

*Original Article***Efficacy of triple therapy with interferon alpha-2b, ribavirin and amantadine
in the treatment of naïve patients with chronic hepatitis C***Hamid Kalantari*, Fatemeh Kazemi**, Mohammad Minakari******Abstract**

BACKGROUND: There is controversy about the efficacy of amantadine in the treatment of chronic hepatitis C. In this study, we evaluated the efficacy of triple therapy with interferon-alpha, ribavirin and amantadine in the treatment of naïve patients with chronic hepatitis C.

METHODS: Forty-eight patients with genotype 3 chronic hepatitis C received a three- drug regimen: interferon alpha-2b, 3 million units, three times a week, ribavirin 1000–1200 mg based on body weight, daily, in divided doses, and amantadine 100 mg twice daily, for six months. End of treatment response (ETR), sustained virologic response (SVR), biochemical response and histologic improvement were evaluated.

RESULTS: Forty-eight patients, 41 male and 7 female, with a mean age of 37.42 ± 16.2 years, were enrolled in the study. During treatment, four patients were excluded from the study due to severe thrombocytopenia, major depression and incompliance. End of treatment response was seen in 38 (86.36%) patients. Among these patients, 34 (77.27%) had sustained virologic response 6 months after the end of treatment and 40 (91%) had improvement in serum level of liver enzyme. Among patients who had response to treatment, liver biopsy was performed for 33 at the end of treatment and 31 patients had histologic improvement. Five non-responsive patients underwent liver biopsy at the end of treatment, and 2 of them had histologic improvement. No major side effects due to amantadine occurred in our patients.

CONCLUSIONS: Triple therapy with interferon-alpha-2b, ribavirin and amantadine is a safe and effective regimen in the treatment of chronic hepatitis C.

KEY WORDS: Interferon alpha, ribavirin, amantadine, chronic hepatitis C.

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Hepatitis C virus (HCV) affects 100-300 million people worldwide. Chronic hepatitis C (CHC) is one of the leading causes of chronic liver disease and related complications such as cirrhosis and hepatocellular carcinoma. 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 (IFN) and ribavirin^{1,2}. Improvements in therapy, using pegylated

interferons have resulted in higher response rates^{3,4}. Once HCV infection is confirmed, the genotype of the HCV virus can be determined. The genotype of the HCV virus could play an important role in planning for treatment, since it can predict the response rate to treatment and can guide the length of treatment²⁻⁵. However, patients infected with genotypes 2 or 3 demonstrated SVR rates of 80%, while genotype 1 patients had only 44% SVR rate with combination therapy regimens consisting of

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pegylated interferon and ribavirin. The SVR rates in genotype 4 patients vary between 55 and 69%^{3,4,6,7}. The current guidelines support the use of a pegylated interferon α plus ribavirin as the first line therapy⁸. For genotype 1, ribavirin should be dosed based on weight (1000 mg/day for weight <75 kg, 1200 mg for weight \geq 75 kg/day), and the duration of treatment should be anticipated for 48 weeks. On the other hand, genotypes 2 and 3 require only ribavirin 800 mg/day, and the recommended duration of treatment is 24 weeks. The variables reported to be associated with higher SVR include a genotype other than 1, viral load <2 million copies/ml, age <40, and lower body weight⁸. Amantadine is a relatively inexpensive antiviral agent with activity noted against the flaviviridae family to which the hepatitis C virus (HCV) belongs⁹. Although a few early reports claimed a good response to amantadine monotherapy⁹, subsequent studies have failed to confirm these observations¹⁰. The role of amantadine in the treatment of CHC remains unclear and is ineffective as monotherapy. Amantadine increased the sustained virologic response of special treatment of 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 therapy¹¹. Brillanti et al. reported that the combination treatment with IFN, ribavirin and amantadine did reach a relatively high-sustained viral eradication rate of 48%¹². There is controversy about the efficacy of amantadine in the treatment of chronic hepatitis C¹³. Pegylated interferons are more effective than conventional interferons, but are also more expensive. Many patients in Iran cannot afford to use pegylated interferons due to the high cost. So amantadine, combined with interferon- α and ribavirin, may be a safe and effective alternative, especially for this group of patients. In this study, we evaluated the efficacy of triple therapy with interferon α , ribavirin and amantadine in treatment of naïve patients with

chronic hepatitis C in the Isfahan province of Iran.

Methods

Forty-eight adult patients with genotype 3 chronic hepatitis C infection who had no previous treatment for CHC were eligible for the study. Genotyping of hepatitis C virus was determined by genotype specific primers¹⁴. Participants were patients who visited Imam Reza Hepatitis Research Clinic of Isfahan, Iran. Patients were enrolled if they had HCV- RNA detectable by polymerase chain reaction (PCR), elevated serum alanine aminotransferase (ALT) level, evidence of inflammation or fibrosis on liver biopsy within three months before treatment, according to Ishak's modified histologic activity index¹⁵ and no known contraindications to treatment with interferon, ribavirin, or amantadine. Exclusion criteria included major psychiatric disorder, decompensated cirrhosis, alcohol consumption, renal failure, autoimmune hepatitis, ischemic heart disease, cerebral vascular accident (CVA), thalassemia, hemophilia, severe anemia, severe thrombocytopenia, thyrotoxicosis, hypothyroidism, hepatitis B, HIV positivity and pregnancy. They received a three drug regimen of interferon alpha-2b (PDferon-B®, Pooyesh Darou, Iran), 3 million units three times a week, ribavirin (Copegus®, Roche pharmaceuticals) 1000 mg (for patients <75 kg) to 1200 mg (for patients \geq 75 kg) daily in divided doses (1,2) and amantadine (Ammorel®, Amin pharmaceuticals, Iran) 100 mg twice daily, for six months. A written informed consent was signed by all patients at the beginning of the study. All patients underwent a comprehensive history taking and physical examination prior to study. Subsequent history, adverse events and vital signs were recorded at 2, 4, and 8 weeks, every 8 weeks thereafter until the end of the treatment and 24 weeks after the end of treatment. Laboratory evaluations including cell blood count (CBC), creatinine and liver function tests were done at the same time.

Thyroid stimulating hormone (TSH) was checked at baseline and at three-month intervals thereafter. Reinforcing the need to practice strict birth control, beta-HCG was checked if doubt every 4 weeks. Additional tests were done as required.

When polymorphonuclear cells (PMNs) count appeared between 500-750 per mm³ or platelet count between 20,000-50,000 per mm³, the interferon-alpha dosage was cut in half and again was returned to normal value when those laboratory findings were repaired. However, at below 500 for PMN and 20,000 for platelet, we stopped the treatment and excluded the patients. In some situations when the hemoglobin (Hb) dropped below 10 g/dl, we decreased the ribavirin dose to 400mg per day, and if we didn't have improvement in Hb concentration, ribavirin was eliminated^{1,2}. Patients with life-threatening, adverse events or non-compliance were excluded from the study. Liver biopsies were performed within three months before the beginning of the study. Patients were also required to have a liver biopsy after completion of the treatment as part of the study design. Pre-treatment biopsy reports were classified based on the degree of fibrosis and the presence of cirrhosis according to the Modified Histologic Activity Index. Histologic improvement was considered as decreasing at least 2 scores of Ishak's histologic activity index and no worsening fibrosis at post-treatment biopsy. Detection of HCV-RNA by RT-PCR [Cobas amplicor monitor version 2 (Roche molecular systems, Branchburgh, NJ)] at the completion of treatment was used to evaluate the end of treatment response (ETR). Virologic response was defined as undetectable level of HCV-RNA with a lower limit of detection of 100 copies/ml. Sustained virologic response (SVR) was evaluated by detecting HCV-RNA 6 months after therapy cessation. Biochemical response was defined as decreasing ALT level to normal value (<40 IU/L) at the end of treatment.

Results

Forty-eight patients with mean age of 37.24 ± 16.2 years and a range of 19 – 61 years were enrolled in the study. There were 41 males and 7 females, making the male to female ratio of 5.86. Table 1 shows characteristics of patients at the base of study. Forty-four patients completed the study. Among 4 patients who were excluded from the study, one had severe thrombocytopenia (<20,000 per mm³), one experienced major depression and two refused to continue therapy. At the end of treatment, ETR was seen in 38 (86.36%) patients. Among these patients, 34 (77.27%) had sustained virologic response. Forty (91%) had normalization of serum ALT. Mean serum AST level decreased from 131.92 to 30.19 IU/L and mean ALT level from 134.37 to 34.11 IU/L. Among 38 patients who had response to treatment, 33 underwent liver biopsy at the end of treatment. Thirty one (93%) patients had histologic response. Of five non-responsive patients who underwent liver biopsy at the end of treatment, 2 had histologic response. On the other hand, among 38 biopsied patients, 33 (86.8%) had histologic response. Table 2 shows the comparison of mean AST, ALT and Ishak's score in all patients before and after treatment, while table 3 shows the characteristics of virologic responders and non-responders at the end of treatment. Table 4 demonstrates the frequency of biochemical response, histologic response, end of treatment response and sustained virologic response. The most frequent adverse events were flu-like symptoms, weight loss, hair loss and pruritus with incidence of 41 (93.2%), 39 (88.6%), 26 (59%) and 16 (36.4%), respectively. We found 12 mild anemic (hemoglobin 10-12 g/dl) and 7 mild thrombocytopenic (platelet 100000-150000) patients. No evidence of thyroid disorder appeared in our patients.

Table 1. Characteristics of patients at base line (n = 48).

Age (mean \pm SD)		37.24 \pm 16.2
Sex	Male	41 (93.2%)
	Female	7 (6.8%)

Table 2. Comparison of mean AST, ALT and Ishak's score in all patients, before and after treatment.

Variables	Before Treatment	After Treatment	P value
AST (mean \pm SD, IU/L)	131.92 \pm 22.38	30.19 \pm 9.32	<0.001
ALT (mean \pm SD, IU/L)	134.37 \pm 26.76	34.11 \pm 13.49	<0.001
Ishak's score (mean \pm SD)	12.28 \pm 3.46	8.41 \pm 2.27	0.02

Table3. Comparison of age, sex, mean AST and ALT and frequency of histologic response at the end of treatment in virologic responders and non-responders.

Variables	Responders	Non-responders
Age (mean \pm SD)*	32 \pm 19.24	34 \pm 16.45
Frequency of male sex (%)*	34 (89%)	7 (70%)
AST (mean \pm SD, IU/L)**	26 \pm 12.24	69 \pm 23.53
ALT (mean \pm SD, IU/L)**	31 \pm 13.74	88 \pm 19.32
Frequency of histologic response**	31 (93%)	2 (40%)

*P>0.05; **P<0.001

Table4. Frequency of biochemical, virologic and histologic response to treatment in chronic hepatitis C patients.

Variables	Number of patients (%)
Biochemical response	40 (91)
End of treatment response (ETR)	38 (86.36)
Sustained virologic response (SVR)	34 (77.27)
Histologic response	33 (86.8)*

*Frequency of histologic response was calculated in 38 biopsied patients.

Discussion

In patients with HCV infection, improvements in therapy have resulted in higher response rates ^{8,9}. The response rate has improved from 10% with interferon monotherapy to 40% with a combination of interferon and ribavirin ^{1,16}. In a study by Poynard T et al. in patients with genotype 2 and 3 chronic hepatitis C, SVR was 66% by a 24-week regimen of interferon-alpha and ribavirin ¹⁷. One of the limitations of our study was the lack of a control group with a standard pegylated interferon α plus ribavirin treatment. Then, we were not able to compare the regimens head to head. If we review the

major trials on pegylated interferon α plus ribavirin treatment, we will find three important studies as follows: A phase III randomized controlled trial included 1,530 interferon-naïve subjects who were randomly assigned to three groups, each of whom received treatment for 48 weeks: standard interferon alfa-2b plus ribavirin (1000 to 1200 mg/day), pegylated interferon alfa-2b (1.5 μ g/kg per week for four weeks followed by 0.5 μ g/kg per week) plus ribavirin (1000 to 1200 mg/day) and pegylated interferon alfa-2b (1.5 μ g/kg per week) plus ribavirin (800 mg/day). SVR was approximately 80 percent in those infected with geno-

types 2 and 3 for all treatment groups⁴. Another multicenter trial involving 1,121 interferon naïve patients compared the efficacy of pegylated interferon alfa-2a (180 µg SC each week) plus ribavirin (1000 to 1200 mg) with that of standard interferon alfa-2b plus ribavirin (Rebetron) and pegylated alfa-2a interferon monotherapy. Patients were treated for 48 weeks. A sustained virologic response was observed significantly more often in the peginterferon/ribavirin group compared to Rebetron or pegylated interferon monotherapy (56 versus 44 and 29 percent, respectively). The response rate was significantly higher for patients with genotype 2 or 3 compared to genotype 1 (76 versus 46 percent)³. The third trial included 1,311 interferon naïve patients who were randomly assigned to pegylated interferon alfa-2a (180 µg SC each week) plus ribavirin (either 800 or 1200 mg daily) for 24 or 48 weeks. For patients with genotype 2 or 3, the sustained virologic response rate with the lower dose of ribavirin (800 mg daily) was 80 percent after 24 weeks⁵. The results of these three studies showed that SVR, after a course of combination therapy with pegylated interferon and ribavirin, is about 75-80 percent, which is comparable to SVR rate (77.27 percent) in our study. We have shown that addition of amantadine to interferon alfa and ribavirin resulted in 83.36% ETR and 77.27% SVR in genotype 3 treatment naïve CHC patients. Amantadine is an antiviral agent that showed its efficacy on hepatitis C years ago¹⁸. Deltenre P, et al. analyzed the effect of amantadine on the end-of-treatment virological response and the sustained response using meta-analysis of 31 randomized controlled trials. Overall analysis revealed a significant effect of amantadine. Triple therapy was the best regimen for improving the sustained response. In subgroup analysis, amantadine did not have a significant effect upon naïve patients or relapsers. In non-responders, combination therapy with amantadine was associated with a significant effect on the sustained response¹⁹. Two

trials (one randomised) in IFN-non-responders demonstrated significant benefits from the addition of amantadine to the combination of IFN and ribavirin^{12,20}. In a study by Thuluvath PJ, et al. of 171 hepatitis C patients, response to triple therapy of interferon alfa, ribavirin and amantadine was similar to standard therapy of interferon alfa and ribavirin, and the authors suggested that amantadine has no role in the management of HCV¹⁸.

Some authors tried to answer this question of whether adding amantadine to peginterferon increased response to treatment of patients with HCV infection. Ferenci P, et al. found that adding amantadine to peginterferon alfa-2a (40KD)/ribavirin combination therapy does not augment virological response rates in genotype 1 patients²¹. A multi-center, open-label clinical trial showed that the addition of amantadine to pegylated interferon alfa-2b and ribavirin does not seem to increase the efficacy of this regimen. They found that in the treatment-naïve group, sustained virologic response (SVR) was 34.3%, versus 19.4% for the group who had previously failed to respond to a course of treatment ($P = 0.01$). Patients with genotypes 1 and 4 had lower response rates than those with genotypes 2 and 3 (SVR, 21 vs. 46%; $P = 0.001$)²². This study showed that the addition of amantadine to pegylated interferon alpha-2b and ribavirin does not seem to increase the efficacy of this regimen, while combination of peg-interferon and ribavirin has resulted in up to 80% SVR among patients with genotype 3 chronic hepatitis C^{3,4}. In our study, SVR was achieved 77.27% in genotype 3 HCV infection by triple therapy with amantadine, interferon-alpha and ribavirin. In our study, we also noted 91% biochemical response and 86.8% histologic improvement, which is nearly the same as ETR and SVR. In addition, there were 2 histologic responses in 5 patients who did not have SVR. This finding shows that treatment, even if is not associated with virologic response, can still have beneficial effects on liver inflammation in

some patients. Controlled trials of combination therapy have demonstrated that a virologic response is associated with improvement in liver histology, including fibrosis. The effect on fibrosis was emphasized in a combined report that included 1,509 patients from three randomized controlled trials who underwent liver biopsies before and after therapy¹⁶. The most striking finding was that treatment was associated with improvement in fibrosis, including reversal of early cirrhosis in 75 patients--49 percent of cirrhotic patients included in the studies²³. In this study, we did not observe any life-threatening side effects. 8.3 percent of patients dropped out of the study, and only half of these, excluded from the study due to side effects of interferon-alfa. Cessation of therapy due to side effects occurred in 4.1% of patients, which is compatible with a study in Europe that had an 8% cessation rate, while a US study had 11% of patients cease the therapy for severe side effects^{24,25}. There was no change of dose to half regarding to PMN, Hb and platelet counts. These findings indicate that amantadine is a safe agent and addition of this medication to therapeutic regimen does not increase the frequency of side effects. Also, oral amantadine was a safe agent in other studies, and it may provide a safe alternative treatment for those patients who are intolerant or unresponsive to interferon²⁶. Health-related quality-of-life analysis showed an improvement in fatigue and vigour scores in patients

receiving combined IFN-alpha and amantadine treatment compared with those treated with IFN-alpha alone^{27,28}. Smith JP, et al. conducted an open-labeled prospective study, starting with amantadine 200 mg daily, and increasing to 500 mg daily while monitoring for safety, toxicity and efficacy. They found that amantadine, given at a dose of 300 mg daily, is safe and significantly lowers ALT blood levels. The enzyme response rate did not significantly improve above 300 mg, but toxicity increased²⁹. Amantadine, if combined with interferon and ribavirin, augments sustained virologic response among naïve chronic hepatitis patients, and may be useful in patients who are unresponsive to other therapeutic regimens. 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. In summary, although combination therapy with peg-interferon and ribavirin is the treatment of choice for chronic hepatitis C, triple therapy with interferon alpha, ribavirin and amantadine, is a safe and effective regimen, and may be an alternative regimen in the treatment of particular patients.

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