To the Editor:

The endothelial protein C receptor (EPCR) is a recently described member of the protein C anticoagulant pathway. The membrane form of EPCR works in concert with thrombomodulin (TM) to augment protein C activation on endothelial cells, whereas a soluble form of EPCR from normal human plasma inhibits the generation and function of activated protein C. The protein C pathway plays a critical role in both anticoagulant processes and in the host response to inflammation, especially bacterial sepsis. TM is a well-known endothelial receptor of protein C activation on endothelial cells, whereas a soluble form of EPCR from normal human plasma inhibits the generation and function of activated protein C. The protein C pathway plays a critical role in both anticoagulant processes and in the host response to inflammation, especially bacterial sepsis. 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The protein C activation complex and soluble TM fragments have been detected in the plasma of patients. In various disease states, increased levels of soluble TM reflect endothelial cell damage that is often correlated with disease severity. 

We examined whether soluble plasma EPCR may serve as an additional marker of endothelial integrity in patients with systemic lupus erythematosus (SLE; American College of Rheumatology classification criteria) or sepsis (ACCP/SCCM consensus conference). These patients have inflammatory processes involving the vasculature, often complicated by thrombotic tendency. Plasma samples from these patient groups were assayed for soluble TM by enzyme-linked immunoabsorbent assay (ELISA). Soluble EPCR levels were determined by ELISA essentially as described, except that the coating and detecting antibodies were reversed and the chromogenic substrate was BluePhos (KPL, Gaithersburg, MD). Citrated plasma samples from the lupus patients were obtained at the time of a scheduled outpatient visit to the clinic. Samples from the sepsis patients were collected into Bauer’s anticoagulant and obtained upon admission to the intensive care unit. The septic patients required hemodynamic support, had [ATIII] less than 70%, no previous liver disease, and no hematologic disease. All samples were obtained with informed consent.

In both patient groups, we found significant elevations in soluble EPCR levels relative to normal volunteers (Fig 1), ranging up to a fivefold increase over the normal average in the SLE group. The soluble TM levels were higher in the SLE patients as reported by others, but, unlike earlier studies, we did not find any difference in soluble TM levels in the septic patients. In the septic patients, there was no correlation between the soluble EPCR levels and multiple organ failure score, survival, or presence of septic shock.

Interestingly, the soluble TM and EPCR levels did not correlate in either the SLE patients (r² = .018) or in the septic patients (r² = .013), despite the fact that both proteins are found primarily on endothelium. Immunohistochemistry studies have shown that membrane-bound EPCR is expressed almost exclusively on the large vessels along with TM but is largely absent in the microcirculation where TM is abundant. Thus, the lack of correlation between the soluble plasma EPCR and TM levels may result from differences in the site of injury, reflecting large-vessel versus small-vessel disease processes. Currently, there are no candidates for an endothelium-specific marker that can show large-vessel disease processes. Clinical studies with defined patient groups will be required to establish the utility of soluble plasma EPCR as a marker of large-vessel disease processes.

**REFERENCES**


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**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 al1 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 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 studies2-4 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 al3 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 hemophiliac patients on the basis of previous reports in nonhemophiliac patients that showed an increase of the chance of a sustained response5 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,6,7 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 α 2a 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 nonresponders 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 hemophiliac 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. Moreover, our patients had a mean age higher than that reported by Rumi et al1 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

We have begun an ongoing multicenter study in Spain to confirm these results. Our intention is now to perform HCV-RNA quantification.
Plasma Levels of Endothelial Cell Protein C Receptor Are Elevated in Patients With Sepsis and Systemic Lupus Erythematosus: Lack of Correlation With Thrombomodulin Suggests Involvement of Different Pathological Processes

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