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PEG IFN alfa-2a vs. alfa-2b: And the winner is . . .?

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Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, Nyberg LM, Lee WM, Ghalib RH, Schiff ER, Galati JS, Bacon BR, Davis MN, Mukhopadhyay P, Koury K, Noviello S, Pedicone LD, Brass CA, Albrecht JK, Sulkowski MS; IDEAL Study Team. N Engl J Med 2009 Aug 6;361(6):580–93.

***Background**: Treatment guidelines recommend the use of peginterferon alfa-2b or peginterferon alfa-2a in combination with ribavirin for chronic hepatitis C virus (HCV) infection. However, these regimens have not been adequately compared.*

***Methods**: At 118 sites, patients who had HCV genotype 1 infection and who had not previously been treated were randomly assigned to undergo 48 weeks of treatment with one of three regimens: peginterferon alfa-2b at a standard dose of 1.5 microg per kilogram of body weight per week or a low dose of 1.0 microg per kilogram per week, plus ribavirin at a dose of 800 to 1400 mg per day, or peginterferon alfa-2a at a dose of 180 microg per week plus ribavirin at a dose of 1000 to 1200 mg per day. We compared the rate of sustained virologic response and the safety and adverse-event profiles between the peginterferon alfa-2b regimens and between the standard-dose peginterferon alfa-2b regimen and the peginterferon alfa-2a regimen.*

***Results**: Among 3070 patients, rates of sustained virologic response were similar among the regimens: 39.8% with standard-dose peginterferon alfa-2b, 38.0% with low-dose peginterferon alfa-2b, and 40.9% with peginterferon alfa-2a (P = 0.20 for standard-dose vs. low-dose peginterferon alfa-2b; P = 0.57 for standard-dose peginterferon alfa-2b vs. peginterferon alfa-2a). Estimated differences in response rates were 1.8% (95% confidence interval [CI, −2.3 to 6.0) between standard-dose and low-dose peginterferon alfa-2b and −1.1% (95% CI, −5.3 to 3.0) between standard-dose peginterferon alfa-2b and peginterferon alfa-2a. Relapse rates were 23.5% (95% CI, 19.9 to 27.2) for standard-dose peginterferon alfa-2b, 20.0% (95% CI, 16.4 to 23.6) for low-dose peginterferon alfa-2b, and 31.5% (95% CI, 27.9 to 35.2) for peginterferon alfa-2a. The safety profile was similar among the three groups; serious adverse events were observed in 8.6% to 11.7% of patients. Among the patients with undetectable HCV RNA levels at treatment weeks 4 and 12, a sustained virologic response was achieved in 86.2% and 78.7%, respectively.*

***Conclusions**: In patients infected with HCV genotype 1, the rates of sustained virologic response and tolerability did not differ significantly between the two available peginterferon–ribavirin regimens or between the two doses of peginterferon alfa-2b. (ClinicalTrials.gov No. NCT00081770) 2009 Massachusetts Medical Society.*

Which pegylated IFN treatment is the best to cure chronic hepatitis C? This long-debated question should have been finally answered by the IDEAL [1], the first large randomized study comparing head-to-head PEG IFN alfa-2a and alfa-2b combined with ribavirin (RBV). Taken at face value, these treatments are an even match: both PEGs bring home about 40% of sustained virological response (SVR) in patients infected with HCV genotype 1. Perhaps the more disturbing finding is that for PEG IFN alfa-2b the registered dosage of 1.5 μg/kg/wk is in excess, since 1 μg will obtain a comparable rate of SVR. Hence, for many years we might have over-treated patients, a practice that in real-life conditions often translates into reduced patient adherence and ultimately in reduced effectiveness.

In 2001 PEG IFN alfa-2b was approved by the FDA and then by the EMEA on the basis of the Manns study [2]. It was felt that the trial design, although showing superiority to the 1.5 μg vs. the 0.5 μg dose, did not indicate whether an intermediate dose would be sufficient. The issue was further clouded by the range of RBV doses used, even if a *post-hoc* analysis suggested higher SVR at an exposure to RBV beyond 13 mg/kg body weight/day. In the US, the latter finding was translated into a recommended dose for RBV ranging between 800 and 1400 mg/day [3]. The lack of information about the minimum effective dose of PEG IFN alfa-2b led the regulatory authorities to request its makers, as a post-approval commitment, to perform a randomized trial comparing 1.5 μg to 1 μg in genotype 1 patients. This was the original core project for the IDEAL. Data in favour of efficacy of the 1 μg dose appeared. In an investigator-driven cohort study [4], PEG IFN alfa-2a at 180 μg was later approved on the basis of Fried's trial [5] which reported rates of SVR for HCV genotype 1 comparable to Manns [2] using a narrow range of RBV doses, from 1000 to 1200 mg/day. Although a further study with PEG IFN alfa-2a by Hadziyannis [6] clarified that 800 mg of RBV were not enough, at least for genotype 1, the highest dose assessed was

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Table 1. RCTs and cohort studies with comparative data on PEG IFNs plus ribavirin.

	Type of study/sponsor	Country	Pts. *n*	Genotype	Ribavirin dose range* A: PEG alfa-2a B: PEG alfa-2b	% SVR PEG alfa-2a vs. alfa-2b	*P* value	Refs.
IDEAL	RCT/Schering – Plough	USA	3070	G1	A: 1–1.2 B: 0.8–1.4	41/40	NS	[1]
Ascione et al.	RCT/investigator initiated	Italy	320	All	A: 1–1.2 B: 1–1.2	68.7/54.4	0.008	[7]
Colombo et al.	RCT/investigator initiated	Italy	431	All	A: 1–1.2 B: 0.8–1.4	66/54	0.02	[8]
PROBE	Prospective cohort/Roche	Italy	1017	G1	A: 1–1.2 B: 1–1.2 (mostly)	36/29	0.002	[9]
PRACTICE	Retrospective cohort/Roche	Germany	1696	All	A: not stated B: not stated	59.3/53	0.008	[10]
US veterans	Retrospective cohort/US government	USA	5944	All	A: 1–1.2 B: 0.8–1.4	31/24	<0.001	[11]

*Ribavirin dose refers principally to genotypes 1 and 4 and is expressed as gm/day. Dose ranging according to body weight.

1200 mg/day. Thus, PEG IFN alfa-2a was approved for use in genotype 1 with 1000–1200 mg of RBV. Since no claim of superiority, or of non-inferiority, could be made without a direct comparison of the two interferons, a comparator arm with PEG IFN alfa-2a was included in the IDEAL design. A post-marketing dose-assessment study then became, at least in the eyes of the physicians and in the nightmares of some marketing experts, the final contest for the best PEG IFN.

A relevant difference found in the IDEAL was the rate of end-of-treatment response (ETR): 73.9% for PEG IFN alfa-2a and 63.4% for PEG IFN alfa-2b (mean of both arms). This did not translate into more SVR for the former, since the relapse rates were, respectively, 27.8% and 17.8%. To a critical eye, the results of this study are marred by the difference in the dosing of RBV, both per schedule and as actually received by the patients. Although the amount of RBV was regulated by the approved prescribing information, the dosing seems inappropriate by current standards. In fact nowadays, many clinicians (at least in Europe) use both PEG IFNs with weight-ranging dosing of RBV as the appropriate way to be sure that patients receive an adequate amount of the latter.

Although the IDEAL is a well constructed study, we must realize some of its limitations. It has been performed in a US population, with a high proportion of overweight and obese patients and 20% of those patients were of African American decent. This prevalence of difficult-to-treat patients might hence hide minor differences in efficacy of the two PEG IFNs by flattening the response curves. Even more important is the fact that, again according to the registered schedules, the rules for RBV reduction in the presence of anemia were different. When Hb level went below 10 mg/dl, patients on PEG IFN alfa-2a received only one dose reduction to 600 mg/day, while those on PEG IFN alfa-2a could have two steps of reduction, each at 200 mg/day. If Hb failed to recover to levels beyond 8.5 g/dl, RBV was stopped altogether and stepping up of RBV after Hb values had improved was not allowed in the two arms of the trial. Again, this policy may be different from everyday practice, where RBV levels are gradually reduced and readjusted individually. Interestingly, 52% of patients should have received the same dose of RBV regardless of the type of PEG IFN; however, amongst the patients actually being treated, the rate receiving an overall amount of RBV >13 mg/day was 56% for PEG IFN alfa-2a and 29–33% for PEG IFN alfa-2b. Since RBV is crucial to obtain viral eradication after early viral response and ETR, it is difficult to reconcile these data with the higher relapse rate in the PEG IFN alfa-2a arm. It is stated that those who had an Hb level below 10 g/dl, albeit requiring a dose reduction, had a better chance of SVR (48.8% vs. 36.7% of non-anemic). Anemia was felt to be a surrogate marker of the actual exposure of RBV and a predictive factor of SVR. Unfortunately, no data are available on the relation between anemia and SVR split by arms of treatment. Finally, the trial was not blinded for the type of PEG IFN used. This could have affected the way some physicians handled treatment.

All available studies that compare the two PEG IFNs, other than the IDEAL (Table 1 and Refs. [7–11]), show a significant trend towards higher efficacy of PEG IFN alfa-2a, with a range of difference of SVR between 6 and 13% and an OR between 1.2 and 1.9. This effect is seen both in randomized clinical trials (RCTs) and in cohort studies. In the two studies where RBV dosage is equal or equivalent between the two arms (1 RCT and one cohort), the difference in favour of PEG IFN alfa-2a is maintained. Although it is difficult to reconcile this uniform trend with the IDEAL results, one is left with a feeling that population-related and dosing-related issues may be more relevant than the type of drug. In order to determine which PEG IFN is the most effective for treatment, we will have to await further data based on more appropriate RBV dosing. However, at a time when triple therapy with small molecules acting as direct viral inhibitors will soon be available, one may ask if this issue is even relevant.

We should bear in mind that small differences in outcomes hyped by the industry, such as the 6.5–7% Δ pre-fixed as primary end-point, are of minor practical relevance and are barely perceptible to the clinician. Ultimately, when translating the results of clinical trials into real-life practice, it is the tolerability and adherence to a regimen which matter most. To this aim, the fact that the lesser dose of PEG IFN alfa-2b is equally effective is probably the most important message delivered by the IDEAL. Last but not least, attention should be placed in all kinds of RCTs to a more individualized dosing of RBV, especially in the difficult-to-treat patient [12], even beyond the FDA-approved prescribing information.

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