

Oral Treatment of Chronic Hepatitis B

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This review deals specifically with the currently available oral antiviral agents for chronic hepatitis B (CHB) virus infection. The different definitions and information are obtained mainly from various recently published regional and international guidelines. The detailed pathogenesis and parenteral treatment with different interferons is beyond the scope of this article. Pegylated interferon, despite its effectiveness in producing durable viral suppression and more sero-conversions, is not a treatment of first choice for internists and family physicians; moreover, use of interferons currently accounts for not more than 10% of all the prescriptions for hepatitis B treatment in US and Europe and is even less in Asia. Contrary to this, a lot of new oral molecules have been introduced recently in the treatment of hepatitis B and are gaining interest among clinicians. Therefore, an overview of treatment of HBV with oral agents alone is presented in order to acquaint general physicians, internists and gastroenterologists with studies in recent years. The literature is modified as per the need of clinicians in local communities.

Key Words

Chronic Hepatitis B, Oral treatment, oral antiviral agents

Introduction

Hepatitis B virus (HBV) is a partially double-stranded circular DNA virus¹. Of the two billion people infected, more than 400 million have chronic hepatitis²

There are different models reported for estimation of HBV-related problems. For the year 2000, the model estimated that 620,000 persons died worldwide from HBV-related causes: 580,000 (94%) from chronic infection-related cirrhosis and hepatocellular carcinoma and 40,000 (6%) from acute hepatitis B.

The results of treatment of CHB are based upon certain indicators, which include elevated serum aminotransferase levels (> 100 IU per milliliter), presence of HBV DNA in serum at a level of < 200 pg per milliliter, and a liver biopsy suggesting moderate or severe inflammatory activity³.

Approved oral treatment for chronic hepatitis B includes lamivudine, adefovir dipivoxil, entecavir, tenofovir and telbivudine—all of which belong to the nucleoside analog family.

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Mechanism of Action of Nucleoside analogs

All nucleoside analogs inhibit viral polymerase activity. The nucleoside analogs act by inhibiting three different enzymes: priming of reverse transcription, minus DNA synthesis (i.e., RNA dependent DNA polymerase activity or reverse transcription), and plus strand DNA synthesis (i.e., DNA dependent DNA polymerase activity) of the viral enzymes.

The effect of nucleoside analogs on viral polymerase activity results in a decreased production of infectious viral particles which therefore limits the spread of virus to uninfected hepatocytes. Intra-hepatic covalently closed circular DNA (ccc DNA) plays a role in determining the fate of hepatitis B viral infection. It has been reported that none of the currently available nucleosides is able to prevent the de novo formation of ccc DNA in infected hepatocytes like interferons⁴.

Terminologies used for hepatitis B infections

CHB is broadly divisible into: HBeAg positive (wild type) and HBeAg negative disease (mutant type) based on the HBeAg status. Important terms used during course of hepatitis B infection are helpful in understanding the phases of disease, such as:

- i) Chronic hepatitis B (i.e. HBsAg positive for >6 months, high serum HBV DNA >10⁵ copies/ml for HBeAg positive, and >10⁴ copies/ml for HBeAg negative), persistent or intermittent elevation in ALT/AST levels, liver biopsy showing chronic hepatitis with necro-inflammatory score = 4.
- ii) Inactive HBsAg carrier i.e. HBsAg positive > 6 months, persistent normal ALT, HBeAg negative, Anti HBe reactive, HBV DNA < 2000 iu/ml and absence of significant hepatitis on liver biopsy.

Outcome measurements of HBV treatment

The ideal outcome of any hepatitis B treatment should be undetectable HBV DNA along with sero-conversion of HBsAg into anti HBsAb. Unfortunately this is not accomplished with even the most effective treatment in a substantial number of patients. Even pegylated interferon given for a year can achieve HBsAg sero-conversion in not more than 7-8% of patients in recently reported trials. The realistic and achievable goals of hepatitis B treatment are divided into two categories:

Short term outcomes: (in order of attainment)

1. Sero-conversion of HBeAg in serum to anti HBeAb (in patients with HBeAg +ve infection).

2. Suppression of HBV DNA level $<10^4$ copies/ml.
3. Disappearance of serum HBV DNA.
4. Improvement in histologic activity index or fibrosis score.
5. Disappearance of HBsAg

Long term outcomes

1. Prevent progression to cirrhosis.
2. If cirrhosis has developed then aim of treatment is to prevent decompensation or hepatocellular carcinoma.
3. If patient is already decompensated then the aim is to stabilize the disease or lower viral load.
4. Improvement in survival and quality of life.

Paradigm shifts in levels of HBV DNA, ALT and CHB complications

There are several controversies related to level of suppression of HBV DNA and ALT levels proposed in most guidelines. There is an argument that if one does not consider patients with HBV DNA levels below 100,000 copies /ml then the number of patients with active underlying liver disease can be excluded from receiving treatment. A study of 165 Chinese patients with HBeAg + ve disease suggests that 89% of patients had HBV DNA levels persistently below 100,000 copies /ml. Moreover, 45 % of HBeAg – ve patients also had levels below $10^{5.6}$. Both groups of patients were found to have active disease during long-term follow up. Similarly in a large study from Greece more than 10% of HBeAg –ve patients with consistently increased ALT levels had serum HBV DNA levels $< 10,000$ copies /ml⁶. All these studies suggest that HBV DNA can falsely indicate the severity of liver disease and can cause misleading interpretation of the disease status.

There is also concern related to the levels of ALT in a patient with CHB and HBeAg – ve status. Guidelines suggest following ALT levels exceeding 1.5 to 2 times upper limit of normal (ULN). Many patients with normal or near normal ALT would be deprived of treatment despite active disease. ALT levels fluctuate in patients with CHB much as they do in chronic hepatitis C patients⁷. Hence, treatment of CHB with HBV DNA and ALT levels below the recommended levels should be individualized according to patients' disease status and wishes.

Previously it was considered that higher the levels of HBV DNA and ALT levels the more are the chances of development of CHB- related long-term complications. The HBV DNA level is a dynamic parameter and has substantial variations day to day, and it is difficult to consider one measurement as a predictor of complications. Several Asian studies focusing on the natural history of CHB have shown that values of HBV DNA of 10,000 copies can be associated with increased risk of complications such as hepatocellular carcinoma (HCC) and higher mortality⁸. HBV DNA levels of $>100,000$ copies have the highest rate of HCC while 10,000 copies have intermediate risk⁹.

Based on these reports there is a place for long-term nucleoside analog treatment for suppressing HBV DNA to lowest possible levels for as long as possible, thus decreasing the chances of development of CHB related complications and improving survival. Stopping therapy based on HBeAg seroconversion and undetectable levels of HBV DNA may not apply, and maintained suppression of HBV DNA may become the new paradigm in the management of CHB patients in future¹⁰.

ORAL THERAPY OF CHRONIC HEPATITIS B

Prior to 1998 the only treatment available was standard interferon in high and difficult to tolerate doses. The first oral nucleoside analog, lamivudine was introduced in 1998. Adefovir dipivoxil was the next oral treatment and after that the array of nucleosides has in quick succession included the licensed drugs entecavir, telbivudine and tenofovir.

Many other new molecules are in the phase II and phase III trials such as clevudine, elvucitabine, valtorcitabine, amdoxovir, racivir, MIV 210, β -L-FddC, alamifovir, and heparvir B.

1) LAMIVUDINE

There is extensive literature available on treatment trials with lamivudine in HBeAg + ve and HBeAg –ve group of patients.

HBeAg positive patients:

In HBeAg +ve patients reductions in HBV DNA concentration, HBeAg seroconversion, ALT normalization, and histological improvement observed after 1-year of treatment reach 44%, 17%, 41%, and 52%, respectively¹¹. Several factors, including genotype and the presence of cirrhosis may predict the durability of response to lamivudine.

HBeAg negative patients

In HBeAg –ve patients after one year of treatment with lamivudine, HBV DNA became “undetectable” with a non-standardised assay in 70% of patients, serum ALT normalized in 75%, and histological improvement was noticed in 60%¹². However, the overwhelming majority of patients relapsed after treatment cessation. Resurgence of ALT and HBV DNA is seen in majority of trials; hence lamivudine must be continued for a long time

Resistance to lamivudine

Lamivudine resistance has been mapped to mutations in the tyrosine-methionine-aspartate-aspartate (YMDD) pattern of the reverse transcriptase (rt) domain of HBV DNA polymerase. Chances of resistance increase with long term administration: 10-15% in the 1st year and 60-70 % after 4-5 years of treatment¹³.

Lamivudine resistance is accompanied by a breakthrough of HBV DNA levels and a subsequent rise of ALT, but this is variable. Adding adefovir before waiting for HBV DNA breakthrough or an ALT rise would be helpful for patients on

long-term lamivudine use. Adefovir, tenofovir and entecavir are active against lamivudine resistant hepatitis B, but it is advisable to continue lamivudine and adefovir in these patients, rather than replacing them¹⁴.

Indications of Lamivudine

Due to high resistance rates lamivudine is no longer recommended for long term administration but its potent anti-viral effects can be used as preemptive treatment. It is still the treatment of choice for avoiding transmission of HBV from mother to newborn in the third trimester of pregnancy¹⁵. It can be used for avoiding the HBV re-activation in patients needing immuno-suppressive therapy. It is also effective in cases of chemotherapy associated with exacerbation of hepatitis B¹⁶. (See algorithm)

Side effects are comparable to placebo in most trials and no dose adjustment is advised.

2) ADEFOVIR DIPIVOXIL

It is not as potent an anti-viral medication as lamivudine, but the advantage is fewer emergences of resistant mutants. Therefore adefovir should be used primarily in HBeAg –ve, lamivudine resistant patients¹⁷.

HBeAg positive disease

Adefovir 10 mg daily, when compared with placebo resulted in reductions in HBV DNA (3.52 vs 0.55 log copies/ml), normalization of ALT (48% vs 16%), and HBeAg seroconversion (12% vs 6%). It is observed that even after 1 year of treatment anti-viral activity is less in cases where HBV DNA level is high. Therefore adefovir is not a good choice in patients with wild type HBV infection¹⁸.

HBeAg negative disease

It has been observed that patients with low viremia and HBeAg –ve respond well to adefovir when given for a longer time. This group of patients requires long term suppressive treatment. Adefovir has low rates of resistance and good long term viral suppression, which is of particular benefit in HBeAg negative HBV infection¹⁹.

Adefovir resistant mutations

The cumulative incidence of resistance in treatment naive patients is 3.9 % to 5.9 % after three years of treatment. In clinical practice higher rates up to 29% are reported after 5 years of treatment²⁰. Patients with previous lamivudine resistance are at greater risk of adefovir resistance²¹. Interestingly, the adefovir resistant mutants are usually susceptible to lamivudine and vice versa.

Indications for Adefovir

Adefovir can be used as monotherapy in both wild and mutant variety of CHB infection, where it can cause a 3 to 4 log

reduction in mean HBV DNA levels. The optimal duration of therapy is uncertain. However, it is suggested that adefovir must be continued for 6 months after HBeAg sero-conversion, even if there is HBV DNA suppression earlier; while patients with HBV mutant infection, who have achieved HBV DNA suppression, must continue it for at least four to five years.

Side Effects

Serum creatinine should be checked prior to start of adefovir. The dose must be adjusted to half of routine dose if the creatinine clearance is < 50 %.

3) ENTECAVIR

Entecavir is safe and well tolerated. Entecavir is recommended in a dose of 0.5 mg daily for patients with HBeAg positive or negative, nucleoside naïve status and 1 mg daily in non-naïve patients.

HBeAg positive disease

is associated with a greater degree of reduction of HBV DNA than . An open-label, comparative trial included 69 antiviral-naïve patients who were randomly assigned to entecavir (0.5 mg daily) or adefovir (10 mg daily) for a minimum of 52 weeks²². The mean HBV DNA change from baseline to week 48 was significantly greater with entecavir (-7.27 versus -5.08 log (10) copies/mL). Similarly, a multinational trial included 715 patients with HBeAg positive CHB who were randomly assigned to (0.5 mg daily) or (100 mg daily) for 48 weeks²³. At week 48, HBeAg seroconversion was observed in 21% of group and 18% of group. Serum HBV DNA decreased from baseline, suppression of HBV DNA and normalization of serum ALT were observed significantly more often in the entecavir group. Serum HBV DNA was undetectable by PCR assay in 67% of the entecavir group compared with 36% in lamivudine group. Histologic improvement (defined as ≥ 2 point reduction in the Knodell necroinflammatory score) was observed significantly more often in the group (72 versus 62%).

HBeAg negative disease

A multinational trial included 648 patients with HBeAg negative HBV who were randomly assigned to (0.5 mg daily) or (100 mg daily) for up to 96 weeks²⁴. At 48 weeks, the mean reduction in HBV DNA was significantly greater in the entecavir group and undetectable HBV DNA by PCR occurred significantly more often (90% versus 72%). Serum HBV DNA decrease and proportion of patients with ALT normalization were significantly higher in the entecavir group.

Entecavir resistance

Viral rebound due to entecavir-resistant mutation develops in approximately 1, 11, 27, and 39% of lamivudine-refractory patients treated for one, two, three, and four years, respectively, and in approximately 1% of nucleoside-naïve patients after up to 4 years of therapy.

Indication for entecavir

Monotherapy with (0.5 mg daily for 52 weeks) in HBeAg positive or HBeAg negative CHB was associated with a 5 to 7 log¹⁰ reductions in mean HBV DNA levels. This degree of reduction is greater than has been observed with dipivoxil, telbivudine, or.

The dose needs to be adjusted if creatinine clearance is below 50 ml/minute^{23, 24}.

4) TELBIVUDINE

Telbivudine belongs to a new class of β-L-configuration nucleoside analogues²⁵. Its antiviral activity is equal to lamivudine and entecavir but the main problem is emergence of resistance at a rate of 10 % per year^{26, 27, 28}.

HBeAg positive patients

A greater therapeutic response with telbivudine at week 104 has been noted in HBeAg positive patients (64% of those receiving telbivudine vs. 48% of those on lamivudine). Limited follow up information suggests that patients may discontinue treatment after HBeAg seroconversion. Responses are durable in approximately 80%²⁹.

HBe Ag negative patients

The mean log¹⁰ decline in a recent trial was -5.0 and -4.2 in telbivudine and lamivudine recipients, respectively. At two years, HBV DNA was undetectable by PCR in 82% of HBeAg negative patients vs. 52% of lamivudine recipients; 78% had normal ALT³⁰.

Telbivudine resistance

Overall resistance reported is 17.8% and 7.3% in HBeAg positive and negative patients at two years, respectively²⁹. Resistance is correlated with the viral response at week 24, but the rates of resistance increased substantially in patients with higher levels of viraemia at this point. Adefovir can be added to patients with resistance to telbivudine. Telbivudine cannot be used for the treatment of lamivudine resistant patients.

It is excreted through the kidney and dose adjustments are recommended for patients with estimated creatinine clearance of < 50 ml/ml^{28, 29}.

5) TENOFOVIR

Tenofovir and adefovir are related molecules with a similar mechanism of action. Majority of literature of tenofovir has reported its efficacy in HIV-HBV co-infected patients and is encouraging³⁰. The drug is active against wild type and pre-core mutant hepatitis B, as well as lamivudine resistant HBV in vitro^{31, 32, 33}. Recent trials show a favorable effect of tenofovir and adefovir in patients with lamivudine resistant HBV infection and high baseline HBV DNA (>10⁶ copies/ml)^{34, 35}.

The pharmacokinetics of tenofovir is altered in patients with

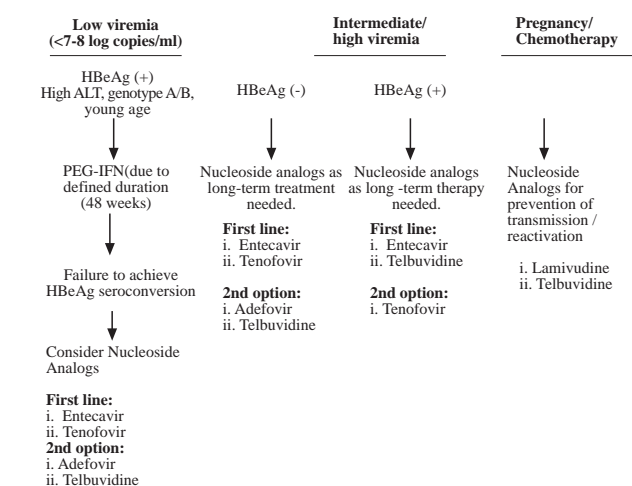
renal impairment and dose needs to be adjusted according to renal clearance.

Approach to a CHB patient and role of combination therapy

The following strategies could be suggested for patients with high levels of viral replication or advanced disease: the physician has to decide about using a nucleoside analogue or pegylated interferon. Young patients with chronic active HBV infection with markedly raised ALT may be the most suitable candidates for interferon. The side effects of pegylated interferon along with response rates should be discussed. The main advantage of interferon is its fixed duration as compared to oral nucleosides. However, it is correct that these patients respond similarly to oral nucleosides.

In HBeAg positive patients with high levels of viral replication, or patients with decompensated cirrhosis, rapid suppression of HBV DNA replication to confer a low risk of primary non-response or resistance is important, and only a single oral agent should be considered. The agent of choice must have a low resistance profile and potent antiviral activity. In the current era entecavir and telbivudine and adefovir may be appropriate as first choice of therapy. Combinations of drugs may be advantageous in some settings, particularly in resistant cases. The main advantage of combination therapy is that it helps avoid drug resistance, which is not a new concept. There is no data to suggest that combination treatment has synergistic action and it will need large and expensive trials. Thus we may need to glean the efficacy of potent monotherapies versus combination therapies from direct clinical experience over the coming years.

Algorithm: for selecting nucleoside analog in a patient with CHB.



Note: Monitor HBeAg (in HBeAg +ve only) and Quantitative HBV DNA copies at 3 months of treatment. If desired reduction of HBV DNA copies not achieved then add or switch to second agent in order to reduce the chances of resistance/mutants.

For patients with lower levels of viral replication, similar questions and arguments apply. Guidelines based on clinical

trial data and experience perhaps suggest that many anti-HBe positive patients could be treated with single agents which have low rates of resistance, for example adefovir, tenofovir, entecavir, and perhaps telbivudine on a long term basis. A suitable additional agent should be added if patients do not show a rapid viral decline — for example, if HBV DNA concentrations are $>10^4$ after 24 weeks—because of the high risk of resistance.

Duration of therapy

The duration of therapy with the oral nucleoside is controversial and debatable. Most of the randomized control trials and cohort studies have limited the treatment duration to 48 weeks. We know from the long term follow up studies and clinical experience of using initial nucleoside analog that there is a resurgence of ALT and HBV DNA in majority of the trials on stopping treatment.

It is suggested that patients with HBeAg positive disease should continue treatment at least 6 -12 months after HBeAg seroconversion and their treatment must not be stopped on only achieving HBV DNA suppression. Similarly, it is suggested in literature to continue treatment for at least four to five years in patients with HBeAg negative chronic hepatitis who continue to have suppression of HBV DNA³⁶.

The optimal duration of therapy is uncertain at the moment but a prolonged HBV DNA suppression which is acceptable to the patients and physician with drugs that cause least resistance is advised. Even AASLD guideline of 2007 has recommended for a long-term treatment but how long is not defined in it.

Once a physician has decided for oral treatment of CHB patient then the approach mentioned in algorithm can be adapted. See Figure.

Monitoring of HBV patients while on treatment

- i) Assess Serum HBV DNA and ALT levels every 3-6 monthly for
 - a. Response to therapy
 - b. Potential development of resistance to anti-viral treatment
- ii) Assess HBeAg status in HBeAg positive patients 3-6 monthly
- iii) Initiate screening for HCC in high risk patients
 - a. Asian men >40 yrs/ women >50 years, cirrhotics, those with family history of HCC, high HBV DNA levels, active hepatic inflammation.
 - b. Ultrasound examination every 6-12 monthly.

Diagnosis and interventions for mutants

The recognition of emerging mutant strains while on treatment is crucial in the management of CHB infection and it may mimic primary non-response to treatment. Serum HBV DNA is the

best available measure for determining the mutant strains. The following is recommended:

- Use a sensitive PCR-based HBV DNA assay
- Use the same assay over time
- Perform PCR with ALT measurement

Three types of drug-resistances are defined in the literature including genotypic, phenotypic and viral breakthrough or rebound. Genotypic resistance is detection of HBV polymerase mutation(s) associated with resistance; phenotypic resistance is defined as decreased in-vitro susceptibility to an antiviral agent in the compliant patient and lastly viral breakthrough or rebound, when there is confirmed increase in plasma HBV DNA $>1 \log^{10}$ IU/mL from nadir along with increase in ALT on treatment.

The drug-resistance mimics primary non response to an antiviral agent which is defined as lack of $= 1 \log^{10}$ decrease in HBV DNA at 6 months. The ideal way to fight resistance is to determine mutants at the outset, i.e, before the start of treatment which is difficult in clinical setting. The AASLD recommendation for management of resistance is shown in Table 1³⁷.

Table 1: AASLD recommendations for treating different resistance with oral neucloside analog.

| Resistance | Rescue Therapy |
|-------------|---|
| Lamivudine | <ul style="list-style-type: none"> § Add adefovir § Switch to entecavir (increased risk of entecavir-R development) § Add tenofovir or switch to emtricitabine/tenofovir |
| Adefovir | <ul style="list-style-type: none"> § Add lamivudine § Switch to or add entecavir § Switch to emtricitabine/tenofovir |
| Entecavir | <ul style="list-style-type: none"> § Add or switch to adefovir or tenofovir |
| Telbivudine | <ul style="list-style-type: none"> § Add adefovir § Switch to entecavir (increased risk of entecavir-R development) § Add tenofovir or switch to emtricitabine/tenofovir |

Conclusion

The oral therapy for hepatitis B has seen a drastic improvement in recent days, after approval of the first agent, lamivudine in 1998. The newer anti-viral drugs introduced in last few years has shown promise and expanded the choices for the clinicians. Entecavir, due to its potent anti-viral activity against HBeAg +ve and -ve patients and less chances of resistance can be considered as treatment of first choice. Lamivudine, which is used widely in Pakistan due to its low cost, free availability and physician familiarity, is no more an option for the long term

treatment in chronic hepatitis B due to the high rates of resistance. Selection of appropriate treatment is key to preventing resistance. The best choice has to be based on the host and viral factors and the evidence available for that drug. All treatment failures should likely be treated with combination of a nucleoside and nucleotide. Lastly, the treatment of hepatitis B has to be individualized based on the epidemiological and financial aspects of the patients.

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