Antiviral therapy against hepatitis C has improved significantly over the past 10 years and the infection is now considered curable. Dual therapy with peginterferon and ribavirin remains the backbone of treatment for all patients with hepatitis C. For patients infected with genotype 1 hepatitis C virus (HCV), adding a first-generation directly acting antiviral — boceprevir or telaprevir — offers better cure rates compared with using only dual therapy with peginterferon and ribavirin. The introduction of these medicines to hepatitis C treatment regimens brings new challenges and offers pharmacists the opportunity to apply their pharmaceutical expertise to patient care and increase their involvement in this therapeutic area.

Treatment aims
HCV replicates entirely within the cytoplasm. It does not establish latency and it is possible, therefore, for the virus to be cleared spontaneously or to be eradicated by treatment — ie, people can be cured of a hepatitis C infection.1 HCV is considered to be eradicated when a sustained virological response (SVR) to treatment has been achieved (see accompanying article, p100). This is defined as having an undetectable level (ie, <50iu/ml) of HCV RNA in the blood 24 weeks after completing treatment.

Viral eradication will prevent any further liver damage and avoid the consequences of liver disease, such as fibrosis, cirrhosis, decompensation, hepatocellular carcinoma and death. Although an SVR is considered the main endpoint of HCV therapy2 and viral eradication is the primary aim of treatment, preventing the transmission of HCV and improving patients' quality of life are also important treatment outcomes.

Antivirals
Peginterferon alfa Interferons are naturally occurring cytokines, that are produced by macrophages and lymphocytes in response to pathogens. Although they are known to have immunomodulatory, antiproliferative, pro-apoptotic and antiviral effects, their specific mechanism of action against HCV is unknown.

Interferon alfa became available as a treatment option for HCV infection in the early 1990s but has since been replaced by peginterferon alfa in all HCV treatment regimens. Peginterferon has better pharmacokinetic and pharmacodynamic properties than interferon and is formed by attaching inert glycol moieties to interferon molecules (known as pegylation).

Peginterferon alfa is administered by subcutaneous injection once a week. There are two preparations licensed in the UK for HCV infection: peginterferon alfa-2a (Pegasys) is prescribed at a fixed dose of 180µg and peginterferon alfa-2b (ViraferonPeg) is prescribed according to weight (1.5µg/kg). Although the efficacy of each brand has been debated over the years, there has been no conclusive evidence supporting one preparation over another and choice should be guided by local policies and patient preference.

Ribavirin Ribavirin is an analogue of the nucleoside guanosine. The exact mechanism of action of ribavirin is unknown; however, it is thought to interfere with viral replication by inhibiting viral mRNA polymerases and subsequently disrupting intracellular nucleotides. It is taken orally twice a day and doses are weight-dependent.

For personal use only not to be reproduced without permission
Boceprevir and telaprevir

Research into the life cycle of HCV has led to the discovery of new therapeutic targets and enabled the development of directly acting antivirals. In 2011, the first generation of directly acting antivirals were licensed in the UK. Boceprevir and telaprevir are peptide-mimetic protease inhibitors that potently and reversibly inhibit HCV NS3/4A serine protease. This enzyme has an essential role in the building of mature viral proteins, and by inhibiting this enzyme viral replication is inhibited.

Acute infection

It is difficult to conduct research into acute HCV infection because most patients will be asymptomatic and difficult to identify in this phase. To prevent chronic disease all patients found to have acute HCV infection should be considered for antiviral therapy. Some patients might clear the virus spontaneously before pharmacological intervention and it is recommended that therapy should be delayed for two to four months after the onset of disease to prevent unnecessary treatment.

Excellent results can be obtained with peginterferon alfa monotherapy — with viral eradication achieved in over 90% of patients with acute infection. No firm recommendations can be made regarding the addition of ribavirin to the treatment regimen, and the decision to do so is made on a case-by-case basis.

Treatment duration is subject to debate; current European practice guidelines recommend 24 weeks, but many clinicians choose to extend this.

Chronic infection

All patients with chronic HCV infection are candidates for antiviral treatment. However, the risks and benefits of therapy must be considered for each individual. The stage of liver disease, HCV genotype, HCV RNA level and IL28B genotype should help determine how a patient will respond to the antiviral regimens available. Clinicians must also take into account:

- Any previous treatment regimens
- The presence of patient comorbidities and their potential effect on disease progression
- Any desired treatment outcomes

Dual therapy

Before the introduction of protease inhibitors dual therapy with peginterferon alfa and ribavirin was the standard of care for all patients with chronic HCV infection. This regimen achieves SVR rates of 40–50% for patients with HCV genotypes 1 and 4 and of around 80% for those with HCV genotypes 2, 3, 5 and 6. Treatment duration can vary from 16 to 48 weeks.

Triple therapy

Boceprevir and telaprevir are licensed for the treatment of patients with HCV genotype 1 in combination with peginterferon alfa and ribavirin. This is known as triple therapy. To date, five published phase III studies have clearly demonstrated the therapeutic benefits of using boceprevir or telaprevir as part of a triple therapy regimen.

There have been no head-to-head studies comparing boceprevir with telaprevir, and the study populations, secondary outcomes and study design in the clinical trials of each drug were different — so neither drug can be recommended over the other.

Patients prescribed boceprevir need to have received at least four weeks of therapy — a lead-in period — with peginterferon alfa and ribavirin before commencing treatment (see Box 1). To use a lead-in with telaprevir is outside its licence, but in selected patients this may be clinically beneficial.

Possible advantages of a lead-in period include: assessment of tolerability to dual therapy; assessment of the likelihood of achieving SVR with, or without, a protease inhibitor; and characterisation of patient response to dual therapy — this is particularly relevant in the context of previous treatment failure.

Box 1: Boceprevir and telaprevir

<table>
<thead>
<tr>
<th>FORMULATION</th>
<th>BOCEPREVIR</th>
<th>TELAPREVIIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOSE</td>
<td>800mg three times a day</td>
<td>750mg three times a day</td>
</tr>
<tr>
<td>DURATION</td>
<td>24-44 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>ADMINISTRATION</td>
<td>Taken with food; doses over six hours late should be omitted</td>
<td>Taken with food containing a high amount of fat (approximately 20g); doses over four hours late should be omitted</td>
</tr>
<tr>
<td>METABOLISM</td>
<td>Aldoketoreductase (primarily)</td>
<td>CYP3A4 (primarily)</td>
</tr>
<tr>
<td></td>
<td>CYP3A4 (to a lesser extent)</td>
<td>P-glycoprotein inhibitor and substrate</td>
</tr>
<tr>
<td></td>
<td>P-glycoprotein substrate</td>
<td>Potent CYP3A4 inhibitor</td>
</tr>
</tbody>
</table>

Do you have a prescribing qualification but lack the business case to develop a pharmacist-led service?
Approach to therapy

The National Institute for Health and Care Excellence has issued several guidelines to support treatment of patients with chronic HCV infection with peginterferon alfa and ribavirin.

In 2012, it issued further guidance on treatment of HCV genotype 1 infection, recommending the use of boceprevir or telaprevir in triple therapy regimens for all such patients. The Scottish Medicines Consortium had issued similar guidance in 2011. Treatment regimens vary for each genotype (see Box 2, p107).

A national meeting of HCV care providers in 2011 led to the development of consensus guidelines on the use of boceprevir and telaprevir. The guidelines provide a concise review of the evidence supporting the use of these medicines and offer recommendations for best practice in the management of chronic HCV patients.

The use of highly sensitive HCV RNA assays and rapid access to results are key for the safe and effective delivery of triple therapy. HCV RNA levels need to be assessed at set intervals to determine treatment duration. For instance, if a treatment-naïve and non-cirrhotic patient taking boceprevir has an undetectable level of HCV RNA at treatment weeks 8 and 24, then he or she can stop therapy after 28 weeks (four weeks of dual therapy followed by 24 weeks of triple therapy). This is known as “response-guided therapy”. However, if HCV RNA is detected at week 8 but not at weeks 12 and 24 then the patient is not eligible for response-guided therapy and treatment should be continued for 48 weeks.

Full guidance on response-guided therapy and instructions on when to stop treatment when it is proving ineffective (also known as futility rules) can be found in the summaries of product characteristics and these recommendations vary between manufacturers.

Some patients with HCV are unsuitable for response-guided therapy and require 48 weeks of therapy. This includes all patients with cirrhosis and patients who have received dual therapy previously but did not respond fully or did not respond at all. Response-guided therapy with telaprevir may be used for patients who have relapsed on previous therapy.

Adverse effects

The main adverse effects associated with peginterferon alfa and ribavirin include:

- Flu-like symptoms (chills, fever, malaise, headache)
- Haematological disturbances (eg, neutropenia, thrombocytopenia, anaemia)
- Psychological conditions (eg, anxiety, depression and irritability)
- Hypo- and hyperthermia
- Nausea, vomiting and diarrhoea
- Decreased appetite and weight loss
- Myalgia
- Hair loss
- Insomnia

The main adverse effects reported with boceprevir are anaemia, neutropenia and taste disturbances. For telaprevir, rash, ano-rectal symptoms (pruritus and
Discomfort) and anaemia are more frequently reported compared with dual therapy. Doses of boceprevir and telaprevir cannot be adjusted; instead, specific strategies are adopted to manage any adverse effects that occur during therapy.

Anaemia Anaemia is a well-documented side effect of dual therapy and is mainly associated with the toxic effect of ribavirin on red blood cells. On average, patient haemoglobin levels drop between 2–3g/dl during dual therapy. Adding a protease inhibitor further increases the occurrence of anaemia and data suggest that haemoglobin levels also, on average, drop by a further 1g/dl.

Epoetin is an unlicensed treatment option for HCV therapy-associated anaemia; the benefits of its use have been debated and its use in practice varies. Recent data suggest that reducing the dose of ribavirin is as effective as epoetin for treating anaemia and does not compromise clinical outcomes in boceprevir- and telaprevir-based regimens. The current recommendation for treating clinically significant anaemia during therapy is a stepwise dose reduction of ribavirin.

Rash An increased incidence of rash was reported in patients treated with telaprevir-based triple therapy regimens compared with peginterferon alfa and ribavirin dual therapy (55% versus 33%, respectively). Over 90% of rashes were graded as mild or moderate. Half of patients who develop a rash on telaprevir will do so within the first month of treatment (although this side effect can occur at any time). The rash is typically pruritic and eczematous and affects less than a third of the surface of the body. A detailed rash management plan is available from the manufacturer of telaprevir. Access to a specialist dermatology service must be available for all patients started on telaprevir and provisions must be put in place before starting therapy.

Treatment issues Resistance The clinical impact of resistance to directly acting antivirals has not been established. It appears that resistant variants of HCV are less capable of replicating and there does not seem to be an archive of resistant mutations. However, all directly acting antivirals carry the risk of selecting resistant variants and so strict adherence to the dosing regimen and futility rules is essential when using antiviral therapy. Both the clinician and the patient should understand this to ensure optimal clinical outcomes. There is currently no place for routine screening for HCV resistant mutations at baseline.

Studies show that co-administration of peginterferon alfa and ribavirin with boceprevir or telaprevir is critical for preventing HCV resistance. Patients who are less responsive to peginterferon alfa and ribavirin demonstrate higher rates of virological failure and resistant mutations compared with patients who respond well.

Adherence As discussed above, adhering to complex dosing regimens is vital for treatment success. The implications of non-adherence, such as treatment failure and resistance, should be explained clearly to patients, and
pharmacists are well placed to do this (see Box 3). Advice on how to manage dosing schedules, including the practicalities of taking boceprevir and telaprevir with the correct amount of fat to aid absorption, should be discussed. It is also important that patients know the possible adverse effects that can occur during treatment and how to manage them.

**Drug interactions** There are relatively few documented drug interactions between peginterferon alfa, ribavirin and other medicines, and managing interactions during HCV dual therapy has not been problematic. However, boceprevir and telaprevir are both potent inhibitors of the cytochrome p450 isoenzyme CYP3A4 and the management of drug interactions in HCV triple therapy regimens has become more complex.

Drug interactions can complicate the management of HCV, and other medical conditions, in many ways. An interaction can increase the risk of side effects, put the patient at a higher risk of toxicity, change the antiviral activity of the HCV regimen (potentially leading to a loss of efficacy and the development of resistance) or alter the effect of concomitant medicines. Boceprevir and telaprevir are contraindicated with drugs that are either potent inducers of CYP3A4 or highly dependent on CYP3A4 for drug clearance (see Box 1, p104).

An accurate medication history (including all prescribed and purchased medicines) should be taken from each patient before they start HCV therapy. A detailed drug interaction management plan should be set out and any new medicines required during treatment should be carefully evaluated before they are started. Recognition and accurate characterisation of interactions is vital to ensure safe and appropriate management of patients on HCV treatment. An excellent resource, with which many pharmacists will be familiar, is the drug interaction database by the University of Liverpool

![www.hep-druginteractions.org](www.hep-druginteractions.org) — a website dedicated to interactions with viral hepatitis medicines.

**Teratogenicity** Ribavirin is known to be teratogenic and, therefore, women and men are advised to use two forms of contraception throughout treatment and for several months after, with the exact duration varying slightly between the sexes.

**Specialist care** Patients with chronic HCV infection who are co-infected with HIV, who have had a liver transplant or have established cirrhosis are also eligible for antiviral therapy. The increased likelihood of drug interactions and adverse effects mean that treating these patients can be complex and they should be managed at specialist centres.

**Future treatments** There is great interest in developing new therapies that have activity against all HCV genotypes, have improved pharmacological parameters, have higher barriers to resistance and, if possible, exclude peginterferon alfa (to avoid unwanted adverse effects and regular injections). Novel dosing strategies with different combinations of directly acting antivirals that shorten treatment durations and maximise SVR rates are currently being explored.

More has been discovered about the life cycle of HCV in recent years and this has led to the identification of several new targets for drug development. There are now over 30 directly acting antivirals in various stages of clinical development. These include protease inhibitors, nucleoside and nucleotide polymerase inhibitors, non-nucleoside polymerase inhibitors, NS5A inhibitors, entry inhibitors and host-targeting drugs. Examples of directly acting antivirals currently in phase III trials include sofosbuvir (a nucleotide polymerase inhibitor), simeprevir (a protease inhibitor) and daclatasvir (a NS5A inhibitor).
References

Boost your continuing professional development by completing our Lifelong Learning modules at www.clinicalpharmacist.com

Hepatitis C

Lifelong Learning questions are available to complete in an online module on the Clinical Pharmacist section of PJ Online — accessible via www.clinicalpharmacist.com.

To complete the module, you will need to log in to the site. If you are a new visitor, it is simple to register as a user (free to all Royal Pharmaceutical Society members).

Questions
This month’s Lifelong Learning questions are based on the CLINICAL FOCUS articles on hepatitis C, which were commissioned from an independent author.

The information in the Box (adjacent) is there to help you identify knowledge gaps and undertake continuing professional development. This online module will close on 18 July 2013.

Answers
When you have completed the online module, your answers will be submitted for marking and Clinical Pharmacist will send you a certificate and your results by email within two weeks of the module closing. The questions in this Lifelong Learning module have been appraised by an independent reviewer for quality assurance.

How to undertake continuing professional development

Our CLINICAL FOCUS articles and the online Lifelong Learning modules can help you plan your CPD and record the benefits of the activity at www.uptodate.org.uk.

Reflect on your gaps in knowledge
- What is hepatitis C virus (HCV) and how is it transmitted?
- What are the clinical features of chronic HCV infection?
- What treatment options are available for patients with chronic HCV infection?

Evaluate the activity
- What have you learnt?
- How has it added value to your practice?
- What will you do now and how will this be achieved?

Act to enhance your practice
- Read the CLINICAL FOCUS articles in this issue (pp100–9)
- Test your knowledge by completing the questions at www.clinicalpharmacist.com