Poster #S1004

Clearance of HCV in Children at 5-Year Follow-up Is Predicted by Sustained Virologic Response at 24 Weeks Post Treatment With Interferon alfa-2b Plus Ribavirin

D. Kelly,[1] B. Haber,[2] R. P. González-Peralta,[3] K. F. Murray,[4] M. M. Jonas,[5] J. P. Molleston,[6] M. R. Narkewicz,[7] F. R. Sinatra,[8] T. Lang,[9] A. Lachaux,[10] S. Wirth,[11] M. Shelton,[12] H. S. Te,[13] H. Pollack,[14] W. Deng,[15] S. Noviello[15]

[1]Liver Unit, Birmingham Children's Hospital, Birmingham, United Kingdom; [2]Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA; [3]University of Florida, Gainesville, Florida, USA; [4]Seattle Children's Hospital and Regional Medical Center, Seattle, Washington, USA; [5]Children's Hospital Boston, Boston, Massachusetts, USA; [6]Indiana University School of Medicine, Riley Hospital for Children, Indianapolis, Indiana, USA; [7]University of Colorado Denver School of Medicine and The Children's Hospital, Aurora, Colorado, USA; [8]Keck School of Medicine of the University of Southern California, Los Angeles, California, USA; [9]Klinikum Starnberg, Starnberg, Germany; [10]Hospices Civils de Lyon, Lyon, France; [11]HELIOS Klinikum Wuppertal, Wuppertal, Germany; [12]Cook Children's Health Care Network, Fort Worth, Texas, USA; [13]University of Chicago Medical Center, Chicago, Illinois, USA; [14]New York University, New York, New York, USA; [15]Schering-Plough Research Institute, Kenilworth, New Jersey, USA

Abstract

Background and Aim: Sustained virologic response (SVR) 24 weeks after treatment of chronic hepatitis C virus (HCV) infection with interferon (IFN) alfa-2b ± ribavirin (RIBA) predicts long-term clearance (>5 years) of HCV from serum in adults (McHutchison et al, *J Hepatol* 2006;44[suppl 2]:S275). The aim of the current study was to confirm long-term HCV clearance in children treated with IFN+RIBA.

Methods: 97/166 (58%) children treated with IFN+RIBA in 2 pediatric clinical trials (González-Peralta et al, *Hepatology* 2005;42(5):1010-8) were assessed annually for up to 5 years for clinical evidence of liver disease progression and virologic evidence of relapse in sustained responders (SRs).

Results: 56 SRs and 41 nonresponders (NRs) entered the study and were followed for a mean of 261 and 238 weeks, respectively. 82% and 75% of SRs and 71% and 63% of NRs completed 3 and 5 years of follow-up, respectively. One SR patient relapsed during the 5-year follow-up at year 1. The patient had a baseline HCV-RNA level of 31,000,000 copies/mL before receiving 48 weeks of treatment with IFN+RIBA 15 mg/kg/day and had genotype 1a prior to treatment and at relapse. Kaplan-Meier estimate for continued sustained response at 5 years is 98% (95%, 100%). Of the 56 SRs at the end of the initial 24-week follow-up, 54 (96%) had normal alanine aminotransferase (ALT) levels during long-term follow-up and 1 (2%) had missing data. The only SR with elevated ALT values during the 5-year follow-up had levels <3 × upper limit of normal. None of the patients had clinical progression of liver disease and no deaths occurred. Serious adverse events were reported for 5 patients; all were considered unlikely related to IFN+RIBA.

Conclusions: SVR 24 weeks following therapy with IFN+RIBA in pediatric patients predicts long-term clearance of HCV. These results confirm those of McHutchison et al. and suggest that successful treatment (SVR) of HCV infection with IFN+RIBA leads to a clinical cure in both adults and children.

Note: Abstract has been revised since submission.

Background

- An estimated 100,000 children in the United States are chronically infected with hepatitis C virus (HCV)[1]
- Sustained virologic response (SVR) rates of 46% to 61% are attained among children or adolescents with chronic hepatitis C who receive conventional interferon alfa (IFN-alfa)-2a or -2b plus ribavirin (RIBA; 15 mg/kg/day) for 12 months[2,3] or 48 weeks[4]
- The durability of SVR in children is unknown; however, studies in adults indicate that up to 99% of patients who attain SVR after treatment with IFN alfa-2b (Intron A®) with or without RIBA remain free of virus during the subsequent 5-year period[5]

Aim

- To assess the durability of SVR (undetectable HCV-RNA 24 weeks after cessation of therapy) and HCV-associated disease progression in children with chronic hepatitis C who were treated for 48 weeks with IFN alfa-2b plus RIBA and completed 24 weeks of follow-up

Patients and Methods

Study Design

- Phase 3b, multicenter, long-term, follow-up study of children 3 to 16 years of age with chronic hepatitis C who were previously treated with IFN alfa-2b (3 MIU/m^2 3 times weekly) plus RIBA (8 mg/kg/day, 12 mg/kg/day, or 15 mg/kg/day) for 48 weeks in 2 international clinical trials[4]
- Patients who completed 24 weeks of follow-up in these treatment studies were invited to participate in a long-term, observational, follow-up study
  - Patients could enroll at any time from 1.5 to 5.5 years after treatment
  - No drug was administered during the follow-up study
    - Patients were discontinued if they received antiviral retreatment for chronic hepatitis C during the study
  - Patients were assessed annually for up to 5 years for virologic relapse in sustained responders and for clinical evidence of liver disease progression

Efficacy End Point

- Primary end point was the durability of virologic response in children with chronic hepatitis C who were previously treated with IFN alfa-2b plus RIBA and were sustained responders 24 weeks after treatment

Assessments

- Long-term follow-up assessments were scheduled for 1 year after the end of the 24-week follow-up period in the initial treatment studies and then yearly for an additional 4 years
  - Visit date windows corresponding to the scheduled visits (**Table 1**) were defined because not all patients attended visits at the scheduled times
- Assessments were as follows:
  - Serum HCV-RNA levels in sustained responders
  - Alanine aminotransferase (ALT) levels
  - Gastrointestinal/liver examination
  - Serious adverse events
- Polymerase chain reaction (PCR) testing for HCV-RNA was performed by Schering-Plough Research Institute using a proprietary TaqMan reverse transcriptase-PCR assay (lower limit of detection, <125 IU/mL) and by Quest Diagnostics, Nichols Institute, using the Roche COBAS TaqMan assay (lower limit of quantitation, <50 IU/mL)

Table 1. Timing of Clinic Visits During Long-term Follow-up

Long-term Follow-up Visit, y	Time Since End of Treatment[a]	
	Years	Days, range
1	1.5	350-730
2	2.5	731-1096
3	3.5	1097-1462
4	4.5	1463-1812
5	5.5	1813-2194

[a] End of treatment was defined as reported by González-Peralta et al.[4]

Results

- 97 of 166 (58%) patients who were treated with IFN alfa-2b plus RIBA were included (**Figure 1** and **Table 2**)
  - 56 patients were sustained responders
    - 43 received RIBA 15 mg/kg/day during initial therapy
  - 41 patients were nonresponders
    - 33 received RIBA 15 mg/kg/day during initial therapy

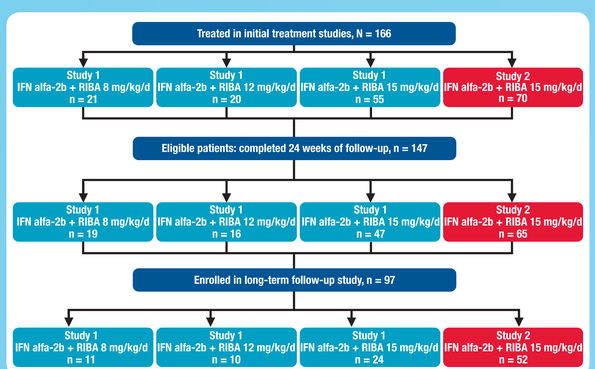

Figure 1. Patient disposition. IFN = interferon; RIBA = ribavirin.

Table 2. Patient Demographics

	Sustained Responders n = 56	Nonresponders n = 41
Male, n (%)	25 (45)	26 (63)
Race, n (%)		
Caucasian	47 (84)	31 (76)
Black	0 (0)	4 (10)
Asian	4 (7)	0 (0)
Hispanic	4 (7)	6 (15)
Other	1 (2)	0 (0)
Mean age, y (range)[a]	12.1 (6-19)	13.3 (5-19)
Mean body weight, kg (range)[a]	39.3 (14-92)	42.4 (10-87)
Source of HCV exposure, n (%)[b,c]		
Vertical transmission	30 (54)	22 (54)
Transfusion associated	19 (34)	17 (41)
Parenteral	5 (9)	2 (5)
Sporadic/other	1 (2)	0 (0)
Mean years since probable exposure (range)[b]	9.4 (1.4-16.9)	10.9 (3.4-16.9)
Genotype, n (%)[b]		
1	35 (63)	40 (98)
2	9 (16)	1 (2)
3	12 (21)	N/A
Mean baseline viral load, copies/mL[b]	2,357,838	3,334,593
HCV-RNA ≤2,000,000 copies/mL, n (%)	24 (43)	14 (34)
HCV-RNA >2,000,000 copies/mL, n (%)	32 (57)	27 (66)

HCV = hepatitis C virus; N/A = not applicable.
[a] Collected on entry to long-term follow-up protocol.
[b] Collected on entry to original treatment protocols.
[c] One sustained responder had no known source of infection.

Duration of Follow-up

- Sustained responders and nonresponders were followed for means of 261 and 238 weeks, respectively
  - 82% and 75% of sustained responders and 71% and 63% of nonresponders completed 3 and 5 years of follow-up, respectively
- In total, 70% (68 of 97) of subjects completed the study
  - More sustained responders (75%; 42 of 56) than nonresponders (63%; 26 of 41) completed long-term follow-up
  - The primary reason for discontinuation was "lost to follow-up"
  - One nonresponder discontinued the long-term follow-up study and was retreated with PEG-IFN alfa-2b (PegIntron®) plus RIBA

Durability of Response

- One sustained responder relapsed during the 5-year follow-up
  - A 6-year-old patient infected with HCV genotype 1a had a baseline HCV-RNA level of 31,000,000 copies/mL before receiving 48 weeks of treatment with IFN alfa-2b + RIBA 15 mg/kg/day
  - The patient relapsed at year 1 of long-term follow-up with an HCV-RNA level of 3,600,000 copies/mL; HCV genotype remained 1a
- The point estimate for the likelihood of maintaining response at 5 years in subjects who initially attained SVR was 98% (95% confidence interval [CI]: 95%,100%) (**Figure 2**)

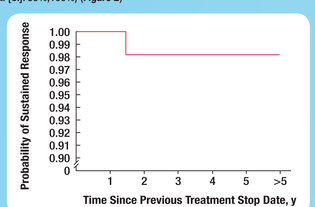

Figure 2. Kaplan-Meier estimate: durability of response.

ALT Levels

- 54 of 56 (96%) sustained responders had normal ALT levels at the last visit of long-term follow-up, and 1 of 56 (2%) had missing data (**Table 3**)
  - One sustained responder had an elevated ALT value (67 U/L) at the end of the 5-year follow-up
    - Hepatomegaly was present and considered not clinically significant, possibly due to obesity

Table 3. Changes in ALT Levels in Long-term Sustained Responders Between Follow-up Week 24 and Last Visit During Long-term Follow-up

	Number (%) of Patients	
	Long-term Follow-up ALT	
Follow-up Week 24 ALT[a]	Normal	Abnormal
Normal (n = 52)	51 (98)	1 (2)
Abnormal (n = 3)	3 (100)	0
Total (n = 56)	54 (96)	1 (2)

ALT = alanine aminotransferase; normal = ≤upper limit of normal; abnormal = >upper limit of normal.
Data missing for 1 patient.
[a] Sustained virologic responders at follow-up week 24.

Safety

- No deaths occurred
- Serious adverse events were reported for 5 patients; all were considered unlikely related to study drugs
- No clinical progression of liver disease was reported

Summary

- All but 1 of the children remained sustained responders for 5 years after the completion of treatment with IFN alfa-2b plus RIBA
- Kaplan-Meier estimate for continued sustained response at 5 years in patients who initially attained SVR was 98% (95% CI: 95%,100%)
- 96% of the children had normal ALT levels at the end of the long-term follow-up
- No clinical progression of liver disease was reported

Conclusions

- Attainment of SVR after treatment with IFN alfa-2b and RIBA predicts long-term clearance of HCV in pediatric patients
  - 98% of patients who attained SVR maintained long-term viral clearance
- These results mirror those obtained in adult chronic hepatitis C patients treated with IFN alfa-2b with or without ribavirin[5]

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Disclosures

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