

TREATMENT OF CHRONIC HEPATITIS B VIRUS INFECTION

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KEY POINTS

- Treatment is considered for patients with high HBV DNA, elevated ALT levels and evidence of inflammation or fibrosis on liver biopsy.
- Patients in the immune clearance and reactivation phases of infection, but not in the immune tolerance phase, are candidates for therapy.
- The primary goal of therapy is control of viral replication. In HBeAg-positive patients, HBe seroconversion is an endpoint of therapy. In HBeAg negative-patients, no therapeutic endpoint exists and therapy is usually indefinite.
- Direct antiviral agents can be chosen according to their potency, their side effects and the chance of resistance. For treatment-naïve patients, entecavir is the best currently available antiviral therapy. For lamivudine-resistant patients, adefovir added to lamivudine therapy is most effective. Long-term therapy is commonly required and resistance is likely, with all agents in current use.
- Pegylated interferon has comparable efficacy to antiviral agents, with the disadvantage of increased side effects and the advantage of a shorter, fixed duration therapy without drug resistance.
- Therapy should be individualised. Regular monitoring is required to identify resistance, hepatitis flares and response.

Goals of therapy

The primary goal of therapy of chronic hepatitis B (CHB) is to reduce and maintain suppression of hepatitis B virus (HBV) replication to the lowest possible level, as evaluated by highly sensitive assays for HBV DNA. The ultimate aim of durable viral suppression is to prevent the progression of liver disease to cirrhosis and reduce (or eliminate) the risk of liver failure or the development of hepatocellular carcinoma (HCC) in those patients who have established liver injury.¹

High viral replication is associated with a worse outcome, as evidenced in natural history studies of untreated hepatitis B surface antigen (HBsAg) positive patients. Adverse liver-related outcomes (i.e. risk of cirrhosis and HCC) in Taiwanese patients with CHB have been reported predominantly in patients with HBV DNA levels $>10^5$ copies/mL ($>20,000$ IU/mL).² These outcome data may not be applicable to younger patients in the immunotolerant phase, where high levels of HBV DNA are not accompanied by necroinflammatory activity

and progressive liver damage. Data from recent clinical trials have shown that prolonged control of viral replication may reduce the likelihood of liver decompensation and death. These results are also reflected in clinical experience, particularly in liver transplant centres, where the clinical recovery of patients with CHB after commencing antiviral therapy is well documented and the proportion of patients undergoing liver transplantation for CHB is decreasing.²

Loss of HBsAg is the only absolute endpoint of therapy in HBeAg-positive and HBeAg-negative chronic disease, but HBsAg seroconversion is uncommon and has not been used as a primary endpoint in most short-term clinical trials.

An objective of antiviral therapy in HBeAg-positive patients is the loss of HBeAg and the development of anti-HBe—the so-called eAg seroconversion. HBeAg seroconversion is infrequent, although rates increase with prolonged antiviral therapy. Sustained HBeAg seroconversion indicates that antiviral therapy may be discontinued after a period of consolidation (six to nine months) and that viral suppression may be maintained even after the cessation of treatment. In some cases, however, the HBeAg loss is not durable and sero-reversion may occur. Thus, all patients require careful ongoing monitoring.

In the majority of patients with HBeAg-positive disease, HBeAg seroconversion does not occur and thus many years of therapy are required. The emergence of drug resistance in these patients can become a significant therapeutic challenge.¹

Therapy for HBeAg-negative patients is more difficult to assess, as HBeAg seroconversion cannot be used as an endpoint. The suppression of HBV DNA and the normalisation of ALT levels are markers of a virological and biochemical response, but both usually rebound shortly after therapy is ceased. In general, the decision to commence a patient with HBeAg-negative disease on a nucleoside analogue is a commitment to indefinite therapy. Problems with viral resistance may emerge, although

the rates of resistance vary with the chosen antiviral agent.

Indications for antiviral therapy

The decision to commence antiviral therapy is based upon a number of factors, including the patient's age, the HBeAg status, the serum HBV DNA concentration, ALT levels, and the risk of HCC. In Australia, liver biopsy remains a compulsory requirement for the reimbursement of therapy (unless the patient has an underlying coagulation disorder) and the histological severity of the underlying liver disease is an important element of the decision-making process to initiate treatment. When choosing the most appropriate anti-HBV therapy, it is important to consider the advantages and disadvantages of each therapy based on the available clinical evidence. The choice of therapy must take into account the drug's efficacy, safety, chance of achieving desired endpoints, anticipated duration of therapy and the likelihood of developing resistance. The likelihood of patient adherence to therapy regimens should be considered, as non-adherence may be associated with significant flares in disease activity.

HBeAg-positive patients

HBeAg-positive patients with an elevated serum ALT greater than two times the upper limit of normal (ULN) and a serum HBV DNA level of greater than 20,000 IU/mL should be considered for antiviral therapy. Under current PBS recommendations, these patients require a liver biopsy demonstrating histological evidence of CHB.³

In general, HBeAg-positive patients with a serum HBV DNA level of less than 20,000 IU/mL are not recommended for therapy, because the vast majority of these patients will have inactive disease and a normal ALT level. The HBV DNA level and the necroinflammatory activity of the liver disease are subject to significant variability and these patients should be monitored to ensure constant levels of HBV DNA and the persistence of a normal ALT level. At present, an annual HBV DNA measurement will be reimbursed by the Australian PBS, although it

is recommended that serum ALT be monitored every three to six months and the HBV DNA level be reassessed if the serum ALT increases. Occasionally, patients with low level viral replication have significant necroinflammatory activity or hepatic fibrosis; antiviral therapy is indicated in these patients.⁴

HBeAg-positive patients with a serum HBV DNA level of greater than 20,000 IU/mL with a persistently normal ALT level are often young and within the immunotolerant phase of their illness. It is advisable to monitor such patients for an extended period to observe changes in ALT levels. However, some patients with normal ALT levels and a markedly elevated HBV DNA level may have significant liver injury. A liver biopsy should be considered in older patients (over 40 years of age) with this laboratory profile, or in those patients in whom a clinical evaluation suggests significant underlying disease. The patient should then be offered antiviral therapy if significant liver injury is discovered.⁴

HBeAg-negative patients

Serum HBV DNA levels are often lower in patients with HBeAg-negative CHB than in patients with HBeAg-positive CHB, but many affected patients have significant necroinflammatory activity or hepatic fibrosis on liver biopsy. Therefore, it is recommended that the threshold serum HBV DNA level for initiating antiviral therapy should be 2000 IU/mL in this group of patients. In general, other recommendations for therapy in HBeAg-negative patients are similar to those for HBeAg-positive disease.⁴

Therapeutic options

There are two main classes of therapy: direct antiviral agents, which inhibit the function of the viral polymerase to prevent viral replication, and the interferons that are synthetic cytokines which act via multiple intracellular biological pathways to eradicate the viral infection.

In practical terms, three agents are currently accepted and approved by the Australian Government's Therapeutic Goods Administration (TGA), and listed on the

Pharmaceutical Benefits Scheme (PBS) for the initial treatment of CHB patients in Australia. These agents are pegylated interferon (180 µg weekly), lamivudine (100 mg daily) and entecavir (0.5 mg daily). A further agent, adefovir dipivoxil (10 mg daily), is licensed by the PBS to treat patients who have developed resistance to lamivudine or entecavir. Entecavir is also approved to treat patients with lamivudine resistance, although the recommended dose is higher than for previously untreated patients.

Several other agents are either currently under evaluation for reimbursement by the Pharmaceutical Benefits Advisory Committee (PBAC) or are in the advanced stages of clinical trial programs, so recommendations for the most appropriate antiviral therapy in different patient populations are likely to change, based on the future availability of these drugs. However, the following discussion will be largely confined to the treatments that are currently registered for use in Australia.

Pegylated interferon

Use of conventional interferon (IFN) has been supplanted by the use of pegylated interferon (PEG-IFN), which has the advantage of weekly dosing and improved efficacy. This drug has a pegylated moiety, which confers improved pharmacokinetics to allow less frequent dosing. PEG-IFN is given weekly for 12 months. The side effects are similar to conventional IFN, including troublesome flu-like symptoms, fatigue, leukopenia, irritability, sleep disturbance and depression.¹ In HBeAg-positive patients, HBe-seroconversion occurs in 32% of patients six months after the end of treatment.⁵ Sustained responses are better in patients with genotype A CHB (47%) than in those with genotype D CHB (25%) infection. Better response rates to IFN-based therapies are seen in patients who are young, female, and have an elevated ALT, a relatively low HBV DNA level and genotype A CHB.^{4,6-8} Long-term studies suggest that HBeAg seroconversion continues to occur in the years after therapy is completed at a greater rate than would be expected to occur naturally.

A small but significant proportion (approximately 5%) of patients treated with IFN also achieves HBsAg seroconversion. This is seen particularly in those with genotype A, the most common genotype in Caucasian patients. Loss of HBsAg is significantly less common with direct antiviral agents (see below).

PEG-IFN also has a role in the treatment of HBeAg-negative patients. A sustained control of viral replication (< 2000 IU/mL) is seen in approximately 30% of patients six months after the completion of therapy.⁹ The control of viral replication at these levels should reduce the progression to clinically significant liver disease.

The main advantage of PEG-IFN is the fixed duration of therapy and the chance for HBsAg seroconversion. The main disadvantage is the side effect profile, predominantly fatigue, irritability and leukopenia. Flares of viral hepatitis can result from the enhanced immune clearance. Flares can be seen in 12%–18% of patients and can be severe in those with advanced underlying liver disease.¹ PEG-IFN is contraindicated in decompensated cirrhosis. The main concern when using PEG-IFN is the ongoing viral replication that persists at the completion of therapy in many patients. It is possible for patients who have ongoing, clinically significant viral replication after the completion of PEG-IFN therapy to receive oral antiviral therapy. However, this approach has not been validated in clinical trials.¹

Lamivudine

Lamivudine was the first antiviral agent available for treatment of HBV infection. It is an oral nucleoside analogue, well tolerated and without significant side effects. It induces profound inhibition of viral replication in almost all patients, which results in improved liver histology, improved liver function in decompensated disease and, in some studies, a reduction in the rate of HCC in patients with advanced fibrosis. It may be taken with or without food, and is well tolerated, with a side effect profile similar to the placebo.¹

The endpoint of therapy for HBeAg-positive disease is HBeAg seroconversion with associated control of viral replication. HBeAg seroconversion only occurs in a minority of patients; this is more likely to occur in those with a markedly elevated ALT. Seroconversion rates continue to increase the longer a patient remains on therapy (17% after one year of treatment, 27% after two years of treatment and 50% by year five of treatment).¹⁰ Therapy is indefinite if HBeAg seroconversion does not occur. Therapy for HBeAg-negative infection is indefinite, as relapse after the cessation of therapy is almost universal. Unfortunately, prolonged therapy with lamivudine is limited by the high rates of viral resistance, occurring in 14%–32% after one year of therapy and in 60%–70% after five years of therapy.¹¹ When resistance develops, efficacy is lost and in some patients severe exacerbations of liver disease can occur.¹ As a consequence, lamivudine is no longer the best option for first-line therapy, now that other agents with an improved resistance profile are available.

Entecavir

Entecavir is a purine-derived nucleoside analogue. It is highly effective at inhibiting viral replication, and early studies confirmed that this inhibition of viral replication was associated with improvements in liver histology. Entecavir has few side effects, the most common being headache (2–4%) and fatigue (1–3%), although adverse events were equally seen in the lamivudine-treated group when the two agents were compared.¹² Unlike other antiviral agents, entecavir must be taken on an empty stomach, two hours before or after a meal.

Compared with lamivudine and adefovir, entecavir has the greatest potency (measured by the decrease in viral load from baseline) of the available direct antiviral agents, compared with lamivudine and adefovir. HBeAg rates of clearance are similar to those seen with other antiviral agents. Importantly, entecavir has the lowest rate of resistance (less than 1% in nucleoside-naïve patients after one to two years).^{1,13} From November 2006, the PBS agreed to support the use of entecavir for treatment-naïve patients with HBV infection. Entecavir has

now largely superseded lamivudine as the first-line therapy of choice for the treatment of CHB in Australia.

Entecavir can be used in patients who have developed resistance to lamivudine. Higher doses of 1.0 mg daily are required to suppress lamivudine-resistant HBV. Despite higher doses, antiviral activity remains lower than that seen with wild-type HBV. Despite its improved potency, patients with lamivudine-resistant mutants are more likely to develop resistance to entecavir (17% after four years of treatment).¹⁴ Entecavir is thus not the best choice for patients with lamivudine resistance, who should ideally be treated with adefovir.¹

Adefovir

Adefovir, an acyclic phosphorate nucleoside analogue, is an effective antiviral agent. The control of viral replication and improved biochemical, histological and clinical outcomes have been demonstrated. Adefovir is orally active and well tolerated at the 10 mg daily dose recommended for use in HBV infection. It may be taken without regard to food. The potency of adefovir at this dose is less than that of other available antivirals. Higher doses, while more effective, cannot be used because of nephrotoxicity. The renal function at the 10mg dose does, however, need to be monitored, as renal toxicity can occur with long-term use.¹

While in the US adefovir is used in the first line setting, currently the PBS requires that adefovir be limited in the setting of lamivudine resistance. In this setting, adefovir is added to lamivudine therapy for the first three months in patients with compensated disease, and for the first 12 months in patients with decompensated disease; adefovir is then used on its own, as monotherapy. The rate of resistance to adefovir in the first line setting is much lower than lamivudine (0% after one year of treatment, 1% after three years and 30% after five years of treatment).¹⁵ Unfortunately, the rates of resistance to adefovir are much higher in patients already resistant to lamivudine. Long term combination therapy with adefovir and lamivudine in patients with lamivudine resistance is associated with much lower rates

of resistance.¹ Although the PBS does not currently fund this approach, combination lamivudine/adevovir in this setting is likely to gain approval in the near future.

Future therapies (not yet approved in Australia)

Emtricitabine, tenofovir and telbivudine are agents not yet available in Australia, but with known efficacy against HBV replication. It is likely that some or all will be available as PBS subsidised therapy in Australia in the near future, depending on their efficacy, tolerability and rates of resistance. Overseas data suggest that tenofovir may have the most beneficial profile of these three new agents.¹

Tenofovir, like adefovir, is an acyclic adenine nucleotide, with potent activity against HBV. It is currently in use for the treatment of HIV infection. As a result of its potency, tenofovir is particularly effective in patients with lamivudine-resistant CHB, and is likely to have an important role in treatment-naïve patients with HBV infection.¹

Emtricitabine, like lamivudine, is an L-nucleoside agent with a level of potency and resistance similar to lamivudine. Telbivudine is also an L-nucleoside agent that may be more potent than lamivudine, with rates of resistance that are lower than those of lamivudine, but substantially higher than those of entecavir and adefovir.¹ Both emtricitabine and telbivudine are ineffective in the setting of a lamivudine-resistant virus. These drugs may find their place in combination therapy regimes, which are under investigation at the present time.

Monitoring patients on antiviral therapy

Patients should be monitored regularly while on therapy to document their response to antiviral therapy, to detect adverse side effects of therapy and to facilitate the early detection of antiviral resistance. Monitoring needs to be more frequent in patients treated with pegylated interferons compared to those treated with nucleoside analogues because of the risk of bone marrow suppression,

neuropsychological side effects and other complications of interferon-based therapy.

For patients treated with pegylated interferon, frequent (e.g. fortnightly) monitoring is recommended until the treatment dose is stabilised. Patients can then reduce the frequency of their visits to every four to six weeks. Particular attention should be paid to the full blood count, white cell count differential and platelet count at each visit, in case dose adjustments are required.

In patients treated with nucleoside analogues, monitoring should occur on a three monthly basis—particularly for patients with advanced fibrosis or cirrhosis, and for those patients on antiviral therapy who have a high incidence of viral resistance. Full blood count, liver function tests and HBV serology (for HBeAg-positive patients) should be performed at each of these visits. The optimal frequency for HBV DNA testing remains to be determined. Three-monthly HBV DNA testing appears appropriate for patients with high viral resistance rates or in those for whom the likelihood of clinical complications due to delaying therapy for resistance is judged to be high. The frequency may be reduced to four or six monthly for patients with low resistance rates and in those for whom the risk of complications of resistance is judged to be low.^{4,16}

Antiviral drug resistance

The emergence of antiviral drug resistance is the major challenge confronting clinicians who manage patients with CHB. Recently, the following definition for antiviral resistance to nucleoside analogue treatment was proposed: a confirmed 10-fold increase in serum HBV DNA level ($> 1 \log_{10}$ IU/mL) from nadir following initially effective treatment constitutes secondary treatment failure which, in the absence of poor adherence or drug substitution, is almost always due to the emergence of the drug-resistant HBV mutants. A rebound in serum HBV DNA always precedes the biochemical and histological markers of increased HBV disease activity, and patients with underlying cirrhosis are at an increased risk of decompensation following

the emergence of resistance. Early diagnosis of secondary treatment failure and the institution of appropriate antiviral therapy remain key to preventing hepatic decompensation, liver failure, death or liver transplantation in patients who develop drug resistant mutations.¹⁶

Predictors of lamivudine resistance include high pre-treatment HBV DNA levels, non-Asian ethnicity, male gender and persistent viral replication with continued antiviral therapy.¹

The molecular characterisation of genotypic changes that confer resistance is not usually performed in clinical practice, and there is no indication that such laboratory analysis will be reimbursed by Medicare in the near future. While the sequencing of HBV drug-resistant mutations is largely regarded as a research tool at present, it can provide important information and influence the selection of the most appropriate therapeutic antiviral strategy.

In relation to reimbursement options by the PBS, the management of patients who develop lamivudine resistance is limited to switching therapy to either adefovir or entecavir. However, the risk of the emergence of subsequent adefovir or entecavir resistance is much higher in this cohort of patients than in treatment-naïve patients. There is now abundant evidence that the addition of adefovir to lamivudine therapy, rather than a switch to adefovir monotherapy, is the preferred management strategy for patients who develop lamivudine resistance. In those patients who have been placed on adefovir monotherapy, (for lamivudine resistance), the development of resistance to adefovir can often be managed by the re-introduction of lamivudine and the continuation of adefovir. At present the PBS will not provide reimbursement for combined therapy in this patient group. However, it is expected that combination therapy with adefovir and lamivudine for this patient group only will be approved in the near future.

The molecular virology of HBV viral resistance is discussed in more detail in Chapter 2: Virology: viral replication and drug resistance.

Treatment-related side effects

The safety profile of nucleoside and nucleotide analogues is similar to that of the placebo. In general, these drugs are remarkably well tolerated. Their major concerns are the risks of resistance and safety in pregnancy.

Tenofovir, an oral nucleoside agent currently in clinical studies, may be the safest option for women in their child-bearing years, given its recent category B pregnancy listing. It is currently only approved for HBV/HIV coinfection, but not for HBV mono-infection.¹ (Category B: Presumed safety based on animal studies, with no controlled studies in pregnant women, or if animal studies have shown an adverse effect that was not confirmed in controlled studies in women in the first trimester and there is no evidence of a risk in later trimesters. Available at: <http://www.tga.gov.au/docs/html/medpreg.htm>).

In contrast, pegylated interferon has many side effects. Anecdotally, it seems to be better tolerated in patients with HBV rather than patients with hepatitis C virus (HCV). Despite this observation, patients taking interferon may experience many different side effects that require careful consideration and appropriate intervention. Treatment is usually supportive and symptom-based. The most common side effects early on are flu like symptoms and the following measures may be of benefit:

- Simple antiemetics, such as metoclopramide, for nausea and vomiting
- Antispasmodics, such as buscopan, for abdominal cramps
- Paracetamol for headaches, fevers, myalgia and arthralgia (avoid NSAIDs because of concomitant thrombocytopenia with treatment).

Mood disturbances become more common as therapy continues and appropriate interventions may include:

- Benzodiazepines or zolpidem for insomnia
- Antidepressants: SSRIs are preferred for anxiety and depression.

If the patient has a history of depression, a low threshold should exist for starting SSRI

therapy pre-treatment. Patients already on antidepressants may need a dose increase during interferon therapy. For patients starting an SSRI during treatment, the SSRI is usually continued for six months post-cessation of interferon therapy.

Skin changes are common during therapy and patients often complain of dry, itchy skin and a multitude of skin rashes. Therapy is usually based on keeping the skin hydrated, with regular use of moisturisers and emollients. Antihistamines can be used, particularly if pruritus is exacerbating insomnia. Steroid-based creams can be trialled for rashes that do not respond to any of the above measures.

Lifestyle issues while on therapy appear to be important. Patients can trial a variety of lifestyle changes during therapy to help with interferon-related side effects. Regular exercise before and during therapy seems to help with lethargy and myalgias. Anecdotally, patients who exercise regularly seem to tolerate treatment better than those who are sedentary. Patients should avoid alcohol if possible.

For information about reimbursed therapy: <http://www.pbs.gov.au/html/healthpro/home>

For information about the listing of drugs in pregnancy: <http://www.tga.gov.au/docs/html/medpreg.htm>

Alternative therapies

The use of complementary, alternative or Chinese medicine has not been well studied in patients undergoing treatment with interferon-based therapies; because of the risk of hepatotoxicity, the use of these therapies should be discouraged while the patient is undergoing interferon-based therapy. Massage, hypnotherapy, acupuncture and other non-medical based therapies may provide symptom-based relief during treatment.

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