

Effect of hepatic iron concentration and viral factors in chronic hepatitis C-infected patients with thalassemia major, treated with interferon and ribavirin

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Background: Beta thalassemia major patients are vulnerable to transfusion-transmitted infection, especially hepatitis C virus (HCV), and iron overload. These comorbidities lead to cirrhosis and hepatocellular carcinoma in these patients. In order to prevent these complications, treatment of HCV infection and regular iron chelating seems to be necessary. The aim of this study was to evaluate the effect of hepatic iron concentration (HIC) and viral factors on the sustained virological response (SVR) in chronic HCV-infected patients, with beta thalassemia major being treated with interferon and ribavirin.

Materials and methods: We enrolled 30 patients with thalassemia major and chronic HCV who were referred to the Hematology Clinic of Guilan University of Medical Sciences, between December 2002 and April 2006. HIC was measured by atomic absorption spectroscopy before treatment. The viral factors (viral load, genotype) and HIC were compared between those who achieved a SVR and nonresponders.

Results: Mean age of the 30 thalassemic patients, was 22.56 ± 4.28 years (14–30 years). Most patients were male (56.7%). Genotype 1a was seen in 24 (80%) cases. SVR was achieved in 15 patients (50%). There were no significant correlations between HIC ($P = 1.00$), viral load ($P = 0.414$), HCV genotype ($P = 0.068$), and SVR. No difference was observed in viral load ($P = 0.669$) and HIC ($P = 0.654$) between responders and nonresponders.

Conclusion: HIC, HCV viral load, and HCV genotype were not correlated with virological response, and it seems that there is no need to postpone antiviral treatment for more vigorous iron chelating therapy.

Keywords: hepatitis C virus, hepatic iron concentration, combination therapy, thalassemia major, interferon alfa, ribavirin

Introduction

Beta thalassemia is the most common inherited single gene disorder worldwide¹ and one of the most common autosomal recessive disorders in Iran where there is tradition of inbreeding and a conservative culture; there are more than 15,000 registered cases in the country.^{2–4} It is caused by point mutations or, more rarely, deletions in the beta globin gene on chromosome 11. This often leads to a decreased or absent synthesis of the beta chains of hemoglobin. Patients usually present within the first 2 years of life with severe anemia, requiring regular red blood cell transfusions.⁵ The life-long need for transfusion renders patients vulnerable to transfusion-transmitted viral infections especially hepatitis C virus (HCV).^{6,7} Up to 80% of adult thalassemic patients are

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infected with HCV infection worldwide.⁸ In Iran HCV infection rate ranges from 2% to 32%.⁹ Transfusion-dependent thalassemic patients have mild liver necroinflammation, mainly attributable to HCV infection. Significant fibrosis is frequent, and its progression is influenced mostly by iron overload which, with current therapy regimens, may be attributable to both erythrocyte catabolism and iron hyperabsorption.^{10,11} Iron overload and HCV infection are independent risk factors for liver fibrosis progression, and their concomitant presence results in a striking increase in risk.^{12,13} Aggressive approaches to the treatment of HCV may be particularly valuable because of the additive risks for cirrhosis and hepatocellular carcinoma that are posed by infection and iron overload.¹⁴ Nowadays, combination therapy with peginterferon (PEG-IFN) plus ribavirin (RBV) is the standard treatment for chronic HCV.^{15–17} In patients with chronic HCV and advanced fibrosis, sustained virologic response (SVR) to treatment is associated with improved clinical outcomes, mainly prevention of liver failure.¹⁸ In previous studies, it has been proved that the mentioned comorbidities such as iron overload negatively affect the outcome of liver disease, often reducing the chance of achieving a SVR with PEG-IFN and RBV treatments in chronic HCV patients.^{19–23} Burt and Cooksley showed that a hepatic iron concentration (HIC) > 1100 µg/g appears to identify a group of patients who are unlikely to respond to IFN- α .²⁴ Some studies have shown that raised ferritin values predicate nonresponse to IFN-RBV therapy in HCV patients.^{25,26} On the other hand, some authors have demonstrated that iron removal does not appear to improve responsiveness to IFN- α therapy.^{27–29} Some studies have shown the impact of iron on the outcome of IFN therapy and indicated that iron removal can improve the rate of response to IFN, especially in patients with lower hepatic iron deposits.^{30,31} There seems a low rate of treatment with IFN and RBV in thalassemic patients. The aim of this study was to evaluate the correlation between HIC and SVR in treatment of chronic HCV infection in thalassemic patients.

Materials and methods

Among thalassemia major patients who were referred to Hematology Clinic of the Guilan University of Medical Sciences between December 2002 and April 2006, 30 patients who met the inclusion criteria and who were HCV RNA positive were studied.

In order to confirm the HCV status of subjects, anti-HCV antibody (anti-HCV Ab) was tested by third-generation enzyme-linked immunosorbent assay (ELISA, Diapro, Diaplus, Italy) and sera of these anti-HCV Ab-positive patients

were analyzed by polymerase chain reaction (PCR, Roche Viral RNA kits, Germany) for detection of HCV RNA.

Exclusion criteria included: coinfection with HIV or hepatitis B virus, immunosuppression, previous antiviral therapy, chronic kidney disease, and alcohol consumption. Finally, after giving written informed consent, 30 beta thalassemia major patients who were HCV RNA positive were enrolled. The protocol of this study conformed to the ethical guidelines of the Helsinki Declaration and was approved by the local ethical committee.

Sera from patients were analyzed by real time reverse transcription polymerase chain reaction assay (Qiagen, Germany) to determine viral load. Consecutively, HCV genotyping was performed by hybridization assay with a Qiagen kit. Viral load was defined as low at <10⁴ copies/mL; intermediate at 50 × 10⁴ copies/mL, and high at >50 × 10⁴ copies/mL.

Liver biopsies were obtained from all patients before treatment. HIC was determined by atomic absorption spectroscopy in formalin-fixed, paraffin-embedded liver samples. The results were expressed as mmol/g dry tissue weight. The mean of two quantifications of iron by spectrometer was calculated and defined as HIC. Patients were divided into three groups according to HIC: low, dry tissue weight < 125 mmol/g; intermediate, dry tissue weight 125 to 400 mmol/g; and high, dry tissue weight > 400 mmol/g.

A total of 30 treatment-naive patients with HCV genotype 1a (n = 24) and 3a (n = 6) infection was enrolled into 48 weeks and 24 weeks of treatment with IFN- α -2a (3 million units 3 times weekly) plus RBV (1000–1200mg/day, based on body weight), respectively. The HCV RNA was quantitatively assessed before treatment, after 12 weeks of treatment, and at end of treatment (48 weeks and 24 weeks respectively). The response to antiviral treatment was evaluated by the detection of HCV RNA in serum by qualitative PCR at 12 weeks of treatment and end of treatment (48 weeks and 24 weeks respectively). Patients who tested HCV RNA negative at 12 weeks of treatment and end of treatment were classified as responders (SVR). All other patients, including those who relapsed, were classified as nonresponders. The patients were compared for HIC, viral load, and HCV genotype according to the response to treatment (SVR or nonresponders).

Statistical analysis

Data were analyzed by using SPSS software version 15. Categorical variables were expressed as frequency and percentages. Continuous variables were expressed as mean

and standard deviation or median and range. Continuous variables were compared by the *t*-test. The Pearson's and Spearman's correlations between HIC, viral load, and SVR were determined. A *P* value < 0.05 was considered statistically significant.

Results

Mean age of the studied patients was 22.56 ± 4.28 years (14–30 years). Most patients were male (56.7%). HCV virus genotyping test resulted in type 1a in 24 (80%) and type 3a in 6 (20%). SVR was achieved in 15 patients (50%) (Table 1).

There was no significant correlation between viral load and SVR (*P* = 0.414), HIC and SVR (*P* = 1.00), or between HCV genotype and SVR (*P* = 0.068) (Table 2). No difference was observed in viral load (*P* = 0.669) and HIC (*P* = 0.654) between responders and nonresponders (Table 3).

Discussion

HCV infection is often associated with an elevation of iron parameters. Free liver iron causes liver damage and liver fibrosis preferentially through induction of reactive oxygen species.^{31,32} In addition, data suggest an effect of iron on the outcome of IFN therapy. Conflicting results have been reported in studies evaluating the relationship between liver iron deposits in chronic HCV patients, and also their effect on the response to therapy in these patients.^{33–36} Tsai et al showed that 15% of chronic HCV patients who previously failed IFN had a sustained response to IFN therapy after iron depletion.²³ Ortiz et al concluded that sustained response to IFN therapy is an infrequent event and is more dependent on viral factors (viral load and genotype) and lowering serum ferritin by phlebotomy does not increase HCV eradication rate after IFN treatment.²⁸ Herrera showed that patients who previously failed treatment with IFN, iron depletion induced by phlebotomy is ineffective in achieving viral eradication in patients retreated with IFN.²⁹

Table 1 Demographic and clinical characteristics of the sample studied

Characteristic	N = 30
Sex	
Male	17
Female	13
Age (years)	22.56 ± 4.28
Viral load (copies/mL)	333432 ± 422285
HIC (mmol/g)	157.34 ± 90.51
HCV genotype (%)	
1a	80
3a	20

Note: Quantitative variables are expressed as mean \pm SD.

Abbreviations: HCV, hepatitis C virus; HIC, hepatic iron concentration.

Table 2 Viral load, HCV genotype, and hepatic iron concentration (HIC) in patients presenting a sustained virological response (SVR) and in nonresponders (NR)

	SVR	NR	P value
Viral load (copies/mL)			
Low	1 (50)	1 (50)	0.414
Intermediate	11 (45.8)	13 (54.2)	
High	3 (75)	1 (25)	
HCV genotype			
1a	10 (41.7)	14 (58.3)	0.068
3a	5 (83.3)	1 (16.7)	
HIC (mmol/g)			
Low	7 (50)	7 (50)	1.00
Intermediate	8 (50)	8 (50)	
High	0 (0)	0 (0)	

Note: Categorical variable expressed as number (percent).

Abbreviation: HCV, hepatitis C virus.

Van Thiel et al suggested that hepatic iron content predicts a response to IFN therapy. They showed that hepatic iron content of nonresponders was almost twice that of responders (1156 ± 283 μ g/g dry weight vs 638 ± 118 ; *P* < 0.05).³⁷ Olynyk et al showed that mean HIC in nonresponders (860 ± 100 μ g/g) was significantly higher than in responders (548 ± 85 μ g/g) (*P* < 0.05). They also found that patients with chronic HCV who have an HIC of > 1100 μ g/g predicted nonresponse in 88% of patients. Response to therapy in that study was defined as normalization of alanine transferase levels at the end of treatment.³⁸ In our study, correlation between HIC and SVR as well as viral factors and SVR were evaluated. Surprisingly, HIC in SVR (164.93 ± 95.06 mmol/g) was higher than nonresponders (149.76 ± 88.37 mmol/g), although there was no significant relationship between HIC and SVR. Nonresponsiveness may be related to definition of SVR in various studies.

Consistent with our findings, Sievert et al, in their study of 28 patients with beta thalassemia major, found no difference in HIC between responders and nonresponders to therapy.³⁹ Pianko et al found that in the combination therapy (IFN and RBV) group, the mean HIC was similar for both SVR and nonresponders (533 ± 86 μ g/g in the NR, and 662 ± 95 μ g/g in the SVR).⁴⁰ Rulyak et al showed no significant difference in median HIC between responders and nonresponders (404 μ g/g

Table 3 Comparison between viral load and hepatic iron concentration (HIC) of responders and nonresponders (NR)

	SVR	NR	P value
Viral load	367223 ± 532418	299640 ± 288912	0.669
HIC	164.93 ± 95.06	149.76 ± 88.37	0.654

Note: Quantitative variables expressed as mean \pm SD.

Abbreviation: SVR, sustained virological response.

and 394 $\mu\text{g/g}$, respectively; $P = 0.31$)⁴¹ Pereira et al found that median HIC was 9.9 and 8.2 $\mu\text{mol/g}$ dry tissue ($P = 0.51$) for SVR and NR patients, respectively.⁴² Differences in median HIC between SVR and nonresponder groups in these studies may be associated with method of tissue staining and technique of determination of HIC. In contrast, Fujita et al found that increased hepatic iron stores in chronic HCV were related to resistance to IFN-RBV treatment.⁴³ Lin et al suggested that positive hepatic iron stain is an independent predictor of non-response to combination therapy with PEG-IFN- α and RBV for patients with chronic HCV.⁴⁴ Bertino et al, in a study of 45 patients with chronic HCV who were taking PEG-IFN- α -2a and RBV, found that HIC negatively conditions the response to therapy with PEG-IFN and RBV. In their study, iron removal was correlated with the response to treatment.⁴⁵

Sievert et al showed that serum HCV RNA was lower in responders than in nonresponders and also showed that genotype 1 was more frequent in nonresponders, and nongenotypes 1 were more frequent in responders, although this was not statistically significant.³⁹ Although in our study genotype 1a was more frequent (58.3%) in nonresponders, we found no correlation between HCV genotype and SVR, and we also found no correlation between HCV viral load and SVR. Souza et al studied 85 patients with chronic HCV who were treated with IFN and RBV and found no association between HCV genotype and response to IFN and RBV therapy.⁴⁶ De Galocsy et al indicated that many genotype 4 HCV patients in Belgium originate from Central Africa, and their response to treatment seems lower.⁴⁷ Alavian et al suggested in their review of 13 articles which included 429 thalassaemic HCV-infected patients treated with conventional or combination therapy with RBV that genotype 1 infection significantly benefits from combination therapy with ribavirin.⁴⁸ Rulyak et al indicated that factors associated with SVR included genotype 2 or 3 (odds ratio [OR] = 12.2; 95% confidence interval [CI] 3.1–47.8) and viral load < 2 million copies/mL (OR = 3.6; 95% CI 1.3–10.0).⁴¹ Effect of viral factors on anti-HCV treatment may be associated with patient factors such as their immune status and duration of treatment. Results of the Jurczyk et al study showed that iron status does not significantly influence the efficacy of treatment with IFN and RBV in patients with chronic HCV.⁴⁹ Taliani et al, who studied retreatment of nonresponders to IFN and RBV in HCV-infected patients, showed that accurate selection of patients, such as those with low viral load and low gamma-glutamyltransferase levels, and prolongation of therapy for more than 24 weeks also in HCV RNA-positive patients, may further increase the rate of SVR.⁵⁰

In conclusion, our study indicated that HIC, HCV viral load, and HCV genotype were not correlated with virological response to antiviral treatment, and it seems that there may be no need to postpone antiviral treatment for more vigorous iron chelating therapy and reducing hepatic iron overload.

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Disclosure

The authors declare no conflicts of interest.

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