Hepatitis C Virus Antibody Seroconversion in Bone Marrow Transplant Recipients Treated With Immune Globulin: The Impact of the Problem

To the Editor:

Immune globulin (IVIg) preparations made by current procedures are believed to be safe products with respect to hepatitis C virus (HCV) transmission. Nevertheless, the presence of HCV RNA and the development of chronic C hepatitis have been recently reported in some IVIg recipients.1,2 Seroconversion for antibody to HCV (anti-HCV) after administration of IVIg in bone marrow transplantation (BMT) recipients has been recently published.3,4 In this clinical setting, the detection of anti-HCV may originate important diagnostic problems because liver disease caused by graft-versus-host disease, venoocclusive disease, and toxic or viral hepatitis may be frequently found. However, the incidence of these seroconversions, the time to detect anti-HCV for the first time after the administration of IVIg, the period of persistence of the anti-HCV, and the potential infectivity of IVIg preparations for HCV has not been widely studied in the BMT setting, especially after the introduction of the routine screening of blood products for HCV.

From 1992 to 1993, 19 consecutive patients with hematologic malignancies were included in a prospective, controlled, randomized study to assess the efficacy of polyvalent IVIg (Polyglobin; Bayer, Berkeley, CA) in the prevention of complications after BMT. Eleven patients were allocated in the IVIg Group (median age, 38 years; 9 male/2 female; 2 allogeneic BMT/9 autologous BMT) and received IVIg intravenously at a dose of 400 mg/kg every 15 days between days +7 and +102 after BMT. The rest of BMT recipients received no prophylactic IVIg (median age, 38 years; 5 male/3 female; 4 allogeneic BMT/4 autologous BMT).

All patients received blood products screened for anti-HCV with a second-generation enzyme immunoassay (ELISA; Ortho, Raritan, NJ). HCV antibodies were not found in any patient just before BMT. After BMT, an ELISA test for HCV antibodies was performed every 15 days up to discharge and every 1 or 2 months thereafter. Positive antibody tests were validated by a second-generation recombinant immunoblot assay (RIBA; Ortho). Polymerase chain reaction (PCR) for viral RNA was performed in all positive sera.

All BMT recipients in the IVIg group seroconverted for anti-HCV, with a median of 10 days after BMT (range, 8 to 41 days), i.e., just after the first dose of IVIg in 10 of 11 cases. The RIBA test was confirmatory in all cases. Yet, polymerase chain reaction (PCR) was always found to be negative. None of the 8 patients in the control group and none of the 52 patients of a historic group who received only HCV-screened blood products (but not IVIg preparations) seroconverted. There were no differences in the median number of transfusions received by the IVIg and control patients in each group (30 [range, 4 to 46] v 25 [range, 9 to 48], respectively).

Nine patients who received IVIg are evaluable for long-term follow-up. ELISA and RIBA tests remained positive for a median period of 9 months (range, 4 to 14), although all then became seronegative at the end. Only 1 patient in the IVIg group developed persistent abnormalities of liver chemistry that were detected before seroconversion for anti-HCV. PCR was always negative. The temporal relationship between liver chemistry abnormalities and cyclosporine dosage suggests toxic liver damage more than HCV infection. Yet, no other diagnostic approach was performed because liver biochemistry normalized and the patient became seronegative by 4 months after BMT.

ELISA and RIBA tests were positive when performed on several batches of two different IVIg preparations (Polyglobin [Bayer] and Gammagard [Baxter, Deerfield, IL]). The PCR assay was always negative in all batches tested. Two different "HCV-negative" IVIg preparations, according to manufacturers' information, were positive in the ELISA test but negative in the RIBA and PCR assays.

So, in our experience, (1) seroconversion to HCV caused by passive transfusion of antibody in the IVIg preparations was observed in all BMT patients to whom prophylactic IVIg was administered; (2) viral RNA was not found either in any patient or in any IVIg...
preparation despite the fact that RIBA and ELISA tests were positive; (3) the notably prolonged period of persistence of anti-HCV positivity, up to 14 months, may originate long-lasting diagnostic problems; (4) routine screening of blood donors for anti-HCV seems to have diminished the prevalence of HCV infection because none of the 52 patients grafted after its introduction were infected, which contrasts with much higher figures between patients who did not receive HCV-screened blood products; and (5) the new “HCV-negative IVIg” may contain anti-HCV because these IVIg preparations include plasma tested only with first-generation ELISA tests that are less sensitive than the assays used currently.

In summary, although we have not found any HCV infection between our IVIg recipients, the high incidence of seroconversion to anti-HCV and the median prolonged time of anti-HCV positivity (9 months in our study) may raise important diagnostic problems in BMT recipients. Moreover, these diagnostic problems caused by the administration of IVIg seem far from being solved, even with the new HCV-negative IVIg preparations.

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REFERENCES
Hepatitis C virus antibody seroconversion in bone marrow transplant recipients treated with immune globulin: the impact of the problem [letter]

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