Effect of interferon alfa-2b and ribavirin treatment on hepatitis C–associated cryoglobulinemia and rheumatoid factor: comment on the article by Vassilopoulos and Calabrese

To the Editor:

We read with interest the review by Vassilopoulos and Calabrese on the relationship between hepatitis C virus (HCV) and vasculitis (1). Herein we report our experience on the effects of combination interferon alfa-2b (IFN alfa-2b) and ribavirin therapy on HCV-associated mixed cryoglobulinemia (MC) and rheumatoid factor (RF) levels.

We prospectively studied the effects of 48-week treatment with IFN alfa-2b (3 million units 3 times weekly) and oral ribavirin (1,000–1,200 mg daily) on MC and RF levels in 30 patients with HCV infection and liver biopsy evidence of active hepatitis. MC, RF (by radioimmunoassay) (2), circulating HCV RNA (by polymerase chain reaction), and alanine aminotransferase levels were measured at baseline and serially for 48 weeks. Thirteen patients had positive serum RF, of whom 5 were able to complete the study. Four patients were excluded from the trial due to persistence of circulating HCV RNA at 12 weeks of treatment, and 4 were lost to followup. Of the 5 remaining seropositive patients, 2 had MC at baseline. One was a 60-year-old man who presented with arthralgias and palpable purpura; the other was a 44-year-old woman who had asymmetric small joint arthritis. Both of these patients had a good response to combination therapy. Their clinical manifestations and circulating MC disappeared at week 12 of treatment.

Biochemical and immunologic features in the 5 RF-positive patients who completed the study are shown in Table 1. Serial determinations of RF revealed a consistent decline in titers in all patients, with a mean 1.6 decrease in RF in the positive patients who completed the study are shown in Table 1.

Combination treatment with IFN alfa-2b and ribavirin for chronic HCV has shown promising results (3,4). Large multicenter trials have demonstrated the superiority of this combination treatment over IFN alfa monotherapy (5). Two open-label studies have addressed the use of combination of IFN alfa-2b and ribavirin in the treatment of HCV-associated cryoglobulinemic vasculitis (6,7). The study by Zuckerman et al (6) showed a substantial improvement in symptoms of refractory symptomatic HCV-related MC, but without complete biochemical or virologic response, in patients who received combination IFN alfa and ribavirin therapy. Our patients had mild symptoms attributable to cryoglobulinemia, and none had recurrence of symptoms related to cryoglobulinemia during the study or at followup 6 months after completion of treatment. Elevated serum RF was seen in 13 of 30 patients in our study (an incidence of 43%, somewhat lower than that seen in other series [8]). In a study that addressed the response to IFN treatment in patients with HCV infection and positive RF, there was no difference in outcome in patients with and those without serologic markers of autoimmune disease. It should be noted that ours is the first study in which RF levels were recorded serially during treatment of HCV with IFN and ribavirin. All 5 patients with positive RF had a decrement in their RF levels, and 2 had disappearance of cryoglobulins and associated clinical manifestations. However, it is likely that even though at 48-week followup these patients had normalization of biochemical parameters and no detectable circulating HCV, the failure to induce seronegativity may indicate incomplete eradication of the virus and eventual recurrence of disease. The rate of recurrence even with combination treatment is still quite significant. It would be of interest to follow up the patients prospectively to study the possible prognostic significance of RF positivity.

Both of our patients with cryoglobulinemia experienced remission of the clinical symptoms related to cryoglobulins and improvement in biochemical, immunologic, and virologic parameters. There was a significant decrease in serum RF titers.

We agree with Drs. Vassilopoulos and Calabrese that combination treatment with interferon alfa-2b and ribavirin is a good therapeutic option for hepatitis C virus–related mixed cryoglobulinemia.

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Table 1. Immunologic, biochemical, and virologic features of patients with positive rheumatoid factor and cryoglobulins who completed the study

<table>
<thead>
<tr>
<th>Patient</th>
<th>RF, ng anti-IgM bound</th>
<th>ALT, IU/liter</th>
<th>HCV, copies × 10^3/ml</th>
<th>MC, mg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Study end</td>
<td>Baseline</td>
<td>Study end</td>
</tr>
<tr>
<td>1</td>
<td>500</td>
<td>240</td>
<td>77</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>140</td>
<td>–</td>
<td>105</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
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<tr>
<td>5</td>
<td>839</td>
<td>169</td>
<td>63</td>
<td>14</td>
</tr>
</tbody>
</table>

* RF = rheumatoid factor; ALT = alanine aminotransferase; HCV = hepatitis C virus; MC = mixed cryoglobulins.
Characterization of flares in patients with systemic lupus erythematosus: comment on the article by Ho et al

To the Editor:

We read with interest the article by Ho et al (1) describing a 1-year study of monthly assessments of systemic lupus erythematosus (SLE) patients to determine the degree to which changes in serum anti–double-stranded DNA (anti-dsDNA) levels were correlated with changes in SLE activity. The authors concluded that a decrease in anti-dsDNA is the most common pattern detected concurrently with a lupus flare. They are certainly to be praised for their rigorous methodology and maneuvers that increase the study reliability. We are, however, surprised by the high prevalence of reported SLE flares in their study population (1.5 flares per patient-year).

Petri et al previously assessed SLE flares occurring during pregnancy (2). Similar to the definition used in the study by Ho et al, disease flare was defined as a change of ≥1 cm in a 0–3 cm visual analog scale of the physician’s global assessment of disease activity, and patients were evaluated on a monthly basis. The flare rate was 1.63 per patient-year of followup. In another epidemiologic study, the incidence of flare in the Johns Hopkins Lupus Cohort was 0.65 per patient-year (3). Unless we assume that the patients in the study reported by Ho and colleagues were pregnant, the flare rate seems intriguingly high.

One explanation would be that it was easier to convince patients with a severe disease course to be closely monitored, compared with patients with mild SLE. Nevertheless, it would be reasonable to expect that monthly followup would result in a somewhat more favorable disease course. Bootsma et al reported that close followup of lupus patients, along with frequent testing, reduced the frequency of flare (4). A fundamental difference in the study by Bootsma et al is that the intention to treat was based on monthly anti-dsDNA evaluations. Relatively conservative treatment practices of the investigators could be another explanation for the high SLE flare rate in the study by Ho and colleagues.

We believe, however, that in addition to the above-mentioned factors, potential bias may have led to an overestimation of SLE flare rate in the study by Ho et al, based on the following: 1) In that study, physicians were blinded to laboratory data. It is not mentioned, however, whether they were also blinded to previous clinical assessment scores at the time of monthly evaluations. Indeed, reported flares were relatively mild and, given the prospective nature of the study, there could have been a potential for bias if the investigators were not blinded to previous scores. 2) We are not sure if the subset of patients labeled as having several flares during the study should be categorized as having 3 or 4 flares per year or should rather be regarded as presenting 1, partially controlled, still evolving flare. Should, for instance, a lupus flare involving the joints, followed 4 weeks later by renal involvement, account for 1 or 2 distinct flares? These events would be regarded as 2 consecutive flares according to the definition of lupus flare in Ho’s study, which relies on significant change in assessment scores at 1-month intervals. While clinical scores represent reliable tools, the time interval between flares warrants further discussion in our opinion, especially in the setting of a chronic disease such as lupus. Indeed, Petri et al have already identified 3 patterns of SLE activity: relapsing–remitting, chronic active, and long quiescent, the chronic active pattern being the most frequent (5). If it holds true that the patients in Ho and colleagues’ series predominantly exhibit the CA pattern, we believe accurate flare identification and flare rate estimation would be particularly delicate to establish, and clinical interpretation of biologic markers rather difficult in this setting. Furthermore, while the chronic active pattern accounts for most of the patients in the Johns Hopkins Lupus Cohort, we hypothesize that if changes in SLE biologic markers were to prove valuable for the clinician, they would be particularly useful in the setting of relapsing–remitting disease.

We believe these are more than theoretical issues since they directly affect the results and conclusions of a study that could have considerable impact on daily clinical practice.

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