Diagnosis and management of hepatitis C

Hepatitis C virus, a bloodborne virus infection, is a major cause of mortality and morbidity worldwide and was until recently a difficult to treat disease. However, rapid treatment advances can now deliver cure rates of >95% and provide the real possibility of eliminating hepatitis C virus.

Hepatitis C virus is a bloodborne ribonucleic acid (RNA) virus that infects an estimated 160 million people worldwide (Lavanchy, 2011). Hepatitis C virus infection only rarely presents with an acute symptomatic hepatitis, but approximately 75–80% of those infected develop chronic infection with persistent viraemia. Chronic infection results in hepatitis and slowly progressive hepatic fibrosis so that over 25–30 years 5–25% of those infected will have progressed to cirrhosis (Thein et al, 2008), with the proportion increasing over even longer durations. Accelerated fibrosis progression is seen with co-factors including alcohol use, immunosuppressive therapy, hepatic steatosis, hepatitis B virus and human immunodeficiency virus (HIV) co-infections. Established hepatitis C virus cirrhosis results in a significant mortality and morbidity burden from complications of portal hypertension (ascites, variceal bleeding and hepatic encephalopathy) and from the 1–3% per annum risk of developing hepatocellular carcinoma. Hepatitis C virus infection can have a number of extra-hepatic manifestations and consequences, including cryoglobulinaemia, renal disease, arthralgia and fatigue, with more recent data suggesting a link between hepatitis C virus and coronary artery disease.

Hepatitis C virus-related cirrhosis is the leading cause of hepatocellular carcinoma in Europe, and the commonest indication for liver transplantation in the United States. In England an estimated 214 000 individuals have chronic infection, with a predicted 8690 affected by compensated hepatitis C virus-related cirrhosis and a further 2530 facing either death or transplantation from their decompensated disease and/or hepatocellular carcinoma (Public Health England, 2014).

Diagnosis of hepatitis C virus

Diagnosing hepatitis C virus infection is straightforward with a number of commercially available 4th generation hepatitis C virus antibody tests, which are both highly sensitive and specific (Chevaliez and Pawlotsky, 2005). Hepatitis C virus antibodies are detectable within a few weeks of infection and remain so long term. Chronic infection is defined by the presence of hepatitis C virus RNA for 6 months or more after infection. Polymerase chain reaction (PCR) techniques for the detection and quantification of hepatitis C virus RNA are able to confirm ongoing viraemia and quantify the viral load down to levels as low as 15 IU/ml. Up to 25% of hepatitis C virus antibody-positive cases will have undetectable hepatitis C virus RNA, having cleared the infection spontaneously. When hepatitis C virus RNA is detected the viral load does not correlate well with disease severity, but is important in assessing treatment response. More recently an HCV core antigen assay has become commercially available, and while it is currently less sensitive than HCV RNA it may have a role as a cost-effective and rapidly available test to confirm which HCV antibody-positive individuals have active infection. Its role in monitoring response to treatment remains to be determined.

Hepatitis C virus shows considerable heterogeneity with seven distinct genotypes (numbered 1 to 7), each with their own subtypes (alphabetical). Genotype 1 is the commonest worldwide, followed by genotype 3, with genotype 5 the least common accounting for <1% of all hepatitis C virus infections (Messina et al, 2015). Determining hepatitis C virus genotype and sub-type is important in guiding treatment choices.

Hepatitis C virus shares similar routes of infection to hepatitis B virus and HIV and therefore all hepatitis C virus-positive patients should also be tested for hepatitis B virus and HIV co-infection.

The symptoms of chronic hepatitis C virus are typically mild and non-specific before developing advanced liver disease so that many cases of hepatitis C virus infection remain undiagnosed. It is hoped that the increasing use of near patient tests that can detect hepatitis C virus

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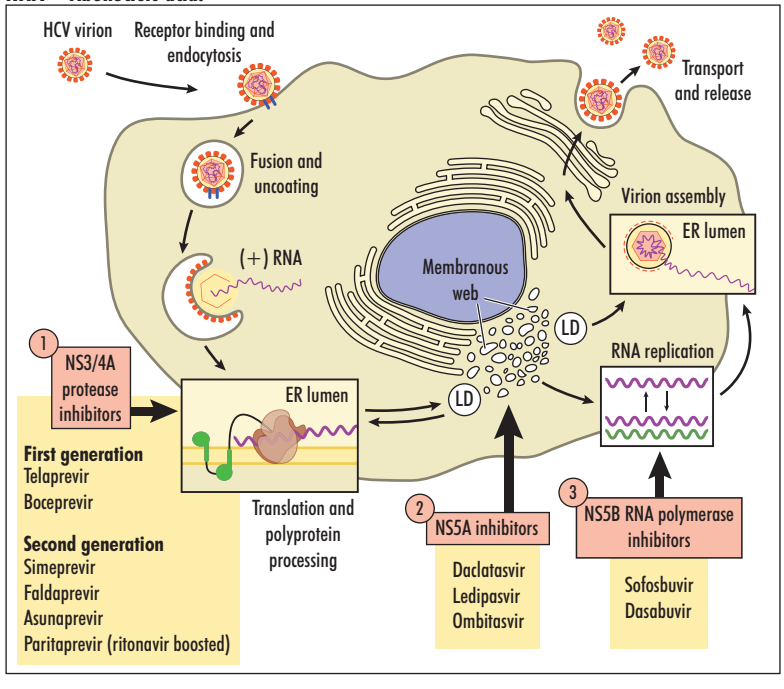
antibodies in a blood spot or saliva specimen within a few minutes will facilitate and expand testing, especially in high risk but hard to reach populations (Lee et al, 2011).

Once hepatitis C virus infection has been diagnosed it is important to define the severity of the liver disease and in particular the degree of hepatic fibrosis. Assessment of the patient should include a careful history of risk factors for disease progression (such as alcohol consumption or obesity predisposing to fatty liver disease) and clinical assessment using physical examination, blood tests and ultrasound imaging. Non-invasive measures of liver fibrosis including transient elastography (Afdhal, 2013) and serological tests such as Fibrotest and ELF (Poynard et al, 2007; Lichtinghagen et al, 2013) are widely used so that liver biopsy is now only rarely needed.

Treatment of hepatitis C virus

The aim of hepatitis C virus treatment is to eradicate the virus permanently, termed a sustained virological response. Sustained virological response is defined as undetectable hepatitis C virus RNA 12 or 24 weeks after treatment completion and long-term studies have confirmed that sustained virological response translates into permanent viral eradication, and importantly into significant patient benefit. In a treated cohort of 530 hepatitis C virus-infected patients with advanced fibrosis and cirrhosis, those achieving sustained virological response had improved all-cause mortality, reduced liver cancer and reduced hepatic decompensation over 10 years follow up (8.9% *vs* 26.0%, 5.1% *vs* 21.8% and 2.1% *vs* 29.9% respectively) as well as improved liver histology (van der Meer et al, 2012).

Figure 1. Hepatitis C virus life cycle and targets of the direct acting antivirals. ER = endoplasmic reticulum; HCV = hepatitis C virus; LD = luminal domain; RNA = ribonucleic acid.



Until recently hepatitis C virus was treated with the non-specific antivirals interferon alpha (given by weekly subcutaneous injection in a controlled release form bound to polyethylene glycol – PEG-IFN) and ribavirin (given as a tablet twice daily), which were used in combination. Sustained virological response rates with PEG-IFN and ribavirin vary widely from under 10% to over 75% according to hepatitis C virus genotype, prior treatment response and disease severity. Treatment duration is up to 48 weeks and the side-effect profile of this combination is both extensive and significant with many patients unable to complete their planned treatment course even with careful support and monitoring. Common side effects of PEG-IFN include flu-like symptoms, myelosuppression, weight loss and depression (it is relatively contraindicated in patients with a significant psychiatric history), while those of ribavirin include haemolysis sufficient to cause anaemia and teratogenicity.

Treatment of hepatitis C virus infection in 2015 is undergoing revolutionary change with the licensing of a number of highly effective hepatitis C virus-specific directly acting antiviral drugs. Currently available and upcoming directly acting antiviral drugs specifically target hepatitis C virus-encoded proteins involved in the replication cycle, and in the future therapies targeting alternative areas involved in replication such as host proteins (e.g. cyclophilin inhibitors) or entry inhibitors as well as small interfering RNAs are likely to be used. *Figure 1* shows the hepatitis C virus life cycle and the areas targeted by the new direct acting antivirals. Directly acting antiviral drugs used in isolation are initially effective but resistant viral strains rapidly emerge so that combinations of drugs are needed to achieve sustained virological response. Various directly acting antiviral drugs were initially used in combination with PEG-IFN and ribavirin with improved sustained virological response rates and shorter treatment durations. Over recent months well tolerated, tablet only, interferon-free combinations of directly acting antiviral drugs have become available with short treatment courses of 8–12 weeks proving highly effective. An understanding of how the major classes of directly acting antiviral drugs work, their effectiveness across different hepatitis C genotypes, and their inherent barrier to viral resistance emerging are important in understanding optimum drug combinations.

Directly acting antiviral drug classes

NS3/4A protease inhibitors

Protease inhibitors were the first class of directly acting antiviral drugs licensed, with telaprevir and boceprevir getting National Institute for Health and Care Excellence approval in 2012 (National Institute for Health and Care Excellence, 2012a,b). Protease inhibitors licensed to date are effective against genotype 1 but only telaprevir and simeprevir (but not boceprevir) have activity against genotype 4. While potent they have a low barrier to resistance emerging, which is most marked in genotype 1a such that treatment outcomes are better in genotype

1b than 1a. First generation drugs were associated with haematological toxicity, rash, many drug–drug interactions and the need for multiple daily doses often with food. The second generation of protease inhibitors include simeprevir and paritaprevir, which have a better pharmacokinetic profile being taken once daily and far less in the way of haematological and skin toxicity. Paritaprevir needs to be boosted with ritonavir (an antiviral agent with marked inhibition of cytochrome P450 iso-enzymes used to act as a pharmacological booster at the low dose of 100 mg where it has no antiviral activity) to achieve sufficient levels to effectively inhibit wild type virus in a once-daily dosing regimen. New protease inhibitors are under development that have a more pan-genotypic spectrum of activity but are yet to be licensed.

NS5B polymerase inhibitors

NS5B polymerase inhibitors are either nucleoside inhibitors with a pan-genotypic effect and high genetic barrier to resistance, or non-nucleoside inhibitors with particular effect in genotype 1 hepatitis C virus and a lower barrier to resistance. Sofosbuvir was approved in Europe and the USA in late 2013 and is the only currently licensed nucleoside NS5B inhibitor. It has a potent effect across all hepatitis C virus genotypes and as yet minimal evidence of viral resistance.

NS5A inhibitors

This class of drugs is characterized by its very high level of activity in low doses against most hepatitis C virus genotypes, but with a low genetic barrier to resistance. Their potent viral suppression means that when used in combination with other directly acting antiviral drugs they have proved highly effective. There are currently three licensed NS5A inhibitors: daclatasvir, ledipasvir and ombitasvir.

Currently licensed treatment options

PEG-IFN and ribavirin with simeprevir

The use of the second generation protease inhibitor simeprevir in combination with PEG-IFN and ribavirin is effective for genotypes 1 and 4 hepatitis C virus infection, but not other genotypes. Twelve weeks of triple therapy followed by a further 12 weeks (sometimes longer) of PEG-IFN and ribavirin without simeprevir is approved by the National Institute for Health and Care Excellence (2015a). Those cases who become hepatitis C virus RNA undetectable from treatment week 4 and remain undetectable to week 12 will achieve a 90% sustained virological response. Simeprevir has an improved toxicity profile compared to boceprevir or telaprevir with fewer drug interactions, but is still metabolized via the cytochrome P450 isoenzyme and therefore has the potential for drug–drug interactions. This combination has cost advantages, but is still a 24-week treatment course and has the toxicity profiles associated with both PEG-IFN and ribavirin.

Sofosbuvir-containing drug regimens

The NS5B polymerase inhibitor sofosbuvir has a high barrier to resistance and a pan-genotypic spectrum of activity. It was first licensed in Europe and the USA for use in combination with PEG-IFN and ribavirin where it is highly effective across genotypes. Interest has centred on its use in combination with other directly acting antiviral drugs to develop very effective, interferon-free, well tolerated, safe and short treatment courses. More recently it has been licensed and marketed in a fixed dose combination with the NS5A inhibitor ledipasvir as a single tablet taken daily. This fixed dose combination has been shown to be highly effective in genotype 1 infection with over 97% sustained virological response with a 12-week course and 96% sustained virological response with just 8 weeks' treatment for previously untreated hepatitis C virus without cirrhosis (Afdhal et al, 2014; Kowdley et al, 2014). There remains uncertainty as to whether shorter duration treatment regimens may increase the risk of relapse in some harder to treat groups, so that current guidelines suggest 8 weeks treatment be used only for treatment naïve non-cirrhotics with baseline viral load under 6 million IU/ml and 24 weeks treatment be considered for treatment experienced cases without other treatment options. Sofosbuvir has also been used in combination with another NS5A inhibitor daclatasvir, again with high sustained virological response rates. In the USA, the effective combination of sofosbuvir with the protease inhibitor simeprevir has been widely used, but this is unlikely to be broadly adopted in the UK because of its expense compared to alternative regimens.

Ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin

This combination has recently been licensed in Europe and the USA for genotype 1 and 4 infection. It consists of three hepatitis C virus-specific directly acting antiviral drugs (protease inhibitor, together with NS5A and NS5B inhibitors), together with ritonavir to boost the level of protease inhibitor, and achieves excellent sustained virological response rates of over 95% with a combination of pills taken once and twice daily (Ferenci et al, 2014; Poordad et al, 2014). This well-tolerated treatment is for 12 weeks in most cases, with ribavirin recommended for genotype 1a or 1b cirrhotic cases and 24 weeks in genotype 1a cirrhotics.

Current position on treatment regimens

National Institute for Health and Care Excellence (2015b) have approved treatment regimens using sofosbuvir in combination with PEG-IFN and/or ribavirin and is currently reviewing several all-oral combination treatments. NHS England have funded an early access scheme for patients with decompensated disease or life-threatening extra-hepatic manifestations of hepatitis C virus using sofosbuvir in combination with ledipasvir or daclatasvir with or without ribavirin (NHS England, 2014).

Simeprevir has both National Institute for Health and Care Excellence approval and an NHS England (2015) interim commissioning policy for its use in combination with PEG-IFN and ribavirin. The conclusions of a recent consensus meeting on best use of currently available hepatitis C virus treatments are presented in *Tables 1–4* (British Association for the Study of the Liver, 2015).

Challenges with new hepatitis C virus-specific directly acting antiviral drugs

Antiviral resistance

As outlined above, the different classes of antiviral drugs and the drugs within each class have differing levels of efficacy against viral genotypes and subtypes and a variable barrier to viral resistance emerging. Despite high sustained virological response rates, a proportion of patients are going to fail to respond to therapy, and concern remains that the selection of highly resistant viral strains could jeopardize a patient's ongoing care. The long-term significance of viral resistance remains unclear and probably varies between the drug classes. As hepatitis C virus is not archived (unlike hepatitis B virus and human immunodeficiency virus) the persistence of a viral mutation is dependent on how well the virus can continue to replicate with that mutation. Continuing treatment after resistance emerges will allow secondary mutations to develop that increase the likelihood of resistance persisting. Early data are emerging of the potential efficacy of alternative combinations of directly acting antiviral drugs following previous failed IFN-free therapy, with sofosbuvir/NS5A inhibitor-containing regimens appearing to be effective in patients who have previously failed to respond to regimens with protease inhibitors.

Viral resistance can emerge as a result of a lack of drug efficacy, but also as a consequence of inadequate drug exposure as either a result of poor adherence to therapy or drug–drug interactions. Treatment programmes will need to focus on ensuring that patients take medications reliably and as prescribed and will need to be vigilant for potential interactions with prescribed and non-prescribed medications including herbal remedies. Drug interactions can be checked at www.hep-druginteractions.org. Careful virological monitoring for early detection of resistance is also important, in order that treatment that is proving ineffective can be stopped at the earliest opportunity to prevent the ongoing selection of increasingly resistant viral strains.

Table 1. Treatment options for patients with hepatitis C virus genotype 1

Patient group	Treatment options	Treatment length	Notes
No evidence of cirrhosis or severe fibrosis*	Sofosbuvir and ledipasvir +/- ribavirin	8 weeks	
	Ombitasvir and paritaprevir(r)/dasabuvir +/- ribavirin†	12 weeks	
	Sofosbuvir and simeprevir†	12 weeks	
	Sofosbuvir and daclatasvir	12 weeks	
Compensated cirrhosis or severe fibrosis or major extra-hepatic manifestations‡	Ombitasvir and paritaprevir(r) and dasabuvir +/- ribavirin	12 weeks	Child Pugh A
	Sofosbuvir and ledipasvir +/- ribavirin	12 weeks	
	or sofosbuvir and simeprevir +/- ribavirin	12 weeks	
	or sofosbuvir and daclatasvir +/- ribavirin	12 weeks	
Decompensated cirrhosis	Sofosbuvir and ledipasvir +/- ribavirin	12 weeks	
	Sofosbuvir and daclatasvir +/- ribavirin	12 weeks	

*If funding for oral direct acting antiviral regimens is not available for this patient population, patients can wait for oral therapy, self-fund or start treatment with an interferon-based regimen; these options are sofosbuvir/pegylated interferon (PEG-IFN)/ribavirin for 12 weeks or simeprevir/PEG-IFN/ribavirin for 12 weeks, for genotype 1b or genotype 1a without Q80K variant an additional 12 or 36 weeks PEG-IFN/ribavirin is used. †Avoid protease inhibitor-containing regimens in patients who have previously failed to respond to protease inhibitors. ‡Include patients in this group who have previously failed to achieve a sustained virological response with 'standard' treatment of PEG-IFN/ribavirin. From British Association for the Study of the Liver (2015)

Table 2. Treatment options for patients with hepatitis C virus genotype 2

Patient group	Treatment options	Treatment length	Notes
No evidence of cirrhosis or severe fibrosis	PEG-IFN and ribavirin	24 weeks*	Treatment naïve
	Sofosbuvir and ribavirin	12 weeks	Treatment experienced and PEG-IFN intolerant
Compensated cirrhosis or severe fibrosis or major extra-hepatic manifestations	Sofosbuvir and ribavirin	12 weeks	Treatment naïve
	Sofosbuvir and ribavirin	12 weeks†	Treatment experienced
Decompensated cirrhosis	Sofosbuvir and ledipasvir +/- ribavirin or sofosbuvir and daclatasvir +/- ribavirin	12 weeks 12 weeks	

PEG-IFN = pegylated interferon. *12 weeks in those with low viral load/rapid viral response; †16 weeks in patients with cirrhosis. From British Association for the Study of the Liver (2015)

Expense

A major challenge with the emerging directly acting antivirals is their cost, with all directly acting antiviral drug combinations being more expensive than previous therapies. Although some of this increased cost can be offset against the shorter treatment duration and reduced toxicity, the broad eligibility for treatment and increasing numbers of patients expected to present for treatment, suggests that hepatitis C treatment costs are likely to increase significantly in the coming years. However, as more drugs become licensed the competitive market forces may well drive down some of this cost. The cost effectiveness of various treatment strategies is currently under close scrutiny by the National Institute for Health and Care Excellence and other bodies.

Who and when to treat

In the UK, early experience of using all-oral combinations to treat hepatitis C has focused on patients with advanced disease, with funding provided mostly for those with hepatic decompensation. Treating advanced disease clearly makes much sense in terms of deferring death and preventing further deterioration in liver function, but it remains to be seen whether viral eradication at this late stage can result in restoration of liver function and hepatic recompensation. Treatment at earlier stages in the course of hepatitis C virus infection before complications have arisen is important.

An important patient group to consider treatment in is those on the liver transplant list, as hepatitis C virus eradication will prevent infection of the new graft and therefore remove the risk of post liver transplant hepatitis C virus-related complications; for many patients this is being achieved via the Early Access Programme with no patients who are RNA negative for 4 weeks or more pre-transplant developing graft infection to date.

A number of models have been developed looking at the numbers of patients needing to be treated, and at what stage of their disease, to have the maximum impact on the epidemic of hepatitis C. One model of treatment

Table 3. Treatment options for patients with hepatitis C virus genotype 3

Patient group	Treatment options	Treatment length	Notes
No evidence of cirrhosis or severe fibrosis	PEG-IFN and ribavirin	24 weeks	Treatment naïve
	Sofosbuvir and daclatasvir +/- ribavirin	12 weeks	Treatment naïve and PEG-IFN ineligible
	or sofosbuvir and ledipasvir +/- ribavirin		
	PEG-IFN and ribavirin and sofosbuvir	12 weeks	Treatment experienced
	Sofosbuvir and daclatasvir +/- ribavirin	12 weeks	Treatment experienced and PEG-IFN intolerant
	or sofosbuvir and ledipasvir +/- ribavirin		
Compensated cirrhosis or severe fibrosis or major extra-hepatic manifestations	PEG-IFN and ribavirin and sofosbuvir	12 weeks	Preferred option
	Sofosbuvir and daclatasvir and ribavirin	12 weeks	If PEG-IFN intolerant
	or sofosbuvir and ledipasvir and ribavirin		
	or sofosbuvir and ribavirin	24 weeks	If PEG-IFN intolerant
Decompensated cirrhosis	Sofosbuvir and ledipasvir +/- ribavirin	12 weeks	
	or sofosbuvir and daclatasvir +/- ribavirin	12 weeks	

PEG-IFN = pegylated interferon. From British Association for the Study of the Liver (2015)

Table 4. Treatment options for patients with hepatitis C virus genotype 4

Patient group	Treatment options	Treatment length	Notes
No evidence of cirrhosis or severe fibrosis	Sofosbuvir and ledipasvir and ribavirin	12 weeks	Preferred option
	or ombitasvir and paritaprevir and ritonavir and ribavirin	12 weeks	Preferred option
	or PEG-IFN and ribavirin and sofosbuvir	12 weeks triple therapy then further 12–36 weeks PEG-IFN and ribavirin	If all-oral treatments not available
	or PEG-IFN and ribavirin and simeprevir		
Compensated cirrhosis or severe fibrosis or major extra-hepatic manifestations	Sofosbuvir and ledipasvir and ribavirin	12 weeks	
	or sofosbuvir and daclatasvir and ribavirin	12 weeks	
Decompensated cirrhosis	Sofosbuvir and ledipasvir +/- ribavirin	12 weeks	
	or sofosbuvir and daclatasvir +/- ribavirin	12 weeks	

PEG-IFN = pegylated interferon. From British Association for the Study of the Liver (2015)

rates for the UK suggests that 95% of all viraemic cases of hepatitis C could be eradicated by 2030 by increasing treatment eligibility to 90–95% of those diagnosed and by increasing current treatment rates 2.7-fold by 2018. This equates to an increase from 5340 to 14 670 cases treated per year which in turn requires enhanced rates of testing and diagnosis. This model predicts an 80% reduction in hepatitis C-related liver deaths, with 5200 liver deaths avoided by 2030 by the early application of these new effective antiviral therapies (Wedemeyer et al, 2014).

Conclusions

This is an exciting time for clinicians dealing with hepatitis C virus infection, with licensed drugs now available that are able to cure the vast majority of patients. In just 25 years since hepatitis C virus was first described it has gone from a disease that was incurable for many to a condition with a nearly 95% cure rate. We now have the ability to largely eradicate the epidemic of hepatitis C within the next 15 years if concerted efforts are made to diagnose and treat infected individuals in accessible treatment programmes designed to maximize adherence. While concerns remain about the risk of antiviral drug resistance, the major issue facing clinicians today in treating hepatitis C virus is that of affordability and securing funding. **BJHM**

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KEY POINTS

- Hepatitis C virus infects an estimated 160 million people and is a major cause of morbidity and mortality worldwide.
- Hepatitis C virus should now be considered a curable disease with the new directly acting antiviral drugs (>95% cure rate).
- The potential emergence of viral resistance to directly acting antiviral drugs is a serious concern and care must be taken in selecting drug regimens and in treatment monitoring.
- Early and widespread use of the new directly acting antiviral drugs is predicted to result in an estimated 80% reduction in hepatitis C virus-related liver deaths, with 5200 liver deaths avoided by 2030.
- The major challenge currently facing clinicians regarding hepatitis C virus treatment remains that of funding.

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