Treatment of acute hepatitis B infection is, in most cases, supportive. The management of chronic hepatitis B (CHB) is focused on drug treatment. Infection with the hepatitis B virus (HBV) cannot be completely eradicated because of the persistence of covalently closed circular DNA in the nucleus of infected hepatocytes (for details of virus life cycle see Box 1 in accompanying article, p12).

This article describes the options for managing patients with CHB in the context of the most up to date guidelines, published in 2009 by the European Association for the Study of the Liver (EASL).1

Currently seven drugs are licensed for treating CHB. They can be divided into two main categories: immune modulators (eg, interferons), which help the immune system mount a defence against the virus; and nucleoside/nucleotide analogues (also known as NUCs), which aim to suppress or destroy the hepatitis B virus (HBV) by interfering with its replication.

There are three main aims when treating a patient who has chronic HBV:

- To improve the patient's quality of life and survival by preventing progression of the disease to cirrhosis, hepatic decompensation, end-stage liver disease, hepatocellular carcinoma (HCC) and death
- To reduce HBV DNA to as low a level of detection as possible to ensure a degree of virological suppression that leads to biochemical remission (demonstrated by normalisation of alanine aminotransferase [ALT] levels) and histological improvement — thereby limiting the risk of complications such as cirrhosis and HCC
- To achieve hepatitis B e antigen (HBeAg) seroconversion if the patient is HBeAg-positive or, if the patient is HBeAg-negative, sustained suppression of HBV DNA to undetectable levels

Interferons

Interferons are naturally occurring cytokines that have immunomodulatory, antiviral and antiproliferative actions. Interferons work by inhibiting viral replication and enhancing the body's immune response to HBV. Standard interferon alfa was licensed in the early 1990s; at that time thrice-weekly subcutaneous injections were required. It has since been largely superseded by peginterferon (pegylated interferon) alfa, which is longer acting.

Pegylation is a process whereby inert polyethylene glycol is bound covalently to the interferon molecules. This alters the pharmacokinetic and pharmacodynamic properties of interferon — increasing its half-life, decreasing immunogenicity, altering metabolism and reducing renal clearance. This allows for once-weekly administration.

Benefits of peginterferon alfa treatment include a fixed length of treatment (48 weeks) and a higher rate of HBeAg seroconversion at one year compared with NUCs (30% versus 21–26%).1 Frequent side effects, weekly subcutaneous injection and the fact that it is not suitable for those with decompensated cirrhosis are the main disadvantages.

Hepatitis B management

By Joyeta Das, DipClinPharm, MRPharmS

When a decision has been made to treat a patient with chronic hepatitis B (CHB) infection, choosing the most appropriate treatment depends largely on whether he or she has compensated or decompensated cirrhosis.

For those with compensated cirrhosis caused by CHB, orally administered nucleoside/tide analogues (NUCs), of which five have been licensed, are the only treatment options. These medicines can also be used for patients with earlier stages of disease (eg, fibrosis, compensated cirrhosis). The greater potency and lower rates of resistance associated with entecavir and tenofovir make these NUCs more appealing first-line treatments than adefovir, lamivudine and telbivudine.

For patients without decompensated cirrhosis who have received no previous treatment, peginterferon alfa-2a is an alternative. This medicine can be given for a finite duration and stimulate a lasting response from the immune system. However, the NUCs cause fewer side effects. As a result, whether to treat with a finite course of peginterferon or an indefinite course of the better tolerated NUCs remains a subject for debate.

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disadvantages of peginterferon therapy. (See Box 1 for summary of advantages and disadvantages of treatments.)

Toxicities Fever after injection, fatigue, myalgia and headache are common side effects early in therapy. These can be relieved with paracetamol and should resolve as treatment progresses; however, some patients continue to experience these side effects throughout treatment. Other adverse effects include neutropenia and thrombocytopenia, which require close blood monitoring and possible dose reduction. Peginterferon alfa-2a can affect serotonin concentrations and cause mood disturbances, which may respond to low-dose selective serotonin reuptake inhibitors and do not usually require interruption of peginterferon treatment.

Nucleoside/nucleotide analogues Treatment with NUCs involves once-daily dosing. Currently there are five oral NUCs licensed in the UK for the management of CHB. Several medicines are also in development. They all inhibit the viral polymerase enzyme to suppress viral replication.

Unlike peginterferon therapy, they do not induce a strong immune response and thus often require long-term administration to prevent relapse. Finite treatment with NUCs is possible for patients who develop HBeAg seroconversion as a result of treatment, although the required duration of therapy cannot be predicted (see “Treatment strategies”, below).

NUCs have the advantage that they can be used with reasonable safety for patients with fibrosis, cirrhosis and hepatic decompensation — unlike peginterferon alfa-2a which is contraindicated in patients with severe hepatic dysfunction or decompensated cirrhosis.2 (For an explanation of hepatic decompensation, see Box 4 of accompanying article, p16.) Resistance is a concern with some of these medicines and, as discussed, treatment durations are hard to define.

Lamivudine Lamivudine was the first oral medicine licensed to treat CHB and has been used widely since the late 1990s. It is a cytidine analogue and a reverse transcriptase inhibitor that directly inhibits HBV DNA polymerase — an enzyme involved in base priming, reverse transcription and DNA synthesis. It is converted intracellularly to its active form lamivudine triphosphate, which is incorporated into the viral DNA causing chain termination and inhibiting replication. Although it is generally well tolerated, lamivudine’s efficacy is limited by high resistance rates — approximately 70% at five years.3

Adefovir In 2003 adefovir became the second oral medicine licensed in the UK for CHB treatment. It is a nucleotide analogue of adenosine monophosphate and is available as the prodrug adefovir dipivoxil. It is phosphorylated to adefovir diphosphate, which is incorporated into viral DNA and inhibits viral replication through DNA-chain termination. Before the availability of tenofovir it was useful for managing lamivudine-resistant infection. However, adefovir resistance is a problem with rates of around 29% at five years and its use is being superseded by tenofovir (see below).

Telbivudine Telbivudine was licensed in the UK in 2007 and is an analogue of thymidine. It is phosphorylated to the active form telbivudine triphosphate and causes viral DNA chain termination, inhibiting viral replication. Its main disadvantage is its high resistance rates — 10–25% at two years.4 In 2008 the National Institute for Health and Clinical Excellence concluded that telbivudine could not be recommended as a cost-effective use of NHS resources for the treatment of CHB.

Entecavir In 2008 entecavir was approved by NICE as a treatment option for adults with CHB for whom antiviral treatment is indicated. Entecavir is a guanosine nucleoside analogue which is phosphorylated intracellularly to entecavir triphosphate, the active drug. Entecavir inhibits the action of HBV DNA polymerase. It is a highly potent inhibitor of viral replication and, in nucleoside-naive patients, has low resistance rates of 1% at five years. For patients who are lamivudine-resistant, entecavir resistance rates are far higher (51% at five years).5

Tenofovir Tenofovir is a nucleotide analogue that has been licensed for HIV treatment since 2001 and for CHB treatment since 2008. In 2009 NICE recommended tenofovir as an option for adults with CHB for whom antiviral treatment is indicated. Tenofovir is available as the prodrug tenofovir disoproxil — it is converted to tenofovir and then phosphorylated to tenofovir.
moderate-to-severe active necroinflammation or fibrosis.

Upper limit of normal (ULN) and liver biopsy shows above 2,000 iu/ml or the serum AL T levels are above the considered for treatment when HBV DNA levels are checking HIV status.

Given to any hepatitis B-infected patient without first against both HIV and HBV these medicines should not be they can be confidently used as first-line therapy.

Inhibitors of HBV with a high barrier to resistance — thus can be confidently used as first-line therapy.

Finite treatments

A 48-week course is recommended for patients suitable for peginterferon alfa-2a treatment (mainly recommended for HBeAg-positive patients).

If the decision is made to use NUCs, the most potent medicines with the highest barrier to resistance (entecavir or tenofovir) should be prescribed to rapidly lower the virus to undetectable levels and avoid the disease “rebounding” because of resistance. Usually once seroconversion is achieved NUC treatment should be continued for six months to, preferably, one year.

When to treat

The EASL clinical practice guidelines for the management of chronic hepatitis B specify the following parameters to inform treatment initiation:

- Serum HBV DNA levels
- Serum ALT levels
- Histological grade and stage

The guidelines recommend that patients should be considered for treatment when HBV DNA levels are above 2,000 iu/ml or the serum ALT levels are above the upper limit of normal (ULN) and liver biopsy shows moderate-to-severe active necroinflammation or fibrosis.

Treatment strategies

EASL recommends two different treatment strategies for patients with CHB treatment of finite duration with either peginterferon alfa-2a or NUCs, and long-term treatment with NUCs. Both strategies are applicable for both HBeAg-positive and HBeAg-negative patients. Based on the safety and efficacy evidence to date, peginterferon alfa-2a and NUCs should not be used in combination. Treatment monitoring is described in Box 2 and definitions of response are set out in Box 3.

Finite treatments

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Box 2: Treatment monitoring

Patients treated with pegylated interferon alfa-2a or nucleoside/nucleotide analogues should undergo regular monitoring for treatment response and the development of resistance. The European Association for the Study of the Liver recommends the following monitoring:

Peginterferon alfa-2a treatment
- Full blood count and serum alanine aminotransferase (ALT) monitored monthly
- Hepatitis B virus (HBV) DNA level monitored at weeks 12 and 24 to verify primary response
- HBeAg-positive patients:
  - HBeAg and HBe antibodies (anti-HBe) at weeks 24 and 48, and 24 weeks post-treatment
  - HBsAg checked every 6 months after HBe seroconversion if HBV DNA is undetectable
- HBeAg-negative patients:
  - Monitor for safety and efficacy throughout 48-week regimen

NUCLEOSIDE/NUCLEOTIDE ANALOGUES

- Finite treatment in HBeAg-positive patients: HBV DNA every 12 weeks
- Long-term treatment (HBeAg-positive and -negative patients): HBV DNA levels at week 12 then every 2 to 24 weeks

Long-term treatment

Long-term treatment is appropriate for HBeAg-positive patients who do not achieve HBe seroconversion and HBeAg-negative patients — ie, for patients who cannot sustain a virological response off treatment — as well as patients with cirrhosis. Again, the most potent NUCs with a high barrier to resistance (entecavir, tenofovir) should be selected.

Antiviral resistance

Resistance to NUCs should be identified as early as possible — usually flagged up by increased ALT and HBV DNA levels. For patients with primary non-response and partial response to antivirals, compliance should be assessed. Once resistance has been identified, therapy should be modified depending on the resistance profiles of the medicines.

Box 3: Definitions of response to treatment

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary non-response</td>
<td>Peginterferon alfa-2a and nucleoside/tide analogues (NUCs): less than 1 log_{10} iu/ml decrease in hepatitis B virus (HBV) DNA level from baseline at three months</td>
</tr>
<tr>
<td>Virological response</td>
<td>Peginterferon alfa-2a: HBV DNA &lt;2,000 iu/ml at 24 weeks. NUCs: HBV DNA undetectable within 48 weeks</td>
</tr>
<tr>
<td>Serological response</td>
<td>Peginterferon alfa-2a: HBe seroconversion in HBeAg-positive patients</td>
</tr>
<tr>
<td>Partial virological response</td>
<td>NUCs: Reduction in HBV DNA of more than 1 log_{10} iu/ml but detectable after 24 weeks (lamivudine) or 48 weeks (adefovir, entecavir, tenofovir)</td>
</tr>
<tr>
<td>Virological breakthrough</td>
<td>NUCs: An increase in HBV DNA level of &gt;1 log_{10} iu/ml compared with lowest level</td>
</tr>
</tbody>
</table>
In general all new patients who are NUC naïve will be started on tenofovir or entecavir monotherapy. For those who go on to develop resistance while on treatment, a second antiviral medicine, which is not associated with cross resistance, should be added (see Figure 1).

Management of special groups

HIV co-infected patients It is recommended that most HIV/hepatitis B co-infected patients are simultaneously treated for both infections. Tenofovir and emtricitabine (both active against HIV) plus a third anti-HIV medicine are indicated. In certain patients HBV can be treated before HIV: adefovir and telbivudine, which are not proven to be active against HIV, are recommended. However, if these medicines with a low barrier to resistance do not reach the goal of undetectable HBV DNA, treatment of HIV infection should be considered. Lamivudine, entecavir and tenofovir have activity against both HIV and HBV and are therefore contraindicated for use as monotherapy against hepatitis B in co-infected patients.

Hepatitis C co-infected patients In most patients co-infected with hepatitis B and C, HBV DNA levels are often low or undetectable and the hepatitis C virus (HCV) is responsible for the activity of chronic hepatitis, although this is variable. Thus patients should receive peginterferon with ribavirin in line with HCV treatment guidelines. Sustained virological response rates for HBV/HCV co-infected patients are broadly comparable to those for HCV mono-infected patients. There is a potential risk of HBV reactivation during or after clearance of HCV; the HBV must then be treated with NUCs.

Pregnancy Adefovir, entecavir and lamivudine are listed by the US Food and Drug Administration as pregnancy category C drugs, and telbivudine and tenofovir as category B drugs (category A is considered the safest for use in pregnancy). These classifications are based on the risk of teratogenicity in preclinical evaluation.

There is a considerable body of safety data for pregnant HIV-positive women who have received tenofovir and/or lamivudine. Recent reports suggest that lamivudine therapy during the last trimester of pregnancy in HBsAg-positive women with high levels of viraemia reduces the risk of intrauterine and perinatal transmission of HBV if the baby is given hepatitis B immunoglobulin and HBV vaccination as soon as possible after birth.1 Although further evidence is needed to confirm the safety of entecavir and tenofovir in pregnancy, these

\[
\begin{array}{|c|}
\hline
\text{LAMIVUDINE} \\
\text{Add tenofovir} \\
\hline
\text{ADEFOVIR} \\
\text{Switch to tenofovir} \\
\text{and add a second} \\
\text{drug without cross-} \\
\text{resistance} \\
\hline
\text{ENTECAVIR} \\
\text{Add tenofovir} \\
\hline
\text{TELBIVUDINE} \\
\text{Add tenofovir} \\
\hline
\text{TENOFOVIR} \\
\text{Resistance not yet} \\
\text{described therefore} \\
\text{cross-resistance} \\
\text{profile should be} \\
\text{performed} \\
\text{Any NUC could be} \\
\text{added if resistance} \\
\text{is suspected} \\
\hline
\end{array}
\]

Figure 1: Summary of European Association for the Study of the Liver recommendations for modification of treatment with nucleoside/nucleotide analogue (NUC) antivirals when resistance occurs

British Liver Trust
www.britishlivertrust.org.uk

European Association for the Study of the Liver
www.easl.eu

American Association for the Study of Liver Diseases
www.aasld.org

Pharmacist input

Pharmacists can provide the following hepatitis B-related input:

- Direct individuals to hepatitis B vaccination and screening services (important for those identified as “at risk” — eg, needle exchange and sexual health service users)
- Raise awareness of hepatitis B among healthcare professionals in the community
- Provide medicines information to doctors and allied healthcare professionals in primary and secondary care
- Work with primary care organisations to develop services for treating hepatitis B in the community
- Practise as independent prescribers to improve treatment provision
- Provide hepatitis B patients with information on treatment
- Offer adherence and treatment support to patients

In most patients co-infected with hepatitis B and C, HBV DNA levels are often low or undetectable.

British Liver Trust
www.britishlivertrust.org.uk

European Association for the Study of the Liver
www.easl.eu

American Association for the Study of Liver Diseases
www.aasld.org
Summary of medicines licensed for treatment of chronic hepatitis B infection

<table>
<thead>
<tr>
<th>MEDICINE</th>
<th>Peginterferon alfa-2a</th>
<th>Adefovir</th>
<th>Entecavir</th>
<th>Lamivudine</th>
<th>Telbivudine</th>
<th>Tenofovir</th>
</tr>
</thead>
<tbody>
<tr>
<td>DESCRIPTION</td>
<td>Immunomodulator</td>
<td>Nucleotide analogue</td>
<td>Nucleoside analogue</td>
<td>Nucleoside analogue</td>
<td>Nucleoside analogue</td>
<td>Nucleotide analogue</td>
</tr>
<tr>
<td>DOSE</td>
<td>180μg once weekly, subcutaneously</td>
<td>10mg daily, orally</td>
<td>0.5mg daily, orally, for nucleoside-naive patients; 1mg daily for lamivudine-resistant patients</td>
<td>100mg daily, orally</td>
<td>600mg daily, orally</td>
<td>245mg daily, orally</td>
</tr>
<tr>
<td>DOSE MODIFICATIONS</td>
<td>Dose should be reduced for patients with creatinine clearance (CrCl) &lt;50ml/min</td>
<td>Dose should be increased for patients with CrCl &lt;50ml/min</td>
<td>Dose should be reduced for patients with CrCl &lt;50ml/min</td>
<td>Dose should be increased for patients with CrCl &lt;50ml/min</td>
<td>Dose should be increased for patients with CrCl &lt;50ml/min</td>
<td></td>
</tr>
<tr>
<td>CONTRAINDICATIONS</td>
<td>Decompensated cirrhosis, autoimmune hepatitis</td>
<td>Breastfeeding</td>
<td>Breastfeeding</td>
<td>Breastfeeding</td>
<td>Breastfeeding</td>
<td></td>
</tr>
<tr>
<td>SIDE EFFECTS</td>
<td>Flu-like symptoms, depression, myelosuppression</td>
<td>Generally well tolerated, minor gastrointestinal effects, rarely lactic acidosis</td>
<td>Generally well tolerated, minor gastrointestinal effects, rarely lactic acidosis</td>
<td>Generally well tolerated, minor gastrointestinal effects, rarely lactic acidosis</td>
<td>Generally well tolerated, minor gastrointestinal effects, rarely myopathy</td>
<td></td>
</tr>
<tr>
<td>ADVICE/MONITORING</td>
<td>Injection in thigh or abdomen for better absorption</td>
<td>Potential for nephrotoxicity: renal monitoring essential</td>
<td>Patients taking 1mg dose must take dose at least 2h before or 2h after food</td>
<td>Advise patients to report muscle pain and tenderness</td>
<td>Potential for nephrotoxicity: renal monitoring essential</td>
<td></td>
</tr>
<tr>
<td>NICE-APPROVED*</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>SMC-APPROVED*</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Not assessed</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>COST PER YEAR</td>
<td>£6,092 (48 weeks)</td>
<td>£3,664</td>
<td>£4,404</td>
<td>£1,015</td>
<td>£3,769</td>
<td>£3,094</td>
</tr>
<tr>
<td>RESISTANCE</td>
<td>None</td>
<td>29% at 5 years</td>
<td>1% at 5 years in NUC-naive patients</td>
<td>70% at 5 years</td>
<td>22% at 2 years</td>
<td>None at 3 years</td>
</tr>
</tbody>
</table>

**HBeAg-positive patients**

| PERCENTAGE HBeAg SEROCONVERSION | 30 | 24 | 22 | 22 | 26 | 21 |
| PERCENTAGE HBV UNDECTECTABLE AT ONE YEAR | 24 | 21 | 67 | 39 | 60 | 74 |

**HBeAg-negative patients**

| PERCENTAGE HBV UNDECTECTABLE AT ONE YEAR | 63 | 51 | 90 | 72 | 88 | 91 |

* NICE = National Institute for Health and Clinical Excellence; SMC = Scottish Medicines Consortium

NUCs could be considered for use in this patient group. All of the licensed NUCs are contraindicated for use while breastfeeding.

**Prophylaxis** Patients who are carriers of HBV and who are being treated with chemotherapy or immunosuppressive therapy are at high risk of their infection reactivating. All patients who are being considered for such therapy should be screened for HBeAg and anti-HBc antibodies before therapy is started. Vaccination against HBV in seronegative patients is highly recommended.

Seropositive patients should be tested for HBV DNA levels; those who test positive for viral DNA should receive prophylactic NUC therapy. The NUC of choice is lamivudine, which should be prescribed during the course of therapy and for 12 months after the course is completed.

**References**