

Interferon and Amantadine in Naive Chronic Hepatitis C: A Double-Blind, Randomized, Placebo-Controlled Trial

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Recent controlled trials on the efficacy of an amantadine/interferon combination in treatment-naive patients with chronic hepatitis C yielded contradictory results. We therefore conducted a large, double-blind, placebo-controlled, multicenter trial in naive patients with chronic hepatitis C: 246 patients were randomized to receive interferon alfa-2a (6 MIU sc thrice weekly for 20 weeks, then 3 MIU sc thrice weekly) and either amantadine sulphate (2 × 100 mg po QD) or placebo. Treatment continued for a total of 52 weeks, if HCV-RNA in serum polymerase chain reaction (PCR) had fallen below detection limit (1,000 copies/mL) at treatment week 10, and stopped otherwise. All patients were followed for 24 weeks off therapy. After 10 weeks of treatment, 66/121 patients treated with amantadine (55%) and 78/125 treated with placebo (62%) had lost HCV-RNA (n.s.). After 24 weeks of follow-up, 25 patients in the amantadine (21%) and 17 (14%) in the placebo group remained HCV-RNA negative (n.s.). During therapy, virologic breakthroughs occurred less often in the amantadine than in the placebo group [14 (12%) vs. 27 (22%) patients; $P = .04$]. Multivariate logistic regression analysis revealed genotype, viremia level, age, and amantadine therapy [risk ratio 0.4 (95%CI 0.2-1.0), $P = .05$] as predictors of sustained virologic response. Adverse events and impact of therapy on quality of life were similar in amantadine and placebo treated patients. Compared with current standard treatment (interferon/ribavirin), the interferon/amantadine combination was not cost-effective. In conclusion, amantadine does not add to a clinically relevant extent to the treatment of naive patients with chronic hepatitis C. (HEPATOLOGY 2002;35:447-454.)

Hepatitis C virus (HCV) infection follows a chronic course in the majority of subjects and leads within decades to liver cirrhosis and hepatocellular carcinoma in a significant proportion of patients.¹ HCV-associated liver disease is a leading cause of liver-related morbidity and mortality and for liver transplantation in Western countries. Although pharmacotherapy of chronic hepatitis C has evolved rapidly in recent years,²⁻⁵ even modern treatment regimens combining pegylated interferons with ribavirin fail to clear the virus in 20% to 50% of patients.^{6,7} More-

over, current therapies frequently cause side effects necessitating dose reductions or discontinuation of treatment.^{2,3} Thus, additional therapeutic options are warranted.

Amantadine is a tricyclic amine exhibiting antiviral activity against influenza A⁸⁻¹⁰ and other viruses including some flaviviridae^{11,12} to which HCV belongs. Whereas its mechanism(s) of action against influenza A is well characterized,¹³ that against other viruses remains ill defined.^{12,14-16} Beneficial effects of amantadine in HCV infection have been reported in some,^{17,18} but not all,¹⁹ clinical pilot studies. In addition, conflicting data have been reported on its efficacy combined with interferon alfa in patients with chronic hepatitis C who failed to respond to or relapsed after a previous interferon alfa monotherapy.²⁰⁻²³ However, triple combination therapy consisting of amantadine, ribavirin, and interferon alfa was found to be more efficacious than double combination of ribavirin and interferon alfa in a recent open-label, randomized, controlled trial in interferon alfa nonresponders.²⁴ Moreover, recent randomized, controlled trials on the combination of amantadine and interferon alfa in treatment-naive patients with chronic hepatitis C yielded conflicting results: Zeuzem et al. observed in their double-blind, placebo controlled trial an – albeit insignificant – negative effect of amantadine,²⁵ Tabone et al.,²⁶ and Caronia et al.,²⁷ detected in their open-label studies no significant benefit, whereas Mangia et al. found in an open-label study that amantadine significantly increases the antiviral efficacy of interferon alfa.²⁸ Although the reason(s) for these conflicting results

Abbreviations: SR, sustained response; HCV, hepatitis C virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; n.s., nonsignificant; SFR, Swiss francs; cps, copies; RT-PCR, reverse transcription-polymerase chain reaction; subcutaneous; po, per oral; MIU, million international units; b.w., body weight; n.s., not significant.

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remain(s) unclear, the study by Zeuzem et al. may have missed a modest treatment effect because of its limited sample size, while because of its open-label design a bias in favor of active treatment may not be entirely ruled out in the trial of Mangia et al.

The aim of the present study was, therefore, to clarify in a large, double-blind, randomized, placebo-controlled trial efficacy, safety/tolerability, and cost-effectiveness of amantadine and interferon alfa for treatment of naive patients with chronic hepatitis C.

Patients and Methods

Patients

Patients of both genders aged 18 to 65 years with biopsy-proven (within ≤ 2 years) chronic hepatitis C who had never been treated before, exhibited elevated ALT within 6 months of entry on at least 2 occasions at least 1 month apart, and tested positive for HCV RNA in serum by RT-PCR (Amplicor HCV Monitor version 2.0, Roche Diagnostics, Basel, Switzerland) were eligible for the study.

Patients with either one of the following were excluded from the study: any other cause of liver disease including HBV-coinfection (HbsAg pos.) and alcohol intake > 20 g/day in females and > 40 g/day in males; a history of or actual decompensation of liver disease (ascites, variceal bleeding, or encephalopathy); cirrhosis ≥ 8 Child-Pugh points; other clinically relevant disorders including cardiovascular, pulmonary, renal, metabolic, hematologic, rheumatologic, neurologic and psychiatric diseases, autoimmune disorders, HIV infection, immunosuppression within 12 months of entry, organ transplantation, malignant neoplastic disease within 2 years of study entry, illicit drug use within 1 year of study entry, or psychosocial instability.

Patients with one of the following laboratory abnormalities were also excluded: leucocytes $< 2,000/\mu\text{L}$, neutrophils $< 1,000/\mu\text{L}$, platelets $< 50,000/\mu\text{L}$, serum creatinine > 1.5 times upper limit of normal, elevated thyroid stimulating hormone, α -fetoprotein above normal limits, and/or focal lesion on ultrasound performed within 1 month of study entry.

Additional exclusion criteria were pregnancy or lactation, refusal to practice effective contraception during treatment and follow-up or treatment with any investigational drug within 6 months of study entry.

Study Design and Conduct

This is a double-blind, randomized, placebo-controlled, parallel-group trial performed on behalf of the Swiss Association for the Study of the Liver (SASL) in 28 Swiss centers (see Acknowledgements). Recruitment started in February 1998 and ended in June 1999. The study was approved by the local ethics committees of all participating centers and conducted in accordance with the Declaration of Helsinki²⁹ and the guidelines on Good Clinical Practice of the Swiss regulatory authorities (Interkantonale Kontrollstelle für Heilmittel, Bern, Switzerland). All patients gave written informed consent before enrollment.

Patients were randomized with a ratio of 1:1 to receive either interferon alfa-2a and amantadine sulphate or interferon alfa-2a and placebo. Randomization was carried out in blocks of 10 using random numbers stratified according to the presence/absence of cirrhosis. Interferon alfa-2a (Roferon A) was provided by Roche Pharma (Schweiz) AG, Reinach, Switzerland, amantadine sulphate

(PK Merz)/Placebo by Adroka AG, Allschwil, Switzerland, respectively. Treatment consisted of interferon alfa-2a 6 MIU sc thrice weekly for 20 weeks, followed by 3MIU sc thrice weekly for an additional 32 weeks and amantadine sulphate 100 mg po twice daily or matched placebo throughout. Treatment was stopped if after 10 weeks HCV RNA in serum remained detectable by RT-PCR (Amplicor HCV Monitor version 2.0, Roche Diagnostics, Switzerland; detection limit: 1,000 copies/mL). Patients were followed for 24 weeks after stopping therapy.

Patients were evaluated on an outpatient basis for safety/tolerability and efficacy at the end of treatment weeks 2, 4, 8, 10, 12, and subsequently every 4 weeks, and at the end of week 12 and 24 after stopping treatment. At each visit a history with emphasis on adverse events was taken, vital signs were recorded, and blood was drawn for lab tests. In addition, overall quality of life was assessed using a visual analogue scale, *i.e.*, the patient was asked to mark with a pen his/her current perception of his/her overall quality of life on a continuous 10-cm-long scale where the left end stood for "I feel very bad" and the right end for "I feel very good," respectively.

Hematologic tests (hemoglobin, leucocyte, neutrophil, and platelet count) and biochemical tests (ALT, AST, alkaline-phosphatase, gammaglutamyl-transferase, creatinine, albumin, and prothrombin time) were performed by local laboratories. HCV RNA was determined centrally (Div. Clinical Immunology, University Hospital, Zurich, Switzerland) by RT-PCR (Amplicor HCV Monitor version 2.0, Roche Diagnostics, Switzerland; detection limit: 1,000 copies/mL) in serum collected at baseline, at treatment weeks 10 and 52, and at follow-up week 24. The same central lab also determined HCV genotype using a reverse hybridization assay (Inno-Lipa HCV II, Innogenetics, Ghent, Belgium).³⁰

A single pathologist (CG) unaware of clinical data including treatment response scored all pretreatment liver biopsies using the extended Knodell score described by Ishak.³¹

Cost-Effectiveness Analysis

Cost-effectiveness was assessed by a decision tree analysis (Decision Maker 7.0).³² Three treatment strategies were tested: (1) interferon alfa 6 MIU sc thrice weekly for 20 weeks, then 3 MIU sc thrice weekly for a total of 52 weeks, *i.e.*, the treatment of our placebo arm; (2) interferon alfa 6 MIU sc thrice weekly for 20 weeks, then 3 MIU sc thrice weekly, and amantadine 2×100 mg po daily for a total of 52 weeks, *i.e.*, the treatment of our amantadine arm; and (3) interferon alfa 3 MIU sc thrice weekly and ribavirin (b.w. ≤ 75 kg: 1,000 mg po daily; b.w. > 75 kg: 1,200 mg po daily) for 24 weeks (genotype 2 or 3) or 48 weeks (genotypes 1, 4, 5, or 6), respectively, *i.e.*, the current standard treatment.³³ Tested treatment strategies included stopping rules at week 10 (interferon and interferon/amantadine combination) or at week 24 (interferon/ribavirin combination), *i.e.*, treatment would be discontinued, if HCV RNA (PCR) would still be above detection limit (1,000 copies/mL) at these time points. Efficacy data for the interferon/ribavirin combination were those from two large trials.^{2,3} Costs were those of ambulatory care and drug retail prizes in Switzerland for the year 1999 from a societal perspective.³³

Data Analysis and Statistics

Two hundred thirty-nine patients are needed for a power to detect an increase in treatment response from an estimated 15% in the interferon alfa and placebo group³⁴ to 24% in the interferon alfa and amantadine group with an α -error of .05 and a β -error of .20.

Data were analyzed for (1) sustained virologic response, *i.e.*, HCV RNA in serum below detection limit (1,000 copies/mL) at the end of follow-up week 24 and (2) initial and end of treatment virologic responses, *i.e.*, HCV RNA below detection limit at end of treatment week 10 and 52, respectively, virologic breakthrough and relapse, *i.e.*, reappearance of HCV RNA during therapy and follow-up, respectively, and for the corresponding biochemical efficacy measures, *i.e.*, normalization of ALT, at the respective time points. Safety and tolerability as reflected by clinical and laboratory adverse events and quality of life were described.

Efficacy analysis is based on the intention-to-treat population of 246 patients who were randomly assigned to treatment and received at least one dose of therapy. Missing data were treated by a worst case method, *e.g.*, missing HCV RNA determinations during/after therapy were taken to have remained above detection limit.

Baseline characteristics and treatment differences between groups were analyzed using the χ^2 -test, Fisher's exact test (two-tailed) or the Wilcoxon rank sum test, as appropriate. Factors potentially associated with sustained virologic response were analyzed by univariate followed by multivariate logistic regression analysis using a backwards selection procedure. Factors with a *P* value \geq .20 were removed from the multivariate model. A *P* value \leq .05 was chosen to indicate statistical significance. All statistical analyses were performed by SAS procedures (version 6.12, SAS Institute Inc, Cary, NC).

Results

Baseline Characteristics

Two hundred fifty-four patients were enrolled, of whom 8 (4 in the amantadine, 4 in the placebo group) withdrew informed consent after baseline evaluation, but before starting treatment. Two hundred forty-six patients started treatment. Figure 1 depicts the overall trial profile of this intention-to-treat population. Whereas baseline variables (Table 1) did not significantly differ between groups, genotype 1 infection and severe fibrosis (Ishak fibrosis scores 5 and 6) tended to be slightly, albeit not significantly, more prevalent in the amantadine group.

Efficacy

Virologic Response. Sustained virologic response tended to be slightly higher in the amantadine (20.7%) than in the placebo group (13.6%) (Table 2). This failed, however, to reach statistical significance. Moreover, initial virologic response (week 10) and end-of-treatment response (week 52) were similar in both groups. Nevertheless, virologic relapse and breakthrough tended to be lower in the amantadine than in the placebo group, the latter reaching statistical significance (*P* = .04).

Biochemical Response. In the amantadine and the placebo group, the proportion of patients with normalized ALT tended at all times to be slightly higher than that with undetectable HCV

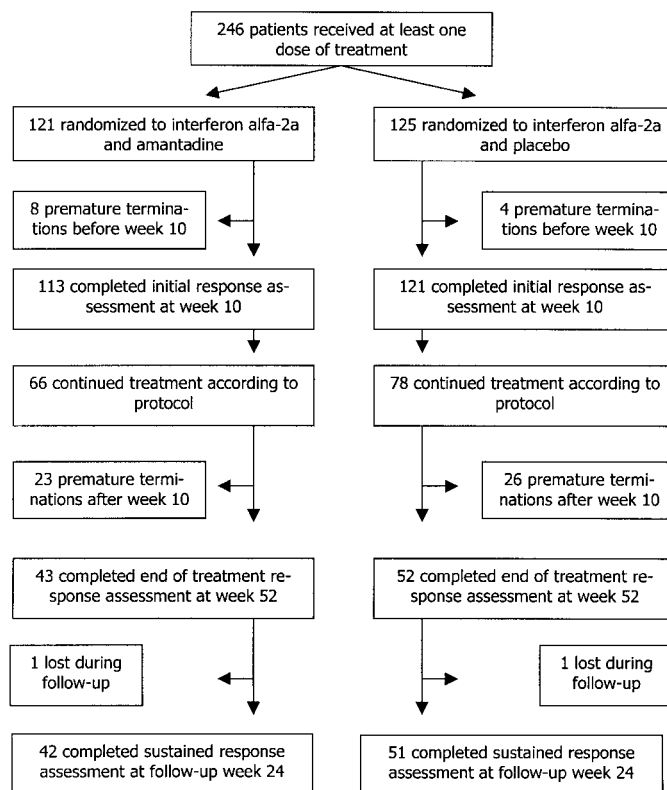


Fig. 1. Trial Profile - Intention to Treat Population. Two hundred forty-six patients received at least one dose of treatment and thus form the intention-to-treat population. One hundred twenty-one patients were randomized to interferon alfa-2a and amantadine and 125 to interferon alfa-2a and placebo. Eight patients in the amantadine group and 4 patients in the placebo group stopped treatment before completing treatment week 10 for noncompliance (*n* = 8) and adverse events (*n* = 4), respectively. Thus, 113 patients in the amantadine and 121 patients in the placebo group were available for initial response assessment at the end of treatment week 10: 66 and 78 patients, respectively, had undetectable HCV RNA in serum (PCR), were thus initial responders, and continued treatment according to protocol. Of these, 23 patients in the amantadine and 26 in the placebo group stopped treatment prematurely between treatment week 11 and 52 for viral breakthrough (*n* = 20), adverse events (*n* = 19), and noncompliance (*n* = 10), respectively. Thus, 43 and 52 patients, respectively, completed treatment up to treatment week 52. One patient each in the amantadine and in the placebo group did not return to the follow-up visits, leaving 42 patients in the amantadine and 51 patients in the placebo group, respectively, available for sustained response assessment at the end of follow-up week 24.

RNA levels. Thus, initial, end-of-treatment and sustained biochemical responses amounted in the amantadine and placebo group to 57.9% and 72.8% (*P* = .016), 28.9% and 29.6% (*P* = n.s.), and 25.6% and 20.8% (*P* = n.s.), respectively. A similar picture emerged, when virologic combined with biochemical response was analyzed as efficacy parameter, initial, end-of-treatment, and sustained combined biochemical and virologic responses in the amantadine and placebo group amounting to 43.0% and 58.4% (*P* = .020), 25.6% and 25.6% (*P* = n.s.), and 18.1% and 12.8% (*P* = n.s.), respectively.

Logistic Regression Analysis - Sustained Virologic Response According to Baseline Characteristics and Treatment. The following parameters were entered into a logistic regression analysis: treatment (amantadine vs. placebo), HCV genotype (1, 4, 5, 6

Table 1. Baseline Characteristics*

	IFN/Amantadine	IFN/Placebo	P†
Number of Patients	121	125	–
Male (% [n])	68 [82]	70 [88]	.681
Body Weight [kg]‡	72 [40-112]	71 [47-100]	.529
Age [years]‡	39 [20-66]	38 [20-65]	.827
ALT [U/l]‡	101 [34-421]	111 [30-768]	.680
Viremia [10 ⁶ copies/ml]‡	2.16 [0.001-38.60]	4.72 [0.02-50.50]	.107
Genotype Distribution			overall: .212
1 (% [n])	55 [66]	42 [52]	.055
2 (% [n])	10 [12]	9 [11]	.829
3 (% [n])	28 [34]	40 [50]	.060
4 (% [n])	4 [5]	5 [6]	1.000
5 (% [n])	0 [0]	0 [0]	–
6 (% [n])	1 [1]	0 [0]	.492
Histologic Activity§			overall: .556
Mild (% [n])	27 [33]	23 [29]	.468
Moderate (% [n])	67 [81]	73 [91]	.333
Severe (% [n])	5 [6]	3 [4]	.535
Histologic Stage			overall: .437
Mild (% [n])	49 [59]	50 [63]	.800
Moderate (% [n])	36 [43]	39 [49]	.599
Severe (% [n])	15 [18]	10 [12]	.244

*One liver biopsy and 3 genotype determinations and 1 liver biopsy and 6 genotype determinations are missing in the amantadine and placebo groups, respectively.

†Wilcoxon rank sum test, χ^2 -test, or Fisher's exact test (two-tailed), respectively, as appropriate.

‡Median [range].

§Activity measured by the interphase inflammatory score according to (29): mild = score 0-1; moderate = score 2-3; severe = score 4.

||Fibrosis stage according to (29): mild = score 0-2; moderate = score 3-4; severe = score 5-6.

vs. 2, 3), HCV RNA level (≤ 2 Mio copies/ml vs. > 2 Mio copies/mL), ALT elevation (≤ 3 times upper limit of normal vs. > 3 times upper limit of normal), gender (female vs. male), age (≤ 40 years vs. > 40 years), weight (≤ 75 kg vs. > 75 kg) and stage of

Table 2. Virologic Response

	IFN/Amantadine (n = 121) % (n) [95% CI]	IFN/Placebo (n = 125) % (n) [95% CI]	P*
Initial Response†	54.5 (66) [45-64]	62.4 (78) [53-71]	.244
End of Treatment Response‡	30.6 (37) [23-40]	28.8 (36) [21-38]	.782
Sustained Response§	20.7 (25) [14-29]	13.6 (17) [8-21]	.175
Breakthrough	11.6 (14) [7-19]	21.6 (27) [15-30]	.040
Relapse**	9.1 (11) [5-16]	15.2 (19) [10-23]	.174

*Fisher's exact test (two-tailed).

†HCV RNA in serum not detectable by PCR (Amplicor HCV Monitor version 2.0) at end of treatment week 10.

‡HCV RNA in serum not detectable by PCR (Amplicor HCV Monitor version 2.0) at end of treatment week 52.

§HCV RNA in serum not detectable by PCR (Amplicor HCV Monitor version 2.0) at end of follow-up week 24.

||HCV RNA in serum again detectable by PCR (Amplicor HCV Monitor version 2.0) during treatment after an initial response had been achieved; virologic breakthroughs occurred in both treatment groups at similar rates prior to and after interferon alfa dose reduction (week 20), i.e., in 0.75% and 0.43% of patients per week of treatment in the amantadine and in 0.90% and 0.80% of patients per week of treatment in the placebo group, respectively.

**HCV RNA in serum again detectable by PCR (Amplicor HCV Monitor version 2.0) at end of follow-up week 24 after an end of treatment response had been achieved.

fibrosis (none to moderate, i.e., Ishak fibrosis scores 0 to 4 vs. severe, i.e., Ishak fibrosis scores 5 and 6), respectively.

In univariate analysis, genotype 2 or 3, HCV RNA level ≤ 2 Mio copies/mL and age ≤ 40 years were strongly associated with sustained virologic response (Table 3). Although amantadine treatment decreased the risk ratio for virologically not responding in a sustained fashion by about 40%, this did not reach statistical significance. Similarly, a trend for lower fibrosis stages to be associated with increased sustained virologic response rates failed to reach statistical significance. The remaining parameters tested, i.e., ALT elevation, gender, and body weight, were also not associated with sustained virologic response.

In multivariate logistic regression using a backwards variable selection procedure, amantadine treatment just reached the level of significance as independent predictor of sustained virologic response ($P = .0498$), whereas genotype, HCV RNA level, and age proved to be strongly and independently related to this favorable outcome (Table 4). All other parameters tested exhibited a P value $\geq .20$ and thus were removed from the model.

Safety and Tolerability

During the first phase of treatment, i.e., until week 10, there were a total of 722 adverse events reported in 206/246 patients (84%), 344 in 98/121 patients (81%) in the amantadine group and 378 in 108/125 patients (86%) in the placebo group, respectively. During the second phase of the treatment, i.e., after week 10, a total of 249 events in 98/144 (68%) patients occurred, 131 in 49/66 patients (74%) in the amantadine group and 118 in 49/78 patients (63%) of the placebo group. Adverse events were mostly mild, attributable to interferon alfa and of similar pattern and frequency in both treatment groups (Table 5). Four hundred and four (40%) adverse events have been judged by the responsible investigators to be definitely related to the study medication, 188 (47%) in the amantadine and 216 (53%) in the placebo group, respectively.

Twenty-four adverse events in 20/246 patients (8.1%) were classified as serious by the investigators: 13 in 10/121 patients (8.3%) in the amantadine group and 11 in 10/125 patients (8.0%) in the placebo group, respectively. In the amantadine group, this consisted of the following: recurrent substance abuse (2 patients), pulmonary arterial hypertension with cor pulmonale, pulmonary fibrosis, pneumonia, tuboovarian abscess, kidney infection and

Table 3. Univariate Analysis of Factors Potentially Associated With Sustained Virologic Response

	P	Risk Ratio	95% Confidence Limits	
			Lower	Upper
Genotype (1, 4, 5, or 6 vs. 2 or 3)	.0024	3.000	1.474	6.106
Age (≤ 40 vs. > 40 years)	.0175	0.416	0.202	0.858
Viremia ($\leq 2 \times 10^6$ vs. $> 2 \times 10^6$ cps/ml)	.0295	0.431	0.202	0.920
Fibrosis (mild-moderate vs. severe)	.1204	0.311	0.071	1.358
Treatment (Amantadine vs. Placebo)	.1436	0.604	0.308	1.187
ALT ($\leq 3 \times$ UNL vs. $> 3 \times$ UNL)	.5513	1.227	0.626	2.407
Gender (female vs. male)	.7073	0.873	0.430	1.772
Body Weight (≤ 75 vs. > 75 kg)	.7354	0.887	0.444	1.774

Table 4. Multivariate Analysis of Factors Potentially Associated With Sustained Virologic Response

	Estimate	P	Risk Ratio	95% Confidence Limits	
				Lower	Upper
Genotype (1, 4, 5, or 6 vs. 2 or 3)	1.1935	.0044	3.229	1.451	7.500
Viremia ($\leq 2 \times 10^6$ vs. $> 2 \times 10^6$ cps/ml)	-0.9099	.0265	0.403	0.180	0.899
Age (≤ 40 vs. > 40 years)	-0.8622	.0458	0.422	0.181	0.984
Treatment (Amantadine vs. Placebo)	-0.8177	.0498	0.441	0.195	0.999

pelvic inflammatory disease (same patient), severe flu-like symptoms, herniated intervertebral disc, methadone withdrawal symptoms, and impaired glucose tolerance. In the placebo group, the following serious adverse events were recorded: death from a ruptured aortic aneurysm with medianecrosis Erdheim-Gsell, relapse of substance abuse (4 patients), luxation of the hip in a car accident, oral abscess, severe depression, methadone withdrawal symptoms, hyperthyroidism, and a suspected pregnancy (which later was disproved). Five of these 24 serious adverse events (3 in the amantadine group and 2 in the placebo group) were classified by the investigators as definitely or probably related to the study treatment.

Adverse events lead to a total of 53 episodes of dose reductions (30 in the amantadine, and 23 in the placebo group). Sixty-one patients (31 in the amantadine and 30 in the placebo group) terminated therapy prematurely: 25 premature terminations (14 in the amantadine, 11 in the placebo group) were for adverse events, the remaining (17 in the amantadine, 19 in the placebo group) for viral breakthroughs recognized during therapy (8 and 12 patients) or for the patient's wish (9 and 7 patients), respectively. Overall quality of life decreased with starting treatment, ameliorated with dose reduction of interferon alfa (week 20), and returned to baseline levels on cessation of therapy (Fig. 2). There were no differences between treatment groups with respect to initial, end of treatment, or sustained virologic or biochemical responses (data not shown).

Cost-Effectiveness

Calculating with the observed numerical – albeit not statistically significant – difference in sustained virologic response between the interferon alone (14%) and the interferon/amantadine combination (21%), interferon alone is dominated by interferon/amantadine, *i.e.*, is less effective at higher costs (Table 6). The

standard interferon/ribavirin combination, however, is twice as effective as the interferon/amantadine (overall sustained virologic response rate of 41% compared with 21%). This outweighs its higher costs, *i.e.*, leads to a marginal cost-effectiveness ratio of SFR 47'123 [or \$26,179 (US)] per each virologic sustained response gained with interferon/ribavirin over and above those achieved with interferon/amantadine.

Discussion

Whether addition of amantadine improves antiviral efficacy of current therapeutic strategies for chronic hepatitis C is controversial.²⁴⁻²⁸ Main observations of our large, double-blind, randomized, placebo-controlled trial in treatment-naive patients with chronic hepatitis are: (1) amantadine increased sustained virologic response numerically, but statistically not significantly (by ~ 7%); (2) amantadine significantly reduced virologic breakthrough (by ~ 10%); (3) in multivariate logistic regression analysis, amantadine treatment just reached the level of significance ($P = .05$) as independent predictor of sustained virologic response; (4) treatment with amantadine was safe and well tolerated; (5) the cost-effective-

Table 5. Number of Adverse Events

	Total	INF/Amantadine	INF/Placebo
Any Adverse Event	971	475	496
Flu-like Symptoms	302	147	155
Nervous System*	214	104	110
Gastrointestinal Tract	130	60	70
Blood†	115	64	51
Skin	99	42	57
Cardiovascular System	42	27	15
Endocrine System	31	15	16
Respiratory System	28	12	14
Urinary Tract	12	4	8

*Including headache, dizziness, irritability, mood changes, and major depression.

†Mostly leucopenia, neutropenia, and/or thrombocytopenia.

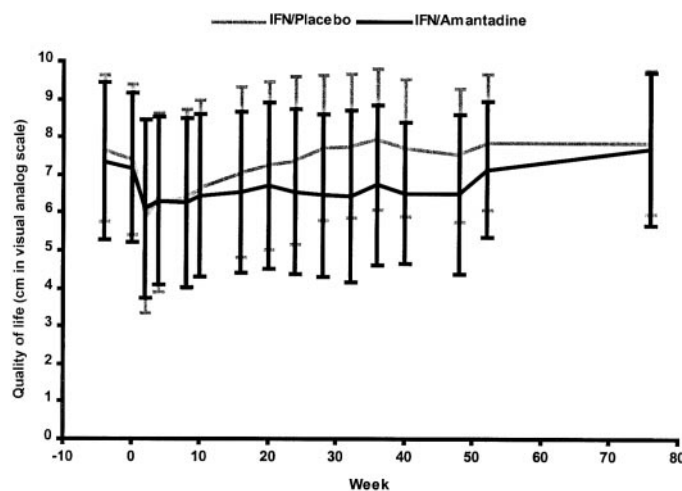


Fig. 2. Quality of Life. Quality of life was assessed at each visit using a visual analogue scale. Mean quality of life scores are depicted over time for both the amantadine (black line) and the placebo group (gray line), respectively. The higher the score, the better the perception of the patients' overall health-related quality of life. Error bars reflect standard deviations. Quality of life decreased on starting therapy in both groups, tended to return towards baseline levels after interferon dose reduction (week 20) in the placebo, but not in the amantadine group, and fully recovered to baseline levels after cessation of treatment (week 52) in both treatment groups. There was, however, no significant difference in overall health-related quality of life between the amantadine and the placebo group.

Table 6. Cost-Effectiveness of an Interferon/Amantadine vs. an Interferon Alone vs. an Interferon/Ribavirin Strategy

	Costs (SFR)	Effectiveness (Sustained Virologic Response Rate)	Average Cost-Effectiveness (SFR/Sustained Virologic Response)	Marginal Costs (SFR)	Marginal Effectiveness (Sustained Virologic Response)	Marginal Cost Effectiveness (SFR/Sustained Virologic Response)
IFN/Amantadine	8446	0.21	40'217			
IFN alone	8888	0.14	63'485	442	-0.07	dominated
IFN/Ribavirin	17'973	0.41	43'604	9527	0.20	47'123

NOTE. For details cf. Text, strategies are in order of rising costs.

ness ratio of the interferon/amantadine combination was less favorable than that of standard interferon/ribavirin.

Amantadine apparently does not affect the activity of HCV protease, helicase, and polymerase.³⁶ However, amantadine seems to be concentrated in the liver compared with plasma³⁷ and was reported to dose-dependently reduce HCV RNA content in cultured peripheral blood mononuclear cells isolated from HCV infected patients, which was significantly augmented by concomitant incubation with interferon alfa.³⁸ Whereas these observations are compatible with antiviral activity of amantadine in HCV infection, the validity of the latter as an *in vitro* model for hepatic HCV infection has to be questioned. Because of the scarcity of *in vitro* models for HCV infection,³⁹ clinical trials remain the mainstay for determining efficacy of anti-HCV strategies.

This study is the second double-blind, placebo-controlled trial on amantadine in treatment-naïve patients with chronic hepatitis C and twice as large as the first such study.²⁵ The sample size of our trial enables detection of a 9% treatment difference, *i.e.*, of an increase in assumed virologic sustained response from 15% in the placebo group³⁴ to 24% with a power of 80%. Thus, there remains the possibility that the 7% increase in sustained virologic response observed with amantadine is real, but escaped statistical detection. However, even taking this observed numerical efficacy difference at face value, it seems small, at best, and would translate into the need to treat ~ 14 patients with amantadine (in addition to interferon alfa) to gain one sustained virologic response.

The interferon alfa dosing schedule used in the present study, *i.e.* 6 MIU sc thrice weekly for 20 weeks followed by 3 MIU sc thrice weekly for the remaining treatment phase, and the stopping rule at the end of week 10 if HCV RNA remained detectable in serum, was at the time the study was initiated a standard treatment schedule in Switzerland based on a consensus of experts and third-party payers. Its rationale was the extrapolation that > 90% of sustained viral responders have lost HCV RNA by the end of week 10 of interferon alfa therapy⁴⁰ and that higher interferon alfa doses increase response rates.⁴¹ Even if in retrospect it may have been optimal to continue with the higher interferon dose and to use a stopping rule at a later time point, we feel confident that the interferon dosing schedule used did not introduce a relevant bias into our study because it affected both treatment groups similarly.

Baseline characteristics of the 2 treatment groups were statistically not different. However, genotype distribution and fibrosis stage tended to disfavor—albeit insignificantly—the amantadine group. Indeed, univariate analysis of potential factors associated with sustained virologic response in our study picked genotype (1, 4, or 6 vs. 2 or 3) as the most significant. Fibrosis failed to be significantly associated with sustained virologic response, most

likely because of the small number of patients with advanced fibrosis/cirrhosis enrolled. When correcting for the aforementioned slight—albeit insignificant—baseline differences by multivariate logistic regression analysis, amantadine treatment just reached the level of significance ($P = .0498$) as independent predictor of sustained virologic response.

Zeuzem et al.²⁵ reported a beneficial effect of amantadine on health-related quality of life during therapy. We were not able to confirm this. Thus, frequency and quality of adverse events were similar in both treatment groups and the patients' overall perception of quality of life was similar in the amantadine and in the placebo group during the entire treatment period. Whereas Zeuzem et al.,²⁵ however, used several sophisticated quality of life questionnaires, we assessed overall quality of life using a visual analogue scale. To check the quality of the patients' rating on the visual analogue scale, patients were asked at each visit whether they feel better, unchanged, or worse compared with the last visit. The change in quality of life ratings on the visual analogue scale was congruent with the answers to this question (data not shown). Thus, we feel confident that the visual analogue scale correctly reflects the patients' perception of overall quality of life. Our crude instrument, however, is certainly not able to detect subtle differences between treatment groups, *e.g.*, in certain domains of health-related quality of life such as fatigue and vigor, as reported by Zeuzem et al.²⁵

Cost-effectiveness considerations do not favor an amantadine/interferon alfa combination in treatment-naïve patients with chronic hepatitis C. Interferon alone is dominated by interferon/amantadine, *i.e.*, is less effective at higher costs. This is because of the fact that the initial virologic response rate with interferon/amantadine was lower—albeit not significantly—than with interferon alone (56% vs. 63%). Because therapy was stopped in case of initial virologic nonresponse, this led to a larger proportion of patients treated for 52 weeks with interferon alone than with interferon/amantadine accounting for higher total costs of interferon monotherapy. Taking into account that amantadine is relatively cheap [SFR 1.- or \$0.55 (US) per day of treatment], and calculating with the observed numerical gain in sustained virologic response (number needed to treat ~ 14), an interferon/amantadine strategy would therefore be more efficient at saving costs than an interferon-alone strategy. However, when efficacy and costs of interferon/amantadine are compared with those of the current standard, *i.e.*, interferon/ribavirin, the latter's higher efficacy outweighs its higher costs, translating into a marginal cost-effectiveness ratio of SFR 47,123 [\$26,179 (US)] per sustained virologic response. Assuming that 7 life years are gained per sustained virologic response (40-year-old HCV-infected patient),^{33,42}

this translates into a marginal cost-effectiveness of SFR 6,732 [\$3,703 (US)] per life-year saved. Marginal cost-effectiveness ratios of less than \$50,000 (US) per life-year saved are generally accepted by society to attest to the cost-effectiveness of a treatment strategy.⁴³ Thus, even when calculating with the numerically favorable – albeit not statistically significant – efficacy data for interferon/amantadine observed in the present study, therapy of treatment-naïve chronic hepatitis C with the current standard interferon/ribavirin combination is more favorable. The even better efficacy of pegylated interferons combined with ribavirin,^{6,7} which presumably will become the therapeutic standard in the near future likely further disfavors interferon/amantadine.

In conclusion, addition of amantadine to interferon alfa-2a is marginally effective at best in treatment-naïve patients with chronic hepatitis C. Although well tolerated, and perhaps cost-effective compared with interferon monotherapy, interferon/amantadine is substantially less effective than the current treatment standard, *i.e.*, interferon/ribavirin. Thus, the routine clinical use of amantadine instead of ribavirin seems not justified in treatment-naïve patients with chronic hepatitis C. While not having been formally explored, it seems doubtful whether addition of amantadine could improve to a clinically relevant extent the efficacy of today's most effective therapy, *i.e.*, the combination of pegylated interferon alfa and ribavirin.

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