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Short communication

Summary: antiviral treatment of hepatitis C virus

G.M. Dusheiko[1]

University Department of Medicine, Royal Free Hospital and School of Medicine, Pond Street, Hampstead NW3 2QG, UK

In 1989, Houghton and co-workers succeeded in isolating nucleic acid of the major NANB agent by recombinant DNA technology (Kuo et al., 1989; Choo et al., 1989; Choo et al., 1990). This virus has been given the nomenclature hepatitis C virus (HCV). Several isolates of hepatitis C have been cloned. The sequence divergence of these isolates indicates that that are several major genotypes of hepatitis C, and component subtypes (Chan et al., 1991; McOmish et al., 1993). Geographic localization of these types has been reported.

The virus has a propensity to cause chronic infection, and it is believed that 10%–20% of patients with chronic hepatitis C infections will progress to cirrhosis within a decade.

In some countries, patients with type II autoimmune CAH appear to have a high frequency of genuine exposure to HCV, and antibodies to liver kidney microsomal antibodies are present in patients (Lenzi et al., 1991; Onji et al., 1991). These patients may also have circulating antibodies to a pentadecapeptide (Gor), an epitope of normal hepatocytes; this phenomenon may represent an auto-immune response peculiar to type C hepatitis (Mishiro et al., 1990). This association has some therapeutic implications, as in some of these patients the disease may be aggravated by alpha interferon and is responsive to corticosteroids.

1. Acute hepatitis C

The disease may be relatively silent in the acute phase, as most (75%) patients are not jaundiced, and have only non-specific symptoms. Current tests should enable a diagnosis to be made in many if the disease is suspected. The diagnosis may require testing for HCV RNA, as some patients may not have anti-HCV at the time that serum aminotransferases are elevated.

Therapeutic trials of alpha interferon have been undertaken. Initial treatment trials of alpha interferon for 12 weeks did not result in lasting benefit by reducing the rate of chronic disease. A trial of beta interferon in Japan, given intravenously for 1–3 months, did significantly reduce the risk of chronic hepatitis however (Omata et al., 1991). Recent phase II trials with alpha and beta interferon, which have included 8 weeks to 12 months of therapy and higher doses (up to 6 mu), have provided more convincing evidence that risk of chronic hepatitis can be reduced. However, it is not always clear whether treatment has benefited those patients who might have been convalescing spontaneously, and whether late relapses will still

[1] Tel.: +44 171 830 2993; fax: +44 171 431 4581.

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occur in those patients who remain HCV RNA positive. However, if a diagnosis of acute hepatitis C can be made, and the patient does not appear to be convalescing 2–4 months after the onset of the disease, alpha interferon can be considered at a dose of 3–6 mu tiw for at least 4–6 months.

2. Chronic hepatitis C

Individuals with chronic hepatitis C with elevated ALT, detectable viraemia and chronic active hepatitis histologically should be considered for antiviral therapy. Preliminary therapeutic trials of alpha interferon indicated that a proportion of patients may respond to treatment with this agent. Larger, placebo controlled studies have indicated that approximately 50% of patients will have normal serum aminotransferases after treatment courses of alpha interferon of approximately 3 million units three times a week for 6 months (Davis et al., 1989; Di-Bisceglie et al., 1989).

Serum HCV RNA may become undetectable in patients after 4–8 weeks of alpha interferon treatment in patients who respond, but an undetectable HCV RNA at the end of treatment does not preclude relapse in patients. However, after stopping treatment after 6 months, one half of the responsive patients will promptly relapse. Serum aminotransferases usually increase in patients who are HCV RNA positive at the end of therapy, although in some cases the relapse may be delayed for several months (Chayama et al., 1991). Our studies at the Royal Free Hospital indicate that 20% of patients have a prolonged response to therapy and do not again develop elevated serum aminotransferases (Varagona et al., 1992). These patients also remain negative for HCV RNA.

There is most information about 3 mu tiw given for 6 months. It is not yet clear whether this dose is optimal. Other regimens are being evaluated, and there is a suggestion initiating therapy with a somewhat higher dose of 15–18 million units per week, and prolonging therapy for a year may result will lower relapse rates. In a Japanese study of alpha 2b, it was concluded that 10 MIU of IFN administered 6 days a week for 2 weeks followed by three times a week for an additional 12 weeks produces the highest rate of both biochemical and virological responses to IFN therapy in patients with chronic HCV (Iino et al., 1993). However, relapses still occur after higher doses. Therefore, studies to stratify for other variables determining response are required to justify the higher cost and increased side effects. Treatment should not be continued beyond 3 months in patients who do not have reduced levels of serum ALT. Responsive patients usually exhibit histological improvement.

Unfortunately, responsiveness to alpha interferon remains somewhat unpredictable. Factors which predict a greater likelihood of response are now being studied. Multivariate analysis of several pre-treatment parameters indicate that patients without cirrhosis are more responsive to interferon, and are more likely to have a sustained response. The influence of genotypes of hepatitis C is the subject of considerable interest at present, as is the association between lower levels of viraemia and response. In Japanese studies on genotypes, it has become apparent that Simmonds 1b, the most prevalent genotype in Europe and Japan, is associated with a poor response to interferon therapy (Okamoto et al., 1992a; Okamoto et al., 1992b). Similar differences in European patients have been reported. However, types 2 and 3 are more sensitive to interferon in a high proportion of patients. Patients with diverse circulating quasispecies may be less responsive to therapy than those with a single major species. Improved responses have been observed in patients with lower levels of circulating HCV RNA (Yamada et al., 1992). Unfortunately, the issue remains complex: there is not yet a standardized system or nomenclature for genotyping hepatitis C, or for quantitating concentrations of HCV RNA in serum. Also, these factors may be interdependent, as particular viral strains may replicate at higher efficiency than others.

When can treatment be considered successful? These criteria vary, but it is reasonable to infer that those patients with normal serum ALT a year after stopping interferon treatment, and negative for HCV RNA a year after stopping therapy, with histologically improved disease activity, and a perhaps normal serum procollagen III peptide

have had a good response. HCV antigens may be cleared from the liver with successful treatment (Krawczynski et al., 1992).

Unfortunately, a proportion of patients may have a good initial response on treatment, but then the ALT rise again despite continuing treatment; it is possible that some patients develop neutralizing interferon antibodies; the timing of antibody development may be a factor in explaining the course of responsive patients who do develop neutralizing antibodies (Dianzani, 1993). Continuing interferon with a second course of treatment with a different interferon may be useful in some patients. Only a small number number of patients have been reported however.

Other patients do not respond to treatment, and no improvement in serum ALT can be discerned. Some patients may actually worsen on treatment with interferon, and develop increased serum aminotransferases. A positive anti-HCV antibody in patients with autoimmune disease remains a pitfall in diagnosis, which has implications for treatment (Davis, 1991). Such patients require confirmation by immunoblot assay, or HCV RNA, as they may optimally require corticosteroid therapy (Czaja et al., 1991). It is possible that such patients have an underlying autoimmune status associated with hepatitis C and exacerbated by interferon treatment. For such patients, and for patients who do not respond to treatment, ribavirin may be an alternative (Reichard et al., 1991).

Immunosuppresed patients and patients with HIV may response although long term responsiveness is uncertain. This is of particular importance in liver transplant patients.

3. Ribavirin

Ribavirin is a synthetic guanosine nucleotide analogue, which possesses a broad spectrum of activity against both DNA and RNA viruses in vitro and in vivo (Fernandez et al., 1986). The drug exerts its action after intracellular phosphorylation to mono, di- and triphosphate nucleotides. The precise mode of action probably includes pertubation of intracellular nucleoside triphosphate pools, interference with the formation of the 5′ cap structure of viral mRNA by competitive inhibition of both guanyltransferase and methyltransferase capping enzymes, direct inhibition of the viral mRNA polymerase complex, and possibly enhancement of macrophage inhibition of viral replication.

The pharmacokinetics of ribavirin have been studied. The bioavailability of oral formulations has been calculated at 19–65% (compared with IV administration). The distribution half-life is 1–3 h, but the terminal half life is prolonged (27–52 h) perhaps due to sequestration within red cells and other tissues. Ribavirin is concentrated 10–50 fold in red blood cells, and crosses the blood brain barrier. Peak plasma levels range from 5–13 uM after single oral doses of 600–2400mg. The excretion of the drug is predominantly renal.

The major side effects of the drug that have been reported include anaemia, a metallic taste, dry mouth, flatulence, dyspepsia, nausea, headaches, irritability, emotional lability, fatigue, insomnia, skin rashes and myalgia. Mild reversible anaemia is common. Modest increases in uric acid have been reported.

3.1. Studies of ribavirin in hepatitis C infection

Tong treated 22 patients with chronic hepatitis NANB with ribavirin 1200 mg daily for 4 weeks; although the details are not published, ALT and AST declined from a median of 145 to 78 and 86 to 52 u/l respectively. After 4–8 weeks follow up, median levels of both ALT and AST had increased to pre-treatment levels. An open label study in Sweden, in which ribavirin was prescribed to 10 patients with chronic hepatitis C (1000–1200 mg/day) for 12 weeks has been completed. Median serum AST levels declined, but rose to pre-treatment levels upon completion (Reichard et al., 1991). A small study, using escalating doses of ribavirin (600–1200 mg) showed a somewhat slower fall in serum aminotransferases, perhaps reflecting the lower starting dose of ribavirin. There was a significant decrease in geometric mean titres of HCV RNA. At the Royal Free Hospital, we treated treated 28 patients with chronic hepatitis C in a pilot study (Rassam and

Dusheiko, 1992). Thirty eight percent had normal ALT during treatment, but a further third had only a 50% decline in ALT. The remaining third were not responsive. The time course of normalization of ribavirin is slower (mean time to normal 5.5 months) in patients with biochemical improvement. Despite the significant improvement in serum ALT, we have not observed a marked decline in serum HCV concentrations quantitated by a branched DNA assay.

In a recent multicenter study, the efficacy and safety of a 24-week course of oral ribavirin in patients with chronic hepatitis C, compared to placebo was assessed; 114 patients were randomized to ribavirin or placebo. Ribavirin was administered in doses of 1000 or 1200 mg/day for 24 weeks. Efficacy was determined in the intention to treat population: 76 received ribavirin and 38 placebo. Ribavirin was significantly more effective than placebo in reducing and normalizing serum ALT levels. Fifty-five percent of ribavirin treated patients vs 2/38 (5%) of placebo recipients had either normalization of ALT levels or a reduction from baseline of at least 50% ($P < 0.001$). ALT levels were normal in 22/76 (29%) of ribavirin treated patients vs 0/38 placebo recipients ($P < 0.001$). However, 24 weeks after stopping ribavirin, the majority of patients had abnormal ALT levels. There was no difference between the treatment groups in reduction or disappearance of HCV RNA levels. More ribavirin than placebo patients showed improvement in total Knodell score (45% vs 31%) but these differences were not statistically significant. Ribavirin was also associated with reversible haemolytic anaemia: A fall in haemoglobin occurred in 32% of treated patients. These data indicate that ribavirin was no more effective than placebo in reducing or eliminating HCV RNA levels, and was not significantly more effective than placebo in improving hepatic histology after 6 months of treatment. The role of 6 months treatment with ribavirin, which is without an effect on HCV RNA, is therefore limited.

More emphasis is therefore being placed on combination therapy with ribavirin and interferon (Table 1). Several small trials have been completed. In each of these studies, patients treated with a combination of interferon alpha and ribavirin (at doses of 800 mg–1.2 gm) for 6 months have improved virological responses. However, the number of patients treated in these regimens have been small, and further follow up for relapses is required. Larger controlled trials are being planned.

4. Antiviral treatment and liver transplantation for hepatitis C

Cirrhosis due to hepatitis C becoming an important indication for liver transplantation, and the number of patients being transplanted for decompensated hepatic disease has increased in the past 5 years. It has become apparent that recurrence of hepatitis C virus infection is common, and that 90% or more of patients transplanted will again be HCV RNA positive. The recurrence is rapid, and HCV RNA can be found in the engrafted liver within 2 weeks of the transplant. A number of studies have investigated the biochemical virological and histological outcome of the transplantation (Zignego et al., 1993; Read et al., 1991; Poterucha et al., 1992; Feray et al., 1992; Wright et al., 1992; Ferrell et al., 1992). Episodes of biochemical hepatitis are more common in patients with recurrence of HCV than in control groups of patients transplanted for cirrhosis not due to chronic hepatitis

Histological hepatitis is also more common, and chronic hepatititis is seen in the approximately 60% of patients at 3 years. Cirrhosis occurs in about 10% of patients after 2–3 years.

Thus although the recurrence is associated with relatively mild disease, follow up of these patients

Table 1
Combination treatments for chronic hepatitis C

Ribavirin and interferon alpha
Interferon and acetylcysteine
Interferon and ursodeoxycholic acid
Interferon and indomethacin
Interferon and zoduvidine
Prednisolone withdrawal and interferon
GCSF and interferon
Iron depletion and interferon
Thymosin and interferon

has been short, and severe sequelae, including cirrhosis and even possibly hepatocellular carcinoma may become more common with the passage of time. This provides the rationale for consideration of treatment. There is as yet little information in these patients. Preliminary studies have indicated that in some treated patients, levels of ALT may improve, along with a decline in concentrations of HCV RNA. As with chronic hepatitis, many patients are unresponsive, and biochemical deterioration may occur. Moreover, interferon is a powerful modulating agent, and there is concern that rejection may be increased with this treatment. Relapse rates are likely to be high. Carefully considered controlled trials are therefore indicated. The timing and dose of treatment will require assessment.

Ribavirin is less likely to be effective for transplanted patients if it is verified that this agent does not decrease circulating HCV RNA concentrations. A small pilot study of interferon and GCSF in patients with cirrhosis due to hepatitis C has been completed, with encouraging results. The toxicity of this regimen in patients with advanced liver disease and portal hypertension will require careful monitoring.

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