Treatment of chronic hepatitis C in patients unresponsive to interferon

Interest of re-treatment combining interferon induction therapy and ribavirin (a multicenter pilot study)

ORIGINAL ARTICLE

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SUMMARY

Aim — About 45% of patients with chronic hepatitis C are unresponsive to the present reference treatment combining pegelated interferon plus ribavirin; before pegylated interferon was available the non-response rate was around 60%. This open multicenter pilot study, initiated before pegylated interferon became available, was designed to evaluate, in patients unresponsive to interferon monotherapy, the rate of biological and virological response and side-effects of the ribivirin- alpha 2b interferon combination.

Methods. The combination protocol was ribavirin (1 to 1.2 g/d) plus alpha 2b interferon at induction doses (9 MU/d the first week; 4.5 MU/d the eleven following weeks; 3 MU/2 days the 36 following weeks).

Results. Among the 27 included patients, 17 (63%) were viremia-negative (PCR) after 12 weeks of treatment, 9 (33%) were complete responders (undetectable viremia and normal transaminases) at the end of treatment (48 weeks) and of follow-up (72 weeks). Patients with non-1, non-4 genotypes who derived full benefit from this therapeutic strategy (6/7 (86%) were complete responders: 4/5 with genotype 3 and 2/2 with genotype 5). Quality-of-life was impaired during treatment, especially during the first 12 weeks of high-dose interferon therapy.

Conclusion. While waiting for new therapeutic possibilities, these good results suggest interferon induction at the beginning of treatment remains a valid option.

RÉSUMÉ

Traitement de l'hépatite chronique virale C chez des malades non répondeurs à l'interféron : intérêt d'une induction par interféron quotidien en association à la ribavirine (étude pilote multicentrique)

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Environ 45 % des malades atteints d'hépatite chronique virale C ne répondent pas au traitement de référence actuel qui associe l'interféron pégylé et la ribavirine. Avant la disponibilité de la forme pegylée de l'interféron le taux de non-réponse avoisinait les 60 %.

L'intérêt de cette étude pilote, ouverte, multicentrique, initiée avant la disponibilité de l'interféron pegylé, était d'évaluer, chez des malades non répondeurs à l'interféron en monothérapie, le taux de réponse biologique et virologique ainsi que la tolérance d'un schéma thérapeutique associant ribavirine (1 à 1,2 g/j) et interféron alpha 2b en induction (9 MU/j la première semaine ; 4,5 MU/j les 11 semaines suivantes ; 3 MU/2j les 36 semaines suivantes).

Parmi les 27 malades inclus, 17 (63 %) ont eu une virémie indétectable par PCR qualitative après 12 semaines de traitement, 9 (33 %) ont été répondeurs complets (virémie indétectable et transaminases normales) à la fin du traitement (S48) et du suivi (S72). Les malades de génotype non-1, non-4 ont été ceux qui ont le plus bénéficié de cette stratégie thérapeutique (6/7 (86 %) étaient répondeurs complets : 4/5 génotypes 3 et 2/2 génotypes 5). La qualité de vie a été altérée pendant le traitement, particulièrement pendant les 12 premières semaines de posologie maximale d'interféron.

En attendant de nouvelles possibilités thérapeutiques, ces bons résultats incitent à réévaluer l'intérêt d'une induction par posologie renforcée d'interféron en tout début de traitement.

Introduction

Chronic hepatitis C virus (HCV) infection is one of the most widespread chronic liver diseases. More than 300 million persons are affected worldwide. Chronic HCV infection can lead to cirrhosis then hepatocellular carcinoma and is the leading indication for liver transplantation in Europe. Despite major advances in antiviral treatments, the problem raised by patients who fail to respond to these treatments remains unsolved: 85% of patients given primary treatment with interferon (IFN) monotherapy and 60% of those given standard alpha-IFN-ribavirin dual therapy are non-responders. Since the introduction of combined pegylated interferon (PEG-IFN)-ribavirin the rate of non-response remains at 45%, particularly for genotype 1 [1].

This pilot study was conducted before PEG-IFN became available. The prior protocol, using alpha-IFN (3 MU 3 times a week) had been found to be inadequate for most patients with HCV infection. During the chronic phase of the infection, viral replication reaches a characteristic plateau with a 3-hr half-life of free HCV virions and a daily production of 10^{12} viral particles. For many patients, the decline in viral load induced 24 hours after a unique injection of 3 MU is insufficient. A higher dose would pro-

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The Fontevraud group is a committee of hepatologists and virologists working with viral hepatitis in the Center-West area France.
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voke a greater fall. Furthermore, intermittent administration of IFN is associated with a rebound in viral replication on day 2, reducing the slope of the viral elimination curve [2]. The aim of our study designed in 1998 was to test, in patients non-responsive to IFN monotherapy, the capacity of combination IFN-ribavirin using daily injections of IFN the first 12 weeks and induction with high-dose IFN the first week, to induce virological response, evaluated at the end of the 12 weeks of high-dose treatment. The advent of pegylated IFN has eliminated the need for studies on daily injections of IFN, but until anti-helicase and anti-protease agents currently under investigation become available, induction treatment using a higher dose of IFN [3, 4] still appears to be a valid option.

Patients and methods

Patient selection

Eligible patients were adults aged 18-55 years who were unresponsive to monotherapy using alpha-IFN. Non-response was defined as the absence of normal serum ALAT levels and absence of viral C RNA clearance at the end of treatment using 3 to 6 MU, 3 times a week for at least 3 months. These patients had not received alpha-IFN (3MU 3 times a week) for more than 18 months. This treatment had to be interrupted for at least 6 months. Active chronic hepatitis was defined as elevated ALAT at least twice the upper limit of normal (ULN). Chronic active hepatitis was defined by the following criteria observed during the 6 months preceding inclusion: presence of anti-HCV antibodies (ELISA 3, Ortho Diagnostics), presence of HCV-RNA determined by qualitative polymerase chain reaction (PCR) (Amplicor HCV 2.0 Roche Diagnostics, detection threshold 50 IU/mL), METAVIR score [5] ≥ A1 and ≥ F1 for liver biopsy performed between two treatments and not more than 24 months before inclusion. Viral genotype was determined by INNOLIPA (Innogenetics). Viremia was measured qualitatively in each center during patient screening, then at weeks 12, 48, 52, and 72. Serum samples drawn weekly during the first month then at weeks 6, 8, 12, and every 4 weeks to the end of treatment as well as 1, 3 and 6 months after treatment end were preserved (-80°C) by each center. These samples were assayed by quantitative PCR (Amplicor Monitor HCV 2.0, Roche Diagnostics, detection threshold 600 IU/mL) at the Orleans center to determine HCV-RNA.

Minimal values required for inclusion were: hemoglobin 12 g/dL for women and 13 g/dL for men, white cell count 3×10^9/L, neutrophil count 1.5×10^9/L, platelet count 100×10^9/L. Normal levels were required for serum bilirubin, serum albumin, serum creatinine, prothrombin time, blood urea nitrogen, and blood glucose.

Patients were not eligible for inclusion in the event of: pregnancy desired in next 18 months, hepatitis B virus (HBV) co-infection, human immunodeficiency virus (HIV) co-infection, uncontrolled cirrhosis, alpha-fetoprotein level > 50 ng/mL or focal liver lesion identified at ultrasonography, history of severe heart disease, diabetes, psychiatric disorder, epilepsy, respiratory insufficiency, hemoglobin disorder, autoimmune disease hyperuricemia, immunosuppressor or hepatotoxic treatment, active or recent drug abuse (less than 6 months abstinence), alcohol consumption > 20 g/d, liver disease unrelated to HCV. All patients who accepted the treatment protocol were included in each center. Inclusions were discontinued as soon as the main objective was reached.

Study design and organization

Five French centers participated in this open multicentric prospective pilot study which was approved by the Tours ethics committee (*comité consultatif de protection des personnes se prêtant à une recherche biomédicale*) in January 1999. All patients provided their informed written consent.

Eligible patients were given a combination treatment with ribavirin (1 g/d for body weight < 75 kg; 1.2 g/d for body weight > 75 kg) for 48 weeks and IFN alpha 2b (9 MU/d the first week; 4.5 MU/d for the next 11 weeks; then 3 MU every 48 hours for 36 weeks). Patients were seen at consultation at weeks 1, 2, 3, 4, 6, 8, and 12 after treatment onset then every 4 weeks to the 48th week, at which time treatment was discontinued. Routine biological and hematological tests were monitored. Therapeutic doses were adapted to the hematological and chemistry results.

If at the end of the 12-week induction phase ALAT levels were > ULN and serum HCV-RNA remained detectable by PCR, treatment could be interrupted and the patient was seen every 3 months for one year.

Efficacy and tolerance

The main outcome criterion was virological response measured at 12 weeks (W12, end of the induction period) by qualitative PCR. Undetectable HCV-RNA at W12 was considered to be the expected favorable response.

The second outcome criterion was complete response defined by the association of undetectable viremia by qualitative PCR and normal ALAT level. Patients were tested for complete response at W48 and 6 months later. Sustained complete response distinguished between responders and relapsers who were viremia-positive again between 48 and 72 weeks.

Secondary outcome criteria included negative viremia at W4, kinetics of the virological response assessed by quantitative PCR, influence of genotype, initial viral load, type of response to first treatment by IFN alone (initial nonresponse or relapse).

Tolerance was determined on the basis of undesirable effects and quality-of-life, measured on a visual analog scale, assessed at each consultation.

Statistical analysis

An independent clinical research group from the Faculty of Medicine at Tours performed the statistical analysis.

The study was designed according to the triangular test method [6] using the Phase II software developed by Bellissant et al. [7]. The highest response rate considered to be sufficient to decide not to progress to phase III (p_o) was set at 0.2. The rate considered to be pertinent to detect clinical benefit (p_a) was set at 0.5. The alpha and beta risks were accepted at 5%. The number of subjects to include in each step of the sequential trial (N) was set at 5. The triangular test thus was a sequential statistical analysis performed every 5 patients (i.e. when the W12 results of 5 new patients were available). The triangular test estimated two statistical values, Z and V (figure 1), which schematically represent the rate of response and the number of inclusions respectively. These values were represented by a point on a plane (V on the x-axis and Z on the y-axis) whose position was compared with the pre-established boundaries defining the rules of trial discontinuation and conclusion of the trial, considered to demonstrate efficacy if the point was above the upper boundary and inefficacy if the point was below the lower boundary.

Results

Patient characteristics (table I)

In this study, the statistical analysis led to the conclusion that the treatment was effective after results were available for the first 10 patients, confirming that the rate of virological response was

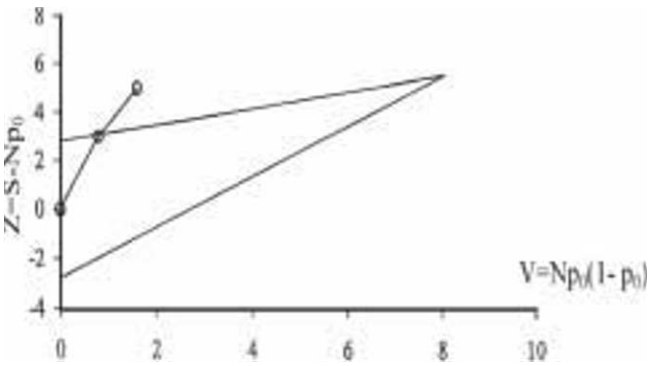

Fig. 1 – *Sequential analysis at week 12 of the virological response.*
Analyse séquentielle à la douzième semaine, de la réponse virologique à l'interféron α2b quotidien associé à la ribavirine ($p_0 = 0,2$ $p_a = 0,5$ $\alpha = \beta = 0,5$ et $N = 5$).

ABBREVIATIONS :

IFN	: interferon
MU	: million units
HCV	: hepatitis C virus
PEG-IFN	: pegylated interferon
HBV	: hepatitis B virus
HIV	: human immunodeficiency virus
ALAT	: alanine aminotransferase
PCR	: polymerase chain reaction
ULN	: upper limit of normal