Treatment Option for Chronic Hepatitis B

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Hepatitis B virus (HBV) infection has a worldwide distribution, with approximately 300 million individuals having chronic infection and are at risk for development of hepatocellular carcinoma[1]. Pakistan and it's neighboring countries, fall in the category of intermediate prevalence for HBV infection (3-50%)[1]. The measures for prevention of HBV infection, by infant and adult immunization, are being aggressively pursued in our country at all levels, since it is the only strategy which is likely to have an impact on the incidence of HBV infection. Unfortunately, people already infected with the virus do not benefit from the present immunization therapy. therefore, it is imperative to be aware about the options that are available for therapy of chronic HBV infection.

It is crucial to be selective in offering treatment for chronic hepatitis B (Cl IB) for three reasons: a) not all patients require therapy. b) spontaneous seroconversions also occur. c) the response to therapy is markedly different in various subgroups. Hence, a brief introduction of the serology in chronic hepatitis B is mandatory before making any comments about antiviral therapy.

Serologic Testing in Chronic Hepatitis B Virus Infection

I lepatitis B surface antigen (HbsAg) is often the first serologic marker which signifies the presence of HBV infection. Clinically, its persistence for longer than six months after an acute infection suggess chronic HBV infection. More commonly, patients present with HbsAg positivit\\ with or without elevation of serum alanie aminotransferase (ALT) in the absence of a history of acute HBV infection tests for virus replication: hepatitis B e antigen (HbeAg). hepatitis B e antibody (anti-Hbe) and HBV DNA (Table 1).

Table 1. Interpretation of serologic markers associated with HBV infection.

Acute Infection	
Early phase	HBsAg, IgM anti-HBc. HBeAg. HBV DNA
Window period	IgM anti-HBC
Resolved infection	anti-HBS. anti-HBC
Chronic Infection	
Carrier state	HBsAg, IgG anti-HBc
Replicative infection	HBsAg, HBeAg, HBV DNA, IgG anti-HBc
Non or low replicative infection	HBsAg, anti-HBe. IgG anti-HBc
Precore variants	HBsAg, anti-HBe. HBV DNA, IgG anti-HBC
Post Immunization	**anti-HBs**

The presence of HbeAg and HBV DNA signifies a replicative HBV infection. Conversely. absence of HbeAg and HBV DNA and seropositivity for anti-Hbe generally indicate a non-replicative infection. The presence of HbsAg and hepatitis B core antibody (lgG) is suggestive of hepatitis B carrier state.

Antiviral Therapy for Chronic Hepatitis B Patient Selection

On the basis of the serologic pattern, three common subgroups of patients can be identilied viz: chronic

}IBV carrier state. replicative chronic hepatitis B infection and non-replicative chronic hepatitis B infection.

The chronic HBV carrier state does not require any treatment even in those patients with minimal ALT elevations. There is data indicating that HBV carriers rarely develop progressive liver disease. However. these individuals are at risk of developing HCC and therefore. screening with atleast yearly serum alpha-feto-protein (AFP) and ultrasound should be considered.

The aims of treatnient in patients with chronic hepatitis B are: sustained suppression of HBV replication. remission of liver disease and improvement in clinical outcome. (Table 2).

Table 2. Aims of antiviral therapy for chronic hepatitis B.

Sustained suppression of HBV	Loss of HBVDNA
	HBeAg to anti-HBe seroconversion
	HBsAg to anti-HBs seroconversion
Remission of liver disease	normalization of serum ALT
	decrease in the necroinflammatory score
Improvement in clinical outcome	decrease in risk for hepatocellular carcinoma
	increased survival

Therefore, treatment of patients with non-replicative HBV infection is not recommended since the endpoint of treatment (HbeAg to anti-Hbe serocon version) has already been satisfied prior to initiation of antiviral agents. Replicative chronic hepatitis B infection without cirrohosis. is the group who potentially benefit the most from interferon therapy. This trend however is changing since the advent of less toxic nucleoside analogs. nowadays treatment of patients with decompensated HBV cirrhosis can also be undertaken safely.

Interferon Therapy in Chronic Hepatitis B

Interferon alpha (IFN) was the first agent to be approved for use in chronic HBV infection. It has antiviral, antiproliferative and immunomodulatory properties. Unfortunately, the cost, adverse effects and limited efficacy restricts its use to a very selective population of CHB patients. Following are best prognostic indicators of response to interferon: female sex, adult acquired HBV infection, low pretreatment HBV DNA, raised pretreatment ALT (> 2-1/2 times normal), active inflammation on liver biopsy, negative serology for delta virus and HIV. Therefore, in general, interferon therapy is restricted to individuals with replicative CHB infection with raised ALT levels in the absence of cirrhosis. Patients with normal ALT should not be considered for IFN despite the presence of active viral replicative markers, because the response in this subgroup of patients is poor. In patients who respond to IFN there is usually a flare in the liver disease prior to response, in those with cirrhosis this flare can precipitate decompensation[2]. Therefore, IFN is avoided in individuals with cilThosis unless administered in a closely monitored setting. Interferon therapy is administered subcutaneously, either 5mU daily or lOmU thrice weekly for 16 weeks. Careful monitoring for hematologic, psychiatric and endocrine side effects is recommended during therapy. Interferon therapy is associated with approximately 35% HBV DNA and HbeAg loss and only 10% HbsAg clearance[3], However, the response is durable and there is also data to support improved histology and clinical outcome together with a decrease in risk for hepatocellular carcinoma in sustained responders to interferon[4]. Children

with raised ALT and replicative infection have response rates similar to adults.

Nucleoside Analogues in Chronic Hepatitis B

The nucleoside analogues work by incorporating themselves into the active binding site of the viral HBV DNA polvmerase. HBV polvmerase is the enzyme primarily responsible for the replication ot HBV by reverse transcription, therefore interference with it's action inhibits virus production. Lamivudine is the only nucleoside analog approved for therapy of CHB. The oral administration and scarcity of adverse effects makes it a very attractive alternative to interferon in most patients. it's cost however may be prohibitive in some patients. Similar to interferon therapy, individuals with replicative HBV infection are candidates for lamivudine therapy. It is administered orally as 100mg once daily for at least one year. Generally lamivudine monotherapy for 1 year is associated ith a 30% HbeAg loss and 16-18% IlbeAg seroconversion rate[5-6]. Once again pretreatment ALT level is also an important determinant of response to lam ivudine therapy. The HbeAg seroconversion rate in patients with pretreatment ALT< 2 times upper limit normal (ULN) is 5% whereae in those with >5 times ULN could be as high as 64%[7]. There is convincing data that responders to lamivudine also have improvement in inflammation and fibrosis in the liver[6].

Lamivudine is equally effective in both interferon native patients as well nonresponders to IFN. In contrast to IFN, lamivudine is safe in patients with HBV cirrhosis. There is data demonstrating efficacy even in patients with advanced liver disease. In these individuals, further deterioration in liver function can be halted and there have been reports of improvement in liver function to the extent that liver transplantation was either postponed or averted[8]. Unfortunately. upto 25% of patients receiving lamivudine for > 1 year will develop lamivudine resistant YMDD mutants. The presence of these mutants during therapy is detected by re-emergence of HBV DNA and elevation of serum ALT levels. Interestingly. recent data suggests that despite the presence of these mutants there is continued improvement in liver histology[6].

Lamivudine monotherapy has been shown to be as effective as IFN and lamivudine combination therapy. Given the choice of two agents for antiviral therapy, it is at times hard to decide which to pick in an individual patient. Careful consideration of the age. comorbidities, liver histology, and patient preferences could be useful guides to choosing the appropriate regimen. Elderly individuals with comorbid illness and cirrhosis mav far better with lamivudine whereas a young patient could have the benefit of trying IFN first and reserve lamivudine for IFN failure.

Other promising agents which are clinical trials include adefovir dipoxivil and entecavir. These agents are in clinical trials presently, and preliminarv results are very encouraging. The future of antiviral therapy for HBV infection lies in combination therapy with two or more nucleoside analogues.

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