Will Ponsegromab Be a Game Changer for Wasting Syndrome?

No drugs are approved in the United States or Europe to treat wasting syndrome, so the results with ponsegromab are promising.

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An experimental drug called ponsegromab may be an effective treatment for a wasting syndrome called cachexia that often affects people with cancer, according to results from a clinical trial.

The hallmark sign that cachexia has taken hold is the unintentional loss of significant amounts of weight, both from fat and skeletal muscle. In addition to harming quality of life, cachexia is also estimated to be responsible for as many as 30% of deaths in some cancer types.

In the clinical trial, nearly 200 people with advanced cancer and cachexia were randomly assigned to receive one of three different doses of ponsegromab or a placebo. Participants treated with ponsegromab gained anywhere from 2 to 6 pounds on average over 12 weeks, depending on the dose they received. By comparison, people treated with the placebo lost an average of 1 pound.

The group of participants treated with the highest dose, 400 mg, in fact, gained back more than 5% of their body weight, reported one of the study's investigators, Jeffrey Crawford, M.D., of the Duke Cancer Institute.

That amount of weight gain is "clinically significant for our patients," said Dr. Crawford, who presented the trial's findings on September 14 at the European Society for Medical Oncology (ESMO) annual congress in Barcelona. The study's results were published the same day in the New England Journal of Medicine.

Trial participants treated with the highest dose also reported having better appetites, fewer cachexia-related symptoms, and were physically more active than those who received a placebo. Ponsegromab caused few side effects, and few people stopped treatment because of them, he explained.

Ponsegromab, a type of drug known as a monoclonal antibody, targets a protein called GDF-15. Several drugs targeting GDF-15 or another that it interacts with in the brain, called GFRAL, are in development as possible treatments for cachexia, but ponsegromab is the first to advance this far in clinical trials.

No drugs are approved in the United States or Europe to treat cachexia, so the results with ponsegromab represent “a big breakthrough in the field of cancer cachexia research,” said Richard Dunne, M.D., of the Wilmot Cancer Center in New York and an investigator on the trial.

In a press release, Pfizer—which makes ponsegromab and funded the trial—said it is planning to launch a larger trial of the drug next year in people with cancer and cachexia. If the trial produces similarly positive results, it could lead to the drug’s approval by the Food and Drug Administration.

A desperate need for an effective cachexia treatment

Cachexia has long been considered an almost insurmountable problem in people with cancer, usually those with advanced disease. It’s also commonly seen in several other health conditions, including heart failure and chronic obstructive pulmonary disease, or COPD.

In its most severe form, with muscle and fat slipping away over a period of months for no apparent reason, it can cause extreme weakness and fatigue, along with unwelcome changes in skin color and overall physical appearance. Its physiologic impact, particularly on the lungs and heart, can lead directly to death.

Although it can occur in many types of cancer, cachexia most commonly occurs in people with pancreatic, colorectal, lung, and head and neck cancers, as well as some blood cancers and sarcomas.

According to E. Ramsay Camp, M.D., of Baylor College of Medicine’s Dan L. Duncan Comprehensive Cancer Center, for oncologists like him who specialize in treating pancreatic and other cancers in which cachexia is common, the condition is always top of mind.

“One of the first things I ask new patients [with these cancers] is whether they’ve lost weight,” said Dr. Camp, who was not involved in the trial. Any weight loss could be a sign that cachexia is starting to set in. Even in people whose cancer is still in early stages, a loss of muscle and fat can affect their ability to tolerate and complete their treatments, he explained.

“Patients often ask me what they can do to help” with their treatment, he said. “And my number one comment is always to maintain your weight, because [your] cancer treatments will take a toll.”

Targeting GDF-15 and GFRAL

For years, researchers struggled to understand cachexia’s biological underpinnings—what happens in cells and organ systems that causes muscle to deteriorate and squelches people’s desire and ability to eat.

Over the last decade, however, cachexia researchers have made substantial headway in

understanding the biologic players involved in cachexia and identified some tangible leads for possible treatments.

Among the most promising treatment leads has been GDF-15, a type of protein known as a cytokine that helps cells adapt and respond to changes in their surroundings. Several studies showed that GDF-15 is often abundant in the blood of people with cachexia.

These and other studies also determined that GDF-15 wasn't just an indicator of cachexia but actively involved in causing it. GDF-15, they showed, travels to a spot in the back of the brain, where it latches on to and activates a protein on neurons called GFRAL. GFRAL, it turns out, plays a critical part in controlling appetite.

Following that discovery, several studies showed that experimental drugs that lock on to either GDF-15 or GFRAL and block their interaction resulted in never-before-seen improvements in weight and survival in studies of mice with cachexia. With these exciting results in hand, human clinical trials of GDF-15 targeted drugs, including ponsegromab, were quickly launched.

Weight gain, improved appetite, and increased activity

The trial of ponsegromab included 187 participants with lung, colorectal, or pancreatic cancer. To be part of the trial, participants had to have unintentionally lost at least 5% of their body weight over the previous 6 months (an accepted definition of cachexia), and to have elevated blood levels of GDF-15.

Participants were randomly assigned to receive one of three doses of ponsegromab (100 mg, 200 mg, or 400 mg), given as an injection, or a placebo injection, once every 4 weeks for 3 months.

Most participants had already received many cancer treatments and nearly all were still undergoing active treatment for their cancer, Dr. Crawford explained. In addition, many had GDF-15 levels that were twice those the trial leaders had established as the minimum required for being in the study, he said.

Participants treated with ponsegromab at any dose gained weight, but the largest increases—in the 6-pound and higher range—were in those treated with the 400 mg dose. In addition to gaining weight, they also put on muscle mass.

Many of these participants reported improved ability to perform everyday physical activities. Some participants taking ponsegromab also wore activity monitors. Of those in the 400 mg group who wore monitors, their activity increased by an average of about 50 minutes a day compared with when they entered the study, Dr. Crawford reported.

Dr. Dunne said he was particularly pleased that ponsegromab appears to have few side effects.

"Even at the highest dose [tested], it was very, very safe—safer than the appetite stimulants we

often use” in people with cachexia, he added.

In addition, ponsegromab didn’t appear to interfere with patients’ responses to their cancer treatments, Dr. Crawford explained. But because the trial was small and people were only treated for 12 weeks, “it’s hard to say definitively” whether that’s the case, he cautioned.

Building on the early promise of targeting GDF-15 in cancer cachexia

Many trial participants have opted to be part of an extension study, during which they will receive treatment weekly for up to a year. The extension study will help provide insights into any potential longer-term safety issues with the drug as well as the extent to which it can help people with cachexia maintain and gain weight and muscle, Dr. Dunne said.

As for these initial findings, Dr. Camp said he was extremely encouraged.

“It brings a lot of hope, honestly,” he said. “It’s really encouraging that just by blocking this one molecule you can see such a huge impact.”

And if ponsegromab can indeed help patients with cachexia gain and maintain their weight, he continued, there’s the possibility of additional benefits. For example, if it can help people tolerate and stay on their cancer-directed treatments, he said, “it could have an effect on their long-term [cancer] outcomes.”

Even with these promising early findings, there’s a lot more research to do, Dr. Dunne cautioned, including on GDF-15.

“We don’t know everything we need to know [about GDF-15] broadly across different cancer types,” he said. That includes the extent to which it influences cachexia in different cancers and whether different levels of GDF-15 are required for it to take hold.

But one thing that has emerged from this trial, he added, is that GDF-15 “has clearly been shown to be an important driver of cachexia.”

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