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Clinical trial: a randomized trial of pegylated-interferon-α-2a plus ribavirin with or without amantadine in treatment-naïve or relapsing chronic hepatitis C patients

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SUMMARY

Background
The combination therapy of pegylated-interferon-α2a plus ribavirin is considered as the standard of care for patients with chronic hepatitis C. A sustained viral response is obtained in 40–50% of naïve patients with genotype 1 and in around 80% of naïve patients with genotype 2 or 3.

Aim
To assess whether amantadine, added to the conventional combination therapy, could improve the treatment efficacy.

Methods
In all, 630 patients (intent-to-treat population) with chronic hepatitis C were randomized into two groups: 316 patients (treatment group) received pegylated-interferon-α2a (180 μg once weekly) plus ribavirin (1000–1200 mg/daily) with amantadine (200 mg/daily); 314 patients (control group) received pegylated-interferon-α2a (180 μg once weekly) plus ribavirin (1000–1200 mg/daily) without amantadine.
The duration of the treatment was 48 weeks for genotypes 1, 4, 5 and 6, and 24 weeks for genotypes 2 and 3.

Results
There was no statistically significant difference between treatments groups for any of the variables tested for. Subgroups of patients likely to take advantage of the addition of amantadine were not identified.

Conclusions
This large study definitely excludes the role of amantadine in addition of conventional combination therapy in the treatment of chronic hepatitis C patients.

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INTRODUCTION

Chronic hepatitis C (CHC) is a major cause of chronic liver disease and related complications such as cirrhosis and hepatocellular carcinoma. Currently, the primary goal of anti-viral therapy in patients with CHC is to obtain a sustained virological response (SVR), defined as an undetectable serum HCV-RNA 24 weeks after the end of the therapy. The combination therapy of pegylated-interferon-α-2a (PEG-IFN) plus ribavirin (RBV) can induce SVR in 40–50% of naïve patients with genotype 1 and in 80% of naïve patients with genotypes 2 or 3. This combination is now internationally considered as the standard of care for CHC.

In the beginning of 2003, various reports suggested that amantadine could improve the SVR rate in naïve patients[1] and could become a valuable option for relapsing patients and patients not responding to conventional anti-viral therapy.[2–4] However, these findings conflicted with other results,[5–7]including a meta-analysis which concluded that combination therapy with amantadine had no effect in naïve and relapsing patients.[8]

Large randomized controlled trials were therefore needed to evaluate the precise potential benefit of a triple therapy in CHC and to identify possible subgroups of patients responding most favourably to it.

As amantadine had been shown to have a good safety and tolerability profile in other indications, a trial including a large number of patients did not raise any ethical concern.

The present trial was designed therefore to investigate, on a large scale and in a randomized design, the effect of adding amantadine to a standard genotype-individualized peginterferon alfa-2a (PEG-IFN) plus ribavirin (RBV) combination therapy on response to treatment of naïve or relapsed patients with CHC. Exploratory analyses were also planned to try indentifying patients' subgroups that could benefit from amantadine addition to PEG-IFN plus RBV combined therapy.

PATIENTS AND METHODS

Selection of patients

Male and female patients ≥18 years of age were eligible if they had serological evidence of CHC (anti-HCV antibody test), a quantifiable serum HCV-RNA of at least 600 IU/mL with the Roche AMPLICOR HCV MONITOR Test v2.0, an elevated serum ALT activity documented on at least two occasions within the 6 months before randomization, histological liver alterations consistent with CHC and, in case of cirrhosis, a compensated liver disease (Child-Plugh Grade A). Pregnancy was an exclusion criterion. Effective contraception was compulsory, including couples where the male partner was the patient. Patients were not allowed to be included if they had been non-responders to a previous therapy or had had a relapse during a previous therapy (breakthrough) or after completion of any previous treatment other than IFN plus RBV. Inclusion was not allowed if the patient had been treated with any systemic anti-viral, anti-neoplastic or immunomodulatory treatment (including supraphysiological doses of steroids and radiation) within 6 months prior to the first dose of the study drug. Patients with a history or any evidence of a medical condition associated with chronic liver disease other than HCV, history of severe psychiatric disease (especially depression), epilepsy, heart failure, thyroid disease, severe retinopathy, and any other evidence of a severe illness, malignancy, or condition which would make him or her, in the investigator's opinion, unsuitable for the study could not be included. The following laboratory results at screening were also exclusion criteria: Positive serology for HAV IgM, haemoglobin <11 g/dL, neutrophil count <1500 cells/mm^3, platelet count <90 000 cells/mm^3, and serum creatinine level >1.5 times the upper limit of normal.

Written informed consent had to be obtained before inclusion.

Sample size

With 278 patients per group, the power was at least 75% to detect an improvement in SVR rate from 55% to 65% at a significance level of 5%, with amantadine added to standard therapy. To take into account protocol violations and dropouts, which might occur in about 15% of the recruited patients and lead to dilution of the expected treatment effects, the number of patients that were to be randomized had to be increased to a total of 640.

Study design

This study was a prospective, phase IV, multicentre, randomized, active control, open-label, parallel group clinical trial conducted in full compliance with Good

Clinical Practices and all applicable laws in Belgium. The study was approved by the ethical committee and patients signed an informed consent for inclusion.

Eligible patients were randomly allocated to one treatment arm. They were treated for 24 or 48 weeks, according to hepatitis C virus (HCV) genotype, either with PEG-INF (180 μg in 0.5 mL) plus RBV (800 to 1200 mg p.o. daily according to HCV genotype and body weight) plus amantadine (100 mg b.d.) (treatment group), or with PEG-IFN plus RBV (same doses, control group). Dose adjustments were allowed in specific circumstances detailed in the guideline provided with the study protocol. Randomization was stratified by HCV genotype (1 vs. 2/3 vs. 4/5/6), cirrhosis status (present vs. absent) and pre-treatment status (naïve vs. relapse). Randomization included a minimization programme by study centre.

Laboratory methods

HCV-RNA was measured at baseline and at 12-week time point using the AMPLICOR HCV MONITOR Test v2.0; this quantitative test is able to detect a viraemia of at least 600 IU/mL. Qualitative HCV-RNA tests were performed at end-of-treatment and 24 weeks after treatment completion with AMPLICOR HCV Test v2.0; this test detects HCV RNA levels as low as 50 IU/mL.

Efficacy variables

The efficacy variables were SVR (primary efficacy variable), sustained biochemical response (SBR) rate, early virological response (EVR) rate, end-of-treatment virological response (EOTVR) rate and mean reduction in HCV-RNA.

Sustained virological response was defined as non-detectable HCV-RNA, 24 weeks after completion of the 24/48-week treatment period. Response rate was calculated as the number of patients with SVR divided by the number of randomized patients. Patients without measurement at the end of the 24-week untreated follow-up period were considered as nonresponders. Patients treated for more than 8 weeks longer than the planned treatment duration (24 or 48 weeks) and patients for whom the last follow-up assessment occurred within 12 weeks after the end of treatment were also considered as nonresponders.

Sustained biochemical response was defined as a normal serum alanine aminotransferase (ALT) level at 24 weeks after completion of the 24- or 48-week treatment period. Patients without measurements at the end of the 24 week untreated follow-up period were considered nonresponders.

Early virological response was defined as either a drop of at least 2 log in HCV-RNA at study Week 12 compared to screening, or non-detectable HCV-RNA at Week 12. A complete EVR (CEVR) was defined as a negative HCV PCR at week 12. A partial EVR (PEVR) was defined as a positive HCV-PCR at week 12, but with a drop of at least 2 logs in HCV-RNA compared to baseline. Nonresponders were patients with positive HCV PCR at week 12 with no change compared to screening or a decrease from screening of less than 2 logs in HCV-RNA.

End-of-treatment virological response was defined as a negative qualitative HCV-RNA, at the end of the 24- or 48-week treatment period. Patients without measurements at the end of the treatment period were considered nonresponders.

Relapse at Week 24 after the end of treatment was defined by an EOTVR followed by a positive HCV-RNA 24 weeks after the end of treatment.

Viral load drop was expressed in the change in $\log_{10}$ (HCV-RNA) at Week 12. For patients without measurement at screening or with non-detectable HCV-RNA at screening or without measurement at week 12, the viral load drop was declared missing.

Safety variables

The evaluation of safety was based on the occurrence of adverse events, results of laboratory tests and vital signs. A serious adverse event was defined as any experience that suggests a significant hazard, contraindication or side effect; this included any experience which is fatal or life-threatening or requires in patient hospitalization or prolongation of an existing hospitalization or results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect or is medically significant or requires intervention to prevent one or other of the outcomes listed above irrespective of its relationship to the treatment received. The severity of an AE was to be considered 'Mild' in case of discomfort noticed but no disruption of normal daily activity, 'Moderate' in case of discomfort sufficient to reduce or affect normal daily activity, 'Severe' if incapacitating with inability to work or perform normal daily activity, 'Life threatening' if representing an immediate threat to life.

Statistical analysis

The primary analysis was to be an intent-to-treat approach. Response rate was to be calculated as the number of patients with a sustained virological response divided by the number of patients who were randomized and who received at least one dose of the study drug. Patients without measurements at the end of the 24-week untreated follow-up period were to be considered nonresponders.

Exact 95% confidence interval from the binomial distribution was to be provided for response rate in individual treatment groups. All categorical variables for pairwise treatment comparisons were to be analysed using the Cochran-Mantel-Haenszel test stratified by genotype (1 vs. 2/3 vs. 4/5/6), pre-treatment status (naïve vs. relapse) and cirrhosis state (present vs. absent). Odds ratios and corresponding 95% confidence intervals were to be given for pairwise treatment comparisons. Change from baseline variables was to be analysed using analysis of covariance. Treatment difference estimates using least square means and corresponding 95% confidence intervals were to be given. Incidence of adverse events and laboratory abnormalities were to be summarized separately for each group of patients.

RESULTS

Patients

Six-hundred and forty-three patients were included into the study in 37 academic and non-academic centres from all Belgian regions. Thirteen patients (all from the control group), who never took any study medication, were excluded from the intent-to-treat (ITT) population. The ITT population (n = 630) comprised all randomized patients who had received at least one dose of (either) study medication. Fifty-five out of 630 patients had one or more major protocol deviations (26 in the treatment group and 29 in the control group) and were consequently excluded from the per protocol (PP) population. Three patients from the ITT population, without any post-baseline assessment, were excluded from the safety population. Seventy-nine patients of the treatment group (25%) discontinued the study prematurely as well as 88 patients of the control group (28.03%). These frequencies were not statistically significantly different (P = 0.417). Population sizes and reasons for discontinuation are summarized in Figure 1.

Baseline characteristics

Baseline characteristics for the whole population and by treatment group are summarized in Table 1. Statistical analysis shows that the differences between treatment groups are not statistically significant for any of the baseline characteristics measured except for the mean heights (171.45 vs. 169.87 cm).

Exposure to treatment

In the treatment group, genotype 2/3 patients were treated for an average of 5.2 months and genotype 1/4/5/6 patients were treated for an average of 9.8 months. In the control group, genotype 2/3 patients were treated for an average of 5.3 months and genotype 1/4/5/6 patients were treated for an average of 9.5 months.

In the treatment group, patients received on average 85.3% of the planned cumulative dose for Pegasys, 86.0% for Copegus, and 86.4% for Amantadine. In the control group, the values were respectively 84.0% for Pegasys and 85.8% for Copegus.

The average compliance for the backbone therapy calculated according to the 80/80/80 rule was 67.4% in the treatment group and 63.7% in the control group. These frequencies are not statistically different (Fisher exact P-value = 0.357). The average compliance for Amantadine (according to the 80/80 rule) was 76.2%.

Virological response

Sustained virological response was observed in 193 patients of the treatment group (61.1%, 95% CI: [0.55; 0.66]) and 192 patients of the control group (61.1%, 95% CI: [0.56; 0.67]). These frequencies were not statistically significantly different (P = 1.000). The analysis of SVR in various subgroups of patients controlling for treatment showed statistically significant treatment effects of treatment status (naïve, 62.4%; relapse, 44.2%; P = 0.019), cirrhosis (no cirrhosis, 64.3%; cirrhosis, 46.7%; P < 0.001), genotype category (genotype 1, 54.7%; genotypes 2/3, 75.3%; genotypes 4/5/6, 54.3%; P < 0.001), age category (<40 years, 66.7%; ≥40 years 57.6%; P = 0.023) and Metavir fibrosis score category (score 0/1/2, 64.3%; score 3/4, 47.2%; P < 0.001). Frequencies of SVR broken down by treatment group and baseline characteristics are in Table 2.

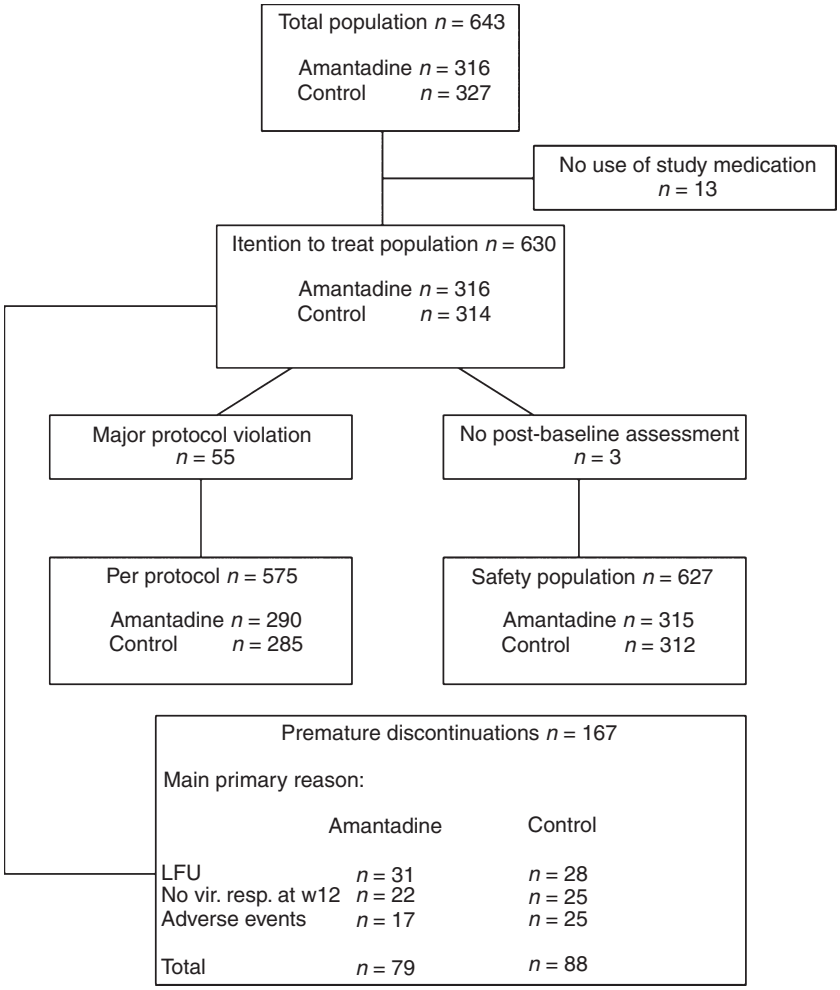

Figure 1. Disposition of patients.

Sustained biochemical response was observed in 187 patients of the treatment group (59.2%, 95% CI: [0.54; 0.65]) and 188 patients of the control group (59.9%, 95% CI: [0.54; 0.65]). These frequencies were not statistically significantly different ($P = 0.871$). The analysis of SVR in various subgroups of patients controlling for treatment showed no statistically significant treatment effect and no interaction effect of treatment with any of the factors. However, overall statistically significant effects were found of treatment status (naïve, 60.8%; relapse, 41.9%; $P = 0.015$), cirrhosis (no cirrhosis, 63.1%; cirrhosis, 44.3%; $P < 0.001$) and genotype category (genotype 1, 55.3%; genotypes 2/3, 71.7%; genotypes 4/5/6, 48.9%; $P < 0.001$).

Early virological response was observed in 246 patients of the treatment group (85.4%, 95% CI: [0.81; 0.89]) and 244 patients of the control group (84.4%, 95% CI: [0.80; 0.88]). These frequencies were not statistically significantly different ($P = 0.816$). The analysis of EVR in various subgroups of patients controlling for treatment showed no statistically significant treatment effect and no interaction effect of treatment with any of the factors. An overall statistically significant effect was found of genotype category (genotype 1, 83.2% genotypes 2/3, 91.9%; genotypes 4/5/6, 77.1%; $P = 0.004$). In the treatment group, CEVR was observed in 220 patients (76.4%), PEVR in 26 patients (9.0%) and 42 patients (14.6%) were nonresponders. In the control group, CEVR was observed in 216 patients (74.7%), PEVR in 28 patients (9.7%) and 45 patients (15.6%) were nonresponders. These proportions were not statistically different ($P = 0.899$).

End-of-treatment virological response was observed in 231 patients of the treatment group (73.1%, 95%

Table 1. Baseline characteristics

	All patients	PEG-INF+RBV+Amantadine (Treatment group)	PEG-INF+RBV (Control group)	*P*-value for difference between groups
Age (years)	44.61 ± 12.32	43.74 ± 12.41	45.48 ± 12.19	0.075
Age category				
<40 years	38.57% (243)	42.41% (134)	34.71% (109)	0.050
≥40 years	61.43% (387)	57.59% (182)	65.29% (205)	
Gender				
Male	57.46% (362)	59.81% (189)	55.10% (173)	0.259
Female	42.54% (268)	40.19% (127)	44.90% (141)	
Race				
Caucasian/ White	87.62% (552)	86.71% (274)	88.54% (278)	0.717
Black	7.62% (48)	7.59% (24)	7.64% (24)	
Oriental	2.54% (16)	2.85% (9)	2.23% (7)	
Other	2.22% (14)	2.85% (9)	1.59% (5)	
Height (cm)	170.66 ± 9.13	171.45 ± 8.87	169.87 ± 9.34	0.031
Weight (kg)	73.07 ± 14.46	73.02 ± 13.63	73.12 ± 15.29	0.933
Weight category				
<75 kg	57.67% (361)	55.24% (174)	60.13% (187)	0.226
≥75 kg	42.33% (265)	44.76% (141)	39.87% (124)	
BMI (kg/m^2)	25.04 ± 4.32	24.78 ± 4.14	25.29 ± 4.49	0.140
BMI category				
≤25 kg/m^2	54.63% (336)	55.99% (173)	53.27% (163)	0.518
>25 kg/m^2	45.37% (279)	44.01% (136)	46.73% (143)	
Viral load				
<800 000 IU/mL	50.65% (310)	49.51% (152)	51.80% (158)	0.573
≥800 000 IU/mL	49.35% (302)	50.49% (155)	48.20% (147)	
HCV genotype				
G1	53.65% (338)	54.43% (172)	52.87% (166)	0.870
G2/3	31.43% (198)	31.33% (99)	31.53% (99)	
G4/5/6	14.92% (94)	14.24% (45)	15.61% (49)	
Mode of HCV acquisition				
Blood transfusion	25.08% (158)	25.95% (82)	24.20% (76)	0.304
IV drug use	32.70% (206)	34.81% (110)	30.57% (96)	
Other or unknown	42.22% (266)	39.24% (124)	45.22% (142)	
Cirrhosis status				
No	80.26% (496)	80.26% (248)	80.26% (248)	1.000
Yes	19.74% (122)	19.74% (61)	19.74% (61)	
Treatment status				
Naive	93.17% (587)	93.35% (295)	92.99% (292)	0.903
Relapsers after combination θ	6.03% (38)	5.70% (18)	6.37% (20)	
Relapsers after mono θ	0.63% (4)	0.63% (2)	0.64% (2)	
Nonresponders	0.16% (1)	0.32% (1)	– (0)	
ALT category				
NL	16.69% (105)	15.24% (48)	18.15% (57)	0.084
>ULN - ≤3*ULN	63.12% (397)	60.95% (192)	65.29% (205)	
>3*ULN	20.19% (127)	23.81% (75)	16.56% (52)	
Metavir activity score				
0/1/2	95.08% (502)	94.30% (248)	95.85% (254)	0.429
3/4	4.92% (26)	5.70% (15)	4.15% (11)	

Table 1. Continued

	All patients	PEG-INF+RBV+Amantadine (Treatment group)	PEG-INF+RBV (Control group)	*P*-value for difference between groups
Metavir fibrosis score				
0/1/2	80.03% (493)	79.87% (246)	80.19% (247)	1.000
3/4	19.97% (123)	20.13% (62)	19.81% (61)	

NL, normal; ULN, upper limit normal; BMI, body mass index; IU, International unit; HCV, hepatitis C virus.
Mean ± standard deviation for continuous variables.
Percentage and (number) for categorical variables.
Statistical testing: Student *t*-test for continuous variables, Fisher exact test for categorical variables.

CI: [0.68; 0.78]) and 224 patients of the control group (71.3%, 95% CI: [0.66; 0.76]). These frequencies were not statistically significantly different ($P = 0.657$). The analysis of EOTVR in various subgroups of patients controlling for treatment showed no statistically significant treatment effect and no interaction effect of treatment with any of the factors. An overall statistically significant effect was found of genotype category (genotype 1, 71.0%; genotypes 2/3, 79.8%; genotypes 4/5/6, 60.6%; $P = 0.002$).

Relapse at week 24 after the end of treatment was observed in 37 patients of the treatment group (17.0%) and 28 patients of the control group (13.3%). These frequencies were not statistically significantly different ($P = 0.346$).

In the treatment group, the mean logarithm of viral load at screening was 5.82, while at week 12, the mean logarithm of viral load was 3.09. In the control group, the respective results were 5.83 at screening and 3.12 at week 12. Consequently, the viral load drop was 2.71 [95%CI: 2.85–2.56] in the treatment group and 2.70 [95% CI: 2.85–2.55] in the control group. The comparison of viral load drop in both groups controlled for treatment status, cirrhosis status and genotype category showed a significant effect of genotype category ($P = 0.002$). In the treatment group, the mean viral load drop was 2.75 for patients with genotype 1, 2.86 for patients with genotypes 2/3, and 2.30 for patients with genotypes 4/5/6. In the control group, the mean viral load drop was 2.69 for patients with genotype 1, 2.93 for patients with genotypes 2/3, and 2.34 for patients with genotypes 4/5/6.

Finally, a multivariate analysis showed that the genotype category had a statistically significant effect on SVR ($P < 0.001$), EOTVR ($P = 0.017$), EVR ($P = 0.003$) and relapse rate at Week 24 after the end of treatment ($P = 0.009$). Similarly, cirrhosis status had a statistically significant effect on SVR ($P < 0.001$), EVR had a statistically significant impact on EOTVR ($P < 0.001$) and age category had a statistically significant effect on relapse rate ($P < 0.001$).

Table 3 below summarizes the frequencies observed for all measured efficacy variables broken down by treatment group. Table 4 presents the results of the multivariate analysis.

All the performed efficacy analyses conclude that there is no statistically significant difference in responses to treatment between both groups for any of the variables tested for. Complementary analyses also indicate that there is no difference in the frequency distribution of either response at week 12 or relapse at week 24 after end of treatment. The analysis of response to treatment (irrespective of the endpoint chosen to evaluate the response to treatment) in various subgroups of patients controlling for treatment, shows no statistically significant treatment effect, nor interaction effect of treatment with any of the factors considered. So, adding amantadine to the back-bone therapy of CHC has no effect on any of the efficacy parameter and in none of the subgroups of patients tested for in the study.

Safety

During the treatment period together with the period of 12 weeks after the last intake of study medication, adverse events were reported for most patients, 303 patients in the treatment group (96.2%) and 297 in the

Table 2. Sustained virological response (SVR) broken down by treatment group and baseline characteristics

	PEG-INF+RBV+Amantadine (Treatment group)	PEG-INF+RBV (Control group)	*P*-value
Treatment status			
Naïve	62.03% (183/295)	62.67% (183/292)	0.972
Relapsers	47.62% (10/21)	40.91% (9/22)	
Cirrhosis status			
No cirrhosis	64.52% (160/248)	64.11% (159/248)	1.000
Cirrhosis	45.90% (28/61)	47.54% (29/61)	
Genotype			
G1	55.81% (96/172)	53.61% (89/166)	0.992
G2/3	73.74% (73/99)	76.77% (76/99)	
G4/5/6	53.33% (24/45)	55.10% (27/49)	
Viral load			
<800 000 IU/mL	63.82% (97/152)	63.29% (100/158)	0.939
≥800 000 IU/mL	58.71% (91/155)	59.86% (88/147)	
Age category			
<40 years	68.66% (92/134)	64.22% (70/109)	0.843
≥40 years	55.49% (101/182)	59.51% (122/205)	
Weight category			
<75 kg	62.07% (108/174)	65.24% (122/187)	0.965
≥75 kg	59.57% (84/141)	55.65% (69/124)	
BMI			
≤25 kg/m^2	64.16% (111/173)	64.42% (105/163)	0.779
>25 kg/m^2	56.62% (77/136)	58.74% (84/143)	
Gender			
Male	59.79% (113/189)	59.54% (103/173)	0.982
Female	62.99% (80/127)	63.12% (89/141)	
ALT			
≤3*ULN	60.00% (144/240)	61.45% (161/262)	0.992
>3*ULN	65.33% (49/75)	59.62% (31/52)	
Metavir activity score			
0/1/2	61.29% (152/248)	60.63% (154/254)	0.699
3/4	66.67% (10/15)	45.45% (5/11)	
Metavir fibrosis score			
0/1/2	64.63% (159/246)	63.97% (158/247)	0.922
3/4	46.77% (29/62)	47.54% (29/61)	

ALT, alanine transaminase; BMI, body mass index; ULN, upper limit normal.
(Number of patients with SVR/Number of patients in this category).
Statistical testing: Student *t*-test for continuous variables, Fisher exact test for categorical variables.

control group (95.2%). Among them, ninety serious (49 in the treatment group and 41 in the control group) adverse events were reported in seventy-three patients (39 in the treatment group and 34 in the control group). Forty-seven of these serious adverse events (23 in the treatment group and 24 in the control group) were, however, considered as not related to the study drugs. None of the reported serious adverse events consisted of leucopenia or thrombocytopenia; anaemia was considered as a serious adverse event in five patients (2 in the treatment group – 1 severe and 1 moderate – and 3 in the control group – 2 severe and 1 life-threatening).

Adverse events reported for at least 10% of patients are listed in Table 5 as well as severity of anaemia, leucopenia and thrombocytopenia.

As for the safety criteria defined by the protocol (e.g. discontinuation rate, adverse event profile and frequency, haemoglobin abnormalities and other clinically significant laboratory abnormalities), no differences were observed between both groups of patients.

Table 3. Efficacy variables broken down by treatment group

	PEG-INF+RBV+Amantadine (Treatment group)	PEG-INF+RBV (Control group)	*P*-value
SVR	61.1% (193/316)	61.1% (192/314)	1.000
SBR	59.2% (187/316)	59.9% (188/314)	0.871
EOTR	73.1% (231/316)	71.3% (224/314)	0.657
Response at week 12			
EVR	85.4% (246/288)	84.4% (244/289)	0.816
Nonresponders	14.6% (42/288)	15.6% (45/289)	
Response at week 12			
CEVR	76.4% (220/288)	74.7% (216/289)	0.899
PEVR	9.0% (26/288)	9.7% (28/289)	
Nonresponders	14.6% (42/288)	15.6% (45/289)	
Relapse at week 24	17.0% (37/218)	13.3% (28/210)	0.346
Mean drop in viral load	2.71 log	2.70 log	0.963

SVR, sustained virological response; SBR, sustained biochemical response; EOTR, end of treatment response rate; EVR, early virological response; CEVR, complete early virological response; PEVR, partial early virological response.
(Number of patients with response/number of evaluable patients).
Statistical testing: Student *t*-test for continuous variables, Fisher exact test for categorical variables.

Table 4. Results of the multivariate logistic regression

Variable entered in model	*P*-value	Odds ratio	95% CI on odds ratio
Sustained virological response – $N = 617$*			
HCV Genotype	$P < 0.001$		
Genotype 2/3 vs. genotype 1		2.89	[1.74; 4.78]
Genotype 4/5/6 vs. genotype 1		1.63	[0.87; 3.06]
End of treatment virological response (yes vs. no)	$P < 0.001$	29.88	[17.46; 51.12]
Cirrhosis (yes vs. no)	$P < 0.001$	0.41	[0.24; 0.68]
End-of-treatment virological response – $N = 577$†			
HCV Genotype	$P = 0.017$		
Genotype 2/3 vs. genotype 1		1.88	[1.11; 3.16]
Genotype 4/5/6 vs. genotype 1		0.76	[0.43; 1.33]
Early virological response (EVR vs. non-responder)	$P < 0.001$	6.60	[4.02; 10.81]
Early virological response – $N = 566$‡			
HCV Genotype	$P = 0.003$		
Genotype 2/3 vs. genotype 1		2.58	[1.34; 4.97]
Genotype 4/5/6 vs. genotype 1		0.68	[0.37; 1.22]
Relapse – $N = 420$§			
HCV Genotype	$P = 0.009$		
Genotype 2/3 vs. genotype 1		0.36	[0.18; 0.72]
Genotype 4/5/6 vs. genotype 1		0.54	[0.23; 1.23]
Age category (≥40 years vs. <40 years)	$P < 0.001$	3.66	[1.84; 7.32]

*Out of the 630 patients, only 617 had data for all predictive variables entered in the model.
†Out of the 630 patients, only 577 had data for all predictive variables entered in the model.
‡Out of the 577 patients for whom early virological response could be defined, only 566 had data for all predictive variables entered in the model.
§Out of the 428 patients for whom relapse could be defined, only 420 had data for all predictive variables entered in the model.

Table 5. Adverse events reported for at least 10% of the patients during treatment period and 12 weeks after last intake

Treatment group			Control group		
Adverse event	Number of patients	% of Patients	Adverse event	Number of patients	% of patients
Anaemia	95	30.2	Anaemia	89	28.5
Mild	37	11.7	Mild	32	10.3
Moderate	51	16.2	Moderate	46	14.7
Severe	7	2.2	Severe	10	3.2
Life-threatening	0	0.0	Life-threatening	1	0.3
Asthenia	93	29.5	Pruritus	87	27.9
Headache	89	28.3	Fatigue	82	26.3
Pruritus	86	27.3	Asthenia	78	25.0
Fatigue	73	23.2	Headache	74	23.7
Neutropenia	70	22.2	Neutropenia	71	22.8
Insomnia	70	22.2	Myalgia	71	22.8
Leucopenia	67	21.3	Leucopenia	68	21.8
Mild	26	8.3	Mild	26	8.3
Moderate	40	12.7	Moderate	38	12.2
Severe	1	0.3	Severe	4	1.3
Anorexia	67	21.3	Thrombocytopenia	65	20.8
Thrombocytopenia	61	19.4	Influenza-like illness	63	20.2
Mild	20	6.3	Mild	29	9.3
Moderate	39	12.4	Moderate	33	10.6
Severe	2	0.6	Severe	3	1.0
Influenza-like illness	59	18.7	Insomnia	58	18.6
Alopecia	55	17.5	Depression	52	16.7
Cough	48	15.2	Alopecia	45	14.4
Myalgia	45	14.3	Cough	43	13.8
Depression	45	14.3	Dyspnoea	40	12.8
Nausea	43	13.7	Anorexia	38	12.2
Dyspnoea	41	13.0	Nausea	38	12.2
			Irritability	36	11.5

DISCUSSION

At the time of study initiation (in early 2003), some reports suggested that amantadine might be effective as supportive drug in the interferon-based treatment of CHC. However, results were conflicting, making larger studies necessary to define precisely the place of this drug in the management of CHC, especially in combination with PEG-IFN and RBV.

A recent meta-analysis[8] reported a significant effect of a triple combination therapy including amantadine in nonresponders, but no effect in naïve or relapsing patients. However, this meta-analysis did not provide details on the genotypes of the hepatitis C virus and did not focus on difficult-to-treat patients.

The aim of the present prospective, controlled and randomized study was to investigate the effect of amantadine added to the standard genotype-individualized combination of PEG-IFN with RBV, in patients with naïve or relapsing CHC. Subgroups should be identified to see which would benefit most from this therapy.

The present large study did not show any difference in efficacy between treatment and control groups. Subgroups likely to take advantage of this triple combination could not be identified.

A previous study by Zeuzem *et al.*[9] has also suggested that amantadine would be able to reduce the intensity of some adverse effects of interferon alpha. This could not be confirmed by our study that shows that adding amantadine does not modify the safety profile of the combined treatment.

For genotype 1 patients, our results are in agreement with the experience of Ferenci who compared PEG-INF plus RBV with or without amantadine in naïve genotype 1 patients.[10] In our study, the SVR in genotype 1

patients is 55.81% (96/172) in the amantadine group compared to 53.61% (89/166) in the control group, confirming in a larger sample of equal group sizes, the data from Ferenci who found that adding amantadine to PEG-INF plus RBV did not increase virological response rates in treatment-naïve genotype 1 patients. The same conclusion was drawn recently by Von Wagner *et al.*[11] with an amantadine dose of 400 mg/days added to PEG-INF plus RBV therapy in previously untreated chronically HCV-1 infected patients.

In our large study, analysis of SVR broken down by treatment and viral load at screening did not show any advantage in adding amantadine to the PEG-INF plus RBV combination for the treatment of patients with high viral load.

Several recent publications[12–16] also suggest that amantadine triple therapy has a role to play in the treatment of hepatitis C patients who failed prior combination therapy. The present study does not bring any additional data for these nonresponders as such patients were not included in this study.

In the group of 44 relapsing patients, taking into account a possible lack of power, SVR was not statistically different between treatment [47.62% (10/21)] and control [40.91% (9/22)] (OR treatment vs. control group = 1.31[0.39; 4.39]). These data in relapsing patients are in agreement with results of three previous randomized trials (Teuber *et al.*,[15] Freilich *et al.*,[17], Herrine *et al.*,[18]) and data from a recent meta-analysis.[8]

Some recent studies[19–23] suggested that the lack of benefit of amantadine might be explained by the efficacy of PEG-INF plus RBV, which has been shown to be superior to other interferon combination treatments used in past. The power of these studies might have been too low to detect a small difference in the virological response in particular in 'hard-to-treat' patients.

Our study, in agreement with the well-conducted, large and randomized trials with amantadine added to PegIFN and Ribavirin, definitely excludes the role of this drug, also in 'hard-to-treat' patients as demonstrated by stratification by genotype, viral load and presence of cirrhosis.

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APPENDIX

List of study participants (who are not authors)

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