LIVER

Randomised, double blind, placebo controlled trial of interferon, ribavirin, and amantadine versus interferon, ribavirin, and placebo in treatment naïve patients with chronic hepatitis C

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Background and aim: In this study, we compared the efficacy of triple therapy (interferon alfa, ribavirin, and amantadine) with standard therapy (interferon alfa and ribavirin) in treatment naïve patients with chronic hepatitis C virus (HCV).

Methods: In this prospective, randomised, double blind, placebo controlled, multicentre study, 85 patients (amantadine group) received a three drug regimen of interferon alfa-2b 3 million units three times per week, ribavirin 1000–1200 mg daily in divided doses, and amantadine 100 mg twice daily, and 86 patients (placebo group) received interferon alfa-2b, ribavirin, and identical placebo. Treatment was discontinued at 24 weeks if patients had detectable HCV RNA by polymerase chain reaction (PCR). All patients were followed for 24 weeks after completion of treatment. The primary end point was undetectable HCV-RNA by PCR at 24 weeks (sustained viral clearance) after completion of treatment.

Results: At the end of treatment, HCV RNA clearance was seen in 32.9% of the amantadine group and 38.4% of the placebo group (p=0.3). Sustained virological response was seen in 24.7% of the amantadine group and in 27.9% of the placebo group by intention to treat analysis; response rate was 30.4% and 34.8%, respectively, in those who completed 24 weeks of treatment. Poor response was seen in both groups among cirrhotics, African-Americans, genotype 1, and those with a higher viral load. By multivariate analysis, genotype 1, high viral load, and low serum albumin were the only predictors of poor response. Addition of amantadine to the standard regimen did not result in any unexpected side effects.

Conclusion: Response to triple therapy of interferon alfa, ribavirin, and amantadine was similar to standard therapy of interferon alfa and ribavirin. Our results suggest that amantadine has no role in the management of HCV.

Hepatitis C affects 100–300 million people worldwide. Chronic hepatitis C is a leading indication for liver transplantation and a major cause of hepatocellular carcinoma in the USA and Europe.[1] Despite major improvements in the treatment of hepatitis C, sustained virological response (SVR) is achieved in less than 50% of patients treated with a combination of interferon and ribavarin.[2 3] Amantadine is a relatively inexpensive antiviral agent with activity noted against the flaviviridae family to which the hepatitis C virus (HCV) belongs. Although a few early reports[4] claimed a good response to amantadine monotherapy, subsequent studies have failed to confirm these observations.[5] Similarly, combination therapy of interferon and amantadine has shown mixed results. In a provocative, randomised, controlled study of 60 patients who had failed interferon monotherapy, Brillianti and colleagues[6] claimed sustained viral clearance in 19 of 40 patients (48%) with triple therapy of interferon alfa-2b, ribavirin, and amantadine compared with only 1 of 20 patients (5%) who received a combination of interferon alfa 2b and ribavirin. However, when we started our study, there had been no large placebo controlled randomised trials to demonstrate the efficacy of triple therapy in treatment naïve patients with chronic hepatitis C.

The objective of our study was to determine if the addition of amantadine to the standard regimen of interferon and ribavirin resulted in an increase in sustained viral clearance rates in treatment naïve patients with hepatitis C.

PATIENTS AND METHODS

Patients

Adult patients with chronic hepatitis C who had no previous treatment for HCV were eligible for the study. Patients were enrolled if they had HCV RNA detectable by polymerase chain reaction (PCR), evidence of liver disease (alanine aminotransferase (ALT) or aspartate aminotransferase above the upper limit of normal), liver biopsy (within three months), and no known contraindications to treatment with interferon, ribavirin, or amantadine. Stress testing was required for patients at high risk for coronary artery disease, and only patients demonstrating euthyroid state were enrolled. Patients with known haemolytic anaemia, hepatocellular carcinoma, renal failure, and seizure disorders were excluded from the trial. Other exclusion criteria were: concomitant hepatitis B virus or human immunodeficiency virus infection, immunosuppressed state, active substance abuse, decompensated liver disease, major psychiatric disorders, life expectancy less than five years, or daily alcohol intake over 10 g/day. Patients with the following laboratory values were also excluded: haemoglobin <12 g/dl, white blood cell count <3000, platelet count <70 000, serum

Abbreviations: HCV, hepatitis C virus; SVR, sustained virological response; PCR, polymerase chain reaction; ALT, alanine aminotransferase; TSH, thyroid stimulating hormone

bilirubin >3 mg/dl, serum creatinine >1.2 mg/dl, and a positive pregnancy test. Women and men of childbearing age were required to practice medically acceptable methods of contraception.

Study design and treatment regimens

This was a double blind, placebo controlled, multicentre trial conducted in nine centres. Patients were randomly assigned (central randomisation at Johns Hopkins University) to receive subcutaneous interferon alfa-2b 3 million units three times a week, ribavirin 1000–1200 mg (based on body weight) daily in divided doses, and amantadine hydrochloride (or identical placebo) 100 mg twice daily. Interferon and ribavirin were prescribed in an open label fashion and amantadine or identical placebo was provided in a double blind fashion. Only amantadine or placebo was provided free of cost to all patients; interferon and ribavirin were given free only if patients did not have insurance coverage. The pharmacy department at the Johns Hopkins Hospital was responsible for randomisation and supplying amantadine or identical placebo to all centres. Unblinding of amantadine was done only when all patients completed treatment or if any patient experienced unexpected side effects (this was not necessary as there were no serious adverse events). Patients were treated for 24 weeks, and treatment continued for an additional 24 weeks for a total of 48 weeks if HCV RNA clearance was noted by PCR at the end of 24 weeks of treatment. All patients were followed for an additional 24 weeks from the end of treatment. Treatment was discontinued if HCV RNA was positive at 24 weeks.

Clinical and laboratory evaluation

All patients underwent a comprehensive history and physical examination prior to enrolment. Subsequent history, adverse events, and vital signs were recorded at 1, 2, 4, 6, and 8 weeks, every four weeks thereafter until the end of the treatment, and at 12 and 24 weeks after treatment. Laboratory evaluations including creatinine, electrolytes, liver function tests, prothrombin time, and urine for protein were done at 0, 1, 2, 4, 6, and 8 weeks as well as every four weeks thereafter. Thyroid stimulating hormone (TSH) was checked at baseline and at four month intervals thereafter. Additional tests were done as required.

Viral genotype was determined at baseline but genotype could not be reliably determined in four patients. HCV RNA levels were checked at baseline, 12, 24, and 48 weeks during treatment, and 24 weeks after treatment. Virological assays were not performed in a central laboratory, and the study was done before routine use of standardised reporting. Therefore, different assays were utilised at the various sites. We have attempted to stratify patients based on viral loads of over 1 000 000 copies/ml or less, but our assumptions may be affected by a 20% rate of discordance between different assays.

Liver biopsies were performed within three months of entry into the study. Patients were also required to have a liver biopsy after completion of treatment as part of the study design. Pretreatment biopsy reports were classified based on the degree of fibrosis and the presence of cirrhosis. For the purpose of analysis, we included patients with septate fibrosis in the cirrhotic group.

Severity of adverse events, specific to interferon, ribavirin, and amantadine, was recorded at each visit using a predesigned questionnaire (20 treatment specific symptom complexes were examined) on a numerical severity scale ranging from 0 (none) to 5 (maximum). For adverse events, the dose of interferon and ribavirin was modified according to preset criteria, as defined in the protocol.

All patients provided written informed consent, and the institutional review board (IRB) of each centre approved both the consent and protocol.

Study end points

The study design was an intention to treat analysis and the primary end point was sustained clearance of HCV RNA from serum at 24 weeks after treatment. Secondary end points included normalisation of ALT, end of treatment clearance of HCV RNA, response rate in those who actually received 24 weeks of treatment, improvement in liver histology, and safety profile of therapy.

Statistical analysis

Sample size was calculated on the basis of previous reports.[2 3 6] We assumed a treatment response rate of 60% in the triple therapy group (as a 48% response rate was noted in non-responders to prior interferon monotherapy, we predicted a higher response rate in the treatment naïve group)[6] and 35% in the group that received standard treatment of interferon alfa and ribavirin.[2 3] We estimated that 85 patients would be required in each arm, assuming an estimated early dropout of about 20%, to achieve 80% power at the 5% (alpha) level of significance.

Categorical variables were analysed using the two tailed Fisher's exact test, and a p value of 0.05 or less was considered statistically significant. Continuous variables were compared by the *t* test. All data were analysed using SPSS version 11.0 (Chicago, Illinois, USA).

RESULTS

A total of 171 patients were enrolled into the study (fig 1). We could not obtain follow up HCV RNA in four patients from the amantadine group, despite repeated attempts to contact them. These four patients with negative HCV-RNA at the end of 48 weeks of treatment were considered non-responders in our intention to treat analysis. Demographics of patients in both groups were similar, as shown in table 1. All African-Americans had genotype 1, and 21% of all patients had cirrhosis. Age, race, genotype 1, presence of cirrhosis, and HCV RNA levels were similar in both groups (table 1). Similarly, there were no differences in liver enzymes, albumin, bilirubin, prothrombin time, haemoglobin, white blood cells, platelets, creatinine, and TSH between groups. A total of 138 (80.7%) patients completed 24 weeks (minimum treatment period) of treatment.

Forty nine patients (28.6%) failed to complete the treatment by protocol (minimum treatment period of 24 weeks, or 48 weeks if they had HCV RNA clearance at 24 weeks) either because of side effects (29/49: 15—amantadine group, 14—placebo group) or for a variety of other reasons (20/49: 11—amantadine group, nine—placebo group). No patient suffered life threatening adverse events. We measured the severity of side effects using a grading scale (0 = none to 5 = most severe) of 20 specific symptom complexes. Incidence and severity of adverse events were similar in both groups throughout the study period (72 weeks). Severity scores for the first 24 weeks for the adverse events that were found to be significantly different from baseline values are given in table 2. In addition, side effects specific to amantadine (even if not significant from baseline) are also shown in table 2. Twenty nine patients had 39 side effects which were severe enough for them to withdraw from study and these included: neutropenia (n = 2), thrombocytopenia (n = 1), depression (n = 9), skin lesions (n = 2), fatigue (n = 6), dyspnoea (n = 1), memory loss (n = 2), insomnia (n = 3), itching (n = 3), gastrointestinal upset or right upper quadrant discomfort (n = 4), diarrhoea (n = 1), nausea or anorexia (n = 4), and angioedema

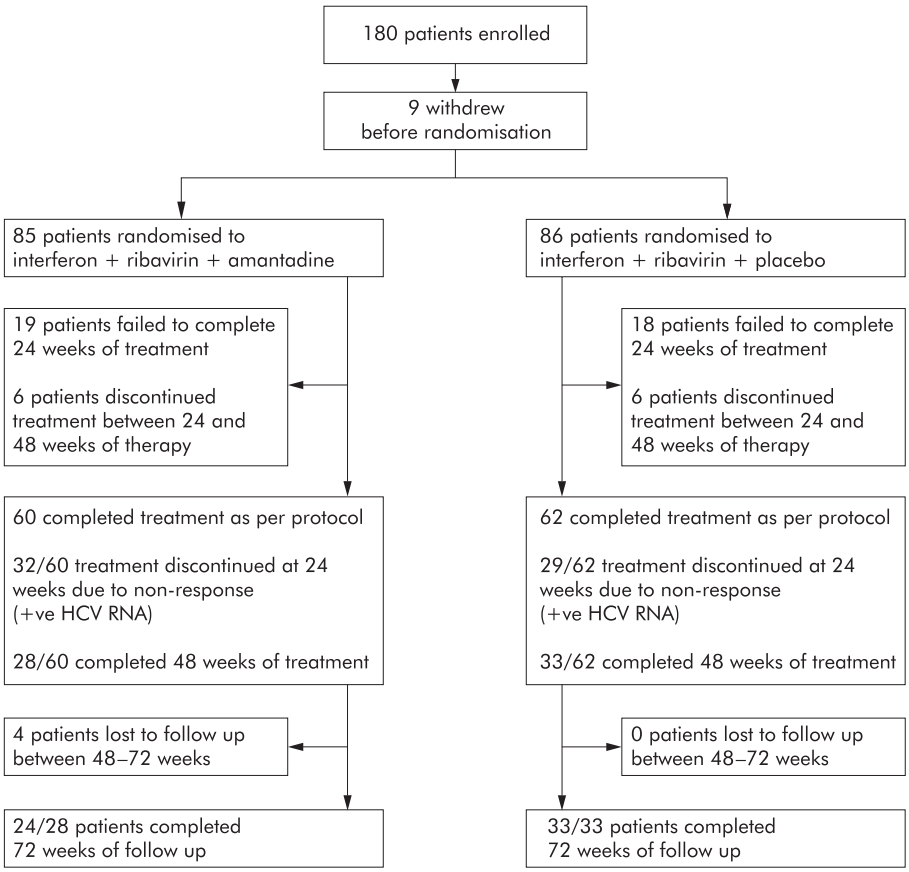

Figure 1 Trial profile.

Table 1 Patients demographics

	Amantadine group (n = 85)	Placebo group (n = 86)	p Value
Age (y)	44.6 (6.9)	43.9 (7.0)	0.5
<50 y	82.4% (n = 70)	75.6% (n = 65)	0.2
>50 y	17.6% (n = 15)	24.4% (n = 21)	
Genotype			
1a/b	87.1% (n = 74)	82.6% (n = 71)	0.3
2, 3	10.6% (n = 9)	15.1% (n = 13)	0.3
4, 5	0	0	
Unable to genotype	2.4%(n = 2)	2.3% (n = 2)	
Race			0.5
Caucasian	78.8% (n = 67)	83.7% (n = 72)	
African-American	20% (n = 17)	14% (n = 12)	
Other	1.2% (n = 1)	2.3% (n = 2)	
Sex (male)	52.9% (n = 45)	61.6% (n = 55)	0.2
Severity of fibrosis			0.2
Cirrhosis/septate fibrosis	18.8% (n = 16)	25.6% (n = 22)	
Minimal/no fibrosis	81.2% (n = 69)	74.4% (n = 64)	
Baseline laboratory results			
ALT	103 (126)	90 (66)	0.4
TSH	1.88 (1.2)	1.93 (1.2)	0.9
Albumin (mg/dl)	4.2 (0.4)	4.1 (0.4)	0.3
Bilirubin (mg/dl)	0.68 (0.4)	0.74 (0.5)	0.4
Haemoglobin (g/dl)	14.6 (1.4)	14.8 (1.2)	0.3
WBC count/mm^3	6482 (1985)	6946 (4479)	0.4
Platelet count/mm^3	201 (71)	188 (64)	0.2
Creatinine (mg/dl)	0.92 (0.2)	0.87 (0.2)	0.1
PT (s)	12 (2.5)	11.7 (1.5)	0.5
HCV RNA level by PCR			0.4
<1 000 000 copies/ml	60% (n = 51)	57% (n = 49)	
>1 000 000 copies/ml	40% (n = 34)	43% (n = 37)	

ALT, alanine aminotransferase; TSH, thyroid stimulating hormone; PT, prothrombin time; WBC, white blood count; HCV, hepatitis C virus; PCR, polymerase chain reaction.
Results are mean (SD) unless otherwise indicated.

Table 2 Severity of side effects†

	Baseline		Month 1		Months 2–3		Months 4–6	
Side effect	Placebo	Amantadine	Placebo	Amantadine	Placebo	Amantadine	Placebo	Amantadine
Fatigue	1.52 (1.48)	1.21 (1.41)	1.99 (1.42)	2.09 (1.35)***	2.09 (1.47)*	2.14 (1.24)***	1.97 (1.59)	1.94 (1.28)**
Anorexia	0.06 (0.4)	0.13 (0.53)	0.46 (0.93)**	0.67 (1.02)***	0.53 (1.06)***	0.5 (0.79)**	0.41 (0.88)**	0.29 (0.7)
Lack of exercise tolerance	0.76 (1.38)	0.81 (1.34)	0.97 (1.38)	1.37 (1.55)*	1.30 (1.61)*	1.47 (1.48)*	1.4 (1.67)*	1.52 (1.53)**
Nausea	0.29 (0.85)	0.23 (0.69)	0.82 (1.08)**	0.81 (1.08)***	0.64 (0.98)*	0.71 (0.94)**	0.46 (0.96)	0.57 (0.93)*
Malaise	0.75 (1.46)	0.44 (1)	1.02 (1.25)	1.16 (1.37)***	1.05 (1.41)	1.15 (1.37)**	1.05 (1.56)	1.01 (1.50)*
Itching	0.63 (1.25)	0.53 (0.97)	0.69 (1.09)	0.92 (1.14)*	0.95 (1.24)	1.12 (1.19)**	1.11 (1.46)	1.44 (1.46)***
Weight loss	0.11 (0.49)	0.08 (0.34)	0.27 (0.51)*	0.39 (0.58)***	0.39 (0.71)**	0.36 (0.53)***	0.36 (0.61)*	0.36 (0.61)**
Depression	0.33 (0.77)	0.31 (0.71)	0.71 (1.1)*	0.84 (1.17)**	0.8 (1.18)**	0.91 (1.14)***	0.95 (1.26)**	0.68 (1.05)*
Insomnia	0.96 (1.47)	0.54 (1.14)	1.05 (1.41)	1.42 (1.4)***	1.18 (1.27)	1.32 (1.31)***	1.41 (1.58)	1.47 (1.33)***
Dizziness	0.09 (0.29)	0.21 (0.69)	0.58 (0.92)***	0.68 (1.05)**	0.63 (1.08)***	0.78 (1.02)***	0.38 (0.79)**	0.61 (0.94)*
Blurred vision	0.48 (0.99)	0.36 (0.89)	0.47 (0.94)	0.6 (1.02)	0.63 (1.2)	0.61 (0.96)	0.55 (1.12)	0.49 (1.03)
Nervousness	0.54 (1.02)	0.51 (1.06)	0.51 (0.89)	0.8 (1.15)	0.66 (0.95)	0.82 (1.23)	0.78 (1.21)	0.66 (1.23)
Dry mouth	0.86 (1.48)	0.57 (1.26)	1.29 (1.52)	1.45 (1.45)***	1.5 (1.65)*	1.58 (1.63)***	1.47 (1.62)*	1.63 (1.51)***

†Severity scored on a scale from 0 (none) to 5 (severe), and results are expressed as mean (SD).
*p<0.05, **p<0.01, ***p<0.001 compared with baseline. There were no significant differences between amantadine and placebo at different time intervals. There were no significant changes in side effects after month 1 in both groups.

(n = 1). Eighteen patients (nine from the amantadine and nine from the placebo group) had dose reduction for development of anaemia (n = 4), neutropenia (n = 6), thrombocytopenia (n = 1), insomnia (n = 3), fatigue (n = 3), or tremors (n = 1). Side effects responded to dose reduction of either interferon or ribavirin as appropriate. Amantadine was not reduced in any patient. An additional 20 (20/49) patients withdrew from the study for personal reasons (n = 6), relapse of intravenous drug abuse (n = 3), relapse of viraemia between 24 and 48 weeks (n = 2), complications of unrelated medical problems (n = 1), inability to swallow or administer medications (n = 2), poor venous access (n = 1), or failure to return for follow up visits despite numerous reminders (n = 5).

HCV RNA clearance rates at 24 weeks and 48 weeks (end of treatment response) were similar in the amantadine and placebo groups (table 3). Intention to treat analysis showed a sustained response rate of 24.7% (21/85) in the amantadine group and 27.9% (24/86) in the placebo group (p = 0.4). Overall response rates were lower in patients with cirrhosis, those with a higher viral load, genotype 1, and those who were older than 50 years, with similar response rates in the amantadine and placebo groups (table 4). There were no differences in response rates based on the patient's weight. Only three of 18 (16%) patients who had dose reductions for side effects had sustained viral clearance. None of the African-Americans (0/28) had sustained HCV RNA clearance (table 4). Logistic regression analysis showed that genotype 2/3 (odds ratio 7.0, 95% confidence interval 2.3–21.7; p = 0.001), low viral load (p = 0.059), and a higher serum albumin (p = 0.016) were the only independent predictors of response to treatment. African-American race, presence of cirrhosis/septate fibrosis, and amantadine therapy (amantadine *v* placebo) were not independent predictors of response.

Sustained clearance rates were higher in patients who completed 24 weeks of treatment; 30.4% (21/69) in the amantadine group (genotype 1—23.7% and genotype 2 or 3—85.7%) and 34.8% (24/69) in the placebo group (genotype 1—23.6% and genotype 2 or 3—81.8%) had sustained clearance of HCV RNA. Of the patients who completed 24 weeks of treatment, mean ALT decreased from 100.9 (105.9) at baseline to 22.7 (17.6) at six months post-treatment (data not shown). Although a secondary end point of our study, histological improvement was not assessed as the majority of patients refused their post-treatment liver biopsy.

DISCUSSION

In this double blind, randomised, controlled study, we have shown that addition of amantadine to interferon alfa-2b and ribavirin did not increase HCV RNA clearance rate in treatment naïve HCV patients. Amantadine was very well tolerated with a similar adverse event profile in the amantadine and placebo groups. Our study corroborated the previous observations of low response rate in older patients, and those with genotype 1, cirrhosis, and a higher viral load. In addition, none of our 28 African-Americans responded to either triple therapy (0/16) or standard treatment (0/12).

Over the past five years there have been major improvements in the treatment of HCV. The response rate has improved from 10% with interferon monotherapy to 40% with a combination of interferon and ribavirin.[2 3] More recently, the use of a combination of pegylated interferon and ribavirin has increased the SVR further to approximately 50%. Our study was inspired by a trial that reported 48% SVR in non-responders of interferon monotherapy using a combination of interferon, ribavirin, and amantadine.[6] In the same study, only 5% of interferon monotherapy

Table 3 Hepatitis C virus (HCV) RNA clearance rates

	HCV RNA clearance rates by PCR					
	Intention to treat analysis (n = 171)			Response among those who completed 24 weeks of therapy (n = 136)		
	Amantadine	Placebo	p Value	Amantadine	Placebo	p Value
24 wks during treatment	40.0% (n = 34)	45.3% (n = 39)	0.3	49.3% (n = 34)	56.5% (n = 39)	0.2
ETR at 48 wks	32.9% (n = 28)	38.4% (n = 33)	0.3	40.6% (n = 28)	47.8% (n = 33)	0.2
SVR at 24 wks post-treatment	24.7% (n = 21)	27.9% (n = 24)	0.4	30.4% (n = 21)	34.8% (n = 24)	0.4

PCR, polymerase chain reaction; SVR, sustained viral response; ETR, end of treatment response.

Table 4 Predictors of response by risk factor (intention to treat analysis)

	SVR at 24 wks post-treatment		
	Placebo (n)	p Value	Amantadine (n)
Overall	27.9% (24/86)	0.4	24.7% (21/85)
Cirrhotic	13.6% (3/22)	0.5	18.8% (3/16)
Non-cirrhotic	32.8% (21/64)	0.3	26.1% (18/69)
Viral load			
<1 000 000 copies/ml	30.6% (15/49)	0.4	35.3% (18/51)
>1 000 000 copies/ml	24.3% (9/37)	0.08	8.8% (3/34)
Race			
Caucasian	31.9% (23/72)	0.5	29.9% (20/67)
African-American	0% (0/12)	N/A	0% (0/17)
Others	50% (1/2)	0.7	100% (1/1)
Genotype			
1a/b	18.3% (13/71)	0.5	18.9% (14/74)
Other (2, 3)	69.2% (9/13)	0.6	66.7% (6/9)
Sex			
Male	28.3% (15/53)	0.5	26.7% (12/45)
Female	27.3% (9/33)	0.4	22.5% (9/40)
Age			
<50 y	32.3% (21/65)	0.4	28.6% (20/70)
>50 y	14.3% (3/21)	0.1	6.7% (1/15)
Weight			
<75 kg	27.3% (6/22)	0.6	32.1% (9/28)
>75 kg	28.1% (18/64)	0.2	21.1% (12/57)

SVR, sustained viral response.

non-responders cleared HCV RNA when retreated with a combination of interferon and ribavirin. Based on the above study, we had postulated that the SVR would be even higher in treatment naïve HCV patients. However, our results showed that amantadine does not improve the response rate when added to a standard regimen of interferon and ribavirin.

Amantadine is a tricyclic amine with antiviral activity against toga, myxo, arena, flavi, and corona families of viruses.[7] In vitro assays suggest that amantadine does not inhibit the HCV protease, helicase, or ATPase enzymes. However, in clinically relevant concentrations, amantadine does cause internal ribosomal entry site specific inhibition.[8] Viral kinetic studies have shown a significant decline in viral load on day 3 of amantadine therapy followed by a rebound on day 7 to baseline titres.[9] In one study, Smith reported SVR in four of 22 (18%) patients who had failed previous interferon monotherapy when retreated with amantadine alone for six months.[4] However, subsequent studies failed to reproduce these results with amantadine monotherapy.[5 10 11] Since then, there have been many small trials using amantadine in combination with either interferon alfa or interferon alfa and ribavirin. These studies in treatment naïve patients or non-responders to interferon alfa have produced conflicting results. In treatment naïve patients, Mangia *et al* reported favourable results with a combination of interferon alfa and amantadine (SVR rates of 29.3% *v* 16.8%) compared with interferon monotherapy.[12] In contrast, several other randomised studies failed to show a better SVR with a combination of interferon and amantadine over interferon monotherapy.[13–16] Studies that had compared interferon alfa and amantadine with interferon and ribavirin have shown consistently better SVR with the latter.[17 18] The focus of treatment has since shifted towards the use of triple therapy using amantadine in combination with interferon alfa and ribavirin. A study in non-responders of interferon monotherapy looked very promising with a 48% sustained response rate in the triple therapy group compared with a 5% response rate in the group that received interferon and ribavirin.[6] Since then two other pilot studies have shown disappointing results with triple therapy in non-responders or relapsers of combination treatment (interferon alfa and ribavirin).[19 20]

Amantadine is an inexpensive well tolerated drug but our study showed that it is ineffective when used in combination with standard interferon alfa and ribavirin. We believe that amantadine should be abandoned as a potential agent for the treatment of HCV based on our study and other previous studies. In a recent randomised controlled trial, Berg *et al* also showed no advantage of triple therapy despite using induction therapy (9 million units daily for first two weeks followed by 6 million units daily for an additional six weeks) and a higher dose of interferon (6 million units daily from 8–24 weeks).[21] Despite similar results, they claimed a questionable benefit with amantadine based on their multivariate analysis. A critical examination of our trial and that reported by Berg *et al* shows that amantadine therapy does not provide any additional benefit over standard interferon and ribavirin combination treatment for treatment naïve chronic HCV patients.[21] One may argue that amantadine has not been tested in combination with pegylated interferons. When we initiated this study, pegylated interferon was not available for clinical use and hence we used standard interferon. However, increasing clinical and experimental evidence indicates that amantadine does not have anti-HCV effects either as monotherapy or in combination with interferon and ribavirin. In some studies, amantadine has shown an improvement in biochemical parameters despite inconsistent and minimal antiviral effects. However, in our study, we failed to demonstrate any significant differences in virological or biochemical improvement between the amantadine and placebo groups.

In our study, we also noted higher withdrawal rates than the registration trials.[2 3] It is likely that the higher withdrawal rate was related to the complexity of the three drug regimen. In addition, our patients incurred out of pocket expenses as part of treatment and travel, which may in part account for our larger dropout rate for ''personal reasons''. However, the withdrawal rates were similar in both groups, and amantadine did not produce any significant additional side effects. The SVR that we have reported in this study is lower than those reported by previous registration trials (38–43%). This could be due to many factors, including a relatively higher proportion of patients with genotype 1 (85% *v* 70%) and African-Americans (17% *v* 3%) in our study compared with

previous trials.[22] Higher withdrawal rates may also have contributed to a relatively lower SVR, but even in those who completed 24 weeks of treatment our SVR was relatively lower than that of the registration trials. In addition, it is important to note that it has been difficult to replicate the results of HCV registration trials in clinical practice.

In this study there was no response among African-Americans although most (except for two patients) completed at least 24 weeks of treatment. Many previous studies had also reported lower response rates in African-Americans.[23–25] Unlike other large trials, including the most recent report on triple therapy, we had a higher proportion of African-Americans in our trial (17% *v* 3% in other studies)[21 23] All African-Americans had genotype 1 and 21% had cirrhosis or septate fibrosis. Although this may partly explain our findings, we do not have any explanation for the complete absence of SVR in African-Americans. It is important to note that African-American race was not an independent predictor of poor response in our study and this may be due to the small sample size. Lower response rates in African-American patients merit continued research and innovative drug trials.

In this double blind, randomised, controlled study, we have clearly shown that triple therapy using a combination of interferon alfa, ribavirin, and amantadine has no role in the management of treatment naïve patients with chronic HCV. We assumed that our study had the power to show a moderate difference if it existed but we did not find even a trend favouring triple therapy. We hope that our observations will dampen the enthusiasm for triple therapy and the interest in amantadine generated by some previous studies.

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