Direct-acting antiviral drugs for the treatment of hepatitis C

KATE STEWART

New direct-acting antiviral drug treatments for hepatitis C are more effective, easier to take and have fewer side-effects than older treatments. New technology appraisals from NICE have recommended specific combinations of these treatments for different patient groups with hepatitis C, meaning that more patients will now have access to these drugs on the NHS.

Hepatitis C is sometimes called the “silent epidemic” because symptoms are often attributed to other illnesses during the earlier stages of infection. In its 2015 report Hepatitis C in the UK, the Department of Health estimates that 214,000 people in the UK are chronically infected with the hepatitis C virus. “Deaths from hepatitis C-related end-stage liver disease and liver cancer have doubled over the last decade – the majority occurring in people under the age of 60 years,” the report adds.

Moreover, there has been more than a five-fold increase in the number of laboratory-confirmed reports of hepatitis C infection over the last two decades in England (see Figure 1). However, the charity Hepatitis C Trust (www.hepctrust.org.uk) and many clinicians UK-wide believe the number of people infected with the hepatitis C virus is much larger with many cases that are currently undiagnosed.

NICE guidance

Drug treatments for hepatitis C infections have advanced greatly in the last few years with a move away from interferon-based treatments to more effective medications that have fewer side-effects, are easier to take and are less debilitating for patients.

These newer, oral, direct-acting antiviral treatments will be made available on the NHS to people living with hepatitis C and, in three recent technology appraisals, NICE has recommended which combinations of these drugs should be used and which patients with hepatitis C should receive them (see Tables 1-3).

The drug combinations now approved by NICE for use as part of the new treatment regimens include ombitasvir-paritaprevir-ritonavir (Viekirax) with or without dasabuvir (Exviera) as a possible treatment for adults with genotypes 1 or 4 of chronic hepatitis C. The combination is

Figure 1. Number of laboratory reports of hepatitis C from England: 1996 to 2014. (NB Statutory notification by diagnostic laboratories was introduced in October 2010)
Hepatitis C

Dasabuvir for treating chronic hepatitis C

NICE technology appraisal recommendations on ombitasvir-paritaprevir-ritonavir with or without dasabuvir

Table 1. NICE technology appraisal recommendations on ombitasvir-paritaprevir-ritonavir with or without dasabuvir for treating chronic hepatitis C

<table>
<thead>
<tr>
<th>Type of hepatitis C</th>
<th>Treatment recommended by NICE</th>
<th>Length of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a, without cirrhosis</td>
<td>Ombitasvir–paritaprevir–ritonavir with dasabuvir and ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>1a, with cirrhosis</td>
<td>Ombitasvir–paritaprevir–ritonavir with dasabuvir and ribavirin</td>
<td>24 weeks</td>
</tr>
<tr>
<td>1b, without cirrhosis</td>
<td>Ombitasvir–paritaprevir–ritonavir with dasabuvir</td>
<td>12 weeks</td>
</tr>
<tr>
<td>1b, with cirrhosis</td>
<td>Ombitasvir–paritaprevir–ritonavir with dasabuvir and ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>4, without cirrhosis</td>
<td>Ombitasvir–paritaprevir–ritonavir with ribavirin</td>
<td>12 weeks</td>
</tr>
<tr>
<td>4, with cirrhosis</td>
<td>Ombitasvir–paritaprevir–ritonavir with ribavirin</td>
<td>24 weeks</td>
</tr>
</tbody>
</table>

Table 2. NICE technology appraisal recommendations on ledipasvir-sofosbuvir for treating chronic hepatitis C

<table>
<thead>
<tr>
<th>Type of hepatitis C</th>
<th>Ledipasvir–sofosbuvir treatment recommended by NICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>If your hepatitis C has not been treated before</td>
<td>8 weeks’ treatment</td>
</tr>
<tr>
<td>1, without cirrhosis</td>
<td>12 weeks’ treatment</td>
</tr>
<tr>
<td>1 or 4, with cirrhosis</td>
<td>12 weeks’ treatment</td>
</tr>
<tr>
<td>If your hepatitis C has been treated before, but has not responded well enough</td>
<td>12 weeks’ treatment, only if the person has a low risk of the disease getting worse</td>
</tr>
</tbody>
</table>

Sometimes taken with ribavirin (see Table 1). Ledipasvir-sofosbuvir (Harvoni) is also recommended as a possible treatment for adults with some genotypes of chronic hepatitis C (see Table 2), as is daclatasvir (Daklinza), in combination with sofosbuvir (Sovud) or peginterferon alfa, and sometimes with ribavirin (see Table 3).

Revolutionary treatments

Consultant hepatologist Dr Kosh Agarwal, who is based at the Institute of Liver Studies, King’s College Hospital, London, has been at the forefront of this new treatment development for patients with hepatitis C.

He tells Prescriber: “These new treatments for hepatitis C represent a significant revolution and improvement in treatment for patient benefit. The important thing to remember is that we are not talking about suppression; we are talking about a cure for hepatitis C.

“Previously, the treatments that we had for hepatitis C were quite arduous; they required injections of interferon and regular visits to the hospital. The treatments had significant side-effects – physical and neuropsychiatric – and had very suboptimal cure rates.

“So for genotype 1 (there are six genotypes of the hepatitis C virus), the previous treatment recommendations would be to give treatment for one year, with an interferon injection every week plus tablets every day. You’d need to be seen in hospital every four weeks and the potential cure rates would be about 35 per cent, which is pretty poor. And for some people, this form of treatment was tantamount to a form of chemotherapy, with significant issues with tolerability.

“We now understand much better how the hepatitis C virus replicates. For the last six years, we have been able to culture it in a laboratory and we therefore understand the enzymes and the steps that it takes for the virus to replicate within a liver cell. This has allowed us to design and deliver drugs that act directly on the virus, known as direct-acting antiviral agents, and there are several clusters of these drugs because they act in different ways on different pathways as the hepatitis C virus replicates.

“We originally used these drugs with interferon, but are now able to avoid that, as well as ribavirin, and we are able to take the duration of treatment down to predominantly 12 weeks. The tablets are taken orally and have very few side-effects; they are very well tolerated and the cure rates are phenomenal – with genotype 1 patients looking at cure rates of 95 per cent and upwards.”

Dr Agarwal adds: “There is no doubt that these drugs are cost effective and, significantly, they are curative – they are not a salve to give you added months or years of survival. The scope of this development is potentially the hottest potato from a financial perspective for all healthcare environments, particularly the NHS, because this truly does represent a game-changing moment for priorities with regard to therapies.

“It is really the best example of research translating to patient benefit. It’s a fantastic opportunity for patients, it’s a fantastic chance for us to discard some of the issues surrounding the stigma associated with hepatitis C and there is no doubt that it gives us a chance to aspire to the eradication of hepatitis C.

“Now we need GPs to target those patients who may be at risk of hepatitis C, to test these patients and refer them to a specialist setting where their care can be managed. Over a period of time, we will see the costs of these treatments go down and greater numbers of patients being treated and their hepatitis C infections being eliminated.”
Dr Agarwal notes that it is vital that primary care practitioners take on the challenge of hepatitis C because at the moment only those with a specialist interest in this area are developing pathways. Dr Agarwal adds: “If you want to eradicate hepatitis C, you have almost got to quadruple the treatment rates we have been seeing. The cost implications of that are immense, so we are trying to focus and target patients in a stepwise fashion.

“The field of treatment will change radically over the next 12 months. All clinicians need to be aware of the types of patients that should be screened for hepatitis C. These patients should be screened and if they are positive, they should be referred.”

Costly but effective

NHS England and NHS Wales have been given extensions in order to raise the money to fund the new hepatitis C treatments, which can cost more than £30,000 for a course of treatment.

Charles Gore, chief executive of the Hepatitis C Trust, says NICE decisions will mean little “if people who are living with hepatitis C in England and Wales do not come forward and discuss their treatment options with their doctor.

“People living with hepatitis C have been eagerly awaiting these new interferon-free treatments and it is now vital that NHS England ensures patients have access to them as quickly and widely as possible.

“These drugs are cost-effective and allow patients to be cured in as little as 12 weeks, so there really is no excuse for delaying treatment and continuing to allow ever-increasing numbers of hepatitis C patients to progress to end-stage liver disease and liver cancer.

“There are too many people living with hepatitis C who are either undiagnosed or not in touch with hospital services, GPs can play an important role in lowering the numbers of unnecessary deaths linked to hepatitis C by ensuring that their patients are tested and on the correct pathway to treatment,” Mr Gore adds.

Dr Steve Ryder, consultant hepatologist, Nottingham University Hospitals NHS Trust and Biomedical Research Unit, agrees that the new drugs would make a huge, positive difference to many patients with hepatitis C. He says: “All tablet treatments for all patients with genotype 1 and genotype 4 hepatitis C are a huge step forward and will increase the proportion of people taking up treatment as there are few or no side-effects. Cure rates have also shown a massive improvement – more than 95 per cent of patients cured.

“There is still a gap for genotype 3 patients, but only because the new drugs don’t work as well for this genotype. This gap is going to close in the next year or so with new drugs,” he predicts. “The drugs are very expensive (£28,000–£37,000 per treatment) and there is lots of ‘payer anxiety’ about whether hepatitis C will break the bank. The budget for treatment in England is £190 million next year and most clinicians feel that will cope with numbers of treatments needed – watch this space.

“The new treatments may make it easier to offer the drugs more widely through primary care than with interferon, but NHS England will want to keep tight control over spend, so there will be limited prescribing opportunities initially in primary care and they would need partnership with hepatitis services in secondary care,” he adds.

Role of primary care

Nottingham City GP and clinical lead for drug misuse and alcohol for NHS Nottingham, Dr Stephen Willett says: “I think these new treatments are very exciting and offer our (often hard to engage) patients with challenging social circumstances a much greater chance of following through with treatment because there are shorter, fewer side-effects and a much greater chance of cure.

“However, because of the high cost, we GPs understand these drugs have to be treated carefully during the likes of multidisciplinary team meetings. But

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<tr>
<td>If your hepatitis C has not been treated before</td>
<td>1, without cirrhosis</td>
<td>Daclatasvir plus sofosbuvir only for people with significant fibrosis.</td>
</tr>
<tr>
<td>4</td>
<td>Daclatasvir plus peginterferon alfa and ribavirin only for people with significant fibrosis or cirrhosis.</td>
<td>24 weeks</td>
</tr>
<tr>
<td>If your hepatitis C has been treated before</td>
<td>1 or 4 without cirrhosis</td>
<td>Daclatasvir plus sofosbuvir only for people with significant fibrosis.</td>
</tr>
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<td>Daclatasvir plus peginterferon alfa and ribavirin only for people with significant fibrosis or cirrhosis.</td>
<td>24 weeks</td>
</tr>
<tr>
<td>If you cannot have interferon</td>
<td>1, 3 or 4 without cirrhosis</td>
<td>Daclatasvir plus sofosbuvir only for people with significant fibrosis.</td>
</tr>
<tr>
<td>1 or 4 with cirrhosis</td>
<td>Daclatasvir plus sofosbuvir, with or without ribavirin.</td>
<td>24 weeks</td>
</tr>
<tr>
<td>3, with cirrhosis</td>
<td>Daclatasvir plus sofosbuvir and ribavirin.</td>
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Table 3. NICE technology appraisal recommendations on daclatasvir for treating chronic hepatitis C

Dr Agarwal notes that it is vital that primary care practitioners take on the challenge of hepatitis C because at the moment only those with a specialist interest in this area are developing pathways. Dr Agarwal adds: “If you want to eradicate hepatitis C, you have almost got to quadruple the treatment rates we have been seeing. The cost implications of that are immense, so we are trying to focus and target patients in a stepwise fashion.

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“However, because of the high cost, we GPs understand these drugs have to be treated carefully during the likes of multidisciplinary team meetings. But
I, for one, welcome the chance to be involved in the treatment of my patients in primary care, which for those with challenging social circumstances (including injecting drug users and perhaps some of the migrant population whose first language is not English), we have a greater chance of them engaging with.”

Grace Everest from HCV Action (www.hcvaction.org.uk) agrees that GPs and those working in primary care have a key role to play in recognising those at risk of hepatitis C. She says: “GPs have a crucial role to play in ensuring greater numbers of people at risk of hepatitis C are tested for the hepatitis C virus. With 90 per cent of all patient contacts in the NHS conducted by GPs and their teams, it is likely that people with hepatitis C will at some point be treated in general practice, yet guidance from both NICE and Public Health England suggests that more needs to be done to raise awareness levels among primary care professionals.

“In particular, GPs should be encouraged to case-find for hepatitis C by proactively enquiring about risk factors such as a history of injecting drug use (for example, baby boomer patients who may have experimented in their youth); offering a test to migrants from high prevalence countries and those from South Asian communities (for example, on registration); and offering a test following an abnormal liver test result.

“The RCGP, together with the Hepatitis C Trust and HCV Action, launched a film in 2015 to raise awareness and increase knowledge of hepatitis C among primary care professionals. The film, which contains information about diagnosing and supporting patients, as well as about the highly effective new treatments available, can be accessed from the HCV Action website.”

Raising awareness
Advanced virology (hepatitis) specialist nurse at Nottingham University Hospitals Trust, Kate Jack says: “Awareness raising among all health professionals about these new hepatitis C drugs is crucial. What makes the new NICE guidance better is that we can offer the direct-acting antiviral drugs to more patients, especially those with genotype 1 who do not have cirrhosis. The side-effects associated with interferon-based therapies can make treatment an extremely debilitating process.

“The new drugs are indeed more expensive, but they also cure people in a short time with very few side-effects, unlike some cancer treatments, which are costly but sadly do not cure the cancer. The regional commissioning processes will ensure that the prices paid by the NHS are lower than the list prices.

“The side-effects are minimal, with tiredness and mild headaches being reported. Most difficulties experienced by patients during treatment are due to ribavirin, which causes a temporary red cell haemolysis and anaemia, which cannot be corrected by ferrous sulfate while taking the ribavirin. However, if people have sufficient ferritin levels then treatment-induced anaemia generally resolves unaided within a month.

“At the moment, [direct-acting antiviral] treatment is prescribed via NHS Operational Delivery Networks with community clinic access in some regions being via a hospital outreach model. There are no current plans for GPs to prescribe these drugs.

“Nurse specialists, GPs and consultants are pleased that these drugs can be more widely prescribed as there are growing numbers of patients who have been waiting for this new option, some for many years. It means that fewer people will develop cirrhosis and require liver transplantation.

“These drugs also highlight how essential is it to take an accurate drug history, including over-the-counter and herbal medication, when planning to prescribe due to the frequency of drug-drug interactions that occur. Although prescriptions and drug history are screened by the pharmacist, nurses need to provide them with very accurate information so they sometimes have to ring the patient’s GP to double check what they are being prescribed. The Liverpool Drug Interaction website (www.hepdruginteractions.org) is an essential tool to aid prescribers.

“These NICE guidelines need to be underpinned in clinical practice by significantly more testing of patients. At-risk groups include those from Asia, Africa and Eastern Europe, previous and current injecting drug users, and those from high prevalence countries such as Pakistan, South Africa and Africa.”

Box. Facts about Hepatitis C (taken from www.hepctrust.org.uk and Public Health England’s Hepatitis C in the UK)¹

- Hepatitis C is a blood-borne RNA virus that predominantly infects the cells of the liver. This can result in inflammation and liver damage and can sometimes lead to cirrhosis, liver cancer or end-stage liver disease
- The course of hepatitis C infection is varied and unpredictable; diagnosis is often delayed because symptoms, eg depression, fatigue, skin problems, insomnia, pain and digestive disorders, are attributed to other illnesses
- Recent research has shown that the hepatitis C virus affects a number of other areas of the body as well as the liver, including the digestive system, the lymphatic system, the immune system and the brain
- There are six different genotypes of the hepatitis C virus – labelled 1 to 6 – and different genotypes predominate in different parts of the world
- An estimated 214,000 people are chronically infected with the hepatitis C virus in the UK, most (90 per cent) being genotype 1 or genotype 3
- Injecting drug use is the most important risk factor for hepatitis C infection in the UK, with half of people who inject drugs thought to have been infected in England and Wales; levels are lower in Northern Ireland (23 per cent) and higher in Scotland (57 per cent)
- In primary care, testing for hepatitis C has risen by 21, 46 and 53 per cent in England, Northern Ireland and Scotland respectively, suggesting that awareness may be increasing in this setting
- Over the last decade, hospital admissions from hepatitis C-related end-stage liver disease and hepatocellular carcinoma have nearly trebled in the UK and deaths from these indications have more than doubled

¹ Prescriber March 2016
rent injecting drug users and people who received blood transfusions prior to September 1991. The hepatitis C virus is underdiagnosed and we can only use these new drugs to prevent people developing liver cirrhosis if we know who is infected,” Ms Jack adds.

Andrew Langford, chief executive of the British Liver Trust agrees. “The new treatments available mean that hepatitis C can now be effectively cured and we have a unique opportunity to eradicate the virus. We know that many people with the virus are undiagnosed; more screening and public health messages are needed to ensure they get diagnosed and treated as soon as possible.

“Everyone living with hepatitis C needs to be made aware of the new treatments available and to speak with their doctor about their options. There is a great deal of stigma surrounding hepatitis C and we also know that there is inequality of care depending on where you live in the UK. It is vital that healthcare professionals are supported and encouraged in identifying and treating everyone currently living with the virus.”

In the 2015 Hepatitis C in the UK report, Dr Mary Ramsay, head of the Immunisation, Hepatitis and Blood Safety Department, National Infection Service, Public Health England, observes: “More people with hepatitis C are getting tested, particularly in primary care, indicating that more and more conversations about hepatitis C infection are happening in community consultations, such as at pharmacies, GP surgeries and drug services.

“While this is promising news, the data on treatment initiation shows that the majority of chronically infected people are not treated successfully in spite of new, highly effective drugs that have the potential to cure most infected people. There is an urgent need in England for clear pathways to help individuals navigate the clinical process so that those who test positive do not fail through the net. Continuing to build an environment where stigma and discrimination does not prevent people from accessing services will underpin success across all areas.”

She adds: “Difficult decisions will need to be made around hepatitis C treatment prioritisation, without losing sight of the impact of hepatitis C infection at the personal and societal level. Through concerted and collective action, we should overcome the barriers to scale up hepatitis C prevention, testing, treatment and care over the next five years.”

Further information
If you have hepatitis C patients who want support or information on how to access treatment or are having any other issues, they can call the Hepatitis C Trust’s confidential helpline on 0845 223 4424 or 0207 089 6221 or email helpline@hepctrust.org.uk.

For more good practice resources on hepatitis C for health professionals, visit HCV Action at www.hcvaction.org.uk.

References

Declaration of interests
None declared.

Kate Stewart is a freelance health journalist

POEMs

ST analysis during labour does not improve neonatal outcomes

Clinical question: Does the use of electrocardiographic ST analysis during labour improve neonatal outcomes compared with tococardiography alone?

Bottom line: The use of electrocardiographic ST analysis during labour does not improve a composite perinatal outcome or rates of neonatal metabolic acidosis, admission to neonatal intensive care unit (NICU), perinatal death, neonatal encephalopathy, caesarean delivery and operative delivery over tococardiography alone. (LOE = 1a)


Synopsis: This meta-analysis of six randomised controlled trials included 26,529 labouring women with singleton pregnancy at term in cephalic presentation. The primary outcome was at least one of the following: intrapartum fetal death, neonatal death, Apgar score of 3 or less at five minutes, neonatal seizure, intubation for ventilation at delivery or neonatal encephalopathy. The primary outcome occurred in 1.5 per cent of neonates in the ST analysis group and in 1.6 per cent of neonates in the tococardiography alone group (relative risk [RR] = 0.90; 95% CI 0.74–1.10). There were no differences in the secondary outcomes studied.