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Different Rx: A Doctor's Push For Drug Pits Him Against Its Maker

Dr. Puder Thinks Omegaven Is Best Option for Sick Babies
Company Prefers New Product
Turnaround for Little Maggie

By Amy Dockser Marcus, The Wall Street Journal, 3339 words
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BOSTON -- Like thousands of children in the U.S., Maggie Leaver has short bowel syndrome. These children can't absorb enough nutrients from food, and some need intravenous feedings to survive.

A baby's digestive system can adapt over time, but that may take months or years. Many of these babies can't wait. For reasons not fully understood, children put on intravenous nutrition may suffer liver damage. Some require liver and small bowel transplants, risky procedures that don't always work. Others die waiting for a transplant.

In July, in a paper in the scientific journal *Pediatrics*, researchers at Children's Hospital Boston reported on a small study that suggested a promising treatment. They found that by switching from the standard intravenous formula to a different kind -- called Omegaven -- babies weren't progressing to liver failure. Omegaven, used in Europe for adults, isn't approved in the U.S. and is considered experimental treatment.

"The kids aren't dying anymore," says Mark Puder, a pediatric surgeon who was lead investigator on the study. "We think we have a good treatment."

But Dr. Puder's effort to get Omegaven widely used in babies has put him in an unusual conflict with the German company that developed the drug. Fresenius Kabi AG, which makes Omegaven, says it isn't interested in bringing the drug to the U.S. market. The company says it doesn't agree that Omegaven is the best drug for these babies and has a new product that it believes is better.

In 28 of 29 babies treated with Omegaven so far at Children's Hospital, Dr. Puder says they were able to stop further liver damage -- and damage that children already incurred seemed to improve. Some babies who were switched to Omegaven rebounded enough that they were taken off the waiting list for an organ transplant. At one point, Maggie Leaver's condition deteriorated so much that her surgeon thought she was going to die. Now the 18-month-old is thriving at home in Hingham, Mass.

Early on, Dr. Puder alienated some colleagues, especially with his inflammatory words that the standard IV nutrition product given to babies may be one of the causes of the liver damage. Fresenius Kabi also makes that product. The company says it has no concerns about its safety.

Omegaven isn't what "we see as the best product for this kind of application," says John R. Ducker, president of the research, development and strategic marketing division of Fresenius Kabi. He says Omegaven, developed 15 years ago, was intended as a supplement, and not to be given alone. The company says it doesn't contain all the essential fatty acids babies need.

Mr. Ducker says the company's new product, called SMOFlipid, "presents a better option for pediatric feeding." The company believes the new product does contain all the essential fatty acids babies need and can be used on its own.

Fresenius Kabi says it doesn't want to invest the resources required to test both products for approval by the U.S. Food and Drug Administration. It hopes to eventually sell the new product in the U.S., Mr. Ducker says, although

no timetable has been set and no trials are under way.

"There is not a whole lot that FDA can do," if a company isn't interested in selling a product in the U.S., says John McCormick, deputy director of the office of orphan-products development at FDA. If the maker of a product has a patent on it, "they can do anything they want with it."

Because Omegaven is considered experimental in the U.S., if hospitals want to try it, they have to ask permission from the FDA for each individual patient. The FDA has regulations that enable doctors to use experimental drugs in certain emergency situations.

If hospitals obtain the required permissions, they must then find a way to buy the drug on their own, since insurers typically won't cover Omegaven because it's experimental. The cost can run from \$50 to \$100 a day per patient. At Children's Hospital Boston, the surgical department has already spent close to \$100,000 to buy Omegaven for babies.

Beyond the cost, many doctors are hesitant to try experimental treatments, especially on babies who are already very sick. There is concern that when the drug is used in greater numbers of patients, dangerous side effects could surface. Early reports of benefits may be proved wrong.

Of the 29 babies Dr. Puder has tested Omegaven on, two have died, one from an infection and one from a congenital heart defect. He says none of the 29 babies showed deficiencies in essential fatty acids. He wants to see if the drug's benefits can be proved in a clinical trial.

Dr. Puder's findings are "one of the most exciting therapeutic options for this condition coming down the pipeline in the last five years," says Paul Wales, a surgeon and director of the Group for the Improvement of Intestinal Function and Treatment at the Hospital for Sick Children in Toronto. But without a clinical trial, he says many doctors will remain reluctant to try it. "All you have is your own anecdotal experience," he says.

Standing in the intensive-care unit, in his blue hospital scrubs after a morning in the operating room, Dr. Puder, 46 years old, checked on one of the babies receiving Omegaven. After five weeks, the baby's bilirubin levels -- which had skyrocketed, indicating severe liver damage -- were starting to decline. The baby's health had now improved enough that he was due to be transferred to a regular floor.

Dr. Puder says he wanted to tell the baby's parents about Omegaven right away, but couldn't because the drug is experimental and another surgeon was overseeing the baby's care. Under hospital practice, the treating physician explains options to parents. Dr. Puder felt frustrated because he believed the baby could have benefited from being put on the drug earlier.

He says he understands the hesitance to test drugs on babies. The first time he discussed the possibility of using Omegaven on an infant with the child's parents, he says, "I kept thinking, 'I hope they say no.'" Despite data he had collected, he was scared of giving the drug to a baby after only testing it in mice.

In a clinical trial, Dr. Puder wants to test his hypothesis that Omegaven both reversed and prevented liver damage; he thinks it should be given to every baby with short bowel syndrome right away, before their livers are damaged. In a conference call in May with Fresenius Kabi officials, he raised his voice about the delay in getting a trial started. "These children are dying," he says he told the company. "We want you to help us."

Fresenius Kabi, in a statement, said it has "never declined to help and always provided Omegaven when requested to do so." The company added that it is convinced its new product "serves the needs of this patient group better than the older product Omegaven."

Fresenius AG, a Bad Homburg, Germany-based provider of products and services for dialysis, hospitals and patient care, reported sales of 7.89 billion euros (\$10.14 billion) last year. Its unit, Fresenius Kabi, which sells clinical nutrition products such as Omegaven, had sales last year of 1.68 billion euros. The company says it doesn't break out results for individual products.

Prices of its products vary, depending on the country. But Fresenius Kabi says based on European markets, where its products are primarily sold, the cost per treatment of its new drug, SMOFlipid, is lower than Omegaven.

Dr. Puder knew he was supposed to act as an objective scientist when discussing his Omegaven data with colleagues and the company, and not get emotional. But as months dragged on without a trial, he found it more difficult to restrain his feelings. "I've always been fairly passive unless it really, really counts," he says.

His effort to figure out why some babies develop liver damage began in 2001. At the hospital, it was a sad time. Several babies had died from liver failure. A surgical resident who helped treat the children asked Dr. Puder to assist her with research on mice. They were trying to find causes of liver damage related to the IV feedings. The question has been studied for decades, with different groups proposing a variety of theories.

This kind of feeding consists of two solutions given at the same time. One contains vitamins and other nutrients. The other is a soy-based formula called Intralipid, designed to provide calories. Intralipid is made by Fresenius Kabi.

At the time the mice experiments were going on, Kathleen Gura, 46, a pharmacy specialist in gastrointestinal nutrition, had been trying to help a teenager with cancer who was unable to eat following a bone-marrow transplant. The boy had a severe soy allergy, so he couldn't use Intralipid. A colleague told Dr. Gura about a fish oil-based formula sold in Europe called Omegaven. She contacted Fresenius Kabi in order to get Omegaven for the 16-year-old.

The teen did remarkably well on Omegaven. After he was released from the hospital, Dr. Gura wrote to Fresenius Kabi and asked permission to give the unused Omegaven to Dr. Puder to test in mice. If it worked in mice, Dr. Gura wrote to the company, "it would justify additional research in our pediatric patients at risk for . . . liver disease."

In July 2003, Dr. Puder says he was amazed by his test results. The mice that got Omegaven by IV had no visual evidence of liver damage. At the hospital, he started showing the other doctors his mouse results. He says they weren't always impressed.

One day, he ran, computer in hand, to the operating room. One of the surgeons had just finished operating on a patient but Dr. Puder could barely contain himself. He called up the data on his computer on the spot as the doctor left the operating room. But he says he was shocked that instead of "the high fives I was expecting," he got a muted reaction.

"Mark was stuck in a lab working on the problem," says Russell W. Jennings, one of the surgeons who eventually became his ally on the Omegaven issue. Many surgeons didn't know what to make of his results or his unbridled enthusiasm. Dr. Puder says colleagues who, unlike him, had worked for years in the field, flat out told him he was wrong in thinking the standard lipid solution was the cause of the liver damage.

He even started calling Intralipid, the standard formula, "the white poison," a term that he says didn't go over well with the other doctors. "It caused a firestorm at the hospital," he recalls.

Fresenius Kabi says it has no safety concerns about Intralipid, which was approved by the FDA in 1975, and has been used longer in Europe. The company says on a volume basis, it sells three million to four million liters of Intralipid a year, compared with 10,000 to 20,000 liters of Omegaven.

In November 2003, at a weekly clinic of those in the short bowel syndrome program, Dr. Gura says colleagues told her Dr. Puder needed to be more judicious in how he presented his findings. Intralipid had been used in patients for decades. His mouse data wasn't even published yet. "The gang is very interested in the findings," Dr. Gura wrote in an email to Dr. Puder, "and it is just a matter of selling the concept so that it can go to the next level without telling them outright that the old way was toxic."

She noted that he seemed angry when he left the hospital the previous day. In her email, she reminded him, "politics always plays into things."

At the company, there was also skepticism about Dr. Puder's conclusions. After a December 2003 conference call with Staffan Bark, senior vice president of medical affairs at Fresenius Kabi about the findings, Dr. Gura received an email from him. It said: "It was nice to discuss these findings, although I am not that negative regarding the potential toxic effects of Intralipid on humans. 41 years of experience tell us something about its safety."

Company officials agreed to meet with the doctors in February 2004 at a conference in Las Vegas. Dr. Gura and Dr. Puder hoped to convince them to join in a clinical trial on Omegaven.

But at that meeting, Dr. Gura recalls, "We felt like we got kicked in the stomach." They were told they shouldn't "jump to conclusions" over their findings, she says. The mouse data was unpublished, and the only clinical data was a single case involving a 16-year-old boy, not a baby.

Ewald Schlotzer, director of medical scientific affairs in the nutrition therapy department for Fresenius Kabi, who was at the meeting, says he doesn't recall that conversation. But he says, "When you see experimental data, they may be fascinating, but you have to discuss the transferability of that data to patients."

In September 2004, Dr. Puder finally got a chance to test his ideas on a baby. Charles Rolfe was born in March 2004, with a hole in his abdominal wall. He was operated on several times, but "his bowels never really worked," says Dr. Jennings, one of the surgeons who operated on the baby.

Charlie, as his parents call him, couldn't eat, so he was put on intravenous feedings. Within a few weeks, he "started turning green" as his liver failed, Dr. Jennings says. Dr. Jennings knew about Dr. Puder's work with the mice, and urged him to give the Omegaven to Charlie.

But Dr. Puder replied: "We are still years away," from a trial in babies.

By August 2004, Dr. Jennings listed Charlie for a liver and small bowel transplant. Dr. Jennings thought Charlie might die before organs became available. "I went back to Mark and pleaded with him," Dr. Jennings says.

Dr. Puder and Dr. Gura approached Fresenius Kabi again, this time to use Omegaven on a five-month-old baby. The company agreed to donate the drug. The FDA allowed them to proceed. Charlie's parents gave their permission.

At first, Omegaven didn't seem to work. Charlie's liver function tests remained unchanged. But after a month, his tests improved and so did his coloring. "He became like a normal baby," says Dr. Jennings. He believes Omegaven "has changed the paradigm for treatment" of short bowel syndrome.

From previous experience, doctors knew they had a six-month window at most before some babies on IV feeding suffered life-threatening liver damage. So the goal had always been "to push food into them as hard as you could, as fast as you could and get them off" the IV feedings, Dr. Jennings says. "But now we don't have a four- or six-month limit. We actually don't know how long we have. Charlie is on Omegaven two years out and is fine."

Yet without a clinical trial, Dr. Jennings worries Omegaven "can be blown out of the water at any time. All it takes is one bad call. Or an adverse effect. Or a processing issue with the fish. This is very tenuous at every level," he says.

In December 2004, Dr. Gura sent Fresenius Kabi's Dr. Bark pictures of Charlie, hoping that the baby's plump cheeks and smiling face would help sway the company to proceed with a trial.

By this time, five more babies at Children's Hospital had been put on Omegaven. Dr. Puder and Dr. Gura believed that Omegaven was saving babies' lives, and they worked to gather data to convince others. On a family vacation in Hawaii, Dr. Gura spent hours online at the hotel's computer, monitoring the babies' test results. In addition to his lab work and surgeries, Dr. Puder checked on every baby taking Omegaven several times a day. He spent hours interviewing parents and compiling their observational data. He asked to see the babies' dirty diapers. "I was looking for signs that the liver was turning on and starting to work," he says.

Children's Hospital buys Omegaven for all the babies except one. The company continues to donate the drug to Charlie, who is now two years old.

Fresenius Kabi says it doesn't want to invest the resources to test both Omegaven and its new drug, SMOFlipid, for approval in the U.S. "We are convinced that SMOFlipid is the better product," says Mr. Ducker. It has already been approved for use in adults in some countries, including Germany and Sweden.

The company has suggested to Dr. Puder and Dr. Gura that they test the new product and has sent them samples to use in mice.

While Dr. Puder says he isn't opposed to testing the new drug, "I have a sense of urgency here," he says. "We have something that works, let's do Omegaven first. Then once we have something approved so these babies don't die, we can test something else." He adds: "We are miles and miles ahead on Omegaven. We have safety data on the patients. We have excellent outcomes on the patients."

Dr. Puder and Dr. Gura continue to search for ways to get a trial done on Omegaven without cooperation from Fresenius Kabi. They are also hoping to find a way to develop a similar product. Children's Hospital has filed a patent in the U.S. and internationally on the use of omega-3 -- which is fish oil, the base of Omegaven -- for the prevention and treatment of liver damage in children on intravenous nutrition. The patent is pending, and the

hospital is talking to companies that might want to develop a product for this use.

After two years with no trial, tensions about whether to use Omegaven remain. Sharyn Leaver, Maggie's mother, says her daughter's initial surgeon, David Mooney, "downplayed Omegaven" and said he didn't recommend it because it was experimental. "I wish we had pushed harder and sooner to get Omegaven for her," says Mrs. Leaver.

Dr. Mooney says he wrestled almost from the beginning about whether to put Maggie on Omegaven. He knew about Dr. Puder's results, which he calls "amazingly great," but the number of children treated was still small. He worried about adverse effects. "It is so easy to get caught in the hype of new things," Dr. Mooney says. Maggie was already fragile. What if he put her on Omegaven, he says, "and there was a horrible side effect that could tip her over the edge?"

But when standard therapies failed, he felt "there was nothing else to do." Given that the treatment is experimental, Dr. Mooney says he believes it was right to wait. But he also feels Omegaven has made a difference. "Five years ago, every single one of the kids taking Omegaven would be dead by now, Maggie included," he says.

In August, Mrs. Leaver took Maggie to Children's Hospital for a checkup. Dressed in a pink cardigan, pink skirt, and pink sandals, Maggie smiled at everyone. When Mrs. Leaver put her on the scale, she kissed her and told her, "Think big!" Maggie was up to 19.6 pounds, but her mother said, "She still doesn't eat like a normal kid."

At the checkup, the doctors reported that some of her liver enzyme levels remained mildly elevated. She might still have some liver damage, but there were no signs of the severe, life-threatening problems that existed before. At the end of the appointment, they concluded Maggie "looks great" and told her mother, "We're very happy."

Christopher P. Duggan, director of clinical nutrition at Children's Hospital, was one of the doctors who examined Maggie that day. He says he understands how parents might feel that Omegaven had saved their child's life. But he cautions that many treatments were given to the babies because they were so sick, making it hard to determine if it was Omegaven or something else that made the difference in their recovery.

"I am a total therapeutic skeptic," Dr. Duggan says. Even with the promising results so far, to really know that Omegaven is working, he says, "I want to see the results of a trial."

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