The Natural History of Chronic Hepatitis C in Haemophiliacs

Makris et al (1996) report that within 22 years of infection with hepatitis C virus (HCV), 19% of patients have cirrhosis and 9% have developed liver failure. The analysis, which shows a non-significant increased risk of progression in those co-infected with HIV, is based on the development of cirrhosis in 19 individuals out of 138 studied, including eight with hepatic failure, of whom four were co-infected with HIV. A number of issues require further comment.

Firstly, the date of the patient's first exposure to clotting factor concentrate was assumed to be the date of HCV infection. However, for 25% of the cohort (35 patients), this date was unknown and has been estimated to be 1 January 1972, or the date of the first birthday in the case of patients born after this date. A number of problems may arise when making this assumption. As seroconversion to HCV from blood product therapy occurred in the U.K. as early as 1965 and as late as 1985, dates of seroconversion to HCV may be inaccurately estimated in some patients. Although it is reasonable to assume that patients with severe haemophilia would have received concentrate by the time of their first birthday, it may be unreasonable to make this assumption in those with mild or moderate forms of the condition for whom the date of first infusion could have occurred at any time. Thus, it would be of interest to see the Kaplan-Meier progression rates calculated only in those 103 patients with documented dates of first exposure to clotting factor concentrate.

Secondly, although the results from this study are consistent with those previously reported (Eyster et al., 1993; Telfer et al., 1994) in confirming an increased risk of progression in co-infected individuals, the hazard ratio associated with co-infection is smaller than that reported in these previous studies. Makris et al. (1996) categorize patients as either being infected or uninfected with HIV. On average, patients in their cohort became infected with HIV in 1983, some 11 years later than infection with HCV. If there is any risk of HCV progression associated with HIV in 1983, some 11 years later than infection with HCV alone and may have underestimated the impact of co-infection on these progression rates. Further analyses of these valuable data will help to clarify these issues.

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REFERENCES


We thank Drs Lee and Sabin for their interest in our paper and for their comments. They suggest that we have shown 'a non-significant increased risk of progression in those co-infected with HIV'. Although we do not think it crucial whether the result was or was not significant, it actually was. The remainder of their comments centre around three areas.

The time of infection with hepatitis C. This is a difficult problem and we can only hazard a guess as to the exact time of infection. Neither the system we used nor that used by Lee and Sabin (Telfer et al., 1994) is likely to be very accurate. Although it is true that almost all concentrates used between 1978 and 1984 transmitted hepatitis C with every batch, this cannot be extrapolated to other periods. Early concentrates, especially those produced in the U.K., were made from only a
small number of donors, so HCV infection was not invariable (Makris et al. 1993). Furthermore, many severe haemophiliacs are likely to have received hundreds of units of plasma or cryoprecipitate prior to exposure to concentrate and may have already been infected with HCV before the assumed infection date.

Lee and Sabin feel that our assumptions may not apply to mildly affected patients and suggest we recalculate our cirrhosis and liver failure rates restricting the analysis to those with known infection dates. We have re-analysed our data by calculating survival curves only for those whose date of HCV infection was known to us, but this did not change the results.

The HIV co-infection risk. We agree that entering HIV-sensitivity for PML-RARα detection in acute promyelocytic leukaemia (APL) may also increase the expression of the chimaeric transcript. They

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### Table 1

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<tbody>
<tr>
<td>Total HCV+ve patients</td>
<td>138</td>
<td>255</td>
<td>156</td>
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<tr>
<td>HIV co-infected patients</td>
<td>4/36 (11.1%)</td>
<td>10/103 (9.7%)</td>
<td>11/97 (11.5%)</td>
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<td>Liver failure patients</td>
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<tr>
<td>HIV-negative patients</td>
<td>5/102 (4.9%)</td>
<td>1/152 (0.6%)</td>
<td>0/59 (0%)</td>
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INTERFERON ENHANCED MINIMAL RESIDUAL DISEASE DETECTION IN ACUTE PROMYELOCYTIC LEUKAEMIA

In their recent paper, Seale et al (1996) reported that PCR sensitivity for PML-RARα detection in acute promyelocytic leukaemia (APL) may be improved by modifying reverse transcription (RT) and PCR conditions. Moreover, an in vitro pretreatment of APL cells with interferon (IFN) may also increase the expression of the chimaeric transcript. They...