sustained responses (5,11). Lamivudine has been well tolerated but prolonged use has resulted in emergence of YMDD mutations and reappearance of HBV DNA and frequent ALT elevation (5). The likelihood of developing resistance increases with duration of therapy and is more likely to develop in individuals with high baseline HBV DNA, high baseline ALT, high HAI score and high body mass index (6).

Other Promising Therapies

The other promising nucleoside analogue which has recently been approved by FDA for treatment of chronic hepatitis B is adipovir depivoxil. In doses of 10 mg per day it causes significant suppression of HBV DNA and results in improved histology (7). It has been effective in lamivudine – and famciclovir – resistant HBV strains. A seroconversion of 12% was found as compared to 6% of placebo (7). So far no resistance has been noted with adefovir dipivoxil. High doses have lead of nephrotoxicity which is dose related and reversible. Entecavir is another nucleoside analogue which is showing promising results in early trials especially in lamivudine – resistant strains (7). There are number of other agents under trial which include thymosine alpha, monoclonal antibodies, therapeutic vaccines, interlukin-12 (4,5, 12) and Chinese herbal medicines (13).

Combination Therapy

Interferon alfa given 9 MU three times a week with lamivudine 100 mg daily for 52 weeks as monotherapy showed that seroconversion was 35 % with combination therapy and 19% with monotherapy and there were significant improvements in HAI score with combination treatment (6). Sequential treatment with lamivudine followed by interferon has also shown encouraging results (6).

Combination of two nucleoside analogues has been tried. Lamivudine 150 mg daily with famiciclovir 500 mg three times daily was compared with lamivudine 150 mg as nonotherapy in HBsAg positive Chinese patients. HBeAg loss was noted in 50% patients on dual therapy compared to 33% on monotherapy and there was sustained loss of HBV DNA is patients on dual therapy (6).

SPECIAL GROUPS:

Children can be treated with lamivudine and interferon. Pregnancy is not a contra-indication for lamivudine. Patients with HIV can also have lamivudine included in their

therapy and has been helpful for effective HBV suppression in these patients (5). The data on patient with concurrent diseases like hepatitis C and hepatitis D is limited.

Table-1. Current Treatment Recommendations

Therapy	Category	Recommendations
Interferon	Normal ALT	No treatment. Observe.
	Elevated ALT (> 2 x normal)	
	• HBeAg – positive	IFN-alfa 5 MU daily or 10 MU thrice weekly x 16 weeks.
	• HBeAg – negative	IFN-alfa 5 MU daily or 10 MU thrice weekly x 12 months
Lamivudine	Normal ALT	No treatment. Observe.
	Elevated ALT (> 2 x normal)	
	• HBeAg – positive	Lamivudine 100 mg daily x 1 year or until clearance of HbeAg.
	• HBeAg – negative	Lamivudine 100 mg daily > 1 year
	• Cirrhosis	Lamivudine 100 mg daily
Interferon + Lamivudine		Not proven to be superior to either mono-therapy regime.
New Agents		
Famciclovir		Low efficacy compared with Lamivudine
Adefovir dipivoxil		10mg/day
Pegylated IFN		Ongoing studies

Modified from Ref-11.

WHO TO TREAT:

Patient with normal ALT respond poorly and should not be treated. Patient with elevated ALT at least twice the upper limits of normal and HBeAg-positive with or without detectable HBV DNA should be considered for treatment. Patient with HBeAg-negative (pre core mutant) should be considered for treatment if ALT is elevated and HBV DNA is present (14).

ROLE OF LIVER BIOPSY:

Liver biopsy is recommended before the treatment to determine the fibrosis stage and extent of necro-inflammation which may be helpful in guiding the anti viral treatment (5) and may help rule out other causes of liver disease (15). Patient should be advised of benefits, risks and limitation of biopsy.

WHICH DRUG TO START:

Patient with ALT level more than five times ULN should be started on lamivudine 100 mg daily. Patient with ALT between 2-5 times ULN and HBeAg positive can be started on either lamivudine or interferon. Patient with positive HBeAg and ALT levels of 1-2 times upper limits of normal are difficult to treat and observation with monitoring of ALT, HBeAg / HBV DNA and serial liver biopsy may be recommended in these patients (Table-1).

HOW TO MONITOR:

Patients on lamivudine should have ALT, HBeAg and /or HBV DNA initially monthly or at least every 2-3 months. After the sero-conversion, they should be monitored every 2-3 months with ALT, HBeAg and HBV DNA. Patient on interferon should be monitored with CBC, ALT, HBeAg and/or HBV DNA every 1-2 months.

After the end of the therapy, patient's ALT and HBV DNA and HBeAg should be checked every two months and HBsAg checked every three months.

WHEN TO STOP THERAPY:

Recommended duration of interferon therapy is 4-6 months irrespective of response. Subsequent follow up may show sero-conversion even at a later date. Patients treated with lamivudine can be advised to stop treatment when there is normal ALT, HBeAg sero-conversion with HBV DNA loss on two consecutive measurements at least one month apart.

GENERAL MANAGEMENT:

In addition to drug therapy, counseling of the patients is an important aspect of management. They should be provided information on infectivity and transmission of HBV and measures that can be taken for prevention. The importance of screening of family members and their vaccination should be stressed. Advice on alcohol use, high-risk behaviour and associated conditions should be provided. The need for regular follow up and monitoring should be meticulously discussed at the outset (5).

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