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Effect of interferon therapy on bile duct inflammation in hepatitis C

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Abstract Inflammation of the bile ducts was studied in liver biopsies from patients with chronic hepatitis C to determine whether the frequency of inflamed bile ducts changes with therapy and correlates with other histological variables and expression of class I and II MHC antigens on ductal epithelium. Twenty patients treated at UMMC between 1991 and 1994 underwent needle biopsies of the liver before and after therapy with interferon alpha 2B (IFN). A complete response to therapy was defined as a return to normal serum alanine aminotransferase levels occurring and persisting during therapy. The number of inflamed bile ducts/total ducts (%IBDs), presence of piecemeal necrosis and lymphoid aggregates, and grade of inflammation were assessed in each high-power field in all areas with bile ducts. The frequencies of these variables were compared in cirrhotics and non-cirrhotics and in patients with complete or incomplete responses to IFN. Frozen sections of biopsies from 5 patients were immunostained using antibodies to HLA-DR and B-2-microglobulin, and positive staining was noted on bile ducts. Before therapy, the %IBD was slightly greater in patients with cirrhosis. After IFN, both %IBD and serum alkaline phosphatase levels decreased in non-cirrhotics who responded to IFN. The change in frequency of IBD with IFN paralleled the changes in the other histological features. No correlation was noted between bile duct inflammation and expression of class I and II antigens. The conclusion is that inflammation of the bile ducts occurs frequently in chronic hepatitis C, correlates with other features of inflammation in the triads, and decreases in response to IFN therapy.

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Introduction

Bile duct inflammation is a prominent feature of chronic hepatitis of diverse causes [1–3, 11, 12, 14, 16, 17, 22]. It has been reported in up to 90% of patients with chronic viral hepatitis C [1, 3, 11, 12, 14, 22] and may be more frequent in C than B chronic viral hepatitis [14]. The pathogenesis of this lesion during the course of infection is not known. It is also unclear whether the lesion may regress, or progress to duct destruction and loss. Clinically, patients with chronic hepatitis C who are treated with standard-dose interferon alpha 2b (IFN), usually 3 MU three times weekly for 24 weeks, show a clinical response in 30–50% of cases. Histologically, response is associated with a decrease in portal and lobular necrosis and piecemeal necrosis [1, 5, 6, 8, 14, 15, 18, 21, 22], but the effect of IFN on the bile duct lesion has not been described.

The aim of this study was to determine whether the frequency of inflamed bile ducts (%IBD) changes in response to IFN therapy, and whether if this correlates with other features of inflammation, such as piecemeal necrosis (PN), lymphoid aggregates (LA), grade of inflammation, and expression of MHC class I and II antigens on ductal epithelium.

Materials and methods

Patients

Between 1990 and 1994, 80 patients with chronic hepatitis C were entrolled in treatment protocols using IFN at the University of Massachusetts Medical Center. Of these, 20 patients had both pre- and post-therapy liver needle biopsies available for review and constituted the final study group. The diagnosis was based on typical historical, clinical, and histopathological features. All patients were seropositive for HCV by RIBA and seronegative for HbsAg. They had normal serum alpha 1-antitrypsin and ceruloplasmin levels, lacked significantly positive anti-smooth-muscle antibody ti-

ters, and had no other demonstrable liver or biliary tract disease. Clinical, demographic and laboratory data were obtained from the patients' reconds. Values for serum alkaline phosphatase (Alk. phos.), aspartate (AST) and alanine (ALT) aminotransferases were obtained within 2 months of the liver biopsies.

The 20 patients consisted of 15 men and 5 women, ranging in age from 29 to 48 years, mean±SE=38±5 years. Risk factors for infection with hepatitis C included a history of intravenous drug use in 12 patients, infected sexual partner in 2 patients, occupational exposure in 1 health care worker, blood transfusion in 2 patients, and unknown factors in 3 patients. All 20 patients completed a course of IFN (IFN 1) in which they received 3 MU s.c. three times weekly. All underwent a second course of IFN (IFN 2), either 5 MU, or 7.5 MU, or 10 MU three times weekly, or 3 MU three times weekly in combination with levamisole (150 mg p.o. three times weekly). Response to treatment was defined as complete (CR) if the serum ALT became and remained normal during therapy (<40 IU/l). A noncomplete response (NCR) was defined as partial change or none at all in the serum ALT levels during therapy. There were no recognizable clinical or histological differences between the patients treated with levamisole and IFN and those treated with IFN alone.

Liver biopsies

In all, 52 biopsies from the 20 patients were reviewed, including 20 pre-IFN biopsies, 20 post-IFN 1 biopsies, and 12 post-IFN 2 biopsies. All 20 patients had a pre-IFN biopsy at intervals ranging from 2 weeks to 1 year (average 5 months) prior to the first course of IFN. The patients had a second biopsy after the first course of IFN, either because they relapsed or because they did not respond to the first course of IFN. The second biopsies were obtained at intervals ranging from a few days to 1 year (average 5 months) after the first course of IFN as part of an evaluation for a second course of therapy. The second course of therapy was given at intervals ranging from days to months after the second biopsy. In 12 patients biopsies were again taken at the end of the second course of therapy.

Tissue processing

Twelve pre-IFN biopsies were fixed in formalin. All other biopsies were fixed in Carnoy's fixative. All were processed routinely using HE, trichrome and Prussian blue stains. All biopsies had three or more portal triads (the number considered minimally adequate), and no biopsies were excluded from analysis. Blocks from pre-IFN and post-IFN 1 biopsies were available for immunostaining in 5 cases, and 4-μm-thick sections were cut from the paraffin blocks and stained on a BioTek Solutions TechMate 1000 automated immunostainer. The slides were pretreated with a proprietary microwave antigen retrieval method and immunostained with an avidin-biotin complex (ABC) staining procedure (BioTek, Santa Barbara, Calif.) using primary antibodies to monoclonal anti-human HLA-DR, alpha chain (DAKO, Carpinteria, Calif., dilution 1:500) and polyclonal anti-human B-2-microglobulin (DAKO, dilution 1:1000).

Histological evaluation

Knodell Scoring. HE and trichrome-stained slides of the pre- and post-IFN liver biopsies were analyzed blind by a GI pathologist (B.B.). Each biopsy was graded for each category of Knodell's Histology Activity Index [13]: I, periportal necrosis; II, lobular degeneration and necrosis; III, portal inflammation; IV, fibrosis; total score=sum of the component grades. For comparison with bile duct inflammation, the total of components I, II, and III was used as the overall grade of inflammation according to the scheme of Desmet et al. [7].

Semiquantitative assessment of inflammation. In each biopsy, all areas with fibrosis were evaluated at 40×. In noncirrhotic biopsies, most portal triads corresponded to a single 40× high-power field (HPF). In cirrhotic biopsies, all fibrous areas were evaluated. In each HPF the following were assessed: grade of inflammation; 1, scattered WBCs, which do not fill the triad; 2, triad full or overflowing; lymphoid aggregates: present or absent; and piecemeal necrosis: present or absent. The bile ducts were counted, and the number of inflamed ducts was noted. In immunostained sections the total number of bile ducts positive for HLA-DR (MHC class II) and the total number of bile ducts positive for B_2-microglobulin (MHC class I) were counted.

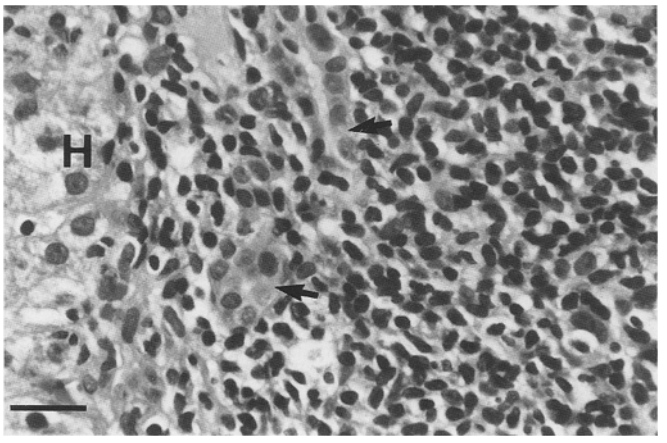

Fig. 1 Photomicrograph of a 40× high-power field (HPF) containing bile ducts (*arrows*) between hepatocytes (*H*) and a lymphoid aggregate in the triad. The longer duct is inflamed. HE, ×400; *calibration bar* 100 μm

Identification of bile ducts

Bile ducts were identified as circular arrangements of cuboidal cells with central round nuclei. Irregular branching ducts were counted as one duct when the epithelium encompassed a single lumen. Because regenerated ducts could not be distinguished from small native ducts in heavily inflamed triads, all ducts were counted equally. Based on the description of "hepatitis-associated bile duct lesion" by Vyberg [22] a bile duct was considered to be inflamed if it showed lymphocytic infiltration and disarray within the epithelium. An example of a typical inflamed bile duct is shown in Fig. 1.

Data analysis

Data are presented as mean±SE. The approximate normality of the differences between pre- and post-IFN biopsies for each variable was evaluated graphically and found to have a reasonably normal distribution. Therefore, comparisons between pre- and post-IFN 1 biopsies were made using a paired Student's *t*-test. The patients were also stratified as cirrhotic (C) or noncirrhotic (NC), and as complete responders (CR) or noncomplete responders (NCR) based on response to IFN 1. The C and NC groups and the CR and NCR groups were compared using the difference between pre- and post-IFN 1 values for each variable in an unpaired Student's *t*-test.

Results

Clinical status and histopathological grading of liver biopsies

All biopsies showed chronic hepatitis. There were 6 patients with cirrhosis in the pre-IFN biopsy, and 14 pa-

Table 1 Mean serum alanine aminotransferase (*ALT*), alkaline phosphatase (*Alk. phos.*), and inflammatory components of the histology activity index for patients grouped by response to interferon (*IFN*) and cirrhosis

Patient group	*n*	ALT	Alk. phos.	Knodell I, II, III
Complete response/no cirrhosis				
Pre-IFN 1	7	151±31	98±57	8±2
Pre-IFN 2	7	124±50	60±13	4±1
Post-IFN 2	4	23±7	48±6	4±1
Noncomplete response/no cirrhosis				
Pre-IFN 1	7	136±59	73±18	5±2
Pre-IFN 2	7	110±42	75±38	5±2
Post-IFN 2	4	41±29	70±42	5±3
Noncomplete response/cirrhosis				
Pre-IFN 1	6	186±86	115±42	7±2
Pre-IFN 2	6	169±78	146±83	7±3
Post-IFN 2	4	166±89	82±28	5±2

tients were noncirrhotic. None of the noncirrhotic patients exhibited cirrhosis in post-therapy biopsies. Seven patients, all noncirrhotic, showed CR to initial standard-dose (3 MU) IFN. They all relapsed when IFN was stopped, and underwent a second course of IFN. In this group, 4 patients had a liver biopsy after the second course of IFN. The other 13 patients, 6 cirrhotics and 7 noncirrhotics, were noncomplete responders. All underwent a second course of therapy, to which 3 patients responded, and 10 did not. Eight patients in the NCR group had a biopsy after IFN 2. In Table 1, the pre-IFN 1, pre-IFN 2, and post-IFN 2 mean serum ALT and Alk. phos. values and inflammatory components (I, II, and III) of Knodell's HAI scores are shown. The patients are grouped as complete responders with no cirrhosis (n=7), noncomplete responders with no cirrhosis (n=7), and noncomplete responders with cirrhosis (n=6). The serum ALT and Alk. phos. values were obtained from 1 to 6 months before the biopsies. The interval between the pre-IFN biopsy and course of IFN 1 ranged from 2 weeks to 18 months. The interval between the biopsy prior to a second course of therapy and the second therapy ranged from a few days to 1 year.

Number of bile ducts/HPF

Since the cirrhotic biopsies were all in the nonresponder group, the number of bile ducts per HPF (BD/HPF) was compared in cirrhotic and non-cirrhotic biopsies to determine whether there was a significantly higher number of bile ducts in the cirrhotics, which might introduce a bias in the comparison of the CR and NCR groups. In the pre-IFN biopsies, the mean numer of BD/HPF for cirrhotics was 3.1±0.06 and that for noncirrhotics 2.5±0.07 (not significant). Post-IFN 1 values for cirrhotics and noncirrhotics were 2.6±1.0 and 2.2±0.05 (not significant). Post-IFN 2 values were 3.1±0.05 and 2.3±0.06 (P=0.03). The pre- and post-IFN biopsies were therefore considered comparable in the density of bile ducts per HPF.

Frequency of bile duct inflammation

Inflamed bile ducts were identified in all except one pre-IFN biopsy (95%), in 17 of the 20 (85%) biopsies taken after IFN 1, and in 10 of the 12 (83%) biopsies taken after IFN 2. By definition, bile ducts were identified as inflamed if they had lymphocytes in the epithelial layer with or without epithelial disarray, as shown in Fig. 1. There was no correlation between the histological appearance of the inflamed ducts and the therapy status of the patients, the degree of portal inflammation around the ducts, or the presence of cirrhosis. The percentage of inflamed bile ducts (%IBD) in pre-IFN 1, pre-IFN 2 and post-IFN2 biopsies and the serum alkaline phosphatase values for individual patients are shown in Figs. 2 and 3. The pre-IFN2 biopsies and serum enzyme levels were obtained when patients were being evaluated for a second course of IFN on the grounds of relapse or nonresponse to the first course of IFN. No data were available

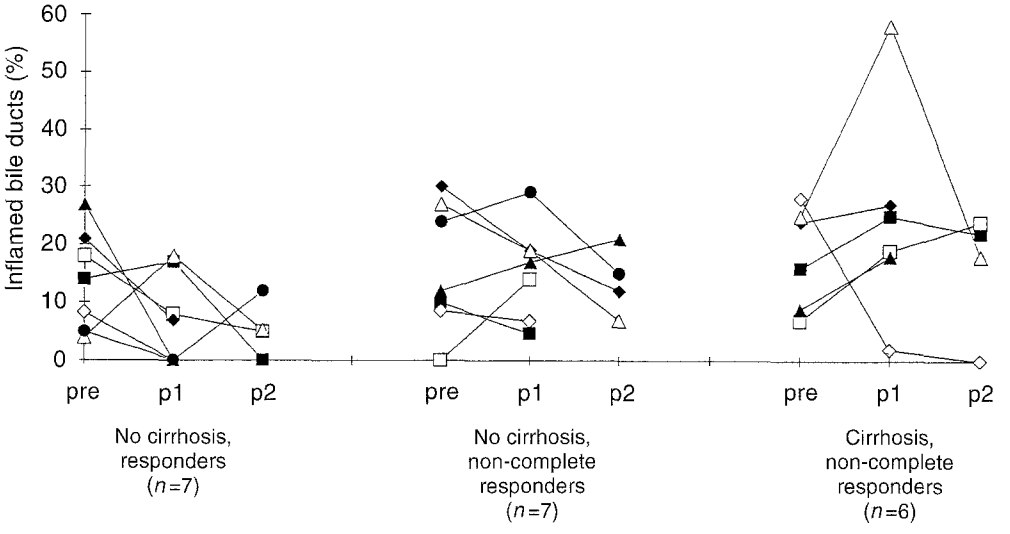

Fig. 2 Percentage of inflamed bile ducts (%IBD) pre- and post-IFN 1 and 2 for each patient. Patients are grouped as complete responders, and noncomplete responders with and without cirrhosis

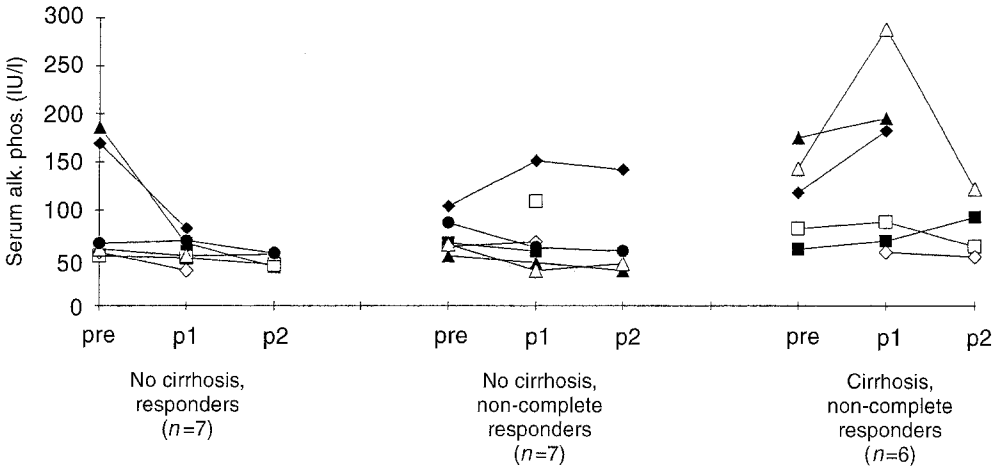

Fig. 3 Serum alkaline phosphatase pre-IFN and post-IFN 1 and 2 for each patient. Patients are grouped as complete responders and non-complete responders with and without cirrhosis

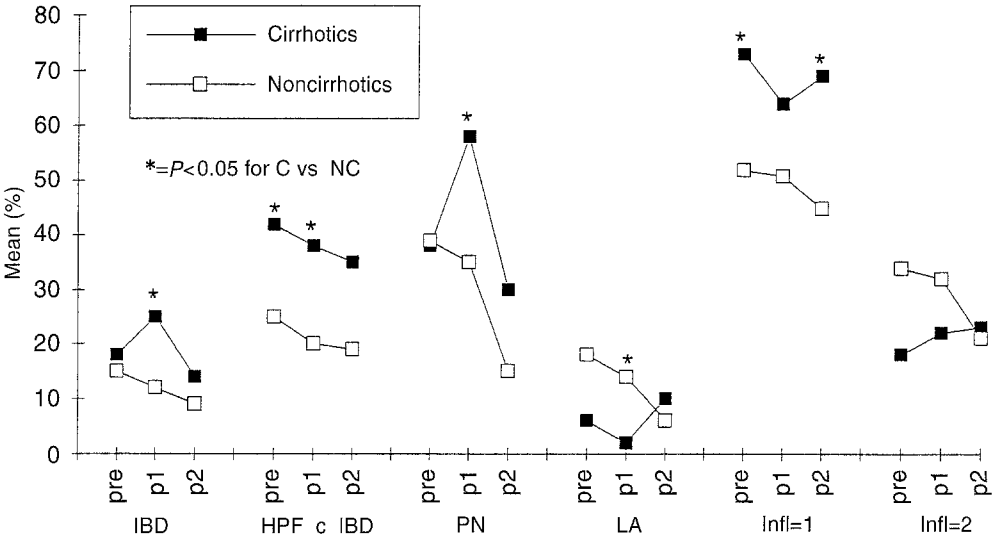

Fig. 4 Comparison of the frequencies of inflamed bile ducts (*IBD*), HPF with IBD, piecemeal necrosis (*PN*), lymphoid aggregates (*LA*), and inflammation grades 1 and 2, in cirrhotics and noncirrhotics pretherapy, and post-IFN 1 (*p1*) and IFN 2 (*p2*). Decrease in bile duct inflammation with IFN therapy correlated with similar trends in PN, LA and grade of inflammation in the noncirrhotic group. No correlation is seen in the cirrhotic group between the histological variables before and after IFN therapy

for these values immediately after the first course of IFN. There was a tendency for the percentage of inflamed bile ducts to decrease over the course of therapy in the noncirrhotics who responded to IFN, particularly high-dose IFN retreatment. Nonresponders, with or without cirrhosis, showed a more variable picture, with poor correlation between %IBD and IFN therapy. Changes in serum alkaline phosphatase after IFN paralleled the changes in frequency of inflamed bile ducts, with a tendency for the serum alkaline phosphatase to decrease eventually after IFN in noncirrhotics who responded to IFN. Cirrhotics showed poor correlation between improvements in serum alkaline phosphatase and response to therapy.

Comparison of the frequency of bile duct inflammation with other histological parameters

A comparison of histological variables between cirrhotics and non-cirrhotics is shown in Fig. 4. Cirrhotics and noncirrhotics did not differ in the mean number of bile ducts per HPF. However, the percentage of inflamed bile ducts, percentage of inflamed bile ducts per HPF and percentage of triads with PN and grade 1 inflammation was higher in cirrhotics than in noncirrhotics. Although not statistically significant after treatment there was a definite trend toward a decrease in bile duct inflammation, PN, LA, and grade of inflammation, particularly in the noncirrhotic group. No correlation between the histological changes before and after IFN therapy was seen in the cirrhotic group.

The comparison of histological features between responders and noncomplete responders is shown in Fig. 5. Again, although not statistically significant, there was a tendency for the percentage of inflamed bile ducts and HPFs with inflamed bile ducts to decrease with IFN therapy in patients with CR. The frequency in patients with NCR was variable. Decrease in bile duct inflammation correlated with a decrease in lymphoid aggregates and inflammation grade 2 in responders. The other variables showed poor correlation between pre- and post-therapy biopsies, and between CR and NCR patients.

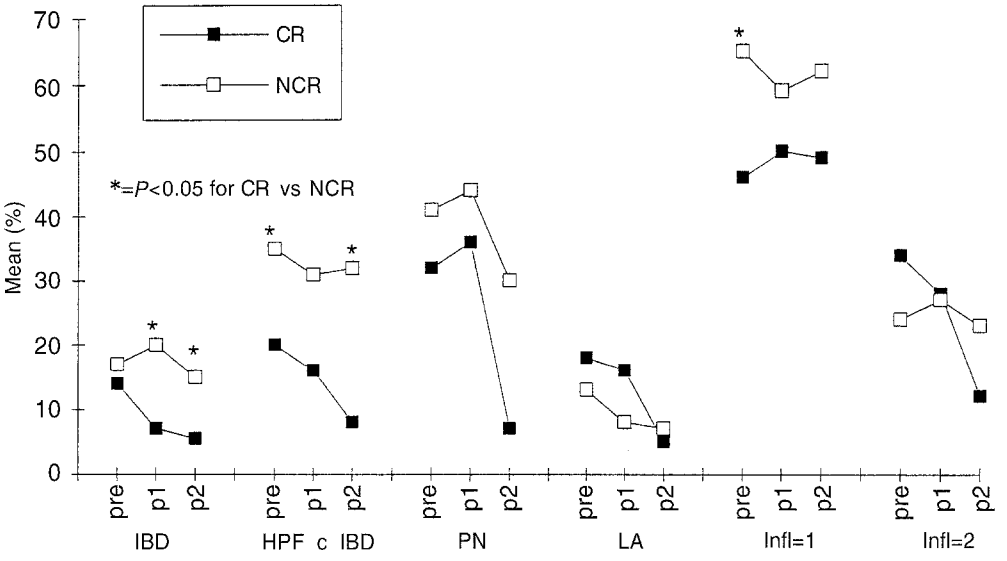

Fig. 5 Comparison of the frequencies of IBD, PN, LA, and inflammation grades 1 and 2, in complete responders (*CR*) and noncomplete responders (*NCR*). There is a tendency for bile duct inflammation to decrease in frequency with IFN therapy in patients with complete response. The frequency in patients with noncomplete response is variable. Decrease in bile duct inflammation correlates with a decrease in lymphoid aggregates and inflammation grade 2 in responders. The other parameters show poor correlation between pre- and post-therapy biopsies, and between CR and NCR

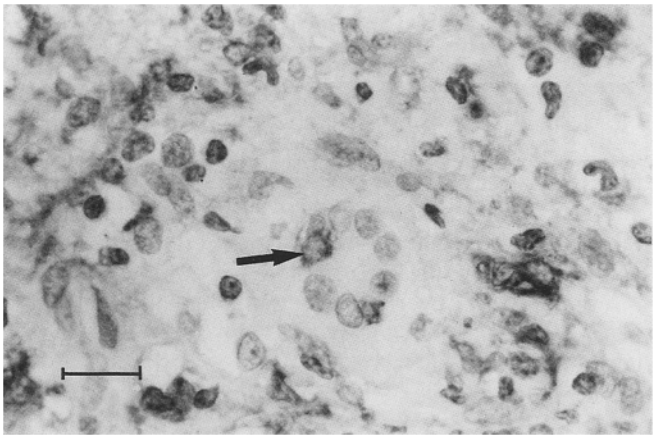

Fig. 6 Photomicrograph of a pre-therapy biopsy showing expression of HLA-DR on bile duct epithelium (*arrow*) and on inflammatory cells in the triad. ABC immunostaining, ×600; *calibration bar* 70 μm)

Expression of class I and II antigens on bile duct epithelium in 5 patients before IFN and after IFN 1 and 2

In 5 patients who were nonresponders (3 cirrhotic, 2 noncirrhotic), expression of class II antigen was found in up to 25% of bile ducts before IFN therapy. After IFN 1, 3 patients showed a decrease in the frequency of positive ducts, and 2 patients showed an increase. Immunostained post-IFN 2 biopsies were available for only 2 patients; one of these showed an increase, and the other a decrease, in frequency of bile ducts positive for class II antigen. Positive staining for HLA-DR was noted on hepatocytes in 4 cases, and diffusely on sinusoidal lining cells and inflammatory cells in all cases. Portal lymphoid aggregates, when present, were also positive for HLA-DR. No change in the expression of HLA-DR with therapy could be detected.

Expression of class I antigen was found in up to 40% of pre-IFN biopsies; in 1 patient 100% of the ducts appeared to be positive. Positive staining was also noted on hepatocytes, particularly in areas of inflammation, inflammatory cells, sinusoidal lining cells, and portal stromal cells. There was no correlation between positive immunostaining for B2-microglobulin and IFN therapy.

Discussion

Inflammation of the bile ducts has long been known to occur in chronic biliary tract disorders. Poulsen and Christoffersen first drew attention to this finding in viral hepatitis, both acute and chronic [16]. In their detailed histological description of the lesion in chronic aggressive hepatitis, Christofferson et al. [2] noted bile duct inflammation in 37% of the biopsies studied. They included patients with hepatitis B, autoimmune hepatitis, and probably hepatitis C. Other studies, including serologically proven patients with hepatitis C, reported bile duct inflammation in 91% [1], 31% [14], 57% [3], and 34% [12] of biopsies. The expected frequency of bile duct inflammation in most series of hepatitis C is 25–30% [22]. The high frequency (91%) in our study may reflect the fact that we focused on the bile duct lesion with careful examination of all the bile ducts in each biopsy. Another factor may have been a bias towards more severe cases in our study, since all 20 patients were under consideration for a second course of IFN. Bile duct damage is thought to be more frequent in hepatitis C than in hepatitis B [14].

Histologically the bile duct lesion has been well described in several studies and reviews [1, 2, 12, 17, 22]. The lesion is characterized by lymphocytic infiltration of bile duct epithelium in small or medium-sized ducts, often in triads that also exhibit inflammation, lymphoid aggregates or PN. The duct epithelium may show multilayering and cellular changes of hydropic swelling and nuclear pyknosis [22]. An example of bile duct inflammation is illustrated in Fig. 1. Bile duct inflammation is

patchy or segmental [15, 17], and not all triads in a biopsy are equally affected. Whether inflammation progresses to loss of bile ducts is not known, but bile duct loss has been reported in some studies [1, 12, 22]. Vyberg [22] suggests that the wide variation in frequency of bile duct inflammation reported may depend on the number of serial sections, care with which the lesions are sought, and the interpretation of findings observed.

In analyzing our data we found that we had to define arbitrarily what would be counted as a single duct, particularly when ducts were buried in inflammation or merging with parenchyma at the edge of the triads. We defined a duct as a circular arrangement of cuboidal cells with central round nuclei. Using these criteria, the only problem was to distinguish ducts from vessels lined by plump endothelial cells. In general, however, endothelial nuclei tended to be relatively larger and fusiform. Another interpretive problem was to distinguish native from regenerating ducts (Vyberg's type I, II, and III lesions), and single irregular ducts from multiple ducts in heavily inflamed triads. Therefore, we arbitrarily counted each duct with epithelium encompassing a single lumen as one duct. Thus, all ducts were equally represented.

Another problem was that the cirrhotic biopsies contained more reduplicated ducts than the non-cirrhotic biopsies. It often was difficult to distinguish native ducts from reduplicated ducts. Therefore, we scanned all the biopsies at 40×, counted all the ducts and inflamed ducts in all fibrous areas, and expressed the counts per HPF. We found that the number of bile ducts per HPF was higher in cirrhotics only after the second course of high-dose IFN. Whether this was due to additional therapy or to the natural progression of cirrhosis is uncertain. Before or after only one course of (standard-dose) IFN, the biopsies with and without cirrhosis appeared to be comparable with respect to the number of bile ducts per HPF.

With data gathered in this manner we detected inflamed bile ducts in 95% of the pre-IFN biopsies. We also noted a tendency for a decrease in frequency of inflamed bile ducts with IFN therapy. As seen in Fig. 2, this was only noticeable in patients without cirrhosis who responded to IFN. We considered the fact that the biopsies and serum enzymes after IFN 1 were not obtained immediately at the end of the course of therapy, but rather at intervals of days to 1 year after therapy, when the patients were being evaluated for a second course of high-cose IFN. The biopsies taken after IFN 2 were taken at much shorter intervals from the end of therapy, from days to 2 months, and were felt to represent the patients' status at the end of a course of therapy more accurately. Given this caveat, there is still a noticeable trend toward a decrease in frequency of inflamed bile ducts and decreased serum alkaline phosphatase levels over the course of therapy, suggesting a resolution of inflammation in response to IFN. The trend toward decreased frequency of bile duct inflammation with therapy correlated with similar trends in PN, LA, grade of portal inflammation, and serum alkaline phosphatase. Previous studies revealed that patients treated with standard-dose (3 MU) IFN show a clinical response in 30–50% of cases. Histologically, response was associated with a decrease in portal and lobular necrosis and PN [5, 6, 8, 15, 18, 21, 22]; an effect of IFN on the bile ducts was not described. Serum HCV-RNA levels were not available for our patients for the time period of this study. However, 4 patients who had a decrease in %IBD with therapy had HCV-RNA levels determined by a branched-chain DNA technique in 1995: these were within the normal range for 3 and elevated for 1. Although we do not know the pre-therapy HCV-RNA levels, it is likely that the first 3 patients cleared the virus, and the 4th did not. Changes in serum HCV-RNA levels have been shown to correlate with changes in serum ALT values after therapy [9]. Thus, serum ALT levels were used in this study to follow response to therapy.

Our study did not address the issue of loss of bile ducts due to inflammation, as reported in some studies [1, 3, 22]. The accepted definition of bile duct loss is absence of the duct of comparable size adjacent to the artery in a triad [1, 3]. However, we found this criterion difficult to use in cirrhotic biopsies and in noncirrhotic biopsies with heavily inflamed triads. Also, our samples did not include a sufficient number of triads with recognizable arteries to assess for loss of ducts. However, we did find that the number of bile ducts/HPF was the same before and after therapy for both cirrhotic and non-cirrhotic biopsies, suggesting that loss of bile ducts was not significant during the time frame of this study. The question remains, however, whether reduplicated ducts differ from native ducts in their potential to become inflamed, damaged, lost, or salvaged by IFN.

The mechanisms of bile duct inflammation in viral hepatitis is not known. Activated lymphocytes are involved [12]. Some observers have noted increased expression of class I and II antigens on bile ducts [19, 20] while others have not [4, 12]. While HLA-DR is expressed on inflammatory cells in portal triads, the mechanism of bile duct injury does not appear to involve increased expression of HLA-DR on bile ducts [4, 12] and thus differs from the mechanism of primary biliary cirrhosis. It has been suggested that bile duct injury may be due to an effect of the virus on the ducts [10]. In our study, attempts to demonstrate class I and II antigen expression showed no correlation with frequency of bile duct inflammation or IFN therapy. Only 5 patients had frozen tissue available for immunostaining, and all had some bile ducts (up to 25%) positive for HLA-DR before IFN. Two patients showed a slight increase in frequency after IFN 1, and 3 showed a decrease. Class I antigen was strongly expressed in ducts, endothelial cells and inflammatory cells, with no apparent correlation with IFN therapy.

In summary, a detailed histological analysis of liver biopsies from 20 patients with chronic hepatitis C showed inflammation of bile ducts in 95% of pre-IFN liver biopsies. The frequency of inflamed bile ducts was greater in cirrhotic patients, showed a tendency to decrease with response to therapy, particularly in noncir-

rhotics, and correlated with similar changes in other variables for inflammation in the triads. Expression of HLA-DR antigen was found in up to 25% of triads in pre-IFN biopsies, but there was no correlation with other variables or response to IFN.

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