Hepatitis C showdown: PEG vs PEG

A head-to-head clinical trial is under way comparing the two leading hepatitis C therapies. Will it be IDEAL?

BY DAVID FILMORE

Peg-Intron and Pegasys. Although they sound like robots that battle every Saturday morning on cartoons, they are actually drugs—developed by Schering-Plough and Roche, respectively—that battle every day in the marketplace. Both target the hepatitis C virus (HCV), which infects about 170 million people worldwide and is a leading cause of liver transplantation. In combination with the broad-spectrum antiviral ribavirin (branded Rebetol by Schering-Plough and Copegus by Roche), either one of these polyethylene glycol (PEG)-modified recombinant interferon α proteins represents the standard of care for chronic HCV.

Schering-Plough is now sponsoring a clinical study in an attempt to differentiate the pair. But Roche strongly questions whether the trial will accomplish this validly.

It's "our regimen versus their regimen," Schering-Plough spokesperson Robert Consalvo says. "We feel very confident in the study and in our product."

Roche, for its part, "would welcome a fair head-to-head study," says company spokesperson Pamela Van Houten. But, she says, Roche believes that Schering-Plough's study design is biased.

Battling back

"A lot of physicians feel that the sustained response rate between the two products is identical," says Bruce Bacon, director of the division of gastroenterology and hepatology at St. Louis University School of Medicine.

This conclusion is backed up by separate pivotal clinical trial results for each formulation, both showing improved efficacy over the non-PEGylated interferon and ribavirin combination with mid-50-percentile sustained virologic responses—the gold-standard end point for determining cure of the infection.

Schering-Plough, however, doesn't buy this. Or, at least, it has a strong motivation to dispute it. In December 2002, when Roche received FDA approval for Pegasys–Copegasys combination therapy, it quickly took a substantial chunk of the market that Schering-Plough had dominated since early 2001 with Peg-Intron/Rebetol, and

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A contender. Roche's Pegasys is being put to the test against its hepatitis C market competitor Peg-Intron, manufactured by Schering-Plough.

before that with a non-PEGylated interferon–ribavirin combination. The fact that ribavirin went generic in April didn't help matters.

These factors, along with the 2002 patent expiration and move to over-the-counter status of its previously high-revenue allergy drug Claritin, contributed strongly to Schering-Plough's 18% drop in 2003 sales and offered a serious incentive to turn around its HCV franchise, still its largest revenue source.

To attempt to set the record straight, the company is sponsoring IDEAL (Individualized Dosing Efficacy vs Flat Dosing to Assess Optimal PEGylated Interferon Therapy), the first large-scale randomized head-to-head comparison of Peg-Intron and Pegasys ribavirin combinations. IDEAL was announced in September 2003 and is currently enrolling patients nationwide.

A PEG is a PEG?

Peg-Intron and Pegasys consist of slightly different proteins—interferon α-2b and interferon α-2a, respectively—that are fastened to different-sized PEG attachments, which influence how long the therapy remains in the body. But perhaps the most significant contrast from a clinical standpoint is that Pegasys is given to all patients in a 180-µg dose, whereas Peg-Intron is prescribed to patients on the basis of their weight in a dose of 1.5 µg/kg. Roche's drug is clearly simpler to prescribe because it doesn't require a separate preparation for each patient, but Schering-Plough asserts that its individualized dosing is more effective, especially in patients who are traditionally more difficult to treat.

IDEAL is the company's means of proving this, Consalvo says.

"There are hints in the existing data, although it is not comparative data, that suggest there might be differences" between the two therapies, he explains.

Bacon, an IDEAL investigator who has consulted for Schering-Plough but has also received research funding from Roche, says, "There are obviously vast differences in how the [Peg-Intron and Pegasys FDA registration] trials were done." Specifically, he points to the facts that Roche's study included a majority of patients who were European, whereas Schering-Plough's included predominantly American patients. Genotype 1, the most resistant-to-treatment form of HCV, is more dominant in the United States than in Europe.

In addition, Bacon says, there were "more patients with low viral load, the [body] weights were lower, there was less fibrosis, and more ribavirin was used in the Pegasys study than in the Peg-Intron study." Each of these factors, he believes, favored better results for Pegasys. IDEAL, on the other hand, is enrolling only U.S. patients with genotype 1 HCV.

Fair play?

"The study is powered to show superiority either way," Consalvo says. "There will be a lot of good data generated to help physicians and their patients make the right choice about what the right treatment is to maximize response."

But Van Houten asserts that the data will be flawed because "the dosing of ribavirin is different for the Pegasys and Peg-Intron arms of the study." In fact, patients in the Peg-Intron arms—there will be two arms because in addition to the Peg-Intron/Pegasys comparison, the study will probe the currently approved Peg-Intron dose against a lower dose to fulfill a postmarketing commitment to the FDA—will receive from 800 to 1400 mg/day of ribavirin depending on their weight, whereas those in the Pegasys arm will receive a weight-based range of 1000–1200 mg/day.

Although ribavirin can't be used to treat HCV on its own, it exerts a transient antiviral action that supplements the antiviral and immunomodulatory activity of interferon to prevent relapses. It is associated with significant increases in sustained response compared with use of PEG-interferon alone.

In IDEAL, Van Houten says, "patients in the Pegasys arm will likely be exposed to lower cumulative doses of ribavirin than patients in the two Peg-Intron arms of the study." This, she says, will put Roche's drug at a disadvantage.

The difference in ribavirin doses, Consalvo says, is a crucial part of the study. "We want to study how we want our drug combination to be used versus the way Roche wants its drug combination to be used," he explains. Also, he adds, the study is required by the FDA to use Roche's labeled doses.

Pegasys is labeled for use with the 1000–1200-mg ribavirin dose, but, as Roche points out, Peg-Intron is currently only labeled for an 800-mg dose. The 800–1400-mg range comes from another Schering-Plough study, called WIN-R (Weight-based Dosing of PEG-Intron and Rebetol), also mandated by FDA postmarketing requirements that compared flat-dose (800 mg) with weight-based (800–1400 mg) ribavirin. WIN-R data reported to the FDA—final study results have not yet been reported publicly—have convinced the agency that the weight-based dosing is appropriate for the IDEAL trial, Consalvo says.

In any case, Bacon suggests that Roche might not have much to worry about regarding the ribavirin dose.

"If you look at the projected weights of the patients in the United States, it is expected that there will be more lighter people receiving 800 mg [of Rebetol] than there will be heavy people receiving 1400 mg," he says. This, he adds, will lead to more "ribavirin given in the Pegasys group than in the Peg-Intron group."

> **"It's our regimen versus their regimen."**

A changing landscape

Whether this turns out to be the case and, moreover, what and how definitive the IDEAL trial results end up being will not be known for several years. There is no guarantee, of course, that Roche's label-recommended dosage won't change at some point, making the results less significant. For instance, Roche is conducting a smaller trial using increased concentrations of both Pegasys and Copegus for patients over 85 kg with genotype 1 HCV and high viral load.

Furthermore, no matter how well the IDEAL trial is carried out, it will not answer the "best treatment" question for a substantial portion of the HCV-infected population.

The trial is only enrolling treatment-naïve patients. About 40–50% of genotype 1 HCV patients who go on PEGylated interferon–ribavirin therapy don't respond to it, Bacon says. This is in addition to people who don't start therapy because of fear of serious side effects, which can include severe fatigue, depression, flulike symptoms, and anemia, and the large population of asymptomatic infected who haven't been identified, he adds.

Both Schering-Plough and Roche are targeting the nonresponder population with trials testing higher doses and longer treatment periods than the current standard of 48 weeks.

Further down the road, new medicines are expected to join in the hepatitis C battle. The closest to market is viramidine, a ribavirin analogue developed by Valeant Pharmaceuticals that is expected to have an improved safety profile and is now in separate clinical trials with Pegasys and Peg-Intron.

A "bio-optimized" interferon α already on the market, called Infergen, is in development by InterMune in combination with an interferon γ protein for nonresponders.

In addition, more targeted HCV viral therapies, such as protease and polymerase inhibitors, are in earlier stages of preclinical and clinical development at Schering-Plough and Roche, as well as at Isis Pharmaceuticals, Idenix Pharmaceuticals, and Boehringer Ingelheim Pharma.

Nonetheless, the current PEG-interferon–ribavirin combination is expected to remain the standard of care for the near future. And Schering-Plough hopes IDEAL will be an important source of information and will prove that its therapy should be the method of choice for physicians.

The company, however, recognizes the risk to the sponsor in this type of head-to-head comparison.

This potential downside was most recently illustrated in Bristol-Myers Squibb's PROVE-IT trial, which put its own statin Pravachol up against Pfizer's Lipitor, only to find that Lipitor prevented heart problems better than Pravachol.

"There is always a risk," Consalvo says. "But you don't know what the results are until you complete the study. We believe we have a good chance of being successful." ■

IDEAL study trial

Arm 1 (n = 960): High-dose Peg-Intron (1.5 µg/kg/week) with weight-based Rebetol (800–1400 mg/day).

Arm 2 (n = 960): Low-dose Peg-Intron (1.0 µg/kg/week) with weight-based Rebetol (800–1400 mg/day).

Arm 3 (n = 960): Pegasys (180 µg/week) with weight-based Copegus (1000–1200 mg/day).