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Mr G Barker
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Dear Mr Barker

Re: Haemophilia and Hepatitis

Thank you for your letter.

The newer second generation hepatitis C tests plus previous epidemiological evidence indicate that all patients treated with unheated or non-virally inactivated factor VIII concentrates and a high proportion of those heavily treated with cryoprecipitate will have been infected with hepatitis C. Early reports using first generation hepatitis C tests gave lower figures and are almost certainly incorrect. Infection with hepatitis C is usually not associated with an episode of jaundice and illness, and the condition is generally asymptomatic. The patients are therefore usually unaware that they have liver disease and must be informed by their clinician. The majority of these patients, if biopsied, have been shown to have chronic persistent hepatitis, a mild and usually non-progressive form of liver disease unlikely to give problems. Liver biopsy studies dating up to the mid 80s showed that about 15% of patients had cirrhosis at that time. It is not known how many have cirrhosis now. It is likely that the proportion will have increased, although I have seen no estimate beyond 25% and in many cases the cirrhosis itself may be relatively benign.

The number of death from liver disease is undoubtedly increasing but it is to some extent masked by the effect of HIV. Many patients dying of AIDS. Cirrhosis may not be the primary cause of death and will therefore not necessarily appear on the death certificate. It is also more difficult to obtain post mortem examinations in HIV seropositive patients, either because of lack of local facilities or because of resistance from the relatives, and many cases of cirrhosis may therefore be missed for this reason. The physical signs of cirrhosis are unreliable and only a proportion of patients with cirrhosis of the liver will be clinically diagnosable.

Since HIV is the major clinical problem it is unlikely that the epidemiological liver biopsy surveys of the mid 80s will be repeated. Bear in mind that the factor VIII required to cover a liver biopsy cost about £5,000.

Liver biopsy is the only reliable means to diagnose the severity of a patient's liver disease. This is unacceptable to clinicians and patients alike, and it seems likely for that reason that severe liver disease will remain under-diagnosed.

It is likely that there may be some interaction between HIV infection and hepatitis C such that liver disease progresses more rapidly in patients with immunodeficiency. This has certainly been shown in patients with hypogammaglobulinaemia and it is expected amongst haemophilic AIDS patients where reactivation of both hepatitis C and B have been documented and in whom a higher prevalence of severe liver disease is found than one might expect.

From the mid 80s, all concentrates have been through hepatitis safety studies prior to licencing and none of the concentrates currently available have been known to transmit hepatitis C. The Adverse Events Working Party of the Haemophilia Directors Organisation has investigated a total of over 20 reports of apparent new hepatitis C in the last 18 months. All of these have proven to be false, almost all being records of first time of testing in patients with established liver disease. We continue to keep a close eye on the situation however. Patients who started their treatment from 1986 onwards should in general not expect to suffer liver disease.

I wrote my MD on haemophilic liver disease and that has some 350 references. I am sure this is far too many for you to wade your way through, but I have included a couple of papers that I wrote at about that time which have most of the key references. I think it would be reasonable to reassure paediatric patients of 5 years old and under that their treatment has been safe throughout their lifetime and that they will not suffer liver disease as a result of factor VIII or IX therapy. For older patients, only qualified reassurance can be provided that the majority, probably of the order of 80-85%, will never suffer any problems from liver disease. Given that most of the patients who do suffer significant liver disease are HIV positive, their liver disease is of secondary concern. Very few patients who are HIV seronegative will actually die from liver disease.

It is part of the normal protocol of the running of the Haemophilia Centre to monitor patients liver function tests on a frequent basis. Hepatitis C and B serology is monitored regularly. Hepatitis B serology is monitored so that patients can be selected for vaccination and for booster vaccination against hepatitis B. In the absence of a vaccine against hepatitis C the regular monitoring of hepatitis C is

far more questionable, although haemophilia directors are increasingly recommending this. My personal view is that it is reasonable that all patients be tested for hepatitis C, particularly now that the more accurate second generation tests are available, just to find out who has been exposed. This will include 100% of the older patients. Newer patients should be tested on a regular basis as part of our surveillance to see if there has been a breakthrough with the newer concentrates. Eventually the hepatitis C vaccine will become available and then the test will become of more practical importance. It is not a substitute for liver function tests or other methods of assessing liver function. Patients should also regularly be examined for evidence of liver disease and possibly have their immunoglobulins measured as suggested in my Blood paper (enclosed). The place of liver biopsies is extremely contentious as are barium swallows in the absence of any particular problem. It is the current policy of the Haemophilia Directors Organisation which will be reinforced at the next annual meeting in 10 days time that all patients with all bleeding diatheses should be vaccinated against hepatitis B. I think your recommendation that vaccination should be made available for sexual partners is more questionable, although were it to be requested I think it would be unlikely to be refused. Certainly sexual partners of people carrying hepatitis B should be vaccinated if not already infected, but if the patients themselves are immune then the risk to their partners or even their relatives handling the factor VIII is so small that I think it would be difficult to make a case.

We are currently reviewing the vaccination policy with Collindale and new guidelines will be issued. Partners and relatives of haemophilic patients were not even discussed in this connection and I will put it to the Adverse Events Working Party to consider. In practice, some centres are better at vaccinating their patients than others. A 100% vaccination policy is never possible due to poor patient compliance and but certainly feel in the Adverse Events Working Party that vaccination policy needs to be tightened up. I am personally unaware of any problems in relation to the availability or cost of the vaccine. I usually arrange for my patients to be vaccinated by their GPs purely for the sake of convenience to them and to improve compliance, but we do also vaccinate patients in the centre. The only available vaccine these days is Engerix B. Unlike the earlier vaccine this is less effective given by the subcutaneous route. This is unfortunate given that this is the route of choice in patients with a bleeding disorder. We would normally give up to 5 shots (3 is the usual) and give up at that point if there was no serological response. The serological response in patients with HIV infection is in any case often very poor and transient.

Interferon is the only practical current treatment for chronic hepatitis C. This is still currently under trial. There is no consensus view as to its usefulness and the length of time for which it

should be given, and to whom it should be given. The dose is used for hepatitis C, is generally agreed and it is small, in contrast with the higher doses used for hepatitis B. There are only minimal side effects. Higher doses give sometimes severe flu like symptoms. There may be some interaction with HIV infection. Interferon is generally available but very expensive. I think it is inappropriate to make any moves to make it more available for haemophilia patients in the absence of proven efficacy. Clinical trials indicating the length of time for which it should be given, and sustained clinical benefit are the most powerful argument for its use and are not yet available.

Eric Preston has more experience than most of liver transplant in haemophilia. Liver transplantation in an HIV seropositive individual would not be considered. The results are absolutely appalling. Hepatic transplant cannot be justified on the basis of a cure for haemophilia. It is only used for terminal liver failure, since most of the patients in this situation with haemophilia are also HIV seropositive, few patients are suitable. It should certainly be considered in seronegative patients with severe hepatic failure although there must be concern that the new liver might also be damaged by hepatitis C. Hepatic transplantation is enormously costly, but I am not aware that financal constraints are limiting its use in this group of patients. Paradoxically, since the patients start to make factor VIII immediately postoperatively you may actually require less factor VIII for a liver transplant than for a liver biopsy! I think hepatic transplantation may be used more in future in haemophilic patients but the numbers will remain small. The procedure does carry a significant mortality, but it is generally used in patients who would otherwise die and where the risk can be justified. Gene therapy which Dr I R Peake (he knows more about this than I do) considers still to be 10 - 20 years away, might offer a more realistic option of cure for haemophilia.

I advise patients with chronic liver disease to avoid alcohol excess, and chronic carriers of hepatitis B either to have their sexual partners vaccinated or to use condoms all the time to prevent sexual spread. We probably ought to arrange for spouses to be tested, but since most of them will not even be tested for HIV, this could be an uphill battle. Patients with bleeding disorders and their immediate relatives should probably refrain from blood donation.

You should not confuse high purity with viral safety. Although monoclonal immunupurification does reduce the viral load by several logs, it has been shown to be inadequate as a method of prevention of viral disease itself. There is no evidence that the currently available products transmit hepatitis. The degree of purity is therefore not directly related to the infectivity of currently available concentrates. Although it has been hypothesized that immunosuppression found in HIV seronegative patients and presumably caused in some way by the concentrate may contribute to the high

prevalence of chronic liver disease in haemophilic patients, there are alternative explanations ie. multiple viral infection. There is as far as I am aware no way of dissecting this out and it remains a hypothesis which cannot be proved. There is therefore no convincing case to argue that haemophilic patients with chronic liver disease should receive only high purity products. I would also point out in relation to the recent rather unbalanced articles on high purity that there are as many clinical trials showing that high purity has no effect on the progression of HIV as there are that show that it has a beneficial effect. There is therefore no consensus that HIV seropositive patients should be on high purity factor VIII. By the same token, there is no evidence that HIV seropositive patients with mild haemophilia (seldom treated) do any better than HIV seropositive heavily treated severe haemophilia tending to suggest that the treatment does not effect the natural history of HIV. Arthur Bloom has long argued that immunosuppression caused by factor VIII concentrate could even be beneficial in HIV infection, since it may reduce the rate of viral replication. There are arguments on both sides and the matter remains unresolved. Clearly even if there is an effect it is not very great. In the present state of knowledge I therefore think that it is wrong for the society to recommend one form of treatment over another, particularly when the inhibitor issued remain unresolved. Clinical trials to resolve this issue continue. This black and white issue, like HIV or hepatitis transmission, and historical comparisons with that situation are probably not fair.

The area of legal compensation is even more difficult than with HIV. There are some similarities however in as much as patients who were treated with factor VIII concentrate rather than either cryoprecipitate or DDAVP where that might have been appropriate, may have some redress in the courts. Most of these patients will have very mild haemophilia. Patients with severe haemophilia should forget it. The clinical significance of this liver disease was still hotly disputed until about the time that heat treated concentrate became available. Until that time many prominent haematologists including P M Mannucci from Milan considered it to be a benign condition.

I think maybe a haemophilia fact sheet about liver disease would be reasonable. I think the contents should be discussed between various people interested. Recent events in relation to product purity and choice made me think that the advisory panel should be reactivated (I understand that it had fallen into disuse) or should perhaps be replaced by some more workable arrangement. I think you should be very wary of making too much of a fuss about it and giving it too high profile since this will just cause distress, and since liver disease is a much smaller problem than HIV that most people affected will not suffer any problems from it. This was a real worry for me when I agreed to write the review for the bulletin on haemophilic liver

disease, and I note that it was followed in the next bulletin by a further article on the subject by Christine Lee.

I will give your comments on research some thought. Feel free to give me a ring to discuss the matter further. My direct line is GRO-C GRO-C

Yours sincerely

GRO-C

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