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

Paul Harmatz,[1] Maureen M. Jonas,[2] Janet L. Kwiatkowski,[3] Elizabeth C. Wright,[4] Roland Fischer,[1,8] Elliott Vichinsky,[1] Patricia J. Giardina,[5] Ellis J. Neufeld,[2] John Porter[6] and Nancy Olivieri[7] for the Thalassemia Clinical Research Network

[1]Children's Hospital & Research Center Oakland, Oakland, CA, USA; [2]Children's Hospital Boston, Boston, MA,USA; [3]Children's Hospital of Philadelphia, Philadelphia, PA, USA; [4]New England Research Institutes, Watertown, MA, USA; [5]New York-Presbyterian Hospital, New York, NY, USA; [6]University College London, London, UK, [7]University Health Network, Toronto, Canada; [8]University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Citation: Harmatz P, Jonas MM, Kwiatkowski JL, Wright EC, Fischer R, Vichinsky E, Giardina PJ, Neufeld EJ, Porter J and Olivieri N for the Thalassemia Clinical Research Network. Safety and efficacy of pegylated interferon α-2a and ribavirin for the treatment of hepatitis C in patients with thalassemia. Haematologica 2008. doi: 10.3324/haematol.12352

Design and Methods

Patient selection

The study was conducted by the Thalassaemia Clinical Research Network, an NIH-funded consortium of 6 clinical centers in North America and Great Britain, and a data coordinating center. Potential patients were identified from the Thalassaemia Clinical Research Network registry. 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 6 months, enrollment in other interventional trials, significant liver dysfunction, major psychiatric illness, alcohol abuse, neutropenia or thrombocytopenia, elevated alpha fetoprotein or liver mass suggesting hepatocellular carcinoma, organ or bone marrow transplant, renal insufficiency, unstable cardiac disease, pregnancy or breastfeeding, substance abuse, inability to comply with prescribed therapy, or male partners of pregnant women.

Study design

This was a prospective, open-label, single arm trial of pegylated interferon-α2a (Pegasys®) and ribavirin (Copegus®, both from Roche Pharmaceuticals, Hoffmann-La Roche Inc., Nutley, NJ, hereafter abbreviated peg-IFN2a/RVN) conducted between August, 2003 and June, 2006. Patients were treated with peg-IFN2a 180 μg subcutaneously once weekly. RVN was administered at 800 mg daily for those weighing ≤50 kg, 1,000 mg daily for those with body weight 51 to 75 kg and 1,200 mg daily for those with body weight >75 kg (minimum RVN dose was 13.4 mg/kg/d, mean dose about 16 mg/kg/d). Patients with genotype 1 were treated for 48 weeks; patients with genotype 2 or 3 were treated for 24 weeks. Duration of treatment as specified in the protocol was independent of virological response. Dose reductions were required for PegIFN2a for neutrophil count less than $0.75nl^{-1}$ (additional dose reductions were allowed at the clinician's discretion), platelet count less than 50×10^9/L, rising ALT, rash, severe depression or disabling symptoms and for ribavirin for a 2-fold increase in blood requirement. Iron burden was measured as liver iron concentration (LIC) from dry weight (dw) biopsy samples obtained at baseline and 48 weeks (formalin fixed, paraffin embedded tissue analyzed by ICP-MS, Mayo, Minnesota). HCV-RNA levels were determined using the Roche COBAS HCV Tests (qualitative and quantitative). Iron- and peg-IFN2a/RVN- related toxicities were assessed by liver pathology, echocardiogram, ECG, fasting blood sugar, thyroid function tests, biochemical parameters, vision and hearing tests, and adverse event monitoring. Blood transfusion volumes and schedules were at the discretion of the treating physicians, but with study-defined guidelines to maintain the pre-transfusion hemoglobin level between 9.0 and 10.5 g/dL. Transfusion volume and hematocrit were recorded for each unit of blood using each blood bank's averaged hematocrit if not individually measured. All subjects received chelation with deferoxamine (DFO). The dose for each patient was at the treating physician's discretion, with guidelines to maintain the dose relatively constant over the course of the trial. Dose adjustments were allowed for patient safety.

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.

Study outcomes

The primary outcome was a change in LIC of 5 mg/g dry wt. or greater from baseline to 48 weeks. This change was considered a clinically significant rise by the participating investigators. Secondary outcomes included change in transfusion requirement, virological response, and development of iron-related toxicities, in particular, cardiac failure, pathological arrhythmias, progression of liver disease and new endocrine diagnoses (hypothyroid, diabetes mellitus).

It is recognized that some toxicities could also be related to the peg-IFN2a/RVN therapy. Viral response was characterized according to Ferenci *et al.*:

RVR: rapid viral response defined by log10(HCV-RNA) decline >2 or negative after four weeks;

EVR: early viral response defined by log10(HCV-RNA) decline >2 or negative after 12 weeks;

ETR: end of treatment viral response with undetectable viremia after 24 and 48 weeks for genotype 2/3 and genotype 1 respectively;

SVR: sustained viral response with undetectable viremia at 24 weeks after the end of treatment.

Liver biopsies were read by a single pathologist blinded to the corresponding treatment week (baseline or 48 weeks) who determined the total iron score (TIS 0–60) using the Deugnier system and the degree of liver inflammation (grade 0–12) and fibrosis (stage 0–6) within the Ishak scoring system.

Determination of total body iron stores and chelator efficacy

Using the Angelucci relationship for ex-thalassemia patients post bone marrow transplantation,[14] total body iron stores were calculated from dry weight LIC and body weight (BW) at baseline and 48 weeks (time interval Δt) according to equation 1:

$$Total\ Body\ Iron\ store\ (TBI) = 10.6 \cdot LIC \cdot BW$$

In the absence of major contributions from gastrointestinal iron absorption, the molar efficacy of DFO was calculated from the molar daily iron input from blood transfusions (FeTx), the molar chelator dose rate (D), and the difference in total body iron stores as defined by equation 2:[13]

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

Under steady-state conditions (iron balance: Fe_{Tx}=total body iron elimination), an approximate efficacy value can be calculated by the ratio FeTx / D (*see Table 1 of article*).

Statistical analysis

As the sample size, especially in the genotype and SVR groups, was relatively small and its distribution often skewed, non-parametric data analysis (median values, interquartile range (IQR), paired Wilcoxon rank test, Wilcoxon-Mann-Whitney's U-test, Spearman rank correlation coefficient R_S) was performed unless otherwise specified. A p value ≤0.05 was considered significant and p value <0.1 was considered a trend. ROC curve plots were used to determine the optimum time and log_{10}(HCV-RNA) decline level for prediction of SVR. The statistical software packages SAS 9.1 (SAS Institute, Inc.) and StatXact (Cytel Software Corporation) were used for all analyses.

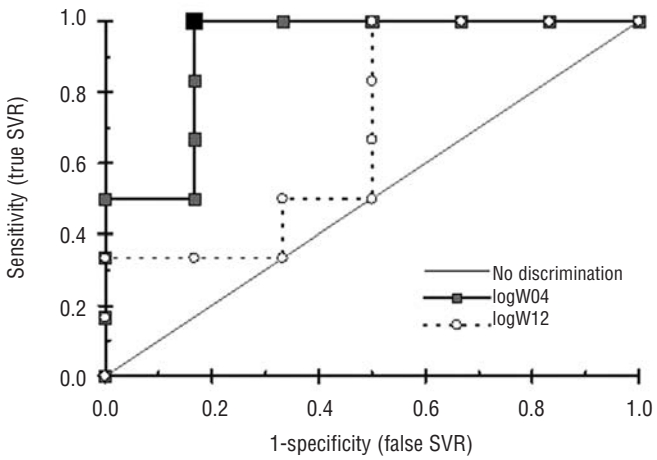
Supplementary Table S1. Patient demographics and baseline characteristics (n=21): percentages or median values and interquartile ranges (IQR).

Characteristics	*Percentage or median (IQR)*	*Range*
Male (%)	48	
Asian ethnicity (%)	24	
Splenectomy (%)	52	
HCV genotype 1 (%)	71	
HCV genotype 2 (%)	24	
HCV genotype 3 (%)	5	
Previous interferon (IFN) alone (%)	14 (genotype 1)	
Previous IFN+ribavirin (%)	10 (genotype 1)	
Age (yrs)	32 (6)	22–44
Log_{10} [HCV-RNA (IU/mL)]	5.7 (0.9)	4.0–6.8
Absolute neutrophil count (nl^{-1})	4.14 (2.05)	1.7–12.5
ALT (U/L)	83 (68)	38–301
Albumin (g/dl)	4.1 (0.3)	3.6–4.6
Prothrombin time, INR	1.1 (0.3)	0.7–2.8
Ferritin (µg/l)	1770 (2756)	408–14380
Liver iron LIC (mg Fe/g dry weight)	7.2 (12.1)	1.1–44.2
Total iron score TIS (Deugnier 0-60)	34 (15)	8–56
Liver inflammation (Ishak grade 0-12)	6 (4)	3–11
Liver fibrosis (Ishak stage 0-6)	2 (2)	1–4
Left ventricle ejection fraction (%)	63 (14)	48–75

Supplementary Table S2. Comparison of viral response to pegIFN2a/RVN treatment between genotype-1 thalassemia and normal patients: mean (± SD) log_{10}(HCV-RNA) decline rate (log-DR) and fraction of patients (%) who had their first undetectable HCV-RNA at weeks 2- 36.

Time	*Thalassemia*		*Normal patients*			
	This study		*Zeuzem et al.**		*Ouzan et al.°*	
	n=12	*with SVR*	*n=235**	*with SVR*	*n=20*	*with SVR*
log-DR (d^{-1})	0.03±0.03	0.05±0.04	n.d.	n.d.	0.08 ± 0.06	0.12 ± 0.07
Week 2	0	0	n.d.	n.d.	10	100
Week 4	8	100	47	89	40	63
Week 12	33	75	26	25	30	40
Week 24	17	0	10	8	n.d.	n.d.
Week 36	17	100	n.a.	n.a.	n.d.	n.d.
All (negative/n)	75	50	83	50	80	40

**Patients were treated with peginterferon alfa-2b plus ribavirin for 24 weeks instead of 48 weeks. *Reference 21; °Reference 20. For each pair of columns, the first column shows the % of patients who first became negative at that week and the second column shows the % of these that achieved SVR.*



Supplementary Figure S1. ROC curves of log_{10}(HCV-RNA) decline in genotype 1 patients after four and 12 weeks of pegIFN2α/RVN treatment with areas under the curve (±SE) of 0.92 (±0.09) and 0.69 (±0.17) respectively. A cut-off value of log_{10}(HCV-RNA) decline >1.83 after four weeks (large solid square) predicts patients achieving SVR with a positive and negative predictive value of 86% and 100%.