Journal of Viral Hepatitis, 2005, **12,** 445–455 doi:10.1111/j.1365-2893.2005.00622.x

REVIEW

Amantadine in treatment of chronic hepatitis C virus infection?

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Received April 2004; accepted for publication June 2004

SUMMARY. Treatment of chronic hepatitis C (CHC) continues to be an important and growing challenge. As the response rate to FDA-approved treatment improved over the past decade, we are facing increasing number of difficult-to-treat patients such as those who have failed prior anti-viral therapy. The role of amantadine in the treatment of CHC remains unclear. Studies thus far have produced conflicting results, and type II error could not be excluded. This review summarized results published in the literature from 1997 to 2003, and reviewed the existing questions and controversies regarding the use of amantadine. Current literature suggests that amantadine is ineffective as monotherapy. Amantadine increased the sustained virologic response of certain treatment naïve patients when used in combination with interferon, and may be effective as an adjunct to interferon-based combination therapy in some patients who have failed or relapsed on prior therapy. Factors such as small sample size, patient characteristics, and differences in treatment protocols including amantadine preparation and duration of therapy might explain the conflicting observations of various studies. Further investigations are needed to define optimal dosing and formulation of amantadine, and its appropriate role in management of CHC infection.

Keywords: amantadine, antiviral, chronic hepatitis, hepatitis C virus, review, treatment.

INTRODUCTION

Hepatitis C virus (HCV) is a major cause of chronic liver disease and hepatocellular carcinoma, and is the leading indication for liver transplantation. In the US alone, approximately 4 million people are infected, of whom 10 000 die each year as a consequence of HCV-related liver disease [1]. The standard of care for treatment of chronic hepatitis C (CHC) infection has evolved in a stepwise progression over the past 10 years. Interferon-alpha 3 million units (MU), given through subcutaneous injection three times weekly, resulted in sustained virologic response (SVR) in 10–20% of patients, whereas combination interferon-alpha/ribavirin achieved overall response rates approaching 30–40% [2–4]. Two forms of a newer, longer-acting pegylated interferon-alpha have provided an incremental advantage over standard interferon, and in combination with ribavirin can achieve SVRs between 40 and 80% depending on the HCV genotype [5,6]. Despite these advances, a significant number of patients fail to respond to the current standard antiviral regimen, especially in patients with unfavourable features such as genotype 1 infection and high viral load, which were the majority of patients in the US with CHC. In the coming years, we will be facing an increasing proportion of such patients and/or treatment failures. While antiviral agents specifically targeting key enzymes of the HCV viral cycle remain under investigation, alternative agents such amantadine may represent important adjunctive treatment options, especially for the growing patient population that have failed prior anti-viral therapy.

The first report demonstrating the efficacy of amantadine in treatment of CHC was published in 1997, when Smith and colleagues described a group of 22 patients who failed interferon-alpha monotherapy and 18% subsequently cleared virus when re-treated with amantadine 100 mg twice daily for 6 months [7]. Since this initial report, clinical studies have provided conflicting results on amantadine when used alone, in combination with interferon-alpha, or with interferon-alpha and ribavirin. Most studies suggest that amantadine has little impact on SVR when used alone, and produces at best a modest improvement in SVR when combined with interferon-alpha or interferon-alpha plus ribavirin. In this review we investigate the potential role of amanatidine, in the treatment of CHC based on results published up to end of 2003.

Abbreviations: CHC, chronic hepatitis C; HCV, Hepatitis C virus; HIV, human immunodeficiency virus; SVR, sustained virologic response.

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MECHANISM OF ACTION

Amantadine (1-aminoadamantanamine) is a water soluble tricyclic amine that has been used clinically to prevent influenza A viral infection, and has known antiviral effects against other families of RNA viruses such as togavirus, myxovirus, coronavirus and flavivirus, of which hepatitis C is a member [8]. This effect is mediated by inhibition of an early step in influenza A viral replication through interaction with the M2 viral membrane matrix protein, which functions as an ion channel, and is required for internalization of the virus by endocytosis [9].

The mechanism of amantadine as an antiviral agent for hepatitis C remains uncertain. Early studies showed that amantadine reduced HCV RNA content in cultured peripheral blood mononuclear cells from infected patients [10], and inhibit the HCV p7 protein, a key component of ion channel formation [11]. Despite this observation, *in vitro* biochemical assays demonstrated that amantadine failed to inhibit key regulatory enzymes and steps of viral replication, including HCV protease, helicase, ATPase, RNA-dependent RNA polymerase, and HCV internal ribosomal entry site translation [12]. Any effect of amantadine on HCV likely involves an immune-mediated process as amantadine may induce the production of interleukins [13]. Therefore, amantadine may be best used as an adjunct to interferon and ribavirin to produce an additive or synergistic effect [14,15]. Additional research is needed to determine if amantadine interacts with other host or viral factors, or modulates the host immune system as a basis for its antiviral effects.

METHODS

A literature search was performed by using the MEDLINE database to identify publications between 1966 and December 2003. A MEDLINE keyword search was conducted using the MeSH terms: hepatitis C virus, chronic viral hepatitis and amantadine. The search was then limited to English-language studies in adult humans. The reference lists of retrieved publications were then examined to identify additional citations. All article abstracts were reviewed to determine relevance to management of CHC infection, after which full text articles were obtained for further analysis. All clinical studies using amantadine for treatment of CHC were published since 1997. Clinical trials published between 1997 and 2003 with the use of amantadine for CHC formed the basis of this review.

RESULTS

Use of amantadine in treatment-naïve patients with chronic hepatitis C infection

Amantadine as monotherapy or in combination with interferon

Thirteen clinical trials have studied the use of amantadine as first-line treatment for CHC infection. Eighty-nine patients in five observational trials were treated with amantadine 200 mg daily alone for 3–12 months; although a biochemical response was seen in some patients, none achieved a SVR [16–20]. Six randomized trials were performed to evaluate interferon-alpha and amantadine combination therapy as first-line therapy. Caronia *et al.* [21] demonstrated in their study of 143 patients that the addition of amantadine to fixed-dose IFN-alpha 4.5 MU three times weekly for 12 months had no additional improvement in SVR (18% without amantadine *vs* 15% with amantadine). In contrast, Mangia *et al.* [22] found in their open-label, prospective study of 200 patients that the addition of amantadine to fixed-dose IFN-alpha 6 MU three times weekly for 12 months resulted in a statistically significant increase of SVR from 16.8 to 29.3% ($P = 0.036$). A recent meta-analysis of individual patient data for these six trials showed that combination interferon-alpha and amantadine appears to be effective, resulting in a pooled SVR of 23.1% ($P = 0.03$) [23]. In this meta-analysis, 481 treatment naïve patients were treated with interferon and amantadine and 491 received interferon monotherapy. Baseline characteristics in favour of the interferon-amantadine combination therapy over monotherapy included genotype 1 or 4 ($P = 0.025$), high viral load ($P = 0.035$), age <40 ($P = 0.023$), low ALT level ($P = 0.007$) and absent to moderate fibrosis ($P = 0.007$). Logistic regression analysis showed interferon-amantadine combination therapy ($P = 0.04$) in addition to age, genotype and baseline viraemia were independent predictors of response. In the most difficult to treat group (genotype 1 or 4, high viral load), the response rate using combination therapy was 10.5% *vs* 4.9% in the monotherapy group ($P = 0.08$), but response was similar among those with favourable genotype (2 or 3) and low viral load. The most important conclusion, perhaps, was the fact that amantadine did improve the response rate of interferon in treatment naïve CHC patients in this meta-analysis. However, this was still below the SVR with current interferon and ribavirin combination therapy.

Amantadine as induction therapy

Four randomized controlled trials evaluated the role of interferon in combination with amantadine induction therapy. Only one of the four trials showed the addition of amantadine to interferon during induction improved the SVR. Nakamura *et al.* [24] studied 31 patients in whom the addition of amantadine 100 mg daily did not increase the SVR in patients receiving interferon-beta 6 MU daily for 6 weeks, followed by 6 MU three times weekly for 26 weeks (0% *vs* 9%) ($P =$ ns). Zeuzem *et al.* [25] studied 119 patients in whom the addition of amantadine 200 mg daily did not increase SVR in patients receiving interferon-alpha 6 MU three times weekly for 24 weeks, followed by 3 MU three times weekly for 24 weeks (10% *vs* 22%) ($P =$ ns). Tabone *et al.* [26] studied 180 patients in whom the addition of amantadine 200 mg daily did not demonstrate a statistically significant increase in SVR in patients receiving interferon-

alpha 6 MU on alternate days for 6 months, followed by 3 MU on alternate days for 6 months (24% *vs* 17%) (P = ns). Helbing *et al.* performed a double-blind study of 246 patients who received interferon-alpha 6 MU three times weekly for 20 weeks then 3 MU three times weekly for the remainder of a 12 month course, with or without amantadine 200 mg daily. The addition of amantadine resulted in a statistically insignificant increase in SVR from 17% to 24% ($P = 0.175$) [27]. These trials suggest that amantadine induction therapy is ineffective.

Amantadine in combination with interferon and ribavirin

Two randomized trials evaluated the role of triple therapy with interferon-alpha, ribavirin, and amantadine in management of treatment-naïve patients. Ullerich *et al.* studied 30 patients in an open-label, prospective study in which amantadine 200 mg daily and ribavirin 1000–1200 mg daily was given to all patients. Patients were then randomized to receive either low induction interferon-alpha 6 MU three times weekly for 12 weeks then 3 MU three times weekly for 36 weeks, or high induction interferon-alpha 9 MU three times weekly for 4 weeks, followed by 6 MU three times weekly for 4 weeks, 3 MU three times weekly for 4 weeks and 1.5 MU three times weekly for the final 36 weeks. The high induction interferon regimen resulted in a large but statistically not significant increase in SVR (67% *vs* 40%) (P = ns) [28]. Berg *et al.* performed a large randomized, double-blind trial of 400 patients, all of whom were given induction interferon-alpha 9 MU daily for 2 weeks, followed by 6 MU daily for 6 weeks and 6 MU three times weekly for 40 weeks, in addition to weight-based ribavirin 1000–1200 mg daily. Patients were then randomized to receive placebo or amantadine 100 mg twice daily. Patients receiving amantadine did not have a statistically significant increase in SVR (52% *vs* 43.5%, P = ns) [29]. The SVR was higher in the amantadine group (39% *vs* 31%) in patients with genotype 1. In addition, multiple logistic regression analysis showed amantadine treatment was an independent factor associated with SVR. The finding of this study and the meta-analysis of the amantadine–interferon combination therapy [23] suggested there might be a beneficial effect of amantadine in genotype 1 patients.

Summary

Current literature does not support the use of amantadine monotherapy as a first line treatment for CHC. Amantadine may have a limited role in combination with interferon-alpha or interferon-alpha plus ribavirin for management of treatment-naïve patients, particularly in patients with genotype 1 and high viral load.

Use of amantadine for interferon nonresponders in hepatitis C infection

Eleven trials have evaluated the use of amantadine in treating patients with CHC infection who have previously failed interferon monotherapy. Three small observational studies involving a total of 44 patients demonstrated that monotherapy with amantadine 200 mg daily failed to result in SVR in any patient (0%) [30–32]. Two small prospective studies evaluated the role of amantadine in combination with interferon-alpha in re-treatment of interferon non-responders.

Interferon and amantadine

Teuber *et al.* performed a randomized, double-blind trial of 55 patients in whom the addition of amantadine 200 mg to interferon-alpha 6 MU three times weekly for 24 weeks then 3 MU three times weekly for 24 weeks did not result in SVR (0%) (P = ns) [33]. In a nonrandomized, prospective, open-label trial in which patients were given interferon-alpha 4.5 MU daily for 1 month then 6 MU three times weekly for 5 months, with or without amantadine 200 mg daily, the addition of amantadine did not result in a single case of SVR (0%) (P = ns) [34]. The first randomized, prospective, open-label trial by Khalili *et al.* [35], who demonstrated in a cohort of 15 patients treated with amantadine 200 mg daily and 3 MU interferon-alpha TIW was inferior to interferon and ribavirin 1000 mg daily (14 patients) for six months with SVR of 0% *vs* 15%, respectively (P = ns). In a randomized, double-blind trial by Younossi and colleagues, 118 patients were re-treated for 24 weeks with either of two regimens: (i) interferon-alpha 3 MU three times weekly and ribavirin 800 mg daily, or (ii) interferon-alpha 3 MU three times weekly and amantadine 200 mg daily. None of the patients receiving amantadine achieved a SVR; only 3.9% of patients receiving combination interferon-ribavirin cleared the virus ($P = 0.16$) [36]. These studies demonstrated that the combination of interferon and amantadine is ineffective.

Amantadine in combination with interferon and ribavirin

The initial study by Berg *et al.* [32] described 14 consecutive interferon nonresponders who were given induction therapy with interferon-alpha 9 MU daily for 1 week, followed by 9 MU on alternate days for 5 weeks, 6 MU three times weekly for 6 weeks, and 3 MU three times weekly for 36 weeks, as well as ribavirin 1000–1200 mg daily and amantadine 200 mg daily. None of these patients achieved SVR. In contrast, three other studies suggested that amantadine triple therapy might be beneficial. In a pilot nonrandomized, prospective, open-label trial of 20 patients, the addition of amantadine to interferon 5 MU on alternate days and ribavirin 800–100 mg daily resulted in a large, statistically significant increase in SVR (30% *vs* 0%) ($P < 0.0001$) [37]. A follow-up randomized, open-label trial of 60 patients by the same research group also demonstrated that the addition of amantadine resulted in a statistically significant increase in efficacy (48% *vs* 5%) ($P < 0.001$) [38]. Adinolfi *et al.* performed the largest randomized trial addressing this question, studying 114 patients who were randomized to three groups: (i) fixed dose interferon-alpha

3 MU three times weekly and oral ribavirin 1000 mg daily, (ii) induction interferon-alpha 3 MU daily (4 weeks) then 3 MU three times weekly plus oral ribavirin 1000 mg daily, or (iii) induction interferon-alpha and ribavirin plus oral amantadine 200 mg daily, resulting in SVR of 2, 4 and 25% respectively ($P = 0.002$) [39]. This study demonstrated that the combination of induction interferon-alpha, ribavirin and amantadine resulted in statistically significant increases in SVR.

Reasons for conflicting results

These conflicting findings are likely the result of uniformly small sample sizes and important differences in the treatment regimens. For example, in the meta-analysis of treatment-naïve patients, a sample size of 500 in each treatment arm was needed to detect the marginal increase in SVR with addition of amantadine [23]. These studies were inadequately powered to detect a small benefit from amantadine. The study by Younossi *et al.* [36] also has several shortcomings. Although the optimal duration of treatment with amantadine and interferon remains unknown, it is possible that the full antiviral effect of combination therapy was underestimated by the short-course of treatment (24 weeks), as other studies have demonstrated that a minimum of 48 weeks of interferon is necessary to achieve sustained viral clearance in patients with genotype 1. Amantadine's antiviral effect may be mediated, in part, by unique synergistic interactions with interferon and ribavirin, and therefore may have been underestimated in trials not evaluating triple therapy. Additionally, its effect may have been underpowered by the low ribavirin dose used in this study (800 mg daily). Previous studies have clearly demonstrated that ribavirin exerts antiviral effects in a dose-dependent manner, and therefore comparison with studies using higher doses cannot be made. In contrast, both the Brillanti [38] and Adinolfi [39] trials evaluated amantadine as a component of triple therapy for a full 48-week course, and demonstrated impressive increases in SVR compared with the standard combination interferon–ribavirin regimen. The trial by Adinolfi [39] was the best powered to address this question (114 patients), and additionally demonstrated that induction therapy with 4 weeks of daily interferon may have incremental benefit. Amantadine may have an important role as an adjunct to combination interferon–ribavirin therapy in interferon nonresponders, although further prospective, randomized trials are needed to further elucidate the optimal dosing and duration, and identify predictive factors for success.

Summary

Current literature strongly suggests that amantadine is not effective as monotherapy or in combination with interferon for re-treatment of interferon nonresponders. It may have a role as an adjunct to standard interferon-alpha and ribavirin therapy in treatment of interferon-nonresponders, although the current data is conflicting.

Use of amantadine in interferon/ribavirin nonresponders

Three small observational studies have evaluated the efficacy of amantadine in treating patients who have failed to respond to combination interferon/ribavirin or both interferon monotherapy and interferon/ribavirin re-treatment. DiMartino *et al.* treated 10 consecutive patients who failed either interferon or interferon/ribavirin with amantadine 100 mg daily for 12 months. Although this resulted in decreased ALT in all patients, none achieved SVR (P = ns) [40]. Thuluvath *et al.* studied 23 consecutive interferon/ribavirin nonresponders by re-treating all patients with triple combination therapy (interferon-alpha 3 MU three times weekly, ribavirin 1000–1200 mg daily, and amantadine 200 mg daily) for 6–12 months. This resulted in a 13% SVR, suggesting that re-treatment with combination therapy and amantadine may result in viral clearance in a small number of patients [41]. Younossi *et al.* treated 20 consecutive interferon monotherapy and combination interferon/ribavirin nonresponders with triple combination therapy (interferon-alpha 3 MU three times weekly, ribavirin 800 mg daily, and amantadine 200 mg daily) for 48 weeks, achieving SVR in two patients (10%) [42].

Summary

Amantadine may result in viral clearance in a small group of patients who have failed both interferon and combination interferon/ribavirin. The results of these trials are limited by small sample sizes, and therefore may be inadequate to support a definitive conclusion on the effects of amantadine in patients failing standard combination interferon/ribavirin.

Use of amantadine in relapsers to interferon and/or interferon/ribavirin

Four trials (three observational studies and one open-label randomized trial) have evaluated the role of amantadine in patients who responded but relapsed on prior therapy with interferon and/or interferon/ribavirin. Tabone *et al.* [43] treated 40 interferon relapsers with amantadine monotherapy (amantadine 200 mg daily for 2 months); none of these patients achieved SVR. Carlsson *et al.* treated both nonresponders and relapsers to interferon/ribavirin combination with triple therapy (interferon 3 MU three times weekly, ribavirin 1000 mg daily, and amantadine 200 mg daily for 24 weeks), finding that 0% and 10% achieved SVR, respectively. This suggested that amantadine has no effect on nonresponders, but may result in SVR in a small number of relapsers to combination therapy [44]. Weeginth *et al.* randomized 37 patients who responded but relapsed to previous interferon or interferon/ribavirin therapy to either of two triple therapy regimens. All patients received an initial 2 weeks of induction therapy with high-dose interferon-alpha 18 MU three times weekly, ribavirin, and amantadine, followed by 22 additional weeks of ribavirin

and amantadine, with or without additional interferon-alpha 3 MU three times weekly. None of the patients who received only 2 weeks of induction interferon achieved viral clearance; in contrast, a very high percentage (44%) of patients completing 24 weeks of triple therapy with induction and then standard interferon-alpha achieved SVR ($P < 0.001$) [45]. This study demonstrated that re-treatment with triple therapy may be highly effective in a small subset of relapsers to previous interferon or interferon/ribavirin therapy who have a non-I genotype and demonstrated a virologic response within 6 weeks of initiating therapy.

Zilly *et al*. performed an observational study of 46 patients who were nonresponders to either interferon or interferon/ribavirin, relapser on interferon, or experienced a breakthrough on interferon or interferon/ribavirin. All patients were treated with triple therapy (interferon-alpha 6 MU three times weekly, ribavirin 1000–1200 mg daily, amantadine 200 mg daily) for 6 months, and then interferon 6 MU three times weekly (monotherapy) for an additional 6 months. Although very few previous nonresponders achieved SVR with this regimen (6%), a significant number of patients who initially responded but relapsed on interferon, or experienced a breakthrough on interferon or interferon/ribavirin did achieve SVR (73, 71 and 66%, respectively) [46]. These results suggested that re-treatment with triple therapy may be highly effective in a select group of patients who have an initial response to interferon or interferon/ribavirin, but may have very little value in initial nonresponders.

Summary

The role of amantadine in treatment of relapsers to interferon or interferon/ribavirin remains unclear. The current literature remains inadequate to properly assess its role in this population. However, these trials suggest that amantadine monotherapy and double therapy (interferon/amantadine or ribavirin/amantadine) do not appear to be effective in clearing virus. More importantly, this data additionally highlights that amantadine triple therapy (interferon/ribavirin/amantadine) may achieve significantly higher rates of sustained viral clearance in relapsers than in initial nonresponders. Although all of these studies were grossly underpowered to demonstrate a statistically significant difference, current data shows that amantadine may be a very promising adjunct in this target population, and should be studied in larger, randomized trials.

Use of amantadine in special populations

Few studies have examined the role of amantadine in special patient populations and these are summarized below.

Elderly patients

The elderly remain an understudied population in the treatment of CHC infection [47]. Most drug trials explicitly exclude patients aged over 60, and therefore little data is available to guide standards of care in these patients [48]. This paucity of data is reflected in the original 1997 NIH Consensus Development Statement on Management of Hepatitis C, which did not support the routine use of interferon-based therapy in patients aged over 60 years 'because of incomplete data' [49]. Although no formal recommendation is made in the most recent Consensus Statement in 2002, it is clear that controversy remains over the safety and efficacy of interferon-based therapy in this population, and the balance between risks and benefits. Newer regimens using antiviral agents with a favourable side effect profile are needed to provide alternative options for patients in whom interferon or ribavirin may be contraindicated. Amantadine is typically well-tolerated, has few side effects (nausea, lightheadedness, decreased concentration, decreased appetite and anxiety), and rarely causes more serious reactions (agitation, hallucinations, seizures) [50]. Torre *et al*. treated 23 consecutive treatment-naïve elderly patients with CHC aged over 65 (mean age 70.1) with amantadine monotherapy [20]. Although treatment was found to be safe with few side effects, amantadine failed to achieve either a sustained biochemical or virologic response. In summary, amantadine appears to be safe, well-tolerated medication for the elderly, but is not effective for CHC.

HCV-HIV co-infection

Treatment of HCV patients co-infected with human immunodeficiency virus (HIV) continues to be an important challenge. As highly active antiretroviral therapy has resulted in markedly improved life spans in patients with HIV infection, liver disease has become an increasingly common cause of morbidity and mortality in this population. There are no therapies currently approved by the United States Food and Drug Administration for HIV-HCV co-infection, and the most recent NIH Consensus Development Conference Statement in 2002 recommended that treatment should be considered on a case-by case basis, particularly in those with stable HIV infection and well-compensated liver disease [51]. Several small trials have suggested that combination interferon-alpha/ribavirin is safe and well-tolerated in these patients, and may achieve rates of sustained viral clearance similar to those of HCV mono-infected patients [52–55]. Pegylated interferon in this population will likely be superior to standard combination interferon-alpha and ribavirin. Sax *et al*. performed a pilot study in which nine patients with HIV co-infection on antiretroviral therapy were treated with interferon-alpha with or without amantadine. Neither treatment regimen resulted in SVR, suggesting that the addition of amantadine to interferon has little effect in this patient population [19].

Recurrent hepatitis C postliver transplantation

Hepatitis C infection recurs in nearly all patients following liver transplantation for HCV-related cirrhosis, and may

Table 1 Summary of clinical trials of amantadine combination therapy in nonresponders

	Study description	No. of patients	Drug regimens used	% HCV-1 genotype	Viral load ($\times 10^6$ copies/mL)	Fibrosis/ cirrhosis	Type of nonresponder	Statistical tests used	Response rate at end of treatment	Percent sustained response at post-treatment follow up
Khalili *et al.* [35]	Randomized, open label	29	IFN-α + ribavirin *vs* IFN-α + amantadine	82.8%	2.85	Fibrosis: 48.3%	IFN-α monotherapy nonresponders	Two-tailed Student's *t* test, Fischer's exact test	36% in IFN-α + ribavirin group; 0% in IFN-α + amantadine group ($P = 0.017$)	15% in IFN-α + ribavirin group; 0% in IFN-α + amantadine group (P = NS)
Younossi *et al.* [36]	Randomized, double-blinded, controlled multi-centred	118	IFN-α + ribavirin *vs* IFN-α + amantadine	77.1%	70.9% >2.0	Cirrhosis: 17.1%	IFN-α monotherapy nonresponders	Wilcoxon rank sum, chi-square, or Fischer's exact test	19.8% in IFN-α + ribavirin group; 14.7% in IFN-α + amantadine group ($P = 0.60$)	3.9% in IFN-α + ribavirin group; 0% in IFN-α + amantadine group ($P = 0.16$)
Teuber *et al.* [33]	Randomized, placebo-controlled, double blinded	55	IFN-α + amantadine *vs* IFN-α + placebo	92.5%	7.6	Fibrosis Mild: 29% Mod: 40.5% Severe: 23.6%	IFN-α monotherapy nonresponders	One-tailed Fischer's exact test	4% in IFN-α + amantadine group; 14% in IFN-α + placebo group (P = not reported)	0% in IFN-α + amantadine group; 7% in IFN-α + placebo group (P = not reported)
Brillanti *et al.* [38]	Prospective, randomized, open-label, controlled	60	IFN-α + ribavirin *vs* IFN-α, ribavirin, + amantadine	56.7%	5.48	Cirrhosis: 25%	IFN-α monotherapy nonresponders	Two-tailed Wilcoxon signed-rank and Fischer's exact tests	10% in dual therapy group; 67% in triple therapy group ($P < 0.0001$)	5% in dual therapy group; 48% in triple therapy group ($P < 0.001$)
Adinolfi *et al.* [39]	Prospective, open-label, randomized trial	114	IFN-α + ribavirin vs. induction IFN-α + ribavirin vs. induction IFN-α, ribavirin, + amantadine	71%	3.0	Cirrhosis: 27.2%	IFN-α monotherapy nonresponders	Fischer's exact and chi-square tests	25% in dual therapy group; 29% in induction dual therapy group; 67% in induction triple therapy group ($P = 0.001$)	2% in dual therapy group; 4% in induction dual therapy group; 25% in induction triple therapy group ($P = 0.002$)
Younossi *et al.* [42]	Open-label, pilot study	20	IFN-α, ribavirin, +amantadine	85%	1.8	No reported	Failed to respond to IFN-α monotherapy and IFN-α + ribavirin dual therapy	Wilcoxon rank, Fischer's exact, and Kaplan–Meier	15% in triple therapy group	10% in triple therapy group

Table 1 Continued

	Study description	No. of patients	Drug regimens used	% HCV-1 genotype	Viral load ($\times 10^6$ copies/mL)	Fibrosis/ cirrhosis	Type of nonresponder	Statistical tests used	Response rate at end of treatment	Percent sustained response at post-treatment follow up
Zilly *et al.* [46]	Open-label, pilot study	46	IFN-α, ribavirin, +amantadine	84.8%	1.85	HAI stage score: 1.76	IFN-α monotherapy nonresponders *vs* IFN-α + ribavirin dual therapy nonresponders	Chi-square test	6.25% of previous dual nonresponders; 11.1% of previous monotherapy nonresponders	6.25% of previous dual nonresponders; 0% of previous monotherapy nonresponders
Berg *et al.* [32]	Open-label, pilot study	14	Induction IFN-α, ribavirin, +amantadine	92.9%	13.6	Mild: 28.6% Mod: 64.3% Cirrhosis: 7.1%	IFN-α monotherapy nonresponders	Not reported	14% in triple therapy group	0% in triple therapy group
Teuber *et al.* [63]	Randomized, open-label	225	Induction IFN-α + ribavirin *vs* Induction IFN-α, ribavirin, +amantadine	92.5%	67% had a high viral load	Mild: 52.6% Mod: 32.1% Severe: 7.9% Cirrhosis: 7.4%	IFN-α monotherapy non-responders or IFN-α + ribavirin or amantidine non-responders	Chi-square test	37% in triple therapy group; 29% in dual therapy group ($P = 0.187$)	25% in triple therapy group; 18% in dual therapy group ($P = 0.201$)
Afdhal *et al.* [64]	Prospective, randomized, controlled, open-label study	118	PEG-IFN-α + ribavirin *vs* PEG-IFN-α + amantadine *vs* PEG-IFN-α, ribavirin, +amantadine	90%	67% had a high viral load	No reported	IFN-α + ribavirin dual therapy nonresponders	Not reported	30% PEG-IFN-α + ribavirin group; 18% PEG-IFN-α + amantadine group; 38% PEG-IFN-α, ribavirin, + amantadine	Not reported
Lawitz *et al.* [65]	Randomized, controlled, open-label	436	PEG-IFN-α + ribavirin *vs* PEG-IFN-α, ribavirin, +amantadine	84%	Not reported	Metrovir fibrosis stage: 44%	IFN-α monotherpay nonresponders *vs* IFN-α + ribavirin dual therapy nonresponder	Not reported	27% in dual therapy-dual nonresponder group; 46% in triple therapy-dual nonresponder group; 43% in dual therapy-mono nonresponder group; 25% in mono nonresponder group	Not reported

contribute to accelerated rates of fibrosis in some patients [56]. Routine chemoprevention and treatment is not currently recommended in this setting in the absence of data [51]. Although the data is limited, small studies have demonstrated that combination interferon-alpha and ribavirin may be effective in some patients, but is poorly tolerated in most, requiring drug reduction or withdrawal [57–60]. Pilot data presented at the September 2003 American College of Gastroenterology conference suggests that pegylated interferon/ribavirin achieves high rates of sustained viral clearance in those patients who are able to complete 12 months of therapy, but treatment withdrawal occurs in nearly 50% of patients [62]. Clearly, newer regimens with better tolerated agents are needed. Andreone *et al.* studied nine consecutive patients with recurrent post-transplantation hepatitis C infection by administering triple therapy (interferon-alpha 3 MU three times weekly, ribavirin 600 mg daily, and amantadine 100 mg daily) for 12 months. Unfortunately, the treatment was very poorly tolerated, with two requiring discontinuation within the first 3 months; only one patient was able to complete 12 months of therapy. During treatment, triple therapy did significantly decrease ALT levels below baseline, but only the patient who completed treatment achieved SVR (11%). Histological improvement on liver biopsy was seen in two patients [61]. This suggests that triple therapy with amantadine in post-transplant patients may result in viral clearance, but few are able to tolerate therapy for 12 months.

Impact of amantadine on the quality of life

One study evaluated the impact of amantadine on health-related quality of life when used in interferon nonresponders. This analysis showed substantial improvement of depression scores, and in the Profile of Mood States scale in the subscales fatigue ($P < 0.05$) and vigour ($P < 0.05$) among patients receiving interferon-alpha and amantadine compared with those receiving interferon-alpha alone [33], most likely because amantadine reduced the side-effects of IFN. Previous studies have demonstrated that interferon-based regimens may significantly improve quality of life scores along all subscales of the SF-36 survey instrument after treatment, particularly in those patients who achieved SVR. Although the mechanisms of action remain unclear, amantadine may improve quality of life by ameliorating symptoms associated with CHC infection and/or side-effects of interferon therapy.

DISCUSSION

Our review of the published data suggested that amatadine may have a minor role in the treatment of CHC, although many issues remain unresolved. The optimal formulation and dosage of amantadine, for example, has been poorly studied. Although amantadine hydrochloride has been the primary drug form studied in research trials, several investigators have used amantadine sulphate in combination regimens. It is possible that the choice of formulation may affect treatment outcomes. In the meta-analysis of interferon–amantadine combination therapy in treatment naïve patients, there was a significant difference in the response rate among patients who received amantadine hydrochloride instead of amantadine sulphate ($P = 0.02$) (64). The typical dose used in these studies ranged between 100 and 200 mg daily, although it is unknown if higher doses would result in higher efficacy. Major drawbacks of existing data include small sample sizes, widely divergent selections of patients and treatment protocols. Several studies did not stratify patients according to genotypes, a major predictor of response to interferon-based therapy. This may explain some of the differences in results observed in different countries, as genotype distribution is largely regional in nature. In addition, several studies used nonstandard doses of interferon with or without induction, making comparison or pooling of data difficult. However, these studies demonstrate that amantadine is not effective as monotherapy, and poorly effective when used with interferon alone.

Amantadine may be useful as a safe, and well-tolerated adjunct to combination interferon/ribavirin therapy in the treatment of some patients who have failed interferon or interferon/ribavirin for CHC infection (Table 1). The major advantage of amantadine is its favourable safety and tolerability profile and low cost. Although it is a weak antiviral agent with indirect effects on viral replication, multiple observational studies and randomized trials suggest that combination regimens with amantadine may significantly increase rates of sustained viral clearance in nonresponders, responder/relapsers, and breakthrough responders to interferon and interferon/ribavirin. In the absence of available therapies which target the HCV viral replication cycle, amantadine may represent a suitable option in the properly selected patient. Larger, randomized trials are needed to further define the role of amantadine in management of hepatitis C infection, particularly in combination with newer pegylated interferon-based regimens, and in special understudied populations such as the elderly, and patients with HIV-coinfection or recurrent HCV following liver transplantation.

REFERENCES

1 Lim JK. Natural history of hepatitis C infection: a concise review. *Yale J Biol Med* 2001; 74: 229–237.
2 McHutchison JG, Gordon SC, Schiff ER *et al.* Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. *New Engl J Med* 1998; 339(21): 1485–1492.
3 Poynard T, Bedossa P, Chevallier M *et al.* A comparison of three interferon alfa-2b regimens for the long-term treatment of chronic non-A, non-B hepatitis. *New Engl J Med* 1995; 332(22): 1457–1463.

4 Poynard T, Marcellin P, Lee SS *et al.* Randomised trial of interferon α2b plus ribavirin for 48 weeks or for 24 weeks versus interferon 2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. *Lancet* 1998; 352(9138): 1426–1432.

5 Manns MP, McHutchison JG, Gordon SC *et al.* Peginterferon alfa-2b plus ribavirin compared with interferonalfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; 358(9286): 958–965.

6 Fried MW, Shiffman ML, Reddy KR *et al.* Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *New Engl J Med* 2002; 347(13): 975–982.

7 Smith JP. Treatment of chronic hepatitis C with amantadine. *Dig Dis Sci* 1997; 42(8): 1681–1687.

8 De Clerq E. Antiviral drugs: current state of the art. *J Clin Virol* 2001; 22: 73–89.

9 Nicholson KG, Wiselka MJ. Amantadine for influenza A. *BMJ* 1991; 102: 425–426.

10 Martin J, Navas S, Fernandez M *et al.* In vitro effect of amantadine and interferon alfa-2a on hepatitis C virus markers in cultured peripheral blood mononuclear cells from hepatitis C virus-infected patients. *Antiviral Res* 1999; 42: 49–70.

11 Griffin SD, Beales LP, Clarke DS *et al.* The p7 protein of hepatitis C virus forms an ion channel that is blocked by the antiviral drug amantadine. *FEBS Letters* 2003; 535(1–3): 34–38.

12 Jubin R, Murray G, Howe A *et al.* Amantadine and rimantadine have no direct inhibitory effects against hepatitis C viral protease, helicase, ATPase, polymerase, and internal ribosome entry site – mediated translation. *J Infect Dis* 2000; 181: 331–334.

13 Wandinger KT, Hagenah JM, Kiner H *et al.* Effects of amantadine treatment on in vitro production of interleukin-2 in de novo patients with idiopathic Parkinson's disease. *J Neuroimmunol* 1999; 98: 214–220.

14 D'Agostini C, Palamara AT, Pavelli C *et al.* Efficacy of combination therapy with amantadine, rhymosin alpha 1 and alpha/beta interferon in mice induced with influenza A virus. *Int J Immunopharmacol* 1996; 18: 95–102.

15 Hayden FG. Combination antiviral therapy for respiratory virus infections. *Antiviral Res* 1996; 29: 45–48.

16 Goff JS, Reveile RM, Johnson J. Treatment of chronic hepatitis C with amantadine. *Dig Dis Sci* 2000; 45(7): 1389–1391.

17 Senturk H, Mert A, Akdogan M *et al.* Amantadine monotherapy of chronic hepatitis C patients infected with genotype Ib. *Scand J Infect Dis* 2000; 32(5): 575–576.

18 Andant C, Lamond J, Devbach JC *et al.* Amantadine for chronic hepatitis C: pilot study in 14 patients. *Eur J Gastroenterol Hepatol* 2000; 12(12): 1319–1322.

19 Sax H, Friedl A, Renner E *et al.* Pilot study of interferon-alpha with and without amantadine for the treatment of hepatitis C in HIV co-infected individuals on antiretroviral therapy. *Infection* 2001; 29(5): 267–270.

20 Torre F, Campo N, Giusto R *et al.* Antiviral activity of amantadine in elderly patients with chronic hepatitis C. *Gerontology* 2001; 47(6): 330–333.

21 Caronia S, Bassendine MF, Barry R *et al.* Interferon plus amantadine versus interferon alone in the treatment of naïve patients with chronic hepatitis C: a UK menticentre study. *J Hepatol* 2001; 35(4): 512–516.

22 Mangia A, Minerva N, Annesse M *et al.* A randomized trial of amantadine and interferon versus interferon alone as initial treatment for chronic hepatitis C. *Hepatology* 2001; 33(4): 989–993.

23 Mangia A, Leandro G, Helbling B *et al.* Combination therapy with amantadine and interferon in naive patients with chronic hepatitis C: meta-analysis of individual patient data from six clinical trials. *J Hepatol* 2004; 40(3): 478–483.

24 Nakamura H, Uyama H, Enomoto H *et al.* The combination therapy of interferon and amantadine hydrochloride for patients with chronic hepatitis C. *Hepatogastroenterology* 2003; 50(49): 222–226.

25 Zeuzem S, Teuber G, Naumann U *et al.* Randomized, double-blind, placebo-controlled trial of interferon alfa-2a with and without amantadine as initial treatment for chronic hepatitis C. *Hepatology* 2000; 32(4 Pt 1): 835–841.

26 Tabone M, Laudi C, Delmastro B *et al.* Interferon and amantadine in combination as initial treatment for chronic hepatitis C patients. *Journal of Hepatology* 2001; 35(4): 517–521.

27 Helbling B, Stamenic I, Viani F *et al.* Interferon and amantadine in naïve chronic hepatitis C: a double-blind, randomized, placebo-controlled trial. *Hepatology* 2002; 35(2): 447–454.

28 Ullerich H, Avenhaus W, Poremba C *et al.* High-dose interferon alpha-2a with ribavirin and amantadine in naïve chronic hepatitis C patients – results of a randomized, prospective, pilot study. *Aliment Pharmacol Ther* 2002; 16(12): 2107–2114.

29 Berg T, Kronenberger B, Hinrichsen H *et al.* Triple therapy with amantadine in treatment-naïve patients with chronic hepatitis C: a placebo-controlled trial. *Hepatology* 2003; 37(6): 1359–1367.

30 Craxi A, Lo Lacono O. Amantadine for chronic hepatitis C: a magic bullet or yet another dead duck? *J Hepatol* 2001; 35: 527–530.

31 Parolin MB, Lacerda MA, Lopes RW. Amantadine-HCl in the treatment of chronic hepatitis C in non-responders to alpha-interferon. *Arquivos de Gastroenterologia* 1999; 36(2): 63–67.

32 Berg T, Naumann U, Wiedenmann B *et al.* Pilot study of interferon-alpha high-dose induction therapy in combination with ribavirin plus amantadine for nonresponder patients with chronic hepatitis C. *Zeitschrift fur Gastroenterologie* 2001; 39(2): 145–151.

33 Teuber G, Berg T, Naumann U *et al.* Randomized, placebo-controlled, double-blind trial with interferon-alpha with and without amantadine sulphate in primary interferon-alpha nonresponders with chronic hepatitis C. *J Viral Hepat* 2001; 8(4): 276–283.

34 Gaeta GB, Stornaiuolo G, Stanzione M *et al.* Interferon-alpha plus amantadine in chronic hepatitis C resistant to interferon alone: a pilot randomized study. *J Viral Hepat* 2001; 8(4): 284–286.

35 Khalili M, Denham C, Perrillo R. Interferon and ribavirin versus interferon and amantadine in interferon nonresponders with chronic hepatitis C. *Am J Gastroenterol* 2000; 95(5): 1284–1289.
36 Younossi ZM, Mullen KD, Zakko W *et al.* A randomized, double-blind controlled trial of interferon alpha-2b and ribavirin vs. interferon alpha-2b and amantadine for treatment of chronic hepatitis C non-responders to interferon monotherapy. *J Hepatol* 2001; 34(1): 128–133.
37 Brillanti S, Foli M, DiTomaso M *et al.* Pilot study of triple antiviral therapy for chronic hepatitis C in interferon alpha non-responders. *Ital J Gastroenterol Hepatol* 1999; 31(2): 130–134.
38 Brillanti S, Levantesi F, Masi L *et al.* Triple antiviral therapy as a new option for patients with interferon nonresponsive chronic hepatitis C. *Hepatology* 2000; 32(3): 630–634.
39 Adinolfi LA, Utili R, Tonziello A *et al.* Effects of alpha interferon induction plus ribavirin with or without amantadine in the treatment of interferon non-responsive chronic hepatitis C: a randomised trial. *Gut* 2003; 52(5): 701–705.
40 DiMartino V, Boudjema H, Delacour T *et al.* Treatment of chronic hepatitis C with amantadine hydrochloride in patient who had not responded to previous treatment with interferon-alpha and/or ribavirin. *Clin Infect Dis* 2001; 32(5): 830–831.
41 Thuluvath PJ, Pande H, Maygers J. Combination therapy with interferon-alpha(2b), ribavirin, and amantadine in chronic hepatitis C nonresponders to interferon and ribavirin. *Dig Dis Sci* 2003; 48(3): 594–597.
42 Younossi ZM, Mullen KD, Hodnick S *et al.* Triple combination of interferon alpha-2b, ribavirin, and amantadine for treatment of chronic hepatitis C. *J Clin Gastroenterol* 2003; 36(5): 427–430.
43 Tabone M, Ercole E, Zaffino C *et al.* Amantadine hydrochloride decreases serum ALT activity without effects on serum HCV-RNA in chronic hepatitis C patients. *Ital J Gastroenterol Hepatol* 1998; 30(6): 611–613.
44 Carlsson T, Lindahl K, Schvarez R *et al.* HCV RNA levels during therapy with amantadine in addition to interferon and ribavirin in chronic hepatitis C patients with previous nonresponse or response/relapse to interferon and ribavirin. *J Viral Hepat* 2000; 7(6): 409–413.
45 Weeginth CJ, Sentjens RE, Beld MG *et al.* Chronic hepatitis C patients with a post-treatment virological relapse re-treated with an induction dose of 18 MU interferon-alpha with ribavirin and amantadine: a two-arm randomized pilot study. *J Viral Hepat* 2003; 10(3): 174–182.
46 Zilly M, Lingenhauber C, Desch S *et al.* Triple antiviral re-therapy for chronic hepatitis C with interferon-alpha, ribavirin and amantadine in nonresponders to interferon-alpha and ribavirin. *Euro J Med Res* 2002; 7(4): 149–154.
47 Eyigun CP, Van Thiel DH, De Maria N. Use of interferon for the treatment of chronic hepatitis C in the elderly. *Hepatogastroenterology* 1998; 45(20): 325–327.
48 Strader DB. Understudied populations with hepatitis C. *Hepatology* 2002; 36(5 Pt 2): S226–S236.
49 National Institutes of Health. NIH Consensus Development Conference Statement: Management of hepatitis C: 1997. *Hepatology* 1997; 26(Suppl. 1): 2S–10S.
50 Centers for Disease Control and Prevention. Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2003; 52: RR08.
51 National Institutes of Health. NIH Consensus Development Conference Statement: Management of hepatitis C: 2002. *Hepatology* 2002; 36(5 Pt 2): S10–S21.
52 Perez-Olmeda M, Nunez M, Romero M *et al.* Pegylated IFN-a2b plus ribavirin as therapy for chronic hepatitis C in HIV-infected patients. *AIDS* 2003; 17(7): 1023–1028.
53 Landau A, Batisse D, Piketty C *et al.* Long-term efficacy of combination therapy with interferon-a2b and ribavirin for severe chronic hepatitis C in HIV-infected patients. *AIDS* 2001; 15(16): 2149–2155.
54 Neau D, Trimoulet P, Winnock M *et al.* Comparison of 2 regimens that include inferferon-a2a plus ribavirin for treatment of chronic hepatitis C in human immunodeficiecy virus-coinfected patients. *Clin Infect Dis* 2003; 36: 1564–1571.
55 Nasti G, di Gennaro G, Tavio M *et al.* Chronic hepatitis C in HIV infection: feasibility and sustained efficacy of therapy with interferon alfa-2b and ribavirin. *AIDS* 2001; 15: 1783–1787.
56 Gane EJ, Portmann BC, Naoumov NV *et al.* Long-term outcome of hepatitis C infection after liver transplantation. *New Engl J Med* 1996; 334(13): 815–821.
57 Firpi RJ, Abdelmalek MF, Soldevila-Pico C *et al.* Combination of interferon alfa-2b and ribavirin in liver transplant recipients with histological recurrent hepatitis C. *Liver Transplant* 2002; 8(11): 1000–1006.
58 Kornberg A, Hommann M, Tannapfel A *et al.* Combination therapy/prophylaxis with interferon and ribavirin for recurrent hepatitis C after liver transplantation: long-term effects on graft function and morphology. *Transpl Proceedings* 2002; 34(6): 2259–2260.
59 Samuel D, Bizollon T, Feray C *et al.* Interferon-alpha 2b plus ribavirin in patients with chronic hepatitis C after liver transplantation: a randomized study. *Gastroenterology* 2003; 124(3): 642–650.
60 Bizollon T, Ahmed SN, Radenne S *et al.* Long term histological improvement and clearance of intrahepatic hepatitis C virus RNA following sustained response to interferon-ribavirin combination therapy in liver transplanted patients with hepatitis C virus recurrence. *Gut* 2003; 52(2): 283–287.
61 Andreone P, Gramenzi A, Cursaro C *et al.* Interferon-alpha plus ribavirin and amantadine in patients with post-transplant hepatitis C: results of a pilot study. *Dig Liver Dis* 2001; 33(8): 693–697.
62 Mukherjee S, Gilroy RK, Rogge J *et al.* Pilot study of pegylated interferon alfa-2b and ribavirin for recurrent hepatitis C after liver transplantation. *Am J Gastroenterol* 2003; 98(9 Suppl. 1): S98.
63 Teuber G, Pascu M, Berg T *et al.* Randomized, controlled trial with IFN-alpha combined with ribavirin with and without amantadine sulphate in non-responders with chronic hepatitis C. *J Hepatol* 2003; 39(4): 606–613.
64 Afdhal N, Flamm S, Imperial JC *et al.* Analyses of 40 kDa peginterferon alfa-2a (Pegasys) in combination with

ribavirin, mycophenolate mofetil, amantadine, or amantadine plus ribavirin in patients that relapsed or did not respond to rebetron therapy: a report of 2 randomized, multicenter, efficacy, and safety studies. *Hepatology* 2001; 34(Suppl. 1): 243A.

65 Lawitz EJ, Cantu NS, Becker S *et al.* Pegylated interferon alfa-2b (PEG-IFN) and ribavirin for hepatitis C patients who were nonresponders to previous therapy. *Gastroenterology* 2002; 122(Suppl. 1): A626.