

Commentary

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Adding interventions to interferon in chronic HCV infections

Interferon alfa is the only licensed therapy for chronic hepatitis C. The response rate with interferon monotherapy in terms of sustained loss of HCV RNA is 20–25%. It is now possible to predict, from baseline host and viral factors and from the early response to interferon, which patients are most likely to respond to therapy.¹ Patients with cirrhosis or type 1b infection, for example, are less likely to respond to interferon. More prolonged treatment courses² and higher doses of interferon are associated with improved response rates but both these approaches are complicated by reduced patient compliance and limited by treatment costs.

Ribavirin monotherapy results in a temporary reduction in the transaminase levels³ but only a modest and transient decrease in the HCV RNA levels. The combination of interferon alfa and ribavirin, however, seems promising treatment for naive patients⁴ and for those who have failed to respond to interferon monotherapy.⁵ Multicentre trials of such dual therapy are in progress. Proteinase inhibitors seem promising for the treatment of HIV infection and are under development for chronic hepatitis C. Antiviral research, however, is limited by the lack of suitable cell culture and animal models. The success with interferon alfa as treatment for chronic hepatitis B and C is thought to relate to its combination of antiviral and immunomodulatory activity. This has led to trials with other cytokines such as interferon beta, gamma, interleukins, and thymus derived polypeptides.

Extract of bovine and porcine thymus has been shown to have immunostimulatory activity. Various peptides have been identified and more recently sequenced and synthesised. Thymus humoral factor, (thymus humoral factor- γ_2), is a synthetic octapeptide and thymopentin is a synthetic heptapeptide. Thymosin α_1 , used in the study on page 679, is a synthesised 28 amino acid peptide, which seems to be a major immunostimulatory component of crude thymus extract. Administration of thymic peptides leads to stimulation of release of interferon alfa, gamma, interleukin 2, increased interleukin-2 receptor expression with increased CD4, and natural killer cell activity.

Thymus extracts and factors have been tried as therapy for chronic hepatitis B in humans and in the woodchuck model. In small studies⁶ seven of 12 patients who received either thymosin α_1 or thymosin factor 5 and three of nine patients⁷ who received thymus humoral factor γ and interferon cleared HBeAg. In a small, uncontrolled study⁸ 15 patients with chronic hepatitis B were given a combination of thymosin α_1 and low dose interferon alfa. Nine of the patients lost HBV DNA.

The next challenge for this group was the treatment of chronic hepatitis C and the results of their study are published on page 679. In this open pilot study 15 patients with chronic hepatitis C received one year of the combination of thymosin α_1 and interferon. Thirteen of the patients had type 1b infection, usually associated with a reduced chance of sustained response, and four had failed to respond to previous treatment courses with interferon monotherapy. A sustained response with clearance of HCV

RNA six months after the discontinuation of therapy was seen in six (40%) of the patients. Following this study larger trials are in progress.

Chronic hepatitis C is a major health challenge for many countries including the United Kingdom. Many patients have progressive disease and without effective antiviral therapy are at risk of developing cirrhosis and hepatocellular carcinoma. Currently available treatment is expensive but has to be balanced against the inevitable clinical and economic burden of the long term complications. It is hoped that early effective antiviral or immunomodulatory therapy, or both, can reduce the morbidity and mortality of chronic hepatitis C. There is much to learn about the host-virus interaction and how this can be modified by cytokines as monotherapy or in combination. Recombinant technology has led to the availability of a number of immune modifiers that have potential for amplifying the host immune response to chronic viral infection. It is only with careful trials that the potential clinical application of these agents can be determined.

Two recent reports suggest that interferon may have other benefits and that treatment with interferon, whether or not successful in clearing hepatitis C virus, may reduce the chance of the development of hepatocellular carcinoma.^{9 10} Interferon has many actions and it may be that the antiproliferative in addition to the antiviral effects are beneficial for patients with chronic viral hepatitis.

In summary the results from these small studies are encouraging but it is only with the results of large, multicentre controlled trials with long term follow up that we can determine the potential clinical benefit of new interventions as treatment for chronic viral hepatitis.

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