Is One Type of Pegylated Interferon More Effective for Treating Chronic Hepatitis C?

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Pegylated interferon plus weight-adjusted ribavirin is standard therapy for chronic hepatitis C, but there has not been consensus about the relative benefits of Pegasys (Roche/Genentech) and PegInton (Schering-Plough). Past research has produced conflicting findings, and data have not always been strictly comparable due to regimen differences such as varying doses of ribavirin, which helps prevent relapse after the end of therapy.

Interferon alpha used for hepatitis C treatment is a genetically engineered version of a natural human cytokine (chemical messenger). It works by enhancing immune system responses against HCV. Pegylated interferon is attached to polyethylene glycol (PEG), which makes it last longer in the body (allowing injections once instead of 3 times weekly). Pegasys and PegIntron have different shapes and sizes (40 kDa vs 12 kDa molecular weight), which influences their pharmacokinetic properties and may affect how well they work.

Study 1

In the first new study, Maria Grazia Rumi from Università degli Studi in Milan and colleagues compared the safety and efficacy of the 2 pegylated interferons in treatment-naive chronic hepatitis C patients stratified by HCV genotype.

The study included 431 participants. About half had hard-to-treat HCV genotypes 1 or 4, and about 19% had liver cirrhosis, another characteristic associated with poorer treatment response.

Participants were randomly assigned (1:1) to receive 180 mcg/week Pegasys or 1.5 mcg/kg/week PegIntron for 24 weeks (genotypes 2 or 3) or 48 weeks (genotypes 1 or 4). In accordance with the drugs' differing prescribing instructions, genotype 1 and 4 Pegasys recipients received 1000-1200 mg/day weight-adjusted ribavirin and genotype 2 and 3 Pegasys recipients received a fixed dose of 800 mg/day; in contrast, all PegIntron recipients received 800-1200 mg/day weight-adjusted ribavirin regardless of genotype.

Results

- In an intent-to-treat analysis, the overall sustained virological response (SVR) rate 24 weeks after completing treatment was significantly higher in the Pegasys group compared with the PegIntron group (66% vs 54%, respectively; P = 0.02).
- Among the 222 patients with HCV genotypes 1 or 4, the corresponding SVR rates were 48% vs 32%, respectively (P = 0.02).
- Among the 143 patients with genotype 2, the SVR rates were 96% vs 82%, respectively (P = 0.01) (there were too few genotype 3 patients to permit a separate analysis).
- The Pegasys and PegIntron groups had similar rates of treatment-related serious adverse events (1% in both) and discontinuation due to adverse events (7% vs 6%, respectively).

- In a logistic regression analysis, use of Pegasys was an independent predictor of SVR (odds ratio 1.88).

Based on these findings, the study authors concluded, "Although the 2 regimens showed a similar safety profile, the [pegylated interferon alpha-2a]-based treatment yielded significantly more SVR than [pegylated interferon alpha-2b]."

Study 2

In the second study, Antonio Ascione from Cardarelli Hospital in Naples and colleagues compared the safety and efficacy of Pegasys versus PegIntron in 320 previously untreated chronic hepatitis C patients.

About 18% of participants had cirrhosis at baseline, and about 55% had high HCV RNA viral load (> 500,000 IU/mL).

Again, participants were randomly assigned (1:1) to receive 180 mcg/week Pegasys or 1.5 mcg/kg/week PegIntron for 24 weeks (genotypes 2 or 3) or 48 weeks (genotypes 1 or 4). In this study, however, all participants -- regardless of genotype -- received ribavirin at doses 1000 mg/day if they weighed < 75 kg (about 165 lb) or 1200 mg/day if heavier.

Results

- In an intent-to-treat analysis, more patients overall achieved SVR in the Pegasys group compared with the PegIntron group (68.8% vs 54.4%; P = 0.008).
- Among genotype 1 or 4 patients, the corresponding SVR rates were 54.8% vs 39.8%, respectively (P = 0.04).
- Among genotype 2 or 3 patients, the SVR rates were 88.1% vs 74.6%, respectively (P = 0.046).
- Among participants without cirrhosis (all genotypes combined), SVR rates were 75.6% with Pegasys vs 55.9% with PegIntron (P = 0.005).
- Among patients with cirrhosis, however, SVR rates were statistically similar (42.4% vs 46.1%, respectively; P = 0.774).
- Among patients with high baseline HCV RNA, SVR rates were again higher in the Pegasys compared with the PegIntron group (75.6% vs 55.9%; P = 0.005).
- Among patients with low baseline viral load, SVR rates did not statistically differ (68.4% vs 65.7%, respectively; P = 0.727).

"In patients with chronic HCV infection, treatment with peginterferon alfa-2a plus ribavirin produced a significantly higher SVR rate than treatment with peginterferon alfa-2b plus ribavirin," the investigators concluded.

Editorial

In an accompanying editorial Stefan Zeuzem from J.W. Goethe University Hospital in Frankfurt, Germany, offered a perspective on the findings from these 2 trials in the context of prior research.

"Owing to greater variations in peak-to-trough ratios for peginterferon alfa-2b than peginterferon alfa-2a, HCV RNA levels tend to fluctuate more (at least within the initial 4 weeks of therapy) in patients treated with peginterferon alfa-2b than in those treated with peginterferon alfa-2a," he noted.

One previous large study, the IDEAL trial sponsored by Schering-Plough, included more than 3000 HCV genotype 1 patients treated with Pegasys or PegIntron according to the drugs' respective label directions (i.e., the ribavirin dose was not consistent). In that study, Pegasys recipients had a higher end-of-treatment response rate (64.4% Pegasys vs 53.2% PegIntron) but PegIntron recipients had a lower relapse rate (31.5% Pegasus vs 23.5% PegIntron) so the sustained response rates ended up being statistically similar (40.9% Pegasys vs 39.8% PegIntron).

A recent systematic review by the Cochrane Collaboration of randomized clinical trials comparing the 2 pegylated interferons, which included a meta-analysis of SVR rates in 8 trials with a total of 4293 participants, found that Pegasys was slightly but significantly more effective than PegIntron (relative risk 1.10; P = 0.004), with similar results for all subgroups; adverse event profiles were similar.

"Taken together, since the publication of the pivotal phase 3 trials for peginterferon alfa-2a and alfa-2b in combination with ribavirin, it took another 8 years to characterize the pharmacodynamic differences between the 2 drugs in detail," Zeuzem wrote. "At the dawn of new direct antiviral drugs against HCV we need now to investigate how important the observed differences between the peginterferons (and other long-acting interferons such as albumin interferon) are in combination with HCV NS3/4A protease and NS5B polymerase inhibitors."

It also remains to be determined whether one form of pegylated interferon works better than the other in HIV/HCV coinfected patients, who tend to respond less well to interferon-based therapy than people with HCV alone.

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Study 2: Department of Gastroenterology, Liver Unit and Pathology Units, Cardarelli Hospital, Napoli, Italy; Department of Medicine, Centre for Liver Disease, Fatebenefratelli Hospital, Napoli, Italy; Gastroenterology Unit, IRCSS de Bellis, Castellana Grotte, Italy.

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