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Amantadine triple therapy for non-responder hepatitis C patients. Clues for controversies (ANRS HC 03 BITRI)☆

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***Background/Aims*: To determine whether addition of amantadine to pegylated interferon/ribavirin improved response rates among chronic hepatitis C patients, non-responders to interferon/ribavirin and study the dynamic of response.**

***Methods*: In a double blind, multicenter, randomized trial, 200 non-responder patients received pegylated interferon 1.5 μg/kg per week and ribavirin 800–1200 mg/day, plus either amantadine 200 mg/day or placebo for 48 weeks. Endpoints were virological responses, ALT normalization, and histological benefit overtime.**

***Results*: Twenty percent of all patients achieved a sustained virological response (SVR). This rate was 8% higher in the triple therapy group (24%) compared with the double therapy group (16%) ($P=0.22$). A better virological response rate at week 24 was observed in the triple regimen group (43 vs 29%; $P=0.06$), which was lost at week 48 suggesting viral escape. The biochemical response rate was also significantly higher with triple therapy at week 12 (63 vs 49%; $P=0.05$) and week 24 (64 vs 49%; $P=0.03$). Fibrosis stabilized or improved in 77% of all patients.**

***Conclusions*: Re-treatment of interferon/ribavirin non-responder patients should be encouraged since a substantial proportion benefits from re-treatment with pegylated interferon/ribavirin ± amantadine. In triple therapy involving amantadine, a time wise response and an increased SVR rate in subgroups less prone to viral breakthrough suggest clues for existing controversies.**

***Keywords*: Hepatitis C; Treatment; Clinical trial; Triple therapy; Amantadine**

1. Introduction

Treating hepatitis C patients who have not responded to a standard interferon/ribavirin combination remains a major challenge [1]. Re-treatment using the same schedule yielded disappointing results. A potential alternative is to use triple therapy combining pegylated interferon/ribavirin plus amantadine, an antiviral drug that has been used for many years for the prevention of influenza A infection. Its effect on RNA viruses suggested a therapeutic potential in chronic hepatitis C [2], probably by a specific antiviral effect on the function of the hepatitis C virus (HCV) p7 protein [3,4], a potential target for antiviral drug therapy [5]. A recent study showed that amantadine could suppress internal ribosomal entry site (IRES)-dependent translation in Huh7 cells containing HCV replicon RNA [6].

Five years ago, Brillanti et al. reported promising results with interferon/ribavirin and amantadine in interferon

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Abbreviations: ALT, alanine aminotransferase; HCV, hepatitis C virus; NR, non-responders; PCR, polymerase chain reaction; SVR, sustained virological response; ULN, upper limit of normal.

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non-responder patients with a sustained virological response (SVR) rate of 48% [7]. Since, then, no other randomized trial on non-responder patients reported such a high rate of SVR. In recent studies in non-responders, SVR ranged from 13 to 25% [8–10], and the benefit of amantadine still remained controversial.

The aim of the present study was to evaluate the benefit of a re-treatment by triple therapy with pegylated interferon/ribavirin plus amantadine compared to double therapy with pegylated interferon/ribavirin plus placebo in non-responders to the standard interferon/ribavirin combination.

In addition, we also undertook careful analysis of responses over time and tried to provide clues for some of the discrepancies previously reported.

2. Patients and methods

2.1. Patients

Patients were eligible if they had failed to respond to a single previous 24-week cycle of interferon/ribavirin combination therapy (at least 3 MIU interferon-alfa three times weekly and ribavirin at a minimum dose of 600 mg/day). Non-response was defined as persistent HCV RNA in the serum during the last month of treatment. Other key inclusion criteria were: elevated serum ALT, detectable HCV RNA, neutrophil count $\geq 1000/mm^3$, platelet count ≥ 100 giga/L, haemoglobin ≥ 10 g/dL. A post-treatment liver biopsy within a year had to show a METAVIR histological score $\geq$ A1F1, and $<$F4.

Exclusion criteria were co-infection with HBV or HIV, any other cause of liver disease, active drug abuse or alcohol consumption >40 g/day, organ grafts, presence of hepatocellular carcinoma, cardiovascular, metabolic, renal, haematological, neurological or psychiatric disease. Patients with previous amantadine use, systemic immunosuppressive or antiviral treatment during the last 24 weeks, and those with a history of interferon and/or ribavirin intolerance were also excluded.

2.2. Study design

This study was a randomized, double blind, prospective multicenter trial. Patients were recruited from 23 hepatology centers in France. The protocol was approved by the French ethical committee and all patients provided written informed consent. Eligible subjects were randomly assigned the two treatment groups in equal proportions. The randomization process was generated by the Department of Biostatistics, Hospices Civils de Lyon, Lyon, France.

The triple therapy group received pegylated interferon alfa-2b (PEG-Intron, Schering-Plough, Kenilworth, NJ, USA) at a dose of 1.5 μg/kg per week subcutaneously, plus oral ribavirin (Rebetol, Schering-Plough) 800–1200 mg/day and oral amantadine hydrochloride (Mantadix, Dupont Pharma SA, Paris) 2×100 mg/day for 48 weeks. The second group received the same dose of pegylated interferon alfa-2b and ribavirin, plus a placebo instead of amantadine. For both groups, the dose of ribavirin was adjusted according to body weight (800 mg up to 65 kg weight, 1000 mg between 65 and 85 kg, and 1200 mg for weight of 85 kg or more). All drugs were started and stopped at the same time. Treatment was administered for 48 weeks regardless of the virological response during therapy. At the end of this treatment period, patients underwent a liver biopsy and were followed up for 24 weeks.

The primary endpoint was a sustained virological response, defined as an undetectable HCV-RNA 24 weeks after treatment discontinuation (week 72). Secondary endpoints were the biochemical response at week 72 defined as ALT normalization, histological benefit, tolerance, as well as virological and biochemical responses during therapy at weeks 12, 24 and 48. The analysis was done on the whole treated population (intention-to-treat strategy), i.e. all patients who received at least one dose of study medication. Patients found missing HCV RNA or ALT values during follow-up were classified as virological or biochemical non-responders, respectively. A per protocol analysis was also performed on the primary endpoint.

2.3. Adverse events

Adverse events were graded as mild, moderate, severe or life-threatening. Therapy was permanently discontinued for life-threatening events. Pegylated interferon dose was lowered to 1.0 μg/kg per week if the neutrophil count fell between 900 and 750×10^6/L. If the neutrophil count fell between 750 and 500×10^6/L and/or the platelet count fell between 90 and 60×10^9/L, interferon dose was reduced to 0.5 μg/kg per week. If neutrophil or platelet counts fell below 500×10^6/L or 60×10^9/L, respectively, interferon was discontinued. Ribavirin dose was lowered to 400 mg/day (at body weight <65 kg) or 600 mg/day (at body weight $>$ 65 kg) if haemoglobin concentration fell between 10 and 8.5 g/dL. If haemoglobin level fell below 8.5 g/dL, ribavirin was discontinued. The amantadine or placebo dose was lowered to 100 mg/day if creatinine level increased between 1.5 and twice the upper limit of normal (ULN). Amantadine or placebo was stopped if this level increased above $2\times$ULN. Once lowered, interferon, ribavirin and/or amantadine remained at the same dose throughout the remaining treatment period.

2.4. Biochemical and virological tests

Patients were evaluated every 4 weeks during therapy and at weeks 4, 12 and 24 after the end of treatment. All haematological and biochemical parameters were determined and genotyping performed in the local laboratories of each study centre. Serum HCV RNA was measured at baseline, during treatment at weeks 4, 12, 24, and 48, and 24 weeks after therapy (week 72), by a quantitative RT-PCR assay performed centrally (detection threshold 615 IU/mL; Cobas Amplicor Monitor v2.0, Roche Diagnostics, Meylan, France). When viral load was below this level, a qualitative PCR was performed (detection threshold 50 IU/mL; Cobas Amplicor v2.0, Roche Diagnostics).

2.5. Histology

Liver biopsies were done at baseline and at week 48 prior to stopping therapy, and were scored locally using the METAVIR scoring system [11]. Histological improvement and impairment were, respectively, defined as a decrease or increase of at least one METAVIR point between baseline and week 48.

2.6. Quality of life

Health status was assessed every 12 weeks throughout therapy using the following question: 'Would you say your health is: very good/good/fair/poor?'

2.7. Statistical analysis

Statistical analysis was performed using SPSS V.11.5.1 for Windows. The number of subjects was calculated using a two-sided hypothesis to detect a 20% difference in SVR rates (40 vs 20%), with 80% power at the 5% level of significance. Expecting 10% of drop-outs, 101 patients were thus necessary in each group. Randomization was done using a random permuted blocks method. To compare the two treatments, Fisher's exact test was used for dichotomous variables, and the Pearson Chi-square test for the other categorical variables. For continuous variables, the Student's *t*-test (with correction if variances were not equal) or Wilcoxon's non-parametric test (when the number of cases was small) were used. A multivariate logistic regression analysis was conducted to control for factors possibly associated with virological response. Estimated odds ratios with 95% confidence intervals were calculated. The statistical significance level was set at $P<0.05$.