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Amantadine Plus Interferon-α Versus Interferon-α Monotherapy for the Treatment of Chronic Hepatitis-C Infection in β-Thalassemia Major Patients: A Randomized Double Blinded Pilot Study in Shiraz, Iran

Mehran Karimi[1], Vahid Emad Marvasti[1], Mohammad Hadi Imanieh[2], Fatemeh Jahaniar Moqadam[1]

1. Thrombosis and Hemostasis Unit, Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.
2. Department of Pediatrics/Gastroenterohepatology Research Center, Nemazee Hospital, Shiraz University of Medical Sciences, Shiraz, Iran

Corresponding author: Mehran Karimi, Hematology Research Center, Department of Pediatrics, Nemazee Hospital, Shiraz University of Medical Sciences, Shiraz, Iran. (Phone: +98 (711) 647-0207, Fax: +98 (711) 647-0207, E-mail: karimim@sums.ac.ir)

Abstract

Background: Hepatitis-C infection is a major problem in chronically transfused patients. We compared Interferon-α (INF-α) monotherapy with combination of INF-α and amantadine in the treatment of β-thalassemia major patients who were chronically infected with HCV.

Materials and Methods: Forty six thalassemia major patients who were chronically infected with HCV were randomly divided into two groups. One group (22 patients) was treated by INF-α, 3 million units every other day plus amantadine 2 mg/kg/day (case group) and the other group (24 patients) was treated by INF-α and placebo tablet (control group). The duration of treatment was 12 months in both groups. PCR for HCV and liver function tests were performed 3 months after beginning of treatment and 6 months after treatment cessation in both groups and the results were compared.

Results: Sixteen patients were excluded from the study (12patietns in case group and 4 patients in control group) due to drug intolerance and inadequate follow up . 20 patients out of 24 patients who were treated with INF-α alone (control group) and 10 patients out of 22 patients who were treated with INF-α plus amantadine (case group) were followed for 18 months . PCR for HCV was performed two times for all patients. Initial PCR revealed that 15 patients (75.0%) became HCV negative in control group while 10 patients (100%) became HCV negative in case group.

The second PCR which was performed 6 months after termination of treatment disclosed that 16 patients (80.0%) in control group were HCV negative compared to 6 patients (60.0%) in case group (P>0.05).

Conclusion: Addition of amantadine to interferon does not improve the remission rate in HCV positive major thalassemic patients.

Keywords: Amantadine, Interferon-α, Chronic hepatitis C, Thalassemia major.

Introduction

Thalassemia is a hereditary disease related to hemoglobin synthesis, presenting with severe anemia, bone changes and splenomegaly. Due to heterogenic nature of genetic abnormalities, the clinical spectrum of β-thalassemia is quite wide, having thalassemia major in one side as a severe transfusion dependent anemia [1]. Although blood transfusion may guarantee blood supply of β-thalassemia major patients but on the other hand poses them to blood borne infections such as hepatitis and Human Immunodeficiency Virus (HIV).

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Despite efforts in screening of blood products, there are still a large number of thalassemia major patients who are chronically infected with hepatitis C virus (HCV). Studies on thalassemia patients in Iran showed that the rate of infection with Hepatitis C virus (HCV) infection was significantly higher than the rate of Hepatitis B virus (HBV).[2,3]

Since the discovery of the hepatitis C virus in 1989, the treatment of hepatitis C has considerably improved. Initially, interferon alpha (INF-α) was used as a single drug, and the sustained virological response rate was below 20%. Then, with the use of combination therapy by interferon with ribavirin, the response rate increased to 41%.

More recently, combination of pegylated interferons (PEG-INF) with ribavirin gave a response rate of about 54-63%. The indication of therapy is mainly based on the results of the liver biopsy which is the best way to assess the prognosis of the liver disease [4, 5]. Therefore, treatment is indicated in patients with moderate or severe necroinflammation or fibrosis [4].

The role of amantadine in the treatment of chronic hepatitis C remains unclear. In this study we compared INF-α monotherapy with combination of INF-α and amantadine in the treatment of β-thalassemia major patients who were chronically infected with HCV.

Materials and Methods

This study is a double blinded prospective, randomized clinical trial which was conducted from June 2004 through March 2007. Selected patients were 36 non-cirrhotic thalassemia major patients who were on regular transfusion and Desferal injections and were chronically infected with HCV. The exclusion criteria were cirrhosis and concurrent medical illnesses.

Cirrhotic patients were excluded from the study by findings in ultrasonography, previous liver biopsies and liver function tests.

The age range of patients was from 3 to 22 years. Out of the total 46 patients, 22 were male and 24 were female. In all patients, positive results of ELISA test for HCV was followed by PCR for HCV and liver biopsy. Participants who were recruited into the study were allocated to the two treatment groups using a computer generated random list based on a simple random selection procedure. One group (22 patients) was treated by INF-α, 3 million units every other day plus amantadine 2 mg/kg/day (case group) and the other group (24 patients) was treated by INF-α and placebo tablet (control group). Medications were administered to patients by a nurse who was blinded to the study. As PEG-INF was not available in Iran's drug market at the time of the research performance, we used conventional interferon for both groups. The duration of treatment was 12 months in both groups. PCR for HCV and liver function tests (LFT) were performed 3 months after beginning of treatment and 6 months after treatment cessation in both groups and the results were compared.

This study was approved by the Ethics Committee of the Shiraz University of Medical Sciences. Informed consents were obtained from all patients.

Data were analyzed with Fisher's exact test by SPSS software ver. 11.5. P-values less than 0.05 were considered statistically significant.

Results

12 patients were excluded from the case group due to drug intolerance and 4 patients were excluded from the control group due to inadequate follow up. The age range of patients was from 3 to 22 years. Out of the total 30 patients, 22(61.1%) were male and 8(26.7%) were female. 27 patients (90.0%) were younger than 15 years and 3 patients (10.0%) were older or equal to 15 years. PCR for HCV was positive in all patients. All patients had abnormalities in LFT and liver biopsy with elevated liver enzymes and necroinflammatory changes in liver biopsy.

30 patients (20 in control group and 10 in case group) finished the 12-month duration of treatment. PCR for HCV was requested two times for all patients. The first PCR was performed 3 months after starting treatment and the second PCR was performed 6 months after termination of the treatment.

The initial PCR in our patients showed greater remission frequency in amantadine group but the results were not statistically significant (P>0.05, Table1).

The second PCR, performed 6 months after termination of the treatment, showed no difference between efficacy of treatments in the 2 groups (P>0.05, Table2).

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***Table 1**. Comparison of PCR results for HCV three months after beginning of treatment in the two study groups*

	HCV Positive in PCR	HCV negative in PCR
Interferon	5(25.0%)	15(75.0%)
Interferon + Amantadine	0(0.0%)	10(100.0%)

***Table 2.** Comparison of PCR results for HCV 6 months after treatment cessation in the two study groups.*

	HCV Positive in PCR	HCV negative in PCR
Interferon	4(20.0%)	16(80.0%)
Interferon + Amantadine	4(40.0%)	6(60.0%)

Discussion

In this study, we compared the combination of INF-α plus amantadine versus INF-α alone in the treatment of HCV infected β-thalassemia major patients. The results revealed that although the preliminary response was better in those who were allocated to the combination therapy but the final results were identical and there was no significant difference in persistent therapeutic response between the two groups. In other words, combination therapy with interferon and amantadine did not guarantee a sustained virological response in our patients.

Amantadine either alone or in combination with a variety of drugs has been evaluated in the treatment of chronic hepatitis C in different populations of patients with conflicting results. The best regimen for achieving a much better and more sustained viral response (SVR) in thalassemia major patients with hepatitis c is reported to be combination therapy with interferon and ribavirin[6].

Although there are few reports supporting the efficacy of amantadine oral monotherapy and even considering amantadine a safe alternative treatment for those patients who are intolerant or unresponsive to interferon [7]; current literature suggests that amantadine is ineffective as monotherapy neither in treatment naive patients nor in the case of HCV recurrence [8,9].

Mangia et al. claimed that in treatment-naive patients with chronic hepatitis C, triple therapy with PEG-INF-α-2a, ribavirin and amantadine produces higher sustained virological response than dual therapy with conventional IFN alpha-2a and ribavirin [10]. Oguz et al. found that the combination regimen of INF-α, ribavirin and amantadine can enhance sustained viral response of IFN-alpha and ribavirin in non-responder patients with HCV [11]. Conversely, Younossi et al. found that the combination of PEG-INF-α-2b, ribavirin and amantadine is ineffective for chronic hepatitis C in both treatment-naive patients and those who had failed a previous course of treatment [12]. In a meta-analysis of 31 randomized controlled trials; combination therapy with amantadine plus ribavarin and INF had no effect on treatment-naive patients or relapsed HCV patients but in non-responders, triple therapy improved the sustained response [13].

Another meta-analysis of six European studies revealed that when genotypes and viremia levels were combined, the response rate after combination therapy (INF and Amantadine) was two times more than that observed with IFN alone in all subgroups, except those with low viremia and genotypes 2 or 3 [14]. In a study of combination therapies in HCV patients who relapsed or experienced a viral breakthrough, the sustained virologic response was higher in patients who were administered PEG-INF-α-2a plus ribavirin (38%) or ribavirin and amantadine (45%) than in those administered PEG-INF-α-2a plus mycophenolate mofetil (17%) or amantadine (10%) alone [15].

In addition to virological response; other factors that have been studied were effects of amantadine on liver enzymes and patients' sense of well being. Torre et al. showed that although amantadine can decrease liver enzymes but had no additional effect on the result of PCR for HCV[16]. Finally Zeuzem compared INF-α alone with INF-α plus amantadine in adult patients and showed that although amantadine will not guarantee a persistent

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response but can be well tolerated and results in decreased fatigue [17].

Most studies used 200 mg of amantadine daily. We also used this amount of amantadine, but Smith et al. stated that amantadine given at a dose of 300 mg daily is safe, and significantly lowers alanine transferase (ALT) blood levels compared to amantadine 200 mg daily. However, the enzyme response rate does not significantly improve above the dose of 300 mg, but toxicity increases [18]. Our study showed that 12 patients (54.5%) developed nausea and vomiting and could not tolerate amantadine with the dose of 2 mg/kg/day.

Despite a transient response, the persistent virological response does not differ in thalassemia patients who have been treated with amantadine plus INF-α versus INF-α alone. 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.

The main limitation that needs to be acknowledged and addressed regarding the present study is that HCV genotypes were not assessed in this study .Various studies strongly indicate that *HCV genotype* is an important determinant of *response to treatment.* Further studies with larger sample sizes, quantitative PCR, HCV genotype determination and liver enzyme monitoring may be required to fully elucidate this subject.

Conclusion

Addition of amantadine to INF-a is not effective for the treatment of chronic hepatitis C in thalassemia major patients.

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