Case Study in the Management of Chronic Hepatitis C in Non-responders to Antiviral Therapy

Jenny Heathcote

CASE

A 39 year old white business man was first found to have abnormal liver biochemical tests in 1990 when he went to see his family physician for a routine checkup. At the age of 17 he had begun injecting drugs and at age 18 he had an episode of acute hepatitis. Despite this he continued to be an injecting drug user for another 3 years. He had never been a heavy drinker, consuming no more than 3 beers per month. He has been overweight since he was a teenager (Body Mass Index 32). He has asthma, and takes local medication to relieve the symptoms. His mother is said to have died of liver cancer.

The patient was first referred to a hepatology clinic in 1997 after being tested and found positive for hepatitis C. At that time, his liver function tests were normal; serum bilirubin 11µmol/L, serum albumin 48g/L, and international normalized ratio (INR) of 1.2. His liver biochemical tests revealed an aspartate aminotransferase (AST) of 81IU/L and an alanine aminotransferase (ALT) of 160IU/L, serum alkaline phosphatase levels were normal. His hemoglobin was 146g/L, white cell count was 4.2×10^6/L, and platelet count was 148×10^6/L. Ultrasound suggested that the liver texture was heterogeneous without focal lesions and the size of the liver and spleen were normal. Bile

ducts were normal. A percutaneous liver biopsy performed in 1998 showed grade 2 activity and stage 4 fibrosis (METAVIR). Genotyping and viral load were not available at that time.

The patient was treated with interferon 3mU 3 times/week for 12 weeks. However his liver biochemical tests never returned to normal, he had headaches, fever and nausea and his white blood count decreased, so after 12 weeks he stopped treatment. The following year he was identified as genotype 1a with a viral load of $9x10^4$IU/L. In 2001 he was retreated with pegylated interferon alpha-2a (180µg/wk) and ribavirin 1200mg daily for a full year with no improvement in either liver biochemistry or viral load. He described the treatment as "brutal".

In 2003 he was reassessed because he was anxious about undergoing long-term therapy. He was recruited for the European prospective investigation into cancer and nutrition (EPIC) program and received a further 12 weeks of treatment with pegylated interferon alpha-2b 1.5µg/kg/wk + ribavirin 1200mg/day. At the end-point of these 12 weeks, his white blood cell count was only $1.5x10^6$ (absolute neutrophil count [ANC] 0.9) and his platelet count $70x10^9$/L. Liver function tests (Alb 4.1g/L, bilirubin 17mmol/L) were normal and his serum aminotransferases remained elevated (AST 149, ALT 252). There was a <2 log decrease in his viral load after 12 weeks of therapy. Treatment was stopped and he was randomized to long-term observation rather than long-term low dose pegylated interferon alpha-2b.

This 46-year old male has a 30 year history of hepatitis C and currently has compensated cirrhosis. He has failed to respond to interferon monotherapy, or pegylated interferon alpha + ribavirin. This case history raises a number of questions.

What are the risk factors for progressive disease?

Factors recognized to influence the rate of progression in chronic hepatitis C include age at acquisition, male gender, co-infection with hepatitis B and/or HIV, regular alcohol consumption and hepatic steatosis. In addition, there may be genetic factors which are unknown as yet [1].

What factors influence response to antiviral therapy?

Lack of response to treatment is influenced by viral genotype (genotype 1a responds particularly poorly), the pattern of quasi species development during treatment, and the viral titer. Genetic factors such as ethnicity (African-Americans respond poorly) and genetic factors controlling interferon responsiveness play a role. There may also be viral factors which influence interferon response genes, e.g. IRF3 inhibited by genotype 1. Host factors influencing antiviral therapy include the degree of hepatic fibrosis, hepatic steatosis, continued alcohol consumption and central obesity [2, 3].

Is antiviral therapy beneficial in patients with persistent viremia?

Short-term follow-up of individuals treated with interferon and ribavirin indicate that in some individuals, there may be a reduction in the degree of hepatic fibrosis, despite persistent viremia. However, long-term follow-up studies of therapy do not show that this improvement is maintained.

In patients with cirrhosis the risk of hepatocellular carcinoma (HCC) is only slightly reduced even in those with a sustained virological response to treatment, i.e. antiviral therapy needs to be given prior to the development of cirrhosis to effectively reduce the risk of HCC [4-7].

What treatment strategies are there for hepatitis C patients with cirrhosis who are non-responders to antiviral therapy?

Preventive strategies such as regular screening for hepatocellular carcinoma on a semiannual or annual basis (and early treatment if HCC is detected) as well as screening for esophageal varices and prophylactic therapy with non-selective beta blockers when varices develop may improve overall survival.

General strategies for patients with cirrhosis include advice on avoiding certain drugs, e.g. benzodiazepines, nonsteroidal anti-inflammatory drugs (NSAIDs), and aminoglycosides. Patients should also always be reminded to have infections treated rapidly. In patients who are not immune to hepatitis A and B, vaccination is recommended to avoid the risk of developing a superimposed acute hepatitis.

Because the risk factors for HCC in cirrhosis due to hepatitis C include iron overload, diabetes/obesity and smoking, attempts should be made to reduce these additional risks.

There are some data which suggest that the use of triple therapy (interferon, ribavirin and amantadine) may be effective in non-responders to antiviral therapies [8, 9].

REFERENCES

1. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet 1997;349:825-832.

2. Layden-Almer JE, Ribeiro RM, Wiley T, Perelson AS, Layden TJ. Viral dynamics and response differences in HCV-infected African-American and white patients treated with IFN and ribavirin. Hepatology 2003;37:1343-1350.

3. Bressler BL, Guindi M, Tomlinson G, Heathcote J. High body mass index is an independent risk factor for nonresponse to antiviral treatment in chronic hepatitis C. Hepatology 2003;38:639-644.

4. Poynard T, McHutchison J, Manns M, Trepo C, Lindsay K, Goodman Z, Ling MH, Albrecht J. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. Gastroenterology 2002;122:1303-1313.

5. Shiratori Y, Imazeki F, Moriyama M, Yano M, Arakawa Y, Yokosuka O, Kuroki T, Nishiguchi S, Sata M, Yamada G, Fujiyama S, Yoshida H, Omata M. Histologic improvement of fibrosis in patients with hepatitis C who have sustained response to interferon therapy. Ann Intern Med 2000;132:517-524.

6. Yoshida H, Shiratori Y, Moriyama M, Arakawa Y, Ide T, Sata M, Inoue O, Yano M, Tanaka M, Fujiyama S, Nishiguchi S, Kuroki T, Imazeki F, Yokosuka O, Kinoyama S, Yamada G, Omata M. Interferon therapy reduces the risk for hepatocellular carcinoma: national surveillance program of cirrhotic and noncirrhotic patients with chronic hepatitis C in Japan. IHIT Study Group. Ann Intern Med 1999;131:174-181.

7. Farci P, Strazzera R, Alter HJ, Farci S, Diogioannis D, Coiana A, Peddis G, Usai F, Serra G, Chessa L, Diaz G, Balestrieri A, Purcell RH. Early changes in hepatitis C viral quasispecies during interferon therapy predict therapeutic outcome. Proc Natl Acad Sci USA 2002;99:3081-3086.

8. Teuber G, Pascu M, Berg T, Lafrenz M, Pausch J, Kullmann F, Ramadori G, Arnold R, Weidenbach H, Musch E, Junge U, Wiedmann KH, Herrmann E, Zankel M, Zeuzem S. Randomized controlled trial with IFN-alpha combined with ribavirin with and without amantadine sulphate in non-responders with chronic hepatitis C. J Hepatol 2003;39:606-613.

9. Foy E, Li K, Wang C, Sumpter R, Masanori I, Lemon S, Gale M. Regulation of interferon regulatory factor-3 by the hepatitis C virus serine protease. Science 2003;300:1145-1148.