



Hepatitis-B : Recent Treatment

Vijay Gupta, Jamil-Ul-Hussain, Shally Vijay

The hepatitis - B virus (HBV) affects an estimated 350 million people around the world and hepatitis-C (HCV) affects an estimated 170 million (1). Many of those infected develop persistent disease and a proportion goes on to develop liver failure and cancer.

Hepatitis B Treatment

About 5% of adults (about 95% of neonates) infected acutely with HBV will go on to develop chronic infection with high levels of HBV DNA and surface antigen (2). These patients are divided into those who have positive HBe antigen (HBe antigen) and those who have HBeAg negative antigen. A proportion of eAg negative individuals have high loads of circulating DNA with precore or core promoter mutants form of virus. Liver Biopsy remains the gold standard in identification of patients with chronic hepatitis who may benefit from treatment. Although high ALT levels are associated with liver damage, patients with normal range may also have significant abnormal liver biopsy. patients with persistent eAg positive for more than six months indicating high level of replication, may be treated with Lamivudine, interferon-alfa or Adefovir. Treating these with HBeAg negative with high circulating HBV DNA levels (> 10 copies), High ALT is more challenging. The main aim of treatment of Chronic HBV infection is to suppress replication of the virus before there is significant, irreversible liver damage.

The initial end points of therapy are :

Sustained clearance of HBe Ag and HBV - DNA in the serum, improvement in the liver disease, indicated by normalization of alanine transferase (ALT) and a decrease in necroinflammation determined on liver biopsy .

The ultimate end points of treatment are sustained clearance of serum HBsAg and HBV DNA (by

PCR assay), decreased incidence of cirrhosis and hepatocellular carcinoma, and prolonged survival.

Interferon - Alfa

IFN-A is the only approved treatment for chronic HBV infection in most countries .IFNs have antiviral ,antiproliferative and immunodulatory effects . IFN-A therapy should be considered for patients with chronic HBV infection (i.e. HBsAg positive for more than six months) , who have evidence of active virus replication (i.e. HBeAg and serum HBV DNA positive by hybridization assay), and active liver disease (i.e. abnormal ALT and chronic hepatitis on liver biopsy).

IFN administered as subcutaneous or intramuscular injections in doses of 5 million units or 10 million units three times weekly for 16 weeks results in seroconversion from replicative to non- replicative HBV infection in approximately 35 % of patients with a concomitant improvement in liver histologic features (4).

Several factors associated with a favorable response to IFN treatment have been identified ;

A high pre treatment serum HBV-DNA level (200pg/ml), adult acquired HBV infection, liver histology indicating active disease, female gender, no concomitant HIV or HDV infection .

Adverse Effects of Interferon Therapy

Initial influenza like illness, fatigue, anorexia, weight loss, hair loss emotional liability & depression, bone marrow depression, induction of antibodies , unmasking or exacerbation of autoimmune disease.

IFN therapy is associated with a wide range of adverse effects. During the first 1-2 weeks of treatment , influenza like symptoms, including chills, fever, headache, malaise, muscle aches, nausea and anorexia are common. These symptoms can be reduced by increasing fluid intake,

Correspondence to: Dr. Vijay Gupta, Principal & Dean, Government Medical College, Jammu (J&K) India



administering IFN at bedtime and pretreatment with acetaminophen. Other possible adverse effects are during the course of treatment include fatigue, low grade-fever, mild weight loss, hair loss and emotional liability or depression. Although emotional problems are more common in patients with a history of neuropsychiatric illness. Mild myelosuppression is common and cell count should be checked during treatment. IFN has been reported to induce formation of a wide range of auto antibodies and to exacerbate previously undiagnosed autoimmune hepatitis; other less common adverse effects include worsening of diabetes, psoriasis and retinopathy. Several approaches have been tried to improve efficacy of interferon. Initially, conventional alpha - interferon has been used, but now PEG- IFN alpha-2a and 2b is being used following its successful trials in chronic hepatitis-C. PEG - IFN consists of a polyethylene glycol (PEG). Polymer which is attached to the interferon molecules resulting in delayed excretion and prolonged half life. PEG-IFN 1alpha-2a has shown in HBeAg positive Chronic hepatitis - B, loss of HBeAg, HBV-DNA suppression and alanine amino transferase normalization, which is twice as compared to conventional interferon, while the severity of side effects is similar (4).

Lamivudine

This nucleoside analogue inhibits reverse transcriptase and HBV -DNA enzyme necessary for HBV replications. Lamivudine is generally given in a dose of 100-300 mg daily. It is cleared by the kidney and adjustments may be necessary in those with impaired kidney function. Results of treatment are better in those with high ALTs levels. Those with initially normal ALT levels should probably not be treated. After 1 year, 45 % of initially positive patients have lost HBV-DNA with normal ALT, but only 15 % remain HBV-DNA negative 16 weeks after stopping the therapy (5). Exacerbations after stopping the therapy are due to viral resistance and to recrudescence of viremia. It is difficult to decide when to stop therapy. This could probably be done following HBsAg seroconversion and 18 months of therapy.

Combination Therapy

The combination of lamivudine with interferon increases the HBeAg seroconversion rate.

ribavirin may also be added in combination therapy.

Lamivudine Resistance

Unfortunately, lamivudine therapy is followed by viral resistance in a high proportion of cases. This develops with the return of viral replication in 27% of patients at 1 year, and 58% after 2 years of treatment and 69% after 5 years (6,7). This resistance is marked by amino acid mutations in a highly conserved YMDD (tyrosine, methionine, aspartate, aspartate) motifs of the active sites of the polymerase. These mutants impair HBV replication, but the virus is still pathogenic (8).

Even after YMDD mutations occur, HBV DNA and ALT levels as well as histologic scores tend to remain lower than baseline levels in immunocompetent patients. Until other antivirals are developed the approach to YMDD variants emerging during lamivudine treatment is to continue therapy (9). Patients on lamivudine who have developed resistant virus may benefit from alternate therapy with adefovir or interferon alpha.

Comparison of Interferon and Lamivudine Therapy

	Interferon	Lamivudine
Route of administration	Injection	Oral
Duration of therapy	4 Months	> 1 year
Tolerability	Poorly tolerated	well tolerated
HBeAg loss	33%	32-33%
HBeAg seroconversion	18-20%	16-20 %
Normalization of ALT	Confined to HBeAg Responders	>40%
HBsAg Loss during therapy	3-8%	2-4%
HBsAg Loss after therapy	80% over 9yrs	To be determined
Histologic improvement	confined to HBeAg responders	>50%
Retardation of fibrosis	Not demonstrated	20%
Viral resistance year	None	15-20%
Natural history	Reduced mortality decompensation, HCC	To be determined.
Pre-core mutant hepatitis-B	Limited response	>60%
Candidate range	Narrow	Broad



Other Anti-Viral Drugs used in Hepatitis-B

Famciclovir

It can effectively reduce serum HBV-DNA levels in patients with chronic hepatitis B and in those who have had a liver transplant, although the overall efficacy of this clinical agent is less than that of Lamivudine. Because of relatively weak potency of Famciclovir and cost associated with daily administration of 1.5 g of drug, it is unlikely that Famciclovir will ever be first line therapy for HBV infection .

Adefovir Dipivoxil

It is the oral prodrug of an acyclic nucleotide monophosphate analogue. Orally administered adefovir dipivoxil exhibits an inhibitory effect on both HIV and HBV reverse transcriptases. Importantly, Adefovir retains activity against various HBV stains that have acquired both Lamivudine and Famciclovir resistance. Adefovir has also been shown to be viral suppressive in patients with HIV/HBV coinfection, many of whom have Lamivudine resistance. Trials of both Adefovir monotherapy and Lamivudine/Adefovir combination therapy are currently underway in previously untreated and Lamivudine resistance patients (10).

In one of the study, it has been shown that the treatment with adefovir dipivoxil improved histological liver abnormalities, reduced serum HBV-DNA levels and normalized ALT levels. The absence of resistance mutations during 48 weeks of therapy is potentially important advantage, since the majority of patients with HBeAg negative chronic hepatitis-B will require long term therapy (11).

Dose of Adefovir dipivoxil: 100 mg/day for 4 weeks. Toxicity of Adefovir include renal insufficiency and frequent development of hypophosphataemia.

Entecavir

It is a carbocyclic deoxyguanosine analogue with potent Anti-Herpes and Anti-Hepadnaviral activity. Adefovir and entecavir are effective against all common Lamivudine-resistant variants, although higher doses of these compounds are necessary to inhibit the variants with multiple rather than single mutations (12).

Fialuridine or Fiau

It is also a nucleoside analogue. It is phosphorylated by viral and cellular enzymes and this phosphorylated analogue is a potent inhibitor of HBV-DNA polymerase activity. However, the clinical trial of more prolonged therapy was not possible because of development of severe toxicity (13).

Therapeutic Vaccines

Theradigm-HBV is a therapeutic vaccine that consists of three components - the viral protein ; a T-helper peptide ,which enhances immunogenicity ; and two palmitic acid molecules. The vaccine is capable of inducing an HBV-specific MHC class I-restricted cytotoxic T-lymphocyte response in healthy volunteers but results of trial of these vaccine in patients with chronic HBV infection showed only modest benefits (14).

Other Immunomodulators

Thymosin derivatives have been shown to regulate multiple aspects of T-cell function. Large randomized trials have failed to show any clear evidence of a sustained clinical or virologic effect (15).

Interferon- β and γ have been used as monotherapy and as combined therapy. Because of the limited sample size, there is insufficient information to determine the efficacy of IFN- β and IFN- γ either alone or in combination (16).

Glucocorticoids have been studied as monotherapy and in combination therapy with IFN-A. Increased viral replication occurs in association with glucocorticoids administration and prolonged therapy can delay seroconversion from HBeAg to anti-Hbe. Glucocorticoids in combination with IFN-A offer no advantage over IFn therapy alone.

Combination Therapy

The combination of Lamivudine and IFN did not show superiority over Lamivudine monotherapy in patients who had previously failed to respond to IFN alone. However, in vitro study and a preliminary in vivo study showed that the combination of Famciclovir and Lamivudine may be more efficacious than therapy with either agent alone. No treatment is indicated or available for asymptomatic non replicative hepatitis B carriers.



Whereas patients with decompensated chronic hepatitis B are not the candidates for IFN therapy, they may respond to Lamivudine, with reversal of signs of decompensations (17).

Special Groups

Patients Receiving Chemotherapy

Patients who are HBsAg positive prior to receiving the chemotherapy are at high risk of reactivation of HBV with high rate of subsequent morbidity and that prophylactic Lamivudine is effective and advisable in those patients (18,19).

Pregnancy

Perinatal transmission of HBV is a significant risk. Lamivudine to high viraemic HBeAg positive mothers in last month of pregnancy have been used with encouraging results (20).

Hepatic and Renal Failure

Interferon therapy in patients with cirrhosis may result in hepatitis decompensation. In contrast, Lamivudine therapy may be beneficial in decompensated liver. Lamivudine is also seen to be well tolerated in CRF patients.

HBV/HIV Coinfection

Chronic Hepatitis-B progress more rapidly in patients coinfecting with HIV than in HIV negative patients. Treatment protocol for antiviral therapy is however, similar to those used in immunocompetent individual; although only a few long term results are available. The Lamivudine in HIV and Hepatitis-B virus infection has been proven in short term studies. In Hepatitis-B and HIV coinfection Hepatitis-B antivirals are best administered with anti-retroviral therapy. Thus preventing the selection of HIV viral species which may be resistant to the drugs used for Hepatitis-B virus (21-23).

Liver Transplantation

For patients with end stage chronic Hepatitis-B, liver transplantation is the only potential lifesaving intervention. Re-infection of new liver is almost universal; however, the likelihood of liver injury associated with hepatitis -B in new liver is variable. Prevention of recurrent hepatitis-B after liver transplantation has been achieved by prophylaxis with hepatitis-B immunoglobulin and with nucleoside analogues such as lamivudine (24-26).

Histological evidence of improvement in liver disease is a significant improvement after therapy, especially when number of patients is low. In one study, it had shown that combination therapy significantly reversed necroinflammatory activity, compared with IFN-A monotherapy (84% versus 27%) The biopsy specimens is scored on the basis of KNOVELL histologic activity score.

Conclusion

As hepatitis-B is global health problem and patients with chronic hepatitis-B (CHB) carry a significant risk to eventually develop cirrhotic liver disease. Selection of appropriate patients for antiviral therapy depends on identification of HBV replication and an elevated alanine aminotransferase levels or histological liver disease. Pegylated interferon Alfa offers potent immunomodulatory and antiviral activity with potential of durability, by also with adverse effects and significant cost. The nucleoside or nucleotide analogs, lamivudine, adefovir and entecavir, suppress HBV replication and are extremely well tolerated but long term or even life long therapy is required. Most experience has been gained with lamivudine, but viral resistance occurs frequently. Newer analogue appears to be relatively free of this problem. Approaches using a combination of agents have promise but have yet to be proven superior to individual drugs alone.

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