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. Further, 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 date. 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 co-infection, then it is unlikely to act during these first 11 years when patients are only infected with HCV. Further, the individuals who become infected with HIV must have survived at least 11 years without developing liver failure. Thus an analysis of this type is biased towards showing a better prognosis in co-infected individuals. A more appropriate analysis which provides an unbiased estimate of the hazard ratio associated with HIV infection would incorporate HIV infection into a Cox proportional hazards model as a time-updated covariate, taking the value of 0 prior to and 1 after the estimated date of seroconversion to HIV.

Finally, the endpoint of cirrhosis was based on performance of a biopsy. The transaminase levels in those biopsied and those not biopsied suggests that a highly selected population may have been chosen for biopsy (Table I).

Thus, the estimate of progression to cirrhosis is likely to be an overestimate of that in HCV-infected haemophilic patients if ALT levels are related to subsequent development of cirrhosis.

These results are of importance for healthcare planning purposes and for advising haemophilic patients about their disease. Although there is no doubt that chronic HCV infection is a progressive disorder, it is likely that Makris *et al* (1996) have overestimated the rapidity of progression for the individual infected 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.

Table I

ALT level	Non-biopsied	Biopsied
Persistently abnormal	43%	70%
Intermittently abnormal	33%	22%
Normal	25%	8%

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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

Table I

	Makris *et al*, 1996	Telfer *et al*, 1994	Eyster *et al*, 1993
Total HCV+ve patients	138	255	156
HIV co-infected liver failure patients	4/36 (11·1%)	10/103 (9·7%)	11/97 (11·3%)
HIV-negative liver failure patients	5/102 (4·9%)	1/152 (0·6%)	0/59 (0%)

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-seropositivity as a time-dependent covariate in the analysis is a worthwhile analytical procedure. When we reanalysed our data by this method, the results did not change. The hazards ratio (relative risk) for cirrhosis in HIV-positive HCV carriers, as compared to HIV-negative patients was 4·1 (CI95 1·4–12·1), whereas the original figure was 3·9. All other estimates also remained unchanged. Two previous cohort studies reported on the rate of liver failure in HIV co-infected patients (Eyster *et al*, 1993; Telfer *et al*, 1994). The crude data based on total patients reported are compared with our data in Table I.

Only one of 211 HIV-negative haemophiliacs developed liver failure in the two other cohorts, which is surprising considering the natural history of HCV in non-haemophiliacs (Tremolada *et al*, 1991). Moreover Darby *et al* (1995) have recently reported an increased liver related mortality among U.K. HCV+ve HIV−ve haemophiliacs.

The selection of patients for biopsy. As we mentioned in our paper (Makris *et al*, 1996), liver biopsies were *not* performed in a random fashion, in that patients with abnormal liver enzymes were more likely to be biopsied. Drs Lee and Sabin are, however, wrong in suggesting that this overestimates the incidence of cirrhosis. In contrast, the opposite is likely to be true. We found 19 cases of cirrhosis in our cohort of 138 patients. Since a liver biopsy was performed in <50% of the cohort, this is almost certainly an underestimate of the true number of patients with cirrhosis. It would be inconceivable that we fortuitously biopsied every case of cirrhosis from the cohort.

We remain convinced that HCV-related liver disease in HIV-negative haemophiliacs is associated with significant morbidity and mortality, a fact supported by the data reported by Darby *et al* (1995) on the entire U.K. haemophilic population.

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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