Antiviral Research 98 (2013) 1–3

Contents lists available at SciVerse ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

Short Communication

Equal efficacy between the two types of peginterferon on HCV: A matter of relapse?

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ARTICLE INFO

Article history:
Received 15 December 2012
Revised 1 February 2013
Accepted 11 February 2013
Available online 16 February 2013

Keywords:
HCV therapy
Pegylated interferon
HCV relapse

ABSTRACT

Two types of peginterferon alfa (2a and 2b) are available for the treatment of chronic hepatitis C genotype 1 or non-1. Comparative studies of bitherapy suggest equivalent results in terms of sustained virologic response for the two types of interferon possibly with a slight advantage in favor of type 2a. However, these studies report only limited data concerning relapse.

We analyzed studies comparing the two types of peginterferon with data concerning relapse. In the 6 studies examined (8538 patients), peginterferon 2a was clearly associated with a much higher rate of end of treatment response but also a higher relapse rate than type 2b (29.3% vs 21.1%; relative risk of relapse with peginterferon 2a:1.54 [1.35–1.76], $p = 0.0024$). These data are highlighted in overweight patients. We tried to explain these differences between these two types of interferon by discussing in terms of pharmacokinetics.

Peginterferon remains the cornerstone of HCV treatment and must be carefully chosen on the basis of the patient's history and cofactors. These data are important and must be considered in the era of DAA.

We recently conducted a prospective study including 154 patients with an undetectable viral load at the end of treatment (EOT). The purpose of this study was to analyze the kinetics of relapse after stopping treatment. Treatment of these patients was based on the synergistic combination of peginterferon α (2a or 2b) and ribavirin. Analysis of follow-up data for these patients revealed a significantly higher relapse rate for patients treated with peginterferon (PEG-IFN) 2a than for those treated with PEG-IFN 2b (38.7% vs 13.3%; $p = 0.004$). The ribavirin doses received by the patients in these two groups were not significantly different: 14.52 mg/kg/d for type 2a and 14.4 mg/kg/d for type 2b. Notably, among patients treated with type 2a, the relapse rate was 29% for patients weighing 75 kg or less and 49% for patients weighing more than 75 kg ($p = 0.04$). In order to more clearly understand these results, we extracted data from randomized trials published in the literature comparing these two types of interferon in terms of relapse rate. This search retrieve six randomized studies comparing relapse rates between these two types of IFN (Table 1).

First of all, in the IDEAL trial (McHutchison et al., 2009), based on 3070 patients with genotype 1, sustained virologic response (SVR) rates were similar between regimens: 39.8% with standard-dose PEG-IFN α-2b, and 40.9% with PEG-IFN α-2a ($p = 0.57$). Relapse rates were 23.5% (95% CI: 19.9–27.2) for standard-dose PEG-IFN α-2b and 31.5% (95% CI: 27.9–35.2) for PEG-IFN α-2a ($p = 0.003$; data not provided but calculated by us). During the treatment period, the mean and median daily ribavirin doses were significantly higher among patients receiving PEG-IFN α-2a than those in the PEG-IFN α-2b group. In particular, the IDEAL study showed that the end of treatment response (ETR) was significantly lower among patients treated with PEG-IFN α-2b: 63.4% for PEG-IFN α-2b vs 73.9% for PEG-IFN α 2a. However, it should be noted that the IDEAL study was performed in a US population, with a high proportion of overweight and obese patients.

Secondly, in a German retrospective study (PRACTICE), including 3470 patients (Witthoeft et al., 2010), the authors concluded that ETR and SVR rates were all higher for PEG-IFN α-2a compared to PEG-IFN α-2b, although a significant difference was not demonstrated on ITT analysis. When the raw data for relapse rate in the two groups were extracted, a marked difference was observed: 30% for 2a and 23% for 2b ($p = 0.0001$).

The third study (Villa et al., 2012) was conducted in 746 Italian treatment-naive patients to compare two types of interferon in relation to gender. Final results showed a slight difference in terms of SVR in favor of 2b. This study also demonstrated a marked difference in terms of relapse rate (31.1% for 2a vs 10.8% for 2b; $p = 2.95 \times 10^{-7}$).

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http://dx.doi.org/10.1016/j.antiviral.2013.02.006

Table 1
Descriptive overview of six studies comparing the two types of peginterferon and reporting relapse data.

Study	Type of study/sponsor	Pts, *n*	Genotype	Weight A: 2a B: 2b	Ribavirin dose range A: 2a B: 2b	% SVR 2a vs 2b	*p* Value	% Relapse 2a vs 2b	*p* Value
IDEAL	RCT/Schering-plough	3070 (ITT)	G1 naive	A: 82.8 B: 84	A: 1–1.2 B: 0.8–1.4	40.9/39.8	0.57	31.5/23.5	0.003
PRACTICE	Retrospective cohort/ Roche	3414 (ITT)	All	A: 74.7 B: 74.3	RBV prescribing recommendation	52.9/50.5	0.18	30/23	0.0001
Villa et al.	Retrospective cohort/ Investigator initiated	746 (ITT)	All naive	NA	RBV prescribing recommendation	43.1/51	0.03	31.1/10.9	2.95e-07
Berenguer et al.	Retrospective cohort/ Investigator initiated	557 (ITT)	All naive – HIV coinfected	A: 68 B: 67	A: 14 mg/kg/d B: 13.3 mg/kg/d	33/31	0.82	36.8/21	0.011
Rumi et al.	RCT/Investigator initiated	431 (ITT)	All naive	A: 72.2 B: 68.9	A: 1–1.2 B: 0.8–1.2	66/54	0.02	15,7/18,5	0.63
Ascione et al.	RCT/Investigator initiated	320 (ITT)	All naive	A: 70.4 B: 69.9	A: 1–1.2 B: 1–1.2	68.8/54.4	0.008	17.9/15.5	0.75

A fourth study comparing both types of IFN was the Spanish retrospective study conducted in HIV coinfected patients (Berenguer et al., 2009), which found that ETR was significantly lower among patients treated with PEG-IFN α-2b (40% vs 52%; $p = 0.006$). No significant difference in terms of SVR was observed between patients treated with PEG-IFN α-2b and those treated with PEG-IFN α-2a (31% vs 33%; $p = 0.82$). Once again, the relapse rate was significantly lower among patients treated with PEG-IFN α-2b than among those treated with PEG-IFN α-2a (21% vs 36.8%; $p = 0.011$).

The fifth study by Rumi et al. included 431 Italian treatment-naive patients (Rumi et al., 2010). Sustained virologic response rate was higher in PEG-IFN α-2a than in PEG-IFN α-2b patients (66% vs 54%, respectively; $p = 0.02$). The relapse rate was very low in the two study arms (15.7% and 18.5%, respectively) and was not statistically different.

The most recent study, conducted by Ascione et al., included 320 Italian patients (Ascione et al., 2010). The conclusions were almost identical to those of the study reported above with an SVR rate in favor of 2a ($p = 0.008$) and no difference in terms of relapse rates. Once again, the overall relapse rate in the study remained very low (16.9%).

These data therefore appear to indicate that there is no difference between the two types of PEG-IFN in terms of SVR, with a possible slight advantage in favor of 2a. A recent systematic review by the Cochrane Collaboration of randomized clinical trials comparing the 2 peginterferons, which included a meta-analysis of SVR rates in 8 trials comprising a total of 4293 participants, found that PEG-IFN α-2a was slightly but significantly more effective than PEG-IFN α-2b (relative risk 1.10; $p = 0.004$) (Awad et al., 2010). In our analysis including studies for which relapse data are available, ETR also appeared to be higher for 2a (69.85% vs 59.6%). However, patients treated with PEG-IFN α-2a were more likely to have a response followed by relapse (29.3% for 2a and 21.1% for 2b; Table 1) after completion of therapy, particularly for studies including overweight patients. We calculated using the forest plot (Fig. 1) the relative risk of relapse for each cohort. We obtain a higher risk with peginterferon 2a (overall relative risk = 1.54 (95% CI: 1.35–1.76); $p = 0.0024$, Cochran test) (Fig. 1). The main limitation of these six head-to-head studies comparing the two drugs is that they derived from different populations of HCV infected patients.

In November 2002, an antiviral drugs advisory committee of the Food and Drug Administration (FDA, 2002) published a document based on analysis of data from the clinical studies of Fried et al. (Fried et al., 2002) and Hadziyannis et al. (Hadziyannis et al., 2004). One of the conclusions of this report was that body weight <75 kg significantly increased a patient's chance of SVR after treatment with fixed-dose PEG-IFN α-2a plus weight-adjusted ribavirin. For PEG-IFN α-2a, heavier weight was associated with a lower SVR with a 29–30% absolute difference in terms of SVR between heavier patients (>98 kg) and lighter patients (<64 kg). This finding confirms that high body weight adversely influences the treatment efficacy of PEG-IFN 2a(Fried et al., 2002).

What factors can explain these data? Failure of IFN-based treatment regimens to eradicate HCV infection is due to a combination of factors. Suboptimal peginterferon pharmacokinetics, with a rebound in viral load as serum levels of IFN decline, may contribute to treatment failure. Differences in pegylation chemistry and structure are associated with significant pharmacokinetic differences. PEG-IFN α-2b has a linear PEG chain of approximately 12,000 Daltons, whereas PEG-IFN α-2a has a branched PEG chain of approximately 40,000 Daltons. The larger and more branched the PEG molecule, the smaller the volume of distribution and the longer the half-life of the drug. Volume of distribution is the volume of bodily fluids throughout which a drug is distributed. The volume of distribution is considerably greater for PEG-IFN α-2b (1 L/kg) than for PEG-IFN α-2a (6–12 L) (Silva et al., 2006). The lower volume of distribution of PEG-IFN α-2a has also been proposed as an argument in support of fixed rather weight-based dosing. Due to its restricted volume of distribution, the PEG-IFN α-2a molecule preferentially accumulates in the blood with highest concentrations occurring in the liver. Pharmacodynamic studies have shown that PEG-IFN α-2a is available at a maximum concentration for up to 168 h after injection compared to only 72 h for PEG-IFN α-2b (Silva et al., 2006). Serum PEG-IFN α-2b concentrations therefore decrease below the detection limit before the end of the period between injections (7 days) (Silva et al., 2006) and plasma viral suppression may sometimes be insufficient to maintain virologic response. Drugs with a high volume of distribution have the best potential to enter several body compartments (both intravascular and extravascular). HCV reservoirs outside the liver may play a role in HCV persistence and reactivation of infection; therefore drugs with a low volume of distribution have a much lower chance of infiltrating extravascular tissue, which may explain the higher relapse rate. In this context, the pharmacokinetics of PEG-IFN α-2b in the body might explain the lower relapse rates observed with PEG-IFN α-2b. However, fixed-dose therapy with PEG-IFN α-2a provides proportionally lower amounts of drug as patient's weight increases (Silva et al., 2006). All of these findings may therefore explain the comparable SVR rates observed in some studies despite an ETR in favor of 2a. Other parameters currently unknown could explain this difference. In the patient subset weighing more than 85 kg, PEG-IFN α-2b therapy was more effective than PEG-IFN α-2a. Conversely, in studies with lighter patients, relapse rates were similar between the two types of IFN, explaining the better SVR rate for 2a.

These data may also be considered for patients who cannot receive and have access to protease inhibitors as well as for patients with non genotype 1 infection so as to optimize the SVR rate. Since

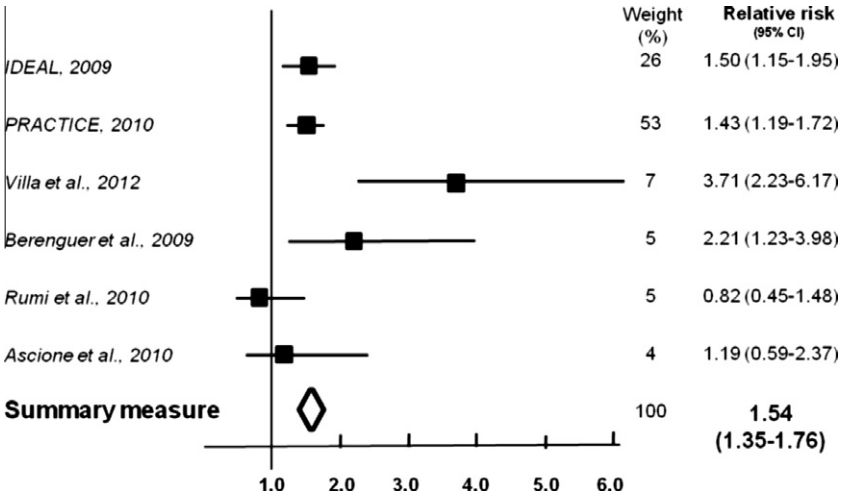

Fig. 1. Forest plot of comparison: peginterferon alpha-2a vs peginterferon alfa-2b, outcome: relapse. Analyses include relative risks and confidence intervals for each study. Weight (%) represents the importance of each cohort relative to the overall analysis based on the number of patients.

the era of direct antiviral agents (DAA), interferon is still required in the treatment against HCV. Peginterferon alpha used in triple therapy may then influence response rate. When prescribing triple therapy, the clinician must now choose between the available protease inhibitors as well as the two types of pegylated interferon. Although the individual DAA used significantly contributes to the likelihood of success with fewer patients relapsed, PEG-IFN α plays a critical role in response rate and optimizing its use therefore remains a major challenge in terms of treatment outcome.

The contribution of each person listed below

Etienne Brochot: analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; administrative.

Eric Nguyen-Khac: drafting of the manuscript; critical revision of the manuscript for important intellectual content; administrative.

Gilles Duverlie: drafting of the manuscript; critical revision of the manuscript for important intellectual content; administrative.

Financial support

The study was carried out as part of our routine work.

Acknowledgments

We are grateful to Dr Anthony SAUL for English corrections.

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