Hepatitis D virus (HDV) is a unique defective RNA virus that requires a helper function provided by hepatitis B virus (HBV) for its assembly and transmission. Although over the past decade, there has been a decline in the incidence of HDV infection in the Mediterranean area, most likely as a result of HBV vaccination programs and improved socioeconomic conditions, chronic hepatitis D still remains a major cause of liver transplantation and death. Infection with HDV causes the most severe form of chronic viral hepatitis, leading to cirrhosis in about 80% of patients. The disease can be rapidly progressive, with cirrhosis developing within 1 to 2 years following acute hepatitis in 15% of cases. The serious nature of chronic hepatitis D and the uniqueness of the delta virus make this disease a difficult target for antiviral therapy. Although treatment is not yet satisfactory, a proportion of patients with chronic hepatitis D benefit from high doses and prolonged courses of interferon α, the only licensed drug that has been extensively evaluated for the treatment of this disease. However, in most clinical trials, the efficacy of interferon has been evaluated on the basis of the short-term biochemical and virologic response, within the first year after termination of therapy. Thus, little is known about the long-term effects of interferon on the natural history of chronic hepatitis D.

Cirrhosis, the final stage of chronic hepatitis, has been considered to be irreversible. However, recent evidence has challenged this belief. Thus, the fibrotic component of cirrhosis may be a reversible process. In the present study, we evaluated prospectively the long-term clinical and histologic outcome of a cohort of patients with chronic hepatitis D. The patients were included in...
a randomized controlled trial, initiated in Sardinia 15 years ago, in which the efficacy of a 48-week course of high-dose (9 million units) or low-dose (3 million units) interferon α was compared with no treatment. Most of the patients had active cirrhosis at the time of enrollment and underwent serial liver biopsies before and at the end of treatment, as well as during follow-up. This cohort provided a unique opportunity to investigate the long-term effects of treatment with interferon α on liver fibrosis, clinical outcome, and survival in chronic hepatitis D.

Materials and Methods

Patients

The subjects of our follow-up study were derived from a cohort of 41 patients with chronic hepatitis D enrolled between 1987 and 1991 in a prospective randomized controlled trial conducted by the Liver Unit of the University of Cagliari, Italy. All patients provided written informed consent for ongoing follow-up evaluations, and the protocol was approved by the Research Review Committee of the Department of Internal Medicine of the University of Cagliari. Patients had been randomly assigned to receive either interferon α-2a at doses of 9 million units (14 patients) or at doses of 3 million units (14 patients) 3 times a week for 48 weeks or no treatment (14 patients). All, except 1 untreated control, completed the treatment period and the short-term follow-up. Of these 41 patients, 36 (88%) were included in the long-term follow-up, although 5 were not evaluated because 4 received treatment after the trial completion, and 1 was lost to follow-up. They consisted of all 14 patients treated with 9 million units, 12 of 14 patients treated with 3 million units (1 was retreated and 1 was lost to follow-up), and 10 of 13 untreated controls (3 were treated). The 10 patients who remained in the control group were not treated for the following reasons: refusal of treatment (2 patients) or the desire to become pregnant (1 patient), leukopenia or thrombocytopenia with or without deterioration of liver function tests (4 patients), arrhythmias (1 patient), varicose hemorrhage (1 patient), and depression (1 patient). In the low-dose group, 12 patients could not be retreated for the following reasons: refusal of treatment (2 patients) or the desire to become pregnant (1 patient), an alanine aminotransferase (ALT) pattern characterized by nearly normal to slightly elevated values during follow-up (6 patients), thrombocytopenia with or without deterioration of liver function tests (3 patients).

Long-Term Follow-up and Evaluations

After completion of the treatment period, patients were seen during the first month, during the third month, and every 3–6 months thereafter, for a mean (±SD) follow-up period of 10.8 ± 3.8 years (median, 13.0; range, 2 to 14.8). Severe liver-related clinical complications were prospectively defined and included the following: death, development of hepatocellular carcinoma (HCC), need for orthotopic liver transplantation (OLT), variceal hemorrhage, hepatic encephalopathy, and ascites. The time of follow-up was calculated from the end of treatment until death or the need for OLT or the last recorded visit before September 2002. At each visit, the patients received a complete physical examination, and blood was taken for routine liver function tests and hepatitis B and D serology. On each occasion, aliquots of serum were stored at −70°C for HDV RNA and HBV DNA testing. Serum HDV RNA was reevaluated in all serial serum samples from each patient by a sensitive nested reverse-transcriptase polymerase chain reaction (RT-PCR). We also determined the HDV titer in selected serum samples obtained at baseline, end of treatment, and at the end of the long-term follow-up. An additional testing was also performed at the time of the last liver biopsy. The HDV genotype was assessed at baseline in 32 patients, by sequencing analysis of hepatitis delta antigen (HDAg). In patients positive for antibodies to hepatitis C virus (anti-HCV), the presence and levels of serum HCV RNA were determined.

Liver Biopsy Studies

The initial trial included 3 liver biopsies for treated patients (before enrollment, at the end of treatment, and at 6 months after the completion of therapy) and 2 for untreated patients (before enrollment and at 6 months of follow-up). During follow-up, all treated and untreated patients who were eligible underwent a fourth and a third liver biopsy, respectively, after a mean (±SD) follow-up period of 11.7 ± 1.1 years (median, 11.4; range, 10.4 to 13.9) from the first liver biopsy. Liver biopsy specimens were fixed, paraffin-embedded, and stained with H&E and picrosirius red for collagen. For each liver biopsy specimen, stage of fibrosis and grade of activity were established according to the scoring system of Knodell. Fibrosis was scored on a scale of 0 to 4, with 0 indicating absence of fibrosis, 1 fibrous portal expansion, 2 bridging fibrosis, and 3 cirrhosis. The intensity of the necroinflammatory lesions was measured by grade of activity, which comprised the sum of 3 scores, including interface hepatitis ± bridging necrosis (0–10), lobular necrosis and inflammation (0–4), and portal inflammation (0–4).

Assays

Hepatitis B surface antigen (HBsAg), antibody to HBsAg (anti-HBs), antibody to hepatitis B core antigen (anti-HBc), hepatitis B e antigen (HBeAg), antibody to HBe (anti-HBe), and IgM anti-HBe were measured with commercial radioimmunoassays (Abbott Laboratories, North Chicago, IL) as were IgG and IgM anti-HD (Sorin Biomedica, Saluggia, Italy). Titers of serum IgG and IgM anti-HD were determined by testing 10-fold serial serum dilutions. Anti-HCV and anti-HIV-1 were tested with commercial enzyme immunoassays (Ortho Diagnostic Sys-
Table 1. Base-line Characteristics of the Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treated patients</th>
<th>Untreated controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9 Million units</td>
<td>3 Million units</td>
</tr>
<tr>
<td></td>
<td>(n = 14)</td>
<td>(n = 14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n = 13)</td>
</tr>
<tr>
<td>Age, yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, No. (%)</td>
<td>35 ± 9</td>
<td>35 ± 8</td>
</tr>
<tr>
<td>Total score (HAI)</td>
<td>151 ± 65</td>
<td>139 ± 33</td>
</tr>
<tr>
<td>Alanine aminotransferase, U/L^g</td>
<td>192 ± 113</td>
<td>209 ± 136</td>
</tr>
<tr>
<td>Aspartate aminotransferase, U/L^h</td>
<td>103 ± 54</td>
<td>118 ± 71</td>
</tr>
<tr>
<td>Bilirubin, mg/dL^i</td>
<td>0.6 ± 0.3</td>
<td>0.8 ± 0.4</td>
</tr>
<tr>
<td>Albumin, g/dL^j</td>
<td>3.9 ± 0.4</td>
<td>3.8 ± 0.5</td>
</tr>
<tr>
<td>γ-globulin, g/dL^k</td>
<td>2.2 ± 0.6</td>
<td>2.1 ± 0.5</td>
</tr>
<tr>
<td>Platelets (10^3/µL)^l</td>
<td>151 ± 65</td>
<td>139 ± 33</td>
</tr>
<tr>
<td>HBeAg, No. (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Antibody to HBeAg, No. (%)</td>
<td>13 (93)</td>
<td>12 (86)</td>
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<td>IgM anti-HBc, No. (%)</td>
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<td>0</td>
</tr>
<tr>
<td>HBV DNA (&gt;400 copies/mL), No. (%)</td>
<td>4 (29)</td>
<td>2 (14)</td>
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<tr>
<td>IgM anti-HDAg, No. (%)</td>
<td>14 (100)</td>
<td>14 (100)</td>
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<tr>
<td>No. of HDV RNA genome equivalent/mL, geometric mean^x</td>
<td>10^6.4</td>
<td>10^6.1</td>
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<tr>
<td>Anti-HCV-positive, No. (%)</td>
<td>2 (14)</td>
<td>1 (7)</td>
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<td>HCV RNA, No. (%)</td>
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<td>0</td>
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<tr>
<td>Liver biopsy findings</td>
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<tr>
<td>Fibrosis</td>
<td>3.8 ± 0.4</td>
<td>3.5 ± 1.0</td>
</tr>
<tr>
<td>Stage</td>
<td>12.5 ± 2.3</td>
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<tr>
<td>0, No. (%)</td>
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<td></td>
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<tr>
<td>1, No. (%)</td>
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<tr>
<td>2, No. (%)</td>
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<td>3, No. (%)</td>
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<tr>
<td>4, No. (%)</td>
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</tr>
<tr>
<td>Activity Grade</td>
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<tr>
<td>Piecemeal necrosis</td>
<td>2.6 ± 1.4</td>
<td>1.6 ± 1.3</td>
</tr>
<tr>
<td>Lobular necrosis</td>
<td>2.9 ± 1.1</td>
<td>2.8 ± 1.0</td>
</tr>
<tr>
<td>Portal inflammation</td>
<td>3.4 ± 0.5</td>
<td>2.9 ± 0.9</td>
</tr>
<tr>
<td>Total necroinflammation</td>
<td>8.9 ± 2.4</td>
<td>7.4 ± 2.5</td>
</tr>
<tr>
<td>Total score (HAI)</td>
<td>12.5 ± 2.3</td>
<td>10.9 ± 2.9</td>
</tr>
</tbody>
</table>

NOTE. Plus-minus values are means ± SD. Percentages may not total 100 because of rounding. None of the differences among the 3 groups of patients were statistically significant.

HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HDAg, hepatitis delta antigen; and HDV, hepatitis D virus.

^aNormal value, ≥60 U per liter.

^bNormal value, ≥42 U per liter.

^cTo convert serum bilirubin values to micromoles per liter, multiply by 17.1.

^dNormal value range, ≥3.6–≤5.0.

^eNormal value range, ≥0.7–≤1.6.

^fNormal value range, ≥159–≤388 (10^3/µL).

^gThe HDV titer was not determined in 1 patient in the high-dose group, in 2 in the low-dose group, and in 2 untreated controls.

Statistical Analysis

The results are expressed as means ± SD. An analysis of variance was used to detect significant differences between mean values of continuous variables whenever data from all 3 groups of patients were analyzed and to determine changes over time within each group; we then used the Newman–Keuls test for comparisons of groups. χ^2 Analysis or Fisher exact test were used to test differences between proportions. Student unpaired t test was used to compare differences between group means. Changes in the levels of viremia at different time points as well as changes in the histologic findings were compared with the use of Wilcoxon test for paired...
samples. The Kaplan–Meier method was used to estimate survival, and differences among the 3 groups were assessed by using the log-rank test; for the calculations of survival times, the need for liver transplantation was combined with death. A P value of less than 0.05 (2-sided test) indicates statistical significance.

**Results**

**Baseline Characteristics of the Study Cohort**

The baseline clinical characteristics of the 3 groups of patients were similar with respect to sex, age, liver function tests, and virologic and histologic features (Table 1). Most of the patients were men, and all were heterosexual. All patients had markers of active HDV replication, as documented by the presence of HDV RNA and IgM anti-HD. The mean baseline titers of IgG and IgM anti-HD did not differ among the 3 groups (range, $10^3$ to $10^5$). All patients were positive for HBsAg, and most (88%) were anti-HBe positive. However, a few patients in each group (Table 1) had signs of HBV replication, albeit at very low levels (mean [± SD] 10,495 ± 14,608; range, 492 to 42,814 copies/mL). All patients were IgM anti-HBc negative at baseline and during follow-up. Four patients (9.5%) were retrospectively found to be anti-HCV positive, but none of them had detectable HCV RNA in serum; in only 1 patient treated with 9 million units, did HCV RNA become transiently detectable. The proportion of patients with active cirrhosis did not differ significantly among the 3 groups, although it was higher in the group that received 9 million units (Table 1). Consistent with their geographic origin, all tested patients had HDV genotype 1.

**Long-Term Effects of IFN-α: Survival**

Survival was significantly longer in the high-dose group than in controls ($P = 0.003$) or in the low-dose group ($P = 0.019$), whereas it did not differ significantly between the low-dose group and the controls ($P = 0.328$). During long-term follow-up, severe clinical complications leading to liver-related death or OLT developed in 2 patients treated with 9 million units as compared with 7 patients treated with 3 million units and 7 untreated controls. Full clinical reports about the cause of death were available for all patients. In the high-dose group, 1 patient died from esophageal variceal hemorrhage, and 1 had liver failure requiring OLT. In the low-dose group, 5 patients died and 2 needed OLT. Three of the 5 deaths were caused by decompensated cirrhosis and 2 by HCC. An additional patient treated with 3 million units died at 10 years of follow-up for liver metastasis secondary to a colon cancer. In the control group, 2 patients died from HCC and 5 developed liver failure necessitating OLT. Estimates of survival without need for OLT at 12 years after treatment were 86% in patients who received 9 million units, 39% in patients who received 3 million units, and 31% in untreated controls (Figure 1).

**Serum ALT and Other Liver Function Tests**

At the end of treatment, serum ALT levels were normal in 10 of 14 patients (71%) treated with 9 million units of interferon as compared with 1 of 13 untreated patients (8%, $P = 0.001$) and 4 of 14 patients treated with 3 million units (29%, $P = 0.029$). At 12 years of follow-up, ALT levels were persistently normal in 7 of 12 surviving patients treated with 9 million units, 5 of whom were sustained responders since the end of treatment. The long-term biochemical response was associated with a progressive increase in the levels of serum albumin and a progressive decrease in γ-globulin levels, both of which became highly significant at 12 years of follow-up (Table 2). By contrast, patients with persistently elevated ALT values showed unchanged albumin and γ-globulin levels over time (Table 2).

In the low-dose group, none of the 4 patients with normal ALT levels at the end of treatment had a sustained biochemical response, and none survived up to 12 years of follow-up. In the remaining 8 patients, including 5 with a partial biochemical response (>50% reduction) and 3 nonresponders at the end of treatment, the
ALT levels returned to nearly normal or slightly elevated values within the second year of follow-up, often following a transient relapse after stopping therapy. This ALT pattern persisted for several years and eventually resulted in 2 different clinical outcomes. In 4 patients, including 2 in whom ALT became persistently normal during the fifth year of follow-up, there was a long-term improvement in the levels of serum albumin and a decrease in γ-globulin levels, which persisted until the present date (Table 2); in the remaining 4 patients, despite low levels of ALT, a progressive deterioration in liver function tests occurred between 7 and 10 years of follow-up, leading to OLT or death. Thus, at 12 years of follow-up, a biochemical response was documented in only 2 of 4 surviving patients; overall, within the low-dose group, there were no significant changes among the clinical variables during the entire follow-up period (Table 2). Among the control group, none of the 3 patients who survived up to 12 years of follow-up showed either a sustained biochemical response or a significant change in any of the clinical parameters (Table 2).

### Serum HDV RNA

Serum HDV RNA, as measured by nested PCR, remained detectable in all patients at the end of treatment and in most during long-term follow-up. However, there was a significant decrease in the high-dose group at the end of treatment compared with baseline ($P = 0.009$), whereas only minor changes were observed in the low-dose group or in the controls (Figure 2A). Remarkably, the significant decrease in HDV RNA seen in the high-dose group was sustained ($P = 0.008$) (Figure 2B), and, in 3 patients with long-term biochemical response, serum HDV RNA was eventually cleared during the last years of follow-up (mean, 11.5 years) (Figure 3). A similar pat-
tern was seen in a single patient treated with the low dose of interferon, whereas, among controls, serum HDV RNA became undetectable in one patient before he died from HCC. In the low-dose group and in controls, no significant changes in viral load were documented during long-term follow-up, although a decline was observed concomitant with the progression to end-stage liver disease (Figure 2B). Serum HBV DNA, which was present in only a minority of patients and at very low levels prior to the onset of therapy (Table 1), remained detectable at 12 years of follow-up in only 2 patients, 1 in the 9 million units group and 1 in the 3 million units group and, in both, the levels were very low (fewer than 1000 copies per mL).

**Serologic Markers**

During long-term follow-up, we did not observe significant changes in the titer of IgG anti-HD in any of the groups. By contrast, the pattern of serum IgM anti-HD did change. All patients with a long-term biochemical response, both in the high- and low-dose group, lost IgM anti-HD (Table 2 and Figure 3), after a mean interval (±SD) of 9.5 ± 2.4 years (median, 9.7; range, 5.1 to 11.9) and 9.5 ± 0.0 years (range, 9.4 to 9.5), respectively, after termination of therapy, whereas IgM anti-HD persisted in all of the other patients. In the high-dose group, the association between sustained biochemical response and loss of IgM anti-HD was highly significant ($P = 0.001$).

Among patients with a long-term biochemical response to 9 million units, HBsAg became undetectable after a mean of 12.8 years in 2 patients, one of whom later seroconverted to anti-HBs, and declined to borderline values at 12.4 years in one patient; in all 3 patients, HDV RNA had become undetectable between 1 and 2 years earlier. In the low-dose group, HBsAg became negative in a single patient after 11.6 years of follow-up, at the time that HDV RNA first

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**Figure 2.** Mean (± SE) change in serum HDV RNA levels from baseline in patients treated with interferon (9 million units or 3 million units) and untreated controls. Data shown are the changes from baseline to the end of treatment (A) and to the last evaluation (B), according to the treatment regimen. Changes in viral load from baseline were statistically significant only in the high-dose group, both at the end of treatment and at the last evaluation. The HDV titer was not determined in 5 patients at the end of treatment (1 treated with 9 million units, 2 with 3 million units, and 2 untreated controls) and in 4 patients at the end of the long-term follow-up (1 treated with 9 million units, 2 with 3 million units, and 1 untreated control).

**Figure 3.** Biochemical, histologic, serologic, and molecular profiles of a representative case of a patient with chronic hepatitis D treated with 9 million units of interferon α-2a, who had a sustained biochemical response. The gray area indicates the values for ALT. The red horizontal bar indicates positive assays for serum HDV RNA by nested PCR assay, and the number inside the bar represents the genome equivalent titer of HDV determined by testing 10-fold serial dilutions of the extracted RNA in the reverse transcriptase-PCR assay. The numbers indicate the titer of serum HBV DNA quantified using Amplicor HBV Monitor test, with a detection limit of 400 copies per mL. The yellow line indicates the reciprocal titers of IgM anti-HD, defined as the highest dilution with a positive result. The arrows indicate the time and results of liver biopsies.
became undetectable. One patient in the control group lost HBeAg at 3 years of follow-up, but he did not seroconvert.

**Liver Histology**

Among 36 patients evaluated in the long-term follow-up, a fourth liver biopsy was performed in 10 of 14 treated with 9 million units (2 did not provide the informed consent and 2 developed major clinical complications that precluded the performance of a liver biopsy) and in 4 of 12 treated with 3 million units (8 developed major clinical complications). Among untreated controls, a third liver biopsy was performed in only 1 of 10 patients (2 did not provide the informed consent, and 7 developed major clinical complications). The last liver biopsy was performed at 11.9 ± 1.2 years (median, 11.4; range, 10.4 to 13.9), 11.2 ± 0.9 years (median, 10.9; range, 10.4 to 12.7), and 11.8 years after the initial biopsy in patients treated with 9 million units or 3 million units and the untreated control, respectively. Patients treated with the high dose showed in the last liver biopsy a significant improvement in the activity grade ($P = 0.0004$) with respect to interface hepatitis ($P = 0.002$), lobular necrosis ($P = 0.004$), and portal inflammation ($P = 0.003$), as well as in the fibrosis stage ($P = 0.007$) and in the total histologic activity index ($P = 0.0004$) (Table 3). Strikingly, in 4 of the 6 patients with a sustained biochemical response, all of whom had active cirrhosis in the first 3 liver biopsies, we documented an absence of fibrosis in the last liver biopsy (Figures 4 and 5), obtained after a mean of 11.5 years following completion of therapy. Interestingly, such regression was associated with a significant decrease in HDV viral load. Viremia became undetectable 13 months before the last liver biopsy in one patient and was cleared after the liver biopsy in another patient. The absence of detectable liver fibrosis was associated with loss of IgM anti-HD, improvement in albumin levels, and decrease in γ-globulin levels. The seventh patient with a long-term biochemical response, who had lost both HDV RNA and HBsAg, refused to undergo a liver biopsy. In the low-dose group, there were no significant changes in liver histology over time. In the single untreated control who underwent a third liver biopsy, the activity grade had deteriorated and the stage of fibrosis (stage 4) did not improve.

**Discussion**

Our long-term follow-up study confirmed that the efficacy of interferon in chronic hepatitis D is related to the dose of the drug. It is remarkable that half the patients who had a biochemical response at the end of treatment with 9 million units of interferon (for 48 weeks) continued to have normal ALT for up to 14 years after the termination of therapy. Interestingly, all patients with persistent ALT normalization had a decline in antibody titer and ultimately a loss of serum IgM anti-
HD, which is considered to be the best marker of resolution of disease activity.\textsuperscript{27}

A surprising finding of our earlier study was that a sustained biochemical response occurred despite the persistence of viremia, as measured by dot-blot hybridization.\textsuperscript{21} Here, in which serum HDV RNA was quantified with a more sensitive technique (PCR), we demonstrated that high doses of interferon exerted, in addition to the early beneficial effects on liver-enzyme values and viral load, later effects that significantly improved hepatic function and liver histology. Remarkably, the histologic improvement seen in patients treated with high doses of interferon correlated with a better long-term clinical outcome and survival. Interestingly, none of the patients treated with high doses of interferon developed HCC, as compared with 2 patients in the low-dose group and 2 in the control group, which suggests that high doses of interferon may also decrease the risk of developing liver cancer, as already reported for chronic hepatitis C.\textsuperscript{28}

In this study, clinical, biochemical, virologic, and histologic features were evaluated longitudinally over a 12-year period in a cohort of patients treated with interferon. However, the high frequency of death and liver transplantation among patients treated with the low dose of interferon and among untreated controls significantly affected the number of patients eligible for a follow-up liver biopsy, providing further evidence of the long-term

Figure 5. Photomicrographs of liver biopsy specimens obtained from a patient with chronic hepatitis D before and 12.8 years after the completion of treatment with 9 million units of interferon $\alpha$-2a. A shows a specimen obtained before treatment. An active micronodular cirrhosis with small nodules surrounded by wide fibrous septa is seen (picrosirius stain, 25\texttimes). B shows a specimen obtained from the same patient 12.8 years after the completion of therapy. Inflammatory activity and fibrosis can no longer be identified in the needle biopsy (picrosirius stain, 25\texttimes). Serum HDV RNA, as measured by nested PCR, became undetectable 13 months prior to the last liver biopsy and HBsAg 14 months after the last liver biopsy; all liver enzymes were normal, and the hepatic function was dramatically improved. At the time of the last liver biopsy, there were no clinical features of portal hypertension: there was no evidence of esophageal or gastric varices at endoscopy, the diameter of the portal vein and of the spleen were normal by ultrasound, and the platelet count was normal.
effects of high doses of interferon on the natural history of chronic hepatitis D. The degree of resolution of the necroinflammatory lesions in patients treated with high doses of interferon was dramatic, even though 71% of them had an initial diagnosis of active cirrhosis. Comparison of the changes in activity grade between the first and the fourth liver biopsy, the latter performed up to 12 years after the end of treatment, showed a highly significant difference. But the most striking finding of this study was the absence of detectable liver fibrosis in the final biopsy of 4 patients who had a long-term biochemical response. Although, in principle, there is no way to exclude the possibility of conversion of active micronodular cirrhosis to less active (or inactive) micronodular variants of cirrhosis in these patients, the absence of fibrosis in the liver biopsy specimens of 4 patients who had an initial diagnosis of active cirrhosis documented in 3 consecutive liver biopsies, is remarkable, especially in that all of the liver biopsy specimens were evaluated without knowledge of the clinical data. Several lines of evidence support the histologic findings of apparent regression of fibrosis. First, the absence of liver fibrosis was associated with persistent normalization of all liver-enzyme values and, more importantly, with a significant improvement in hepatic function. Second, it was associated with a significant loss of IgM anti-HD and a significant and sustained decrease in the levels of HDV replication, leading in some patients to the eradication of HDV (as well as HBV). Third, patients whose biopsy specimens were devoid of fibrosis did not show any clinical features of portal hypertension (data not shown): There was no evidence of esophageal or gastric varices at endoscopy, the diameter of the portal vein and the spleen were normal by ultrasound, and the platelet count was normal. Of note, eradication of both HDV and HBV, associated with an apparently complete reversion of liver fibrosis, has recently been reported in a single patient with active HDV cirrhosis treated with continuous interferon therapy, 5 million units daily for up to 12 years. Likewise, there is a growing list of liver diseases in which specific interventions have been associated with histologic improvement, including regression of fibrosis. Finally, the observations in humans have recently been supported by experimental studies in animal models, which have provided evidence that even advanced fibrosis is reversible.

In this study, within the limitations of our data set, we did not find any determinants or predictive factors that distinguished patients whose advanced fibrosis reversed from those who did not. Moreover, reversion of fibrosis did not occur in all patients with a long-term biochemical response. Whether the progression of liver disease may reach a threshold point, after which fibrosis becomes irreversible, is presently unknown. However, in our study, cirrhosis was diagnosed in all subjects at an early stage by percutaneous liver biopsy because patients with advanced or decompensated cirrhosis (Child–Pugh class B or C) were excluded from this trial. Thus, these data support the hypothesis that not all types of fibrosis are the same and that fibrosis in early cirrhosis may be reversible.

In conclusion, our long-term study provides evidence that high doses of interferon significantly improve the long-term clinical outcome and survival of patients with chronic hepatitis D, even in the presence of initial cirrhosis. Such improvement was substantiated by a significant amelioration in liver-enzyme values, hepatic function, and liver histology. Although this study strongly suggests that reversion of liver fibrosis in not too far advanced cirrhosis (Child Pugh A) is possible, additional studies, both in humans and in animal models, are needed to determine to what extent advanced cirrhosis may be reversible.

References

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