GDOL/MG

09 February 2005

Dear Dr Keel

Further to your email of 02/02/06 to the Haemophilia Centre Directors in Scotland, we have done our best to contact ex-colleagues and predecessors who worked in Haemophilia Centres in Scotland during the 1990s and seek their recall of hepatitis C testing and information given to patients with haemophilia, as knowledge of hepatitis C evolved over that period of time.

As you know, the SEHD enquiry in 1999-2000 included this question, which was discussed during a meeting in 2000 between SEHD and some Haemophilia Centre Directors and is addressed in the published report (October 2000).

From the 1970s it was well recognised that viral hepatitis was a frequent complication of treatment with blood products, including fresh frozen plasma, cryoprecipitate and factor VIII and factor IX concentrates. Hence all patients with haemophilia who had received such products were routinely screened for hepatitis as part of routine blood testing at clinic reviews. Hepatitis testing included liver function tests (non-specific markers of liver damage) and testing for hepatitis A and hepatitis B. Some patients had intermittently or persistently elevated levels of liver function tests which could not be attributed to hepatitis A or B: such findings raised the possibility of non-A, non-B viral hepatitis, although there are several other common causes for such findings (e.g. alcohol, drugs, obesity). It is important to note that

diagnosis of non-A, non-B hepatitis in individual patients was therefore very difficult. Because of the bleeding risk of liver biopsy in patients with haemophilia, this procedure was rarely indicated. There was no effective treatment or advice for non-A, non—B hepatitis, apart from avoiding excessive alcohol intake.

In 1990 several international papers were published showing that almost all patients who had received treatment with blood products (before effective viral inactivation procedures were introduced in 1980s) had a positive antibody test for hepatitis C, which indicates previous exposure to the hepatitis C virus (HCV). It was subsequently established that HCV was the commonest cause of non-A, non-B virus hepatitis. In retrospect, it is likely that most patients with haemophilia were exposed to hepatitis C at the time of their first treatment, often as a small child and with blood products used before the introduction of concentrates.

The UK Haemophilia Directors Organisation (UKHCDO) recommended from 1990 that HCV antibody testing should be added to routine screening for hepatitis in patients with haemophilia who had previously received blood products. It was however recognised that the first-generation HCV antibody test was unreliable for establishing whether or not an individual patient had been exposed to hepatitis C.

It was also recognised that full evaluation of hepatitis C would require complex clinical and laboratory evaluation over the next few years. Such evaluation would include annual testing for HCV antibody (using more reliable second-and third-generation tests), followed by further blood tests to establish whether or not patients were actually infected (carriage of the HCV virus in the blood, as detected by the polymerase chain reaction (PCR) test), furthermore, whether or not HCV carriers had chronic hepatitis would require repeated blood testing over several years, supplemented as appropriate by other tests (e.g. liver scans, endoscopy, liver biopsy) and by repeated clinical examinations. Therefore," hepatitis C testing and information given to patients" is a complex process that takes several years.

In 1993, the UK Haemophilia Society distributed its first booklet for patients on Hepatitis, which noted the above developments and encouraged patients to discuss hepatitis with their Haemophilia Centre staff. This and subsequent patient information booklets from the Haemophilia Society, the British Liver Trust and other sources were given to patients at routine clinic reviews and were freely available at Haemophilia Centres.

In 1995, UKHCDO produced its first "Guidelines on the diagnosis and management of chronic liver disease in haemophilia" (Preston et al, Haemophilia, 1995, 1, (Suppl 4), 42-44), which together with other UKHCDO guidelines were distributed to Haemophilia Centre staff and kept at Haemophilia Centres. Recommendations for testing in this guideline included:

- Close collaboration should be established between the Haemophilia Centre Director and a consultant hepatologist, and that the latter should play an important role in the management of haemophiliacs with chronic liver disease.
- The patients should be kept fully informed of the results of all laboratory tests, including antibody status. The clinical implications of the findings should also be discussed.
- All patients who have been treated with blood products should be tested by a second/third-generation HCV antibody test. It is recommended that, for those individuals who are HIV-antibody positive and HCV-antibody negative a diagnosis of HCV infection should be sought by detection of HCV RNA by polymerise chain reaction (PCR). For this group of patients in particular, decisions with respect to treatment with interferon should be made through consultation with a hepatologist.
- Sexual transmission of hepatitis C is possible. Currently the risk is estimated at 3%, although the possibility of higher transmission risks under some circumstances cannot be excluded.

  The current data on the rate of sexual transmission and the advantages of barrier contraception should be discussed. Patients should be encouraged to take a joint decision with their sexual partners.

- Anti-HCV antibody testing should be offered to all sexual partners of HCV-antibody-positive patients. Although there is little evidence of vertical HCV transmission, HCV testing of children of HCV-positive mothers should be offered, but the interpretation of this may be difficult.
- HCV-infected patients known to have abnormal aspartate aminotransferase/alanine transaminase (AST/ALT) levels should attend for review at approximately 4-monthly intervals.

  For those HCV-antibody-positive patients without documented liver biochemistry results, ALT/AST levels should be determined on three occasions over a period of 6 months. If all three determinations are normal then, wherever possible, PCR should be performed for HCV RNA. This is to establish whether the patient has detectable viraemia, despite normal serum ALT. If HCV RNA is detected, the results and therapeutic implications should be discussed with a hepatologist. Patients with abnormal AST/ALT levels should attend for review at approximately 4-monthly intervals.

  It is important to stress that no definite relationship exists between liver enzymes (ALT/AST) levels and liver histology.

These Guidelines were updated in the second UKHCDO Guideline (Makris et al, Haemophilia 2001, 7, 339-345).

As far as current Haemophilia Centre Directors in Scotland can recall or establish from discussions with ex-colleagues or predecessors, these guidelines were available at all Haemophilia Centres and were generally followed. Patients were offered information and counselling about hepatitis C by Haemophilia Centre staff (including doctors, nurse specialists and at Comprehensive Care Centres social workers and counsellors trained in HIV and hepatitis counselling). As noted above, patient information leaflets on hepatitis, and contact addresses for local counselling services, were provided for patients. Each Haemophilia Centre established close relationships with local consultant hepatologists (and subsequently

also with hepatitis C nurse specialists) to whom patients were referred at an appropriate stage. Many patients have received anti-viral treatment for hepatitis C. Hepatitis services have been included in national UKHCDO Audits since the 1990s. A Haemophilia Centre Director is a member of the SIGN guideline development group that is currently writing the national hepatitis C guidelines.

Haemophilia Centre staff have spent much time over the last 15 years discussing hepatitis C with their patients. As we have described above, evaluation of patients for their hepatitis C status is not "a simple blood test". It has evolved over the years and is a complex process involving repeated blood tests, other tests and clinical examinations. Likewise knowledge about hepatitis C, its complications and its prognosis has evolved over the years. As with any other condition, patients vary widely as to the amount of information they want. Some have wished detailed discussion at every clinic visit. At the other end of the spectrum, some patients have declined review clinic appointments (some for years) or appointments at local Liver Clinics for specific discussion on hepatitis C.

With regard to transmission of virus infections, since 1985 all UK patients with haemophilia who have received blood products have been advised by Haemophilia Centre staff to take care with handling of blood and to discuss and practice safe sex with their partners (including use of barrier contraception) irrespective of the results of any tests for HIV or hepatitis viruses.

Finally, Haemophilia Centre Directors in Scotland have worked hard since the mid- 1980s, together with their patients, the Scottish National Blood Transfusion Service, NHS Scotland and the Scottish Executive to establish first that virally inactivated clotting factor concentrates used in NHS Scotland were safe, and second that these blood products were largely replaced by recombinant (non-human-derived) clotting factor concentrates from 1996 onwards.

We are happy for you to make this response public, but we are copying it to our Health Board Medical Directors whom you may wish to consult before doing this, because we are

employees of our Health Boards who were and are responsible for haemophilia treatment in NHS Scotland.

Yours sincerely

pp: Dr R.C.Tait

Secretary on behalf of Haemophilia Centre Directors in Scotland

c.c. Haemophilia Centre Directors in Scotland