PENROSE ENQUIRY

4.11.2011

Report from Professor Peter Hayes

re: Itemised questions received from Lindsey Robertson with regard to the Penrose Enquiry C6

1. Regarding the first treatment for patients found to have acquired Non-A Non-B hepatitis

With regard to this question it is important that Non-A Non-B hepatitis when it was used before 1989, when the hepatitis C virus was identified, was not a specific diagnosis. It tended to be used for people who became jaundiced or had abnormal liver tests after a blood transfusion, where hepatitis A and B could be excluded, but also tended to be used for unexplained hepatitis. For example the term "enteric" Non-A Non-B hepatitis is referred to in the textbook Diseases of the Gastrointestinal Liver Tract, Shearman and Finlayson 2nd edition published in 1989, which is clearly not hepatitis C. Therefore not all Non-A Non-B hepatitis before 1989 represented hepatitis C.

With regard to treatment, the first that was found successful in some cases was human alpha Interferon and was reported in the New England Journal of Medicine in 1986 volume 315; page 1575-8. This reported treatment in 10 patients believed to have Non-A Non-B hepatitis and we would now consider likely to be hepatitis C. These individuals had had either blood transfusions, drug abuse or, in one, employment in North Africa. The treatment appeared partially successful but was

monitored for improvement in liver enzymes rather than eradication of a virus, as this was not able to be identified at that time. It should be recognised that many patients with abnormal liver function tests, in whom no obvious cause could be found, would potentially have been labelled as Non-A Non-B hepatitis. We recognise this far more nowadays with non alcoholic fatty liver disease causing abnormal liver function tests and is associated with obesity. This condition was not significantly recognised in the pre hepatitis C era.

With regard to what was the purpose of the treatment this would obviously be to eradicate a putative virus and the paper mentioned above records that prolonged treatment was associated with sustained improvement in aminotransferase levels and improvement in liver histology was seen in some.

With regard to who was responsible for providing such treatment, this would generally be Gastroenterologists with an interest in hepatology. My understanding is that such treatment was unusual before 1989, presumably because of the lack of precision in making a diagnosis. I have no personal recollection of using this treatment in the setting of Non-A Non-B hepatitis at this time.

2. This will be answered in two sections, firstly, related to Non-A Non-B hepatitis and then hepatitis C

Effective treatment for chronic Non-A Non-B hepatitis before human alpha Interferon was not effective. The publication referred to in question 1 was the

first publication I am aware of reporting the use of alpha Interferon in Non-A Non-B hepatitis. This publication involved only 10 patients was very different to more recent drug trials for hepatitis C which are much larger and randomised controlled studies.

With regard to hepatitis C once the virus could be identified, drug trials showed in turn that alpha Interferon alone, three times weekly, appeared effective in clearing the virus in a minority of patients. This was followed by the combined use of three times weekly alpha Interferon with Ribavirin and more recently with the use of once weekly pegylated alpha Interferon along with Ribavirin. With each of these changes the success rate in clearing the virus i.e. curing the patient increased incrementally with the last treatment inducing cure between 50 and 75% depending upon viral genotype. Until recently, there were two main sources of clinical trials namely two pharmaceutical companies Schering Plough (now part of MSD) and Roche. Companies carried out large randomised controlled trials for drug licensing purposes and which provided a solid base of evidence for guidelines to be developed and advances to be recorded.

3. Regarding treatment of the hepatitis C virus over the years please see answer to question 2. The original treatment with alpha Interferon three times a week was introduced in clinical practice around 1991/2 with Ribavirin being added around 1995/6 and pegylated Interferon around 2000. I will mention the new drugs Boceprevir and Telaprevir below.

With regard to the question about counselling and other holistic care, this is difficult to give a simple answer, as it will have varied from Unit to Unit and over time. However, generally patients when they would have had a diagnosis of hepatitis C made would have had counselling about natural history, infectivity and treatment options and some patients might be interested in alternative medicine or herbal medicines. I suspect the advice they will receive from medical practitioners may vary. The evidence base for using these agents is minimal and unconvincing. Regarding alcohol intake, generally patients are advised, certainly in our Unit, that if they have cirrhosis they should be teetotal but if their liver disease is short of cirrhosis then drinking within sensible limits of 21 units for men and 14 units a week for women is considered safe. Nowadays we locally advise patients it is best not to be overweight and more recently give information that coffee may be protective to the liver.

It as been known for many years that Non-A Non-B hepatitis and hepatitis C can progress to cirrhosis and in the early days there was discussion about what proportion of patients may progress over time. A figure of 20% being cirrhotic after 20 years was quoted. I believe it true to say that many thought the majority of patients would not develop cirrhosis. Recent data by Foster in London suggests that 71% of Asian patients develop cirrhosis over 60 years (Clinical Gastroenterology & Hepatology 2005,3:840-2). Our understanding of the natural history of the condition changed and this affected patient selection for treatment. In the early days with regard to funding treatment NICE recommended that only those patients with severe disease i.e. not early, should be treated and that this should be based on liver biopsy. It was agreed at a Consensus Conference in

Edinburgh in April 2004 that the histology should not have such a key place. In Scotland there was an emphasis to increase the number of people being treated in the Scottish Hepatitis C Action Plan published in 2005. Because of the seriousness of the condition once cirrhosis has been reached in relation to progressive liver disease, including complications of portal hypertension, such as variceal haemorrhage and the development of liver cell cancer, treating people earlier was believed important. Patients once they have cirrhosis even if they can be cured of the hepatitis C still require long term hepatocellular carcinoma screening and long term follow up.

With regard to guidelines for treatment of hepatitis C there have been many and they have changed with time. Guidelines tend to be produced by a large organisations such as the American Association for the Study of Liver Disease, the European Association for the Study of the Liver and relatively recently the Scottish Intercollegiate Guidelines Network (SIGN) (published December 2006 www.sign.ac.uk). As response to treatment has been identified as varying, with such factors as age, severity of liver disease and genotype of the virus, protocols have become more complicated and tailored. For example, in 2006 the Sign guidelines the treatment of patients is based on genotype and also stopping rules in patients who respond to treatment were included. The stopping rules are likely to be even more of a feature as the newer orally active drugs are introduced.

From the above therefore it can be seen that guidelines have developed over the years and treatments have improved. One of the early guidelines was an EASL International Consensus Conference statement in the Journal of Hepatology 1999

volume 30:956-961. Treatment guidance before that tended to be based on results of clinical trials and reviews of trials.

Regarding your question about having been diagnosed with hepatitis C at what stage should the patient receive treatment has evolved over the years.

As mentioned previously it was originally proposed by NICE that patients, on the basis of a liver biopsy, should only have treatment if they did not have mild disease. Emphasis on liver biopsy was downgraded in the Scottish Consensus meeting and this is now widely accepted, and the most important determinant is whether the patient wishes treatment or not. Patients may decide for a variety of reasons they do not wish treatment, particularly if they are asymptomatic. Where patients have more advanced disease, particularly if they have cirrhosis, then we are keen to encourage them to treatment compared with, for example, an elderly patient who is asymptomatic and had no clinical, biochemical or imaging features of cirrhosis.

4. The effectiveness of treatment

Hepatitis C treatment has significantly improved over the past 20 years. Overall effectiveness with Interferon monotherapy was probably around 10-20% and this improved with the addition of Ribavirin to around 30-40% and with pegylated Interferon and Ribavirin to around 50% in genotype 1 patients and over 70% in genotype 3. The addition of the new oral agents Boceprevir and Telaprevir, which are both indicated in genotype 1 patients only, will improve the effectiveness i.e. sustained virological response i.e. cure from around 50% to 75%. Other than the

treatment and the genotype, factors such as age, cirrhosis, co-infection with HIV virus effect treatment success rates. With regard to patients having more than one genotype of virus in clinical practice this is extremely rare. It would appear that although theroretically patients may be infected by more than one genotype but in clinical practice only one genotype is detected.

5. I am unaware of haemophilia per se affecting the modern treatment response. Our experience with monotherapy in the 1990s suggested perhaps response less than figures in the literature in non haemophliacs, but I do not believe this has been borne out subsequently. Factors such as age and gender, given that nearly all haemophiliacs are male, would have a minor effect on treatment response. A recent publication in Liver International (2010 volume 30(8): page 1173-80) shows sustained virological response in haemophiliac patients of 51% in genotype 1 and 71% in genotype non 1. Age less than 24 with a BMI of less 25 and a viral load less than 600000 IU/ml and genotype non 1 were the major determinants of SVR achievement in these patients.

6. With regard to individuals response to treatment who are co-infected with HIV this is generally believed to be reduced compared with patients without HIV. The response rate of 48 weeks of pegylated Interferon and Ribavirin is around 60% in patients with genotype 2 and 3 and between 14-29% in patients with genotype 1. This latter figure improved in patients with a low HCV viral load (New England Journal of Medicine 2004 351:451-9, JAMA 2004 292:2839-48 and New England Journal of Medicine 2004 351:438-50).

7. Side effects with antihepatitis C drugs are significant. I mention here the more important ones related to Interferon and Ribavirin and the newer agents which are likely to be used soon. With Interferon and Ribavirin flu-like symptoms are common as are anaemia and neutropenia. Anaemia is primarily related to Ribavirin and more recently rather than reducing doses of Ribavirin, Erythropoietin has been used. Granulocyte colony stimulating factor may stop drug-induced neutropenia. Depression is a relatively unusual side effect but can be serious and antidepressants can be used successfully in this setting. In patients with a psychiatric history a psychiatric consultation is invaluable before starting treatment. As with many drugs skin reactions may occur including dry skin, itch, eczema in a significant proportion. Thyroid dysfunction may occur with Interferon and Ribavirin manifest as either overactive or underactive thyroid. This side effect is not always reversible. Other side effects such as weight loss, breathlessness, retinopathy, hair loss and poor concentration are recognised.

With regard to new treatments, Boceprevir is now licensed and SMC approved. Its most frequently reported adverse reactions are; fatigue, anaemia, nausea, headache and dysgeusia (abnormal taste). Telaprevir is now licensed but has not been SMC approved and the main side effect with this drug is skin rashes which can be severe even life-threatening.

As can be seen from the above there are many side effects related to treatment and considering treatment involves weekly injections and is taken generally for either 6 or 12 months this undoubtedly impacts on patients quality of life. Stopping

roles are designed to reduce drug exposure and side effects in those very likely not to respond. Patients reaction to treatment is variable ranging from intolerable side effects to having little impact on quality of life.

8. It can be seen from the above that there are now two licensed new orally active treatments for patients with genotype 1 which significantly improve success rate of treatment. However, currently these agents are used in combination with pegylated Interferon and Ribavirin it will probably be several years before regimes have developed that are Interferon free. These new orally active agents have their own side effects and are currently very expensive. Their use will require closer monitoring and significant resources.