Hepatitis C: tackling the silent epidemic

Chronic hepatitis C virus infection is responsible for a significant and growing burden on NHS services. It is one of the commonest causes of liver cirrhosis and hepatocellular carcinoma, and the leading indication for liver transplantation. Major advances have been made in treatment, which can eradicate the virus in more than 50% of patients and reduce complications, but progress is hampered by inadequate detection and access to treatment.

Chronic hepatitis C is a slowly progressive disease of the liver caused by the blood-borne hepatitis C virus (HCV) that was formally identified in 1989 (Choo et al, 1989). As yet its natural history is not fully understood, largely because its onset is rarely recognized and its course is prolonged and insidious.

The virus may be transmitted a number of ways, most commonly through intravenous drug use or transfusion of infected blood products before the introduction of blood screening in 1991; other possible routes of infection include tattoo needles, electrolysis, body-piercing, acupuncture and needle stick injuries. Sexual infection and transmission from mother to child can occur, while concomitant human immunodeficiency virus (HIV) infection is thought to increase the risk of transmission.

Six major genetic types of HCV have been identified. Genotype 1 (G1) is the most common in the UK, and is found in about 40–50% of cases, usually among people infected through blood products. The G2 and G3 genotypes are more common among injecting drug users (IDUs), and make up another 40–50% of cases. The G4 and G5 genotypes constitute the remaining 5%.

Following HCV infection only 25–35% of patients show symptoms in the early stages and may develop acute hepatitis with malaise, weakness and anorexia. In most patients infection remains undetected. While some will spontaneously clear the virus, as many as 85% of patients develop chronic hepatitis (Thomas et al, 1996). The rate of progression is slow and variable; symptoms may not appear for up to 30 years after infection. Symptoms are generally non-specific and include fatigue, irritability, depression, nausea, headache, muscle ache, anorexia, abdominal discomfort and right upper quadrant pain, while there is also evidence to suggest cognitive impairment in patients with mild disease (Shepherd et al, 2003). Living with chronic hepatitis C is associated with a clinically and socially relevant reduction in health-related quality of life that can be improved by eradication of the virus (Bonkovsky and Woolley, 1999) with a consequent reduction in demand for health-care services and an increase in productivity of affected individuals (Neary et al, 1999).

Severe liver disease affects 20–50% of those who are infected; about 20–30% develop cirrhosis within 20 years (Poynard et al, 1997) and 1–4% of these are at high risk of hepatocellular carcinoma (Di Bisceglie, 1998). HCV infection is the main cause of liver transplantation (Detre et al, 1997). About 15% of liver transplants in England happen because of liver damage caused by chronic HCV infection.

HCV infection: the tip of the iceberg?

HCV infection can remain asymptomatic for long periods, making accurate prevalence rates difficult to estimate. Prevalence varies across different groups according to risk factors such as injecting drug use. Nevertheless, worldwide it is thought that as many as 170 million people are infected with hepatitis C, some 3% of the world's population (World Health Organisation (WHO), 1997).

Published prevalence data for HCV infection in the UK vary from 0.08% to 0.72% but these figures are mainly derived from selected populations such as organ donors, tertiary referral centres, blood donors and antenatal clinics. For instance, reported prevalence rates are 0.04% in blood donors, 0.4% in people attending antenatal clinics (in London), 1% in people attending genitourinary clinics and up to 50% in IDUs. Data from the Trent HCV Study group suggest a population-based prevalence of 0.05% (Mohsen et al, 2001), although this figure is based on reporting of positive tests, and so excludes those patients who are asymptomatic and who have not been tested.

Government estimates suggest that the prevalence of chronic hepatitis C in England is 0.5% – equivalent to some 250 000 patients. About 20% eradicate the virus without treatment, so 0.4% of the population (200 000 people) is chronically infected. To date, doctors in England have diagnosed only 38 000 cases of chronic HCV, suggesting that most cases remain undiagnosed.

However, hepatologists feel this is an underestimate. In its 2002 report *Hepatitis C – the Public Stealth Disease*, the British Liver Trust estimated that some 400 000 people in the UK were infected and undiagnosed in the UK. It said 60 000 would progress towards serious liver disease each year, with about 460 requiring a liver transplant and at least 1600 dying from liver cirrhosis.

HCV infection is more common in inner cities than rural areas, reflecting the greater number of IDUs in urban areas. The Health Protection Agency (2003) report stated that more than two in five IDUs had been infected with HCV, while in Glasgow the estimated incidence of infection among recent initiates to injecting was approximately 30% per year. Data for England and Wales indicate that HCV transmission among injectors has increased recently, and in 2002 one in seven of those who had started to inject since the beginning of 2000

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had been infected. By the end of 2002 there had been around 50 000 reported laboratory diagnoses of hepatitis C in the UK, with the majority of these reports associated with injecting drug use. Of those injectors with hepatitis C almost three-fifths were unaware of their infection.

Management of HCV infection

Management of HCV must focus on avoiding high alcohol consumption and tobacco, and ensuring that metabolic disorders (diabetes, overweight, steatosis, steatohepatitis) are treated. In addition, patients should be assessed for antiviral treatment.

Treatment is regarded as successful if elevated serum levels of alanine aminotransferase (a surrogate marker of inflammatory liver damage) return to normal and HCV disappears from the blood, and these levels are maintained for at least 6 months after treatment. Such a response is assumed to prevent progression of liver disease and development of cirrhosis, portal hypertension, liver failure and possible hepatocellular carcinoma.

HCV was initially treated with standard interferon alpha monotherapy via subcutaneous injection on a minimum of 3 days a week for 48 weeks although response was limited (Myers et al, 2002). Dual therapy consisting of interferon alpha and the nucleoside analogue ribavirin (which has broad spectrum antiviral activity against RNA viruses) achieved sustained virological response rates of 41% in treatment-naive patients (Poynard et al, 2000) and 49% in those who had relapsed following previous interferon treatment (Davis et al, 1998).

More recently, standard interferon has been superceded by pegylated interferon. PEG (polyethylene glycol) is a large branched molecule that encircles interferon alpha-2, substantially extending its half-life. This permits once-weekly dosing by subcutaneous injection, because of reduced renal clearance and more sustained absorption. The size of the PEG moiety influences the relative antiviral activity of peginterferon alpha-2: peginterferon alpha-2b (12 kDa) has an in-vitro antiviral specific activity 25–35-fold higher than peginterferon alpha-2a (40 kDa). In addition, the antiviral activity of pegylated interferon alpha-2 is also governed by the site of pegylation of the interferon alpha core proteins (Grace and Cutler, 2004). While peginterferon alpha-2a is given as a flat dose to all patients regardless of body weight, peginterferon alpha-2b is administered to individual patients using weight-based dosing (between 40–100 kg bodyweight). The IDEAL trial (Individualised Dosing Efficacy *vs* flat dosing to Assess optimal pegylated interferon therapy) involving 2880 patients is directly comparing the efficacy and safety of the two peginterferons in HCV G1 patients.

The National Institute for Clinical Excellence (NICE) approved the combination treatment of peginterferon alpha and ribavirin for treatment of all people aged 18 years or older with moderate-to-severe HCV (significant fibrosis, significant necrotic inflammation or both) in 2004 (NICE, 2004). However, peginterferon alpha alone should be used if ribavirin is contraindicated or not tolerated; ribavirin monotherapy is ineffective.

Combination therapy successfully clears the infection in over 50% of patients (Poynard et al, 2003), but is influenced by genotype; patients with G1 and G4–6 should receive therapy for 48 weeks and G2 and G3 for 24 weeks. Measuring viral load by polymerase chain reaction at 12 weeks should determine if patients with G1 need further therapy. Age, gender, disease stage and compliance also affect treatment success. Re-treatment is recommended for patients previously treated with interferon monotherapy who have relapsed, but not for primary non-responders.

Side-effects and compliance with treatment

Interferon alpha, whether non-pegylated or pegylated, and ribavirin both produce side effects of varying severity in most patients, particularly in the early stages of treatment. These generally include mild 'flu-like' symptoms such as fatigue, headache and fever but may also include anaemia and other haematological disturbances, gastrointestinal complaints (particularly anorexia and nausea) and psychiatric disturbances such as anxiety and depression. While most people find any side-effects resolve after a few weeks, some patients may be unable to tolerate a full dose or a full course of treatment. In clinical trials as many as 20% of patients discontinue combination therapy, usually because of haematological events (NICE, 2004).

Because of the high frequency of side effects such as anaemia, and because various blood tests are needed during treatment, patients require support throughout treatment in the form of regular clinic appointments so that progress can be carefully monitored. Poor compliance is common, particularly among former IDUs, who often face considerable health and social problems. As a result, it is important to make administration of treatment as simple and straight forward as possible. Some interferons are available in a pen delivery system that allows precise, individualized weight-based dosing. A self-priming action automatically removes air bubbles before self-administration, while the small needle minimizes discomfort.

Cost of treatment

HCV treatment is costly although the precise costs vary depending on which interferon (alpha-2a or alpha-2b) is used, the delivery system used and on weight (the ribavirin dose is weight-adjusted). *Table 1* shows the prices (excluding VAT) listed in the *British National Formulary* (Joint Formulary Committee, 2005). A 4-week cycle of interferon alpha at 3 million units three times a week costs around £215, and ribavirin for the same period costs around £590. Therefore, the net cost of 24 weeks of combination therapy of interferon alpha plus ribavirin is around £4830, excluding monitoring costs.

Public health implications

Given the high cost of drug treatment for HCV, other medical interventions and liver transplants, HCV represents a substantial burden on the NHS and one that is likely to increase. While more than half of all patients can be cured provided an early diagnosis is made, there are significant geographical inequalities in access to care in the UK, particularly compared with other countries. The British Liver Trust estimates that in 2001 just 1300

Table 1. Costs of HCV treatments as listed in *British National Formulary* (all prices are net)

Treatment		Preparation	Amount	Cost
Interferon alpha	Interferon alpha-2b (Intron A)	For sc or iv injection	10 million units/ml, 2.5 ml vial	£135.00
		For sc or iv injection, powder for reconstitution	10 million unit vial (with injection equipment and water for injections)	£53.96
		Pen cartridge for sc injection	15 million units/ml, 1.5 ml	£97.20
			25 million units/ml, 1.5 ml	£162.00
			50 million units/ml, 1.5 ml	£324.00
	Interferon alpha-2a (Roferon-A)		6 million units/ml, 0.5 ml (3 million-unit)	£15.07
			9 million units/ml, 0.5 ml (4.5 million-unit)	£22.60
			12 million units/ml, 0.5 ml (6 million-unit)	£30.12
			18 million units/ml, 0.5 ml (9 million-unit)	£45.19
			36 million units/ml, 0.5 ml (18 million-unit)	£97.19
		Cartridge for intramuscular injection by Roferon pen device	30 million units/ml, 0.6 ml (18 million-unit)	£90.39
	Interferon alpha-2b (Viraferon)	For sc injection	6 million units/ml, 3 ml vial	£97.20
		Injection pen	15 million units/ml, 1.5 ml cartridge	£97.20
	Peginterferon alpha-2a (Pegasys)	For sc injection	135 μg prefilled syringe	£114.39
			180 μg prefilled syringe	£132.06
	Peginterferon alpha-2b (PegIntron)	For sc injection, powder for reconstitution (all with injection equipment and water for injections)	50 μg vial	£67.50
			80 μg vial	£108.00
			100 μg vial	£135.00
			120 μg vial	£162.00
			150 μg vial	£202.50
	Peginterferon alpha-2b (ViraferonPeg)	For sc injection, powder for reconstitution (all with injection equipment and water for injections)	50 μg vial	£67.50
			80 μg vial	£108.00
			100 μg vial	£135.00
			120 μg vial	£162.00
			150 μg vial	£202.50
		For sc injection, prefilled pen, powder for reconstitution (all with needles and swabs)	50 μg pen	£74.25
			80 μg pen	£118.80
			100 μg pen	£148.50
			120 μg pen	£178.20
			150 μg pen	£222.75
Ribavirin	Ribavirin (Copegus)*	200 mg tablets	42 tablet pack	£115.62
			112 tablet pack	£308.31
			168 tablet pack	£462.47
	Ribavirin (Rebetol)†	200 mg capsules	84-cap pack	£296.40
			140-cap pack	£494.00
			168-cap pack	£592.80

* Dose (in combination with interferon alpha or peginterferon alpha): adult over 18 years, body weight <75 kg, 400 mg in the morning and 600 mg in the evening; body weight ≥75 kg, 600 mg twice daily (NB: HCV genotype 2 or 3 requires a lower dose of Copegus (in combination with peginterferon alpha), usual dose 400 mg twice daily; † Dose (in combination with interferon alpha or peginterferon alpha), adult over 18 years, body weight <65 kg, 400 mg twice daily; body weight 65–85 kg, 400 mg in the morning and 600 mg in the evening; body weight >85 kg, 600 mg twice daily. HCV = hepatitis C virus; IV = intravenous; SC = subcutaneous. From Joint Formulary Committee (2005).

people received treatment for the disease in the UK, compared with 15 000 in Germany, 22 000 in Italy and 18 000 in France.

The *Hepatitis C Strategy for England* (Department of Health, 2002) aimed to improve prevention, diagnosis and treatment and was followed by the *Hepatitis C Action Plan for England* in June 2004. However, professional and advocacy groups doubt its likely effectiveness. The action plan fails to address the widespread need for more hepatologists and more specialist nurses. It also has no timetable for implementation and sets no targets for maximum waits and levels of diagnosis and treatment against which primary care trusts must deliver. While it stresses the need for primary care trusts (PCTs) to provide funding and access to medication, the action plan takes little account of the financial disincentive on PCTs to treat: a liver transplant with complications could cost £200 000–300 000 but as transplants are funded centrally, costs are not met by the PCT budget. Adequate funds need to be clearly allocated if treatment is to be delivered to all patients who need it.

In addition, significant resources need urgently to be directed towards preventive efforts. With no effective vaccine against HCV, prevention of new infections is particularly important. Explicit campaigns are needed, designed to raise awareness among the general public and particularly within at-risk groups such as IDUs, to ensure that people understand the benefits of knowing their HCV status. Infected individuals need to know that early modification of lifestyle and monitoring with a view to timely treatment can help the course of the disease. In addition, they need to understand how to avoid infecting others.

Conclusions

The management of patients with HCV clearly provides significant challenges to health-care services because of the scale of the epidemic and because most patients are asymptomatic and/or undiagnosed. Services are already struggling to cope with the burden of infection and liver disease, and that significant resources must urgently be directed at improving prevention and the delivery of care.

KEY POINTS

- Hepatitis C virus infection is a common cause of liver cirrhosis and hepatocellular carcinoma and the leading indication for liver transplantation.
- The disease already represents a significant and growing burden on the NHS but is compounded by under-diagnosis.
- Effective treatment is available and can eradicate the virus in more than 50% of patients, reducing the likelihood of complications.
- Insufficient funds are being made available to ensure equitable access to treatment.
- Failure to raise awareness of the disease and to offer treatment to many more patients will simply store up trouble for the future.

Antiviral treatment has, to date, had only a limited impact on the burden of disease. The latest figures suggest that only about 2000 people in England and Wales each year are currently treated for HCV infection with some form of interferon or peginterferon alpha therapy (NICE, 2004). Given the high cost of managing end-stage liver disease, access to treatment should be broadened to all those who might benefit if the NHS is to avoid storing up trouble for the future. **BJHM**

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