Viral Kinetics during Induction *versus* Standard Alfa Interferon Mono-therapy in Lithuanian Patients with Chronic Hepatitis C Virus Infection

Ligita Balčiūnienė[1], Arvydas Ambrozaitis[1], Ola Weiland[2]

[1] Department of Infectious Diseases of Vilnius University and Vilnius University Hospital for Infectious Diseases, Birutės 1, Vilnius LT-2004, Lithuania
[2] Division of Infectious Diseases, Department of Medicine, Karolinska Institutet at Huddinge University Hospital, Stockholm, Sweden

The viral kinetics in genotype 1 and non-1 infected Lithuanian patients with chronic hepatitis C virus (HCV) infection was studied during treatment with Lithuanian alfa interferon (IFN). Thirty-six patients with a mean age of 37 years (range, 19–66 years) were given IFN mono-therapy either as a standard regimen during 48 weeks or with an increased IFN dose daily during a 10-day induction phase followed by standard three times a week (t.i.w.) dosing with 3 or 6 MU during totally 24 weeks. Induction IFN therapy followed by standard or high dose t.i.w. of IFN used as mono-therapy was not better than standard t.i.w. treatment from onset in achieving a decline in HCV RNA levels at weeks 4, 8 or 12 during treatment. Patients with genotype 2 or 3 infections had a much more pronounced decline in HCV RNA levels, irrespective of treatment schedule given, than genotype 1 patients, reflected by a mean 3 log and 1 log decline, respectively, of the HCV RNA levels already at week 4. No patient treated with induction and a low follow-up IFN dose during only 24 weeks achieved sustained virological response (SR), whereas patients treated with induction and a high follow-up dose achieved SR in 36%, a difference which nearly reached significance, $p = 0.067$. Patients treated with the standard scheme during 48 weeks had an overall SR of 42%, not significantly different from the result in the combined induction groups (17%, $p = 0.1$). It is concluded that genotype non-1 infections respond with a much more pronounced decline in viral levels early during treatment than genotype 1 patients, and that a short induction period does not translate in a higher sustained response rate.

Key words: chronic hepatitis C, hepatitis C virus RNA, hepatitis C virus dynamics, alfa interferon, induction therapy

INTRODUCTION

Chronic infection with hepatitis C virus (HCV) is estimated to affect almost 4 million people in the United States, approximately 8–9 million in Europe, and 170 million worldwide (1, 2). Many of these patients eventually will develop cirrhosis and its sequela (3). Alfa interferon (IFN) treatment of chronic HCV infection has been used during the last decade and yet the optimal treatment schedule has not been firmly established (4). Recently the turnover of HCV in serum has been shown to be very rapid, with a daily production of HCV particles of 10^{12} (5). The decline of HCV RNA levels during IFN therapy of HCV-infected patients has shown that three times per week dosing is less effective to reduce the viral levels than daily dosing, and that the decline is dependent on the IFN dose given (5, 6). During IFN treatment HCV RNA levels fall more slowly in genotype 1 than genotype 2 infections (7), both during the initial rapid decline phase reflecting clearance of the virus from serum and during the subsequent slower decline phase which starts on the second day of treatment, which is thought to reflect the elimination of infected hepatocytes. The standard treatment regimen with IFN 3

Correspondence to: Prof. Ola Weiland, Division of Infectious Diseases I73, Karolinska Institutet at Huddinge University Hospital, 141 86 Stockholm, Sweden. Fax: +46 8 585 819 16. E-mail: ola.weiland@medhs.ki.se

MU thrice weekly offers a low efficacy in patients with genotype 1 infections, where induction treatment potentially could improve the results (8). One important prerequisite to achieve a sustained response seems to be an early clearance of HCV RNA from the circulation, which is achieved more frequently with a more aggressive initial therapy (9). In Japan thus initial daily IFN administration during 2–4 weeks followed by administration three times a week (t.i.w.) during the following 5 months has been widely used and resulted in comparatively high sustained response rates also in genotype 1 infections (10). It is firmly established that patients with genotype non-1 (genotype 2 or 3) will respond better to IFN mono-therapy or IFN in combination with ribavirin than genotype 1 patients (4, 8). The reason for this difference and the more rapid viral decay rate in genotype non-1 versus 1 strains is unknown (7).

The aim of this study was to assess the viral kinetics in patients with genotype 1 and non-1 chronic HCV infection during treatment with a Lithuanian IFN utilised as mono-therapy and given as a standard regimen during 48 weeks or with an increased IFN dose daily during an induction phase followed by standard three times a week dosing with 3 or 6 MU during totally 24 weeks.

MATERIALS AND METHODS

This study was an open trial evaluating HCV RNA kinetics during standard t.i.w. dosing or initial once a day (induction) dosing followed by t.i.w. dosing of Lithuanian IFN alfa-2b during treatment of patients with chronic HCV infection. It was performed at the Department of Infectious Diseases, Vilnius University and University Hospital for Infectious Diseases during 1997–1999. The study was approved by the Ethics Committees at the Karolinska Institutet, Stockholm, Sweden, and Vilnius University, Vilnius, Lithuania.

Patients

Patients with chronic HCV infection were eligible to enter the study if negative for HBsAg and anti-HIV in serum, and if clinical, laboratory or histological signs of autoimmune or metabolic liver disease were lacking. Patients with clinically obvious abuse of alcohol were excluded as were patients with liver cirrhosis. All patients were anti-HCV and HCV RNA positive in serum and had had raised liver enzymes for more than 6 months prior to inclusion. A liver biopsy with findings consistent with chronic hepatitis C had been performed within 6 months prior to entry in all patients. No patient had previously received antiviral therapy for hepatitis C.

Treatment

Treatment was given with Lithuanian recombinant Interferon alfa-2b (Realdiron, Biotechna AB, Lithuania) i.m. Patients were entered consecutively to the individual treatment groups, standard IFN treatment with 3 MU t.i.w. during 48 weeks (group I); daily induction IFN treatment with 6 MU during 10 days followed by standard (3 MU) follow-up dosing (group II) or high (6 MU) follow-up dosing t.i.w. during totally 24 weeks (III). The follow-up period after treatment stop was 24 weeks, hence, the total study period was 72 weeks for group I, and 48 weeks for groups II and III.

METHODS

Sera for determination of HCV RNA levels were drawn at baseline (day 0) and at week 4, 8, and 12 during treatment (for all groups), at end-of-treatment (ETR) (week 24 for groups II and III and 48 for group I) and at the end of follow-up (24 weeks after treatment stop). Analyses for ALT levels, hemoglobin, white cell, differential, and platelets counts were performed at the same time points and also every 4th week during treatment and analysed by standard methods. Sera were immediately frozen at −70 °C and later analysed for HCV RNA levels at the Division of Virology, Huddinge University Hospital, Karolinska Institutet, Stockholm, Sweden.

HCV RNA quantification

HCV RNA levels were analysed by the Cobas Amplicor HCV Monitor version 2.0. Roche Diagnostics, Mannheim, Germany. This assay has a sensitivity of approximately 600 IU/ml serum (11). For high titre sera a dilution of 1/10 was used to give accurate levels.

Genotyping

HCV genotyping was performed by a line probe assay (Inno-Lipa HCV II, Innogenetics, Brussels, Belgium) (12) or an in-house method (13).

Liver biopsy

A liver biopsy was performed in all patients within 6 months prior to entry and again at treatment stop. Histological evaluation was performed according to the Ishak scoring system separating stage and grade (14). In short, the scoring system ranked liver in-

flammation (grade) on a scale 0–18 and fibrosis (stage) on a scale 0–6.

Statistical methods

For a 2-group comparison of continuous data the Mann-Whitney U test and for a 3 group comparison the Kruskal–Wallis test were used when appropriate. The Fisher's exact two-tail test or chi-square methods were used to test categorical variables. A $p < 0.05$ was considered statistically significant.

RESULTS

Thirty-six patients (26 males and 10 females) with a mean age of 37 years (range, 19–66) were included. Sixteen were infected with genotype 1 (1a n = 3; 1b n = 13, including one with mixed genotype 1b/2), and 20 were infected with genotype non -1 (2a n = 9, 2b n = 1, or 3a n = 10). The baseline patient demographics are given in Table 1.

No statistically significant difference among the groups was noted for age, sex, baseline HCV RNA level, genotype distribution, baseline ALT level, baseline stage or grade. Thus the median HCV RNA level at baseline was 593,000 IU/ml in genotype 1 patients and 915,500 IU/ml in genotype non-1 patients, a difference that was not significant. The distribution of genotypes, however, was somewhat skewed so that a low number of genotype 1 patients was allocated to group I. The mean baseline viral load was also higher in the two induction groups (II and III) than in the standard treatment group (I), but not at a significant level.

All patients completed the treatment, and 30 (83%) had a control liver biopsy performed at end-of-treatment (ETR). A follow-up visit was completed for 29 (81%) patients, and only 3 who were negative for HCV RNA at ETR were lost to follow-up and regarded as non-responders in the outcome analysis. The four patients who were HCV RNA positive at ETR and did not come for follow-up were also regarded as non-responders.

HCV RNA levels during the 12 initial treatment weeks

The mean HCV RNA levels according to genotype 1 or non-1 in the treatment groups according to treatment week are shown in Table 2. No statistical-

Table 1. **Baseline demographics according to treatment groups**

	Group I (n = 12)	Group II (n = 13)	Group III (n = 11)	p value
Sex M/F (n)	7/5	10/3	9/2	
Mean age (range), yrs	40 (21–66)	33 (20–43)	37 (19–56)	ns
Mode of acquisition (n) IVDU/PTH/ SURG/SPOR/ HOSP/SEX	2/2/1/7/0/0	3/2/3/5/0/0	2/1/2/4/1/1	
Plasma donor	7	3	5	
Genotype 1/ non-1	4/8	7/6	5/6	ns
Mean HCV RNA (range) IU/ml				ns
Total	848.833 (24.000–2.600.000)	1.424.153 (22.000–6.100.000)	1.730.182 (56.000–4.000.000)	
Genotype 1	931.250 (24.000–2.400.000)	595.429 (22.000–1.900.000)	1.840.200 (56.000–4.000.000)	
Genotype non-1	807.625 (120.000–2.600.000)	2.391.000 (232.000–6.100.000)	1.638.500 (367.000–4.000.000)	
ALT mean (range)	158 (45–500)	133 (49–450)	138 (41–390)	ns
Histology				ns
Grade mean (range)	4.1 (2–8)	3.9 (2–7)	3.6 (3–4)	
Stage mean (range)	0.5 (0–2)	1.0 (0–3)	1.4 (0–3)	

Group I = 3MU t.i.w. for 48 weeks; Group II = 6MU daily for 10 days (induction phase) followed by 3MU t.i.w. until week 24.
Group III = 6MU daily for 10 days (induction phase) followed by 6MU t.i.w. until week 24.

Table 2. **HCV RNA levels according to treatment group and genotype 1 *versus* non-1 at baseline, weeks 4, 8 and 12 during treament**

Genotype / treatment group	Mean HCV RNA IU / ml			
	Baseline	Week 4	Week 8	Week 12
Genotype 1				
Group I	931,250	90,650	36,325	96,150
Group II	595,429	119,628	149,114	166,828
Group III	1.840,200	805,260	617,640	296,440
Genotype non-1				
Group I	807,625	4187	599	8,949
Group II	2,391,000	4066	12,866	899
Group III	1,638,500	799	649	599

Group I = 3MU t.i.w. for 48 weeks; Group II = 6MU daily for 10 days (induction phase) followed by 3MU t.i.w. until week 24
Group III = 6MU daily for 10 days (induction phase) followed by 6MU t.i.w. until week 24

ly significant difference in mean HCV RNA level was noted between the groups with induction (II and III) and standard treatment (I) at any time point during the 12 initial weeks of treatment. The HCV RNA levels in the two induction groups did not differ significantly during this period. Hence, these groups were combined for comparison with group I, the standard treatment group, when analysing the kinetics during the initial 12 weeks of treatment.

Viral decline with induction or standard treatment according to genotype

The median viral load in all patients did not differ significantly at any time point between the induction and standard treatment groups (Fig. 1, a and b). The HCV RNA levels, however, declined more substantially for genotype non-1 than for genotype 1 patients, irrespectively whether induc-

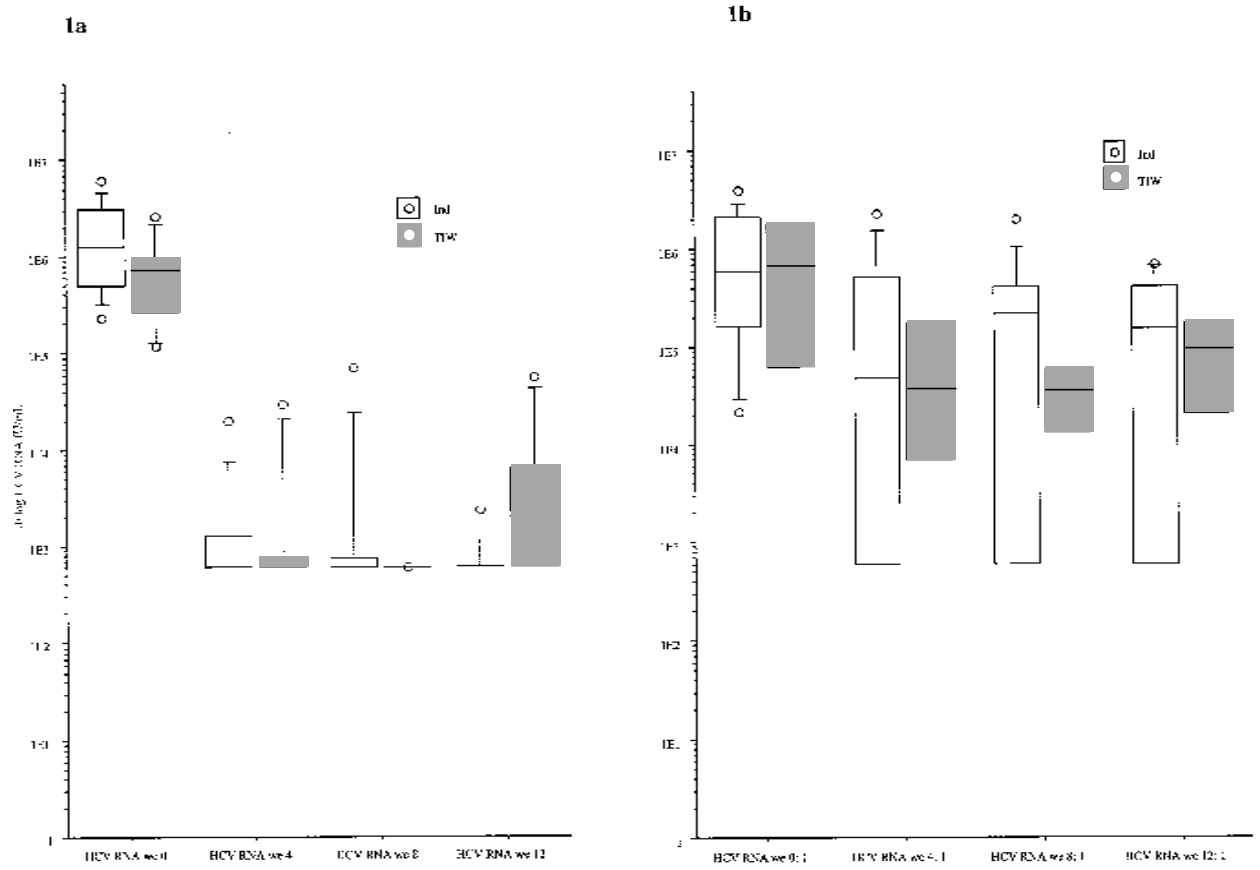

Figure. Box plotting of the median 10 log HCV RNA level (the bar within the box) during treatment with interferon-alfa according to treatment schedule and time point during treatment. Patients received either standard thrice-weekly treatment from start (black box, n = 12) or daily induction therapy during 10 days followed by thrice-weekly treatment (open box, n = 24). The box shows the 25th through 75th percentile, the lower and upper bars the 10th and 90th percentile, respectively. Figure 1a depicts genotype non-1 (genotype 2 or 3) infected and Figure 1b genotype 1 infected patients.

Table 3. **Mean HCV RNA levels according to genotype 1 *versus* non-1 at weeks 4, 8 and 12 during treatment**

Genotype	Mean HCV RNA IU/ml			
	Baseline	Week 4	Week 8	Week 12
Genotype 1	1,068,375	326,643	267,330	189,662
Genotype non-1	1,531.900	3134	4294	4029
p value	0,1864	0,0177	0,0015	0,0056

tion or standard treatment had been given (Fig. 1, a and b). Hence, genotype non-1 patients had a mean 3 log decline already at week 4, whereas genotype 1 patients only declined 1 log. Accordingly, the mean HCV RNA levels at weeks 4, 8 and 12 during treatment showed significantly lower levels in genotype non-1 patients as compared to genotype 1 patients (Table 3).

Overall virological response

The overall virological response at end-of-treatment (ETR) and at follow-up (sustained response (SR) are given in Table 4. At the end of treatment 58%, 23%, and 73% in groups I, II, and III, respectively, had levels of HCV RNA below the detection limit of the test. The corresponding SR figures showed that no patient treated with induction and a low follow-up IFN dose during only 24 weeks achieved a lasting response, whereas patients treated with induction and a high follow-up dose achieved SR in 36%, a difference that nearly reached significance, p = 0.067. Patients treated by a standard scheme during 48 weeks had an overall SR of 42%, not significantly different from the result in the combined induction groups (17%, p = 0.1).

Virological response at different time points in the combined induction group *versus* standard treatment group according to genotype 1 or non-1

Already at week 4 HCV RNA had become undetectable in serum (less than 600 IU/ml) in 7/12 (58%), 7/13 (54%), and 6/11 (55%) of patients in groups I, II, and III, respectively (data not shown). In genotype 1 patients HCV RNA became undetectable in 5/12 (42%) given induction therapy as compared to 1/4 (25%) treated by standard treatment, a difference that was not significant (Table 5). The corresponding figures for genotype non-1 patients at week 4 were 8/12 (67%) and 6/8 (75%) treated by induction and standard treatment, respectively. These data, if combined, show that genotype non-1 patients more often became HCV RNA negative than genotype 1 patients already at week 4 (14/20 *versus* 6/16, p = 0.051) (Table 5). At ETR the corresponding figures were 13/20 *versus* 5/16, p = 0.9.

Table 4. **Virological end-of-treatment response (ETR) and sustained response (SR) according to treatment groups and genotype 1 and non-1**

Treatment group	Virological ETR number total (%)	Virological SR number total (%)
Group I		
Total n = 12	7/12 (58%)	5/12 (42%)
Genotype 1 n = 4	1/4 (25%)	1/4 (25%)
Genotype non-1 n = 8	6/8 (75%)	4/8 (50%)
Groups II and III		
Total n = 24	11/24 (46%)	4/24 (17%)
Genotype 1 n = 12	4/12 (33%)	2/12 (17%)
Genotype non-1 n = 12	7/12 (58%)	2/12 (17%)
Group II		
Total n = 13	3/13 (23%)	0/13 (0%)
Genotype 1 n = 7	2/7 (29%)	0/7 (0%)
Genotype non-1 n = 6	1/6 (17%)	0/6 (0%)
Group III		
Total n = 11	8/11 (73%)	4/11 (36%)
Genotype 1 n = 5	2/5 (40%)	2/5 (40%)
Genotype non-1 n = 6	6/6 (100%)	2/6 (33%)

Group I = 3 MU t.i.w. for 48 weeks; Group II = 6 MU daily for 10 days (induction phase) followed by 3 MU t.i.w. until week 24. Group III = 6 MU daily for 10 days (induction phase) followed by 6MU t.i.w. until week 24.

Liver histology

Liver histology was evaluated in all patients before treatment and in 30 patients (83%) at end of treatment (ETR).

Overall in the total material a significant decline in the grade score was seen from baseline to the ETR biopsy, p = = 0.0001 (Table 6). This decline when analysed according to genotype was significant only for genotype non-1 patients (p = 0.0004) but not for genotype 1 patients (p = 0.1562).

Adverse events

Generally, the adverse events were those commonly noted in IFN treatment. In the induction high dose follow-up group (III), nearly half of the patients had thrombocytopenia ($< 75 \times 10^9$/l).

Table 5. **Number of patients (%) in the combined induction and standard treatment groups with undetectable HCV RNA levels (<600 IU/ml) at week 4, 8, 12, end-of-treatment (ETR) (week 24 for the combined induction group and week 48 for the standard treatment group) and follow-up week 24**

Week	4	8	12	24/48	24 (f-u)
Induction group (n = 24)	13 (54%)	14 (58%)	15 (63%)	11 (46)	4 (17%)
genotype 1 (n=12)	5 (42%)	5 (42%)	5 (42%)	4 (33%)	2 (17%)
genotype non-1 (n = 12)	8 (67%)	9 (75%)	10 (83%)	7 (58%)	2 (17%)
Standard treatment group (n = 12)	7 (58%)	8 (67%)	7 (58%)	7 (58%)	5 (42%)
genotype 1 (n = 4)	1 (25%)	0 (0%)	1 (25%)	1 (25%)	1 (25%)
genotype non-1 (n = 8)	6 (75%)	8 (100%)	6 (75%)	6 (75%)	4 (50%)

Six patients in induction treatment group and one patient in standard treatment group lost to follow-up are all regarded as non-responders; three of them (two in induction group and one in standard treatment group) were HCV RNA negative at ETR.

Table 6. **Stage and grade before treatment and at treatment stop in 30 patients with follow-up biopsy**

	Stage	Grade
Before treatment		
Mean (range) Total n = 36	0,9 (0–3)a	3,9 (2–8)b
Genotype 1, n = 16	0,8 (0–2)	3,2 (2–4)c
Genotype non-1, n = 20	1,1 (0–3)	4,5 (2–8)d
After treatment		
Mean (range) Total n = 30	1,0 (0–3)a	2,4 (0–5)b
Genotype 1, n = 13	0,6 (0–1)	2,6 (1 – 5)c
Genotype non-1, n = 17	1,3 (0–3)	2,2 (0–4)d

A–a) p = NS; b-b) p = 0.0001; c – c) p = NS, d – d) p = 0.0004; c – d before treatment p = 0.0013 after treatment, p = NS.

DISCUSSION

We found that the median viral load in our patients did not differ significantly between the induction and standard treatment groups at any measured time point during the initial 12 weeks of treatment. Hence, no difference in viral kinetics was seen no matter induction or standard treatment had been given; the levels however, were not analysed during the initial 4 weeks when such a difference might have been detected as described earlier (15). HCV RNA levels, however, decreased more substantially for genotype non-1 than for genotype 1 patients, irrespectively if induction or standard treatment had been given. Hence, genotype non-1 patients had a mean 3 log decline in viral levels already at week 4, whereas genotype 1 patients only declined 1 log. These results are in line with the findings in other studies and show that patients infected with genotypes 2 or 3 (non-1) respond better to IFN than genotype 1 patients (5, 16). Hence, Neumann et al. found that the T 1/2 was shorter for genotype 2 than for genotype 1 infections during IFN treatment, both during the initial rapid decline phase and during the second slower decline phase reflecting the infected hepatocyte cell death rate. During the latter phase the mean T1/2 was 2.3 *versus* 8.7 days for genotype 2b and 1 infections, respectively (7). These authors, however, did not correlate these findings with the long-term outcome and sustained response rates.

The turnover rate of HCV has mathematically been calculated and found to be very fast, – 10^{12} viral particles are produced and cleared every day. Furthermore, the half-life of HCV has been estimated to be only 3 h (17). An exponential decline of HCV RNA with a mean half-life of approximately 2 days has been described in patients receiving a dose of 3 MU IFN alfa three times per week (17).

By increasing the dose to 6 MU IFN daily, Yasui et al. noted a mean T1/2 of only 8 h (18). The decline in HCV RNA levels in serum during IFN treatment is thought to be dose-dependent (6). A very rapid clearance of HCV RNA with a mean half-life of 5 h has been noted with a dose of 10 MU IFN during the first day (9). The aforementioned studies performed in naļve patients, taken together with the study performed in non-responders suggest that a dose of 10 MU IFN per day will block HCV virion production more completely than a standard 3 MU dose given three times a week. Furthermore, the HCV RNA levels will rise already 48 h after the first IFN injection before the second dose is given when a t.i.w. scheme is used

(6). It has thus been proposed that daily dosing, induction treatment, should offer better results than t.i.w. dosing.

The findings of Bekkering et al., furthermore, suggests that early clearance of HCV RNA can be achieved by daily induction treatment with a high dose of IFN when used also in IFN non-responders (9). In line with this, Japanese researchers reported a high efficacy when utilising daily initial IFN administration during 2 weeks rather than the intermittent t.i.w. dosing from the start used as a standard therapy in Europe (10). An early clearance of HCV RNA from serum thus seems to be a prerequisite for achieving a sustained response.

In our study, the induction treatment did not translate into a higher sustained response rate nor did it result in a faster decline in viral levels at the time points measured. The induction groups (group II and III), however, got only a 24-week treatment, whereas the standard treatment group was treated for 48 weeks, favouring a higher sustained response rate in this group (4). In fact, no patient in group II with the low dose short follow-up treatment after 10 days of induction treatment had a sustained response, whereas those with a high follow-up dose had sustained response in 36%, not statistically different from 42% noted in group I treated for 48 weeks, reflecting that a higher follow-up dose might offer a better response rate also when the treatment lasts only 24 weeks. In a similar study where patients after 14 days of induction treatment with IFN mono-therapy were offered a 24-week standard combination therapy with addition of ribavirin, a higher sustained response rate was seen in patients initially treated with induction than in those treated with standard IFN t.i.w. dosing (15).

The 3 log decline in HCV RNA levels in our genotype 2 and 3 patients within 4 weeks as compared to only 1 log decline observed for the genotype 1 patients confirms a more rapid decline in genotype non-1 infected patients noted by others (7, 16). This difference can be explained by a greater effectiveness of IFN in blocking the production of HCV virions in genotype 2 infections and by a more rapid clearance rate, reflected by the shorter half-life of virions noted in genotype 2 infections (7). Of clinical importance is the fact that a faster viral decay during treatment correlates with an earlier eradication of HCV RNA from serum, hence, most genotype non-1 patients will have cleared their viremia by week 12 during treatment, which in turn indicates a better chance to achieve a sustained virological response (19).

In conclusion, we found that a 10-day induction IFN monotherapy followed by standard or high dose t.i.w. IFN monotherapy was not better than standard t.i.w. treatment from onset in achieving a decline in HCV RNA levels at weeks 4, 8 or 12 during treatment. Patients with genotype 2 or 3 infections, on the other hand, had a much more pronounced decline in HCV RNA levels, irrespective of treatment schedule, than genotype 1 patients, reflected by a mean 3 log and 1 log decline already at week 4, respectively. A significant histological improvement was noted only in genotype 2 and 3 infected patients.

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L. Balčiūnienė, A. Ambrozaitis, O. Weiland

VIRUSO KINETIKA TAIKANT INDUKCINĘ ARBA STANDARTINĘ ALFA INTERFERONO MONOTERAPIJĄ LIETUVOS PACIENTAMS, SERGANTIEMS LĖTINE HEPATITO C VIRUSO INFEKCIJA

S a n t r a u k a

Buvo nagrinėti Lietuvos pacientų, sergančių lėtiniu hepatitu C, viruso kinetikos skirtumai užsikrėtus hepatito C (HC) viruso pirmu ir ne pirmu genotipu gydymui taikant lietuvišką alfa interferoną (IFN). Trisdešimt šešiems ligoniams, kurių amžiaus vidurkis 37 metai (nuo 19 iki 66 metų), buvo taikyta interferono monoterapija: standartinė dozė (po 3 milijonus vienetų (mln. TV) tris kartus per savaitę injekcijomis į raumenis) 48 savaites arba indukcinė vaisto dozė po 6 mln. TV gydymo pradžioje (10 dienų kasdien), vėliau tęsiant injekcijas tris kartus per savaitę po 3 arba 6 MV iki 24 savaičių. Indukcinės interferono dozės taikymas, vėliau tęsiant gydymą standartine ar didele interferono doze, nebuvo efektingesnis mažinant hepatito C viruso RNR koncentraciją serume po 4, 8 ar 12 gydymo savaičių už standartinį gydymą interferonu nuo gydymo pradžios. Tačiau jau po 4 savaičių gydymo ligonių, užsikrėtusių 2 ir 3 genotipo HC virusu, kraujo serume HCV RNR koncentracija gerokai sumažėdavo, (3 kartus) lyginant su užsikrėtusiais pirmo genotipo HC virusu, nepriklausomai nuo taikyto gydymo (standartinio ar su indukcine doze pradžioje). Nei vienam ligoniui, gydytam indukcine doze, o vėliau tęsiant interferono injekcijas po 3 MV tris kartus per savaitę 24 savaites, nebuvo gautas ilgalaikis gydymo atsakas. Ligoniams, kurie po indukcinės dozės gavo didesnę interferono dozę (6 mln. TV) tris kartus per savaitę iki 24 savaičių, gautas ilgalaikis atsakas sudarė 36% ir šis skirtumas beveik pasiekė statistiškai patikimą ($p = 0,067$). 42% pacientų, gydytų standartine interferono doze 48 savaites, buvo gautas ilgalaikis gydymo atsakas ir tai statistiškai nesiskyrė ($p = 0,1$) nuo ilgalaikio gydymo atsako susumavus abiejų indukcinių grupių rezultatus (17%). Apibendrinus gautus rezultatus galima teigti, kad ne pirmo HCV genotipo infekcija, lyginant su pirmu genotipu, į gydymą interferonu reaguoja daug ryškesniu viruso koncentracijos sumažėjimu jau gydymo pradžioje ir kad trumpas indukcinis gydymo periodas nepagerina ilgalaikio gydymo atsako.

Raktažodžiai: lėtinis hepatitas C, hepatito C viruso RNR, hepatito C viruso dinamika, interferonas alfa, indukcinė terapija