High dose daily interferon-alpha induction and secondary adjunction of ribavirin in treatment-naive patients with chronic hepatitis C

A multicentric, randomised, controlled trial

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Objectives — To evaluate in naive patients with chronic hepatitis C 1- the efficacy and safety of one month interferon alpha (IFN-α) induction regimen; 2- the potential virological benefit of a secondary adjunction of ribavirin among HCV RNA negative patients after 20 weeks of IFN therapy, with or without an initial 4-week IFN induction.

Material and methods — 151 naive HCV-RNA positive patients presenting with biopsy- proven chronic hepatitis C and elevated ALT were randomised in a 2:1 ratio in two arms: IFN-α 3 MU thrice a week (two for 24 weeks (non-induced patients); IFN-α 6 MU daily for two weeks, then 3 MU daily for two weeks then 3 MU tiw for 20 weeks (induced patients). At week 24, HCV-RNA negative patients were randomised to receive in addition or not ribavirin 1-1.2 g daily for 24 additional weeks. Induction efficacy was assessed on the early viral response (EVR) defined as undetectable HCV RNA at week 4 then week 20. Ribavirin efficacy was assessed on the proportion of maintained complete response until the end of follow-up, 24 weeks after discontinuation of treatment. Data were analysed on an intent-to-treat basis.

Results — Efficacy of IFN-α induction: 104 patients were randomised to the non-induction group, 47 to the induction group. Gender, age, genotype distribution and HCV viral load at baseline did not differ significantly between the two groups. There was one treatment discontinuation because of adverse events in induced patients versus four in non-induced patients (P > 0.05). The 4 week EVR was significantly greater in induced patients in patients with HCV genotype 1, 4 or 5 (47% vs 12%, P = 0.0002) only. There was no impact of induction in patients with HCV genotype 2 or 3. Efficacy of ribavirin: at week 24, 28 and 26 HCV-RNA negative patients were randomised to addition of ribavirin or not, respectively. Patients randomised to secondary additive ribavirin were more often HCV-RNA negative at the end of follow-up than patients treated with IFN-α alone: 18/28 (64%) vs 10/26 (39%), P = 0.06. Among patients randomised to bitherapy, the relapse rate was significantly lower in patients with genotype 2 or 3 (0/12 vs 6/13, P = 0.01) and not in those with genotype 1, 4 or 5 (5/11 vs 3/6, P = 0.99).

Conclusion — A 4 week IFN-α induction significantly increases the EVR rate in patients with HCV genotype 1, 4 or 5. Late secondary adjunction of ribavirin to IFN-α for 6 months in HCV-RNA negative patients after 6 months of IFN-α significantly decreases the relapse rate in patients with HCV genotype 2 or 3, but not in patients with genotypes 1, 4 or 5.

SUMMARY

Impact of the induction by interferon alpha and of the adjunction secondaire de ribavirine chez les malades naïfs atteints d’une hépatite chronique C. Une étude multicentrique randomisée

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Introduction

Hepatitis C Virus (HCV) infection has become one of the most common chronic blood-borne infections. Treatment recommendations in patients never treated before have been worked out from the results of many clinical trials [1, 2]. Ribavirin in doses of 1 000-1 200 mg daily in two divided doses combined with IFN-α 3 million units (MU) thrice in week (tiw) was found to significantly improve the sustained virological response (SVR) rates [3, 4]. The long-term response rates have been further improved with pegylated IFN-α [5, 6]. Combination therapy with pegylated IFN-α and ribavirin for 24 or 48 weeks is now the standard treatment for chronic hepatitis C [1, 2]. However, this pegylated combination therapy elicits a long-term response in only approximately 50% of patients treated.

Before the emergence of pegylated IFN-α, several trials had evaluated the potential benefit of an IFN-α induction with varying results. In some studies [7-9], induction regimens improved the early virological response (EVR) but did not enhance the long-term response whereas a significant improvement of the long-term response in patients receiving high-dose IFN-α induction was reported in other trials [10-13].

In the first controlled study and the following large trials comparing the combination of standard IFN-α and ribavirin to IFN-α monotherapy, the greater SVR obtained in the combination therapy arms was mainly related to a decreased relapse rate after discontinuation of treatment [3, 4, 14].

Our hypotheses when designing this study were based on the followings: 1 that 4 weeks IFN-α induction may increase the primary response rate; 2 a secondary introduction of ribavirin in complete responders to IFN-α may help in maintaining the virological response until the end of treatment (to reduce breakthroughs) and the end of follow-up (to decrease the relapses). Our aims were to evaluate the efficacy and the safety of a one month IFN-α induction regimen on the EVR, and to evaluate the potential benefit on the SVR of a secondary adjunction of ribavirin in treatment-naive patients with chronic hepatitis C undergoing IFN-α monotherapy.

Methods

Patients

Previously untreated patients, 18 years or older, HIV and HBV negative, presenting with a biopsy-proven chronic hepatitis C, serum alanin aminotransferase (ALT) level higher than the upper limit of normal values and positive for HCV RNA were eligible for the study. Criteria for non-inclusion included an alcohol intake higher than 40 g per week, decompensated cirrhosis, other causes of chronic hepatitis, and contraindications to interferon or ribavirin.

Study design

This randomised controlled trial was approved by the Ethical Committee on July 1997. All included patients provided written informed consent. Enrolment began in February 1998, and the trial ended in March 2001. The study was carried out in 24 French centres.

Two-hundred and forty patients were randomly allocated with a 2:1 ratio to receive subcutaneously IFN-α 2b (Schering-Plough) 3 MU tiw for 24 weeks (non-induced patients) or IFN-α 2b 6 MU daily for 2 weeks, then 3 MU daily for 2 weeks, and 3 MU tiw for the remaining 20 weeks (induced patients). Randomisation was stratified on viral load (> 2x10^6 copies /mL; ≤ 2x10^6 copies /mL). At week 12, patients with elevated ALT values were tested for HCV-RNA (the protocol was amended on June 1999 and since that date, all included patients were tested for HCV-RNA at week 12). Treatment was stopped in patients remaining HCV RNA positive and was continued in HCV RNA negative patients. At week 20, all patients were tested for HCV-RNA. Patients remaining HCV-RNA positive were withdrawn from the study. HCV-RNA negative patients were further randomised with a 1:1 ratio to receive ribavirin 1 000 mg (bodyweight < 75 kg) or 1 200 mg (bodyweight ≥ 75 kg) daily in addition to IFN-α for 24 weeks. Treatment was stopped at week 48 in both monotherapy and combination therapy arms.

The occurrence of adverse events was assessed during treatment and follow-up. The IFN-α dose was decreased to half-dose in case of severe adverse events. Ribavirin was reduced to 600 mg per day when haemoglobin concentration decreased to less than 10 g/dL and discontinued when haemoglobin concentration fell below 8.5 g/dL.

Patients were evaluated in an outpatient basis at baseline and monthly thereafter until the end of follow-up. An additional blood count was performed at week 2 in induced patients. Serum was collected and stored under appropriate conditions to optimise HCV RNA detection [15]. Serum HCV-RNA was determined using a genotype independent reverse transcription polymerase chain reaction assay with a sensitivity of 100 copies/mL. Quantification of HCV viral load was obtained at baseline, using branched DNA signal amplification assay (bDNA Quantiplex HCV RNA 2.0 Bayer Diagnostics, Puteaux, France), according to the manufacturer’s instructions. HCV genotypes were determined by INNO-LiPA HCV II (Innogenetics, Zwijnaarde, Belgium). Viral quantification and genotyping were centralised.

All patients underwent a liver biopsy within 12 months before enrolment. The degree of inflammation was assessed using both METAVIR and Knodell’s scores [16]. Under METAVIR score, fibrosis was staged as follows: 0 = no fibrosis, 1 = portal fibrosis without septa, 2 = few septa, 3 = numerous septa without cirrhosis, 4 = cirrhosis. The grading of activity (intensity of necro-inflammatory lesions) was classified as follows: A0 = no histological activity, A1 = mild activity, A2 = moderate activity, A3 = severe activity.

Statistical analysis

The primary efficacy endpoints were for IFN-α induction the early viral response (EVR) defined as the loss of detectable serum HCV-RNA at week 4 then week 20; for the combined ribavirin arm the percentage of maintained complete viral response defined

Conclusion — Une induction par IFN-α pendant 4 semaines augmente la RVP chez les malades ayant les génotypes 1, 4 ou 5, mais pas chez les malades ayant les génotypes 2 ou 3. L’adjonction secondaire et tardive de ribavirine à l’IFN-α, pour une durée de 6 mois chez les malades HCV-ARN négatif après 6 mois d’IFN-α, réduit significativement le taux de rechute après l’arrêt du traitement uniquement chez les sujets ayant les génotypes 2 ou 3.
as undetectable HCV RNA at the end of the 24-week follow-up period. The secondary endpoint was the end of treatment response (ETR) defined as undetectable serum HCV-RNA at week 48. The sample size was estimated to show a relapse rate decreasing from 65% to 20% with combined ribavirin. Based on a type I error of 0.05, and a type II error of 0.20, it was necessary to recruit 35 patients in each arm at week 24. Given an estimated response rate of 70% in the induction group versus 50% in the non-induction group, a total of 240 patients was necessary with a 1:2 ratio. Finally, it was necessary to recruit 80 patients in the induction group, and 160 in the non-induction group. The analysis was performed on an intent-to-treat basis. The analysed study populations differed at weeks 20 and 72. At week 20, all induced and non-induced patients were analysed. At week 48 and 72, only HCV RNA negative patients at week 24 were analysed.

All data analyses were conducted using SAS (SAS Institute, Cary, USA, version 8.12). Due to the absence of its distribution normality, viral load data was log-transformed. Comparisons were analysed using t-test and chi-square test for quantitative and qualitative variables, respectively. Fisher’s exact test was used in case of small numbers of expected patients in contingency tables. P value of less than 0.05 was considered to be statistically significant.

Results

Characteristics of the patients

A hundred and fifty-one patients were randomised and underwent treatment. Patients’ baseline characteristics were similar among the two groups (table I). Two thirds of the patients were male, 82 patients (54%) had been infected through IV drug use, 32 (21%) had been infected for 20 years or more, and 84 (62%) were HCV genotype 1. Viral load was greater than 2 x 10^6 copies/mL in 103 patients (68%). Liver biopsy scored at least A2 for intensity of necro-inflammatory lesions in 86 patients (57%), and at least F3 for fibrosis in 30 patients (20%). The average Knodell’s score was 8.6.

Analysis of efficacy and safety of interferon induction regimen

Forty-seven patients received an IFN-α induction and 104 received a 3 MU IFN-α tiw regimen. The early virological response rate (EVR) was significantly higher among induced patients than in non-induced patients, both at weeks 4 and 20 (table II).

In patients with HCV genotype 2 or 3, there was no significant impact of the IFN-α induction on the EVR (table II). In contrast, among patients with HCV genotype 1, 4 or 5, those randomised to induction were more likely to present a viral clearance at week 4 than non-induced patients (47% vs 12%, P = 0,0002). The latter did not sustain however until week 20 (44% vs 25%, P = 0,06). The SVR rate did not differ significantly among induced patients (with or without ribavirin) and non-induced patients (12/20 vs 16/34; P = 0,35) at the end of follow-up.

In patients with serum HCV-RNA viremia higher than 2 x 10^6 copies/mL, virological response at week 4 was likely to be more frequent among patients who received IFN-α induction than those who did not (41% vs 14%, P = 0.003). However the impact was no longer observed at week 20 (41% vs 28%, P = 0.21).

Table I. – Baseline characteristics according to IFN induction dosing.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No interferon induction</th>
<th>Interferon induction</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>N = 104 (%)</td>
<td>N = 47 (%)</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>65 (63)</td>
<td>34 (72)</td>
<td>0.24</td>
</tr>
<tr>
<td>Age &gt; 40 years</td>
<td>45 (43)</td>
<td>15 (32)</td>
<td>0.19</td>
</tr>
<tr>
<td>Route of transmission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous drug use</td>
<td>57 (55)</td>
<td>25 (53)</td>
<td>0.79</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>19 (18)</td>
<td>S(17)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>3 (3)</td>
<td>1 (6)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>25 (24)</td>
<td>11 (23)</td>
<td></td>
</tr>
<tr>
<td>Duration since contamination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 20 years</td>
<td>18 (17)</td>
<td>7 (15)</td>
<td>0.94</td>
</tr>
<tr>
<td>Unknown</td>
<td>30 (30)</td>
<td>14 (30)</td>
<td></td>
</tr>
<tr>
<td>HCV genotypes 1, 4 and 5</td>
<td>65 (63)</td>
<td>32 (68)</td>
<td>0.51</td>
</tr>
<tr>
<td>HCV genotype 2</td>
<td>11 (11)</td>
<td>1 (2)</td>
<td>0.08</td>
</tr>
<tr>
<td>HCV genotype 3</td>
<td>28 (27)</td>
<td>14 (30)</td>
<td>0.72</td>
</tr>
<tr>
<td>Serum HCV-RNA &gt; 2 X 10^6 copies/mL</td>
<td>71 (68 %)</td>
<td>32 (68 %)</td>
<td>0.95</td>
</tr>
<tr>
<td>Mean serum HCV-RNA (10^6 copies/mL)</td>
<td>13.5 (15.8)</td>
<td>9.1 (9.7)</td>
<td>0.27</td>
</tr>
<tr>
<td>Metavir score&gt; A1</td>
<td>63 (61)</td>
<td>23 (49)</td>
<td>0.35</td>
</tr>
<tr>
<td>Metavir score&gt; F2</td>
<td>21 (21)</td>
<td>9 (19)</td>
<td>0.96</td>
</tr>
<tr>
<td>Mean Knodell score (±SD)</td>
<td>8.6 (2.9)</td>
<td>8.8 (3.5)</td>
<td>0.72</td>
</tr>
</tbody>
</table>
During the first 24-week treatment period, IFN-α was discontinued in two and six patients in the induced and non-induced groups, respectively ($P = 0.99$). Reasons for discontinuation in induced patients were: patient's refusal ($N = 1$) and depression ($N = 1$). In non-induced patients, they included: patient's refusal ($N = 1$), psoriasis ($N = 1$), depression ($N = 1$), injecting behaviour ($N = 1$) and unidentified ($N = 2$). There was no IFN-α discontinuation during the one-month induction period. No reduction in IFN-α dosing occurred in both groups during the first 24 weeks.

Analysis of efficacy and safety of the addition of ribavirin.

Among the 59 patients HCV-RNA negative at week 20, 54 were randomised to either combination of ribavirin and IFN-α ($N = 28$) or IFN-α alone ($N = 26$) (table III).

At the end of treatment (week 48), 42 among 54 patients (78%) were HCV-RNA negative. There was no significant difference between patients who had received ribavirin and those who had not (82% vs 73%, $P = 0.42$). After treatment withdrawal, the relapse rate was lower in the combination therapy group than in the IFN-α monotherapy (22% vs 47%) but the difference did not reach statistical significance ($P = 0.08$). At the end of follow-up (week 72), 28 among 54 patients were still HCV-RNA negative. Patients with combined ribavirin were more likely to remain HCV-RNA negative than patients randomised to pursue IFN-α monotherapy (64% vs 39%), the difference being almost significance ($P = 0.06$).

The impact of adding ribavirin on the virological response differed according to HCV genotype. Patients initially infected with an HCV genotype 2 or 3 randomised to adjunctive ribavirin were more likely to remain HCV RNA negative until the end of follow-up than those randomised to pursue IFN-α monotherapy.
Interferon-α induction and secondary adjunction of ribavirin

The relapse rate after interruption of treatment was significantly lower in patients with genotype 2 or 3 who had received adjunctive ribavirin than in those who had not (0% vs 46%, P = 0.01). In the genotype 1, 4 or 5 group, there was no significant difference in the SVR between patients with adjunctive ribavirin and those treated with IFN alone.

During the second 24-week treatment period, treatment was discontinued in one and two patients in the IFN-α monotherapy and IFN-ribavirin combination therapy groups, respectively (P = 0.99). Treatment was discontinued in one patient in the monotherapy group because of a suicidal attempt. In the combination therapy group, one patient refused to continue treatment and in another a severe cutaneous eruption occurred and required treatment discontinuation. There was no IFN-α dose reduction in both groups. Ribavirin dosing was reduced to 600 mg for one month in one patient because of a hemoglobin concentration lower than 10 g/dL. It was reduced to 600 mg for four months in another one. A hemoglobin count below 10 g/dL was observed in two patients in the combination therapy group.

Analysis of the efficacy of additive ribavirin according to IFN-α induction

Among non induced patients, the number of patients remaining non viremic until the end of treatment did not differ whether or not patients had received ribavirin from week 24 to week 48. However the relapse rate after treatment withdrawal was significantly lower in the combination therapy arm (14% vs 69%, P = 0.004) leading to a significantly greater rate of patients remaining HCV RNA negative until the end of follow-up (63% vs 27%, P = 0.03).

In contrast among induced patients, all patients randomised to secondary additive ribavirin from week 24 to week 48 remained HCV RNA negative until the end of treatment whereas 6 patients among the 11 allocated to IFN-α monotherapy presented a breakthrough during treatment (P = 0.04). The relapse rate after interruption of treatment was comparable in both monotherapy and bitherapy arms.

Overall induced patients (with or without ribavirin) did not differ significantly from non induced patients for the percentage of patients with HCV RNA negative at week 20 remaining complete responders until the end of treatment (15/20 vs 27/34, P = 0.70), and until the end of follow-up (12/20 vs 16/34, P = 0.35).

Discussion

Here we report here a prospective study on treatment of HCV infection consisting of secondary adjunction of ribavirin in patients with complete virological response after six months of IFN-α monotherapy, with or without an initial 4-weeks interferon induction. The trial was designed before the era of pegylated interferon and bitherapy. Although our results cannot be extrapolated to current pegylated bitherapy, several points deserve discussion and bring arguments on the mechanisms of action of the anti-viral treatments on the clearance of HCV.

A major drawback of this study is that the number of included patients was less than calculated. We based our sample size calculation upon the hypothesis of an early virological response of 70% in the induction group and 50% in the standard IFN-α regimen group. However, due to pejorative viral parameters (68% of included patients had a high viral load and 58% had an HCV genotype 1), the five months complete response rates observed in the induction and standard arms were respectively of 51 and 34%, hence dramatically decreasing the number of patients eligible for the second treatment period. Secondly, the emergence of new treatment recommendations during the enrolment period made it impossible to propose IFN monotherapy to...
naive patients. Inclusions were prematurely stopped. Consequently our study, especially when looking at sub-groups, should be considered as a pilot study.

Our main finding is that late secondary introduction of ribavirin in patients non-viremic for sometimes several months can significantly decrease their relapse rate after treatment withdrawal and improve the sustained virological response. We observed that this beneficial impact of additive ribavirin differed with the IFN regimen. Late addition of ribavirin in patients who received a 4-week IFN induction prevented HCV resurgence until the end of treatment whereas in patients treated with a standard 3 MU tiw IFN regimen the value of additive ribavirin was observed after treatment was withdrawn with significantly less viral relapses in the combination therapy arm.

Addition of ribavirin to ongoing IFN-α monotherapy in non-treated HCV infected patients has been examined in several trials [13, 17, 18]. In one study, all patients whether or not responders were randomised to receive ribavirin in addition to IFN after 4 weeks of a 10 MU daily IFN [13]. Clearance of HCV RNA was significantly greater both at the end of treatment and at the end of follow-up in the combination therapy arm. Breakthrough during treatment was observed in the IFN-α monotherapy arm only. In another study, ribavirin was introduced on second intention in patients who did not respond after three months of IFN-α [18]. HCV viral kinetics in this trial showed that, when added to an ongoing IFN treatment, ribavirin can exert an additional antiviral effect sufficient to clear the virus in patients presenting a breakthrough under IFN monotherapy. In both studies, addition of ribavirin in patients clearly non responders to IFN did not enable them to clear HCV suggesting that the additive value of ribavirin depends on the effectiveness of IFN. In this study, we took the approach to introduce ribavirin in complete responders to an ongoing IFN-α monotherapy in order to prevent HCV resurgence during treatment and/or after treatment. We observed a significant impact on the relapse rate of additive ribavirin whereas the drug is introduced in non-viremic patients, after six months of IFN-α therapy, therefore several months after clearance of HCV in the early responders. These results suggest that at least part of the action of ribavirin, or the synergy between IFN-α and ribavirin does not require detectable HCV RNA in the serum. They suggest that ribavirin exerts its anti-HCV action through enhancement of the clearance of infected cells, possibly in HCV reservoirs outside the blood. It was reported that ribavirin addition to IFN increases the loss rate of productively infected cells observed in late phases of the viral decline [19]. The mechanisms by which addition of ribavirin to interferon increases the SVR remain unknown. Ribavirin alone exerts either a transient early decline or no decrease of the HCV viral load [20, 21]. In a recent study, the drug was found to induce a slow significant second slope of the viral decline in approximately half of patients treated. This antiviral effect correlated with the ribavirin pharmacokinetics [22]. Whether this additive moderate antiviral effect continues over time and explains the improved efficacy of bitherapies and particularly the reduced relapse rate observed after treatment discontinuation in large trials is not known.

The beneficial impact of adding ribavirin observed here depended on the HCV genotype. Six months combination therapy following six months of IFN-α monotherapy significantly improved the SVR in patients infected with an HCV genotype 2 or 3, but not in those with an HCV genotype 1, 4 or 5. The six month duration of bitherapy compares favourably with the con-

<table>
<thead>
<tr>
<th>Total population (all genotypes)</th>
<th>Ribavirin (n= 28)</th>
<th>No ribavirin (n= 26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virological response at Week 48 n (%)</td>
<td>23 (82)</td>
<td>19 (73)</td>
<td>0.42</td>
</tr>
<tr>
<td>Virological response at Week 72 n (%)</td>
<td>18 (64)</td>
<td>10 (39)</td>
<td>0.06</td>
</tr>
<tr>
<td>Relapsers at Week 72 among responders at Week 48 n (%)</td>
<td>5/23 (22)</td>
<td>9/19 (47)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

| Genotypes 2 or 3 | | | |
| Virological response at Week 48 n (%) | 12/14 (86) | 13/15 (87) | 0.99* |
| Virological response at Week 72 n (%) | 12/14 (86) | 7/15 (47) | 0.05* |
| Relapsers at Week 72 among responders at Week 48 n (%) | 0/12 (0) | 6/13 (46) | 0.01* |

| Genotypes 1,4 or 5 | | | |
| Virological response at Week 48 n (%) | 11/13 (85) | 6/11 (55) | 0.18* |
| Virological response at Week 72 n (%) | 6/13 (46) | 3/11 (27) | 0.42* |
| Relapsers at Week 72 among responders at Week 48 n (%) | 5/11 (45) | 3/6 (50) | 0.99* |

*: Fisher’s exact test.
conclusions of large trials examining combination therapy of different duration [3, 4, 23]. It was demonstrated in these studies, using either standard IFN-α or pegylated IFN-α, that in patients infected with an HCV genotype 2 or 3, a six months course of bitherapy is sufficient to significantly increase the SVR whereas in case of HCV genotype 1, 4 or 5, 48 weeks of bitherapy are needed to reach a greater SVR.

We observed that the 4-week IFN-α induction increased the early virological response only in patients infected with an HCV genotype 1, 4 or 5. In this subgroup, induced patients were more likely to clear HCV at 4 weeks than non-induced patients (45% vs 10%, P = 0.005). This greater early viral clearance with induction in genotype 1 has been previously reported [11]. This finding is also in agreement with a large trial comparing, in naïve patients, two bitherapy arms using either IFN-α 2b or pegylated IFN-α 2b [5]. In this study, optimal SVR were obtained with standard IFN-α without any benefit of pegylation in patients with HCV genotype 2 or 3. Pharmacokineticists suggest indeed that pegylation of IFN may increase the virological response because of an induction like effect [24, 25]. Finally, our conclusions regarding the poor impact of a short IFN induction on the sustained virological response are in agreement with previous studies [7-9].

We did neither observe an increased number of adverse events nor treatment discontinuations in the induction group. The rate of treatment discontinuation for adverse events was within the range reported in trials using IFN regimen 3 MU tiw [3, 4].

In conclusion, our results confirm that a 4 week daily IFN-α induction increases the early virological response in patients HCV genotype 1, 4 or 5 but does not improve the sustained virological response. Addition of ribavirin for six months in complete responders to INF-α significantly decreased the relapse rate after discontinuation of treatment in patients with HCV genotype 2 or 3. The beneficial impact of adding ribavirin was observed whereas the drug is introduced in non viremic patients suggesting that ribavirin increases the clearance of productively infected cells. Although our results are difficult to extrapolate to the current pegylated bitherapy, they support an immune modulatory mechanism for at least part of the anti-HCV effect of ribavirin.

ACKNOWLEDGEMENTS - This work was supported by a research grant from Schering-Plough, France. We thank Dr S. Erlinger for his constructive comments. In addition to the authors, the members of this viral hepatitis study group include the following : Dr V. Auray-Cartier (Creteil), Dr S. Bellon (Avignon), Dr P. Berthelémuy (Pau), Dr N. Biron (Maubeuge), Dr C. Bouet (Pau), Dr JF. Cadranel (Creil), Dr O. Boute (Pontoise), Dr N. Delas (Montfermeil), Dr J. Denis (Corbeil), Dr F. Deuard (Turbes), Dr O. Dubuhamel (Bézières), Dr S. Gayno (Pontoise), Dr P. Gower (Valenciennes), Dr D. Labayle (Evry), Dr B. Lesguenguere (Montfermeil), Dr B. Mesnard (Tourcoing), Dr T. Pauuard (Dunkerque), Dr C. Plane (Béthune), Dr D. Platino (Bourg-en-Bresse), Dr E. Poncin (Auch), Dr A. Soupison (Chalon/saône), Dr AM. Weiss (Colmar), Dr Y. Zarka (Evry).

RÉFÉRENCES


