

Old Drug May Yield New Alzheimer's Treatment

By JON KAMP

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Alzheimer's disease is tough by any measure for the millions of victims and their loved ones. It can also frustrate doctors, who don't have lasting tools to fight the age-related brain disorder and who face a surge in cases as the population ages.

Researchers and a host of companies are in competitive pursuit of treatments that push beyond the handful of Alzheimer's drugs currently available, which generally can delay the worsening of symptoms. A key next step would be finding methods to actually slow or stop the disease's progression.

Study of the intravenous drug Gammagard, made by Baxter International Inc., has drawn particular attention because it is a decades-old and well-known product. The research also stands out because it involves using natural, human-produced antibodies.

Researchers at Cornell University have been exploring the effectiveness of these antibodies against various features of Alzheimer's. A particular target is a protein fragment called beta-amyloid that can collect in the brain and is believed to be an Alzheimer's hallmark. A small-scale Phase I study has hinted at positive treatment of cognitive decline, and results from a bigger Baxter-backed Phase II study are due later this year.

If that study looks good, the drug would progress to a more complex Phase III trial, which can be a stepping stone to seeking regulatory approval.

"I think we've already learned quite a bit," said Norman Relkin, who is researching the issue and directs the Memory Disorders Program at New York-Presbyterian Hospital/Weill Cornell Medical Center. "It's been a remarkable journey so far."

Gammagard is one of multiple intravenous immunoglobulin, or IVIG, drugs, and it is commonly used today to treat malfunctioning immune systems. The aim of using the drug against Alzheimer's is, essentially, to replenish what may be a depleted reservoir of natural antibodies that can remove the brain-harming amyloid.

There are multiple efforts under way on the antibody front, including a joint venture between Wyeth and Elan Corp. that is headed for Phase III study later this year and is also drawing attention. But multiple Alzheimer's experts have noted the unique aspects of the Gammagard-related study.

"This is a product that's been used for decades," said Neil Buckholtz, chief of the Dementias of Aging Branch within a National Institute on Aging program. "There's a lot of experience with safety with this product. That's the reason this is so unique."

There are reasons for caution, particularly because data are limited thus far. Gammagard for Alzheimer's patients would also be quite expensive and, as a human-derived product, potentially in short supply.

Solutions to such issues are under consideration as research presses on. The National Institute on Aging will fund the Phase III study, but Baxter and researchers have discussed additional funding to lengthen the study and add people, according to Dr. Relkin.

From there, Baxter could potentially get an answer from the U.S. Food and Drug Administration on using Gammagard for Alzheimer's patients in 2011, said Robert Davis, Baxter's chief financial officer. Baxter doesn't want to speculate yet on the potential business impact, but will know more as the Phase II trial proceeds, said company spokesman Chris Bona.

A Growing Issue

Message boards on the Alzheimer's Association's Web site pulse with stories of the disease and its impact. The efforts of family members who care for afflicted loved ones, and endure the pain of watching memories slip away, is a common theme.

Alzheimer's threatens to increase as Baby Boomers age and benefit from advancements elsewhere in health care. According to the Alzheimer's Association, an estimated 5.1 million Americans have the disease, the vast majority of whom are at least 65 years old. By 2050, the number of Americans older than 65 with the disease could reach up to 16 million.

The biggest known risk factor for Alzheimer's is age.

"In a way, we're making bodies very healthy but opening the way for these bodies to have sick minds. This is an incredible paradox," said Marsel, director of the Cognitive Neurology & Alzheimer's Disease Center at Northwestern University's Feinberg School of Medicine in Chicago.

"If we don't come up with a solution soon, it's really going to become a problem of proportions one can hardly imagine," he said.

Alzheimer's patients today are typically put on one of three "cholinesterase inhibitors" - Aricept by Eisai Co. and Pfizer Inc., Exelon by Novartis AG, and Razadyne by Johnson & Johnson. They are approved to treat Alzheimer's cognitive symptoms by preventing the breakdown of an important chemical messenger. These drugs are often used in

conjunction with Forest Laboratories Inc.'s Namenda, which works differently but delivers a similar benefit, according to experts.

The cholinesterase drugs tend to delay the symptomatic decline by six to 12 months for about half the patients who take them, according to the Alzheimer's Association. But they aren't approved by the FDA as tools to actually modify the progression of the disease.

Fighting Clusters

Stopping or slowing Alzheimer's progression is a key focus for researchers. At Cornell, researchers have recently discovered that IVIG contains antibodies that work against certain clusters of amyloid that appear very toxic to brain cells. This is important because, while there is some debate around amyloid's role, it appears amyloid itself isn't dangerous but that clusters are, Relkin said.

"IVIG represents a kind of guided missile against the forms of amyloid that we believe to be the most toxic," he said.

Winnowing out the particular antibodies within Gammagard that work best could be key for fashioning a new Alzheimer's weapon from Baxter's drug. There is no way supplies could meet the demand of the vast and growing Alzheimer's population, according to researchers. But it may be possible to isolate the effective antibodies and manufacture them through other means.

In that way, Baxter's drug may represent a bridge to the next development.

"My sense is that Gammagard will teach us how better to design our synthetic forms of therapy," said Sam Gandy, associate director of the Mount Sinai School of Medicine's Alzheimer's Disease Research Center. Gandy also chairs the Alzheimer's Association's Medical and Scientific Advisory Council.

According to Baxter spokesman Mr. Bona, the company believes supply and demand are in balance today for Gammagard's current users, to whom the company is committed. Baxter is also committed to supporting studies for new products, approval for new indications and new product delivery systems, he said.

There is clear need for something new against Alzheimer's.

Don Hayen, 73 years old, a retired dermatologist and HMO medical director, was diagnosed with early onset Alzheimer's in the spring of 2005. He visited his doctor when his family noticed signs of unusual behavior, including uncharacteristic anger, and he became alarmed by periods of disorientation while driving.

Dr. Hayen is now an active Alzheimer's Association member with an interest in better early diagnosis and securing more federal funding for research and social services. He has benefited so far from Aricept and Namenda, but knows he shouldn't expect long-term results, and he hopes for treatment that can "hold people in some reasonable position."

Major research is being conducted into how to detect Alzheimer's quickly, which is critical because when the disease kills brain cells, they don't return. Dr. Hayen understands where the disease can lead.

He remembers a patient of his who was severely disabled by advanced Alzheimer's. Her elderly husband was frustrated with trying to deal with it, and she was rendered unable to reach out and help, or lend sympathy.

"I picture myself that way," Dr. Hayen said. "And the fear and angst I have isn't what happens to me, because I won't be there."