Hepatitis C virus infection—prognosis and treatment

Natural history

Hepatitis C virus (HCV) is responsible for most post-transfusion non-A, non-B hepatitis (PT-NANB). Prospective studies of transfused patients conducted before the availability of HCV serological tests highlighted two important characteristics of this infection—it is usually asymptomatic (identified by transaminase elevation without jaundice) and chronic hepatitis is a common sequel. Studies examining the natural history of chronic HCV infection have included patients recruited in prospective studies of PT-NANB, patients with sporadic icteric infection and asymptomatic patients referred to specialist clinics. Since the introduction of routine blood-donor screening for HCV antibodies, patients in these three groups now comprise only a small minority of known HCV-infected patients.

Routine screening of blood products for anti-HCV was introduced in the UK in September 1991. Preliminary studies in the UK suggested that as many as 0.1% of blood donors are anti-HCV positive, i.e., confirmed by recombinant immunoblot (RIBA) and detection of HCV RNA in serum by the polymerase chain reaction (PCR). Asymptomatic anti-HCV-positive blood donors now comprise the majority of new referrals to many hepatology clinics. The entire spectrum of liver disease associated with HCV infection can now be defined. Although some asymptomatic blood donors have advanced liver disease, chronic HCV infection can occur in the absence of significant liver pathology. Liver biopsy is performed as part of the assessment of all anti-HCV-positive blood donors referred to the Liver Unit at the Queen Elizabeth Hospital, Birmingham, including those with normal liver function tests. Few biopsy samples have appeared "normal", but histological changes have usually been mild and none has been cirrhotic. The prognosis of patients in this group is uncertain. They are asymptomatic, have no history of jaundice, and only a minority (e.g. 10%) have a history of blood transfusion. It may not be valid to extrapolate the natural history of anti-HCV-positive blood donors from previous studies, which included patients with PT-NANB, and patients with symptomatic infection or history of jaundice.

Despite a high prevalence of HCV infection, HCV-associated liver disease is an uncommon cause of liver failure in British patients (< 1% of patients referred to the Queen Elizabeth Hospital Liver Unit for consideration for liver transplantation). One possible explanation is that the prevalence of HCV infection may have increased rapidly in the 1960s and 1970s in association with parenteral drug abuse; this cohort may yet emerge with symptoms of liver failure after a prolonged asymptomatic phase. An alternative explanation is that the majority of HCV infection is relatively benign, and does not progress to liver failure. Long-term prospective studies are needed to define the natural history of HCV infection.

Treatment and patient selection

Alpha-interferon (IFN-z) is now widely prescribed for patients with chronic HCV infection. The aim of therapy is "normalisation" of serum transaminases, which is frequently accompanied by clearance of HCV RNA from the serum. Sustained transaminase elevation during IFN-z treatment is associated with persistence of serum HCV RNA. Fifty percent of patients respond to treatment, but many relapse when treatment is withdrawn. The follow-up period in most studies has been brief, and relapse rates will be underestimated by those studies relying on biochemical (transaminases) rather than virological (HCV RNA) assessment.

IFN-z is expensive and response rates of patients with chronic HCV infection are disappointing. Sustained side-effects are usually minimal at the recommended schedule of 3 million units three times weekly for 6 months. Transaminase levels fall briskly in "responders", and treatment should be stopped if serum transaminases remain elevated after 12 weeks of therapy. In contrast to chronic HBV infection, in which clinical, biochemical, histological and virological features can identify those patients who are most likely to respond to IFN-z, predictors of response and relapse in HCV infection are poorly defined. The severity of the histological changes appears to be the best predictor of response in patients with HCV infection; sustained response is seldom observed in patients with established cirrhosis, and response rates are best in patients with minimal histological abnormalities.

It seems likely that IFN-z will soon be licensed in the UK for the treatment of chronic HCV infection facing the physician with the dilemma of selecting patients who are suitable for therapy. Most potential candidates in UK practice will be asymptomatic donors referred from the Blood Transfusion Service. The majority of these patients have mild histological changes, and a good response to interferon would be...
predicted. However, many may have non-progressive disease and will not require treatment. In contrast, those patients with clearly progressive disease, and established cirrhosis, are least likely to respond to treatment. Those patients with potentially progressive disease that might benefit from IFN-α-therapy need to be identified at an early stage. Long-term prospective study of asymptomatic HCV-infected blood donors should help redefine the natural history of chronic HCV infection, and rationalise the selection of patients for interferon therapy.

Liver transplantation is an established treatment for patients with end-stage HCV-related cirrhosis. However, re-infection of the graft is probably inevitable. De novo infection may also occur in association with the use of HCV-contaminated blood products. Indeed, HCV infection was a common complication of liver transplantation in areas of high endemicity before the availability of serological testing.8 Re-infection and de novo infection appear to be associated with similar patterns of allograft hepatitis. Acute resolving (uncommon in the first month after transplantation), acute progressing to chronic, and chronic hepatitis may all occur. Although fairly rapid progression to cirrhosis has been described,9 many patients have no significant hepatitis and have normal histological appearances, despite persistent viraemia. The role played by immunosuppression in the modulation of graft infection is unclear.

In summary, the natural history of chronic HCV infection is poorly defined. Many patients have benign infection and require no treatment. Some patients may benefit from treatment with IFN-α, but response and relapse rates are discouraging. Liver transplantation can be offered to those few patients who develop liver failure as a consequence of long-standing infection.

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References