

Historical treatment of chronic hepatitis B and chronic hepatitis C

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Abstract

Interferon is currently considered to be the only accepted effective treatment for chronic viral hepatitis. A history of the treatment of chronic hepatitis B and C before the use of interferon is presented here. Hepatitis B virus does not seem to be directly cytopathic and the disease is known to be modulated largely by the host's immune response. Experience with immunosuppressant and immunostimulant drugs and a wide variety of antiviral agents, however, has indicated that none of these are of any benefit in patients with chronic hepatitis B, with the possible exception of adenine arabinoside. In view of the much more recent identification of the hepatitis C virus, studies of therapy for chronic hepatitis C are inevitably less extensive. A pilot study using acyclovir in patients with chronic non-A, non-B hepatitis did not show any benefit, although the treatment period may have been too short for the results to be conclusive. The only agent other than alpha interferon to be tried in chronic hepatitis C is ribavirin, which may have some activity. Many of the agents studied in chronic hepatitis B should also be investigated for the treatment of patients with chronic hepatitis C.

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In reviewing the history of the treatment of chronic viral hepatitis one has to keep in mind that treatment of any disease depends on a precise understanding of pathogenetic mechanisms and the availability of drugs able to interfere with these. As with other diseases, there has been an explosion in knowledge on

viral hepatitis within the past two decades. Landmarks in the development of current pathogenetic concepts and understanding of the viral aetiology of chronic hepatitis are summarised in Table I. Before identification of the various hepatitis viruses and the development of precise diagnostic techniques, treatment of viral hepatitis with a wide variety of drugs was empirical. Their mode of action was poorly defined and their effects were not proved by valid, randomised controlled studies. Furthermore, studies may have included patients with liver diseases of different aetiologies, which means they cannot be compared with therapeutic trials conducted currently. The history of treatment of chronic hepatitis starts with the discovery of the hepatitis B virus (HBV). A wide variety of drugs with established benefit in the treatment of other chronic diseases, or with known antiviral effects towards other viruses, were screened for their potential to influence the course of chronic viral hepatitis. Most of these drugs were tested only in small pilot trials which may have been insufficient to detect efficacy. This overview considers these efforts, excluding the development of interferon treatment, which was first used for the treatment of chronic hepatitis B in 1976.¹ Today, interferon is considered to be the only accepted effective treatment for chronic viral hepatitis.

Treatment of chronic hepatitis B

The discovery of HBV in 1967² and the subsequent development of useful diagnostic tests facilitated the study of both the natural history of chronic viral hepatitis B and of the pathogenetic factors contributing to its progression. HBV is not directly cytopathic, and immune mechanisms are important in both the persistence of, and recovery from, HBV infection. Eradication of infected hepatocytes is mediated by cytotoxic T cell lysis. Chronic hepatitis may result from an inadequate immune response to HBV. Thus, treatment is aimed at modulation of the immune response (by suppression or stimulation) or inhibition of viral replication.

IMMUNOMODULATION

Immunosuppression

It was assumed that immunosuppressant drugs might be of value in the treatment of chronic active hepatitis, given their beneficial effects in autoimmune chronic active hepatitis.

TABLE I Landmarks in viral hepatitis

What is hepatitis?	
Hippocrates	- epidemic jaundice
Virchow (1865)	- catarrhal jaundice
1940s	- epidemic jaundice is a true inflammation of the liver
	- may cause chronic liver disease
What causes hepatitis?	
<i>Viral hepatitis:</i>	
Epidemic studies in the 1940s and 1950s	- two types of virus
1965-1967	- discovery of HBsAg by Blumberg
1973	- hepatitis A virus (Feinstone)
1977	- delta-agent (Rizzetto)
1987-1989	- hepatitis C virus (Houghton <i>et al.</i>)
1989	- hepatitis E virus (Krawczynski)
<i>Non-viral hepatitis:</i>	
1950-1956	- autoimmune hepatitis (Waldenstroem, MacKay)
1972	- Wilson's disease (Sternlieb)
1970s	- drug induced hepatitis

Corticosteroids. Corticosteroids were the first drugs to be used for the treatment of chronic hepatitis in the 1950s. Three controlled trials were conducted in patients with chronic active hepatitis in the 1960s,³ and although at this time an aetiological classification of chronic hepatitis was not possible, all three showed an improvement in survival after treatment with corticosteroids. Further analysis of these studies showed that most patients had autoimmune hepatitis, but about 10% were found to be hepatitis B surface antigen (HBsAg) positive. These patients did not respond as well to steroid treatment as the patients who were HBsAg negative.⁴ Subsequent controlled trials in patients with chronic hepatitis B indicated that steroid treatment was not only ineffective but even detrimental.^{5,6} The reason for the poor response of chronic hepatitis B to steroids may be partly explained by an increase in viral replication.⁷ Spontaneous seroconversion of hepatitis B e antigen (HBeAg) to anti-HBe positivity and disappearance of HBV-DNA occurs less frequently in steroid treated patients than in placebo treated or untreated patients (15% per year). Stopping steroid treatment usually leads to a rebound in hepatic disease activity but may be followed by termination of viral replication within a few months.⁸ Thus, despite the decrease in transaminase activity, steroids have no beneficial (and sometimes a detrimental) effect on liver histology, morbidity, and mortality,⁵ and should not be used for the treatment of chronic hepatitis. Their only role may be the enhancement of the efficacy of interferon or adenine arabinoside (ARA-A) treatment by prior steroid withdrawal in patients with mild inflammatory activity.⁹

Other immunosuppressive drugs. Other immunosuppressive agents such as azathioprine or 6-mercaptopurine were not better than placebo in the treatment of chronic hepatitis, but in combination with steroids exerted a steroid sparing effect.⁴

Immunostimulation

Hepatocytes containing replicating or integrated HBV are destroyed by cytotoxic T cells that recognise foreign or changed liver membrane determinants. An ineffective immune response may be one of the key factors responsible for development of chronic hepatitis B. Therefore, in chronically infected subjects, various immunostimulants listed in Table II have been used to assist the immune system in clearing infected cells. Most of these compounds were tested in only a small number of patients and produced few beneficial effects. Immunostimulation with repeated intradermal applications of *Bacillus Calmette Guérin* (BCG) was followed by disappearance of HBsAg in a few patients,¹⁰ but these findings were not confirmed by others.

A drug of potential interest is levamisole which produces increased T cell con-

TABLE II *Immunostimulatory substances for the treatment of chronic hepatitis B*

Substance	Introduced	Efficacy	
		Anecdotal	Randomised controlled trial
Levamisole	1974		+
Transfer factor	1976	-	ND
anti-HBs	1973	-	ND
Freund's adjuvant	1977	-	ND
BCG	1978	+/-	ND

ND: not determined, +: effective, -: no effect, +/-: conflicting data.

centrations, and therefore induces non-specific immune stimulation. Short term treatment has led to an increased destruction of infected cells but all patients have remained HBsAg-positive.¹¹ Chronic treatment with levamisole has resulted in a higher rate of HBV-DNA elimination and HBeAg-anti-HBe seroconversion than that found in placebo treated patients.¹² These data await confirmation by other randomised, controlled trials in a larger group of patients.

Immunomodulation by cytokines

An improved understanding of the control of the immune response by humoral factors, and the synthesis of these compounds by recombinant gene technology, may allow a more targeted enhancement of the immune response with cytokines such as interleukin-2, tumour necrosis factor (TNF), or interferon gamma in patients with chronic hepatitis B. Interleukin-2 causes cytotoxic T cells to mature and increase in number and may thereby enhance elimination of infected hepatocytes. An open study in 11 patients suggested that it may be beneficial for the treatment of chronic hepatitis B,¹³ although these results need confirmation by randomised, controlled studies. Interferon gamma, which has low antiviral activity, enhanced the effects of interferon beta in chronic hepatitis, probably as a result of its immunomodulatory properties.¹⁴ Tumour necrosis factor is an immunoregulatory cytokine with antiviral properties. Its effect in chronic HBV infection is complex and cannot be explained by its antiviral properties. A clinical study has shown that HBV replication is inhibited by low doses of tumour necrosis factor but increased by higher doses.¹⁵

ANTIVIRAL TREATMENT

A variety of antiviral drugs inhibit HBV-DNA production *in vitro*. Those that have been tested in patients with chronic hepatitis B are listed in Table III.

Adenine arabinoside (ARA-A; vidarabine) and adenine arabinoside monophosphate (ARA-AMP; vidarabine phosphate)

ARA-A and ARA-AMP, its water soluble form, are purine analogues with potent antiviral activity. They block DNA polymerase activity by acting as a faulty substrate, and are

TABLE III Antiviral agents used for the treatment of chronic hepatitis B

Substance	Introduced	Efficacy			Major toxicity
		In vitro	Randomised controlled trial	Anecdotal	
ARA-A	1976	+	+/-		Neuromuscular
ARA-AMP	1984	+	+/-		Neuromuscular
Acyclovir	1981	+	-		
Foscarnet	1986	+	ND	?	?
Suramin	1987	+/-	ND	-	Liver failure
Zidovudine	1988	+	ND	?	
Ribavirin	1978	+	?	-	
Phyllanthus amarus	1987	+	ND	+	
Interferon alfa	1976	+	+		

ND=not determined, +=effective, -=no effect, +/-=conflicting data, ?=not clear or incomplete data available.

ARA-A=adenine arabinoside; ARA-AMP=adenine arabinoside monophosphate.

selectively more potent against viral than against mammalian cell polymerase. ARA-A must be administered by slow intravenous infusion, while ARA-AMP can also be given intramuscularly. Both compounds have a robust antiviral activity (including an effect on HBV-DNA), both *in vivo* and *in vitro*. ARA-A was first used for the treatment of chronic hepatitis B in 1978.¹⁶ Since then, the results of controlled trials with ARA-A or ARA-AMP have been conflicting. Studies from the USA failed to show a benefit of treatment,^{17 18} while European trials demonstrated an increased HBeAg-anti-HBe seroconversion rate with ARA-A or ARA-AMP.^{19 20} A meta-analysis based on the eight published randomised, controlled trials calculated an overall odds ratio for HBeAg seroconversion of 2.37 for ARA-A/ARA-AMP therapy.²¹

Side effects with ARA-A are common and dose related. The most relevant clinical side effect is neuromuscular toxicity, which is associated with severe pains mainly in the paravertebral and lower limb muscles. Combination with human leukocyte interferon has been shown to enhance toxicity and does not improve the overall efficacy.²²

Acyclovir and dascyclovir

Acyclovir and dascyclovir, the oral pro-drug, are non-cyclic guanosine analogues that specifically inhibit viral but not host cell DNA synthesis. They inhibit DNA polymerase activity in Peking ducks infected with hepatitis B. Two small, randomised controlled studies have been performed in patients with chronic hepatitis B, where acyclovir showed transient inhibition of HBV replication but no significant effect on the HBeAg seroconversion rate.^{23 24} The enhancement of the antiviral effects of alpha lymphoblastoid interferon by acyclovir and possibly by dascyclovir^{25 26} has to be confirmed by appropriate trials.

3'-azido-3'-deoxythymidine (Zidovudine) and Suramin

Since reverse transcriptase activity is a prerequisite for HBV replication, inhibitors of reverse transcriptase may be useful for the treatment of hepatitis B. Zidovudine and suramin (a drug used for the treatment of trypanosomiasis) inhibit HBV replication *in*

vitro. Zidovudine has decreased HBV replication in patients with hepatitis B.²⁷ Suramin was tried in three patients with severe hepatitis B but was associated with unacceptable, life threatening side effects.²⁸

Trisodium-phosphonoformat (Foscarnet)

Foscarnet inhibits HBV-DNA polymerase *in vitro* and has been administered to a few patients with fulminant hepatic failure due to hepatitis B. It seemed to decrease mortality in these patients^{29 30} and, in the largest study, six of eight patients survived.³⁰ No reports are available on the potential effects of this drug in patients with chronic hepatitis B.

Extract of *phyllanthus ninuri* (*amarus*)

An extract of this plant had been used traditionally in southern India to treat jaundice, and has been shown to inhibit viral replication in woodchuck hepatitis.³¹ In a randomised, placebo-controlled study using the dried, powdered, and sterilised plant, high rates of HBsAg seroconversion were observed. No serious side effects were reported. However, only incomplete follow up data were given.³²

Ribavirin

Ribavirin is a nucleotide analogue which inhibits the *in vivo* synthesis of DNA. In a short-term trial, ribavirin failed to decrease HBV-DNA polymerase activity or HBsAg concentrations, and had no effect on liver function in six HBsAg positive patients.³³ In the light of the apparent beneficial effects of this drug in chronic hepatitis C,³⁴ it has recently been re-evaluated in the treatment of hepatitis B, and now seems to be effective (Fried *et al* (abstract presented at the Annual Meeting of the American Gastroenterological Association, San Francisco, 1992).

OTHER DRUGS USED FOR TREATMENT OF CHRONIC HEPATITIS B

D-penicillamine

D-penicillamine, a chelating agent, is the treatment of choice in patients with Wilson's disease. It has also been used in primary biliary cirrhosis. In addition to its copper-chelating actions, it has anti-inflammatory properties and may stimulate fibre removal from the liver. It has been tried successfully in some patients with chronic hepatitis³⁵ but not in controlled trials.

Hepatoprotective agents

Hepatoprotective agents are substances which are able to prevent toxic liver cell injury. They are used widely in Europe for the treatment of a variety of liver diseases. (+)-Cyanidanol-3, a flavoid extracted from the plant *Uncaria gambir*, was tested in a large, double blind study involving 338 HBeAg positive patients.

It was found to enhance the HBeAg sero-conversion rate after 14 weeks of treatment.³⁶ However, in another controlled trial which included various forms of chronic active hepatitis, no effects of this drug were observed in HBsAg-positive patients.³⁷ Similarly, subgroup analysis of a large, placebo-controlled prospective trial in patients with various forms of liver cirrhosis, indicated that silymarin, an extract from the milk thistle fruit, *Silybum marianum Gaertneri L*, did not affect the outcome of HBsAg positive patients.³⁸

Treatment of chronic hepatitis C

Hepatitis C virus (HCV) infection is responsible for most chronic cases of non-A, non-B (NANB) hepatitis. Because HCV was discovered only four years ago, the history of its treatment is very short. In 1984, Alter and Hoofnagle concluded that there was no effective treatment available for chronic NANB hepatitis.³⁹ Because of the lack of serological tests, systematic treatment protocols could not be performed. Only a few drugs were tested for their ability to improve chronic, blood transfusion associated NANB hepatitis before the discovery of antibodies against HCV in 1989. In a pilot study, five patients with NANB hepatitis received a short treatment course of acyclovir. None of the patients tested improved.³⁹ In the light of our current knowledge that antiviral treatment has to be administered to patients with chronic hepatitis C for many months to be effective, this short treatment may not have been sufficient to conclude that acyclovir is ineffective in the treatment of hepatitis C. In 1986, Hoofnagle reported the beneficial effects of interferon alfa in a pilot study of the treatment of chronic NANB hepatitis.⁴¹ This enthusiastic study prompted many randomised, controlled trials worldwide, which have since proved the efficacy of this treatment.^{42 43}

Another successful approach may be antiviral treatment with ribavirin.³⁴ It should be stressed, however, that many of the agents which were studied in chronic hepatitis B need also to be investigated in the treatment of chronic hepatitis C.

Conclusions

Interferon remains the only accepted treatment for chronic viral hepatitis caused by either HBV or HCV. Despite a large number of trials with a wide range of agents, no other effective treatment has yet been confirmed for patients with chronic hepatitis B. In chronic hepatitis C, it seems that ribavirin may have some benefit, but studies with other agents are awaited.

- 1 Greenberg HB, Pollard RB, Lutwick LI, *et al*. Effect of human leucocyte interferon on hepatitis B virus infection in patients with chronic active liver disease. *N Engl J Med* 1976; **295**: 517-22.
- 2 Blumberg BS, Gerstley BJS, Hungerford DA, *et al*. A serum antigen (Australia antigen) in Down's syndrome, leukemia, and hepatitis. *Ann Intern Med* 1967; **66**: 924-31.

- 3 Wright EC, Seeff LB, Berk P, *et al*. Treatment of chronic active hepatitis - an analysis of three controlled trials. *Gastroenterology* 1977; **73**: 1422-30.
- 4 Schalm SW, Summerskil WHJ, Gitnick GL, *et al*. Contrasting features and responses to treatment of severe chronic active liver disease with and without hepatitis Bs antigen. *Gut* 1976; **17**: 781-6.
- 5 Lam KC, Lai CL, Ng RP, Trépo C, Wu PC. Deleterious effect of prednisolone in HBsAg-positive chronic active hepatitis. *N Engl J Med* 1981; **304**: 380-6.
- 6 European Association for the Study of the Liver. Steroids in chronic hepatitis B. Randomized double-blind multinational trial on the effect of low dose long-term treatment on survival. *Liver* 1986; **6**: 227-32.
- 7 Sagnelli E, Manzillo G, Maio G, *et al*. Serum levels of hepatitis B surface antigen and core antigens during immunosuppressive treatment of HBsAg-positive chronic active hepatitis. *Lancet* 1980; **ii**: 395-7.
- 8 Nair PV, Tong MJ, Stevenson D, *et al*. A pilot study on the effects of prednisolone withdrawal on serum hepatitis B virus DNA and HBeAg in chronic active hepatitis B. *Hepatology* 1986; **6**: 1319-24.
- 9 Perrillo RP, Regenstein FG, Peters MG, *et al*. Prednisolone withdrawal followed by recombinant alpha interferon in the treatment of chronic type B hepatitis. A randomised controlled trial. *Ann Intern Med* 1988; **109**: 95-100.
- 10 Brzosko WJ, Deboski R, Derecka K. Immunostimulants for chronic active hepatitis. *Lancet* 1978; **ii**: 311.
- 11 Thomas HC. Immunostimulants in treatment of HBsAg positive chronic active hepatitis. In: Eddleston ALWF, Weber JCP, Williams R, eds. *Immune reactions in liver disease*. Tunbridge Wells: Pitman Medicals, 1979: 281.
- 12 Fattovich G, Broll L, Pontisso P, *et al*. Levamisole therapy in chronic type B hepatitis - results of a double-blind randomised controlled trial. *Gastroenterology* 1986; **91**: 692-6.
- 13 Onji M, Kondoh H, Yamaguchi S, *et al*. Effect of recombinant interleukin-2 on hepatitis B e antigen positive chronic hepatitis. *Gut* 1987; **28**: 1648-52.
- 14 Caselman WH, Eisenburg J, Hofschneider PH, Koshy R. β and gamma interferon in chronic active hepatitis B; A pilot trial of short-term combination therapy. *Gastroenterology* 1989; **96**: 449-55.
- 15 Sheron N, Lau JYN, Daniels HM, *et al*. Tumor necrosis factor to treat chronic hepatitis B virus infection. *Lancet* 1990; **336**: 321-2.
- 16 Pollard RB, Smith JL, Neal A, *et al*. Effects of vidarabine on chronic hepatitis B virus infection. *JAMA* 1978; **143**: 1648-50.
- 17 Hoofnagle JH, Hanson RG, Minuk GY, *et al*. Randomized controlled trial of adenine arabinoside monophosphate for chronic type B hepatitis. *Gastroenterology* 1984; **86**: 150-7.
- 18 Perrillo RP, Regenstein FG, Bodicky CJ, *et al*. Comparative efficacy of adenine arabinoside 5' monophosphate in the treatment of chronic active hepatitis type B. *Gastroenterology* 1985; **88**: 780-6.
- 19 Trépo C, Ouzan D, Fontages T, *et al*. Therapeutic activity of vidarabine in symptomatic chronic active hepatitis related to hepatitis B virus. *J Hepatol* 1986; **3**(suppl 2): S97-105.
- 20 Bassendine MF, Chadwick RG, Salmeron J, *et al*. Adenine arabinoside therapy in HBsAg positive chronic liver disease: A controlled study. *Gastroenterology* 1981; **80**: 1016-22.
- 21 de Man RA, Berk L, Schalm SW, Stijnen T. Treatment of chronic viral hepatitis. *Dig Dis Sci* 1991; **9**: 17-35.
- 22 Garcia G, Smith CI, Weisberg JL, *et al*. Adenine arabinoside monophosphate (vidarabine phosphate) in combination with human leukocyte interferon in the treatment of chronic hepatitis B. A randomized, double-blinded, placebo-controlled trial. *Ann Intern Med* 1987; **107**: 278-85.
- 23 Alexander GJ, Fagan EA, Hegarty JE, *et al*. Controlled clinical trial of acyclovir in chronic hepatitis B virus infection. *J Med Virol* 1987; **21**: 81-7.
- 24 Guarescio P, Felipe AP, Migliorini D, *et al*. Treatment of chronic HBeAg-positive hepatitis with acyclovir. *J Hepatol* 1986; **3**(suppl 2): S143-7.
- 25 Schalm SW, van Buuren HR, Heijtkink RA, *et al*. Acyclovir enhances the antiviral effects of interferon in chronic hepatitis B. *Lancet* 1985; **ii**: 358-60.
- 26 de Man RA, Schalm SW, Heijtkink RA, *et al*. Interferon plus dascyclovir in chronic hepatitis type B: Incidence of virus marker elimination and reactivation. In: Zuckerman AJ, ed. *Viral hepatitis and liver disease*. New York: Liss, 1988: 913-6.
- 27 Berk L, Schalm SW, Heijtkink RA, Zidovudine in chronic hepatitis type B. *Proc IV International Symposium on Viral Hepatitis*, Madrid 1989.
- 28 Loke RHT, Anderson MG, Coleman JC, *et al*. Suramin treatment for chronic active hepatitis B - toxic and ineffective. *J Med Virol* 1987; **17**: 97-9.
- 29 Price JS, France AJ, Moaven LD, Welsby PD. Foscarnet in fulminant hepatitis B. *Lancet* 1986; **ii**: 1273.
- 30 Hedin G, Weiland O, Lunggren K, *et al*. Treatment with foscarnet of fulminant hepatitis B and fulminant hepatitis B and D coinfection. In: Zuckerman AJ, ed. *Viral hepatitis and liver disease*. New York: Liss, 1988: 947-52.
- 31 Venkateswaran PS, Millman I, Blumberg BS. Effects of an extract from Phyllanthus niruri on hepatitis B and woodchuck hepatitis viruses. *Proc Natl Acad Sci USA* 1987; **84**: 274-8.
- 32 Thyagarajan SP, Subramanian S, Thirunalasundari T, *et al*. Effect of Phyllanthus amarus on chronic carriers of

- hepatitis B virus. *Lancet* 1988; **ii**: 764–6.
- 33 Jain S, Thomas HC, Oxford JS, Sherlock S. Trial of ribavirin for the treatment of chronic HBs antigen positive liver disease. *J Antimicrob Chemother* 1978; **4**: 369–71.
- 34 Reichard O, Andersson J, Schvarcz R, Weiland O. Ribavirin treatment of chronic hepatitis C. *Lancet* 1991; **337**: 1058–61.
- 35 Lange J, Schumacher K, Witscher HP. Treatment of chronic active hepatitis with D-penicillamine. *Dtsch Med Wochenschr* 1971; **96**: 139–45.
- 36 Suzuki H, Yamamoto S, Hirayama C, *et al.* Cianidanol therapy for HBe-antigen positive chronic hepatitis: A multicenter, double-blind study. *Liver* 1986; **6**: 35–44.
- 37 Bar-Meir S, Halpers Z, Gutman M, *et al.* Effect of (+)-cyanidanol-3 on chronic active hepatitis: a double blind controlled trial. *Gut* 1985; **26**: 975–9.
- 38 Ferenci P, Dragosics B, Dittrich H, *et al.* Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. *J Hepatol* 1989; **9**: 105–13.
- 39 Alter HJ, Hoofnagle JH. Non-A, non-B: Observations on the first decade. In: Vyas GN, Dienstag J, Hoofnagle JH, eds. *Viral hepatitis and liver disease*. Orlando: Grune & Stratton, 1984: 343–54.
- 40 Pappas SC, Hoofnagle JH, Young N, *et al.* Treatment of chronic non-A, non-B hepatitis with acyclovir: Pilot study. *J Med Virol* 1985; **15**: 1–9.
- 41 Hoofnagle JH, Mullen KD, Jones DB, *et al.* Treatment of chronic hepatitis non-A, non-B with recombinant human interferon-alpha: A preliminary report. *N Engl J Med* 1986; **315**: 1575–8.
- 42 DiBisceglie AM, Martin P, Kassianides C, *et al.* Recombinant interferon alfa therapy for chronic hepatitis C: a randomized, double-blind, placebo-controlled trial. *N Engl J Med* 1989; **321**: 1506–10.
- 43 Davis GL, Balart L, Schiff E, *et al.* Treatment of chronic hepatitis C with recombinant interferon alfa: A multicenter, randomized, controlled trial. *N Engl J Med* 1989; **321**: 1501–6.