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Guidelines on the diagnosis and management of chronic liver disease in haemophilia

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Virtually all haemophiliacs treated with clotting-factor concentrates before 1985 have been exposed to the hepatitis C virus (HCV) and almost 100% of these are HCV-antibody positive. A major problem of HCV infection is its propensity to cause chronic liver disease and it is generally acknowledged that this will occur in at least 50–75% of infected subjects [1]. Hepatocellular carcinoma is now emerging as a complication of chronic HCV infection, but this is usually a development of cirrhosis and hepatitis C [2].

Fluctuating abnormalities of liver enzymes are a chararacteristic feature of HCV-related chronic liver disease but it should be stressed that there is no definite relationship between the degree of abnormality of enzyme levels and liver histology. To date, interferon is the only drug of proven value for the treatment of chronic liver disease but sustained responses are limited to no more than 25% of most treated patients. Factors associated with poor response include HCV genotype 1 [3], high HCV viral titre, cirrhosis and increasing age [4].

The Working Party wish to stress that wherever possible, 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 patient 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.

Diagnosis of HCV infection

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 polymerase 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 HCV

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.

HCV testing of 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.

Follow-up of HCV-infected patients

1 HCV-infected patients known to have abnormal aspartate aminotransferase/alanine transaminase (AST/ALT) levels should attend for review at approximately 4-monthly intervals.

2 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.

Treatment with interferon alpha

Although interferon is of proven value in chronic HCV-

related liver disease, sustained remissions are achieved in only approximately 20% of patients treated with this drug. Recently a number of factors have been identified which influence this response rate. Of particular importance are HCV genotype, HCV viral titre, and the presence or absence of cirrhosis. Poor sustained responses, i.e. less than 1:4, can be anticipated in subjects infected with HCV genotype 1, in those with high levels of circulating virus and in subjects with cirrhosis. With respect to viral titres, it has been suggested that a virus level of 10^6 copies/ml might represent a threshold above which conventional treatment with interferon may be unsuccessful.

With this background, the Working Party on Chronic Liver Disease in Haemophilia wish to make the following recommendations.

Patients with biochemical and serological evidence of chronic HCV-related liver disease should be considered for treatment with interferon. However, for patients with ascites, variceal haemorrhages and/or cirrhosis, interferon is of little therapeutic value and may be hazardous.

Because treatment protocols recommended by hepatologists are very likely to be influenced by HCV genotype and HCV viral titre, these should be determined before treatment decisions are taken. Where individuals are infected with HCV genotype 1 and/or with high levels of circulating HCV viral titres (see above), it is strongly recommended that the results be discussed with a consultant hepatologist as it may be advisable for these patients to be treated for longer periods of time and with higher doses of interferon. Alternatively, better responses may be obtained by combination therapy with interferon and ribavarin. It should be appreciated, however, that the latter drug is not currently licensed for this indication.

Standard interferon treatment schedules are recommended for those patients who fulfil the criteria for treatment with interferon and who are infected with HCV genotypes other than type 1 and with high levels of circulating virus. Currently, Roferon-A (Roche) and Viraferon (Schering-Plough) are both licensed for the treatment of chronic HCV-related hepatitis. Recommended dose schedules are provided by the manufacturers.

Dr Peter Simmonds, Department of Medical Microbiology, The University of Edinburgh Medical School, Teviot Place, Edinburgh EH8 9AG, has kindly agreed to undertake, for UK Haemophilia Centre Directors, HCV genotyping by a highly standardized restriction fragment length polymorphism (RFLP) method designed to detect HCV genotypes1–6 and to differentiate between the common subypes of types 1, 2 and 3.

Co-infection with HIV

Irrespective of tests of liver enzymes, a polymerase chain reaction for HCV RNA should be undertaken in patients who are HIV-antibody positive and HCV-antibody negative. HCV genotype and viral quantification should be further undertaken in those who prove to be HCV RNA positive. Treatment decisions should be made following discussion of the results with a consultant hepatologist.

Role of liver biopsies

The Working Party felt that most patients can be managed without the necessity for a liver biopsy. A liver biopsy is indicated where a focal lesion has been identified by ultrasound examination, or where there is doubt regarding the aetiology of the chronic liver disease. It is strongly recommended that liver biopsies in haemophiliacs be performed by experienced operators.

Where liver biopsies are considered necessary we suggest the treatment regime provided below.

Day 0: Pre-biopsy dose: give calculated dose of factor VIII/IX to increase FVIII/IX to 1.0 U/ml (100%).
Dose 2 (p.m.): (FVIII). Further infusion to increase FVIII to 1.0 U/ml (100%).

Day 1: Assay FVIII/IX: give calculated dose of FVIII/IX to increase FVIII/IX to 1.0 U/ml (100%).

Day 2: Assay FVIII/IX: give calculated dose to increase FVIII/IX to 0.5 U/ml (50%).

Other investigations

Endoscopy is recommended every 5 years for patients over the age of 45 years, and/or those who have been infected with HCV for 30 years. Because there are suggestions that the progression of HCV-related chronic liver disease may be accelerated by co-infection with HIV this interval could be reduced in this group of patients.

Abdominal ultrasound is of little value in the staging of chronic HCV-related liver disease. In patients over the age of 45 years it is useful for screening for hepatocellular carcinoma. In patients known to have cirrhosis, an abdominal ultrasound examination and alpha fetoprotein determination are recommended at approximately 4-monthly intervals.

Role of alcohol

Excessive alcohol intake in patients known to be HCV-antibody positive is associated with an increased likelihood of the development of cirrhosis and hepatocellular carcinoma. Patients should be advised not to exceed a weekly consumption of 21 units of alcohol in men, and 14 units of alcohol in women. This is not an all or nothing

phenomenon, and the lower the alcohol intake the better the outcome. (One unit of alcohol is equivalent to 1/2 pint of beer, or 1 glass of wine, or 1 measure of spirits.)

Liver transplantation

Liver transplantation is of proven value in some patients with end-stage liver disease due to hepatitis C. However, recurrence of hepatitis C occurs in 90% of patients. Recommendations for this treatment option will be made by the consultant hepatologist in collaboration with the Haemophilia Centre Director.

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