

Interferon Monotherapy in Major Thalassemic Patients with Hepatitis C Infection

Farhad Zamani¹, Ramin Shakeri², Masoomeh Islam³, Hassan Taheri⁴, Mehdi Mohamadnejad¹, Reza Malekzadeh⁵

¹ Assistance Professor, Gastrointestinal and Liver Disease Research Center, Iran University of Medical Sciences, Tehran, Iran

² Research Fellow, Digestive Disease Research Center, Tehran University of Medical Sciences, Tehran, Iran

³ Research Fellow, Imam Reza Hospital, Amol, Iran

⁴ Research Fellow, Babol University of Medical Sciences, Sari, Iran

⁵ Professor, Digestive Disease Research Center, Tehran University of Medical Sciences, Tehran, Iran

ABSTRACT

Background

Major thalassaemia is the most common form of anemia requiring blood transfusion in Iran. Since ribavirin provokes anemia in the treated patients, interferon monotherapy may be an appropriate treatment in major thalassaemic patients. The aim of this study was to determine the safety and efficacy of interferon monotherapy in thalassaemic patients with hepatitis C virus infection.

Materials and Methods

Forty major thalassaemic patients (20 male), with hepatitis C infection (detectable HCV RNA* by qualitative PCR** amplification assay) and elevated liver enzymes were enrolled. Liver biopsy was done for all patients. Then the patients were treated with interferon (3 MU, three times per week) for six months. They were followed by HCV RNA at the end of treatment, and at 6, 12, 24, 36, and 48 months later. Primary outcome measure was sustained virologic response defined by undetectable serum HCV RNA 6 months after end of treatment. Secondary endpoint was negative HCV RNA at the end of follow up (48 months post-treatment).

Results

Mean age of the patient at the beginning of the study was 17.37±5 years. Three patients discontinued treatment because of interferon side effects. Twenty six (65% on intention to treat analysis) had undetectable HCV RNA 6 months after end of treatment but eleven of them became HCV RNA positive on follow up. Finally, 15 patients (37.5%) had undetectable HCV RNA at the end of follow up.

Conclusions

Interferon monotherapy is an effective treatment for major thalassaemic patients with HCV infection. Definition of sustained virologic response for hepatitis C may require revision in high risk patients.

Keywords: Interferon, Major thalassaemia, Hepatitis, Monotherapy, Iran

Govaresh/ Vol. 10, No. 3, Autumn 2005; 178-182

BACKGROUND

Major thalassaemia (MT) is the most common form of anemia requiring blood transfusion in Iran. HCV infection is found in more than 60% of MT

Corresponding author: Digestive Disease Research Center, Shariati Hospital, Kargar-e-Shomali Avenue, Tehran 14114, Iran.

Telefax: +98 21 88012992

E-mail: malek@ams.ac.ir

patients throughout the world.(1-3), The probability of transmission of the virus has been reduced significantly due to recent vigilant screening of blood donors(4); however, similar to the other part of the world, more than 60% of multitransfused patients with major thalassaemia are infected by the virus in Iran.(5)

* Hepatitis C Virus Ribonucleic Acid

** Polymerase Chain Reaction

Beta thalassemic patients may have a different response to interferon treatment compared with other patient group. This can be attributed to the multiple viral infections in these patients, the repeated transfusions, the frequent need for splenectomy, iron overload, factors that alter immune capability and influence liver function.(6; 7)

Absence of cirrhosis and short duration of disease, low levels of HCV viremia, and infection with non-1b HCV type, are the main clinical and virologic predictors of therapeutic efficacy.(8-10)

Combination therapy with ribavirin and interferon is the standard treatment of Hepatitis C infection in non-thalassemia patients(11), but hemolysis is one of the most common complications of treatment with ribavirin, and the 1999 Consensus Statement of the European Association for the Study of the Liver (EASL) listed anemia as an absolute contraindication to ribavirin in hepatitis C. Therefore, Interferon monotherapy may be an appropriate treatment in major thalassemic patients.

Interferon monotherapy has been reported to achieve a virological response rate of 40% in TM patients, following 6-18 months of treatment(12;13). In spite of high prevalence of HCV infection among Iranian major thalassemic patients; there has been no report of interferon-alfa monotherapy for the treatment of HCV infected TM patients in the country.

This study aimed to investigate the safety and efficacy of interferon monotherapy in a group of Iranian HCV infected MT patients.

MATERIALS AND METHODS

The study protocol was approved by the ethics committee of the Digestive Disease Research Center, Tehran University of Medical Sciences and observed the principles of the ethical standards for Human experimentation.

Between September 2000 and August 2002, forty consecutive treatment naïve HCV infected TM patients were enrolled in thalassemia center of Amol, Iran. All patients were regularly transfused

every 3 to 4 weeks.

All patients gave informed written consent for participation in the study.

Patients were considered eligible for the study if they had the following conditions: 1) diagnosis of MT; 2) seropositivity for antibodies to HCV (anti-HCV) and positive qualitative HCV RNA PCR; and 3) exclusion of other causes of liver damage, and human immunodeficiency virus infection.

All patients had percutaneous liver biopsy within the previous 3 months before treatment. The biopsy specimens were stained with hematoxylin and eosin, Masson's trichrome, and reticulin, and were scored with the use of modified hepatitis activity index by an expert pathologist.(14), Necroinflammation was graded from 0 to 18. Fibrosis staged from 0-6 (0, no fibrosis; 1-2, portal fibrotic expansion; 3-4, bridging fibrosis; 5-6, cirrhosis).

Virological investigation was also performed. Serum HCV RNA was detected by qualitative reverse transcription-polymerase chain reaction (RT-PCR).

The following laboratory tests were performed at baseline: Serum ferritin level, HCV-Ab, HCV RNA PCR, complete blood count, platelet counts, T3, T4, thyroid stimulating hormone (TSH), alanin aminotransferase (ALT), aspartat aminotransferase (AST), alkaline phosphatase, serum total bilirubin, prothrombin time, partial thromboplastin time, serum albumin, blood urea nitrogen, serum creatinin, and urinalysis.

HCV genotyping was not performed since the test was not locally available at the time of beginning of the study.

All patients received 3 MicroUnit subcutaneous interferon alfa-2b (Intron® A-Schering) three times per week for 6 months. During treatment, all patients were visited regularly. At each visits a physical examination and following laboratory tests were performed:

Complete blood count and platelet count were detecting every week during first month of therapy and then twice per month, up to termination of treatment.

Dose adjustment was allowed for interferon if the patients developed leukopenia, thrombocytopenia, significant psychologic disorder, thyroiditis and hypothyroidism or hyperthyroidism. AST and ALT were checked once a month and thyroid function test were performed three months after beginning of treatment. Any observed side effects of treatment were recorded at each visit.

The virological response was assessed by serum HCV RNA detection at the end of treatment and 6, 12, 24 and 48 months after end of treatment.

Primary outcome measure was sustained virologic response defined by undetectable serum HCV RNA, 6 months after end of treatment.

Secondary efficacy endpoint was negative qualitative HCV RNA at the end of follow up (month 48 post-treatment). Safety endpoints were incidence of clinical adverse events; rate of dose reduction or discontinuation of study drugs; changes in hemoglobin level ($<9.5\text{mg/dl}$), neutrophil (less than $750/\text{ml}$), and platelet counts ($<100,000/\text{ml}$).

RESULTS

The mean age of the patient at the beginning of the study was 17.37 ± 5 years (range, 8-27 years). Twenty (50%) were male. The patients were diagnosed with MT at a mean age of 18.4 (SD ± 16.93) months.

Patients were being treated with subcutaneous desferoxamin 45-50 mg/Kg of body weight 5 days per week. All patients had undergone splenectomy. The mean ferritin value before the study began was 2607 ± 1409 ng/ml.

Table 1 shows baseline characteristics of patients before enrollment into the study.

Table 1. Characteristic of forty patients.

| | ALT before treatment | ALT at the end of treatment | grade | stage |
|------|----------------------------|-----------------------------------|----------|----------|
| Mean | 121.925 | 50.92308 | 6.325 | 2.85 |
| SD | 72.99856 | 47.72806 | 1.979219 | 1.791003 |

All patients were Anti HCV and HCV RNA positive by two repeated examination during the year before initiation of treatment.

Histologic evaluation of liver biopsy specimens showed 2 patients had minimal necroinflammation (grade 0-2); 12 had mild (grade 3-6), 22 had moderate (grade 7-12) and 4 patients had severe (grade 13-18) inflammation. Mild fibrosis (stage 0 to 2) was detected in 21 patients; significant fibrosis (stage 3 to 4) in 17, and 2 patients had stage 5 of fibrosis.

Three patients discontinued the drug because of severe interferon side effects (i.e., one because of psychosis, one because of coombs positive hemolytic anemia, and another because of hyperthyroidism). Needs to blood transfusion increased in one patient. Other side effects were hypothyroidism in one, weight loss of more than 5 kg in 10, thrombocytopenia (platelet counts $< 100,000 / \text{ml}$) in 5, and significant neutropenia (absolute neutrophil count of less than $750 / \text{ml}$) in 1 patient.

Six months after end of treatment HCV RNA disappeared in 26 patients (sustain viral response (SVR) of 65% on intention to treat analysis), transaminase levels became normal in 17 of 26 patients and decrement of transaminase was seen in other 9 patients.

Eleven out of 26 patients with undetectable HCV RNA became HCV RNA positive (six cases at 12 months four at 24 months and one at 48 months after the end of treatment) on follow up. They developed simultaneous increase in serum transaminase values as well. Therefore, 15 patients (37.5%) had undetectable HCV RNA at the end of follow up.

Of the 3 patients who received only 3 months course of therapy (due to side effects), only one patient came to SVR.

DISCUSSION

Hepatitis C virus is responsible for the majority of cases of post-transfusion hepatitis in patients with thalassemia major. The prevalence of HCV

infection was reported to be 60% in Italian thalassemic patients(3), and 63.8% of patients suffer from HCV infection in Iran.(5)

Interferon monotherapy has been reported to achieve a sustain virological response rate of 25-40% in TM patients, following 6-18 months of treatment(12;13), the sustain virological response rate of this study is even better than interferon monotherapy in non-thalassemic patients (e.g. SVR of 15% or less).(15;16), In the only previous study of interferon monotherapy in Iranian thalassemic patients, SVR of 25% has been achieved.(17), Interestingly, the SVR in our study was high. According to the definition used for SVR, 26 subjects (65% on intention to treat analysis) achieved SVR. The reason for this difference is unknown, but it may be related to the genotypes of HCV in our patients. Although, we could not determine the genotypes of HCV.

Another important and interesting point in our study is that 11 out of 26 (42%) of those who achieved SVR, became HCV RNA positive on 48 months of follow up, and finally, 37.5% of studied patients remained PCR negative at the end of follow up.

High relapse rate in our study may be due to re-infection during multiple transfusions or low level infection which did not detect by RT-PCR. Thus long term follow up of responded patients (HCV RNA negative) may be appropriate in multi-transfused thalassemic patients.

Previous studies have suggested that iron overload may reduce rate of treatment response in chronic hepatitis C.(18), However, our response rate was good to interferon monotherapy (37.5% at the end of follow up) despite high level of iron overload in our patients (i.e., mean serum ferritin level of 2607 ng/ml). This finding is in accordance with more recent studies which found iron overload does not influence treatment response in chronic hepatitis C.(19)

In our trial the treatment was well tolerated, and discontinued in only 3 of 40 (7.5%) of subjects. Weight loss was the most prevalent adverse reaction but was reversible in patients who

continued therapy.

It has been reported that combination therapy with interferon and ribavirin for a 6-month period results in a high rate of SVR.(20;21), However, the addition of ribavirin for treatment of chronic hepatitis C in TM patients carries the potential risk of hemolytic anemia.(20;21), Nevertheless, pilot trials of combination IFN* and ribavirin have been conducted and resulted in 46 to 72% rate of SVR.(11;22)

In the only report of pegylated interferon in HCV infected thalassemic patients, peginterferon alfa-2a (Pegasys) monotherapy led to 60.8% of SVR.(23), While peginterferon is probably more effective treatment in TM patients; however, given the high cost of peginterferon in Iran, treatment can be started with IFN in the country.

CONCLUSION

In conclusion, IFN monotherapy is safe and effective in Iranian HCV infected thalassemic patients. Further studies of IFN combination, or peginterferon combination therapies should be performed in TM patients infected with hepatitis C virus.

References

1. Angelucci E. Antibodies to hepatitis C virus in thalassemia. *Haematologica* 1994; 79: 353-5.
2. Resti M, Azzari C, Rossi ME, Vullo C, Zammarchi E, Vierucci A. Hepatitis C virus antibodies in a long-term follow-up of beta-thalassaemic children with acute and chronic non-A non-B hepatitis. *Eur J Pediatr* 1992; 151: 573-6.
3. Lai ME, De Virgili S, Argioli F, Farci P, Mazzoleni AP, Lisci V, *et al.* Evaluation of antibodies to hepatitis C virus in a long-term prospective study of posttransfusion hepatitis among thalassemic children: comparison between first- and second-generation assay. *J Pediatr Gastroenterol Nutr* 1993; 16: 458-64.
4. Donahue JG, Munoz A, Ness PM, Brown DE Jr., Yawn DH, McAllister HA Jr., *et al.* The declining risk of post-transfusion hepatitis C virus infection. *N Engl J Med* 1992; 327: 369-73.
5. Ansari MM, Kooloobandi A. Prevalence of hepatitis C virus infection in thalassemia and haemodialysis patients in north

* Interferon

- Iran-Rasht. *J Viral Hepat* 2002; 9: 390-2.
6. Lai ME, Mazzoleni AP, Argioli F, De Virgili S, Balestrieri A, Purcell RH, *et al.* Hepatitis C virus in multiple episodes of acute hepatitis in polytransfused thalassaemic children. *Lancet* 1994; 343: 388-90.
 7. Weatherall DJ. The thalassaemia syndromes. *Tex Rep Biol Med* 1980; 40: 323-33.
 8. Pagliaro L, Craxi A, Cammaa C, Tine F, Di MV, Lo IO, *et al.* Interferon-alpha for chronic hepatitis C: An analysis of pretreatment clinical predictors of response. *Hepatology* 1994; 19: 820-8.
 9. Chemello L, Alberti A, Rose K, Simmonds P. Hepatitis C serotype and response to interferon therapy. *N Engl J Med* 1994; 330: 143-6.
 10. Magrin S, Craxi A, Fabiano C, Simonetti RG, Fiorentino G, Marino L, *et al.* Hepatitis C viremia in chronic liver disease: Relationship to interferon-alpha or corticosteroid treatment. *Hepatology* 1994; 19: 273-9.
 11. Li CK, Chan PK, Ling SC, Ha SY. Interferon and ribavirin as frontline treatment for chronic hepatitis C infection in thalassaemia major. *Br J Haematol* 2002; 117: 755-8.
 12. Donohue SM, Wonke B, Hoffbrand AV, Reittie J, Ganeshaguru K, Scheuer PJ, *et al.* Alpha interferon in the treatment of chronic hepatitis C infection in thalassaemia major. *Br J Haematol* 1993; 83: 491-7.
 13. Di Marco V, Lo Iacono O, Almasio P, Ciaccio C, Capra M, Rizzo M, *et al.* Long-term efficacy of alpha-interferon in beta-thalassaemics with chronic hepatitis C. *Blood* 1997; 90: 2207-12.
 14. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, *et al.* Histological grading and staging of chronic hepatitis. *J Hepatol* 1995; 22: 699.
 15. Di Bisceglie AM, Hoofnagle JH. Optimal therapy of hepatitis C. *Hepatology* 2002; 36: S121-S127.
 16. Poynard T, Leroy V, Cohard M, Thevenot T, Mathurin P, Opolon P, *et al.* Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: Effects of dose and duration. *Hepatology* 1996; 24: 778-89.
 17. Mirmomen S, Ghofrani H, Forootan Pishbijary H, Ebrahimi Daryani N, Farahvash MJ, Sharifian RA, *et al.* Safety and efficacy of interferon alfa for the treatment of chronic hepatitis C infected subjects with transfusion dependent thalassaemia in Iran. *Medical journal of the Islamic republic of Iran* 2003; 17-22.
 18. Fargion S, Fracanzani AL, Sampietro M, Molteni V, Boldorini R, Mattioli M, *et al.* Liver iron influences the response to interferon alpha therapy in chronic hepatitis C. *Eur J Gastroenterol Hepatol* 1997; 9: 497-503.
 19. Hofer H, Osterreicher C, Jessner W, Penz M, Steindl-Munda P, Wrba F, *et al.* Hepatic iron concentration does not predict response to standard and pegylated-IFN/ribavirin therapy in patients with chronic hepatitis C. *J Hepatol* 2004; 40: 1018-22.
 20. McHutchison JG, Gordon SC, Schiff ER, Shiffman ML, Lee WM, Rustgi VK, *et al.* Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. *N Engl J Med* 1998; 339: 1485-92.
 21. Davis GL, Esteban-Mur R, Rustgi V, Hoefs J, Gordon SC, Trepo C, *et al.* Interferon alfa-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. International Hepatitis Interventional Therapy Group. *N Engl J Med* 1998; 339: 1493-9.
 22. Telfer PT, Garson JA, Whitby K, Grant PR, Yardumian A, Hoffbrand AV, *et al.* Combination therapy with interferon alpha and ribavirin for chronic hepatitis C virus infection in thalassaemic patients. *Br J Haematol* 1997; 98: 850-5.
 23. Mirmomen S, Ebrahimi Daryani N, Malekzadeh R, Zali MR, Haghpanah B, Poursamimi P, *et al.* The efficacy and safety of peginterferon alpha-2a (PEGASYS) monotherapy in the treatment of chronic hepatitis C infected subjects with transfusion dependent thalassaemia. *Hepatitis Monthly* 2004; 4: 70-6.