Parkinson patients want experimental drug on market

November 21, 2004

By Jamie Talan

All Robert Suthers wants is the experimental drug that he believes was dramatically improving his symptoms of Parkinson's disease.

But the drug maker has taken it away, saying Suthers' improvement was nothing more than a placebo effect. Suthers' experience is at odds with that finding.

In April, only weeks after he began receiving the drug, Suthers was able to clean out his garage for the first time in years -- no small feat for the 69-year-old Greenlawn man, a former marathon runner.

He was diagnosed in 1998, a year after his left hand started shaking. In September 2003, two holes were drilled into his skull and two pumps implanted in his stomach, each connected to a catheter snaking into the brain region hard hit by the disease. During the next six months, the pump would deliver either the drug or a saline solution -- a placebo.

Suthers was one of 34 patients in a study to determine whether the medicine, a growth factor critical to brain health, would delay or stop the brain cell death associated with Parkinson's.

For the first six months, Suthers received the saline solution -- something he didn't know at the time. He says he felt no improvement.

In April, he began receiving the experimental drug -- and the change was dramatic. "I could go out for dinner without fear of stumbling," he said. "I could write again. I had my life back."

But two months ago, the drug maker, Amgen, halted the experiment, and his access to the drug was shut off. Amgen scientists said improvements had been noted in patients receiving the placebo as well as the drug, and that they had other concerns about developing the substance for Parkinson's: Studies in monkeys had found evidence the drug may be contributing to brain damage, and some of the patients developed antibodies to the drug.

Doctors involved in the trials said they have seen no harmful signs among the patients, many of whom reported dramatic improvement. Now patients are writing letters to company officials begging to have access to the medicine. And many of the doctors are urging the company to redesign the study and make the drug available to the participants.

"The patients aren't getting a fair deal," said Don Gash of the University of Kentucky. Gash ran one section of the study where all patients received the drug for more than a year.

"It's hard to credit a placebo response in all of our 10 patients," he said. "A placebo effect doesn't last a year."

The drug in the study is a substance called glial cell line-derived neurotrophic factor, GDNF for short. Amgen brought GDNF to the top of its list of hot drugs in the company's pipeline after doctors in Bristol, England, showed significant improvement in five patients with advanced disease. The dosage was three times higher than the one in the just-ended study.

But Amgen executives say that company scientists have analyzed the data from the new study, conducted at seven sites in the U.S. and England, and found no significant difference between those who had received the drug and those who hadn't.

"We were surprised when we unblinded the study and saw there was no benefit," said Dr. Roger Perlmutter, the executive vice president of research and development at Amgen. "There was a large placebo effect," meaning patients on and off the medicine showed signs of improvement.

What's more, he said, monkey studies analyzed as the clinical trial was under way revealed small lesions in the cerebellum, an area of the brain that governs movement and balance. While similar damage has not been seen on any brain scans of patients, some of whom have been on the medicine for more than two years, Perlmutter said it raised concerns. The monkeys were exposed to doses 15 times higher than the ones given to patients in the trial.

With no evidence of benefit, and the toxic brain findings in the monkeys, he said, "It is no longer ethical to administer it to patients."

But this clinical trial, and the way it was ended -- Amgen executives did not discuss the problems with study investigators before they went to the Food and Drug Administration with their concerns -- has sparked a response not usually seen in clinical drug testing.

Rarely do doctors involved in such trials rally publicly against a decision to stop a study, especially after a statistical analysis shows that patients on the drug fared no better than those on a saline dose, and questions emerged about its safety in animals. But these doctors believe that the company should have consulted with them before taking their concerns straight to federal drug regulators.

Many believe that the study design was flawed, and thus the analysis was off, as well as the interpretation.

Dr. Michael Hutchinson, associate professor of neurology at New York University School of Medicine and one of the study investigators, did his own analysis of the numbers and found that there was a significant improvement in those with moderate to advanced Parkinson's patients who received GDNF. He believes that the study failed to reach its primary target, symptom improvement, because the milder patients were included in the company's analysis -- an artifact of weak study design, he said.

University of Kentucky neurologist Dr. John Slevin and other investigators said that they watched patients post-GDNF walk comfortably and over long distances for the first time in years. At other centers, one man said he could smell his wife's cooking again. There were others who

basked in the experience of reclaiming intimacy with their life partners.

"I follow the Hippocratic oath," said Hutchinson, who enrolled and followed four New Yorkers, including Suthers, in the study. When he was told in early September to shut off the pumps, he questioned Amgen's decision to stop a drug that looked like it was working. He asked his hospital to seek an injunction that would allow saline to drip through the pump, ensuring that the last bits of the growth hormone could get into the brains of his patients. He also felt that the monkey findings suggested there could be possible risks of stopping the medicine abruptly. "We have to ask: Are we doing the right thing?"

Slevin agreed. "It's a little draconian," he added. "It's frustrating for me to have something in hand that could ultimately change the natural history of this disease and see its use abruptly stopped. I see a benefit in my patients. They see improvements. We have an incredibly devastating, progressive disease."

Indeed, patients who underwent brain surgery and have the cumbersome pumps protruding beneath their bellies have made numerous calls to Amgen executives. "We want the drug. We'll sign away on the risks for these benefits," said Suthers, who suffered a seizure following the first surgery, then a stroke.

"I want the drug," he said. His pumps haven't been refilled since the summer, and he feels his symptoms are getting worse.

Only four of the seven centers participating in the Amgen trial have complied with the company's orders to shut off the pumps. Last week, the company called a meeting in its headquarters in Thousand Oaks, Calif., to rehash the findings and the company's decision.

The clinical benefit wasn't the only concern addressed at the meeting, Amgen's Perlmutter said. There was another potentially troublesome finding. A few of the patients had antibodies in their bloodstream, an indication that the body may have waged an immune response against the foreign protein. No one really knows whether these so-called neutralizing antibodies are harmful, Hutchinson said, and many approved drugs have also triggered similar antibodies with no ill effects.

But Amgen's popular erythropoietin, which was approved in 1989 for the treatment of renal anemia and triggers neutralizing antibodies in some patients, did cause serious problems. In recent years, scientists reported that several patients were harmed when the antibody attacked the body's own erythropoietin, which is crucial in building red blood cells. These patients required blood transfusions to combat severe anemia.

While Perlmutter said that "GDNF could be exposing patients to untold risks," Slevin said it would be easy enough to monitor these patients while still providing the drug.

GDNF's potential of replenishing the Parkinson's brain was first observed in the early '90s, when scientists found that the growth factor worked uniquely on the brain cells affected by the disease. In 1995, four separate teams published findings that GDNF infused into the brain arrested disease symptoms in mice and monkeys.

A million Americans have Parkinson's, a condition that causes rigidity, muscle stiffness, tremor and slowed movements. People with Parkinson's lose brain cells that produce dopamine, a chemical involved in movement and emotion.

Treatments that replace dopamine do not alter the underlying degenerative process, which eventually leads to complete disability.

Robert Green was 36 years old when he was diagnosed with Parkinson's. At 50, his tremors, freezing spells and slowed movements were so bad that last year he opted for the experimental brain surgery to deliver the promising growth factor.

"When I signed on, my wife was lifting me in and out of bed," Green said. After the surgery, when the pump was filled with GDNF, "things got progressively easier for me. I was almost self-sustained again. It was a wonderful feeling."

In September, his hope for his former self was dashed when his Kentucky doctors told him about Amgen's decision. Now, after a few months off the drug, he feels the weakness in his legs returning. He knows what to expect. Recently, his wife has had to help dress him once again.

Parkinson's patients have symptoms that fluctuate minute by minute, hour by hour, making a normal life impossible. "We are desperate," Suthers said. "It's not fair to take something away that is helping people."

Everyone in his family has witnessed his improvements. His wife, Elaine, said that the facial muscles of Parkinson's patients often become rigid, unexpressive. Her husband's face relaxed on GDNF. "He was smiling more, laughing again," she said.

University of Kentucky's Gash said that he asked the company to let his university license the drug. Amgen executives said no. Even if patients signed waivers should something fatal occur, makers of the substance would still be a target for lawsuits, experts say. Doctors are also planning on taking their concerns to the FDA, the drug regulatory agency that could make the medicine available under a "compassionate use" clause.

In other laboratories, scientists are developing other ways to deliver GDNF into the brain. In Chicago, Rush University Medical Center's Jeffrey H. Kordower is working with Ceregene, a California biotech company, testing a gene therapy approach. Others are looking to see whether GDNF could be housed in encapsulated cells and then transplanted into the region where dopamine cells are dying.

Amgen's Perlmutter said that the placebo effect is an amazing thing, especially in a disease like Parkinson's. The field watched for 10 years as scientists tested the benefits of another approach -- fetal cell transplants -- and trumpeted its successes. In the end, it was discovered that the transplants didn't work, and worse, they left many of the patients with uncontrollable dyskinesias, or involuntary movements.

"The incentive to get better is quite striking," said Dr. Anthony Lang, director of the movement disorders center at Toronto Western Hospital,

another study site for Amgen. "We need better animal studies before we take this further in humans." However, he added, "I am not certain that it is just a placebo effect."

NYU's Hutchinson added that if one looks carefully at the data, "the placebo effect was not very strong."

And Suthers said that he'd be willing to be "the human guinea pig" if he could resume feeling like he had only weeks ago.