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Recent advances in viral hepatitis

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Introduction

In the UK deaths from chronic hepatitis C viral (HCV) infection are increasing and deaths from chronic hepatitis B viral (HBV) infection are predicted to increase due to changing immigration patterns.[1,2] This review focuses on recent advances in the epidemiology, progression and therapy of these increasingly important infections.

Epidemiology of chronic viral hepatitis

The hepatitis C virus is blood borne and in the developed world transmission is common in those who use illicit drugs or who received blood or blood products before screening was introduced in 1991. In the UK many of those infected by contaminated blood/blood products have been identified by national 'look back' studies and the greatest burden of disease resides in current or past illicit drug users. Information and awareness campaigns have therefore focused on advising ex and current drug users to come forward for testing and treatment, but, to date, only a minority of the estimated 250,000 infected people in the UK have been identified.[1]

Worldwide, chronic HCV infection is common, affecting over 170 million people. Globally the routes of transmission are diverse and include contaminated medical equipment (used in treatment or immunisation) as well as contaminated non-medical equipment (such as barbers' razors).[3] In the UK end-stage liver disease and death from chronic HCV infection is common in those who were born abroad, but whether this is due to more aggressive variants of the disease or a higher prevalence is unclear.[4] The prevalence of HCV infection in immigrants in the UK is unknown but community screening studies suggest that over 3% of people born in Pakistan are infected and World Health Organization estimates suggest that many immigrants may be at risk (Table 1).[5]

For chronic HBV infection the pattern of infection also differs in developed and developing nations. In the Western world sexual transmission is common whereas in the developing world materno-fetal and early childhood infection predominate, leading globally to very large numbers of chronically infected individuals.

There is growing concern in the UK and elsewhere that the burden of infection with HCV and HBV may be increased in immigrant groups who are not widely recognised as 'high risk'. In the UK, the Department of Health advisory group on hepatitis is investigating this issue and recommendations on testing and case finding are likely in the near future. For the present it is important to be aware of the high rates of chronic viral hepatitis in immigrants and the diagnosis should always be considered in patients from high-risk countries, even if the liver function tests are normal.

Outcome from infection

Chronic infection with HCV leads to a slowly progressive hepatitis that causes significant liver disease in a minority of those who are infected for 30 years. A recent meta-analysis concluded that the

Table 1. The estimated number of people with chronic viral hepatitis in immigrants to the UK from selected high prevalence countries. Figures on the prevalence of viral hepatitis are derived from the World Health Organization (WHO) prevalence estimates and the total number of immigrants born in that country living in the UK is derived from the 2001 census.

Country	Number of people living in the UK	WHO estimated prevalence of HBsAg positivity (%)	WHO estimated prevalence of HCV (%)	Number of people in the UK who are HBsAG positive	Number of people living in the UK who are infected with hepatitis C
India	467,634	4.00	1.8	18,705	8,417
China	149,010	12.00	3	17,881	4,470
Pakistan	321,164	3.00	2.4	9,635	7,708
Kenya	129,635	12.00	0.9	15,556	1,167
South Africa	141,404	8.00	1.7	11,312	2,404
Nigeria	88,378	12.00	1.4	10,605	1,237
Bangladesh	154,354	4.00	2.4	6,174	3,704
Zimbabwe	49,529	10.00	7.7	4,953	3,814
Ghana	56,113	12.00	2.8	6,734	1,571
Uganda	55,207	12.00	1.2	6,625	662
Egypt	24,705	4.00	18.1	988	4,472
Philippines	40,123	10.00	3.6	4,012	1,444
Total infected				**113,181**	**41,071**

probability of developing cirrhosis from HCV was less than 20% after 20 years of infection and for patients with cirrhosis 3–6% per year will develop life threatening complications – either liver failure or liver cancer.[6,7] Both of these complications can be treated by transplantation if detected at an early stage. However the progression of chronic HCV infection is non-linear and the rate of fibrosis progression increases with age, suggesting that middle-aged patients with early disease remain at risk of fibrosis progression. Studies in a cohort infected during plasma donation over 35 years ago and hospital-based cohorts infected for many decades indicate that the incidence of cirrhosis and decompensation or death may increase with age (Fig 1).[8,9] The reassurance from early cohort studies indicating that severe liver disease was probable only in a minority of HCV-infected patients has been replaced by concerns that, with prolonged infection, the proportion developing severe liver disease will increase.

The outcome of chronic HBV infection is complex (Fig 2) – most patients are infected in early childhood and initial infection leads to inactive HBeAg-positive disease with high-level viraemia and minimal liver damage. With advancing age many patients develop an immune response that leads to liver inflammation, progressive disease and, often, seroconversion to the inactive HBeAg-negative phase of infection. This phase is characterised by low-level viraemia and normal liver function tests. A proportion of patients go on to reactivate their infection and develop HBeAg-negative disease with fibrosis progression. HBeAg-negative infection is often regarded as benign and such patients are referred to as 'inactive carriers'.[10]

The inactive management of 'inactive carriers' has recently been questioned. Many studies have shown that a proportion of patients with HBV and 'inactive disease' (based on a single blood test) have active disease on liver biopsy.[11] A recent Taiwanese study followed several thousand untreated patients for many years. Progression to cirrhosis was strongly influenced by the level of viraemia and, over 11 years, even patients with very low levels of HBV DNA (<300 copies per ml) had an increased risk of cirrhosis (Fig 3).[12] As expected cirrhosis was common in those with high levels of viraemia but the finding that low-level viraemia is associated with progression indicates that long-term liver mortality in 'inactive carriers' is increased. This increase in morbidity may be due to inaccurate diagnosis – many patients with HBeAg-negative disease have fluctuating viraemia and liver function tests that confound the diagnosis if only a single test is used. Alternatively the increase in cirrhosis may be due to unidentified disease reactivation or to an increase in liver damage in patients with low level viraemia. Whatever the cause for the inaccurate classification of 'inactive carriers' it is clear that patients who are HBsAg positive, HBeAg negative with low-level viraemia and normal liver function tests require specialised management and follow-up, although probably not treatment. Current guidelines recommend that such patients undergo three-monthly assessments for the first year (measurement of HBV DNA and liver function tests) to avoid misdiagnosing fluctuating disease and then undergo annual review (HBV DNA assessment

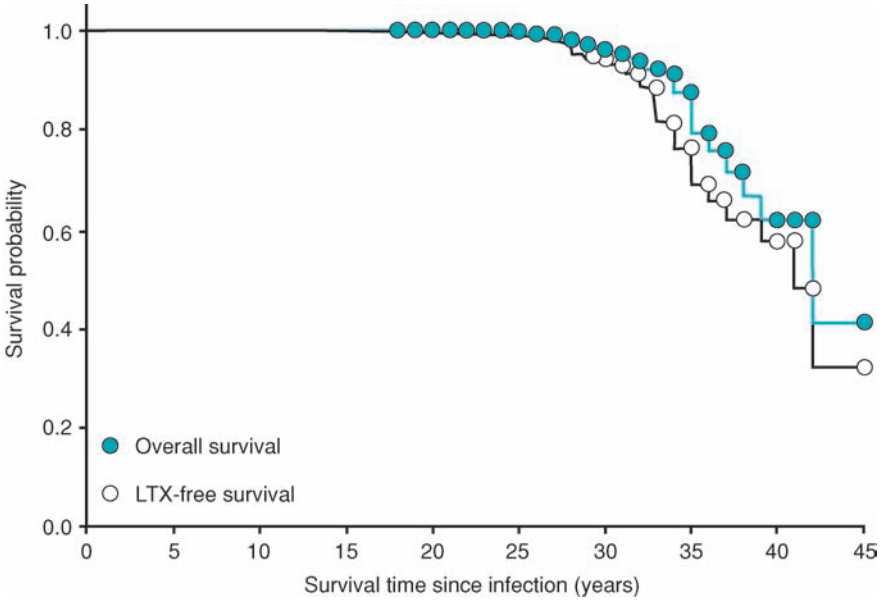

Fig 1. End-stage liver disease in a cohort of patients infected during plasma donation in Austria. Note the rapid deterioration in outcomes after 30 years of infection. LTX = liver transplantation. Reproduced with permission from Elsevier.[8]

Key Points

Viral hepatitis is common in immigrants to the UK

Chronic viral hepatitis causes progressive liver damage in a substantial proportion of those who are infected

Treatment for chronic hepatitis C is curative in many patients and involves a long acting interferon and ribavirin

Treatment for chronic hepatitis B is evolving and therapies include long-acting interferons or direct antivirals that have a low probability of resistance, such as entecavir and tenofovir

KEY WORDS: disease progression, hepatitis B, hepatitis C, natural history

and liver function tests) to detect conversion from 'inactive' to more active disease.[13]

Treatment for chronic viral hepatitis

Chronic HCV infection can be eradicated with a long-acting (pegylated) interferon combined with the antiviral agent ribavirin. Response to therapy is dependent upon viral genotype – a 48-week course of therapy is required for genotype 1 infection and leads to a sustained virological response (which probably equates to a cure) in up to 50% of patients. Genotype 2 or 3 infection requires treatment for 24 weeks and response rates of over 70% are probable.[14] The cost effectiveness of antiviral therapy for chronic HCV has been assessed by the National Institute for Health and Clinical Excellence (NICE) and treatment is recommended for patients with early infection as well as those with advanced disease.[15] Therapy is associated with a wide range of side effects but most patients cope reasonably well and even in socially challenged cohorts (such as homeless injecting drug users) successful therapy is possible.[16] Recent virological monitoring suggests that tailoring the duration of therapy to the rate of early virological response may improve both the cost and clinical effectiveness of therapy.[17]

Within the next five years therapy for HCV will be transformed by direct antiviral agents. Several such drugs are in development and a viral protease inhibitor, telaprevir, is in phase 3 trials.[18] Telaprevir is combined with pegylated interferon and ribavirin for three months and this is followed by a further three months of consolidation therapy. Response rates of 65% have been reported at international meetings and this, or related drugs, may allow improved response rates with reduced duration of therapy. Other protease inhibitors are in development as are drugs with alternative modes of action, including polymerase inhibitors. These drugs will initially be combined with pegylated interferon and ribavirin and then used in novel combinations. The costs, tolerability and durability of these new regimes remains to be determined as does their activity against genotypes other than genotype 1.

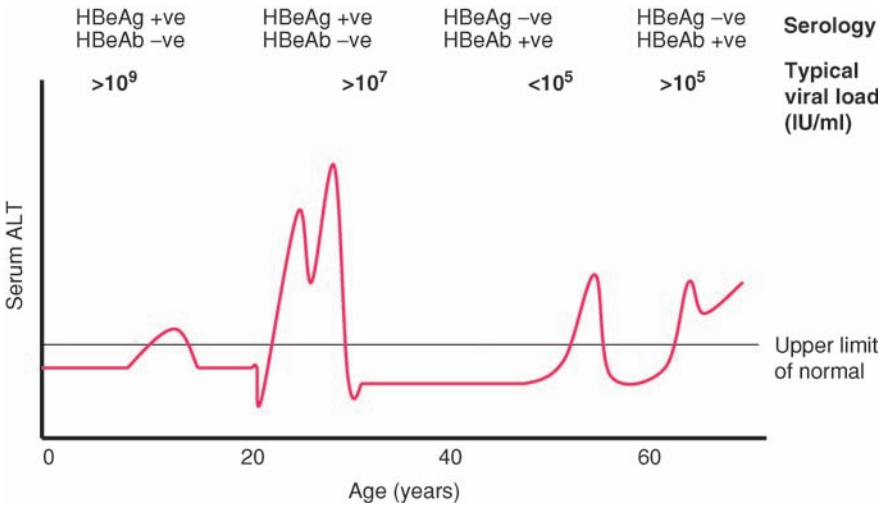

Fig 2. Outline of natural history of chronic hepatitis B virus infection. ALT = alanine aminotransferase.

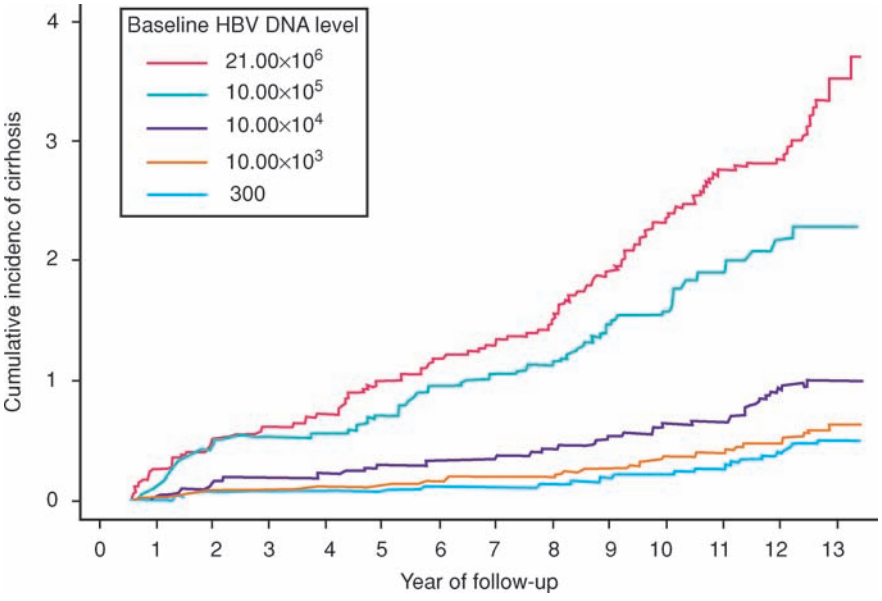

Fig 3. Development of complications from hepatitis B virus (HBV) in a cohort of patients followed for over 11 years. Note that even patients with low-level HBV DNA (traditionally not treated or monitored) had high rates of serious complications. Reproduced with permission from Elsevier.[12]

The management of chronic HBV infection

Therapy for chronic HBV infection should be restricted to patients with active inflammation. For HBeAg-positive disease, pegylated interferon is widely used – it does not induce resistance and leads to seroconversion, to inactive disease, in over 30% of patients. For HBeAg-negative disease, remission rates are disappointing (less than 20%) and studies to define factors that predict response are needed.[13]

Alternatives to interferon for chronic HBV infection are available. The oral antiviral agent lamivudine has long been

used to control viral replication. However, the drug has a very high rate of resistance (up to 70% after five years) and the compensatory mutations associated with resistance make alternative treatment regimes much less robust. Lamivudine is no longer recommended as a first-line agent for chronic HBV and the use of this cheap, well tolerated drug should be reduced to avoid the problems of long-term resistance.[13] Alternatives include entecavir and tenofovir. Both drugs are very potent, well tolerated and rapidly reduce viral replication to undetectable levels in the vast majority of patients. Resistance rates are very low in the medium term – much less than 5% for entecavir after four years – but the long-term resistance rates remain unclear. Equally unclear is whether or not there are benefits to combination therapy with these new, potent, antiviral agents.

Conclusion

Chronic infection with HBV or HCV is increasingly common in the UK. Part of the observed increase in disease is due to better diagnosis and referral but it is probable that current immigration patterns will lead to real increases in prevalence. For both viruses long-term studies have shown that the incidence of severe liver disease increases with increasing duration and the disease burden is predicted to rise sharply. Fortunately the predicted increase in end-stage liver disease can be reduced by appropriate use of the current antiviral agents that are approved by NICE for widespread use. The challenge facing clinicians over the next few years will be to identify and treat the many thousands of patients who require antiviral treatment regimes.

References

1 Health Protection Agency. *Hepatitis C in England: The Health Protection Agency annual report 2007*. London: HPA, 2007.
2 Hepatitis B Foundation. *Hepatitis B: out of the shadows*. London: Hepatitis B Foundation, 2007.
3 World Health Organization. Global surveillance and control of hepatitis C. *J Viral Hep* 1999;6:35–47.
4 Mann AG, Trotter CL, Adekoyejo Balogun M, Ramsay ME. Hepatitis C in ethnic minority populations in England. *J Viral Hepat* 2008;15:421–6.
5 Uddin G, Shoeb D, Solaiman S *et al.* Prevalence of chronic viral hepatitis in people of south Asian ethnicity living in England: the prevalence can not necessarily be predicted from the prevalence in the country of origin. *J Viral Hepatitis* 2009; in press.
6 Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. *Hepatology* 2008;48:418–31.
7 Fattovich G, Giustina G, Degos F *et al.* Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997;112:463–72.
8 Ferenci P, Ferenci S, Datz C *et al.* Morbidity and mortality in paid Austrian plasma donors infected with hepatitis C at plasma donation in the 1970s. *J Hepatol* 2007;47:31–6.
9 D'Souza R, Glynn MJ, Ushiro-Lumb I *et al.* Prevalence of hepatitis C-related cirrhosis in elderly Asian patients infected in childhood. *Clin Gastroenterol Hepatol* 2005;3:910–7.
10 D'Souza R, Foster GR. Diagnosis and treatment of chronic hepatitis. *B J R Soc Med* 2004;97:318–21.
11 Kumar M, Sarin SK, Hissar S *et al.* Virologic and histologic features of chronic hepatitis B virus-infected asymptomatic patients with persistently normal ALT. *Gastroenterology* 2008;134:1376–84.
12 Iloeje UH, Yang HI, Su J *et al.* Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. *Gastroenterology* 2006;130:678–86.
13 Lok AS, McMahon BJ. Chronic hepatitis B. *Hepatology* 2007;45:507–39.
14 D'Souza R, Foster GR. Diagnosis and treatment of hepatitis C. *J R Soc Med* 2004;97:223–5.
15 National Institute for Health and Clinical Excellence. *Peginterferon alfa and ribavirin for the treatment of mild chronic hepatitis C*. London: NICE, 2006.
16 Wilkinson M, Crawford V, Tippet A *et al.* Community based treatment for chronic hepatitis C in drug users: high rates of compliance with therapy despite on-going drug use (HCV in drug users). *Aliment Pharmacol Ther* 2009;29:29–37.
17 Ferenci P. Pegylated interferon plus ribavirin for chronic hepatitis C: the role of combination therapy today, tomorrow and in the future. *Minerva Gastroenterol Dietol* 2006;52:157–74.
18 Kieffer TL, Sarrazin C, Miller JS *et al.* Telaprevir and pegylated interferon-alpha-2a inhibit wild-type and resistant genotype 1 hepatitis C virus replication in patients. *Hepatology* 2007;46:631–9.

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