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PEGylated Interferon Alfa-2b and Ribavirin Treatment in Patients With Hepatitis C Virus–Related Systemic Vasculitis

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Objective. **Type II mixed cryoglobulinemia (MC) is a systemic vasculitis usually associated with hepatitis C virus (HCV), which may involve the skin, kidneys, and nervous system. Molecular evidence of antigen-driven B cell proliferation is definitively provided in HCV-associated type II MC, and HCV appears to be the key trigger. The present trial was established to investigate the efficacy of therapy with PEGylated interferon alfa-2b (PEG–IFN alfa-2b) plus ribavirin in patients with HCV-related MC vasculitis.**

Methods. **Nine consecutive patients with HCV-related MC received PEG–IFN alfa-2b (1.5 μg/kg/week) subcutaneously plus oral ribavirin (800–1,200 mg/day) for at least 6 months. The response to treatment was analyzed by comparing clinical, immunologic, and virologic parameters at the initial evaluation with those observed during followup.**

Results. **The mean ± SD duration of therapy with PEG–IFN alfa-2b plus ribavirin was 13.5 ± 2.8 months. After a mean period of 18.6 months following discontinuation of treatment, all 9 patients are alive. Seven patients (78%) had a sustained virologic response and were complete clinical responders. Serum cryoglobulin disappeared in 5 of 9 patients (56%), and complement levels normalized in 80% of the patients. One patient had a partial virologic response with a complete clinical response. In another patient, a clinical relapse of MC vasculitis occurred in association with the reappearance of HCV RNA. Treatment was well tolerated, and no patient had side effects for which discontinuation of therapy was required.**

Conclusion. **Treatment with PEG–IFN alfa-2b plus ribavirin can achieve a complete clinical response in most patients with HCV-related MC vasculitis. Complete clinical response correlates with the eradication of HCV and requires a shorter treatment period than that previously reported for IFNα plus ribavirin.**

Mixed cryoglobulinemia (MC) is a systemic vasculitis characterized by the proliferation of B cell clones producing pathogenic IgM with rheumatoid factor (RF) activity (1). MC leads to clinical manifestations ranging from the MC syndrome (purpura, arthralgia, asthenia) to more serious lesions with neurologic and renal involvement (2). Hepatitis C virus (HCV) infection is associated with most cases of MC. Sixty to 80% of patients with MC are HCV infected (2). The primary role of HCV in the mechanism of cryoprecipitation is mainly suggested by its selective concentration in cryoglobulins (3).

Limited data are available regarding the treatment of patients with HCV-related systemic vasculitis. Interferon-α (IFNα) monotherapy is associated with a relatively poor response and a high relapse rate, especially in severe cases (4–7). Clinical improvement of HCV-related vasculitis correlates with virologic response, i.e., negative or significant decrease in the serum HCV RNA level. Combination therapy with IFNα plus ribavirin seems to provide much better short- and long-term results (8,9). In comparison with IFNα plus ribavirin, other treatment strategies (i.e., corticosteroids or cytotoxic agents) have not shown superior efficacy. More recently, Italian investigators reported on the efficacy of anti-CD20 monoclonal antibody (rituximab) in patients with HCV-related MC vasculitis resistant or intolerant to IFNα monotherapy (10,11). However, rituximab had a "deep impact" on hepatitis C viremia (in responders,

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Table 1. Baseline characteristics of the 9 patients with HCV-related MC vasculitis*

Parameter	Value
Age, mean ± SD years	60.8 ± 14.2
Male sex	6 (67)
Arthralgia	5 (56)
Sicca syndrome	3 (33)
Cutaneous involvement	7 (78)
Nerve involvement	7 (78)
Renal involvement	2 (22)
Genotype 1	7 (78)
ALT, × ULN	2.2
HCV RNA, mean ± SD $\log_{10}$ IU	5.6 ± 0.4
Metavir activity score, mean ± SD (0–3 scale)	1.4 ± 0.5
Metavir fibrosis score, mean ± SD (0–4 scale)	1.8 ± 1.2
Type II cryoglobulinemia	8 (89)
Cryoglobulin, mean gm/liter	0.98
Rheumatoid factor	7 (78)
Low C4 serum level	5/7 (71)

* Except where indicated otherwise, values are the number (%). HCV = hepatitis C virus; MC = mixed cryoglobulinemia; ALT = alanine aminotransferase; ULN = upper limit of normal value.

HCV RNA levels increased ~2-fold compared with baseline levels).

The addition of a polyethylene glycol (PEG) molecule to IFNα produces a biologically active molecule with a longer half-life than that of the natural molecule and more favorable pharmacokinetics. These characteristics allow for greater efficacy in terms of a sustained virologic response and more convenient once-weekly dosing (12). The combination of PEGylated IFNα plus ribavirin is the current standard for the treatment of patients with chronic HCV infection (13). The present trial was established to investigate the efficacy of PEGylated IFNα plus ribavirin in patients with HCV-related MC vasculitis.

PATIENTS AND METHODS

Patients. The study group comprised 9 consecutive patients with HCV-related MC (Table 1). All patients showed positivity for MC in serum (cryoglobulin level >0.05 gm/liter) on at least 2 determinations, associated with the triad of purpura–arthralgia–asthenia and sometimes with renal or neurologic involvement. All patients were positive for HCV RNA and negative for hepatitis B surface antigen and anti–human immunodeficiency virus antibodies. All of the patients had histologically proven chronic active liver disease. Inclusion criteria for the study were as follows: 1) chronic active HCV infection, 2) signs of MC vasculitis in the absence of any alternative condition known to cause vasculitis, 3) treatment with PEGylated IFNα plus ribavirin for a minimum of 6 months, and 4) a minimum of 6 months of followup after stopping anti-HCV treatment.

Six of the 9 patients had histologically confirmed systemic vasculitis. The remaining patients without histologic confirmation of systemic vasculitis presented with typical signs of "essential" MC vasculitis, i.e., arthralgia, asthenia, purpura of the lower extremities, and/or polyneuropathy.

For each patient, clinical and biologic data were recorded at the time of the initial evaluation, at the end of antiviral treatment, 6 months after stopping antiviral treatment, and at the end of followup. The clinical data included age, sex, neurologic involvement, recent-onset hypertension, cutaneous involvement (Raynaud's phenomenon, purpura, livedo, distal ulcers), arthralgia, myalgia, and clinical signs of hepatic involvement. The laboratory evaluation included a complete hemogram, a serum chemistry profile, and determination of the C3 and C4 fractions of complement, RF, and cryoglobulin. A urinalysis was also completed to screen for hematuria, and a 24-hour urine collection was performed to quantify daily excretion of protein.

Virologic and immunologic serum markers. HCV antibodies and RNA were detected as previously described (8). HCV genotyping was performed using a second-generation line probe assay (LiPA; Innogenetics, Brussels, Belgium). Liver biopsy specimens were evaluated according to the previously validated Metavir scoring system (14). Cryoglobulin levels were measured and classified as previously described (8). The immunologic evaluation included determination of RF and complement components, using standard methods.

Treatment. All patients received PEG–IFN alfa-2b at a dosage of 1.5 μg/kg/week subcutaneously plus oral ribavirin (800–1,200 mg/day) for at least 6 months. In cases of renal insufficiency and/or severe polyneuropathy, corticosteroids were given in a short-term, low-dose regimen (prednisone 0.5 mg/kg/day for 2 weeks, with a rapid decrease to 10 mg/day within 6 weeks).

The main treatment-related data are summarized in Tables 2 and 3. Seven patients had not been treated prior to initiation of therapy with PEG–IFN alfa-2b plus ribavirin. The 2 remaining patients had received first-line antiviral treatment with standard IFNα (3 million IU 3 times weekly) and ribavirin (800–1,000 mg/day) for HCV-related MC (patients 1 and 5). Eight patients did not receive additional treatment, and 2 received low-dose corticosteroids (patients 6 and 8). The response to treatment was analyzed by comparing clinical, immunologic, and virologic parameters at the initial evaluation, at the end of antiviral treatment, and 6 months after discontinuation of antiviral treatment.

Clinical response was defined by analyzing the evolution of the following main clinical signs: skin involvement (absence of purpura), peripheral neuropathy (clinical and/or electrophysiologic improvement at 2 successive examinations), renal involvement (normalization of serum creatinine level and disappearance of proteinuria), and absence of arthralgia. A complete clinical response was defined by an improvement in all baseline clinical manifestations. A partial response was defined by an improvement in at least half of the baseline clinical manifestations. All other patients were classified as nonresponders. Relapse was defined as the reappearance of clinical signs of vasculitis. A sustained virologic response was defined by the absence of detectable serum HCV RNA 6 months after the discontinuation of antiviral treatment; the remaining patients were classified as virologic nonresponders.

Table 2. Treatment-related characteristics of the 9 patients with HCV-related MC vasculitis*

Patient	No. of months after EOT	Duration of antiviral therapy, months	Clinical symptoms		Viremia		Cryoglobulins, gm/liter	
			Entry	6 months after EOT	Entry	6 months after EOT	Entry	6 months after EOT
1	6	26	N, S, A, R	None	Pos.	Pos.	0.08	0
2	24	12	N, S, A	None	Pos.	Neg.	1.08	0.15
3	23	12	N, S	None	Pos.	Neg.	0.78	0
4	28	17	N, S	None	Pos.	Neg.	1.2	0
5	20	13	S, A	S, A	Pos.	Pos.	2.07	0.45
6	33	10	N, S, R	None	Pos.	Neg.	0.53	0
7	8	12	S, A	None	Pos.	Neg.	0.32	0.03
8	15	12	N, R	None	Pos.	Neg.	2.07	0.5
9	11	17	S, A	None	Pos.	Neg.	0.74	0.16

* HCV = hepatitis C virus; MC = mixed cryoglobulinemia; EOT = end of therapy; N = nerve involvement; S = skin disease; A = arthralgia; R = renal disease.

A complete immunologic response was defined by the absence of serum cryoglobulin, and a partial immunologic response was defined by a decrease of >50% in the baseline cryoglobulin level.

RESULTS

Nine patients with HCV-related MC (6 men and 3 women, mean ± SD age 60.8 ± 14.2 years [range 35–77 years]) were included (Table 1). The mode of contamination with HCV was blood transfusion in 3 patients, intravenous drug use in 1 patient, and unknown in 5 patients. The distribution of HCV genotypes was genotype 1 (n = 7) and genotype 2 (n = 2). Clinical manifestations included purpura in 7 patients (78%), arthralgia in 5 patients (56%), sensory polyneuropathy in 4 patients (44%), and sensorimotor polyneuropathy in 3 patients (33%). Three patients (33%) had sicca syndrome. Renal insufficiency was observed in 1 patient (11%), whereas all patients had a mean ± SD creatinine concentration of 79.7 ± 26.2 μmoles/liter (range 58–144). Severe hypertension was noted in 1 patient (11%).

Table 3. Efficacy and tolerance of antiviral treatment in the 9 patients with HCV-related MC vasculitis*

Parameter	Value
Duration of antiviral therapy, mean ± SD months	13.5 ± 2.8
Corticosteroid use	2 (22)
Duration of followup, mean ± SD months	18.6 ± 9
Clinical response	
Complete	8 (89)
Partial	0
None	0
Relapse	1 (11)
Virologic response	
Complete	7 (78)
Partial	1 (11)
None	0
Relapse	1 (11)
Immunologic response	
Complete	5 (56)
Partial	4 (44)
None	0
Relapse	0
Side effects	2 (22)
Leukopenia	1 (11)
Thrombocytopenia	1 (11)
Depression	1 (11)
Discontinuation	0
Dose reduction	1 (11)

* Except where indicated otherwise, values are the number (%). HCV = hepatitis C virus; MC = mixed cryoglobulinemia.

Five patients (56%) had an elevated serum alanine aminotransferase (ALT) level, and the mean ALT concentration in these patients was 2.2-fold the upper limit of normal. Glomerular proteinuria was noted in 2 patients (22%) and was associated with an abnormal urinary sediment in 1 patient. All patients had MC, with a mean cryoglobulin level of 0.98 gm/liter (range 0.08–2.1). Eight patients had type II MC, and 1 patient had type III MC. The serum levels of C4 and CH50 were low in 71% of patients. RF activity was observed in 7 patients (78%).

The mean ± SD HCV RNA level was 5.6 ± 0.4 $1\log_{10}$ IU (range 5–6.4). Liver biopsy revealed that all patients had signs of chronic active hepatitis, with a mean ± SD Metavir activity score of 1.4 ± 0.5 and a mean ± SD fibrosis score of 1.8 ± 1.2. Only 1 patient (11%) had cirrhosis.

Renal biopsy specimens showed membranoproliferative glomerulonephritis in 2 patients. Skin biopsy specimens revealed leukocytoclastic vasculitis in 2 patients. Neuromuscular biopsy specimens showed severe axonal degeneration and an inflammatory process involving nerve in 2 patients.

All 9 patients received combination treatment

with PEG–IFN alfa-2b and ribavirin. The mean ± SD duration of therapy with PEG–IFN alfa-2b plus ribavirin was 13.5 ± 2.8 months (range 10–26 months). After a mean followup of 18.6 months (range 6–33 months) after discontinuation of antiviral therapy, all 9 patients are alive. Seven patients (78%) had a sustained virologic response and were complete clinical responders. In 1 patient who had a complete clinical and virologic response, a relapse of HCV-related MC coincided with the reappearance of serum HCV RNA. Reinstitution of combination therapy with PEG–IFN alfa-2b and ribavirin led to a second complete clinical and virologic response. One patient with persistent HCV viremia was also a complete clinical responder, while exhibiting a 1 $\log_{10}$ reduction of his viral load. The absence of HCV viremia was observed after 3 months of antiviral therapy in all except 1 patient.

For 3 of the 7 patients with peripheral neuropathy, results of serial electrophysiologic studies obtained before and after antiviral treatment showed a dramatic improvement. Disappearance of proteinuria was observed in both of the treated patients. One patient, with nephrotic syndrome and renal insufficiency, also demonstrated normalization of creatininemia and albuminemia.

Following antiviral therapy, serum cryoglobulin disappeared in 5 patients and decreased >50% from the baseline level in 4 patients. Complement levels normalized in 80% of patients (patients 2, 4, 6, and 9). Treatment was well tolerated in 7 of the 9 patients. In the 2 remaining patients, side effects included cytopenia (n = 2) and depression (n = 1). The dosage of PEG–IFN alfa-2b was reduced in 1 of 9 patients, because of leukopenia.

DISCUSSION

The current standard initial therapy for patients with chronic HCV infection is PEGylated IFNα in combination with ribavirin. The response rate for combination therapy with PEGylated IFNα plus ribavirin (48–88%) is higher than that reported in the initial standard IFNα/ribavirin trial (35–60%) (13).

The efficacy of combination therapy with PEG–IFN alfa-2b plus ribavirin has never been reported in patients with HCV-related MC. In previous studies with IFNα plus ribavirin, a sustained virologic response was obtained in 22–59% of patients (8,9,15). Clinical response is correlated with virologic response and generally requires a prolonged period of antiviral therapy (18–24 months) to obtain efficacy and avoid vasculitis relapse (8). Different clinical response rates were observed during antiviral therapy regarding the vasculitic manifestations (i.e., cutaneous 85–100%, renal 50%, neural 25–50%) (8,9). Apart from antiviral therapy, use of corticosteroids, cyclophosphamide, and plasmapheresis may lead to life-threatening complications that are difficult to manage in the long term for patients with HCV-related MC (4,6,7). More recently, a complete clinical response of MC vasculitis (skin vasculitis, peripheral neuropathy, arthralgias) was observed in 80% of patients treated with the anti-CD20 monoclonal antibody rituximab (10,11). However, one potential concern regarding the use of such therapy is its propensity to worsen HCV viremia, which may lead to further development of more severe HCV-induced liver lesions and/or cryoglobulinemic relapses.

The results of this study indicate that the combination of PEG–IFN alfa-2b plus ribavirin is an effective therapy for HCV-related MC vasculitis. After a mean followup of 18.6 months, all patients are alive. Complete clinical response was achieved in 8 of 9 patients (89%), and a sustained virologic response was observed in 7 patients (78%). This virologic response rate is higher than the 22–59% rate previously observed with IFNα plus ribavirin (8,9,15). This outcome was seen despite the fact that 78% of patients had genotype 1 (a major unfavorable pretreatment characteristic) compared with only 48% in our previous trial of IFNα plus ribavirin (8). Furthermore, our patients were treated for a shorter period of time compared with that in patients in a previous trial (13.5 months versus 20.0 months) (8). Tolerance of PEG–IFN alfa-2b plus ribavirin was good, although a reduction in the dose of PEG–IFN alfa-2b was required in 1 patient because of leukopenia. None of the 9 patients required discontinuation of therapy.

In 1 patient, clinical relapse of HCV-related MC vasculitis was associated with relapsing HCV viremia. These results are much better than those reported in studies with IFNα monotherapy (relapse rate 40–100%) (4–7) but are quite similar to those reported in trials of IFNα plus ribavirin (8,9). In our series, the patient who experienced a relapse achieved clinical remission of disease following another course of PEG–IFN alfa-2b plus ribavirin.

In conclusion, treatment with a combination of PEG–IFN alfa-2b plus ribavirin can achieve a complete clinical response in most patients with HCV-related MC vasculitis. A complete clinical response correlates with the eradication of HCV and requires a shorter period of treatment with PEGylated IFN/ribavirin than that previously reported with IFNα and ribavirin. Therapy is well

tolerated, and tolerance apparently is not different from that observed in patients without vasculitis.

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Dr. Lockshin to Handle Review of Manuscripts Submitted On or After April 1

Dr. Michael Lockshin of the Hospital for Special Surgery in New York will officially assume the full responsibilities of Editor, *Arthritis & Rheumatism*, on July 1, 2005. However, as part of the transition from the editorship of Dr. David Pisetsky, Dr. Lockshin will handle the review process for all new manuscripts submitted on or after April 1, 2005. Manuscripts will continue to be submitted online, through Manuscript Central (URL: http://rheumjournal-wiley.manuscriptcentral.com/).