Longterm Efficacy of Interferon-α for Extrahepatic Disease Associated with Hepatitis C Virus Infection

MICHAEL NAARENDORP, USHA KALLEMUCHIKKAL, GERARD J. NUOVO, and PETER D. GOREVIC

ABSTRACT. Objective. To investigate longterm responsiveness to interferon-α (IFN-α) of patients with extrahepatic manifestations of hepatitis C virus (HCV) in a nonendemic area.

Methods. We prospectively evaluated 11 patients with extrahepatic manifestations of HCV infection, including 10 with Type II cryoglobulins, treated with IFN-α — 9 had cutaneous vasculitis, 6 arthralgias, 7 neuropathy, and 4 glomerulonephritis. Liver biopsies were performed on all patients, although 6/11 had normal liver function tests. All received 3 M units IFN-α tiw, with total length of treatment ranging from 3 mo to 5 yrs. Periodic assessments were made of clinical activity, biochemical variables, cryoglobulin quantitation, and HCV copy number.

Results. Three patients were withdrawn because of toxicity. Three were nonresponders at 6, 16, and 17 mo of therapy, based on persistence of HCV RNA in blood, cryoprecipitates, and peripheral blood mononuclear cells. One patient was a partial responder at 3 yrs, with 2 major flares of cutaneous vasculitis occurring on separate attempts to withdraw IFN-α. Three patients (27.2%) were complete responders based on resolution of symptoms (purpura, neuropathy) and disappearance of cryoprecipitates and HCV RNA, but only one successfully tapered IFN-α after 3 yrs of treatment, with sustained resolution at followup 15 mo later.

Conclusion. IFN-α is safely tolerated for prolonged periods in patients with extrahepatic HCV infection, and is particularly effective for treatment of cutaneous vasculitis. Careful monitoring is needed for evolution of liver pathology to cirrhosis, or for progression of renal or neurologic disease. (J Rheumatol 2001;28:2466–73)

Key Indexing Terms: INTERFERON-α CRYOGLOBULINEMIA HEPATITIS C VIRUS

Chronic infection by hepatitis C virus (HCV) may be associated with several overlapping extrahepatic clinical syndromes, including cutaneous vasculitis, neuropathy, arthralgias and/or frank arthritis, and membranoproliferative glomerulonephritis1,2. The precise association varies with the specific syndrome, being most striking among patients with mixed cryoglobulinemia (MC) — the syndrome of purpura, arthralgias, and renal disease — 60–80% of whom are infected with this virus, often for long periods of time3,4. Conversely, 13–54% of patients chronically infected with HCV are found to have cryoglobulins when screened for this laboratory abnormality5,6. Overall, it has been estimated that clinical features of MC develop in only 1–2% of HCV infected persons.

Among patients with chronic hepatitis due to HCV, standard therapy with interferon-α (IFN-α), 3 M units 3 times a week for 6 months, produces a biochemical response in 40–50% and a sustained response in 15–20%. In the same group of patients, the virologic response is 30–40% and 10–20%, respectively; 10–40% of patients require a reduction in dose because of side effects, and treatment must be discontinued in 5–10%6,9. Predictors of favorable response to IFN-α include younger age/lower body weight; short duration of disease; lower (< 1 M/ml) initial viral copy number in serum; absence of fibrosis on liver biopsy; and genotype 2 or 38,10. The first clinical trial of IFN-α for MC was reported in 198711, the description of the HCV genome in 198912. During the early 1990s, clinical series originating almost entirely from Italy, from areas where HCV is endemic, reported short term responsiveness of the clinical manifestations of MC to evolving treatment regimens of IFN-α monotherapy13–18. Subsequent longterm followup studies have shown that most responders relapse, usually within the first 6 months after discontinuation of IFN-α, and a sustained response is seen in only 4–20% of patients19–22.

We investigated the efficacy of IFN-α for patients with extrahepatic disease due to HCV in a nonendemic area, to characterize the clinical and biochemical responses of a well defined group of patients requiring longterm treatment.
MATERIALS AND METHODS

Patients. Clinical, laboratory, and pathologic features of 11 patients are summarized in Table 1. They included 6 men and 5 women, average age 48 years (range 39–68) at the time of diagnosis. Clinical manifestations were purpura in 9 (81.8%), arthralgias/arthritis in 6 (54.5%), neuropathy in 7 (63.6%), and nephritis in 5 (40%). In each case, purpura was documented as due to a leukocytoclastic vasculitis, and nephritis was shown to be membranoproliferative, by biopsy; neurologic involvement was confirmed by nerve conduction studies to be sensorimotor and diffuse or a mononeuritis multiplex in all 7 cases by electrophysiologic testing. Four patients had coexisting sicca syndrome, and one long-standing Crohn’s disease. Duration of disease based on clinical manifestations varied from 5 months to 15 years, with 6 patients having received prior therapy with other agents, including corticosteroids in 5 cases.

Serologic testing revealed that all patients had antiglobulin, i.e., rheumatoid factor (RF), activity restricted to the IgM isotype (positive IgM RF), and 8 (72.7%) had a polyclonal increase in serum IgM that generally reflected disease activity. Ten out of 11 (90.9%) had significant levels of type II (IgMκ-IgGκ) mixed cryoglobulins; one patient treated for ulcerating vasculitis, livedo reticularis, peripheral gangrene of several toes, and progressive peripheral and autonomic neuropathy was repeatedly negative on testing for serum-cryoglobulins, both at diagnosis and throughout the period of followup. Six of 11 patients had evidence of complement activation in blood, based on low levels of the 3rd and 4th components of complement (C3 and C4). Three of the 6 (50%) patients undergoing bone marrow aspiration and biopsy were found to have increased numbers of lymphoid aggregates and/or clonal populations of B cells on flow cytometry, as described in patients with MC without overt non-Hodgkin’s lymphoma23,24.

Evidence of liver disease and HCV infection. No patient gave a history of chronic hepatitis, either previously or corresponding to the onset of symptoms. Only one gave a history of intravenous drug use; 5 patients had received blood transfusions before institution of routine testing of the blood supply for HCV. Laboratory evidence indicating ongoing HCV infection in each patient is summarized in Table 2.

All sera and cryoglobulins were seropositive by Western blot analysis using recombinant HCV antigens, with antibody activity largely restricted to the IgG isotype in isolated cryoglobulins; all contained viral RNA by polymerase chain reaction (PCR) amplification following reverse transcription (RT); none was positive for hepatitis B surface antigen or for other serologic indicators of hepatitis B virus infection. Liver biopsies were performed on all patients before initiation of IFN-α therapy, although only 5/11 were found to have modest elevations of transaminases on serial testing. All biopsies showed chronic hepatitis, with prominent lymphoid infiltrates in 5 and varying degrees of fibrosis in 6; 9/10 biopsies studied by RT in situ PCR25 were found to have viral RNA in hepatocytes in a largely perinuclear distribution (Figure 1). In 7/9 patients studied, HCV RNA was repeatedly present in washed peripheral blood mononuclear cells (PBMC) isolated from heparinized venous blood samples on Ficoll-Hypaque (Pharmacia) density gradients. Genotype analysis was carried out by direct sequencing of the 5′ untranslated (5′ UTR) region of the HCV genome, with one patient being Ia, 3 Ib, 2 Ifb, 3 III, and one IV (Table 2).

Laboratory testing. Cryoglobulins were isolated as described, and were characterized for clonality after rigorous washing by immunofixation and immunoelectrophoresis. The level of cryoglobulin in blood was quantitated by Bradford assay for total protein, and specific immunoglobulin (Ig) isotypes, C3, C4, and RF determined by nephelometric assays26. All patients entering this protocol were PCR positive for HCV RNA, using primers to amplify the 5′ UTR as described22, as well as less conserved NS3/NS4 sequences, in 2 step “nested” amplifications.

The copy number of HCV RNA was assessed by competitive PCR using the Amplicor system (Roche Molecular Systems, Somerville, NJ, USA). Values given for serum are total copy number/ml; to determine the percentage HCV RNA coprecipitating with the cryoglobulin and that remaining in the fluid phase, copy numbers were determined on whole serum, on supernatant remaining after cryoprecipitation, and on cryoglobulins brought to a uniform concentration of 1 mg/ml. Percentage cryoprecipitation refers to the ratio of HCV copy number in the cryoprecipitate to that found for whole serum kept at 37°C before testing; 5–10% cryoprecipitable counts were lost on repeated washing of cryoprecipitates to remove adherent serum proteins. Serial time points for each patient were determined in single runs, and the interassay variability was < 5%.

Human subjects and definition of response to IFN. Enrollment in this study followed a defined protocol; all patients gave informed consent following institutional review board approval. Exclusion criteria were: active alcohol or drug abuse, with abstinence for at least 2 years; other causes of chronic hepatitis; hepatic failure; history of variceal bleeding; debilitating cardiovascular or pulmonary disease; diabetes mellitus; coagulation disorders; history of depression or severe psychiatric disorder; pregnancy; known cryoglobulins; evidence of thyroid disease; known hypersensitivity to IFN-2α, or clinically significant retinal abnormalities. Patients were treated with recombinant interferon-2α (Roferon-A; Hoffmann-La Roche, Nutley, NJ, USA) at a dose of 3 million units 3 times weekly injected subcutaneously. They were seen at 2 and 4 weeks after initiating treatment, and at 4 week intervals thereafter.

Table 1. Clinical, laboratory, and pathologic features.

<table>
<thead>
<tr>
<th>Patient Sex/Age, yrs</th>
<th>Clinical</th>
<th>Duration of Disease, yrs</th>
<th>Prior Therapy</th>
<th>IgM, mg/dl*</th>
<th>Cryoglobulin, mg/ml**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 F 44</td>
<td>P,N,A</td>
<td>5 mo</td>
<td>None</td>
<td>830</td>
<td>1.5–2.7</td>
</tr>
<tr>
<td>2 M 42</td>
<td>A</td>
<td>17</td>
<td>S</td>
<td>112</td>
<td>1.5–2.2</td>
</tr>
<tr>
<td>3 M 52</td>
<td>P,R,A</td>
<td>10</td>
<td>S,A,C</td>
<td>349</td>
<td>0.05–0.38</td>
</tr>
<tr>
<td>4 F 46</td>
<td>P,R,A</td>
<td>12</td>
<td>S,A,H,C</td>
<td>270</td>
<td>0.04–0.84</td>
</tr>
<tr>
<td>5 F 68</td>
<td>P.U,N,R</td>
<td>15</td>
<td>S,A,C</td>
<td>525</td>
<td>2.5–4.2</td>
</tr>
<tr>
<td>6 M 52</td>
<td>P,N,R</td>
<td>12</td>
<td>None</td>
<td>375</td>
<td>1.8–2.5</td>
</tr>
<tr>
<td>7 M 47</td>
<td>P,N,A</td>
<td>4</td>
<td>None</td>
<td>258</td>
<td>0.01–0.08</td>
</tr>
<tr>
<td>8 M 49</td>
<td>N</td>
<td>2.5</td>
<td>S</td>
<td>116</td>
<td>0.08–0.56</td>
</tr>
<tr>
<td>9 F 40</td>
<td>–</td>
<td>7</td>
<td>None</td>
<td>1930</td>
<td>4.4–6.7</td>
</tr>
<tr>
<td>10 F 39</td>
<td>P.U,N</td>
<td>1</td>
<td>H,C</td>
<td>720</td>
<td>0</td>
</tr>
<tr>
<td>11 M 49</td>
<td>P,N,A</td>
<td>1</td>
<td>None</td>
<td>192</td>
<td>0.88–1.4</td>
</tr>
</tbody>
</table>

P: purpura; U: leg ulcers; N: neuropathy; R: renal disease; A: arthralgias/arthritis; H: corticosteroids; A: apheresis; H: hydroxychloroquine; C: cytotoxics. * Normal range for serum IgM 60–370 mg/dl. ** Cryoglobulin quantitation includes range of values obtained at various times over the duration of disease before IFN-α therapy. All patients had RF activity in serum and cryoglobulins.
Response to IFN-α therapy was defined for the initial 6 month treatment protocol, response to reinduction following relapse, and sustained response on long-term followup after discontinuation of IFN-α. A complete response was defined as improvement or disappearance of neuropathy or kidney involvement, disappearance of purpura, normalization of serum alanine aminotransferase (ALT), a 50% reduction in cryocrit, and serum negative for HCV RNA by PCR; a partial response is 10–50% reduction in cryocrit and one (but not all) of the clinical and laboratory signs of systemic disease. Nonresponders were patients not manifesting significant clinical, virologic, biochemical, or immunologic changes during the course of therapy; sustained responders did not have recurrence of any variable over a period of followup > 6 months after discontinuation of IFN-α.

RESULTS
The 11 patients enrolled in this study were all HCV RNA positive and had pathologic evidence for chronic hepatitis, assessed by liver biopsy (Figure 1). Cryoglobulin levels immediately before therapy among the 10 patients found to have Type II cryoglobulinemia ranged from 0.08 to 6.7 mg/ml, and HCV RNA levels quantitated by the Amplicor competitive PCR assay varied from 24,359 copies/ml to 1,204,874 copies/ml (Figure 2). Percentage HCV RNA coprecipitating from serum with highly purified cryoglobulin ranged from 30 to 85%. Notable features among these 11 patients included long duration of prior clinical disease (5 mo to 15 yrs); high incidence of chronic neuropathy (63.6%) and immune complex nephritis (40%); and high incidence of fibrotic changes (45.5%) on liver biopsy. Baseline liver function tests (LFT) were consistently normal in 45.5% before initiation of IFN-α, and alternately normal or minimally elevated in several of the remaining patients (Table 2). Five of 11 were genotype 1a (n = 1) or 1b (4), versus an overall incidence of 58% and 21% among HCV infected persons in the US27; 2/11 (18.2%) were 2b and 3/11 (27.3%) genotype 3, versus 13% and 5% nationally. One patient, an Egyptian male, was genotype 4, most likely reflecting the prevalence of this pan-African genotype in Egypt29.

Initial response to IFN. The initial response to therapy over the first 6 months of treatment is summarized in Figure 2. Prior treatment included corticosteroids (5 patients), plasmapheresis (3), hydroxychloroquine (2), dapsone (1), and cytotoxic agents (4) (Table 1). The total length of treatment with IFN-α ranged from 3 months to 5 years. During the initial period of therapy, 3 patients withdrew because of toxicity (severe depression with suicidal ideation; anemia and leukopenia) or progression of disease (leg ulcers and pulmonary infiltrates), the first at 3 months and the other 2 at 5 months (Figure 2). Two of the 3 had abnormal LFT and fibrotic changes on biopsy before starting IFN-α. At the end of 6 months, the remaining 8 patients were found to be complete (3) or partial (4) responders, and only one patient was a nonresponder. Overall, pretreatment HCV copy number and cryoglobulin level were lower in responders than nonresponders. Serial studies of 2 nonresponders (Patients 1 and 5, Figure 2) showed a striking redistribution of HCV RNA from the cryoglobulin to the fluid-phase fraction of serum in spite of sustained viremia (Figure 3). Of those responding to IFN-α, the most consistent clinical response observed was either partial or complete clearing of purpura during the initial time period; all responders were found to have a progressive drop in ALT and cryoglobulin levels on monthly testing, and 6 patients appeared to have cleared HCV completely from blood, isolated cryoprecipitate and PBMC; 3 of these 6 patients still had significant levels of cryoglobulin on serial testing (Figure 2).

Longterm followup (Figure 4). IFN-α therapy was continued in all partial responders, and was subsequently resumed in complete responders, all of whom relapsed within 6 months after discontinuation of treatment. In spite of the initial response, 3 patients were considered to be overall nonresponders at 6, 16, and a total of 17 months of therapy, based on persistence of HCV RNA in blood, cryoprecipitates, and PBMC — one developed membranoproliferative glomerulonephritis while undergoing treatment and

Table 2. Evidence of liver disease and HCV infection.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Alt*</th>
<th>Liver Biopsy</th>
<th>RT-PCR</th>
<th>HCV PBMC</th>
<th>Genotype</th>
<th>Copies/ml**</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>42–78</td>
<td>H,C,L</td>
<td>+</td>
<td>+</td>
<td>Ib</td>
<td>511,628</td>
</tr>
<tr>
<td>2</td>
<td>71–174</td>
<td>H,F</td>
<td>+</td>
<td>+</td>
<td>IIb</td>
<td>1,204,874</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>H,C,L</td>
<td>+</td>
<td>ND</td>
<td>III</td>
<td>234,320</td>
</tr>
<tr>
<td>4</td>
<td>45–136</td>
<td>H,L</td>
<td>+</td>
<td>+</td>
<td>Ib</td>
<td>1,013,960</td>
</tr>
<tr>
<td>5</td>
<td>30–40</td>
<td>H,L</td>
<td>+</td>
<td>+</td>
<td>Ib</td>
<td>1,013,960</td>
</tr>
<tr>
<td>6</td>
<td>34–68</td>
<td>H,C</td>
<td>ND</td>
<td>+</td>
<td>IV</td>
<td>24,350</td>
</tr>
<tr>
<td>7</td>
<td>24</td>
<td>H</td>
<td>–</td>
<td>–</td>
<td>III</td>
<td>168,170</td>
</tr>
<tr>
<td>8</td>
<td>48–78</td>
<td>H</td>
<td>+</td>
<td>–</td>
<td>III</td>
<td>28,892</td>
</tr>
<tr>
<td>9</td>
<td>30–40</td>
<td>H</td>
<td>+</td>
<td>+</td>
<td>Ib</td>
<td>722,125</td>
</tr>
<tr>
<td>10</td>
<td>35</td>
<td>H</td>
<td>+</td>
<td>+</td>
<td>Ib</td>
<td>64,069</td>
</tr>
<tr>
<td>11</td>
<td>22–92</td>
<td>H,F,L</td>
<td>+</td>
<td>ND</td>
<td>IIb</td>
<td>89,397</td>
</tr>
</tbody>
</table>

H: hepatitis, C: cirrhosis, L: prominent portal lymphoid infiltrates, F: fibrosis. * Normal range 0–40 IU/l. ** HCV copies/ml are values obtained for whole serum just before starting IFN-α therapy. PBMC: peripheral blood mononuclear cells, ND: not done.
one developed clinical and biochemical hyperviscosity syndrome requiring aggressive plasmapheresis. One patient, who had a 12 year history of clinical disease, was a partial responder at 3 years, based on improvement in liver function tests, decrease in HCV RNA, and cryoglobulin quantitation, with 2 major flares of cutaneous vasculitis occurring on separate attempts to withdraw IFN-α. Three patients (27.2%) were complete responders, based on resolution of symptoms (purpura, neuropathy) and disappearance of cryoprecipitates and HCV RNA, but only one successfully tapered IFN-α after 3 years of treatment, with sustained resolution at followup 15 months later. Flares of cutaneous vasculitis appeared in 4 patients after withdrawal of IFN-α, each responding promptly to the reinstitution of therapy. All 3 complete responders were genotype III. Autoimmune phenomena that have been reported to occur with increased frequency with hepatitis or therapy with IFN-α (anti-nuclear/anticardiolipin/antithyroid antibodies) or cutaneous vasculitis (antineutrophil cytoplasmic antibodies) were negative prior to initiation of treatment, and were not found on repeat testing, even after prolonged therapy or clinical disease.

DISCUSSION

The efficacy of IFN-α in achieving clinical, biochemical, and virologic responses in patients with the syndrome of mixed cryoglobulinemia (MC) has been reported in case histories and large series, mostly originating from Italy, Switzerland, and France, from areas in which HCV infection is endemic, both among patients presenting with this

Figure 1. Representative liver biopsy obtained before IFN-α therapy in which HCV RNA was observed after RT-PCR in most hepatocytes at the interphase of cytoplasm and nucleus, and occasionally in Kupffer cells (inset, arrow).
syndrome and in the general population. IFN-\(\alpha\) has also been found to be effective therapy for specific disease manifestations that are associated with MC, or that occur as separate clinical entities associated with HCV infection, including severe vasculitis with leg ulcers, mononeuritis multiplex, and membranoproliferative glomerulonephritis.

We provide long-term followup data regarding the use of IFN-\(\alpha\) for sporadic MC in a nonendemic area among patients presenting for evaluation of extrahepatic disease found to be productively infected by HCV in the course of their initial evaluations. The latter was established by the identification and characterization of HCV RNA in blood, isolated cryoprecipitates, PBMC, and liver, and by serial measurements during the course of treatment.

Significant factors likely to adversely affect outcome include a long duration of disease before initiation of therapy, reflected also in pathologic evidence of chronicity on liver biopsy, and previous therapy with other agents, notably including corticosteroids (Table 1). Two controlled studies have shown improved responses when groups of patients with MC receiving IFN-\(\alpha\) were compared to others receiving steroids alone, and one study found no additional benefit when steroids were added to IFN-\(\alpha\); in addition, steroids have the potential for masking laboratory evidence of hepatic inflammation, reflected in a decrease of abnormally elevated LFT, while raising the level of virus in blood.

As reported, clinical manifestations of cutaneous vasculitis (i.e., purpura) are a particularly sensitive indication of responsiveness to IFN-\(\alpha\), and may begin to clear within weeks of initiation of therapy. This response is usually accompanied by a decrease in the level of cryoglobulin from baseline. The initial level of cryoglobulin is not predictive of the severity of the liver disease (Tables 1 and 2).
and may vary in untreated patients (Table 1), reflecting in turn spontaneous fluctuations in the viral copy number and elevations of transaminases34,35 (unpublished observations). Patient 10 in our series exemplifies the difference that may exist in individual patients between cryoglobulinemia per se and clinical vasculitis — although the activity of her skin lesions (which had previously also manifested as gangrene of several toes) and her HCV copy number varied in parallel, on starting and after withdrawal of IFN-α on 2 occasions, she did not develop detectable cryoglobulin at any time. Similarly, patients have been noted in previous series who clear vasculitis following the initiation of IFN-α without a concomitant decrement in cryoglobulin level 13, and others relapsed after discontinuation with regard to recurrence of cryoglobulins but not of purpura15.

Measurements of HCV copy number are complicated by concentration of viral RNA in cryoprecipitates — 80% and higher36 at baseline — presumed to be due to binding to IgG antibodies directed to various HCV antigens37. Concentration of HCV RNA in the cryoprecipitate allows the possibility that false low or even false negative results may be obtained if care is not taken to avoid loss of cryoprotein during processing38. Among patients with MC responding to IFN-α during the initial 6 month period of treatment, both early and late patterns of viral clearance have been noted that were unrelated to HCV genotype21. This has not been correlated with the kinetics of clearance of viral RNA, particularly with regard to the presence of minus strand replicative intermediates, from PBMC, and the possibility remains that there may be a dissociation between the latter and clearance from the serum in sustained responders39. In 2 patients that we characterized as nonresponders, a significant shift in viral RNA from the cryoprecipitate to the serum supernatant was observed, without concomitant change in the total viral copy number (Figure 3). These preliminary observations, which need to be confirmed at early time points for complete or partial responders, may be due to changes in the stoichiometry of cryoprecipitable HCV.
immune complexes induced by IFN-α, reflecting in turn the level of viral antigens in the complexes or the specificity of the immune response to these antigens. Stoichiometric changes may in turn affect the thermal amplitudes of the cryoglobulins and be manifest particularly in the cutaneous microcirculation, where temperature shifts may directly affect or precipitate ischemic vasculopathy or vasculitis. Thus, clinical and biochemical responses may be observed without clearance of the virus from the circulation or sustained clearance from the host.

By contrast to the cutaneous response to IFN-α monotherapy, which is often rapid and striking, neurologic and renal manifestations, which were prevalent among our patients, are often slow to respond; electrophysiologic improvement may lag considerably behind clinical improvement in paresthesias. Patients may drop out because of progression of neuropathy or because of the apparent de novo development of nephritis. The latter was the case for Patient 6 in our series, who subsequently went on to hepatic failure and died after combined renal and liver transplant. Significant worsening of these clinical manifestations of HCV related extrahepatic disease with IFN-α have been described in several case reports; in addition, paradoxic worsening of cutaneous vasculitis after initiation of IFN-α has also been reported. These adverse reactions could be due to a shift in the stoichiometry of the immune complexes with therapy, uncovering of autoimmunity by IFN-α, or other toxicities.

The biological efficacy of IFN-α may be due to its antiviral, antiproliferative, or immunologic effects. The importance of the antiproliferative effect may be reflected in the regression of B cell proliferation in some patients with MC responding to this agent. Lack of response to IFN-α may be a function of host and viral factors noted above; the development of a host immune response directed against recombinant protein, and/or preexisting genetic polymorphisms that might affect IFN signal transduction, or response elements of cytokines critical to hepatic inflammation or other genes that modulate the various immunologic effects of this agent.

Almost all the patients with MC reported previously and in this study were found to have Type II (IgMk-IgG) mixed cryoglobulins. The clonality of the IgM component of the cryocomplex is even more striking with respect to selective Ig V region gene usage, and may be reflected in the 50–60% incidence of monotypic aggregates noted on bone marrow examination in this series and other studies. Other reports examined the effect of IFN-α on cryoglobulinemia occurring among larger groups of patients with chronic HCV infection being treated primarily for liver disease. In these studies, the overall incidence of cryoglobulinemia among patients with chronic hepatitis due to HCV was 39–46%, 56–67% typable cryoglobulins were Type III (i.e., polyclonal), the incidence of concomitant extrahepatic disease among the cryoglobulin patients was 17–28%, and the sustained response rate was 8–35%.

Thus IFN-α is effective therapy for both type II and type III cryoglobulinemia, but longterm effects are limited by significant occurrence of relapse. Because of difficulty achieving sustained remission off IFN-α, 4 of our patients are currently receiving combination treatment with ribavirin; other protocols, including modified preparations of IFN-α, may increase initial and sustained response rates.

REFERENCES


