

Approximately one-third of patients with chronic hepatitis C have normal or near-normal aminotransferase activity; although one-third to one-half of these patients have chronic hepatitis on liver biopsy, the grade of liver injury and stage of fibrosis tend to be mild in the vast majority. In some cases, more severe liver injury has been reported—even, rarely, cirrhosis, most likely the result of previous histologic activity. Among patients with persistent normal aminotransferase activity sustained over  $\geq 5$ –10 years, histologic progression has been shown to be rare; however, approximately one-fourth of patients with normal aminotransferase activity experience subsequent aminotransferase elevations, and histologic injury can be progressive once abnormal biochemical activity resumes. Therefore, continued clinical monitoring is indicated, even for patients with normal aminotransferase activity.

Despite this substantial rate of progression of chronic hepatitis C, and despite the fact that liver failure can result from end-stage chronic hepatitis C, the long-term prognosis for chronic hepatitis C in a majority of patients is relatively benign. Mortality over 10–20 years among patients with transfusion-associated chronic hepatitis C has been shown not to differ from mortality in a matched population of transfused patients in whom hepatitis C did not develop. Although death in the hepatitis group is more likely to result from liver failure, and although hepatic decompensation may occur in  $\sim 15\%$  of such patients over the course of a decade, the majority (almost 60%) of patients remain asymptomatic and well compensated, with no clinical sequelae of chronic liver disease. Overall, chronic hepatitis C tends to be very slowly and insidiously progressive, if at all, in the vast majority of patients, whereas in approximately one-fourth of cases, chronic hepatitis C will progress eventually to end-stage cirrhosis. In fact, because HCV infection is so prevalent, and because a proportion of patients progress inexorably to end-stage liver disease, hepatitis C is the most frequent indication for liver transplantation (**Chap. 368**). In the United States, hepatitis C accounts for up to 40% of all chronic liver disease, and, as of 2007, mortality caused by hepatitis C surpassed that associated with HIV/AIDS. Moreover, because the prevalence of HCV infection is so much higher in the “baby boomer” cohort borne between 1945 and 1965, three-quarters of the mortality associated with hepatitis C occurs in this age cohort. Referral bias may account for the more severe outcomes described in cohorts of patients reported from tertiary care centers (20-year progression of  $\geq 20\%$ ) versus the more benign outcomes in cohorts of patients monitored from initial blood-product-associated acute hepatitis or identified in community settings (20-year progression of only 4–7%). Still unexplained, however, are the wide ranges in reported progression to cirrhosis, from 2% over 17 years in a population of women with hepatitis C infection acquired from contaminated anti-D immune globulin to 30% over  $\leq 11$  years in recipients of contaminated intravenous immune globulin.

Progression of liver disease in patients with chronic hepatitis C has been reported to be more likely in patients with older age, longer duration of infection, advanced histologic stage and grade, more complex quasispecies diversity, increased hepatic iron, concomitant other liver disorders (alcoholic liver disease, chronic hepatitis B, hemochromatosis,  $\alpha_1$  antitrypsin deficiency, and steatohepatitis), HIV infection, and obesity. Among these variables, however, duration of infection appears to be one of the most important, and some of the others probably reflect disease duration to some extent (e.g., quasispecies diversity, hepatic iron accumulation). No other epidemiologic or clinical features of chronic hepatitis C (e.g., severity of acute hepatitis, level of aminotransferase activity, level of HCV RNA, presence or absence of jaundice during acute hepatitis) are predictive of eventual outcome. Despite the relatively benign nature of chronic hepatitis C over time in many patients, cirrhosis following chronic hepatitis C has been associated with the late development, after several decades, of HCC (**Chap. 111**); the annual rate of HCC in cirrhotic patients with hepatitis C is 1–4%, occurring primarily in patients who have had HCV infection for 30 years or more.

Perhaps the best prognostic indicator in chronic hepatitis C is liver histology; the rate of hepatic fibrosis may be slow, moderate, or rapid. Patients with mild necrosis and inflammation as well as those with limited fibrosis have an excellent prognosis and limited progression to cirrhosis. In contrast, among patients with moderate to severe

necroinflammatory activity or fibrosis, including septal or bridging fibrosis, progression to cirrhosis is highly likely over the course of 10–20 years. The pace of fibrosis progression may be accelerated by such factors as concomitant HIV infection, other causes of liver disease, excessive alcohol use, and hepatic steatosis. Among patients with compensated cirrhosis associated with hepatitis C, the 10-year survival rate is close to 80%; mortality occurs at a rate of 2–6% per year; decompensation at a rate of 4–5% per year; and, as noted above, HCC at a rate of 1–4% per year. **A discussion of the pathogenesis of liver injury in patients with chronic hepatitis C appears in Chap. 360.**

*Clinical features* of chronic hepatitis C are similar to those described above for chronic hepatitis B. Generally, fatigue is the most common symptom; jaundice is rare. Immune complex–mediated extrahepatic complications of chronic hepatitis C are less common than in chronic hepatitis B (despite the fact that assays for immune complexes are often positive in patients with chronic hepatitis C), with the exception of essential mixed cryoglobulinemia (**Chap. 360**), which is linked to cutaneous vasculitis and membranoproliferative glomerulonephritis as well as lymphoproliferative disorders such as B-cell lymphoma and unexplained monoclonal gammopathy. In addition, chronic hepatitis C has been associated with extrahepatic complications unrelated to immune-complex injury. These include Sjögren’s syndrome, lichen planus, porphyria cutanea tarda, type 2 diabetes mellitus, and the metabolic syndrome (including insulin resistance and steatohepatitis).

*Laboratory features* of chronic hepatitis C are similar to those in patients with chronic hepatitis B, but aminotransferase levels tend to fluctuate more (the characteristic episodic pattern of aminotransferase activity) and to be lower, especially in patients with long-standing disease. An interesting and occasionally confusing finding in patients with chronic hepatitis C is the presence of autoantibodies. Rarely, patients with autoimmune hepatitis (see below) and hyperglobulinemia have false-positive immunoassays for anti-HCV. On the other hand, some patients with serologically confirmable chronic hepatitis C have circulating anti-LKM. These antibodies are anti-LKM1, as seen in patients with autoimmune hepatitis type 2 (see below), and are directed against a 33-amino-acid sequence of cytochrome P450 IID6. The occurrence of anti-LKM1 in some patients with chronic hepatitis C may result from the partial sequence homology between the epitope recognized by anti-LKM1 and two segments of the HCV polyprotein. In addition, the presence of this autoantibody in some patients with chronic hepatitis C suggests that autoimmunity may be playing a role in the pathogenesis of chronic hepatitis C.

**Histopathologic features of chronic hepatitis C, especially those that distinguish hepatitis C from hepatitis B, are described in Chap. 360.**

## TREATMENT CHRONIC HEPATITIS C

Therapy for chronic hepatitis C has evolved substantially in the two decades since IFN- $\alpha$  was introduced for this indication. The therapeutic armamentarium has grown to include PEG IFN with ribavirin and, in 2011, the introduction of protease inhibitors telaprevir and boceprevir used in combination with PEG IFN and ribavirin in patients with HCV genotype 1. When first approved, IFN- $\alpha$  was administered via subcutaneous injection three times a week for 6 months but achieved a sustained virologic response (SVR) (**Fig. 362-2**) (a reduction of HCV RNA to undetectable levels by PCR when measured  $\geq 6$  months after completion of therapy) below 10%. Doubling the duration of therapy—but not increasing the dose or changing IFN preparations—increased the SVR rate to  $\sim 20\%$ , and addition to the regimen of daily ribavirin, an oral guanosine nucleoside, increased the SVR rate to 40%. When used alone, ribavirin is ineffective and does not reduce HCV RNA levels appreciably, but ribavirin enhances the efficacy of IFN by reducing the likelihood of virologic relapse after the achievement of an end-treatment response (**Fig. 362-2**) (response measured during, and maintained to the end of, treatment). Proposed mechanisms to explain the role of ribavirin include subtle direct reduction of HCV replication, inhibition of host inosine monophosphate dehydrogenase activity (and associated depletion