Commentary

Hope for haemophilic patients with hepatitis

The high incidence of hepatitis after treatment with large pool clotting factor concentrates was first reported by Kasper and Kipnis in 1972. However, there was an initial gross underestimate of its prevalence because most cases of acute and chronic non-A, non-B hepatitis (NANB) were asymptomatic. Two prospective studies showed that virtually 100% of patients who received clotting factor concentrate for the first time, developed NANB hepatitis - which has now been identified as hepatitis C (HCV). The scale of HCV infection among people with haemophilia is large. In the UK it has been the practice since 1977 to register all treatment administered nationally at a registry based at Oxford, and it has been established that, in 1994, there were at least 3122 patients living who had been infused with large pool clotting factor concentrate and thereby infected with HCV between 1977 (when records began) and 1985 (when sterilisation of concentrates began).

The ultimate treatment for liver failure is liver transplantation. As this is clearly a treatment option, an understanding of the natural history of chronic HCV infection in haemophilia is required to direct the appropriate resources in the future.

In a cohort of 183 haemophiliac patients where the data of first infusion with large pool clotting factor concentrate (and hence HCV infection) was known, the Kaplan-Meier progression to liver failure at 20 years was 11% (confidence intervals 14–18%). On average, patients with haemophilia were infected in 1978 (range 1965–85). Thus, we are only now seeing the beginnings of the impact of the epidemic.

Furthermore, as yet, progression to liver failure is much more common in people co-infected with HIV and HCV - using a Cox proportional hazards model, the relative hazard of developing liver failure after HIV infection is 21 times. Indeed, in the study by Telfer, 10 of 11 patients who developed liver failure were co-infected: the remaining patient who was HIV negative, was a chronic alcoholic. All people who became infected with HIV from clotting factor concentrate must also be infected with HCV - either with the same infusion or before. Thus in the UK, the 50% survivors among those with HIV infection (1227 subjects) must have co-infection and be at risk of developing liver failure. Thus conversely, in a cohort of HIV infected patients, 10% of deaths have been in liver failure.

The paper by McCarthy et al in this issue reports a further four liver transplantations to those already in the literature, approximately nine in number. These experiences have identified some of the features of liver transplantation that are peculiar to haemophilia.

In the past, perioperative therapy with clotting factor concentrate has been by bolus injection: twice daily for factor VIII, which has a half life of 12 hours and less frequently for factor IX, which has a half life of 16–20 hours. However, experience is now considerable for the use of constant infusion to maintain levels at 100%, particularly for factor VIII replacement. This was used for patients 1 and 3 in the reported study. The issues are complex because of concern of 'sticking' of the clotting factor to plastic tubing and pump driven syringes, as well as induction of inhibitors to factor VIII. Thus, treaters are cautious. However, there are tremendous advantages to constant infusion - maintenance of a clotting factor at 100% without peaks and troughs, as well as cutting the cost by one third. (For a 70 kg man with severe haemophilia A, factor VIII <2 U/dl requires 3500 U twice daily - about £1000 twice daily).

Of course, one of the great advantages of liver transplantation in haemophilia is phenotypic cure - the ultimate in 'gene therapy'. Thus in this series, the clotting factor levels were substantially increased in all four patients by 12 hours post transplantation. In the series reported by Bontempo et al one patient showed increase in the clotting factor at six hours. This also means that the operation of liver transplantation is far less daunting: both from the reduced bleeding risk and the cost of clotting factor concentrate compared with other surgery for the haemophilic patient.

The most difficult issue in the management of such patients is co-infection with HIV, and it is these patients who are predominantly presenting currently. Patient 3 in this series was infected with HIV and successfully transplanted: however, it may be significant that his immunity was well preserved with CD4+ at 300/µl. Perhaps co-infected people should be considered at an earlier state of liver compromise than those with HCV infection alone. Patients with HIV infection can now expect increased survival, particularly with a large array of anti-HIV viral therapy becoming available. It is of note that patient 3 had not been treated with interferon 'because he was infected with HIV'. Although the response to interferon in HIV infected subjects is poor, it should be considered, particularly for type III HCV where it may be possible to clear the virus (unpublished data).

Thus, it is likely that liver transplantation will become more common in the management and treatment of end stage HCV disease in haemophilia. The cost-benefit is obvious: the failing liver results in multi clotting deficit in a patient with a single inherited coagulation deficiency and potential bleeding varices - after transplantation, the haemophilia is cured and the liver functions. Even if the patient has HIV infection and the transplant becomes infected with HCV, he can expect a much better quality of life, as well as saving perhaps £30 000 a year in clotting factor concentrate.

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3 Kernoff PFA, Lee CA, Karayiannis P, Thomas HC. High risk of non-A non-B hepatitis after a first exposure to volunteer or commercial clotting


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