Safety and efficacy of pegylated interferon α-2a and ribavirin for the treatment of hepatitis C in patients with thalassemia

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ABSTRACT

Antiviral treatment of hepatitis C virus in thalassemia has raised concerns of ribavirin-induced hemolysis and increased iron loading. This study examined the change in liver iron concentration, transfusion requirement, virological response, and iron-related toxicities after pegylated interferon α-2a/ribavirin treatment in patients with thalassemia. Median transfusions increased by 44%. However, only 29% (4/14) of patients showed an increase of liver iron concentration > 5mg/g dry wt. and overall liver iron remained stable. One of 4 patients with genotype 2 or 3 demonstrated sustained viral response, compared with 50% with genotype 1 (6/12). No patient developed cardiac, liver or endocrine toxicities, although neutropenia occurred in 52%. The molar efficacy of deferoxamine improved with reduction in liver inflammation on biopsy (p=0.001). In conclusion, antiviral treatment is safe if transfusion requirement, iron toxicities and neutropenia are monitored.

Key words: hepatitis C, iron overload, β thalassemia, pegylated interferon α, ribavirin.

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Introduction

Patients with β-thalassemia major receive chronic blood transfusions and have an increased prevalence of chronic Hepatitis C virus (HCV) infection,[1] particularly if transfused before HCV serological testing became available. These patients frequently have increased hepatic iron concentrations and iron-induced liver damage, even given optimal iron chelation therapy.[2] Furthermore, iron overload and HCV infection have been shown to be independent risk factors for progression of liver fibrosis.[3] Patients with hemoglobinopathies have traditionally been excluded from large studies of therapy of HCV,[4] particularly studies that include ribavirin because of the associated hemolysis[5] leading to an increase in transfusion requirement, iron accumulation and risk of iron-related toxicities. Furthermore, increased iron stores have been associated with poor response to interferon-ribavirin treatment.[6]

The association between iron stores and response to HCV treatment has been particularly controversial in transfused patients with thalassemia.[7-10] Prior studies in thalassemia reporting treatment of HCV with interferon α (IFN) and ribavirin (RVN)[8,10] or peg-IFN and RVN[11] were limited in size, reported few end-of-treatment liver iron concentrations (LIC), and did not examine for iron-related toxicities. The present study quantifies the response to combined peg-IFN-2a and RVN treatment in patients with β-thalassemia major as measured by viral response, hepatic iron burden, transfused blood consumption, chelation efficacy, and iron-related liver, heart, and endocrine toxicity.

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The online version of this article contains a supplemental appendix.

Design and Methods

(*Additional method details can be found in the Online Supplementary Appendix*)

Patient selection

The study was conducted by the Thalassaemia Clinical Research Network. Inclusion criteria included age ≥18 yrs, HCV RNA positive by PCR, HBsAg and HIV negative, and willingness to use contraception until six months after stopping ribavirin. Exclusion criteria included use of interferon-α within the previous six months, enrollment in other interventional trials, pregnancy or breastfeeding, significant liver dysfunction, or other disease-related exclusions.

Study design

This was a prospective, open-label, single arm trial of pegylated interferon-α 2a (Pegasys®) and ribavirin (Copegus®, both from Roche Pharmaceuticals, Hoffmann-La Roche Inc., Nutley, NJ, USA hereafter abbreviated peg-IFN2a/RVN). Patients were treated with peg-IFN2a with 180 μg subcutaneously once weekly. RVN was administered as 800 mg daily for those weighing ≤50 kg, 1,000 mg daily for those with body weight 51 to 75 kg and 1200 mg daily for those with body weight >75 kg (minimum dose 13.4 mg/kg/d). Treatment duration was 48 weeks for genotype 1 and 24 weeks for genotypes 2 or 3. Dose reductions were required for ribavirin for a 2-fold increase in blood requirement and for PegIFN2a for standard indications; GCSF was initiated if neutropenia required prolonged dose reduction. All subjects received blood transfusion therapy (maintaining a pre-transfusion hemoglobin level at approximately 10 g/dL) and chelation treatment with deferoxamine (DFO). Compliance with treatment was monitored using patient diaries, questionnaires, returned vials for peg-IFN2a and pill counts for RVN. The protocol was approved by the NIH appointed Protocol Review Committee and Data Safety Monitoring Board, and each institution's Institutional Review Board. All patients provided written informed consent.

Liver iron concentration (LIC) was measured from paraffin embedded biopsy samples obtained at baseline and 48 weeks (Mayo, MN, USA). Total iron score (Deugnier system), liver inflammation and fibrosis (Ishak scoring system) were determined by a single pathologist blinded to treatment week. HCV-RNA was determined using the Roche COBAS (qualitative and quantitative). Viral response was characterized[12] by a rapid viral response (RVR: $\log_{10}$(HCV-RNA) decline > 2 or negative after four weeks) and a sustained viral response (SVR: undetectable viremia at 24 weeks after the end of treatment).

Determination of total body iron stores and chelator efficacy

The chelator efficacy characterizes the iron excreted from the total body iron stores in relation to the chelator dose. As total body iron excretion cannot be measured long-term, the molar efficacy of DFO was calculated from the daily iron input from blood transfusions (Fe_{Tx}), the chelator dose rate (D), and the difference in total body iron stores (TBI) as defined by equation,[1,13] with TBI calculated from dry weight LIC and body weight at baseline and 48 weeks (time interval Δt).[14]

$$\text{molar efficacy} = [Fe_{Tx} + (TBI_{baseline} - TBI_{48\,w})/\Delta t] / D$$

Table 1. Clinical data of patients (genotype 1: n=12, genotype 2 or 3: n=4) completing combined peginterferon α-2a/ribavirin treatment: median values (interquartile range) of pre-transfusion hemoglobin (pre-Tx Hb), blood transfusion normalized to a hematocrit of 70 % (Tx), liver function, iron and chelation (deferoxamine) parameters.

	Baseline[1]	*Weeks 1-24*	*Weeks 25-48*	*Weeks 49-72*
pre-Tx Hb (g/dL)	10.4 (0.9)	9.5 (0.9)*	9.8 (1.2)	10.6 (1.0)
Tx (Hct=70 %) (mL/kg/yrs)	152 (37)	226 (77)**	169 (123)*	161 (99)
Daily iron input (mg/d)	19.1 (4.5)	27.3 (11.2)**	20.1 (11.7)*	21.1 (6.1)
Mean chelator dose (mg/d)[2]	1642 (991)	1754 (723)	1717 (776)	1920 (820)
Peg-IFN dose (%)[3]	na	89 (27)	98 (50)	na
RVN dose (%)[3]	na	99 (7)	100 (4)	na
Ferritin (μg/L)	1541 (3006)	2039 (1622)	1969 (1810)	1297 (1523)
ALT (U/)	74 (69)	45 (39)**	35 (49)	40 (53)
LVEF (%)	64 (15)	65 (12)	65 (13)	66 (4)
LIC (mg/g dry wt)[4]	5.8 (14.0)	nd	8.9 (14.0)	nd
Total iron score TIS	30 (9)	nd	33 (12)	nd
Liver inflammation grade	6 (2)	nd	5 (2)	nd
Liver fibrosis stage	2 (2)	nd	2 (2)	nd
Molar chelator efficacy (%)	11.8[5] (11)	12.2 (15), range 1.5 - 43.8		nd

[1]Baseline parameters were assessed over the previous six months, significance relative to baseline values was tested by paired Wilcoxon test (p<0.05+, p<0.01, p<0.001**); [2]prescribed chelator dose; [3]percentage of scheduled treatment dose; [4]LIC assessed at baseline and after 48 weeks (n=14, p=0.079); [5]assuming iron balance: approximate efficacy = ratio of daily iron input to mean chelator dose.*

Statistical analysis

Due to the sample size, non-parametric data analysis (median values, interquartile range (IQR), paired Wilcoxon rank test, Wilcoxon-Mann-Whitney's U-test, Spearman rank correlation coefficient RS) was performed. A p value ≤0.05 was considered significant.

Results and Discussion

Patient enrollment and study course

Twenty-one patients were enrolled and started peg-IFN2a/RVN treatment. Baseline characteristics are shown in Table 1 of the *Online Supplementary Appendix*. All patients had a viral load of $\log_{10}$[HCV-RNA(IU/mL)] >4.0. No patients had cirrhosis (Ishak Fibrosis score 5 or 6). Sixteen patients (age: 22–44 yrs, 76% treatment naïve) completed the treatment protocol. One patient died at week 9 after being admitted to hospital from presumed sepsis (ANC at admission 4.9 nl^{-1} and without a history of neutropenia). Three participants dis-

Table 2. Adverse effects in enrolled patients (n=21): rates of withdrawals, dose reduction of peginterferon α-2a (pegIFN2a) and ribavirin (RVN), and side effects.

Adverse events	*Week*	*N*[2]	*Percent*[3]
Withdrawal from treatment		5	24%
Flu, neutropenia, thrombopenia	4	1	5%
Exclusion criteria (wife pregnant)	6	1	5%
Death (presumed sepsis)	8	1	5%
Flu, persistent cough	16	1	5%
Flu, rash, sadness	36	1	5%
Dose reduction			
Neutropenia (peg-IFN2a)[1]		11	52%
Anemia (RVN)		1	5%
Other (rash, weight loss, depression)		3	14%
Side effects			
Flu-like symptoms		11	52%
Headache		11	52%
Fatigue		10	48%
Nausea		9	43%
Cough		9	43%
Insomnia		7	33%
Rash		7	33%
Abdominal pain		6	29%
Back pain		5	24%
Neck pain		4	19%
Crying or sadness		4	19%
Irritability		4	19%
Diarrhea		3	14%
Depression		3	14%
Sore throat		2	10%
Weight loss		2	10%
Alopecia		2	10%
Anxiety		2	10%
Other		17	81%

[1]Dose reductions were required if ANC reached 0.75nl^{-1}, but some patients had reductions at 0.9nl^{-1}; 5 patients received granulocyte colony stimulating factor
[2]N=number of patients. [3]Percent of patients (n=21).

continued between weeks 4 through 16 (one each for persistent cough, extreme fatigue, and pregnant spouse), and one participant dropped out at 36 weeks (fatigue, rash, sadness). The follow-up liver biopsy at 48 weeks was obtained in 14 of the 16 patients.

Iron accumulation and related toxicity during pegylated interferon α-2a/ribavirin treatment

The median blood transfusion requirement increased (Table 1), while the median LIC increase of 1.7 mg/gdw was not significant (p=0.08). In 4 out of 14 participants, LIC increased by more than 5 mg/gdw. The change in LIC did not correlate with the change in daily iron input averaged over the 48 weeks.

Left ventricular ejection fractions remained stable (Table 1) and no pathological arrhythmias were reported. No participant developed diabetes mellitus or thyroid disease. Liver fibrosis and inflammation did not change significantly. There was a trend between change in LIC and reduction in the liver inflammation grade (RS=0.55, p=0.051).

Viral response

Sustained viral response (SVR) was achieved by 1 out of 4 of genotype 2 or 3 patients and in 6 out of 12 of genotype 1 patients after 48 and 72 weeks respectively. In genotype 1 patients, SVR could be best predicted by a $\log_{10}$(HCV-RNA) decline > 1.83 after four weeks with a sensitivity of 100 % and a specificity of 83 % (*Figure 1, Online Supplementary Appendix*). SVR was not related to baseline LIC, change in LIC, transfusion requirement, peg-IFN or RVN dose reduction. However, median increase in daily iron input from baseline to 48 weeks was predictive of SVR (p=0.04).

Liver enzymes and chelator efficacy in response to viral treatment

After 48 weeks, a significant decrease in ALT levels (Table 1) was accompanied by reduction in histological inflammation (RS=0.60, p=0.03). The molar efficacy of deferoxamine (Equation) correlated with the decrease in ALT (RS=-0.73, p<0.01), and more strongly with the reduction in liver inflammation (RS=-0.80, p<0.001) (Figure 1). The calculated molar efficacy of DFO ranged from 1.5 to 43.8 % (Table 1).

Adverse events

Most adverse events were those commonly reported in other trials of peg-IFN2a/RVN (Table 2). Of 21 patients, 11 developed neutropenia (ANC <0.9 nl^{-1}) which led to peg-IFN2a dose reduction. Neutropenic patients had significantly lower median LIC (4.7 *vs.* 13.4 mg/g$_{dw}$, p=0.01). Ten serious adverse events were reported in 5 patients including 4 febrile events, central line infection, acute cholecystitis, transfusion reaction, antibiotic reaction, an event including high blood pressure, headache and neck pain. Most of the serious adverse events were judged either unrelated or remotely related to HCV treatment drugs by the investigator, and resolved with specific medical therapy.

Ribavirin induced hemolysis, liver function, iron toxicity, and adverse effects

Contrary to an expected primary endpoint result of a significant increase in liver iron, only 29% of patients (4/14) had a LIC increase >5 mg/gdw (5.9-9.7). Overall, LIC actually remained stable, although transfusion requirements rose by 44%. The resulting increase in daily iron input did not correspond with the change in LIC. Changes in prescribed chelation treatment regimens did not account for this finding. Peg-IFN2a/RVN treatment induced hemolysis was compensated by intensifying the transfusion treatments. A similar increase in transfusion requirement of 30 to 40% in thalassemia patients receiving combined interferon and ribavirin (approximately 16 mg/kg/d) treatment for 6-12 months was observed in other studies.[8,10,11] In the present study, chelator efficacy of DFO improved as liver inflammation decreased (Figure 1) which is supported by the correlation between the change in molar efficacy (assuming iron balance at baseline, see Table 1) and the reduction in liver inflammation (RS=-0.67, p=0.025; *data not shown*). However, the molar chelator efficacy of DFO in thalassemia major patients was lower in the present study than reported for well-chelated patients,[13] but was similar to that reported in 230 patients in the ICL670-107 trial.[15] We cannot exclude that patients improved compli-

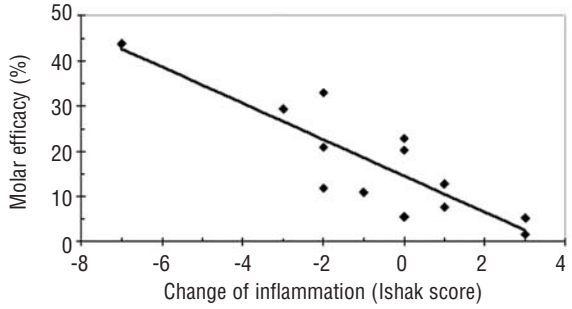

Figure 1. Reduction of inflammation as indicated by a negative change of the Ishak inflammation score from baseline to 48 weeks under pegIFN2a/RVN treatment correlates with molar efficacy of deferoxamine (R_s=0.80, p=0.001).

ance during study without a change in prescribed dose.

The present study found a similar profile of adverse events as other reports.[16-18] Furthermore, no iron-related heart, liver, or endocrine toxicities were noted during the treatment period despite the increased transfusion requirement. Flu-like symptoms appear to be the most common side effect (52%) from peg-IFN-2a/RVN treatment in thalassemia patients similar to non-thalassemia patients.[7,17] Treatment-related neutropenia is more common in thalassemia than in other patient populations[17] (52% *vs.* 21%, p<0.003) and this toxicity should be monitored for closely.

Viral response and predictors of SVR

Fifty percent of genotype 1 patients demonstrated sustained viral response, a rate similar to that reported in studies using either combined IFN/RVN or peg-IFN2a/RVN in patients with β-thalassemia major,[8,10,11] and recent studies in non-thalassemic patients using combined treatment for 48 weeks.[17,19] The response rate of subjects with genotype 2 or 3 in our study after 24 weeks of therapy (25%) was lower compared with non-thalassemia populations (85%) treated similarly,[16] although the analysis is limited by the small sample size. The poorer response in patients with genotype 2 or 3 in our study suggests that longer treatment duration may be needed in these patients. In addition to genotype, viral kinetics as defined by $\log_{10}$(HCV-RNA) decline or by complete viral response (HCV-RNA < detection limit) after 2-12 weeks is a strong predictor of viral response and an important factor in determining the length of treatment in non-thalassemic patients.[12,20] In our thalassemia patient group with genotype 1, a $\log_{10}$(HCV-RNA) decline >1.83 after four weeks of treatment was highly predictive for SVR (*Figure 1, Online Supplementary Appendix*). In non-thalassemic genotype 1 patients naïve to treatment, the best predictor was a log-decline >1.39 after two weeks.[20] This is also highlighted by the percentage of patients with relatively late first undetectable HCV-RNA (*Table 2, Online Supplementary Appendix*) who still develop SVR in contrast to non-thalassemic patients.[20,21] Prior studies have shown a variable impact of total body iron burden on HCV treatment response.[6] In the present study, we did not find a correlation between SVR and iron burden, although severe iron overload (LIC >17 mg/g dw) may delay viral response kinetics. These different results may be explained by the recent finding of impairment of HCV viral replication by high iron concentrations and iron dependent attenuation of antiviral immune response.[22]

To summarize, total body iron stores (LIC) did not increase in HCV infected thalassemia patients as expected from increased blood consumption induced by peg-IFN2a/RVN treatment, mainly due to reduced liver inflammation leading to a higher chelation efficacy for deferoxamine. Despite an increase in iron burden in some participants, it appears that peg-IFN2a/RVN combination therapy has an acceptable safety profile in patients with thalassemia. Increased monitoring of iron-related toxicities and neutropenia should be standard in these patients. The response rates for participants with genotype 1 after 48 weeks of treatment were similar to the non-thalassemia population. Genotype 2 or 3 patients appear to have a lower SVR rate after 24 weeks of therapy despite rapid viral response; therefore, 48 weeks of therapy should be considered.

Appendix

This is publication number five of the Thalassemia Clinical Research Network (TCRN). The following TCRN sites and investigators contributed to the Hepatitis C Treatment Study (listed in alphabetical order): Children's Hospital Boston: Ellis Neufeld, MD, PhD, Principal Investigator, Melody Cunningham, MD, Co-Principal Investigator, Jennifer Braunstein, RN, Study Coordinator; Children's Hospital of Philadelphia: Alan R. Cohen, MD, Principal Investigator, Janet L. Kwiatkowski, MD, Coinvestigator, Catherine S. Manno, MD, Coinvestigator, Marie Martin, RN, Nurse Coordinator, Debra Hillman, Regulatory Affairs Coordinator; Satellite: Children's Memorial Hospital: Alexis Thompson, MD, Principal Investigator, Dena Haddad, Study Coordinator; Children's Hospital & Research Center Oakland: Elliott Vichinsky, MD, Principal Investigator, Sylvia Singer, Co-Principal Investigator, Nancy Sweeters, Study Coordinator, Dru Foote, NP, Study Coordinator; Eun-Ha Pang, Study Coordinator; Satellite: University of California San Francisco, Laura Quill, RN, Study Coordinator; Toronto General Hospital: Nancy Olivieri, MD, Principal Investigator, Jennifer Breaton, Clinical Research Manager, Jennifer Yang, Study Coordinator; University College London: John Porter, MD, Principal Investigator, Cindy Bhagwandin, Study Coordinator; Weill Medical College of Cornell University: Patricia J. Giardina, MD, Principal Investigator, Jeffrey E. Mait and Dorothy Kleinert, NP, MPH, MA, Study Coordinators; Data Coordinating Center, New England Research Institutes: Elizabeth Wright, PhD, Principal Investigator, Eric Macklin, PhD, Statistician, Ellen McCarthy, Project Coordinator; National Heart Lung and Blood Institute oversight: Charles Peterson, MD.

Authorship and Disclosures

PH: designed the research, recruited and administered procedures to patients, analyzed the data and wrote the paper; MJ: designed the research, analyzed

the data and wrote the paper; JLK: designed the research, recruited and administered procedures to patients and wrote the paper; EW: designed the research, administered the project, analyzed the data, and wrote the paper; RF: analyzed the data, wrote the paper; EV: designed the research, recruited and administered procedures to patients and wrote the paper; PJG: designed the research, recruited and administered procedures to patients and wrote the paper; EJN: designed the research, recruited and administered procedures to patients and wrote the paper; JP: designed the research, recruited and administered procedures to patients and wrote the paper; NO: designed the research, recruited and administered procedures to patients and wrote the paper.

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