

# Safety and Efficacy of Pegylated Interferon Alfa-2a for the Treatment of Hepatitis C in Patients with Major Thalassemia

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## Abstract

**Background:** Hepatitis C virus (HCV) infection is the most common transfusion transmitted disease in poly-transfused patients worldwide. In this study we aimed to evaluate the effects of pegylated interferon alfa-2a (PEG-IFN A-2a) in reducing serum ALT and eradicating serum hepatitis C virus (HCV) RNA in HCV infected polytransfused thalassemic patients.

**Materials and Methods:** A cohort of 51 HCV-RNA positive thalassemic patients were enrolled to our study and received 180 µg PEG-IFN A-2a once-weekly for 48 weeks. The primary end point was sustained virological response (SVR). The secondary outcome was normalization of ALT. Patient safety was assured by monthly, and if needed, weekly laboratory assessment and visits.

**Results:** Of 52 patients, 42 participants completed the treatment schedule. A sustained virological response (SVR) was attained in 22/51 (43%) cases. Among non-responders or relapsers to previous HCV antiviral therapy, 9/27 (33%) attained an SVR. Five patients died during treatment and 3 subjects discontinued the therapy because of adverse effects. Adverse events were generally mild, and laboratory abnormalities were rare.

**Conclusion:** A course of 48-week PEG-IFN A-2a monotherapy is effective in eradicating HCV-RNA during treatment. But about one third of thalassemic patients would relapse within 6 months of treatment schedule completion, in whom combination therapy is needed.

**Keywords:** Chronic hepatitis C, Thalassemia, Peginterferon alfa-2a.

## Introduction

Thalassemia major (TM) is the most frequent transfusion dependent anemia in the world. Transfusion-transmitted chronic hepatitis C virus (HCV) infection is common in these patients, particularly those who received blood transfusion before the implementation of blood products screening. HCV infection can be found in more than 60% of thalassemic patients throughout the world and accounts for 90% of acute hepatitis infections

in these patients.<sup>1,2</sup> Despite iron chelation therapy, iron overload, a usual consequence of multiple transfusions, is a negative prognostic factor for antiviral treatment. Iron overload is also an independent risk factor for liver fibrosis in polytransfused thalassemic patients.<sup>3-5</sup> Combination therapy containing ribavirin is a frontline treatment in non-thalassemic patients. However, data on combination treatment in TM patients are limited because of the associated hemolysis leading to an

increase in transfusion requirement, iron accumulation, and risk of iron-related toxicities.<sup>6</sup> To date, conventional interferon is the most widely investigated treatment protocol in thalassemic patients. In non-thalassemic patients, this drug has been shown to normalize serum ALT levels, as well as eradicating serum HCV RNA, and improvement in liver histological findings in about 50% of treated patients.<sup>7</sup> However, 50% of responders may relapse within 6 to 12 months after cessation of therapy.<sup>7,8</sup> We previously reported that about 40% of thalassemic patients responded to conventional interferon monotherapy.<sup>3</sup> Peginterferon treatment has been shown to be more effective than conventional interferon as an antiviral agent in non-thalassemic patients. Information about peginterferon treatment in polytransfused patients with chronic HCV-related hepatitis is limited.

This study aimed to investigate the efficacy and complications of pegylated interferon alfa-2a (Pegasys®) (PEG-IFN A-2a) in a group of Iranian thalassemic patients. We also evaluated, along with other clinical and laboratory features, the affect of HCV type and iron overload on treatment outcome.

## Materials and Methods

### Patient selection

This study was carried out by Baqiyatallah Research Center for Gastroenterology and Liver Diseases (BRCGL). Patients with positive HCV RNA (determined by PCR), who were HBsAg and HIV negative were included in the study. Exclusion criteria included use of interferon-alfa within the previous six months, pregnancy or breastfeeding, liver decompensation, other severe disease-related morbidities, alcoholic liver disease, severe retinopathy, history of inflammatory bowel disease, history of suicidal attempt, and severe and uncontrolled depression.

### Study design

This was a prospective, open-label single arm trial of pegylated interferon alfa-2a (Pegasys®) monotherapy in major thalassemic subjects with chronic hepatitis C. Patients received 180 µg PEG-IFN A-2a subcutaneously once weekly. Treatment duration was 48 weeks for all genotypes. All subjects have been receiving regular blood transfusion in 2 to 4-week intervals to maintain

hemoglobin level at 10–13 g/dL, along with regular therapy with Deferoxamine. Compliance with treatment was monitored using telephone consults, questionnaires and returned vials for PEG-IFN A-2a. The protocol was approved by the ministry of health appointed Protocol Review Committee, as well as, other involved research centers' Institutional Review Board. All patients also provided written informed consent.

### Histology

All subjects underwent percutaneous liver biopsy by Menghini needles. Each biopsy specimen was evaluated according to the modified Knodell score grading and staging system. A scale of 0–18 (modified HAI grading) was applied for necroinflammatory activity grading, and a scale of 0–6 (modified staging) was applied for liver fibrosis and architectural disturbances staging. Then, liver damage staging and grading were categorized in three levels of mild, moderate and severe. 0-6 for grading and 0-2 for staging were designated as mild, 7-12 and 3-4 as moderate, and 13-18 and 5-6 as severe. Perls' staining with scores of 0-4 was applied to assess hepatic siderosis. 0-1 was designated as mild, 2-3 as moderate, and 4 as severe.

### Assessment of efficacy

Serum HCV RNA was measured at weeks 12, 24 and 48 during treatment and after 24 weeks of untreated follow-up. Viral response was characterized by an early viral response (EVR: negative HCV-RNA after 12 weeks of treatment), end of treatment response (ETR: negative HCV-RNA at the end of treatment) and sustained viral response (SVR: undetectable viremia 24 weeks after the end of treatment). Biochemical response was characterized by normalization of serum ALT activity at the end of treatment (EBR) and after 24 weeks of untreated follow up (SBR).

### Assessment of safety

Safety was assessed by monthly laboratory tests and evaluation of adverse events during treatment and follow up. Laboratory criteria for dose reduction were as follows: neutrophils < 500 cells/mm<sup>3</sup>, platelets < 50000/mm<sup>3</sup>, or hemoglobin < 7 g/dL. Treatment was discontinued, if neutrophil count declined to below 2000 cells/mm<sup>3</sup>, or

platelet count was below 30000/mm<sup>3</sup>. G-CSF was initiated, if neutropenia required prolonged dose reduction.

### ***Virological methods***

All polymerase chain reaction (PCR) and genotyping procedures were performed as described previously.<sup>9</sup>

### ***Statistical analysis***

Continuous variables are presented as mean values with 95% confidence interval, qualitative and discrete variables are presented as absolute and relative frequencies in the form of percentage. Chi-squared test was applied to assess correlations between categorical variables. Due to sufficiency of sample size and power, comparison between continuous and categorical variables was performed using student's t-test and one-way ANOVA regardless of distribution or homogeneity of variances. Survival curves were provided according to Kaplan Meier method, and analyzed by the log-rank test. Multiple logistic regression analysis was performed to identify features predicting SVR. All computations were carried out using SPSS version 16. The probability value (P) <0.05 was regarded statistically significant.

## **Results**

### ***Features on admission***

Fifty one chronic HCV infected thalassemic patients who met our inclusion criteria were recruited, and received PEG-IFN A-2a monotherapy for 48 weeks. Twenty eight subjects (55%) were male. Our subjects' mean age was 25 (range: 23-27) years. Twenty four (51%) subjects were naïve, 15 subjects (29%) were non-responder to previous interferon monotherapy, and 12 subjects (23%) were non-responder to previous combination therapy with ribavirin. Cirrhosis was present in 8 (19%) cases. Histologic degree of siderosis was mild in 6 (14%), moderate in 18 (43%), and severe in 14 (33%) subjects. Twenty one (49%) subjects were infected by HCV type 1a. Non-1a HCV types (type 1b: 2, type 2a: 2, type 3a: 19, and type 3b: 1) were found in 30 (51%) subjects. Mixed infections with different HCV types (type 1a /1b/3a, 1; type 1a/3b, 1) were found in 2 (3.9%) subjects.

### ***Pattern of response to PEG-IFN A-2a***

Forty two subjects completed treatment schedule. At their last follow-up visit (24 weeks after the end of treatment), 22 (52%) were HCV-RNA negative, thus fulfilled the definition of SVR. ALT normalization among 22 SVR subjects was obtained within 3 months in 12 subjects (54%), and the end of therapy in another 3 (13.6%). The other 5 SVR subjects (17.9%) reached normal ALT levels within 3 months of stopping PEG-IFN A-2a. Totally twenty-six (62%) subjects developed normal ALT during treatment or within 3 months after stopping PEG-IFN A-2a. The degree of liver siderosis affected the kinetic of biochemical response in a slightly significant manner (figure 2). Almost all the patients with mild degrees of liver iron overload showed normal ALT within 10 months of therapy, whereas those with severe siderosis were biochemically late responders or did not have normal ALT at all (figure 2).

Six subjects (14%) who developed normal ALT during treatment had an ALT relapse within 6 months of follow up. All of these patients were HCV-RNA positive at their last observation. Ten subjects (23.8%) had abnormal ALT over the entire treatment and follow-up period. Two of these were HCV-RNA negative at the end of follow up. Seven subjects had normal ALT prior to and during PEG-IFN A-2a therapy and remained with normal ALT over the 6-month follow-up. But one of them was HCV-RNA positive at her last observation.

### ***Virological response***

Sustained viral response (SVR) was achieved in 11 out of 22 genotype 2 or 3 patients and in 11 out of 29 genotype 1 patients after 72 weeks. The overall SVR rate was not significantly higher in naïve patients (13/24, 51.4%, 95% confidence interval [CI], 30–71.8%) versus non-responders to previous antiviral therapy (9/27, 33.3%, 95% CI, 15.3–51.3%) (OR 0.4, 95% CI, 0.1–1.5). Figure 1 presents rate of HCV RNA clearance during the treatment and 6-month follow up.

### ***Previously treated patients***

Twenty one of 27 previously treated patients completed treatment schedule. An SVR to PEG-IFN A-2a monotherapy was attained in 9 previously treated subjects (9/21, 42.8%, 95% CI, 32.1–53.5%). Of patients who had received previous

**Table 1.** Summarized characteristics of the thalassemic patients at baseline according to antiviral response.

Characteristics	SR (n=22)	NR (n=20)	P
Mean age (means $\pm$ SD) (yr)	21 $\pm$ 3.4	28 $\pm$ 7.6	0.002
Sex (m)	9 (41%)	14 (70%)	0.059
Splenectomy	9 (41%)	14 (70%)	0.059
ALT activity (means $\pm$ SD)	85 $\pm$ 81	96 $\pm$ 58	0.6
AST activity (means $\pm$ SD)	58 $\pm$ 42	78 $\pm$ 49	0.1
Ferritin (mean $\pm$ SD)	1971 $\pm$ 1230	1464 $\pm$ 1434	0.2
HCV-RNA (log <sub>10</sub> copy/ml) (mean $\pm$ SD)	5.3 $\pm$ 0.8	5.6 $\pm$ 0.4	0.2
HCV type			
1	11 (50%)	11 (55%)	0.7
Non-1/mixed	11 (50%)	9 (45%)	
Grade of liver siderosis			
0-1	0	6 (30%)	0.04
2-3	10 (55%)	8 (40%)	
4	8 (44%)	6 (30%)	
Stage of liver fibrosis			
Mild (0-2)	3 (15%)	9 (45%)	0.03
Moderate (3- 4)	14 (70%)	6 (30%)	
Severe (5-6)	3 (15%)	5 (25%)	
Grade of liver necroinflammatory activity			
Mild (0-6)	10 (55%)	15 (75%)	0.1
Moderate (7-12)	8 (45%)	4 (20%)	
Severe (13-18)	0	1 (5%)	
Prior antiviral treatment	9 (43%)	12 (57%)	
Non-responder	7 (54%)	6 (46%)	0.1
Relapser	2 (25%)	6 (75%)	

SR (sustain responder): Negative HCV viremia 6 months after treatment cessation.

NR (non-responder): Positive HCV viremia 6 months after treatment cessation.

monotherapy and combination therapy, 2/9 (22%) and 7/12 (59%) achieved SVR, respectively ( $p=0.098$ ). Relapse was seen in 6/12 and 2/9 patients with previous interferon monotherapy and combination therapy, respectively. Efficacy was lower in relapsers than in non-responders to previous interferon or ribavirin combination therapy, however, this difference did not reach statistical significance (table 1, figure 3). Serum baseline HCV RNA in relapsers and non-responders to previous treatment was similar, and almost half of treatment naïve patients ( $p=0.08$ ) (figure 4). Efficacy was similar in HCV genotype 1 and non-genotype 1 infected patients with history of HCV antiviral treatment (36% vs. 50%,  $p=0.5$ ). Whereas, none of the genotype 1-infected relapsers achieved SVR however 4/7 genotype 1-infected non-responders attained SVR. Serum ALT became

normal in 18/21 patients, and was similar in both relapsers and non-responders (table 2). Rate of SVR was lower in patients who failed to attain HCV clearance after 48 weeks of combination therapy with ribavirin than those who failed to attain HCV clearance after 48 weeks of interferon monotherapy (table 2, figure 5).

#### **Independent factors associated with a SVR**

Analysis using multiple logistic-regression models found that none of the variables significant in univariate analysis (table 1) significantly and independently influence the odds of achieving an SVR.

#### **Predictive value of an early virological response (EVR)**

EVR (undetectable HCV RNA after 12 weeks' treatment) was attained in 37/42 (88%) patients

**Table 2.** Prevalence of genotype 1 and rates of SVR, ETR, and ALT normalization in thalassemic patients with previous HCV antiviral therapy

Variables	Previous monotherapy		Previous combination therapy		Total	
	Non-responder	Relapser	Non-responder	Relapser	Non-responder	Relapser
No. of Patients	6	6	7	2	13	8
Genotype 1 No. (%)	2 (33)	3 (50)	5 (71)	1 (50)	7 (54)	4 (50)
SVR No. (%)	5 (83)	2 (33)	2 (28)	0 (0)	7 (54)	2 (25)
ETR No. (%)	6 (100)	5 (83)	5 (71)	2(100)	11 (85)	7 (87)
ALT normalization No. (%)	5 (83)	5 (83)	7 (100)	1 (50)	12 (92)	6 (75)

**Table 3.** Adverse effects in enrolled patients (n=51).

Adverse events	Weeks	No.	Percent
<b>Withdrawal from treatment</b>		4	8
Uncontrolled DM	32	1	2
Intractable musculoskeletal pain	24	1	2
Lower limb paralysis (myopathy)	36	1	2
<b>Death</b>		5	10
Heart failure	12, 28	2	4
DM complications	4	1	2
Sepsis	12	1	2
Severe Anemia	40	1	2
<b>Side effects</b>			
Flu-like symptoms		15	36
Fatigue		31	74
Musculoskeletal pain		28	67
Psychological		29	68
Gastrointestinal		12	29
Weight loss		5	12
Hair and skin		36	86

(per protocol), of whom 20 (54%) attained SVR. Among 5 patients not achieving EVR, two patients (40%) developed SVR. The negative predictive value of absent EVR at week 12 was 60%, decreasing to 50% at week 24.

### Safety

Three males and 2 females died during treatment. One patient with type 2 diabetes mellitus died because of diabetic complications. Two patients deceased because of heart failure apparently unrelated to treatment. One patient with aplastic anemia died two months after cessation of therapy because of severe anemia. One splenectomized patient died with septic shock manifestations possibly due to treatment related leukopenia. One patient discontinued the

treatment without giving any reason. One patient withdrew the treatment as a result of persistent uncontrollable high serum glucose level. One patient developed lower extremities proximal myopathy to the extent that she was unable to bear her weight. One patient stopped treatment due to frequent severe leukopenia and musculoskeletal pain. Overall three patients discontinued therapy due to side effects. Except these three patients, patients neither needed dose reduction nor developed neutropenia requiring G-CSF administration. Almost all patients experienced one or more side effects during therapy, however, adverse events were generally mild in severity and typical of those associated with interferon-based treatment (table 3). Hair and skin related side effects such as alopecia and dry skin were the most

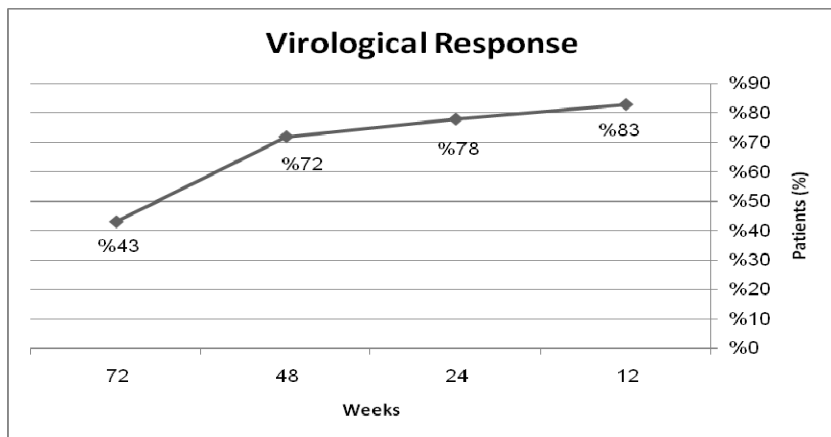
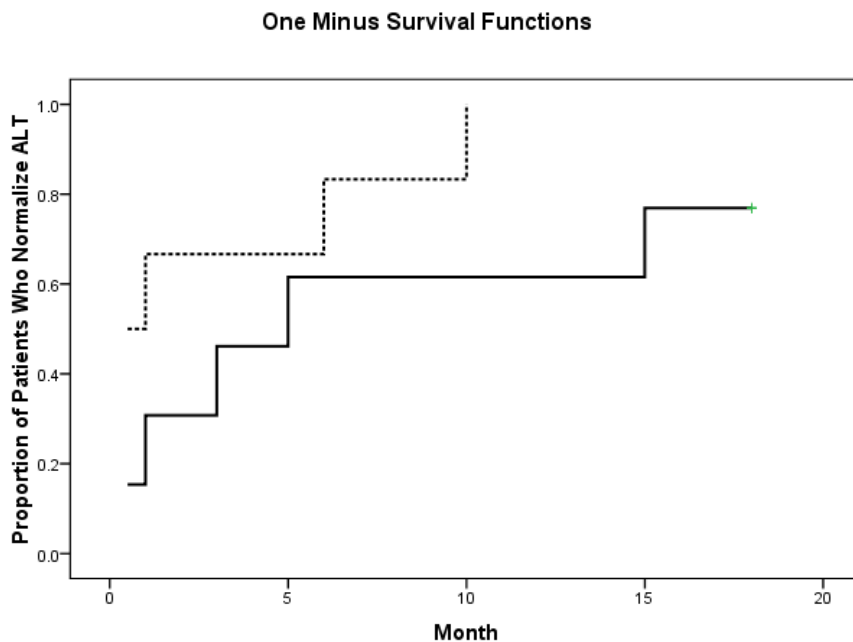


Figure 1. Rate of HCV RNA clearance during the study (intention to treat analysis).



Mild liver siderosis .....  
 Severe liver siderosis \_\_\_\_\_

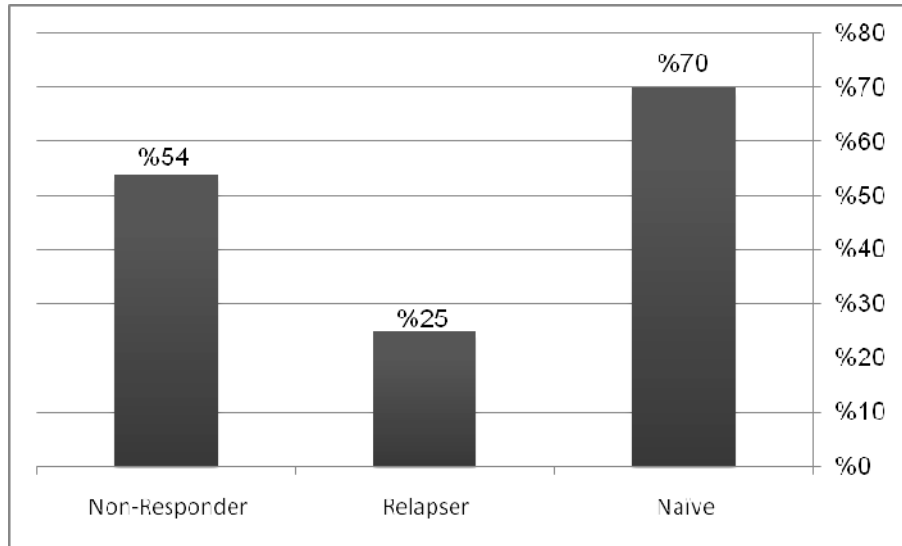
Figure 2. Kinetics of ALT normalization in patients according to grade of liver siderosis at histology. dotted line: siderosis grade 0-1 (6 patients); Solid line: siderosis grade 4 (13 patients) (P = 0.08 by log-rank test).

frequent side effects followed by fatigue, musculoskeletal pain, and psychological problems such as irritability and depressed mood.

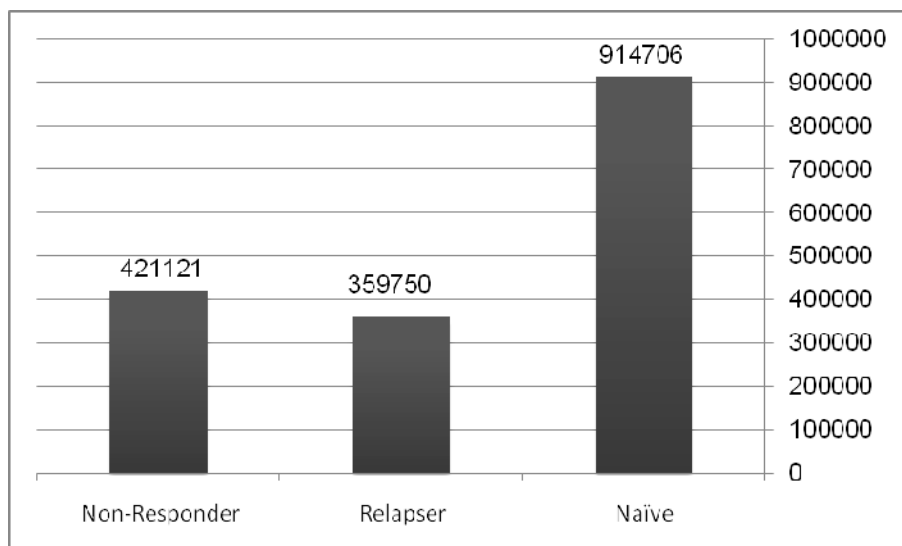
### Discussion

Our data suggests that peginterferon is effective and safe in eradicating HCV viremia and normalizing liver enzymes during treatment course. About one

third of thalassemic patients would relapse during 6-month of treatment cessation. In comparison with current literature on conventional interferon therapy in thalassemic patients, our results are consistent with existing evidence for greater efficacy of PEG-IFN A-2a versus conventional interferon in patients infected with HCV.<sup>10-12</sup> SVR in our trial was also comparable to studies on



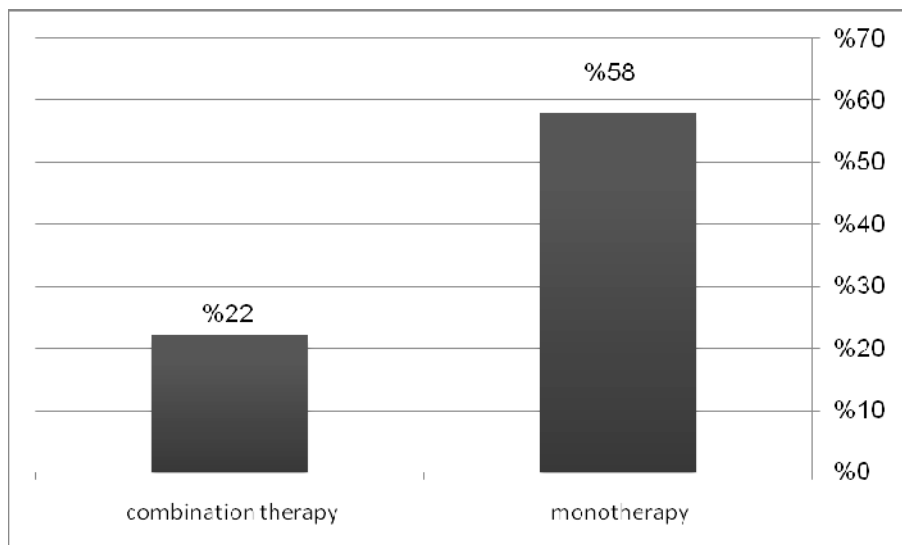
**Figure 3.** SVR rate of PEG-IFN A-2a monotherapy according to outcome of previous antiviral treatment in patients who completed 48 weeks of treatment.



**Figure 4.** Serum baseline HCV RNA in treatment naïve and patients with history of HCV antiviral treatment. Despite higher HCV RNA in treatment naïve patients SVR was higher in these subjects (figure 3).

thalassemic patients with ribavirin combination therapy.<sup>13,14</sup> There are a few reports of PEG-IFN A-2a monotherapy in thalassemic patients. One report from Iran has reported SVR rate of 43% and 3 reports from Spain, Lebanon, and Japan have reported SVR of 13%, 33%, and 26% , respectively.<sup>15-18</sup> Moreover, SVR rate obtained in the current study was almost identical for genotype 1, non-genotype 1, and mixed genotype infections. This result is noteworthy, because patients with HCV genotype 1 infection are generally regarded to

be relatively difficult to treat.<sup>19</sup> We also previously, in a meta-analysis, showed that odds ratio (OR) of SVR rate with interferon monotherapy in genotype 1 versus non-genotype 1 infections was 0.46 (95% CI, 0.22–0.95).<sup>3</sup> It was reported that Asian patients with chronic hepatitis C achieved higher rates of SVR, particularly those with HCV genotype 1 infection.<sup>20-23</sup> Different body compositions, as well as, discrepancies in viral kinetic decay curve in different races are believed to yield this different SVR rates in different ethnic groups.<sup>20-23</sup> In the



**Figure 5.** Rate of SVR according to previous therapeutic protocol ( $p=0.09$  by chi-squared test).

present study, PEG-IFN A-2a monotherapy was effective in approximately half of HCV genotype 1 and non-genotype 1 infected patients.

Peg-IFN A-2a was also effective in patients who had failed to respond to, or had relapsed following previous treatment with conventional interferon monotherapy or combination therapy with ribavirin. SVR was higher in patients with previous monotherapy than combination therapy (figure 5). This implies patients who failed to achieve SVR with ribavirin combination therapy have lower likelihood of HCV clearance with PEG-IFN A-2a retreatment. Patients who relapsed following previous treatment also seems to have lower HCV clearance rate than non-responders (figure 4). Previous studies have described that an EVR at week 12 of treatment can accurately identify patients unlikely to achieve a SVR.<sup>24</sup> In comparison with combination therapy the negative predictive value of EVR was lower in our study (60% vs. 83%).<sup>17</sup>

## Conclusion

A course of 48-week PEG-IFN A-2a monotherapy is effective in eradicating HCV-RNA during treatment. The majority of thalassaemic patients would attain early and end of treatment virological response, however, about one third of them would relapse during 6-month of treatment cessation and need combination therapy with ribavirin.

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## References

1. Dienstag JL. Non-A, non-B hepatitis. I. Recognition, epidemiology, and clinical features. *Gastroenterology*. 1983; 85: 439-62.
2. Mirmomen S, Alavian SM, Hajarizadeh B, Kafae J, Yektaparast B, Zahedi MJ, et al. Epidemiology of hepatitis B, hepatitis C, and human immunodeficiency virus infections in patients with beta-thalassemia in Iran: a multicenter study. *Arch Iran Med*. 2006; 9: 319-23.
3. Alavian SM, Tabatabaei SV. Treatment of chronic hepatitis C in polytransfused thalassaemic patients: a meta-analysis. *J Viral Hepat*. 2010; 17: 236-44.
4. Alavian SM, Tabatabaei SV. Therapy of hepatitis C in thalassemia: the influence of iron on achieving sustained viral response. *Ann Hematol*. 2010; 89: 215-6.
5. Mirmomen S, Alavian SM. Treatment of HCV Infection in Multitransfused Thalassaemic Patients: Does Liver Iron Status Affect the Outcome of Response? *Hepat Mon*. 2005; 5: 11-113.
6. De Franceschi L, Fattovich G, Turrini F, Ayi K, Brugnara C, Manzato F, et al. Hemolytic anemia induced by ribavirin therapy in patients with chronic hepatitis C

virus infection: role of membrane oxidative damage. *Hepatology*. 2000; 31: 997-1004.

7. Pizzarelli G, Di Gregorio F, Romeo MA, Carboni F, Gallisai D, Solinas A, et al. Interferon-alpha therapy in Sicilian and Sardinian polytransfused thalassaemic patients with chronic hepatitis C. *Biodrugs*. 1999; 12: 55-63.

8. Malaguarnera M, Di Fazio I, Restuccia S, Pistone G, Restuccia N, Trovato BA. Efficacy of different schedules in the management of chronic hepatitis C with interferon-alpha. *Ann Med*. 1998; 30: 213-7.

9. Samimi-Rad K, Shahbaz B. Hepatitis C virus genotypes among patients with thalassemia and inherited bleeding disorders in Markazi province, Iran. *Haemophilia*. 2007; 13: 156-63.

10. Mirmomen S, Ghofrani H, Pishbijary HF, Daryani NE, Farahvash MJ, Sharifian RA, et al. Safety and efficacy of interferon alfa for the treatment of chronic hepatitis C infected subjects with transfusion dependent thalassemia in Iran. *Medical Journal of Islamic Republic of Iran*. 2003; 17: 87-95.

11. Clemente MG, Congia M, Lai ME, Lilliu F, Lampis R, Frau F, et al. Effect of iron overload on the response to recombinant interferon-alfa treatment in transfusion-dependent patients with thalassemia major and chronic hepatitis C. *J Pediatr*. 1994; 125: 123-8.

12. Sievert W, Pianko S, Warner S, Bowden S, Simpson I, Bowden D, et al. Hepatic iron overload does not prevent a sustained virological response to interferon-alpha therapy: a long term follow-up study in hepatitis C-infected patients with beta thalassemia major. *Am J Gastroenterol*. 2002; 97: 982-7.

13. Harmatz P, Jonas MM, Kwiatkowski JL, Wright EC, Fischer R, Vichinsky E, et al. Safety and efficacy of pegylated interferon alpha-2a and ribavirin for the treatment of hepatitis C in patients with thalassemia. *Haematologica*. 2008; 93: 1247-51.

14. 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.

15. Inati A, Taher A, Ghorra S, Koussa S, Taha M, Aoun E, et al. Efficacy and tolerability of peginterferon alpha-

2a with or without ribavirin in thalassaemia major patients with chronic hepatitis C virus infection. *Br J Haematol*. 2005; 130: 644-6.

16. Kountouras D, Koskinas J, Berdoussi H, Vgontza N, Karagiorga M, Lagiandreou A, et al. Efficacy and safety of PEG-IFN alpha-2B treatment for 48 weeks in adult thalassaemic patients with chronic HCV infection. *J Hepatol*. 2007; 46: 190S-1S.

17. Makoto Kuboki, Shiro Iino, Tadao Okuno, Masao Omata, Kendo Kiyosawa, Hiromitsu Kumada, Norio Hayashi, et al. Peginterferon a-2a (40 KD) plus ribavirin for the treatment of chronic hepatitis C in Japanese patients. *J Gastroenterol Hepatol*. 2007; 22: 645-52.

18. Mirmomen S, Ebrahimi DN, Malekzadeh R, Zali MR, Alavian SM, Haghpanah B, et al. The Efficacy and Safety of Peginterferon Alpha-2a (PEGASYS) Monotherapy in the Treatment of Chronic Hepatitis C infected Subjects with Transfusion Dependent Thalassemia. *Hepat Mon*. 2004; 4: 65-70.

19. Puoti C, Guarisco R, Bellis L, Spilabotti L. Diagnosis. Management, and treatment of hepatitis C. *Hepatology*. 2009; 50:322.

20. Dev AT, McCaw R, Sundararajan V, Bowden S, Sievert W. Southeast Asian patients with chronic hepatitis C: the impact of novel genotypes and race on treatment outcome. *Hepatology*. 2002; 36: 1259-65.

21. Hepburn MJ, Hepburn LM, Cantu NS, Lapeer MG, Lawitz EJ. Differences in treatment outcome for hepatitis C among ethnic groups. *Am J Med*. 2004; 117: 163-8.

22. Conjeevaram HS, Fried MW, Jeffers LJ, Terrault NA, Wiley-Lucas TE, Afdhal N, Brown RS, et al. Peginterferon and ribavirin treatment in African American and Caucasian American patients with hepatitis C genotype 1. *Gastroenterology*. 2006; 131: 470-7.

23. Alavian SM. Are the Real HCV Infection Features in Iranian Patients the Same As What Is Expected? *Hepat Mon*. 2005; 5: 3-55.

24. Davis GL, Wong JB, McHutchison JG, Manns MP, Harvey J, Albrecht J. Early virologic response to treatment with peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C. *Hepatology*. 2003; 38: 645-52.