Efficacy and Safety of Pegylated Interferon Alfa-2a or Alfa-2b Plus Ribavirin for the Treatment of Chronic Hepatitis C in Children and Adolescents: A Systematic Review and Meta-analysis

Eric Druyts,[1] Kristian Thorlund,[2] Ping Wu,[1] Steve Kanters,[1] Sanni Yaya,[1] Curtis L. Cooper,[3] and Edward J. Mills[1,2]

[1]Faculty of Health Sciences, University of Ottawa, [2]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, and [3]Division of Infectious Disease, University of Ottawa, Ottawa Hospital, Ontario, Canada

Background. A systematic review and meta-analysis were conducted to examine the efficacy and safety of pegylated interferon (peg-IFN) alfa-2a and peg-IFN alfa-2b plus ribavirin (RBV) in children and adolescents with chronic hepatitis C virus (HCV).

Methods. Medline, Embase, and Cochrane Central Register of Controlled Trials were searched. Clinical trials examining peg-IFN alfa-2a or peg-IFN alfa-2b plus RBV among persons ages 3–18 years with HCV were included. Data were abstracted for complete early virologic response (EVR), sustained virologic response (SVR), relapse, treatment discontinuations, hematologic and dermatologic adverse events, and growth inhibition.

Results. Eight trials met the inclusion criteria. Results indicate that 70% of subjects (95% confidence interval [CI], 58%–81%) achieved EVR, and 58% (95% CI, 53%–64%) achieved SVR. EVR and SVR were higher for those with HCV genotypes 2/3 than 1/4. Discontinuation due to adverse events and discontinuation due to viral breakthrough were each 4%, discontinuation due to a lack of response was 15%, and relapse was 7%. Anemia, neutropenia, leukopenia, and thrombcytopenia were 11%, 32%, 52%, and 5%, respectively. Alopecia, injection site erythema, and pruritus were 13%, 27%, and 10%, respectively. Small growth inhibitions were observed during treatment.

Conclusions. The results of this meta-analysis indicate that peg-IFN/RBV combination treatment is effective and safe in treating children and adolescents with HCV.

Keywords. hepatitis C; children; peg-interferon; ribavirin; meta-analysis.

The efficacy of the combination of pegylated interferon (peg-IFN) alfa and ribavirin (RBV) for the treatment of hepatitis C virus (HCV) infection has been well established in adult populations [1–4]. However, there remains a dearth of evidence of such treatments in child and adolescent populations. Although some drug regulatory authorities have approved the use of the peg-IFN/RBV combination for the treatment of HCV in children and adolescents, [5–7] the majority of evidence to support such approvals has likely come from randomized controlled trials (RCTs) in adult populations and open-label single arm clinical trials in children and adolescents [5]. To date, only 1 RCT conducted among children and adolescents with HCV has been presented in the published literature [8]. Comparable to those conducted in adult populations, this RCT found that the combination of peg-IFN alfa-2a and RBV was superior to peg-IFN alfa-2a alone in persons aged 5–17 years [8].

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Correspondence: Edward Mills, PhD, Faculty of Health Sciences, University of Ottawa, 43 Templeton St, Ottawa, ON, Canada K1N 6X1 (edward.mills@uottawa.ca).

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Although others have assessed the efficacy of the peg-IFN and RBV combination in child and adolescent HCV populations through the use of a systematic review methodology [9, 10], no comprehensive meta-analysis of clinical trial data, examining peg-IFN alfa-2a and peg-IFN alfa-2b in combination with RBV, has been conducted. To this end, the present study utilized meta-analytic techniques to compare the efficacy and safety of these treatment combinations in children and adolescents with HCV. Specifically, the present study examined the effectiveness of the 2 treatment combinations in terms of commonly reported virologic outcomes. Given concerns regarding safety and tolerability of peg-IFN/RBV therapy in the child and adolescent population, the risk of treatment discontinuation, adverse events, and growth inhibition were also assessed.

METHODS

Eligibility

Clinical trials were eligible if they assessed the efficacy of peg-IFN alfa-2a or peg-IFN alfa-2b in combination with RBV in children and adolescents (aged 3–18 years) with confirmed HCV infection. Eligible clinical trials had to provide a full treatment course to patients (typically 48 weeks for HCV genotypes 1 and 4 or 24 weeks for HCV genotypes 2 and 3). Eligible clinical trials had to present data on the outcome sustained virologic response (SVR), the primary variable of interest. Studies assessing outcomes among individuals coinfected with any other viruses (eg, human immunodeficiency virus, hepatitis B virus) were excluded. Furthermore, observational studies and conference abstract data were excluded.

Search Strategy

In consultation with a medical librarian, 2 researchers (E.D., K.T.) working independently, in duplicate, conducted a systematic literature search. The following electronic databases were searched (from inception to week 40 [1–7 October 2012]): Medline, Embase, and EBM Reviews–Cochrane Central Register of Controlled Trials. In addition, the bibliographies of published systematic reviews and relevant included clinical trials were also searched. Searches were not limited by language, and were structured in such a way as to accommodate the controlled vocabulary and search language of each database. An example search strategy is presented in Supplementary Appendix Table A.

Study Selection

Two investigators (E.D. and K.T.) working independently, in duplicate, scanned all abstracts and obtained the full text reports of records potentially meeting the inclusion criteria. After obtaining full reports of the candidate studies, the same investigators independently assessed eligibility via full text review. Where required, a third investigator (E.J.M.) provided arbitration. For articles published in a language other than English, translation services were provided to us through contacts at the University of Ottawa.

Data Extraction

Two investigators (E.D. and K.T.) working independently, in duplicate, abstracted data on SVR (defined as an undetectable HCV RNA level at the end of the 24-week posttherapy follow-up period), the primary variable of interest. Data were also abstracted on complete early virologic response (EVR; defined as an undetectable HCV RNA level at treatment week 12), relapse (defined as a recurrence of HCV RNA within the 24-week posttherapy follow-up period), and treatment discontinuations (discontinuation of treatment due to a lack of virologic response to treatment, discontinuation due to the reappearance of HCV RNA in serum while still on treatment [also called virologic breakthrough], and discontinuation due to an adverse event). Where possible, data on each of these efficacy outcomes were abstracted by HCV genotype. Data were also abstracted on hematologic (ie, anemia, neutropenia, leukopenia, and thrombocytopenia) and dermatologic (pruritus, alopecia, and injection site erythema) adverse events, as reported in the source trial publications, as well as growth inhibition. Additionally, trial characteristics were abstracted from each included trial: study design, study setting, study year, study duration, and dosing regimens. Baseline patient characteristics, such as HCV genotype and treatment experience, were also abstracted.

Data Analysis

The phi statistic (ϕ) was used to assess interrater reliability on inclusion of articles. For each outcome, pooled proportions were calculated for treatment combinations peg-IFN alfa-2a plus RBV and peg-IFN alfa-2b plus RBV together, as they are generally thought to be of comparable efficacy in adult populations [1, 11]. Sensitivity analyses looked at each of the treatment combinations separately, and pooled confidence intervals for difference in proportions analyses were conducted to assess whether meaningful differences existed between these combinations. A further sensitivity analysis assessed differences in the outcomes by HCV genotype, where possible.

The pooled weighted proportions were calculated by stabilizing the variances of the raw proportions using a Freeman-Tukey–type arcsine square root transformation, and applying a random-effects model. This is a variance-stabilizing transformation that removes the dependence of the variance on the mean of the transformed proportion (ie, it corrects for overdispersion). All analyses were conducted using StatsDirect (version 2.7.8) and R (version 2.12.2).

Table 1. Characteristics of Included Clinical Trials

Trial	Study Type	Type of Treatment and Dose	Treatment Duration	Genotype: No. (%)	No.	EVR, No. (%)	SVR, No. (%)	Relapse, No. (%)	Treatment Discontinuation due to Lack of Virologic Response, No. (%)	Treatment Discontinuation due to Virologic Breakthrough, No. (%)	Treatment Discontinuation due to an Adverse Event, No. (%)
Wirth et al, 2005 [12]	Nonrandomized trial	• peg-IFN alfa-2b (1.5 μg/kg/wk) • RBV (15 mg/kg/d)	• G1, G4: 48 wk • G2, G3: 8 patients for 48 wk, 5 patients for 24 wk	• G1: 46 (75) • G2, G3: 13 (21) • G4: 2 (3)	62	38 (61)	36 (58)	3 (5)	18 (29)	6 (10)	1 (2)
Zhang et al, 2005 [13]	Nonrandomized trial	• peg-IFN alfa-2a (104 μg/m^2/wk) • RBV (15–20 mg/kg/d)	• peg-IFN: 48-52 wks • RBV: 6-12 mo[a]	• G1: 30 (63) • G2: 3 (6) • G1, G2: 4 (8) • G2, G3: 1 (2) • Unknown: 10 (21)	54	42 (78)	29 (54)	NR	NR	NR	0
Jara et al, 2008 [14]	Nonrandomized trial	• peg-IFN alfa-2b (1.0 μg/kg/wk) • RBV (15 mg/kg/d)	• G1, G4: 48 wk • G3: 24 wk	• G1: 26 (87) • G3: 3 (10) • G4: 1 (3)	30	15 (50)	15 (50)	1 (3)	4 (13)	2 (7)	3 (10)
Al Ali et al, 2010 [15]	Nonrandomized trial	• peg-IFN alfa-2b (1.5 μg/kg/wk) • RBV (15 mg/kg/d)	• G4: 48 wk	• G4 12 (100)	12	10 (83)	9 (75)	1 (8)	0	0	1 (8)
Pawlowska et al, 2010 [16]	Nonrandomized trial	• peg-IFN alfa-2b (1.5 μg/kg/wk) • RBV (15 mg/kg/d)	• G1, G4: 48 wk • G3: 24 wk	• G1: 27 (50) • G3: 2 (4) • G4: 24 (46)	53	26 (49)	26 (49)	9 (17)	NR	NR	NR
Sokal et al, 2010 [17]	Nonrandomized trial	• peg-IFN alfa-2a (100 μg/m^2/wk) • RBV (15 mg/kg/d)	• G1, G4, G5: 48 wk • G2, G3: 24 wk	• G1: 45 (69) • G2: 2 (3) • G3: 16 (25) • G4: 1 (2) • G5: 1 (2)	65	NR	43 (66)	0	8 (12)	0	2 (3)

Table 1 continued.

Trial	Study Type	Type of Treatment and Dose	Treatment Duration	Genotype: No. (%)	No.	EVR, No. (%)	SVR, No. (%)	Relapse, No. (%)	Treatment Discontinuation due to Lack of Virologic Response, No. (%)	Treatment Discontinuation due to Virologic Breakthrough, No. (%)	Treatment Discontinuation due to an Adverse Event, No. (%)
Wirth et al, 2010 [18]	Nonrandomized trial	• peg-IFN alfa-2b (60 μg/m^2/wk) • RBV (15 mg/kg/d)	• G1, G4: 48 wk; • G2: 24 wk; • G3 with viral load ≥600 000 UI/mL: 48 wk; • G3 with <600 000 I/mL: 24 wk	• G1: 72 (67) • G2: 15 (14) • G3: 15 (14) • G4: 5 (5)	107	73 (68)	70 (65)	9 (8)	NR	NR	1 (1)
Schwarz et al, 2011 [8][b]	Randomized controlled trial	• peg-IFN alfa-2a (180 μg/1.73 m^2/wk) • RBV (15 mg/kg/d)	• G1, G2, G3: 48 wk	• G1: 45 (82) • G2: 4 (7) • G3: 6 (11)	55	NR	29 (53)	9 (16)	NR	NR	4 (7)

Abbreviations: EVR, early virologic response; G1, G2, G3, G4, G5, genotype 1, genotype 2, genotype 3, genotype 4, genotype 5; NR, not reported; peg-IFN alfa-2a, pegylated interferon alfa-2a; peg-IFN alfa-2b, pegylated interferon alfa-2b; RBV, ribavirin; SVR, sustained virologic response.

[a] The article did not state the reason for the variable treatment durations.

[b] Data are presented for only the peg-IFN alfa-2a plus RBV arm.

Table 2. Random-Effects Proportional Meta-analysis of Each Efficacy and Safety Outcome Assessed

Outcome	No. of Arms	Proportion (95% Confidence Interval)
All genotypes		
Early virologic response	6	0.70 (.58–.81)
Sustained virologic response	8	0.58 (.53–.64)
Relapse	7	0.07 (.03–.14)
Treatment discontinuation due to lack of virologic response	4	0.15 (.06–.27)
Treatment discontinuation due to virologic breakthrough	4	0.04 (.01–.12)
Treatment discontinuation due to an adverse event	7	0.04 (.01–.07)
Anemia	6	0.11 (.05–.19)
Neutropenia	6	0.32 (.22–.44)
Leukopenia	4	0.52 (.16–.87)
Thrombocytopenia	3	0.05 (.01–.15)
Pruritus	3	0.10 (.05–.16)
Alopecia	5	0.13 (.10–.17)
Injection site erythema	6	0.27 (.18–.38)
Genotypes 1/4		
Early virologic response	3	0.61 (.48–.74)
Sustained virologic response	7	0.52 (.46–.57)
Genotypes 2/3		
Early virologic response	2	0.87 (.76–.95)
Sustained virologic response	6	0.89 (.80–.96)

RESULTS

Eight trials met the inclusion criteria (Table 1) [8, 12–18]. The interrater reliability for study inclusion was high ($\phi = 0.94$). Twenty additional studies retrieved for detailed evaluation were excluded (Supplementary Appendix, Table B) [19–38]. A schematic of study selection process is provided in Supplementary Appendix, Figure A.

Most subjects who achieved an EVR (70%) also achieved an SVR (58%) (Table 2). The rate of relapse was low (7%), as were discontinuations due to a virologic breakthrough (4%) and discontinuations due to an adverse event (4%). Treatment discontinuation due to a lack of virologic response, however, was higher (15%) (Table 2). Neutropenia and leukopenia were the most common hematologic adverse events evaluated (32% and 52%, respectively), whereas anemia and thrombocytopenia were less frequent (11% and 5%, respectively). Injection site erythema was the most common dermatologic adverse event evaluated (27%), whereas pruritus and alopecia occurred less frequently (10% and 13%, respectively) (Table 2).

The sensitivity analysis comparing peg-IFN alfa-2a and peg-IFN alfa-2b indicated that these 2 treatments were comparable in terms of efficacy and safety (results available upon request). Data by HCV genotype were only available for the EVR and SVR outcomes. The results of this sensitivity analysis indicate that EVR and SVR were each higher for genotypes 2/3 (87% and 89%, respectively) than for genotypes 1/4 (61% and 52%, respectively) (Table 2).

Table 3. Growth Inhibition Results

Trial	Reported results
Wirth et al, 2005 [12]	No data reported.
Zhang et al, 2005 [13]	No data reported.
Jara et al, 2008 [14]	22 of 26 patients experienced an average of 1.6-cm reduction in growth (compared with 50th percentile for age and sex) during the treatment phase. During the 24-week follow-up period, growth velocity was entirely normal.
Al Ali et al, 2010 [15]	No data reported.
Pawlowska et al, 2010 [16]	"No influence on height was observed at follow-up and 2 years after follow-up vs baseline."
Sokal et al, 2010 [17]	No statistically significant difference in growth was observed (baseline vs follow-up: *z* score −0.4 ± 1.0 vs −0.5 ± 1.1).
Wirth et al, 2010 [18]	75 (70%) patients experienced growth inhibition (growth velocity below 3rd percentile) during the treatment phase. During the 24-week follow-up period, most patients experienced faster than normal growth.
Schwarz et al, 2011 [8] Jonas et al, 2012 [39]	Decrements of up to 0.5 *z* score were observed for weight, height, and body mass index in many patients during the treatment phase. Longer treatment durations were associated with greater decreases. For instance, 29 (33%) patients treated for 48 weeks had >0.5-unit decrement in their height-for-age score at 1 or more time points during the study. The effects were generally reversible with the cessation of therapy, although the height-for-age score had not returned to baseline after 2 years of observation in some patients.

Growth inhibition was reported in a subset of the eligible trials (Table 3). Data were inconsistently reported and therefore no meta-analysis could be performed. Generally, small growth inhibitions were observed during treatment. Most studies concluded that growth returned to normal after cessation of therapy. However, the one RCT found that height-for-age had not returned to baseline values after 2 years of observation in some patients.

DISCUSSION

The current meta-analysis indicates that peg-IFN plus RBV is effective in the majority of children and adolescents with

HCV. Efficacy is improved for those infected with genotypes 2/3 compared to those with genotypes 1/4. Adverse events are common, but seldom result in discontinuation of treatment. It is possible that minor growth inhibitions may occur with treatment, but in most cases growth returns to normal with cessation of therapy.

There are limitations to the current study's analysis that should be considered when interpreting the results. The systematic review identified a small number of trials meeting the inclusion criteria. However, this was somewhat expected given what has been found in 2 previous systematic reviews conducted [9, 10]. Given this limited number of trials, the data pooled together represent various clinical trial designs, only one of which was an RCT. Furthermore, it would have been meaningful to assess outcomes by treatment duration. Although patients with HCV genotypes 1/4 are typically treated for 48 weeks, and those with HCV genotypes 2/3 are typically treated for 24 weeks, this was not always the case in some of the included trials. It was also not possible to examine outcomes by treatment experience. Although some trials only included children and adolescents naive to peg-IFN alfa plus RBV therapy, others included both those naive to therapy and those with prior experience to peg-IFN or IFN and/or RBV.

Although the doses of peg-IFN alfa-2a, peg-IFN alfa-2b, and RBV differed across the included trials, the variability of these data combined with the limited number of included trials meant that it was not possible to conduct meaningful sensitivity analyses related to dosage. Moreover, it is important to recognize that the data on treatment discontinuation due to lack of virologic response could have been affected by the different definitions and stopping rules defined in the different trials; however, these definitions were not universally reported in the source trial publications. Additionally, the manner in which each of the selected adverse events was defined in the source trial publications may have differed; however, definitions for each of these selected adverse events were not reported in most trials.

In conclusion, the results of this meta-analysis indicate that peg-IFN plus RBV combination treatment is effective in treating children and adolescents with HCV. Although hematologic and dermatologic adverse events are common, treatment discontinuations due to these and other adverse events are infrequent.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://cid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Note

Potential conflicts of interest. K. T. has served as a consultant to Merck & Co, Pfizer, Nycomed, Takeda, Novartis, and GlaxoSmithKline. E. J. M. has served as a consultant to Merck & Co, Pfizer, Nycomed, Takeda, Novartis, and GlaxoSmithKline. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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