Placebo-Controlled Trial of 400 mg Amantadine Combined with Peginterferon Alfa-2a and Ribavirin for 48 Weeks in Chronic Hepatitis C Virus-1 Infection

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The impact of amantadine on virologic response rates of interferon-based treatment of chronic hepatitis C is controversial. The aim of this study was to compare virological response rates in patients with chronic hepatitis C virus (HCV)-1 infection treated with 400 mg amantadine or placebo in combination with peginterferon alfa-2a (40 kD) and ribavirin for 48 weeks. Seven hundred four previously untreated chronically HCV-1–infected patients (mean age, 46 ± 12 years) were randomized to (A) amantadine-sulphate (400 mg/day) (n = 352) or (B) placebo (n = 352), both in combination with 180 μg peginterferon alfa-2a once weekly and ribavirin (1000-1200 mg/day) for 48 weeks. End of treatment and sustained virological response after a 24-week follow-up period were assessed by qualitative reverse transcription polymerase chain reaction (RT-PCR) (sensitivity, 50 IU/mL). Demographic and baseline virological parameters were similar in both treatment groups. In groups A and B, 231 of 352 patients (66%) and 256 of 352 patients (72%) achieved an end of treatment response, and 171 of 352 patients (49 %) and 186 of 352 patients (53 %) a sustained virological response, respectively. On-treatment dropout rate in the amantadine group was significantly higher than in the placebo group (32% versus 23%; $P = 0.01$). However, adverse events and laboratory abnormalities were similar between both groups. Per-protocol analysis revealed similar sustained virological response rates in both treatment groups (53% versus 55%). *Conclusion:* In this large placebo-controlled multicenter study, amantadine even at a dose of 400 mg/day did not improve virological response rates of peginterferon alfa-2a and ribavirin in patients with chronic genotype HCV-1 infection. (HEPATOLOGY **2008; 48:1404-1411.**)

Abbreviations: HCV, hepatitis C virus; PEG IFN-α-2a, pegylated interferon-alfa-2a.

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Hepatitis C virus (HCV) infection may progress to chronic hepatitis, cirrhosis, and its sequelae.[1-3] Interferon-based treatment of patients with chronic hepatitis C can achieve viral clearance and thereby improve histology and prognosis.[4,5] Thus, the primary aim of antiviral therapy in patients with chronic hepatitis C is a sustained virological response, defined as undetectable serum HCV RNA 24 weeks after the end of therapy by a sensitive molecular assay.

Despite recent advances, approximately half of the patients chronically infected with genotype HCV-1 do not achieve a sustained virological response by antiviral treatment with peginterferon alfa (PEG IFN-α) and ribavirin.[6-8] Over more than 10 years, the antiviral efficacy of amantadine in combination with interferon alfa alone or interferon alfa and ribavirin has been evaluated in numerous yet underpowered clinical trials.[9-14] Randomized placebo-controlled multicenter clinical trials revealed controversial results for treatment-naïve patients, and meta-analyses suggested a slight improvement of sustained virological response rates for interferon-based treatment with amantadine.[15] In addition to results from clinical trials, *in vitro* examinations suggested inhibition of the HCV p7-protein by amantadine and an association of specific amino acid variations in the p7-protein with virological response to amantadine in combination with PEG IFN-α and ribavirin.[16-19]

In most previous clinical trials in patients with chronic hepatitis C, amantadine was administered at a dose of 200 mg amantadine sulfate or hydrochloride per day. However, a dose finding study for amantadine monotherapy suggested an amantadine dose-dependent increase in biochemical response.[10] Normalization of alanine aminotransferase values was observed in 35%, 49%, 53%, and 56% of the patients receiving 200 mg, 300 mg, 400 mg, and 500 mg amantadine per day, respectively. However, more than 50% of the patients receiving more than 400 mg/day amantadine required dose reduction or treatment discontinuation. Therefore, the aim of the current study was to compare efficacy and safety of 400 mg/day amantadine sulfate versus placebo in combination with standard doses of PEG IFN-α2a and ribavirin for 48 weeks in patients chronically infected with genotype HCV-1.

Patients and Methods

Patients. Male and female patients older than 18 years with compensated chronic genotype HCV-1-infection not previously treated with interferon alfa or ribavirin were eligible for enrollment. Eligible patients tested positive for anti-HCV antibody and for HCV RNA (>600 IU/mL by quantitative reverse transcription polymerase chain reaction), had a liver biopsy taken within 24 months before the screening visit showing chronic hepatitis, and had at least one serum alanine aminotransferase level elevated during the screening period. Entry neutrophil and platelet counts had to be at least 1500/μL and 90,000/μL, respectively. Hemoglobin values at entry visit had to be at least 12 g/dL for females and at least 13 g/dL for males.

Patients with the following criteria were excluded: any other cause of liver disease or other relevant disorders including human immunodeficiency or hepatitis B virus co-infection, clinically significant hematological, hepatic, metabolic, renal, rheumatological, neurological, or psychiatric disease, clinically significant cardiac or cardiovascular abnormalities, organ grafts, systemic infection, clinically significant bleeding disorders, evidence of malignant neoplastic disease, concomitant immunosuppressive medication, excessive daily intake of alcohol, or drug abuse within the past year, pregnancy and lactation, and male partners of pregnant women. Further exclusion criteria were cardiomyopathy, higher degree of atrioventricular block, bradycardia (heart rate <55 beats/min.), an implanted pacemaker, prolonged Q-T-interval, or a U wave in electrocardiogram, or concomitant intake of medication with long Q-T-interval as a known side effect, concomitant medication with thiazides, known history of severe ventricular arrhythmia, and Parkinson's disease.

Study Design. Forty-five centers in Germany took part in this study designed as a randomized, double blind, placebo-controlled phase IIIb study comparing efficacy and safety of treatment with amantadine or placebo in combination with PEG IFN-α-2a plus ribavirin in previously untreated patients with chronic hepatitis C who were infected with genotype HCV-1. Eligible patients were randomized into one of two treatment groups and were treated with amantadine-sulfate 400 mg/day orally (group A) or placebo (group B) in combination with PEG IFN-α-2a (Pegasys, Hoffmann-La Roche, Grenzach, Germany) 180 μg once per week subcutaneously plus ribavirin (Copegus, Hoffmann-La Roche, Grenzach, Germany) 1000 to 1200 mg/day orally according to body weight (<75 kg: 1000 mg; ≥75 kg: 1200 mg). The ribavirin dose was based on the patient's body weight at study entry.

Before onset of antiviral treatment with PEG IFN-α-2a and ribavirin, amantadine/placebo was dose escalated within 2 weeks in 100-mg steps weekly starting at 200 mg/day. Before every dose increase, the Q-T-interval was measured. In case of an increase of the Q-T interval during this period (increase of Q-T-interval > 60 milliseconds or absolute Q-T-interval > 480 milliseconds), amantadine/placebo medication was stopped.

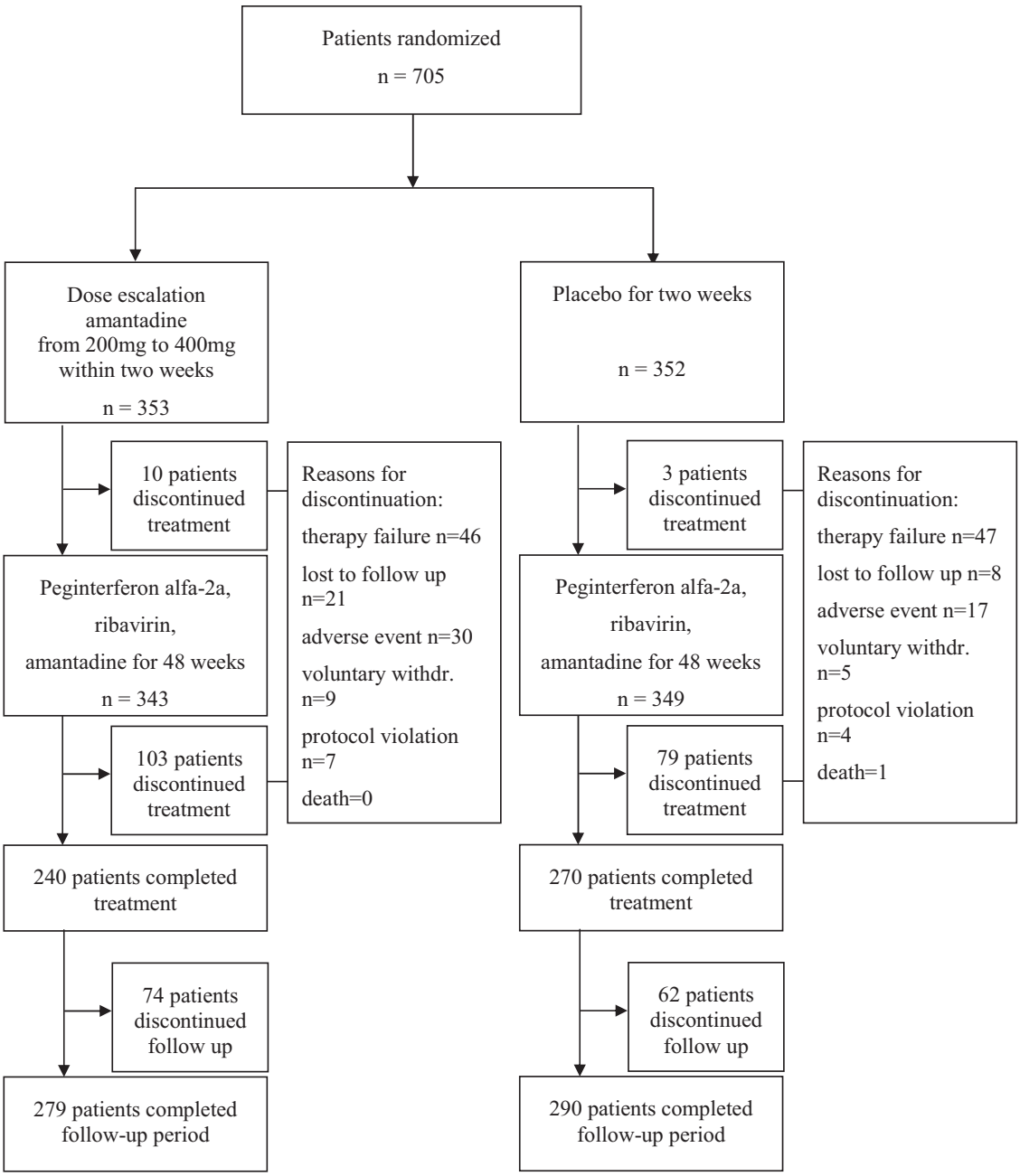

Fig. 1. Trial profile. Patients were randomized before amantadine escalation was initiated. Patients who withdrew prematurely from treatment were encouraged to return for follow-up visits. For this reason, the number of patients who completed follow-up is higher than the number of patients who completed treatment.

In patients without an early virological response (<2 log drop of HCV RNA in first 12 weeks of combination treatment), treatment was discontinued at week 18 of combination treatment. After the end of treatment all patients were followed for an additional 24-week period (Fig. 1). The primary efficacy endpoint for this study was the proportion of patients with a sustained virological response, defined as HCV RNA undetectable in a qualitative HCV RNA reverse transcription polymerase chain reaction (lower limit of detection, 50 IU/mL).

The study was approved by the ethics committees of the participating centers and carried out according to the Declaration of Helsinki and the International Conference on Harmonisation/Committee for Proprietary Medicinal Products (ICH/CPMP) guidelines "Good Clinical Practice." All patients gave written informed consent before enrollment.

Patients were evaluated as outpatients for safety, tolerance, and efficacy at weeks 0 and 1 of amantadine dose escalation, weeks 0, 1, 2, 4, 8, 12, 16, 24, 32, 40, and 48

Table 1. Demographic, Biochemical, Molecular, and Histological Profile of Patients With Chronic Hepatitis C at Baseline

	Group A (Peginterferon Alfa-2a, Ribavirin, Amantadine)	Group B (Peginterferon Alfa-2a, Ribavirin, Placebo)
Demography		
No. (M/F)	352 (185/167)	352 (183/169)
Body weight (kg)*	76.7 ± 14.5	74.0 ± 15.2
Body mass index (kg/m^2)	25.8	25.2
Age (years)*	46.3 ± 12.0	45.4 ± 12.2
Caucasian	346 (98.3%)	344 (97.7%)
Biochemistry		
ALT (× ULN)	2.7 ± 2.0	2.4 ± 1.6
GGT (× ULN)	1.5 (0.3–33)	1.4 (0.2–40)
Molecular parameters		
Genotype HCV-1 (subtype not specified)	52 (14.8%)	69 (19.6%)
HCV-1a	74 (21%)	68 (19.3%)
HCV-1b	226 (64.2%)	215 (61.1%)
Log_{10} pretreatment HCV RNA (IU/mL)†	5.9 (3.1–7.7)	5.8 (2.5–7.9)
Fibrosis (Ishak score 0–6)[20]*	1.6 ± 1.4	1.6 ± 1.1

ALT, alanine aminotransferase; ULN, upper limit of normal.
*Mean ± SD.
†Median (range).

during treatment with amantadine/placebo in combination with PEG IFN-α-2a and ribavirin, and at weeks 12 and 24 after the end of combination treatment. During treatment, HCV RNA was quantified by polymerase chain reaction assay (Amplicor Monitor HCV version 2.0; lower limit of detection, 600 IU/mL). End-of-treatment and sustained virological response were assessed by qualitative polymerase chain reaction assay (Amplicor HCV, Roche Molecular Systems; lower limit of detection, 50 IU/mL). HCV genotyping was performed by reverse hybridization (Inno LiPA HCV, Innogenetics, Gent, Belgium). Histological results were classified by local pathologists according to internationally standardized criteria.[20]

In the current study, only adverse events of special interest had to be reported. Adverse events of special interest were defined as serious adverse events and as all nonserious adverse events unknown for pegylated interferon, ribavirin, or amantadine, and any adverse events leading to dose modification or treatment discontinuation.

Statistical Analysis. Chi-squared tests were applied to compare different rates. Multivariate logistic regression was used to identify independent predictors of virological response. If not stated otherwise, *P* values below 5% were considered significant. A per-protocol analysis was performed for patients who received at least 80% of the assigned PEG IFN-α-2a, ribavirin, and amantadine dose and who completed the planned (±4 weeks) treatment duration and the follow-up period.

Results

Characteristics of the Patients. This study was performed between July 2003 and February 2007 in 45 German centers. According to the inclusion and exclusion criteria, 705 genotype HCV-1–infected patients were enrolled within 24 months. In one patient, HCV RNA was undetectable already at screening and baseline and, therefore, this patient was taken into consideration only for the safety analysis. One hundred forty-two (20%) and 441 patients (63%) were infected with subtype HCV-1a and HCV-1b, respectively, whereas in 121 patients (17%), differentiation between subtypes HCV-1a and HCV-1b was not reported. All baseline characteristics of patients included in the efficacy analysis are summarized in Table 1.

Virological and Biochemical Response. Before the onset of treatment with PEG IFN-α-2a and ribavirin, patients received amantadine and placebo, respectively, for 2 weeks with a dose escalation of 100 mg amantadine every week. HCV RNA was quantified at screening before onset of amantadine dose escalation as well as at baseline, weeks 12, 24, and 48 of combination treatment, and at week 24 of follow-up. In case of an HCV RNA level below the detection limit for quantification (600 IU/mL) during combination therapy, each serum sample was tested by qualitative assay with a lower detection limit of 50 IU/mL.

No change in HCV RNA serum concentration was detectable during amantadine dose escalation (ΔHCV RNA: 0.05 log10 in group A versus −0.02 log10 in group B). However, in three patients receiving amantadine (1%) and one patient receiving placebo (0.3%), HCV RNA was undetectable in the HCV RNA quantification assay (600 IU/mL) at baseline of combination treatment. All of these patients achieved sustained virological response. An early virological response (>2 log drop at week 12 of

Table 2. Virologic Response Rates in Patients Receiving 400 mg/day Amantadine-Sulfate or Placebo, Peginterferon Alfa-2a, and Ribavirin According to Pretreatment Viremia

	Group A (Peginterferon alfa-2a, Ribavirin, Amantadine) n = 352	Group B (Peginterferon alfa-2a, Ribavirin, Placebo) n = 352
Virologic response		
> 2 $\log_{10}$ decrease at week 12	279 (79.3%)	282 (80.1%)
≤ 800,000 IU/mL	141 (82.0%)	154 (83.2%)
>800,000 IU/mL	138 (76.7%)	128 (76.7%)
<50 IU/mL at week 48	231 (65.6%)	256 (72.7%)
≤800,000 IU/mL	120 (69.8%)	133 (71.9%)
>800,000 IU/mL	111 (61.7%)	123 (73.7%)
<50 IU/mL at End of follow up-period	171 (48.6%)	186 (52.8%)
≤800,000 IU/mL	92 (53.5%)	105 (56.8%)
>800,000 IU/mL	79 (43.9%)	81 (48.5%)

combination therapy), end of treatment virological response, and sustained virological response was achieved in 561 patients (80%), 487 patients (69%), and 357 patients (51%), respectively (Table 2). Virological response rates were similar in patients randomized to either amantadine (group A) or placebo (group B). In groups A and B, 231 of 352 patients (66%, CI: 60.4%-70.6%) and 256 of 352 patients (73%, CI: 67.8%-77.3%) achieved a virological end-of-treatment response and 171 of 352 patients (49%, CI: 43.3%-53.9 %) and 186 of 352 patients (53%, CI: 47.5%-58.2 %) achieved a sustained virological response, respectively. Sustained biochemical response was observed in 167 of 352 patients (59%) randomized to the amantadine (group A) and 181 of 352 patients (63%) randomized to the placebo (group B).

According to the per-protocol analysis, end-of-treatment and sustained virological response rates were 217 of 305 (71%) and 161 of 305 (53%) in group A and 243 of 321 (76%) and 175 of 321 (55%) in group B, respectively.

Virological Response According to Baseline Characteristics. The sustained virological response rate was significantly higher in patients with pretreatment viremia lower than 800,000 IU/mL than in patients with pretreatment viremia higher than 800,000 IU/mL (55.2% versus 46.1 %; $P < 0.05$). End-of-treatment and sustained virological response rates were similar in groups A and B regarding pretreatment viremia and HCV subtype (Table 2).

Virological response rates were also found to be dependent on fibrosis score. The sustained virological response rate was significantly lower in patients with transition to cirrhosis or complete cirrhosis compared with patients without cirrhosis (26.2% versus 53.3 %; $P < 0.05$). For patients showing transition to cirrhosis or complete cirrhosis who were receiving amantadine in combination with PEG IFN-α-2a and ribavirin (group A), the sustained virological response rate was lower than in patients receiving placebo (group B) (18.9% versus 37.5%).

Other Predictors of Response. From multivariate logistic regression analysis of all patients, pretreatment viremia higher than 800,000 IU/mL, elevated pretreatment gamma-glutamyltransferase (GGT) levels, transition to cirrhosis/cirrhosis, and higher age (>40 years) were negative predictive factors for sustained virological response. Independent positive predictive factors for sustained virological response were elevated cholesterol levels and female sex.

Adverse Events and Dose Modifications. Fifty-nine serious adverse events in 52 of 705 patients (7.4%) enrolled into this study were reported. The number of serious adverse events was similar between both treatment groups (n = 31 versus n = 28). One patient died in week 8 of treatment. Unfortunately, despite intensive efforts, further information about the reason for death was not available for the responsible center. This patient received placebo in combination with PEG IFN-α-2a and ribavirin.

The number of patients who prematurely withdrew from therapy was significantly higher in the group of patients receiving amantadine in combination with PEG IFN-α-2a and ribavirin than in the group of patients receiving placebo [113/353 (32.0%) in group A and 82/352 (23.3 %) in group B; $P = 0.01$].

According to the study protocol, only adverse events of special interest were reported. In Table 3, the adverse events of special interest are summarized according to the treatment group. In general, frequency and severity of adverse events were similar between both treatment arms.

One hundred forty-six of 705 patients (21%), 200 of 705 patients (28 %), and 105 of 705 patients (15%) required dose reduction or treatment discontinuation of PEG IFN-α, ribavirin, and amantadine/placebo, respectively. Although the number of patients who prematurely

Table 3. Adverse Events of Special Interest and Dose Modifications According to Treatment Group

	Group A (Peginterferon alfa-2a, Ribavirin, Amantadine) n = 353	Group B (Peginterferon alfa-2a, Ribavirin, Placebo) n = 352
Discontinuation*	113 (32.0%)	82 (23.3%)
Dose modification for adverse events or laboratory abnormalities		
Peginterferon alfa	79 (22.4%)	67 (19.0%)
Ribavirin	108 (30.6%)	92 (28.1%)
Amantadine	59 (16.7%)	46 (13.1%)
Adverse events†		
Neutropenia	43	65
Anemia	43	59
Depression	13	13
Thrombopenia	9	14
Exanthema	10	11
Pruritus	13	8
Headache	9	10
Alopecia	6	11
Fatigue	9	8
Urinary tract infection	8	8
Leukopenia	4	10
Hypothyreoidism	6	7
Coughing	10	2
Bronchitis	10	1
Nausca	5	6
Dizziness	3	7
Diarrhea	5	4
Dermatitis	3	5
Dyspnea	5	3
Hyperthyroidism	4	4
Arterial hypertension	3	4
Dry skin	4	3

*Difference in discontinuation is statistically significant ($P = 0.01$) between both treatment groups.

†Adverse events of special interest that occurred in at least 1% of the patients who received at least one dose of study medication. Adverse events of special interest were defined as serious adverse events and as all nonserious adverse events uncommon for pegylated interferon, ribavirin, or amantadine and adverse events leading to dose modification.

withdrew from treatment was significantly higher in group A, no significant difference was observed between both treatment groups regarding rates of dose reduction. Rates of dose reduction and treatment interruption for amantadine and placebo, respectively, were only slightly different (16.7 versus 13.1 %; P = NS).

Discussion

Despite recent advances in the development of antiviral treatment of chronic hepatitis C, up to 50% of the patients infected with genotype HCV-1 do not achieve a sustained virological response.[6-8,21,22] Clinical trials revealed conflicting results on the antiviral efficacy of amantadine in combination with PEG IFN-α with or without ribavirin. Combination treatment with standard interferon alfa and amantadine showed sustained virological response rates of 10% to 30% almost similar to interferon monotherapy.[14,23,24] By antiviral triple therapy containing amantadine, PEG IFN-α and ribavirin sustained virological response rates of 25% to 60% were achieved compared with 28% to 44% observed in patients receiving dual combination with PEG IFN-α and ribavirin.[11,25,26] A meta-analysis comprising 3257 treatment-naïve patients enrolled in 17 controlled clinical trials showed that amantadine augments the response to interferon alfa in treatment-naïve patients, albeit to a lesser extent than most clinical trials assumed for sample size calculation.[15] In the largest randomized, placebo-controlled trial, 400 treatment-naïve patients with chronic hepatitis C were enrolled.[11] Sustained virological response rates observed in patients receiving triple therapy with 200 mg amantadine per day in combination with interferon alfa induction therapy and ribavirin for 48 weeks were 52% compared with 44% in patients receiving placebo plus interferon alfa induction and ribavirin; however, the difference did not reach statistical significance.

In previous trials evaluating amantadine in combination with interferon-based treatment, amantadine was administered in a standard dose of 200 mg/day as for the prophylaxis of influenza. In one prospective randomized study, Smith et al.[10] reported an increase in biochemical response with higher daily doses of amantadine from 200

mg/day up to 500 mg/day in monotherapy. However, in more than 50% of the patients with doses higher than 400 mg/day a dose reduction was necessary, and a dose-dependent increase in side effects was observed. Therefore, in the current study, amantadine at a daily dose of 400 mg was evaluated in combination with standard doses of PEG IFN-α-2a and ribavirin in chronically HCV-1–infected patients.

The overall sustained virological response rate in the current study was 51% and, thus, was similar to sustained virological response rates in HCV-1–infected patients in previous pivotal trials.[6,8] No improvement in end-of-treatment and sustained virological response rates was found with triple therapy including amantadine compared with standard combination therapy. These results are in accordance with one recently published smaller clinical trial revealing similar virological response rates in patients receiving 200 mg amantadine per day or placebo in combination with PEG IFN-α-2a and ribavirin.[27]

In the intent-to-treat population of the current study, even a trend toward lower virological response rates in the group of patients receiving amantadine was observed. Lower rates of virological response in the amantadine group can be explained by a significantly higher dropout rate compared with the placebo group (32% versus 23%; $P = 0.01$). Indeed, the per-protocol analysis considering only patients who received at least 80% of the overall drug dose showed similar sustained virological response rates between both groups (53% versus 55%). The reported rates of adverse events of special interest were similar in both treatment groups. This discrepancy might be explained by the fact that, according to protocol, only adverse events unknown to PEG IFN-α-2a, ribavirin, and amantadine, respectively, or serious adverse events or adverse events leading to dose modifications had to be reported.

Confirming previous findings, elevated pretreatment GGT levels, transition to cirrhosis/cirrhosis, higher age (>40 years), and pretreatment high viral load (>800,000 IU/mL) were found as negative predictive factors for sustained virological response in the current study.[28,29] Elevated cholesterol levels were identified as a positive predictive factor for sustained virological response.[28,29] This finding is also accordant with previous observations.[30] HCV RNA replication *in vitro* has been found to be dependent on intracellular lipid metabolism; however, influence of serum cholesterol levels on virological response to antiviral treatment *in vivo* has not yet been understood.[31,32]

In conclusion, in this large placebo-controlled, double-blinded multicenter study in patients with chronic hepatitis C, amantadine even at a dose of 400 mg/day was not able to improve virological response rates of PEG IFN-α-2a and ribavirin. Therefore, amantadine has no relevance in the antiviral treatment of chronic hepatitis C. Currently, direct antiviral agents such as inhibitors of the HCV serine protease and the RNA-dependent RNA polymerase are under clinical investigations, and initial phase I/II trials have shown that the combination of PEG IFN-α and ribavirin together with a direct antiviral compound can increase sustained virological response rates in genotype HCV-1–infected patients.[33-37]

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