Hepatitis C infection: the quest for new treatment strategies
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Retreatment of chronic hepatitis C non-responder patients with 18 MU daily Interferon-α induction in combination with ribavirin and/or amantadine A pilot study

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Summary

**Purpose:** High dose interferon induction could play a role in hepatitis C virus eradication in patients who failed interferon mono- or interferon/ribavirin combination therapy. Our pilot study explored this approach with various treatment regimens.

**Methods:** Thirty four chronic hepatitis C patients, 26 with a viral non-response after interferon-α therapy and 8 with a viral non-response after interferon-α/ribavirin therapy, received all interferon induction therapy during 2 weeks in a dosage of 18 MU daily, and interferon maintenance therapy during 22 weeks in a dosage of 6 MU three times a week. In a randomized fashion patients who had failed interferon therapy also received ribavirin (group 1 n=9), amantadine (group 2 n=10) or ribavirin and amantadine (group 3 n=7). Patients who had failed interferon/ribavirin therapy were not randomized and received all ribavirin and amantadine (group 4 n=8).

**Results:** Sustained viral response was achieved in 3/9 (33%) of group 1 patients, in 0/10 of group 2 patients, in 3/7 (43%) of group 3 patients and in none of group 4 patients. A viral load decline of less than 2.5 log, after the 2 week interferon induction period was predictive for a non-response in 90% of the patients.

**Conclusion:** Six month interferon/ribavirin or interferon/ribavirin/amantadine therapy including very high dose interferon (18 MU daily) induction may result in a 30–40% sustained viral response. This pilot study demonstrates the importance of early viral kinetics for prediction of response. A viral load decline of less than 2.5 log after 2 weeks was predictive for a viral non-response in 90% of these patients.
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Introduction

Retreatment of chronic hepatitis C patients with a viral non-response (VNR) after interferon-α (IFN) monotherapy with standard dose IFN in combination with Ribavirin (Riba) during 6 months is not very successful. Achieved sustained viral response (SVR) rates varying from 14-18% (1;2). Higher IFN doses and longer treatment duration enhances the SVR rate (28%), but also side effects (3). Nevertheless, a majority of VNR patients fail to achieve a SVR after a retreatment course. In the search for new treatment options for VNR patients high dose IFN induction schedules were introduced. These schedules were based on the IFN dose dependent initial viral responses in difficult to treat HCV patients (4;5). Recently we reported the outcome of an IFN retreatment course of 24 weeks including a 18 MU daily IFN induction treatment schedule for 2 weeks in combination with Riba and Amantadine (Ama) in patients with a previous virological relapse (VR). After the induction period 52% of the patients were HCV-RNA negative by qualitative PCR testing and 44% of the patients achieved a SVR. However, neither viral load decline during induction, nor HCV-RNA negativity after the induction period was predictive for a SVR in these patients (6). Because VNR patients are a different population from VR patients, our aim in this pilot study was to evaluate the efficacy of 24 weeks IFN retreatment with the same 18 MU IFN induction dose for 2 weeks, combined with Riba and/or Ama in VNR patients to previous IFN monotherapy or IFN/Riba combination therapy. Furthermore, early viral kinetics during the induction period was studied to establish if viral decline was a predictor of response or non-response.

Methods

Study design

This study was designed as a randomized open labelled pilot study for retreatment of chronic hepatitis C patients with a VNR to previous IFN monotherapy and a VNR to IFN/Riba combination therapy. The study was approved by an institutional ethics committee. All eligible patients received IFN (Roferon-A, Roche) 6 MU every 8 hours for 2 weeks induction therapy and 6 MU IFN thrice weekly (tiw) maintenance therapy for 22 weeks. In a randomized fashion patients with a VNR to IFN monotherapy received in addition Riba 1000-1200 mg per day (group 1), Ama 100 mg per day (group 2) or the combination Riba 1000-1200 mg and Ama 100 mg per day (group 3) during 24 weeks. Patients with a VNR to IFN/Riba combination therapy were not randomized and received all Riba/Ama combination (group 4). After the 24 weeks treatment period there was a follow-up period of 24 weeks in all groups.

Definition of VNR patients

Chronic HCV patients with a VNR after IFN monotherapy were defined as having had an initial treatment of IFN of at least 200 million units (MU) without loss of HCV-RNA. Chronic HCV patients with a VNR after IFN/Riba combination therapy were defined as having had an initial treatment of IFN of at least 200 MU in combination with Riba (1200-1000 mg daily) of at least 4 months (range 4-18) without loss of HCV-RNA.
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Patient selection
Patients were eligible for inclusion when they fulfilled the following criteria: HCV-RNA positive by qualitative PCR, a treatment free interval of at least 24 weeks after initial antiviral therapy, age between 18 and 75 years and a signed informed consent form. Exclusion criteria were: pregnancy or not willing to practise adequate contraception during treatment and up to 6 months thereafter, HBsAg or HIV antibody positive, decompensated liver cirrhosis, history of alcohol or drug abuse within 6 months prior to study entry, severe mental depression or other major psychiatric illness, any significant systemic disease other than liver disease, pre-existing bone marrow depression, a history of auto-immune hepatitis, a history of seizure or other significant CNS dysfunction.
A normal alanine amino transferase (ALAT) level at the beginning of therapy was not an exclusion criterion.

Patient monitoring
Patients were examined at least 2 weeks before the start of the study, the day the study medication started, and 1 and 2 weeks after initiation of IFN induction. Daily telephone contact with the medical trial coordinator was offered and when uncommon side effects were mentioned, patients were seen more frequently. After completion of the induction period the patients were seen every 2 weeks until week 8, and every 2 months until end of treatment (ET) (week 24). In the follow-up period patients were seen 4 weeks after stopping the study medication (week 28) and at the end of follow-up (EFU) (week 48). At each visit, a medical history, a physical examination and routine blood tests were performed. Before the start of the study, at week 24 and 48, sera were tested for autoantibodies and thyroid-stimulating hormone (TSH). When side effects occurred, the IFN and/or Riba dose was reduced or discontinued depending on the progression and seriousness of the side effects. If appropriate the dose of Riba was reduced in steps of 200 mg, or IFN reduced to half dose and maintained at this dose, if tolerated, until the end of the treatment period. Samples for HCV-RNA measurements were taken at every visit and stored at -70°C.

Detection of HCV-RNA
Qualitative HCV-RNA measurements were performed with a Cobas Amplicor HCV 2.0 test (qual-PCR), lower limit of detection 50 IU/mL (Roche Diagnostic Systems INC., Branchburg NJ, USA) and by Transcription Mediated Amplification (TMA), lower limit of detection 5 IU/mL (Bayer, Berkely, CA, USA).
Quantitative HCV-RNA measurements were performed with the HCV 3.0 bDNA assay (quant-bDNA), lower limit of detection 615 IU/mL (Bayer Versant™ HCV 3.0 assay, Berkeley, CA, USA). HCV genotype was determined by direct sequencing using the TruGene™ Genotyping assay and the OpenGene™ automated DNA sequencing system (Visible Genetics Inc., Toronto, Canada). All tests were performed according to the manufacturer’s manual. The Cobas Amplicor HCV 2.0 test was used on all pre-treatment plasma samples and samples at week 0, 2, 6, 24 and 48. The week 6, 24 and 48 samples with a negative qual-PCR outcome were retested in TMA. The quant-bDNA was used on the plasma samples obtained at week 0, 1 and 2.
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Definition of response
The main endpoint of this study was SVR at the end of follow-up (EFU). SVR was defined as non-detectable HCV-RNA by TMA at EFU (48 weeks). The end of treatment response (ETR) was defined as non-detectable HCV-RNA at week 24 by TMA. Virological relapse (VR) was defined as non-detectable HCV-RNA at the end of treatment (24 weeks) by TMA but recurrence of detectable HCV-RNA within 6 months after cessation of treatment (48 weeks). All other patients were classified as having a virological non-response (VNR). A sustained biochemical response was defined as a normal ALAT value (< 45 U/L) at ET and lasting at least 6 months thereafter.

Viral kinetics
Quantitative HCV-RNA measurements, performed at the beginning of treatment (t=0), after 1 week of treatment (t=1) and after 2 weeks of treatment (t=2) were log transformed. A value of 615 IU/mL (2.8 log) was used when samples were negative in the quant-bDNA. When at week 2 the quant-bDNA had a value of <615 IU/mL, a qual-PCR was performed. If the qual-PCR had a negative outcome, a value of 50 IU/mL (1.7 log) was used. The decline in viral load between t=0 and t=1 week and between t=0 and t=2 weeks was measured.

Liver biopsy
When no liver biopsy was available 2 years before the start of the retreatment, a liver biopsy was obtained, except in 2 patients with haemophilia A. All patients had histologically proven chronic hepatitis and were classified as cirrhotic or non-cirrhotic for this study. The 2 haemophiliac patients had no signs of cirrhosis on ultrasound and were classified as non-cirrhotic.

Statistical analysis
All patients who received at least one dose of study medication became subject of outcome analysis (Intention to treat). Patients who discontinued treatment were considered to be NR patients. Data analysis was conducted using the statistical package SPSS for Windows (version 9.0). Univariate analysis was performed using the Mann-Whitney test for rank ordered data. The chi-square test or the Fisher’s exact test was used for categorical variables. All tests of significance were two-tailed and a P-value <0.05 or <0.025 in case of multiple testing, was considered significant. Confidence intervals of predictive values were calculated and subsequently compared with the prior probability of virological response, to define predictors of SVR and VNR.

Results
A total of 40 patients were included in the study. Eleven were randomized into group 1, 11 into group 2 and 10 into group 3. Eight patients were included in group 4. Six patients discontinued participation in the study before treatment was started: 2 had been randomized for treatment 1, 1 for treatment 2 and 3 for treatment 3. The reason that these patients did not participate in the study was that they had little confidence in the outcome of their second treatment. Four patients (12%) discontinued treatment due to side effects, 1 during treatment 2 and 3 during treatment 4, all because of psychological problems. The intention-to-treat analysis was performed on 34 patients, 9 patients in group 1, 10 patients in group 2, 7 patients in group 3 and 8 patients in group 4.
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The 4 patients who stopped treatment were considered to have developed a VNR. Pretreatment characteristics of the 34 enrolled patients are summarized in table 1.

Table 1  Pretreatment characteristics of 34 treated patients.

<table>
<thead>
<tr>
<th>Pretreatment characteristics</th>
<th>Initial IFN-monotherapy</th>
<th>Initial IFN/Riba therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1 IFN/Riba (n=9)</td>
<td>Group 2 IFN/Ama (n=10)</td>
</tr>
<tr>
<td>Male</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>39 (28-58)</td>
<td>43 (35-49)</td>
</tr>
<tr>
<td>Weight (kg)*</td>
<td>94 (62-111)</td>
<td>79 (58-126)</td>
</tr>
<tr>
<td>ALAT (U/L)*</td>
<td>92 (35-345)</td>
<td>76 (47-188)</td>
</tr>
<tr>
<td>Compensated Cirrhosis</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Cumulative IFN dose (MU)*</td>
<td>252 (216-648)</td>
<td>216 (216-780)</td>
</tr>
<tr>
<td>Mode of acquisition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bloodproducts/ Bloodtransfusion</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Intravenous drug</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Mean duration of infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10years</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>&lt;10 years</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>HCV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>genotype 1</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>genotype 3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>genotype 4</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>genotype 5</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Pretreatment HCV-RNA (10^6 IU/mL)*</td>
<td>0.4 (0.1-8.3)</td>
<td>1.8 (0.1-5.2)</td>
</tr>
</tbody>
</table>

*Median (min-max)
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Virological response
As depicted in table 2 in group 1 (IFN/Riba) 3/9 (33%), in group 2 (IFN/Ama) 0/10, in group 3 (IFN/Riba/Ama) 3/7 (43%) patients developed a SVR. None of the group 4 patients (IFN/Riba/Ama) achieved an ETR and thus a SVR.

Table 2
Intention to treat virological responses at week 1, week 2 and week 6 during therapy, at the end of therapy (ET) and at the end of follow-up (EFU). HCV-RNA was tested with quant-bDNA, qual-PCR and TMA. Patients of group 1, 2 and 3 were non-responders to previous IFN monotherapy and were randomized. Patients of group 4 had a non-response to IFN/Riba combination and were not randomized.

<table>
<thead>
<tr>
<th>Treatment schedule</th>
<th>week 1</th>
<th>week 2</th>
<th>week 6</th>
<th>week 24 (ET)</th>
<th>week 48 (EFU)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>quant-bDNA</td>
<td>quant-bDNA</td>
<td>qual-PCR</td>
<td>TMA</td>
<td>TMA</td>
</tr>
<tr>
<td>Group 1 IFN/Riba (n=9)</td>
<td>2/9</td>
<td>5/9</td>
<td>0</td>
<td>2/9 (geno 3,4)</td>
<td>4/9 (geno 1,1,3,4)</td>
</tr>
<tr>
<td>Group 2 IFN/Ama (n=10†)</td>
<td>2/10</td>
<td>4/10</td>
<td>1/10</td>
<td>1/10 (geno 4)</td>
<td>2/10 (geno 4,5)</td>
</tr>
<tr>
<td>Group 3 IFN/Riba/Ama (n=7)</td>
<td>2/7</td>
<td>3/7</td>
<td>2/7</td>
<td>2/7 (geno 1,3)</td>
<td>3/7 (geno 1,1,3)</td>
</tr>
<tr>
<td>Group 4 IFN/Riba/Ama (n=8‡)</td>
<td>0</td>
<td>1/8</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

HCV-RNA negative [n/total]
† 1 patient dropped out
‡ ‡ 3 patients dropped out

Biochemical response
One of the 9 patients included in group 1 had a normal ALAT value at the beginning of treatment and this value remained normal till the end of the follow up period, despite a virological relapse. Three of the 8 patients with an elevated ALAT at the start of therapy in group 1 developed sustained biochemical response and a SVR. All 10 patients of group 2 had an elevated ALAT level at the beginning of therapy, 1/10 developed a biochemical sustained response, but no SVR. None of the 7 patients of group 3 had a normal ALAT level at the start of treatment, 5/7 achieved a biochemical sustained response, including the 3 patients with a SVR. None of the patients of group 4 had a normal ALAT level at the beginning of therapy, and none developed a biochemical or viral sustained response.

Viral kinetics
In figure 1, the mean HCV-RNA viral load decline of the evaluable patients (n=30) of the 4 treatment groups during induction is depicted. The viral load decline in group 1, 2 and 3 patients tended to be larger than in group 4 patients, but this difference was not significant.
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Figure 1  Mean log HCV-RNA IU/mL decline during induction therapy of 18 MU IFN daily for 2 weeks in the 4 treatment groups (n=30).

Markers for viral response in group 1 and 3 patients

Before treatment
The mean weight of the 6 SVR patients was 71 kg (range 57-108) versus 89 kg (range 76-111) of the 10 VNR/VR patients (p=0.02). No other baseline characteristics as mentioned in table 1 were associated with SVR.

During treatment
The mean log decline of HCV-RNA during induction of the 16 patients is depicted in figure 2, according to their viral response at EFU. After 1 week of induction the mean viral load decline of the 6 SVR patients was 2.7 log (range 1.3-4.1 log), the mean decrease in viral load of the 9 VNR patients after 1 week induction was 1.3 log (range 0.6-2.0 log) (p=0.01). After 2 weeks of induction these values were for SVR patients 3.3 log (range 2.1-4.1 log) and for VNR patients 1.7 log (range 0.6-3.1 log) and this difference was highly significant (p=0.007). The one VR patient had a decline in viral load of 2.2 log after 1 week and 2.3 log after 2 weeks. Five of the 6 SVR patients achieved a >2.5 log decline in viral load after 2 weeks of induction therapy in contrast to 1/9 VNR patients. Patients with a decline in viral load of ≥2.5 log after 2 weeks of retreatment had an 80% chance to achieve a SVR (95% CI 40-100%), with a prior probability of SVR in this group of 40%.
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Patients with a decline in viral load of <2.5 log after 2 weeks of induction treatment had a chance of 90% to achieve a NR (95% CI 60 - 100%), with a prior probability of VNR in this group of 60%.

A positive TMA test at week 6 of treatment was not predictive for a VNR, since 2/6 SVR patients were still TMA positive at week 6 of treatment.

**Figure 2** Mean log HCV-RNA IU/mL decline during 2 weeks induction therapy of 18 MU IFN daily according to virological responses in group 1 and 3 patients (n=16).

**Side effects**

All 34 patients completed the 2 week 18 MU IFN induction phase. In one patient of group 2 dose reduction of IFN was necessary during the second week of induction due to a low thrombocyte count. None of the patients treated with Riba needed a Riba dose reduction during the induction phase. Four patients dropped out of the study before completing the 6 months of therapy: One patient in group 2, at week 12, due to a depressive mood and 3 patients in group 4 (at week 3, at week 8 and at week 9): One because of anger-hostility and 2 because of a depressive mood due to disappointment of the absence of a viral load decline. In 3/9 patients of group 1, 2/7 patients of group 3 and 2/5 patients in group 4, the dose of Riba had to be reduced after the induction phase. The reasons for Riba dose reduction were low hemoglobin level (3), persistent cough (2), general fatigue (1) and skin eruptions. In only 1 patient of group 2 the dose of IFN had to be reduced at week 16, due to thrombocytopenia.
The effect of the 4 treatment schedules on the hemoglobin level is shown in figure 4a. At week 6 of treatment, the mean hemoglobin level of group 2 IFN and Ama (without Riba) and the other treatment groups (with Riba) was significantly higher ($p < 0.05$). The mean hemoglobin level at the end of treatment in group 1 (without Ama) was higher than the mean hemoglobin level of the patients in group 3 and 4 (with Ama). This difference was not significant. As expected the hemoglobin level returned to pretreatment levels after stopping the Riba medication in the 3 Riba containing treatment schedules. The effect on the thrombocytes and leukocytes counts is shown in figure 4b and 4c. During the first week of the induction period the mean decline in thrombocytes was 46% for group 1, 26% for group 2, 42% for group 3 and 33% for group 4 patients. The mean decline in leukocytes during the first week was 53% for group 1, 48% for group 2, 49% for group 3 and 32% for group 4 patients. After the first week of treatment levels of both thrombocytes and leukocytes stabilized and returned to pretreatment levels after stopping the medication.

Figure 3 Mean hemoglobin value (Fig. 3a), mean thrombocytes count (Fig. 3b) and mean leukocytes count (Fig. 3c) during 24 weeks of treatment and after 24 weeks of follow-up for patients in the 4 treatment groups (n=30).
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### 3b

![Graph showing mean leukocytes over time for different treatments.](image)

- **Weeks**: 0, 1, 2, 6, 24, 48
- **Mean leukocytes**: 0 to 350
- **Legend**:
  - Treatment 1
  - Treatment 2
  - Treatment 3
  - Treatment 4

### 3c

![Graph showing mean leukocytes over time for different treatments.](image)

- **Weeks**: 0, 1, 2, 6, 24, 48
- **Mean leukocytes**: 0 to 9
- **Legend**:
  - Treatment 1
  - Treatment 2
  - Treatment 3
  - Treatment 4
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Discussion

This pilot study shows that only 24 weeks retreatment of VNR patients to previous IFN monotherapy, with IFN in combination with Riba or Riba/Ama including IFN high dose (18MU) induction for 14 days, resulted in a SVR of 33% and 43% respectively. No SVR was achieved when VNR patients were retreated with the same IFN schedule in combination with only Ama. Also no SVR was achieved when VNR patients after previous IFN/Riba combination therapy were retreated with the same IFN schedule in combination with Riba/Ama. Recently results of several VNR retreatment studies, including high dose IFN induction in combination with Riba, were presented. IFN induction doses were 10 MU daily, except in 1 study were 20 MU daily for 2 days was given. All treatment schedules were given longer than 24 weeks, varied from 36-48 weeks. In these studies the SVR rates (30-40%) were comparable with these of our study (7-9). In another VNR study 5 or 10 MU IFN induction for 14 days was compared with standard IFN for 38 weeks, all 3 treatment arms in combination with Riba. SVR rates in the 3 groups of patients were comparable, approximately 30%, indicating no additional value of IFN induction therapy (10). Although IFN induction may not increase SVR rates, it allows the early prediction of response or non-response within 2 weeks, as shown in our study. The mean HCV-RNA viral load decline after the 2 week induction period was 3.3 log IU/mL in patients with a SVR and 1.7 log IU/mL in patients with a VNR, a highly significant difference. Despite the small number of patients in our study we found that after 2 weeks patients with a viral load decline of 2.5 log IU/mL or more had 80% chance to achieve a SVR. Whereas declines of less than 2.5 log IU/mL was 90 % predictive for a non-response. These findings are in contrast with those observed in VR patients when retreated with the same treatment schedule. The mean log decrease in viral load, achieved in these patients after 2 weeks of induction was 3.5 log. However, this initial viral load decline during induction was not predictive for SVR or for VNR. On the other hand, TMA negativity at week 6 in VR patients was highly predictive for SVR, but not, as shown in this study, for VNR patients (6). It is clear that VNR and VR patients are different populations, with their own markers for response during treatment. In terms of side effects, frustration and costs, it is highly desirable to identify patients who most likely will not benefit from the treatment, as early as possible during therapy. It is generally accepted that naive chronic hepatitis C patients can discontinue therapy when the viral load decline after 12 weeks of therapy with Pegylated IFN and Ribavirin is less than 2 log (11). Berg et al. showed that, independent from the therapeutic regimen applied (IFN or Pegylated IFN with or without Riba), naive patients can discontinue treatment at 12 weeks when the absolute viral load was above 30,000 IU/mL (12). However, so far no published data are available on the initial viral load decline during high dose IFN induction in VNR patients and the predictive value of this decline in the outcome of therapy. This study indicates that in VNR patients viral decline after 2 weeks high dose IFN induction can predict SVR or VNR. A stopping rule after 2 weeks is of great value for this difficult to treat patient group, preventing unnecessary side effects of an unsuccesfull therapy.

As observed earlier in VR patients (6), the 18 MU IFN daily for 14 days was also well tolerated by VNR patients. None of them had to stop treatment during the induction phase. In only 1 patient (with cirrhosis) an IFN dose reduction during the induction period was necessary, due to a low thrombocytes count. In none of the patients the dose of Riba had to be reduced during this period.
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A decline of a mean of 37% in thrombocytes count and a mean of 45% in leukocytes count was observed during the first week of induction therapy with stabilisation of these levels during the second week.

At present no data are available yet of the efficacy of retreatment with Pegylated IFN (in standard dose or with high induction dose included) in combination with Riba in VNR patients. Several studies are ongoing. Whether non response could be predicted as early in the course of these new retreatment schedules remained to be seen.

Acknowledgements

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