ORIGINAL ARTICLE

The Efficacy and Safety of Peginterferon Alpha-2a (PEGASYS) monotherapy in the Treatment of Chronic Hepatitis C Infected Subjects with Transfusion Dependent Thalassemia

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Abstract

BACKGROUND AND AIMS: Interferon monotherapy is currently the only approved treatment for chronic hepatitis C (CHC) infection in transfusion dependent thalassemic patients, in whom ribavirin has limited use because of its hematologic complications. Our aim was to evaluate the efficacy and safety of pegylated Interferon monotherapy for the treatment of HCV infection in transfusion dependent thalassemic patients.

METHODS: The trial was a multicenteric, open label, single treatment prospective study of Peginterferon alfa-2 a (PEGASYS, 180 micg per week) for a period of 48 weeks. 32 subjects, 18 to 42 years old (mean ± SD: 24.1 9.44 years), whose serum HCV RNA was positive and mean ALT remained greater than 1.5 times upper limit of normal were enrolled. A percutaneous liver biopsy was performed before treatment and all patients underwent monthly assessment of any adverse events and were monitored for serum ALT. Efficacy was assessed by measuring serum HCV RNA following 24 week treatment-free period . One patient missed follow up and another died due to a drug unrelated cause and 30 patients were evaluated.

RESULTS: Liver biopsy showed mild fibrosis in 31.2%, moderate fibrosis in 53.1% and cirrhosis in 15.6% of patients. Siderosis was severe in 16 patients (50%). In 26 out of 30 patients (86.6%) HCV RNA was negative at the end of treatment (ETR response). Data about 24 weeks post treatment was available in 23 patients, which showed a sustained virological response (SVR) of about 14/23 (60.8%). Two patients had an elevated end of treatment serum ALT instead of negative HCV RNA but their ALT returned to normal assoon as the treatment stopped. These 2 patients were considered to have INF toxicity.

CONCLUSION: Our experience indicates that the cure of HCV-related liver disease in thalassemic patients is not an unrealistic aim and may be reached with Peginterferon alfa-2a monotherapy in a sizable portion of cases.

KEYWORDS: Hepatitis C Virus – Thalassemia – Pegylated Interferon alfa-2a – Pegasys

Introduction

Transfusion dependent thalassemia (TDT) is a genetic condition in which patients require regular blood transfusion program throughout their life to sustain their growth and development. Transfusion puts them at increased risk of blood borne viruses of which the most important one is HCV infection. [1, 2] Iran is located on thalassemia line with more than 25000 registered TDT cases. Epidemiologic studies have shown that 20 to 30% of TDT patients are infected with HCV virus. [3, 4]

Interferon alfa (INF alfa) monotherapy is currently approved as the first line treatment for HCV infection in TDT cases. Because of hemolytic complications of ribavirin, currently combination of INF and ribavirin is preserved for INF non-responders and only under investigational situations.[5] Attaching a large polyethylene glycol (PEG) molecule to the interferon-alfa protein (pegylated interferon) was a major advance in the treatment of hepatitis C. It causes a sustained therapeutic concentration of interferon over the weekly dosing intervals and prolonged biological activity, which in term has shown to increase (nearly doubles) the sustained response of conventional INF in non-thalassemic subjects.

To date the combination of Peginterferon alfa-2a and ribavirin is approved as the first line therapy of HCV infection in non-thalassemic patients[7], but till now there is no published data regarding the use of PEG-INF in thalassemic patients. This study was designed to evaluate the efficacy and safety of PEG-INF in the treatment of HCV infection in TDT patients.

Patients and Methods

The trial was a multicenteric, open label, single treatment study. This study provided the opportunity to prospectively evaluate the efficacy and safety of peginterferon alfa 2a in a cohort of subjects with thalassemia major treated in Tehran.

PATIENTS: Study took place in Tehran Adult Thalassemic Clinic, Tehran Hepatitis center, Imam Khomeini general hospital and Digestive Disease Reaserch Center (DDRC).Subjects were enrolled in the study if they met the following inclusion criteria: (1) diagnosis of beta thalassemia and being under regular transfusion program (2) age above 18 years old (3) positive serum HCV RNA measured qualitatively by RT-PCR (reverse transcriptase polymerase chain reaction) (4) serum ALT above 1.5 times as much as normal value at least in two different occasions in last 6 months prior to study (5) histological staging more than 2/18 according to Modified Histological Activity Index (HAI) scoring system.[6] The main exclusion criteria were: decompensated cirrhosis, HIV infection or any other immunocompromized condition, critically illness, thrombocytopenia (PLT< 50 x 10^9 /L) medications, which may cause Bone marrow suppression (Hydroxyurea, cotrimoxazol…), or positive HBsAg or HBVDNA. The clinical trial was devised in accordance with the ethical principles outlined in the Decleration of Helsinki and laws and regulations of the Islamic Republic of Iran. Informed consent was obtained from each eligible subject prior to any procedures. 35 patients were screened concerning the possibility for participation in the clinical trial and 32 were enrolled.

HISTOLOGICAL EVALUATION: A percutaneous liver biopsy was performed for all patients prior to start of therapy; samples were preserved in formalin solution and reviewed by a single pathologist. Hepatic inflammation was reported according to modified histological activity index scoring system (Modified HAI), which expresses inflammation from a minimum (grade 1) to a maximum (grade 18). We also considered those less than grade 4 to have mild (grade) and those above grade 4 to have moderate to severe hepatic inflammation.

According to the above scoring system, hepatic fibrosis (stage) is expressed from stage 1 (No fibrosis) to stage 6 (cirrhosis)and we considered those with stage 1 or 2 as mild ; stage 2 or 3 as moderate and stage 5 or 6 as severe fibrosis. [8] All samples were stained with pursian blue for iron staining as well and were divided to mild, moderate and severe.[9]

Genotype evaluation

HCV genotyping was done before the start of treatment, whenever possible. RT nested PCR was performed and based on genomic differences among various genotypes of HCV, restriction fragment length polymorphism (RFLP) was followed to determine genotypes of amplified viral RNA extracted from patients sera.

Treatment

Patients received Peginterferon alfa-2a (Pegasys, Hoffmann-La Roche Inc., Basel, Switzerland) 180 micg weekly, injected subcutaneously at deltoid region. A trained nurse injected the first dose of medication and patients were allowed to inject later doses by themselves as required.

MONITORING SCHEDULE: The treatment phase of the study lasted 48 weeks, during which patients received regular clinical and laboratory evaluation. All patients were followed for 24 weeks post treatment.

SAFETY MONITORING: All patients underwent assessment of any adverse events or use of concurrent medications and probable dose adjustments every 4 weeks. ALT levels and complete blood counts were measured at every visit and other tests such as thyroid function tests were performed every 12 weeks. Patients were also asked to report any significant adverse event on telephone during the study duration.

EFFICACY MONITORING: Early virologic response (EVR) was defined as negative HCV RNA on week 24, end of treatment virologic response (ETR) as negative HCV RNA on week 48, and sustained virologic response (SVR) as negative HCV RNA on week 72 (24 weeks after end-of-treatment). Biochemical response was defined as normalization of ALT levels

STATISTICAL METHODS: A per-protocol approach was used for statistical analysis of the data: SVR was considered the ideal end point of the study. The statistical analysis was performed using SPSS for windows (ver11).

Results

Mean age of 32 patients who enrolled in the study was 24.1 years ±9.44 sd (range18 to 42 years). 19 patients were male (59.3%) and 13 were female. One patient, who was diabetic and under insulin therapy, died during the study due to hypoglycemic coma and respiratory arrest. This event was not considered to be treatment related. Another patient missed follow up and did not come back for visits after week eight. 30 patients finished the 48 weeks of study but in 7 patients we still do not have the 24 week post follow up data. The genotype was available in 20 patients and 1a and 1b were dominant genotypes in them (table 1). Histological evaluation of all 32 patients prior to beginning of therapy showed that 17 patients (53.1%) had mild hepatic inflammation (4 grade) while 15 patients had moderate to sever hepatic inflammation (grade >4). Liver fibrosis was severe in 5 patients (15.6%), moderate in 17 patients (53.1%) and mild in10 patients (31.2%). Histological Iron staining showed that only one patient had mild Iron deposit. Iron staining was severe in 16 (50%) and moderate in 15 (46.8%) patients. Mean serum ferritin value prior to beginning of therapy, was 1712± 1200 micg/L (table 1). All patients were anti-HIV negative at the time of enrollment. Ten patients were reported to be HBc-antibody positive but all patients were HBs-Ag negative at baseline. Serum globulin value was more than 3 gr/l in 24 patients (75%) and mean serum globulin value was 3.4 0.7 sd. We also checked serum autoantibodies in all 32 patients before start of therapy and results showed that 2 patient had ANA titer of 1/20 and 2 other patients had ANA titer of 1/40. Anti-smooth muscle antibody (anti-sm) was positive in 1 patient (1/20), But none of the patients had Revised International Autoimmune hepatitis score more than 15 (table 1).[10]

Table 1

Pretreatment characteristic of transfusion deoendent thalassemic patients treated with PEGASYS

	Mean	Std. Deviation
Age(years)	24.1	±9
Sex(female: male)	19:13	
Mean Transfusion Years	18.62	±6
Duration of HCV infection(months)	44.1	±21
Genotype (20 patients)		
1a	7	±2
1b	8	±1
3	3	±0.8
4	0	
Non-typeable	2	
Liver Biopsy		
Histological grade[8]	5.3	±2
Histological staging[8]	3.7	±1
Iron Staging[9]	3.1	±0.8
serum ALT(IU/L)	92.1	±32.1
serum Albumin (gr/L)	4.6	±0.5
serum Globulin (gr/L)	3.6	±0.8
serum Ferritin (micg/L)	1712	± 1200

SAFETY EVALUATIONS: Adverse reactions were reported in 31 patients (excluding one patient who missed the follow up). Most frequent adverse events include: flu-syndrome, fever, weakness, headache and weight loss, which caused a temporarary dose reduction in 2 cases. Neutropenia was reported in 5 patients which warranted a temporarary drug withdrawal in 2 of them. One case experienced subclinical hypothyroidism on week 32 of treatment who was managed with replacement therapy. Serious adverse event was not reported during the study, but in one case a severe coombs positive hemolytic anemia occurred on week 12 of treatment. This event was managed with PEG-IFN withdrawal, intravenous immunoglobulin injection, and oral glucocorticoid and after 3 weeks the treatment restarted and continued thereafter. This event was unexpected and we still do not know whether it was drug related or not. Table 2 summarizes all adverse reactions reported during the study.

Table 2
Frequency of adverse events in 31 thalassemic patients treated with PEGASYS

Adverse Events	PATIENTS N	(%)
	31	100
General		
Flu Syndrome	31	100
Chills	10	32.2
Weakness	10	32.2
T>39	9	29
Headache	6	16.3
Sever Flu Like Syndrome	2	6.4
Skin	21	67.7
Alopecia	15	48.3
Local injection pain	10	32.2
Local induration	2	6.4
Generalized rash	3	9.6
Utricaria	1	3.2
Pruritus	5	16.1
Exaggeration of skin reaction		
of Desferal	5	16.1
Vitiligo	1	3.2
Acne (Comodon)	1	3.2
Gastrointestinal	17	54.8
Anorexia	9	29
Weight loss	10	32.2
Dry Month	3	9.6
Nervous system	10	32.2
Mood change	9	29
Somnolence	7	22.5
exitability	5	16.1
Endocrine	2	6.4
Hypothyroidism	1	3.2
Hematology	5	16.1
Leukopenia	5	16.1
Thrombocytopenia	4	12.9
Coombs positive	1	3.2
hemolytic anemia		
Musculoskeletal	2	6.4
Arthralgia	2	6.4
Ocular	2	6.4
Photosensitivity	2	6.4

EFFICACY RESULTS: Omitting the two patients who did not finish the study, we analyzed the efficacy result in 30 patients by a per-protocol approach.
26 out of 30 patients (86.6%) attained an EVR which did not match with biochemical response in 3 of them; ie, serum ALT did not return to normal. At the end of treatment period ETR was the same as EVR (86.6%), but at this point 4 patients had a raised ALT which retuned to normal in 2 of them, after drug discontinuation. These two patients were considered to have Interferon toxicity. Data about 24 weeks post treatment was available in 23 patients, which showed an SVR of about 14/23 (60.8%).

Conclusion

Previous studies in thalassemic patients with chronic HCV infection reported that INF monotherapy could produce a high rate of SVR (25-40%) comparable or even better than non-thalassemic patients. [11- 16] A recent study with INF alfa monotherapy in Iran showed that in TDT patients SVR was about 25%.[17] Efforts and trials are going on to increase the rate of SVR by using INF alfa and ribavirin [18- 20], but as mentioned above ribavirin is not yet approved in thalassemics due to risk of hemolytic anemia. Combination of INF alfa and amantadine (AMA) which has shown to be superior to INF alfa monotherapy in non thalassemic patients[21] could potentially be another option in thalassemic patients. In a randomized controlled study we showed that, although there was no significant difference between the ETR of patients receiving INF alfa plus AMA versus INF alone, but the SVR was significantly increased in INF+AMA group.[22] This study, which was the first one using Pegylated INF in thalassemic patients, confirms that an SVR as high as 60% can be achieved with peginterferon monotherapy in Genotype 1 dominant HCV infected thalassemic patients and also shows that peginterferon alfa-2a is safe and tolerable in these patients. Till now there is no published study worldwide about using peginterferon alfa in thalassemics, so we have no reference to compare our study with. In our opinion the reasons that thalassemic patients achieve a better SVR not only by INF but also by PEG-INF, compared with to non-thalassemics is that: Thalassemic patients should be checked yearly for all viral markers including HCV antibody[3]. So early detection and treatment of HCV infection might be one the reasons for this promising result. Jackel E et al has recently shown that treatment of acute HCV infection in non-thalassemic subjects can results in over 90% SVR.[23] The mean duration of HCV infection in this study was 4 years (Table 1), which is less than what we usually see in non-thalassemic subjects. Looking from patient's view; thalassemic patients are a suffering group who are not only are forced to bear a Desferroxamine pump under their skin many hours per day, in order to get rid of the extra iron out of their body, but also should receive packed cell transfusion every 15-25 days to attain their growth and development. For these special patients, we think weekly INF makes a lot of difference with a 3 time per week regimen. Looking from physicians side, our experience indicate that the cure of HCV-related liver disease in thalassemic patients is not an unrealistic aim and may be reached with the safe and tolerable peginterferon alfa-2a preparation (PEGASY) in a sizable portion of cases (60%, SVR), especially when HCV infection is diagnosed in an early phase by patient screening program.

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REFERENCES

1. Wonke B, Hoffbrand AV, Brown D, Dusheiko G. Antibody to hepatitis C virus in multiply transfused patients with thalassaemia major. J Clin Pathol 1990 Aug;43(8):638-40
2. Tong MT, El-Farra NS, Reikes AR, Co RL: Clinical outcomes after transfusion-associated hepatitis C. N Engl J Med 332:1463
3. Mirmomen SH, Gofrani H, Drayani N, Niknami H. Prevalence of chronic hepatitis C virus in adult multitransfused thalassemic patients in Iran. Govaresh, 1380, vol 33,34:120-124
4. Mirmomen SH, Alavian SM, Hajarizadeh B, et al. Hepatitis B and C among thalassemic patients in Iran; a multicenteric study [Abstract]. Govaresh 2003; 8 (43): 37
5. Thalassemic international federation. Guidelines for the clinical management of thalassemia, April 2002,(www.thalassemia.org)
6. Treatment of hepatitis C. The 2002 French consensus. Gut 2003;52:1784–1787
7. Hadziyannis et al, Peginterferon-á 2a and Ribavirin Combination Therapy in Chronic Hepatitis C , Ann Intern Med, Mar 2004; 140: 346 - 355.
8. Ishak K, Baptista A, Bianchi L, et al. Histological grading and staging of chronic hepatitis. J Hepatolo 1995;22:696-9
9. Seaele JW, Kerr JFR, Halliday JW, et al. Iron storage disease.In: MacSween RNM, Anthony PP, Scheuer PJ, (eds.), Pathology of liver, 2nd ed, Edinburg:Churchill Livingstone, PP, 185-6, 1987
10. International Autoimmune hepatitis Group Report. Review of criteria for diagnosis of autoimmune hepatitis. J hepatol 1998, 18: 929-938
11. Donohue SM, Wonke B, Hoffbrand AV, Reittie J, Ganeshaguurun K, Scheuer PJ, Brown D, Dusheiko G: Alfa INF in the treatment of chronic infection in thalassemia major. Biochemical response J Haematol 1993 Mar; 83(3):491-497
12. Di marco V, Lo Lanco O et al: Alfa-INF treatment of chronic hepatitis C in young patients with homozygous beta-thalassemia. Haematologica 1992 Nov-Dec;77(6):502-6
13. Di Marco, O. Lo Iacono, P. Almasio, C. Ciaccio, M. Capra, M. Rizzo, R. Malizia, A. Maggio, C. Fabiano,F. Barbaria, and A. Crax•D. Long-Term Efficacy of a-INF in b-Thalassemics With Chronic Hepatitis C, Blood, Vol 90, No 6 (September 15), 1997: pp 2207-2212
14. Clement MJ, Congia M, Lai ME, 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 Jul;125(1):123-128
15. Wonke B, Donohue SM, Hoffbrand AV, Scheuer PJ, Brown D, Dusheiko G. Recombinant alpha 2B interferon(INF) in the treatment of chronic hepatitis C disease in thalassemia major (TM). Bown Marrow Transplant 1993; 12:24-25
16. Sipiliopoulou I, Repanti M, et al. Response to interferon alfa-2b therapy in multitransfused children with beta-thalassemia and chronic hepatitis C. Eur J Clin Microbiol Infect Dis 1999 Oct;18(10):709-15
17. Mirmomen S, Ghofrani H, Forootan Pishbijary H, Ebrahimi Daryani N, Jafar Farahvash M, Sharifian R.A, Azmodeh F, Malekzadeh R. Safety and Efficacy of Interferon Alfa for the Treatment of Chronic Hepatitis C Infected Subjects with Transfusion Dependent Thalassemia in Iran. Medical Journal of The Islamic Republic of Iran August 2003 , Vol 17 No 2
18. Telfer PT, et al. Combination therapy with INF alpha and ribavirin for chronic hepatitis C virus infection in thalassaemic patients. Br J Haematol 1997 Sep;98(4):850-5
19. Li CK, et al. Combination therapy as frontline treatment for chronic hepatitis C in thalassemia. Presented in 8th international conference on thalassemia and the hemoglobinopathies(abstract form). October 18-21 Athens-Greece
20. Wonke B, et al New approaches to the management of hepatitis and endocrine disorders in Cooley's anemia. Ann N Y Acad Sci 1998 Jun 30;850:232-41
21. Mangia A, Minerva N, Annese M, Leandro G, Villani MR, Santoro R, Carretta V, Bacca D, Giangaspero A, Bisceglia M, Ventrella F, Dell'Erba G, Andriulli A. A randomized trial of amantadine and interferon versus interferon alone as initial treatment for chronic hepatitis C. Hepatology. 2001 Apr;33(4):989-93.
22. S. Mirmomen, R. Malekzadeh, N.E. Daryani, M.R. Sohrabi. Amantadine and Interferon versus Interferon alone as initial treatment of chronic hepatitis C infected thalassemic patients: a pilot randomized study. Gut 2002; 51 (Suppl III) A11.Best abstract in UEGW 2002
23. Jackel E, et al. Early treatment of acute HCV infection with Interfron á2b monotrapy prevents development of chronic HCV infection. Presented at 51st American Association for Study Liver Disease (AASLD) Oct 2001.