Hepatitis C infection: the quest for new treatment strategies
Weegink, C.J.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE (Digital Academic Repository)

UvA-DARE is a service provided by the library of the University of Amsterdam (http://dare.uva.nl)

Download date: 08 Dec 2018
Viral kinetics of HCV-RNA in patients with chronic hepatitis C treated with 18 MU interferon alpha daily

Roel E. Sentjens¹, Christine J. Weegink¹, Marcel G. Beld², Michel C. Cooreman¹, Henk W. Reesink¹

¹ Department of Gastro-Enterology and Hepatology
² Department of Medical Microbiology, Laboratory of Clinical Virology
Academic Medical Center, University of Amsterdam
The Netherlands.

Eur J Gastroenterol Hepatol 2002; 14(8):833-40
Chapter 6

Summary

Background: A rapid decrease of HCV-RNA is interferon dose dependent and a 3 log decline of HCV-RNA is a strong predictor of sustained virological response. In this study viral kinetics of HCV-RNA in patients treated with 18 MU IFN-α daily for 2 weeks are presented.

Methods: Thirteen treatment-naive patients with chronic hepatitis C received Interferon α-2a 6 MU 8 hourly for two weeks. Samples were obtained daily during the treatment period. HCV-RNA levels were determined using the quantitative VERSANT™ 3.0 bDNA assay (detection limit 520 IU/mL). When results were below the detection limit, HCV-RNA was measured by qualitative PCR using the COBAS AMPLICOR™ HCV test, version 2.0 (detection limit of 50 IU/mL).

Results: In patients infected with genotype non-1 a 3-log decline of viral load was found 2.4 days after the start of induction therapy. On the other hand, only 1 out of 3 patients infected with genotype-1 had a 3-log decline in viral load within 14 days of the start of therapy. In four patients a third phase of viral decline was observed. At the end of treatment 10/13 (77%) and 7/13 (54%) patients were HCV-RNA negative in quantitative assay and qualitative PCR respectively. Only one 1/13 achieved a sustained virological response.

Conclusion: Daily administration of 18 MU IFN-α to patients infected with genotype non-1 induces a 3 log decline of viral load within 2.4 days of the start of treatment. In patients infected with genotype 1 only 1/3 patients had a 3 log decline at 11 days.
Introduction

The current treatment of choice for chronic hepatitis C is a combination of IFN-α and ribavirin for 24 or 48 weeks and such therapy is associated with a sustained virological response (SVR) rate in 38-43% of patients. Patients who are HCV-RNA negative by qualitative PCR test, three months after starting IFN-α therapy, are most likely to achieve a SVR (21). If HCV-RNA is still detectable after one month of treatment it may be considered to discontinue or modify standard therapy (3). A decrease of at least 3 log in viral load during the first 4 weeks of therapy is a strong predictor of SVR. The number of patients with a SVR at the end of therapy may be increased by giving higher doses of IFN-α during the induction period (23). Viral kinetics in patients who respond to IFN-α therapy is biphasic (18). A rapid decrease of HCV-RNA the first 48 hours of therapy can be explained by an inhibitory effect of IFN-α on production and/or release of virus by infected cells. This phenomenon, is dose-dependent (13;15). In patients who respond to IFN-α after the initial phase of steep decline of HCV-RNA, there is a second phase observed in which HCV-RNA decreases less rapidly. It is assumed that this second phase is attributable to the death of infected hepatocytes. The half life of infected hepatocytes varies in different patients. Hence there is also variability in the decline of HCV-RNA between patients (15). The rate of decline of HCV-RNA in the second phase is a predictor of early viral clearance (14). In a recent study a third phase (between 32-120 hrs after start of therapy) during viral decline was described, this third phase is observed directly after the first phase and is marked by an increase in HCV-RNA. Several possible mechanisms may account for this third phase. One explanation is that the immune mediated second phase does not appear directly after the first phase and therefore a period with less immune suppression is present (1). HCV-RNA has a half life of approximately 1.5-4.6 hours in blood or plasma. The daily production of HCV-RNA is $4.1 \times 10^{-1} - 1.1 \times 10^{13}$ copies (10). Because IFN-α has a plasma half life of approximately 8 hours, IFN-α concentrations fluctuate substantially when IFN-α is administered thrice weekly (t.i.w.). When IFN-α is given i.w. there are periods in which IFN-α levels are low or undetectable, and viral replication may be less suppressed (13). It is possible that even when IFN-α is injected once a day HCV viral replication may occur during periods between the injections. Higher doses of IFN-α as induction therapy may prevent the intermittent viral replication. High doses of IFN-α 18-20 MU per day administered to patients with AIDS related Kaposi sarcoma, were shown to be safe and well tolerated in this patient group (8). Since the high rate of adverse events during IFN-α therapy, shorter duration of therapy will be much better tolerated by patients. In some cases SVR was achieved when IFN-α was given for only 2 weeks (2). This observation suggested that in some patients a short course of IFN-α, may be sufficient to clear the virus.

The aim of our pilot study was to determine in patients with chronic hepatitis C the kinetics of HCV-RNA during therapy 18 MU IFN-α, given as 6 MU 8 hourly daily for two weeks and to establish the number of patients with SVR.

Material and Methods

Study design

The study was an open label pilot study. The protocol of the study was approved by Medical Ethics Committee of the Academic Medical Center, University of Amsterdam.
All participating patients had signed a comprehensive informed consent form. All patients received 6 MU IFN-α 8 hourly for 2 weeks. All patients were admitted in the hospital for the first 2 days of the trial. At day 4, 8, 11 and 14 the patients came at the outpatient clinic for monitoring the safety and tolerance of this treatment schedule. Patients were also assessed 3, 4, and 6 weeks and 6 months after start of therapy.

Patients
Criteria for patient selection were: age between 18-70 years, chronic hepatitis C, treatment naïve, anti-HCV and HCV-RNA positive, histopathological confirmation of chronic hepatitis within 6 months prior to start of the therapy, and elevated serum aminotransferase (ALAT) at least ≥ 1.5 times the upper limit of normal.
Exclusion criteria included: evidence of decompensated liver disease (e.g. albumin < 32g/l, PTT > 4 seconds prolonged, conjugated hyperbilirunaemia, ascites, a history of GE bleeding or encephalopathy), HIV infection, coinfection with hepatitis B, severe mental depression, seizures, clinically significant CNS dysfunction, malignant disease, congestive heart failure, uncontrolled diabetes mellitus, renal failure (serum creatinine >2 mg/dl), autoimmune disease, a bone marrow depression (hematocrit <32%, white blood cell count 2.5x10⁹/L, and/or platelets < 80x10⁹/L) and a history of active substance abuse.

Patient characteristics
All 13 patients studied fulfilled the study criteria. Three had genotype 1 and 10 had genotype non-1. Nine were male. Their mean age was 40 years old (range 29-49). Nine of the 13 patients probably had been infected with HCV during previous intravenous drug abuse. In the remaining 4 patients no potential source of infection was identified. The mean duration of infection was 20 years and the mean pre treatment HAI (12)score was 6. The pre treatment ALAT levels and viral load are listed in table 1 and 2.

Sample collection
EDTA blood was collected at the following time points: 2 weeks before start of therapy, during each of the first 2 days of therapy just before the first dose of IFN-α and 8, 24, and 32 hours thereafter, and at days 3, 4, 7, 8, 9, 10, 11, 14, 15 during therapy. During follow-up serum samples were obtained 3, 4, and 6 weeks after starting IFN-α therapy and 6 months after the end of treatment.
EDTA-plasma samples were stored at -70 °C within 4 hours after blood collection.

Serological test
Plasma samples were tested for the presence of anti-HCV antibodies using a 3rd generation Enzyme Immunoassay (EIA 3.0; Abbott Laboratories, Chigaco, IL) according to the manufacturer’s instructions.

Detection of HCV-RNA
Quantitative detection: A quantitative bDNA assay (Versant 3.0 Bayer, Berkeley, CA, USA) which uses 50 µL of plasma or serum and which has a dynamic range of 520-8.3 x10⁶ IU/mL, respectively. This bDNA technology utilises a sandwich nucleic acid hybridisation procedure. Briefly, the HCV 3.0 bDNA assay provides an improved assay in singular measurements of plasma and serum samples.
Viral kinetics of HCV-RNA

Qualitative detection: HCV RNA was detected by RT-PCR using the COBAS AMPLICOR™ system according to the manufacturer’s instructions (Roche Diagnostic Systems, Inc., Branchburg, NJ). The detection limit of this assay is 50 IU/mL.

Genotyping
HCV genotypes were determined by direct sequencing using the TrueGene™ Genotyping assay and the OpenGene™ automated DNA sequencing system (Visible Genetics Inc., Toronto, Canada).

Viral kinetics
The rate of viral clearance ($T_{1/2}$) was calculated using standard methods (13;24). The half-life of the virus is calculated for each patient from the exponential decline in the viral load, in particular from slope (S) between the initial viral load (HCV-RNA) and the viral load (HCV-RNA) 24 h after the start of treatment.

$$S = \log \left( \frac{\text{viral load } T_0}{\text{viral load } T_{24}} \right)$$

$$T_{1/2} \text{ (hours)} = \frac{\log(2)}{S} \times 24$$

Assuming that distribution of the virus reaches equilibrium in extracellular fluid, viral production and clearance per day can calculated according to the following equation:

$[\text{viral production or clearance per day}] = \frac{[\text{extracellular volume in liters}] \times [\text{pretreatment viral load in IU/L}]}{[T_{1/2} \text{ in day}]}.$

Extracellular volume was calculated according to the equation:

$[\text{extracellular volume in liters}] = 20\% \times [\text{body weight in Kg}].$

All viral load data were log_{10} transformed. The decline in viral load between the different time points is expressed as log decline. Due to the log transformation of the viral load a linear model of decline of viral load for each patient was adopted.

In calculations the arbitrary value of 500 IU/mL (2.7 log) was used when values were negative using the quantitative assay but positive using qualitative PCR. When the samples were negative in the qualitative PCR, a value of 50 IU/mL (1.7 log) was used in the calculations.

Statistics
Data are expressed as means ± standard deviation (SD). Mean values were compared using an independent sample T-test. All data analysis was conducted using the Statistical Package for Social Sciences (SPSS for windows 9.0.1). P-values of <.05 were considered to be significant.

Results

Virological response during and after treatment
At the end of treatment 10/13 (77%) patients, all genotype non-1, were HCV RNA negative as measured using the quantitative assay. Seven of these 10 patients were also HCV RNA negative as measured using the qualitative PCR at the end of treatment. The mean viral load for patients who were HCV RNA negative or positive at end of treatment was $1.7 \times 10^6$ IU/mL and $2.6 \times 10^6$ IU/mL respectively (p=NS). One week after stopping treatment, only 2/13 (15%) patients remained HCV RNA negative and at 4 weeks only 1 (patient F) of the 13 patients was HCV RNA negative. This patient was still HCV RNA negative 6 months after stopping therapy and, consequently, has been classified as a SVR.
Chapter 6

**Viral kinetics**

The results of the viral kinetic studies are summarized in figures 1, 2, 3, 4 and in tables 1, 2 and 3. In the first 8 hours (after injection of 6 MU interferon) all patients, independent of genotype, had a reduction of viral load. The mean log decrease was 0.081. After the first 24 hours, patients with genotype non-1 had a mean log viral load decline of 1.9 (SD ± 0.7 range 0.65-3.09) and a mean viral load reduction of 98.2%, whereas patients with genotype 1 had a log decline of 0.91 (SD ± 0.60 range 0.43-1.59) and a mean viral load reduction of 80.3%. In four patients (patient B and M figure 3, and patient H and J, figure 2) a third phase viral load decline was seen during treatment which occurred 32 after hours after start of treatment. Between day 1 and day 15 the log viral load decline was 1.62 (SD ± 0.89 range 0.00-2.54) for patients with genotype non -1, and 1.07 (SD ± 0.63 range 0.56-1.75) in patients with genotype 1. All patients had a reduction in viral load during treatment. The mean log viral load decline during 14 days of treatment was 3.42 (range 1.29-5.00). Between patients who became HCV RNA negative and patients who remained positive at the end of treatment, there were no significant differences in the half-life of HCV RNA, in the first 24 hours and between day 1 and 15.
### Table 1  
Viral kinetics of patients infected with HCV genotype non-1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Geno</th>
<th>Age</th>
<th>Sex</th>
<th>Pre treatment ALAT (U/L)</th>
<th>Pre treatment viral load (log)</th>
<th>Decrease in viral load day 1</th>
<th>$T_{1/2}$ (hrs)§</th>
<th>Viral production and clearance per day x 10^9 IU§</th>
<th>Time point &gt;3 log decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>3</td>
<td>45</td>
<td>M</td>
<td>91</td>
<td>6.43</td>
<td>3.09</td>
<td>2.32</td>
<td>495</td>
<td>1 day</td>
</tr>
<tr>
<td>B</td>
<td>3</td>
<td>40</td>
<td>F</td>
<td>56</td>
<td>6.7</td>
<td>2.46</td>
<td>2.88</td>
<td>539</td>
<td>32 hrs</td>
</tr>
<tr>
<td>C</td>
<td>2</td>
<td>49</td>
<td>M</td>
<td>87</td>
<td>6.43</td>
<td>2.21</td>
<td>3.26</td>
<td>386</td>
<td>2 days</td>
</tr>
<tr>
<td>D</td>
<td>3</td>
<td>34</td>
<td>F</td>
<td>287</td>
<td>5.51</td>
<td>1.88</td>
<td>3.84</td>
<td>39</td>
<td>32 hrs</td>
</tr>
<tr>
<td>E</td>
<td>3</td>
<td>37</td>
<td>M</td>
<td>210</td>
<td>6.54</td>
<td>1.9</td>
<td>3.8</td>
<td>309</td>
<td>32 hrs</td>
</tr>
<tr>
<td>F</td>
<td>3</td>
<td>35</td>
<td>F</td>
<td>90</td>
<td>4.89</td>
<td>1.13</td>
<td>6.39</td>
<td>4</td>
<td>3 days</td>
</tr>
<tr>
<td>G</td>
<td>3</td>
<td>39</td>
<td>M</td>
<td>97</td>
<td>6.84</td>
<td>2.39</td>
<td>3.00</td>
<td>900</td>
<td>8 days</td>
</tr>
<tr>
<td>I</td>
<td>4</td>
<td>49</td>
<td>M</td>
<td>412</td>
<td>4.26</td>
<td>1.56</td>
<td>4.61</td>
<td>0.16</td>
<td>1 day</td>
</tr>
<tr>
<td>L</td>
<td>3</td>
<td>38</td>
<td>M</td>
<td>344</td>
<td>5.75</td>
<td>0.65</td>
<td>11.1</td>
<td>20</td>
<td>4 days</td>
</tr>
<tr>
<td>M</td>
<td>3</td>
<td>41</td>
<td>M</td>
<td>110</td>
<td>5.12</td>
<td>2.5</td>
<td>2.88</td>
<td>19</td>
<td>1 day</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td></td>
<td></td>
<td></td>
<td>41</td>
<td>178</td>
<td>$5.85 ± 0.87$</td>
<td>$1.9 ± 0.7$</td>
<td>$4.4 ± 2.6$</td>
<td>$271 ± 308$</td>
</tr>
</tbody>
</table>

§ All values calculated during the first 24 hours.  
* Upper limit of normal 45 U/L

### Table 2  
Viral kinetics of patients infected with HCV genotype 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Geno</th>
<th>Age</th>
<th>Sex</th>
<th>Pre treatment ALAT (U/L)*</th>
<th>Pre treatment viral load (log)</th>
<th>Decrease in viral load day 1 §</th>
<th>$T_{1/2}$ (hrs)§</th>
<th>Viral production and clearance per day x 10^9 IU§</th>
<th>Time point &gt;3 log decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>J</td>
<td>1</td>
<td>29</td>
<td>M</td>
<td>125</td>
<td>6.51</td>
<td>1.59</td>
<td>4.53</td>
<td>284</td>
<td>11 days</td>
</tr>
<tr>
<td>K</td>
<td>1</td>
<td>37</td>
<td>F</td>
<td>74</td>
<td>5.86</td>
<td>0.43</td>
<td>16.8</td>
<td>13</td>
<td>Not achieved</td>
</tr>
<tr>
<td>H</td>
<td>1</td>
<td>47</td>
<td>M</td>
<td>60</td>
<td>6.29</td>
<td>0.73</td>
<td>9.88</td>
<td>72</td>
<td>Not achieved</td>
</tr>
<tr>
<td>Mean ±SD</td>
<td>38</td>
<td>86</td>
<td></td>
<td>$6.22 ± 0.33$</td>
<td>$0.91 ± 0.60$</td>
<td>$10.4±6.15$</td>
<td>$123 ± 142$</td>
<td>unknown</td>
<td></td>
</tr>
</tbody>
</table>

§ All values calculated during the first 24 hours.  
* Upper limit of normal 45 U/L
Table 3  Comparison of viral kinetics between patient with HCV genotype 1 and genotype non-1

<table>
<thead>
<tr>
<th>Patients infected with:</th>
<th>n</th>
<th>Viral decline during treatment 14 days</th>
<th>Decrease in viral load day 1</th>
<th>T_{1/2} (hrs)</th>
<th>Viral production and clearance per day x 10^{9} IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype non-1</td>
<td>10</td>
<td>3.85 log</td>
<td>1.9</td>
<td>4.4</td>
<td>271</td>
</tr>
<tr>
<td>Genotype 1</td>
<td>3</td>
<td>2.02 log</td>
<td>0.91</td>
<td>10.40</td>
<td>123</td>
</tr>
</tbody>
</table>

*All values calculated during the first 24 hours*

Figure 1  Mean HCV viral load and ALAT during treatment and follow up in patients infected with genotype non-1
Viral kinetics of HCV-RNA

Figure 2  Mean HCV viral load during treatment and follow up of patient F with sustained virological response

Figure 3  HCV viral load during treatment and follow up in patients infected with genotype 1
**Biochemical response during treatment**

The mean pretreatment ALAT values of the 7 patients who became HCV RNA negative at the end of treatment was significantly higher than the 6 patients who were HCV RNA positive at the end of treatment (220 U/L vs. 92 U/L; p=NS). At the end of treatment the mean ALAT value was 98 U/L and 3/13 (23%) of the patients had levels of ALAT within normal range. One week after treatment the mean ALAT value was 50 U/L and 9 (69%) of the patients had ALAT values within the normal range. Four weeks after treatment the mean ALAT value was 90 U/L and only the one patient, who had a SVR had a normal ALAT value.

**Side effects**

All 13 patients completed the therapy protocol, indicating that the treatment was well tolerated. However, all patients initially experienced mild flu like symptoms (headache, fatigue, myalgia) which improved within the first few days with the use of conventional dose of paracetamol. In the second week of treatment most patients discontinued paracetamol. All patients developed mild lymphopenia and thrombocytopenia. The reduced levels of lymphocytes and thrombocytes did not necessitate dose modification and within one week after stopping the treatment, white blood cell and platelet count had returned to the values within normal range. All patients had reversible hair loss 3-4 months after stopping high dose IFN-α treatment. The hair loss resolved within 6 months of the first sign of hair loss. In one patient the dose of IFN-α was reduced after one week because of skin rash. The rash disappeared within 3 days after stopping IFN-α.
Discussion

With the treatment schedule of 6 MU IFN-α 8 hourly, a mean 3 log decline in viral load (HCV-RNA) was achieved within 3.2 days of the start of treatment. Eleven of 13 (85%) patients achieved at least a 3 log decline in viral load within 14 days of start of therapy. An initial 3 log decline of HCV RNA in the first 4 weeks is regarded to be one of the strongest predictor of virological sustained response. When 6 MU IFN-α t.i.w. was administered only, 27% of the patients, had at least a 3 log decline in HCV-RNA 4 weeks after treatment (23). In our study 54% of patients were HCV-RNA negative at the end of treatment. In other studies, 6-12 months of treatment with IFN-α monotherapy was associated with an end of treatment response (HCV-RNA negative) of 24-33% (16;19). A positive HCV-RNA test at week 4 and 12 has been reported to have a high predictive value (98-99%) for virological non-response (3;21). Since we stopped treatment after 2 weeks, the predictive value of a rapid 3 log decline in HCV-RNA and/or an early negative HCV-RNA test could not be established in our study.

At the end of follow up only one of 13 (7.7%) patient had a SVR. In studies in which patients were treated with IFN-α for 6 or 12 months, a SVR rate of 6-19% had been reported (4;16;19;20). In the first 24 hours of treatment we demonstrated that the half life of HCV RNA was 5.79 hours and the calculated daily mean production and clearance of HCV was 237x10^9 IU/day. Other studies have reported a daily production and clearance of HCV of 66.7x10^9 copies/day (24), 367x10^9 copies/day (13), 1276 x 10^9 copies/day (18). In our study patients infected with genotype non-1, the viral decline was more rapid in the first 24 hours (first phase) then in the remainder of the treatment period (second phase). This finding is in accordance with other studies (17;18). Our data confirm that patients infected with genotype-1 are less responsive to IFN-α treatment as was observed by others (5). However a study by Ferenci et al described significant higher SVR rate in patients with genotype 1 receiving high dose induction therapy (7). During the first 24 hours we found a mean reduction in viral load of 80.3%, a half life of HCV RNA of 0.4 days and a daily HCV production and clearance rate of 123 x10^9 IU. Lam et al demonstrated a IFN-α dose dependent decline in viral load for patients infected with genotype 1 in the first 24 hours of treatment. Patients receiving 10 MU IFN-α had a 85.5% reduction of viral load, a half life of HCV RNA of 0.3 days and a daily HCV production and clearance of 370x10^9 copies in the first 24 hours of treatment. Despite the relatively constant levels of IFN-α there were no differences between our study and previous studies of HCV kinetics during the first phase in patients infected with genotype 1 (13;18;24). However, a high density of interferon receptors in the liver correlates with the viral response to IFN-α (22). Therefore, it is possible that most of the interferon receptors were already blocked by a dose of 10 MU IFN-α a day, and that a high constant level of IFN-α had no additive beneficial effect on the clearance of the virus (13)

The first phase of the treatment response is dose dependent (13) but the rate of viral decline in the second phase was found to be not dose dependent (15). However, the slope of HCV RNA levels with respect to time in the second phase is dependent on the viral load achieved after the first phase. A recent study showed that none of the patients with less than 70% viral load decline 24 hours after the first dose of IFN-α had a SVR 6 months after standard therapy (11). In our study most patients rapidly became HCV-RNA negative below the detection level of the quantitative bDNA assay and accordingly no viral load could be detected during the second phase. In four patients infected with genotype 1 and 3 a third phase was observed.
In a study by Bekkering et al. (1), all patients receiving high dose Interferon for 4 weeks showed a short rise in viral load between 32 – 120 hrs after initiation of therapy, the so-called third phase. In our study, the four patients with a third phase appeared to have a delayed start of the second phase. Since the viral decline in the first phase was extremely rapid in most patients and the HCV-RNA load was around or just below the cut-off of the bDNA within 48 hours, therefore a third phase could not be observed. Another possible explanation for the lacking third phase in most patients may be the constant high level of IFN-α and therefore a constant immuno-modulating process in the hepatocytes. Beckering et al (1), postulated 2 mechanisms for the third phase, the efficacy of interferon may change after the first 24-32 hours due to down regulation of Interferon receptors therefore the immune mediated response in the second phase does not start and a lag period of viral suppression is present. The second explanation may be that HCV viral species for which Interferon has a lower efficacy may emerge after the first phase. Another possible explanation is that after rapid clearance of the HCV from the serum (first phase), the second phase which is clearance of the infected hepatocytes starts. In the beginning of the second phase a large number of infected hepatocytes are cleared therewith releasing HCV-RNA in the serum which may contribute for the viral load rise in the third phase. However a raise in ALAT is not observed during the third or second phase. More research is necessary for explanation of the third phase.

It is surprising that patients receiving 8 hourly injections of 6 MU IFN-α had only mild flu like side effects after the initiation of interferon therapy. The observed side effects are comparable to dose occurring 6 to 8 hours after one injection of IFN-α. These side effects can be ameliorated by paracetamol (6). However, in our trial most patients felt they had no need for paracetamol after the first week of treatment. It is possible that due to the injections being given every eight hours, the level of IFN-α is more stable, and patients may not experience symptoms associated with a drop or rise in IFN-α levels and/or a sudden increase of IFN-α levels every other day.

In conclusion, treatment of IFN-α naïve patients with chronic hepatitis C with 6 MU IFN-α 8 hourly for 2 weeks induces a mean 1.6 log decline in HCV-RNA during the first phase and a 1.35 log decline during the second phase of treatment. This high dose induction schedule may potentiate SVR in patients with chronic HCV when prolonged IFN-α treatment in combination with ribavirin is subsequently given.
Viral kinetics of HCV-RNA

References