High-Dose and Long-Term Therapy of α Interferon in Hemophiliac Patients With Chronic C Virus Hepatitis

To the Editor:

We have read with interest the work by Rumi et al\(^1\) reporting very low success rates in the treatment with α interferon in human immunodeficiency virus (HIV)-negative hemophilic patients with chronic hepatitis C despite prolonged therapy. Hepatitis C virus (HCV)-associated chronic liver disease is a major complication in multitransfused persons with hemophilia and is attributed to the use of coagulation concentrates introduced in the early 1970s. Almost all hemophiliacs who have been treated with non–virus-inactivated factor VIII or IX concentrates have evidence of past or current HCV.

Interferon has been used to treat chronic HCV in both nonhemophiliacs and hemophiliacs. Response to treatment has been assessed by serial serum alanine transaminase (ALT) levels, clearance of viremia by polymerase chain reaction (PCR), and direct assessment of liver histology. Clearance of viremia is a prerequisite for a long-term response rather than normalization of ALT. To date, there has only been a few studies on the efficiency of interferon α for the treatment of HCV infection in individuals with hemophilia. Some of these studies\(^2-4\) have suggested that the response to interferon in hemophiliacs may be lower than in other groups infected with HCV.

Interestingly, response rates in the earliest studies are superior to those performed more recently. This may be a reflection of the relatively small number of patients studied or may have been caused by progression of liver disease in cohorts of hemophiliacs leading to diminished responses to interferon. The study of Rumi et al\(^1\) is the first trial with randomized controlled study of interferon therapy that has enrolled exclusively hemophilic patients with chronic hepatitis C not coinfected with HIV-1. On the other hand, it is the first time that interferon therapy has been extended to 12 months instead of the standard period of 6 months in hemophilic patients on the basis of previous reports in nonhemophilic patients that showed an increase of the chance of a sustained response\(^5\) but at dose of 3 × 10\(^6\) units three times a week.

Among factors implicated by the investigators in the poor treatment outcomes observed in the previous studies in hemophiliacs are HIV disease,\(^2-4\) excess virus load,\(^5,7\) duration of HCV infection,\(^8\) high prevalence of genotype 1 infection,\(^9\) and inadequate initial dose of interferon therapy. It is believed that they are implicated in the low rates of sustained remission achieved.

In this way, 3 years ago we began a pilot study (open label cohort format) of treatment with high-dose and prolonged α interferon treatment in patients with congenital coagulopathies and hepatitis C in our Hemophilia Unit. We enrolled 26 patients with hemophilia A (17 patients), hemophilia B (4 patients), von Willebrand disease (3 patients), and other congenital coagulopathies (2 patients). The mean age was 39 ± 10 years. All patients had serum anti-HCV, HCV-RNA using a polymerase chain reaction (PCR) method, and ALT values greater than twice the upper limit of normal range on three consecutive occasions 6 months apart before enrollment. All patients were negative for HIV antibody. Patients were monitored each month for serologic test for HCV and HBV, liver function tests, and complete blood counts and every 3 months for PCR for HCV-RNA. Genotypes were performed in the pretreatment sera. It was not possible to perform the quantification serum levels of HCV-RNA. Fourteen patients were undergoing transjugular liver biopsy for assessment of liver histology (10 patients before and 4 after).

The schedule used was 6 million units of recombinant interferon α2a or 2b administered by subcutaneous injections three times per week for 1 year. Patients who did respond to therapy were followed-up for at least 12 months after cessation of treatment.

According to the definition of response by Rumi et al,\(^1\) we found the following results. Fifteen (58%) treated patients had a complete biochemical and virologic response at the end of treatment (12 months). Ten (38%) had sustained complete remission and the end of follow-up (24 months) and 5 (19%) had biochemical and virologic relapse after cessation of interferon therapy. Four of these patients received another course of interferon treatment at the same schedule and 2 of the 4 achieved a sustained complete remission with a follow-up of at least 6 months. Six of the total (23%) were nonresponses and 5 (19%) left the treatment (2 cases for interferon toxicity).

In addition, we found surprisingly higher complete response and complete sustained response rates than rates reported until now in hemophilic patients treated with other schedules of interferon.

Factors that could be involved in these results were unknown until now. Genotype distribution is the same as in other groups, with a high prevalence of both genotype 1 infection and mixed infections. In our group, it was not possible to perform the HCV-RNA quantification assay. However, there is agreement that hemophiliac patients had higher levels of HCV-RNA. This may result from several factors such as an impaired immunologic status or an accumulation of multiple virus strains.\(^8\) Moreover, our patients had a mean age higher than those reported by Rumi et al\(^1\) and a longer duration of HCV infection, another well-recognized predictor of poor response in nonhemophiliac patients.\(^8\) The last issue is the high degree of genetic variations in HVR1 of HCV specimens isolated from hemophiliacs compared with another population of HCV patients and the biological significance of sequence diversity of the interferon sensitivity determining region (ISDR). Both topics may have affected the final results in our pilot study.\(^10\)

No previous experience exists about treatment with high doses and long-term treatment with interferon α in hemophiliac patients. In nonhemophiliac patients, previous reports\(^5,11-14\) showed that sustained response rates may be improved by longer and higher-dose interferon courses.

We have begun an ongoing multicenter study in Spain to confirm these results. Our intention is now to perform HCV-RNA quantification
to monitor the possible disappearance of HCV charge in long-term therapy.

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