Hepatitis C: Recent advances

Since the initial publication of the discovery of Hepatitis C virus (HCV) by Choo et al (1) from Chiron Corporation in April 1989, much has been learned about the biology, epidemiology and clinical features of HCV infection. In this edition of the notes, we highlight some of the more recent findings.

Better serological testing: Second generation serological tests are now in use. The second generation enzyme immunoassay (EIA) is more sensitive than the first generation assay (2). Furthermore, the second generation recombinant immunoblot assay (RIBA), used by many laboratories as a confirmatory test for HCV infection, is more specific than earlier assays (2,3). Although the second generation tests permit earlier detection of HCV antibody than first generation tests, the diagnosis of HCV infection can seldom be made serologically in the first six weeks following infection.

Screening of blood donors: There is now conclusive evidence that excluding blood donated by individuals who test HCV-seropositive substantially reduces the incidence of post-transfusional non-A, non-B hepatitis to a greater extent than the use of serum alanine aminotransferase (ALT) and hepatitis B surface antigen antibody as surrogate markers (6).

Transmission: The most established route of transmission of HCV is parenteral, with high rates of infection in injection drug users and recipients of large quantities of blood products, such as hemophiliacs. Consistent with this route of transmission, occupational HCV infection of health care workers via needlestick injuries is well documented (7,8), and likely accounts for the higher rate of HCV-seropositivity reported in dentists, compared with controls (9). The risk of HCV infection with a single needlestick injury has been reported at 4% in one study (7) and 10% in another (8); thus the risk is intermediate between that of human immunodeficiency virus at approximately 0.3% and hepatitis B virus (HBV) at 20 to 40%.

Transmission via organ transplantation has also been documented with high rates of transmission reported in two studies (10,11), and a low rate of transmission reported in another (12). Given the limited supply of organs for transplantation, some programs permit the transplantation of organs other than the liver from HCV-seropositive donors into recipients who are already HCV-seropositive. Sexual (13) and vertical (14) transmission of HCV remain infrequent but both clearly occur. Of note, the route of transmission remains unknown in about 40% of cases (15), a proportion comparable to that for HBV.

HCV RNA: Since the report of the initial polymerase chain reaction (PCR) assay for HCV RNA by Weiner et al (16) from Chiron, many research laboratories now perform this assay. However, the significant interlaboratory variability of this assay suggests that standardization and proficiency testing will be required (17).

Several investigators have developed quantitative assays for HCV RNA. A particularly promising quantitative assay is the novel technique of branched DNA signal amplification (18), which has recently been assessed clinically (19).

HCV RNA assays offer the potential of earlier diagnosis and high specificity where serology is equivocal. Quantitative assays are now essential in clinical trials assessing antiviral therapy (20).

Essential mixed cryoglobulinemia (EMC): EMC is a relatively rare condition characterized by purpura, arthralgia and weakness, often together with glomerulo-
nephritis. The diagnosis of EMC requires the demonstration of serum cryoglobulins made up of polyclonal immunoglobulin (Ig) G and monoclonal IgM rheumatoid factors.

Several groups of investigators have demonstrated a high prevalence of HCV seropositivity in patients with EMC (21,22), with concentration of both HCV RNA and anti-HCV in the cryoprecipitate (22,23). Some of these patients also have membranoproliferative glomerulonephritis (23).

HCV in liver disease: Recent studies indicate that a majority of HCV-seropositive individuals have liver disease, despite the fact that most are asymptomatic (24). Normal serum aminotransferase levels do not exclude the presence of chronic hepatitis (25). Furthermore, whereas individuals with chronic hepatitis usually have detectable HCV RNA in serum, circulating HCV RNA may remain detectable for several years in the absence of liver disease (26). Thus, the assessment of asymptomatic HCV-infected individuals with persistently normal serum aminotransferases has become confusing, and arguments can be made for and against performing a liver biopsy in such individuals, largely influenced by one’s belief regarding the efficacy of treatment.

Treatment of HCV: Currently, the only approved treatment for chronic HCV infection is with interferon-alpha. However, interferon-alpha is expensive, toxic and has limited efficacy. No more than 50% of patients experience improvement with this therapy and relapses are very common (27,28). Unfortunately, as with recent antiretroviral drugs, interferon-alpha was licensed for the treatment of HCV on the basis of surrogate data, i.e., improvement in ALT, rather than convincing data demonstrating either a sustained antiviral effect or long term clinical benefits. Thus, it remains to be determined whether interferon-alpha prevents the development of cirrhosis or hepatocellular carcinoma. Furthermore, a recent study indicates that individuals who are followed an average of 18 years after developing transfusion-associated non-A, non-B hepatitis have no increase in mortality from all causes, compared with two control groups (29). There was a small, statistically significant increase in deaths related to liver disease, but 71% of these occurred in chronic alcoholics (29). Therefore, the potential for an effective HCV therapy to reduce mortality is limited. Until placebo controlled trials demonstrate that interferon-alpha results in a sustained clearance of HCV RNA from serum in a substantial proportion of patients and/or reduced progression to cirrhosis and/or hepatocellular carcinoma, its use in HCV must still be considered experimental (30).

Oral ribavirin has also been evaluated in the treatment of chronic HCV infection in two open-label pilot studies (31,32). In both studies, nearly all patients experienced a significant fall in serum ALT, and the drug was well tolerated. Furthermore, a fall in quantitative HCV RNA was observed (32), although HCV RNA did not disappear completely. Unfortunately, virtually all patients relapsed following discontinuation of therapy (31,32). In contrast, some patients treated with interferon-alpha achieve sustained virological remissions with undetectable HCV RNA over a period of several years (33).

Prospect for vaccine: Although about 50% of HCV-infected individuals clear the virus spontaneously, the determinants of immunity in such individuals have not been defined. Furthermore, at least five HCV genotypes are now recognized (34), and it is unknown whether immunity to one type confers cross-immunity to one or more of the other genotypes.

Even more discouraging is the observation that chimpanzees inoculated with HCV who clear the virus do not develop protective immunity to repeat intra-venous challenge with either homologous or heterologous HCV (35). Interestingly, chimpanzees who become chronically infected with HCV are resistant to super-infection with heterologous HCV (35). These data suggest that HCV vaccine development will be considerably more challenging than the development of vaccines for hepatitis A virus and hepatitis B virus.

REFERENCES

12. Roth D, Fernandez JA, Babischkin S, et al. Detection of hepatitis C virus infection among cadaver organ donors:


