Correspondence

Significance of Repeatedly Normal Aminotransferase Activities in Hepatitis C Virus-Infected Patients

To the Editor:

The significance of repeatedly normal aminotransferase activity in hepatitis C virus (HCV)-infected patients is still a matter of debate, and data are discrepant and confusing.[1-4]

Puoti et al. should be congratulated for their interesting and informative study on HCV-infected subjects with persistently normal transaminase levels published in the December 1997 issue of HEPATOLOGY.[5] We also evaluated aminotransferase activity in 1,200 anti-HCV–positive immunocompetent patients. Thirty-six (3%) had repeatedly normal aminotransferase activities, defined by at least four normal values of aminotransferase over a minimum period of 6 months (mean 31 ± 2) without any abnormal value. Eleven were men and 25 were women and the mean age was 45 ± 15 years. The risk factors for HCV contamination were blood transfusion in 36%, intravenous drug use in 17%, and unknown in 47%. Twenty-three (64%) had detectable HCV viremia by polymerase chain reaction (PCR). Fifty-seven percent were genotype 1a or 1b, 26% were genotype 2, and 17% were genotype 3. Histologic analysis in 17 yielded a mean Knodell score of 5.6 ± 3.5 (range, 1-14), <5 in 9 (53%), ≥5 in 8 (47%), including extensive fibrosis or cirrhosis in 2 patients each.

A comparison of immunocompetent viremic subjects with (n=23) and without (n=564) repeatedly normal serum aminotransferase activities showed a significant predominance of females (70% vs. 44%, $P < .05$) and genotype 2 (26% vs. 7%, $P < .05$) in the first group, but no difference in quantitative viremia, alcohol comsumption, or prevalence of individual of risk factors. Interestingly, as observed by Puoti et al. there was no significant difference in mean Knodell and fibrosis scores; about 20% of patients had extensive fibrosis or cirrhosis. Genomic diversity according to biologic and histologic patterns of chronic hepatitis C did not correlate with either severity of liver damage or aminotransferase activity (Leone F, unpublished observations, February 1998).

Factors involved in this peculiar biologic profile are unknown but may include virologic (predominance of genotype 2) or host-related factors. One could hypothesize that the predominance of women indicates an involvement of hormonal factors in the regulation of aminotransferases. Indeed, aminotransferase levels have been reported to be related to hormonal factors,[6] and the normal values of these patients do differ according to sex.

Our study shows that the true healthy carrier state is rare, whereas the persistent normality of aminotransferase activity can be associated with quite severe liver lesions. This leads us to propose liver biopsy in any viremic patient, regardless of aminotransferase values, to evaluate the severity of the liver disease. This recommendation would be strengthened if effective therapy were available for this group.[7] The relative contribution of virologic and host factors in such a biologic pattern remains to be determined.

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Aprotinin in Liver Transplantation

To the Editor:

We have read the paper by Lucia García-Huete et al. on aprotinin in liver transplantation with great interest[1]; this is an important study. In a placebo-controlled trial, the Barcelona group evaluated the effect of aprotinin on intraoperative blood loss in patients undergoing orthotopic liver transplantation. No significant effect on blood loss or hemostasis tests (except for TAT levels) was found; however, the conclusions of this paper may have been adversely affected by data that was omitted.

First, the authors do not describe aprotinin levels in their patients. The effect of aprotinin is dose dependent and, therefore, plasma levels are important for interpreting the

results. From the presented data it can be deduced that the investigators may not have obtained therapeutic aprotinin levels in their patients, which may very well explain the negative outcome represented in this study. Based on the α2-antiplasmin levels, one is able to estimate aprotinin levels, as the activity assay is influenced by the presence of aprotinin.[2] It has been well documented that aprotinin at levels in the therapeutic range (100-200 KIU/mL) increases the measured α2-antiplasmin values by 30% to 40%, as it interferes with the activity assay.[2] Indeed, in a comparable study, Segal et al. found significantly increased and supra-normal α2-antiplasmin levels in the aprotinin group, with an identical curve pattern as found in the aprotinin levels.[3] Although García-Huete et al. did acknowledge this effect of aprotinin on the α2-antiplasmin assay in their paper, they surprisingly found only slightly higher α2-antiplasmin levels in the aprotinin group, compared with the placebo group. This difference never reached statistical significance and α2-antiplasmin levels remained within the normal range throughout the entire operation.[1] Therefore it can be questioned whether adequate aprotinin levels have been achieved in the current study. The relative high number of red blood cells (mean 13.0 U) and fresh frozen plasma (mean 26.0 U) transfusions may have caused a dilutional effect and contributed to this finding.

It is also important to know what happened with the one patient that died intraoperatively and to which group this patient belonged. According to the principles of "intention-to-treat," this patient should have been included in the analysis. Furthermore, 16 patients had to be excluded because of unavailability of aprotinin and 17 patients were excluded because of lack of data to fulfill the analysis. If these 17 patients as well as the one who died, however, were initially enrolled in the study (making a total of 98 randomized patients) this represents an almost 20% drop-out, which is fairly high for a prospective study.

Referring to the importance of this study and to the impact it may have on clinical practice, we conclude that some very important information that should have been included in this paper is currently not available to the reader. Therefore the conclusions should be interpreted with great caution.

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On behalf of the investigators group of the European Multicenter Study on the use of Aprotinin in Liver Transplantation (EMSALT).

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Reply:

We appreciate the comments of Porte and Molenaar on our paper related to the clinical efficacy of aprotinin in orthotopic liver transplantation. The regimen of aprotinin we used is considered a high-dose regimen, which was 2 million KIU bolus plus a continuous infusion of 0.5 million KIU/h, starting at anesthesia induction and maintained during the whole procedure. The difference in α-2-antiplasmin levels between treated and control groups reached 30% after the initial bolus, and this difference was maintained throughout (data expressed in Table III in the original text). Also, this difference was commented on in the Discussion.[1] Although administration of blood products may have led to some dilution of the administered aprotinin, this does not appear to explain its lack of effect in our patients.

Furthermore, Himmelreich et al.[2] investigated the hemostatic changes produced by a low-dose regimen in continuous infusion (0.1-0.4 million KIU/h) or a regimen of three separate boluses of 0.5 million KIU. They showed an increase in PAI activity and α-2-antiplasmin levels with either regimen; however, in their study, the continuous low dose infusion of aprotinin was superior to bolus for preventing biological fibrinolysis (explored by measuring activity of t-PA), but the requirement for intraoperative blood products was identical in both groups. On the other hand, Soilleux et al.[3] were not able to demonstrate an additional benefit of large-dose aprotinin therapy compared with low-dose administration.

The patient who died was excluded because the death happened during the hepatectomy and was related to gas embolism, diagnosed by evidence of inferior caval tear, sudden decrease of end-tidal CO_2, and cardiac arrest.

The intraoperative blood product requirements for those patients excluded because of lack of data were 13.4±7.5 red blood cell U, 20 ± 12 FFP U; 72% received platelets and 48% received cryoprecipitate. Also, for those patients excluded because aprotinin was not available, the blood product requirements were 15.4 ± 9 red blood cell U, 28.5 ± 15 FFP U; 70% received platelets and 52% received cryoprecipitate.

In summary, health care providers involved in orthotopic liver transplantation need more information about the clinical efficacy of aprotinin, as well as other drugs that may reduce blood product transfusion. Only randomized controlled studies may increase our knowledge in this area; thus, we eagerly await the results of the European Multicenter Study on the use of aprotinin in Liver Transplantation (EMSALT).

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