# Quantitative hepatitis C virus RNA and liver histology in chronic hepatitis C patients treated with interferon alfa

G Yamada, M Takahashi, H Endo, T Doi, R Miyamoto, H Shimomura, K Yamamoto, T Tsuji

**Abstract**

**Seventy patients with hepatitis C virus (HCV) infection received alpha interferon at doses ranging from 3 to 10 million units (MU) daily for eight weeks, three times weekly for 12–24 weeks, or daily and three times weekly for 12–24 weeks. The efficacy of interferon was closely related to the initial blood HCV-RNA values in that these were lower in those who responded completely and partially compared with non-responders. Continuous reductions in HCV-RNA and improvements in the histology activity index score were seen in those who responded completely. In contrast, most of the partial and non-responders remained HCV-RNA positive.**

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**First Department of Internal Medicine, Okayama University Medical School, Okayama, Japan**
G Yamada
M Takahashi
H Endo
T Doi
R Miyamoto
H Shimomura
K Yamamoto
T Tsuji

Correspondence to:
Dr G Yamada,
First Department of Internal Medicine
Okayama University Medical School
Okayama, Japan.

In order to discriminate potential interferon responders from non-responders among patients with chronic hepatitis C virus (HCV) infection, we compared background factors such as baseline serum HCV-RNA levels and liver histology.

## Patients and methods

Seventy hepatitis B surface antigen (HBsAg) negative patients were diagnosed as having hepatitis C infection by the presence of anti-HCV antibodies (anti-c100-3, anti-CP-9[1], and anti-GOR) and HCV-RNA (on polymerase chain reaction). Chronic hepatitis was confirmed histologically and five patients were found to have cirrhosis.

All patients were treated with natural or recombinant interferon alfa-2b, interferon alfa-2a, or human lymphoblastoid-alpha interferon at dosages ranging from 3 to 10 million units (MU) daily for eight weeks (n=5), three times a week (TIW) for 12–24 weeks (n=54), or daily *and* three times weekly for 12–24 weeks (n=11). In each case, interferon was given intramuscularly.

The response to treatment was defined as follows:

Complete response: return to normal serum alanine aminotransferase (ALT) activity during or within six months of completing treatment, and maintenance of normal values for one year or longer.

Partial response: return to normal ALT activity during treatment but relapse after completion.

No response: abnormal ALT activity during and after stopping treatment.

## Results

Patient characteristics according to the response to interferon alfa treatment are shown in Table I. There were no significant differences between those who responded completely, partially or not at all in terms of age, sex, anti-HCV positivity, gamma globulin values, or liver histology at baseline, even in patients with cirrhosis (Student's $t$ test and $\chi^2$ test). Both complete and partial responders had slightly lower ALT activities at the start of treatment compared with non-responders, and a higher percentage of responders were anti-nuclear antibody positive compared with those who showed no response.

HCV-RNA titres[2] were estimated in 46 patients by testing 10 fold serial dilutions of RNA extracted from the patient's serum before treatment, and were found to be lower in

TABLE I *Patient characteristics according to response to treatment*

| | *Complete response* | *Partial response* | *No response* |
|---|---|---|---|
| No of patients | 32 | 20 | 18 |
| Men/women | 21/11 | 7/13 | 9/9 |
| Average age (y) (mean (SD)) | 48 (10) | 46 (12) | 54 (7) |
| Serum, anti-HCV +ve: | | | |
| Anti-c100-3(+) | 25 | 20 | 10 |
| Anti-CP-9(+) | 30 | 18 | 12 |
| Anti-GOR(+) | 28 | 18 | 14 |
| ALT (IU/l) at start (mean (SD)) | 120 (84) | 150 (110) | 179 (90) |
| Gamma globulin (g/dl) (mean (SD)) | 1·54 (0·38) | 1·38 (0·24) | 1·62 (0·31) |
| ANA +ve (%) | 20 | 23 | 7 |
| Liver histology; | | | |
| CPH | 13 | 8 | 3 |
| CAH | 17 | 12 | 12 |
| CAH with cirrhosis | 2 | 0 | 3 |

ANA: anti-nuclear antibody; CPH: chronic persistent hepatitis; CAH: chronic active hepatitis; ALT=alanine aminotransferase.

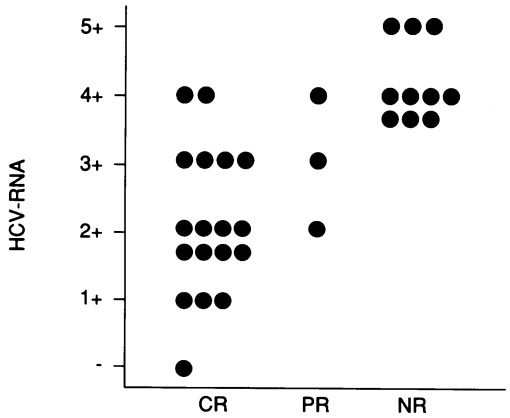


*Figure Serial dilution testing to determine hepatitis C virus (HCV)-RNA titres, in complete (CR), partial (PR) and non-responders (NR).*

TABLE II *Serum hepatitis C virus RNA positivity* before and after interferon treatment*

| *Response* | *Before* | *At end* | *Six months later* |
|---|---|---|---|
| Complete | 21/23 | 1/14 | 3/14 |
| Partial | 10/10 | 3/6 | 8/9 |
| None | 12/13 | 6/9 | 7/10 |

*By polymerase chain reaction.

TABLE III *Changes in histology activity index score before and six months after interferon treatment*

| *Score* | *Complete response (n=12)* | | | *Partial response (n=7)* | | | *No response (n=10)* | |
|---|---|---|---|---|---|---|---|---|
| | *Before* | *After* | *p Value* | *Before* | *After* | *p Value* | *Before* | *After* |
| I | 2·2 (1·9) | 0·4 | (0·7)* | 3·0 (1·4) | 1·5 | (2·1)† | 3·8 (1·6) | 3·9 (2·0) |
| II | 2·4 (1·0) | 0·7 | (0·5)‡ | 2·7 (0·4) | 2·3 | (0·8) | 2·3 (0·9) | 2·0 (1·1) |
| III | 2·2 (0·8) | 1·0 | (1·0)* | 2·8 (0·6) | 1·9 | (1·1) | 2·6 (0·9) | 2·4 (1·1) |
| IV | 2·1 (1·2) | 2·1 | (1·2) | 2·1 (1·1) | 2·2 | (1·0) | 3·2 (0·4) | 3·1 (0·2) |
| Total | 8·9 (3·8) | 4·1 | (2·9)* | 10·7 (2·8) | 7·8 | (4·2)† | 12·0 (2·7) | 11·4 (3·8) |

*p<0·01, †p<0·001, ‡p<0·05 compared with values before treatment (Student's *t* test (paired)).

complete and partial responders compared with non-responders (Figure). HCV-RNA was found to have become undetectable by polymerase chain reaction in most complete responders who were retested at the end of treatment and six months later (Table II). In contrast, most of the partial and non-responders remained HCV-RNA positive. Similarly, the greatest improvements in histology activity index score were seen in patients with a complete response to treatment (Table III).

There were no significant differences in the results obtained with the different types of interferon.

## Conclusions

These findings suggest that the efficacy of alpha interferon is closely related to the initial blood HCV-RNA values. Continuous reductions in serum HCV-RNA and improvements in liver histology activity index scores are observed in those who respond completely.

1 Okamoto H, Tsuda F, Machida A, *et al.* Antibodies against synthetic oligopeptides deduced from the putative core gene for the diagnosis of hepatitis C virus infection. *Hepatology* 1992; **15:** 180–6.

2 Okamoto H, Okada S, Sugiyama Y, *et al.* Detection of hepatitis C virus RNA, by a two-stage polymerase chain reaction with two pairs of primers deduced from the 5'-noncoding region. *Japan J Exp Med* 1990; **60:** 215–22.