biologic parameters, particularly no autoantibodies or defined autoimmune diseases, significantly associated with interferon treatment.

Discussion

This prospective study of 321 patients chronically infected with HCV found a high prevalence of both clinical and biologic extrahepatic manifestations, and an association between some manifestations and the presence of mixed cryoglobulins. The extrahepatic clinical manifestations were particularly frequent: 38% of patients presented at least 1, with a preponderance of rheumatic (19%) and cutaneous (17%) symptoms. Purpura of the lower limbs, Raynaud phenomenon, and pruritus were the primary cutaneous symptoms, concordant with previous results (24, 25, 67, 68). On the other hand, in the present study the frequency of porphyria cutanea tarda, lichen planus, and psoriasis did not exceed those noted in the general population (1% to 2%). Previous studies (20, 21, 28) found a higher frequency of HCV infection in groups of patients with chronic porphyria cutanea tarda, and our results regarding this manifestation may thus appear contradictory. Nonetheless, other studies have also found much lower prevalences (0 to 18%) of porphyria cutanea tarda in HCV patients (49, 60, 76, 82). It seems that the frequency of HCV infection in patients with porphyria cutanea tarda is greater when cirrhosis is present: 60% and 91% in previous studies (22, 43). In our study, the low prevalence of porphyria cutanea tarda may be due to moderate intensity of liver lesions with relatively few cases of cirrhosis. The prevalence of psoriasis and lichen planus were similar to those previously reported by other French teams (20, 46) but lower than those found in Italian and Spanish studies (59, 77).

Sicca symptoms of mouth and/or eye were noted in approximately 10% of our cases. It has been reported (5, 40, 54) that 10%–20% of HCV patients present either mouth or eye sicca symptoms, whereas less than 5% of patients with defined Sjögren syndromes are carriers of HCV (3, 45). Characterized Sjögren syndromes (defined by xerostomia, xerophthalmia, histologic stages III or IV in the Chisholm scale, and anti-SSA or anti-SSB antibodies) were much rarer in HCV patients (9, 45, 47, 88) and were only observed in 1% of our patients. Rheumatologic symptoms were frequent, as 19% of patients suffered from arthralgia. Arthritis and myalgia were rare (2%) and were attributed to nonerosive and nonrheumatoid arthritis, as has been previously noted (83, 78, 86). Connective tissue or autoimmune diseases were observed in 14% including 15 cases of symptomatic mixed cryoglobulinemia, 9 cases of systemic vasculitis, and 6 cases of systemic lupus erythematosus. These relatively high prevalences might reflect enrollment bias, as they came exclusively from internal medicine departments where severe extrahepatic manifestations such as systemic vasculitis are more frequently encountered. However, the severe symptomatic cryoglobulinemia and systemic vasculitis correspond to that noted in other studies (11, 17, 23, 53). The frequency of symptoms in patients with cryoglobulins was 20% (24, 52). Other autoimmune or connective tissue diseases such as rheumatoid arthritis (8, 51) and dermatomyositis (33) are uncommon in HCV-positive patients, suggesting a chance association.

Mixed cryoglobulins are the predominant extrahepatic biologic manifestation of chronic HCV infection, identified in 56% of all patients (1, 4, 12, 15, 31, 57, 90). Their frequent association with a positive rheumatoid factor (36%), essentially in type II cryoglobulins, was expected given its accredited rheumatoid activity. The only significant clinical symptom associated with cryoglobulins following the multivariate analysis is vasculitis (11, 17, 23, 53). We found no association between positive cryoglobulins and the severity of liver histologic damage (24, 29, 52), or HCV genotypes (35, 89, 91).

Systematic search for a multitude of autoantibodies in all our HCV-infected patients revealed high prevalences of antinuclear, antinuclear, antihy- roglogulin, and antismooth muscle cell. These results are in agreement with most (2, 14, 67, 71, 75) though not all (7) previous studies. For several reasons this overproduction of autoantibodies does not appear to be related to a nonspecific polyclonal activation of B lymphocytes by the HCV itself. Only some autoantibodies among all of those tested were found positive (see Table 2). While 70% of patients carried at least 1 autoantibody, only 13% had 3 or more antibodies. Other studies have shown similar results with high prevalences of specific antibodies including antinuclear (20% to 4%), antismooth muscle cell (20% to 22%), antihyoglogulin (8% to 12%) and antinuclear (20% to 22%) (14, 67, 71, 75, 85). When 1/80 is defined as the minimal threshold for positive antinuclear (84), 42% of our patients tested positive, whereas with a threshold of ≥1/160, only 11% did (2, 67, 68). In our study the presence of antinuclear antibodies was not correlated with HIV status since 42% of HIV-negative and 34% of HIV-positive patients tested positive for these antibodies. The case of antinuclear antibodies is noteworthy because in our HCV patients, antinuclear antibodies seemed to be directed against an unidentified antigen, as specificity usually excluded antibodies to DNA, histones, soluble nuclear antigen, or nucleosome. The prevalences of these specific antibodies in our series was between 2% and 3% (see Table 2). One explanatory
hypothesis is that HCV directly or indirectly modifies the configuration of nuclear antigens. The high prevalence of antinuclear antibodies antibodies compared to those already noted in 2 previous studies (2, 68). In our previous study (14), where 20% of the HCV patients carried antinuclear antibodies, there were no associated significant increases in anti-β2 glycoprotein 1 antibodies, thrombocytopenia, or arterial or venous thrombotic events. These antinuclear antibodies can presumably be regarded as "postinfectious" without pathologic potential. Therefore, the few cases of associated HCV and antiphospholipid syndromes are likely coincidental.

Some authors (16, 63) have reported increased prevalence of diabetes mellitus in patients with HCV chronic infection. However, such association was reported in patients with non-insulin-dependent diabetes mellitus. It is then not surprising that in our cohort of HCV patients we did not find an overproduction of autoantibodies usually present in patients with autoimmune insulin-dependent diabetes mellitus such as antiinsulin, antiLangerhans islet, and antilutamic acid decarboxylase antibodies.

The only association observed between clinical and biologic extrahepatic manifestations was in patients with mixed cryoglobulins. Multivariate analysis showed that such patients presented more systemic vasculitis and rheumatoid factors (see Table 3). There was no other association observed between biologic and clinical symptoms (noted in Table 1), including all cases of autoantibody positivity.

A significant proportion of patients were on interferon treatment at the time of enrollment for various durations. This would have skewed the overall prevalence of clinical manifestations and biologic abnormalities, some of which may improve with interferon treatment. Multivariate analysis, however, revealed that interferon alpha treatment was positively associated with vasculitis and negatively associated with HIV positivity. The association with vasculitis is to be expected because interferon alpha therapy was often prescribed to treat systemic vasculitis, often associated with a cryoglobulin (58), and because no vasculitis occurred subsequent to interferon treatment. The negative association with HIV positivity is less surprising given that at the time of study, anti-HIV triple therapy was not applied. There was no association between interferon alpha therapy and defined autoimmune diseases or autoantibodies, including antinuclear which were positive in 41% and 43% of treated and nontreated patients, respectively. Although interferon alpha has been reported in animal models (38, 79) and suspected in humans (65, 66) to induce autoimmune diseases, there has been no clinical evidence or any large prospective studies in humans validating this effect. Since the number of patients with a connective tissue or autoimmune disease was small and about half were treated with interferon alpha, this study does implicate interferon alpha as a causal factor.

Although coinfections of HCV and HIV are frequent (ranging from 20% to 50%) (26, 27, 42, 44, 72–74, 81), few studies have attempted to evaluate the differences between HCV patients who are either HIV positive or HIV negative (44, 93). In this series multivariate analysis showed several significant differences between the 242 HIV-negative and 74 HIV-positive cases. The lower prevalence of arthralgia and myalgia in HIV-negative patients might be related to an underestimation of these symptoms considering the numerous more severe complications associated with HIV infection. The far lower percentage of HIV-positive patients receiving interferon alpha was due to the absence of anti-HIV triple therapy at the time of this study. Considering the relatively short life expectancy of these HIV-positive patients, treatment of their HCV infection was not then considered a priority. The relatively high prevalence in HIV-positive patients of antiphospholipid antibodies and thrombocytopenia has already been reported, and appears to be amplified due to the coinfection of HCV and HIV (27, 44). Subsequent to the discovery of anti-HIV triple therapies and increased survival rates of HIV patients, the evaluation of the severity of HCV infection in such cases appears particularly relevant. In our study the hepatic effects of HCV seemed more severe in the cases of HIV-positive patients, who had higher Knodell (p = 0.0004) and Metavir scores (p = 0.0003). However, the small number of HIV-positive patients who underwent liver biopsies limits the scope of this conclusion. Our finding that HIV-positive patients appear to have more severe HCV infections implies they might benefit from early management of the HCV.

Due to lymphotropism of HCV, a possible role of this viral agent has been suggested in the development of B-cell non-Hodgkin lymphoma, in particular in patients with HCV-mixed cryoglobulinemia (30, 32, 55, 56, 92). Conflicting results have been reported, probably depending on geographic origin of patients and type of malignant lymphoproliferative disease (37, 41). In this cross-sectional study, we did not study specifically the prevalence of lymphoproliferative disease. However, it is conceivable that only a long-term study would show a significant increase in the prevalence of non-Hodgkin lymphoma in HCV patients (34).

Summary

From January 1996 to January 1997, 321 patients with an average age of 46 ± 16 years and chronically infected with hepatitis C virus (HCV) were prospec-
tively enrolled in a study designed to determine the prevalence of extrahepatic manifestations associated with HCV infection in a large cohort of HCV patients, to identify associations between clinical and biologic manifestations, and to compare the results obtained in human immunodeficiency virus (HIV) - positive versus HIV-negative subsets. In a cross-sectional study, clinical extrahepatic manifestations, viral coinfections with HIV and/or hepatitis B virus, connective tissue diseases, and a wide panel of autoantibodies were assessed.

Thirty-eight percent (122/321) of patients presented at least 1 clinical extrahepatic manifestation including arthralgia (60/321, 19%), skin manifestations (55/321, 17%), xerostomia (40/321, 12%), xerophthalmia (32/321, 10%), and sensory neuropathy (28/321, 9%). Main biologic abnormalities were mixed cryoglobulins (110/196, 56%), thrombocytopenia (50/321, 17%), and the presence of the following autoantibodies: antinuclear (123/302, 41%), rheumatoid factor (107/280, 38%), antiparticle (79/298, 27%), antithyroglobulin (36/287, 13%) and anti-smooth muscle cell (27/288, 9%). At least 1 autoantibody was present in 210/302 (70%) of sera. By multivariate logistic regression analysis, 4 parameters were significantly associated with cryoglobulin positivity: systemic vasculitis (p = 0.01, odds ratio [OR] = 17.3), HIV positivity (p = 0.0006, OR = 10.2), rheumatoid factor positivity (p = 0.01, OR = 2.8), and sicca syndrome (p = 0.03, OR = 0.27). A definite connective tissue disease was noted in 44 patients (14%), mainly symptomatic mixed cryoglobulinemia and systemic vasculitis. HIV coinfection (23%) was associated with 3 parameters: antiparticle (p = 0.003, OR = 4.18), thrombocytopenia (p = 0.01, OR = 3.56), and arthralgia or myalgia (p = 0.017, OR = 0.23). HIV-positive patients presented more severe histologic lesions (p = 0.0004).

Extrahepatic clinical manifestations in HCV patients involve primarily the skin and joints. The most frequent immunologic abnormalities include mixed cryoglobulins, rheumatoid factor, antinuclear, antiparticle, and anti-thyroglobulin antibodies. Cryoglobulin positivity is associated with systemic vasculitis and rheumatoid factor and HIV positivity. HIV coinfection is associated with arthralgia or myalgia, antiparticle antibodies, and thrombocytopenia.

References

6. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, Healey LA, Kaplan SR, Liang MH, Luthra HS. The American Rheuma-
tism Association 1987 revised criteria for the classification of rheuma-
dies and liver disease in patients with porphyria cutanea tarda. Hepa-
23. Deny F, Bonacorsi S, Guirliev L, Quist L. Association between he-
27. Eyster ME, Diamondstone LS, Lien JM, Ehmam WC, Quan S, Goedert JJ. Natural history of hepatitis C virus infection in multidrug-fused he-