Long term treatment of chronic hepatitis C with interferon alfa-2b: disappearance of HCV-RNA in a pilot study of eight haemophilia patients

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Abstract

This pilot study was designed to establish the effect of long term alpha interferon treatment in haemophilia patients with chronic hepatitis C. Overall, three of eight (37.5%) patients showed a complete response, three of eight (37.5%) a transient response, and two of eight (25.0%) no response. HCV-RNA detection by polymerase chain reaction was more sensitive in detecting relapse than alanine aminotransferase (ALT) activity measurement, suggesting that current interferon schedules based on the ALT response should be re-evaluated critically.

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A pilot study was undertaken to establish the effect of long term alpha interferon treatment in eight haemophilia patients with chronic hepatitis C virus (HCV) infection, with particular reference to prevention of long term complications of HCV infection (that is, cirrhosis) and effect on HCV viraemia.

Patients and methods

Patients were included in the trial if they had haemophilia A or B and chronic hepatitis C, with serum alanine aminotransferase (ALT) activities greater than 2.5 times the upper limit of normal on at least two occasions within six months and serum HCV-RNA detectable by cDNA polymerase chain reaction (PCR) testing.

All eight patients received subcutaneous interferon alfa-2b in a reducing dose for 24 weeks, according to the following schedule:

5 million units (MU) daily, weeks 0-2
2.5 MU daily, weeks 3-6
1.5 MU thrice weekly, weeks 7-24

During treatment, assessments included plasma HCV-RNA detection by means of cDNA-PCR using primers in the 5' untranslated region,^{1,2} serum ALT activities, clinical evaluation, liver function tests, and ultrasound. Complete response was defined as undetectable HCV-RNA (PCR negative), transient response as renewed HCV-RNA detection after a PCR negative result at some point during treatment, and no response as continuing HCV-RNA positivity.

Results

Serum ALT activities and detection of HCV-RNA are shown in the Table. At week 24, three (37.5%) of the eight patients had a complete response (including one patient who stopped interferon after only two weeks, (patient 3)), and three others had a transient response according to PCR.

After week 24, interferon treatment was stopped in responders, while those with only transient or no response were continued on interferon 5 MU (three times weekly). HCV-RNA remained undetectable in the three complete responders, that is, response was sustained during a follow up of 36 weeks after stopping of treatment. In only one of the three transient responders a renewed response (that is, HCV-RNA no longer detectable) was maintained during treatment. The other two transient responders seemed to need a higher dose of interferon to suppress viral replication.

In responders (according to PCR) ALT activities also decreased. Only one patient,

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TABLE Serum alanine aminotransferase (ALT) activities (IU/l) and hepatitis C virus (HCV)-RNA positivity S (by polymerase chain reaction)

Patient no	Week 1 (5 MU daily)		Week 2 (5 MU daily)		Week 6 (2.5 MU daily)		Week 12 (1.5 MU TIW)		Week 24 (1.5 MU TIW)		Week 36*		Week 48*		Week 60*	
	ALT	HCV- RNA	ALT	HCV- RNA	ALT	HCV- RNA	ALT	HCV- RNA	ALT	HCV- RNA	ALT	HCV- RNA	ALT	HCV- RNA	ALT	HCV- RNA
1	173	+	51	-	47	-	38	-	39	-	17	-	82	-	12	-
2	112	+	32	-	24	-	51	-	45	-	24	-	69	-	17	-
3†	123	+	27	-	15	-	13	-	14	-	NT	NT	15	-	11	-
8‡	40	+	29	+	27	+	53	+	37	+	35	+	35	+	19	+
4	134	+	51	+	38	-	15	-	26	+	42	+	17	-	46	-
5	92	+	94	+	55	-	48	-	71	+	103	+	33	-	21	+
6	86	+	15	-	13	+	192	+	123	+	45	+	97	+	89	+
7	302	+	285	+	233	+	203	+	330	+	160	+	213	+	203	+

*Patients 1, 2, 3, and 8 stopped treatment, patients 4, 5, 6, and 7 received IFN 5 MU three times weekly for the remainder of the study.

†Stopped interferon after two weeks.

‡Patient refused further treatment after week 24.

NT Not tested.

however, (patient 3) showed a complete ALT normalisation at week 24.

Even in complete responders, ALT fluctuation above the upper limit of normal, not accompanied by renewed HCV-RNA detection, was seen and is difficult to explain.

Conclusions

From the results of this study, we conclude that HCV-RNA detection by cDNA-PCR is a better criterion for relapse than serum ALT measurement. Current interferon alpha

treatment schedules for patients with chronic hepatitis C are based on the ALT response and should be critically re-evaluated for their ability to clear HCV-RNA.

- 1 van der Poel CL, Cuypers HTM, Reesink HW, *et al.* Confirmation of hepatitis C virus infection by second generation four-antigen recombinant immunoblot assay and polymerase chain reaction. *Lancet* 1991; **337**: 317–19.
- 2 Han JH, Shyamala V, Richman KH, *et al.* Characterization of the terminal regions of hepatitis C viral RNA: identification of conserved sequences in the 5' untranslated region and poly(A) tails at the 3' end. *Proc Natl Acad Sci USA* 1991; **88**: 1711–15.