



Tesamorelin Update

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Since it first became available in the mid-1990s, highly active anti-retroviral therapy (HAART) has saved lives and improved health and quality of life for countless people living with HIV—but the drugs are not without their downsides. One of these became clear within a few years after HAART was introduced, when people taking the new drugs began to experience dramatic and disturbing body shape changes caused by shifts in where fat accumulates.

Tesamorelin (brand name Egrifta), a new treatment to reduce one type of fat accumulation linked with antiretroviral treatment, has been in the works for a few years and was approved by the Food and Drug Administration (FDA) on November 11, 2010. This article explains how tesamorelin works, and why it represents an important development in HIV medicine.

FAT AND VAT

Fat, also called “adipose tissue,” can be stored subcutaneously (just below the skin) or more deeply. Loss of subcutaneous fat from the face, arms, legs, and buttocks is collectively called “lipoatrophy.” Fat accumulation, or “lipohypertrophy,” can occur in the breasts (in both men and women), in the upper back and at the base of the neck (known as “buffalo hump”), and in the belly. This kind of deep belly fat is known as “visceral adipose tissue” (VAT)—in other words, fat (adipose tissue) that surrounds the abdominal organs (viscera).

Lipohypertrophy (abdominal obesity, in particular) is linked to metabolic issues such as insulin resistance (a precursor to diabetes), hypertriglyceridemia (abnormally high levels of certain fats in the blood), decreased HDL (“good”) cholesterol, and cardiovascular disease. And the emotional pain and stigma around VAT are not inconsequential.

Clinicians and researchers are still trying to understand exactly what causes lipohypertrophy. Unlike lipoatrophy, which can be traced to specific antiretrovirals, fat accumulation is seen in individuals on a variety of treatment regimens. Duration of anti-HIV therapy is implicated, as is progression to AIDS, but so are other risk factors unrelated

to HIV or its treatment, including older age and body composition before taking anti-HIV drugs.

Neither is it clear just how many people on HIV treatment have some form of lipodystrophy—reports range from 11% to as high as 83%.

What is clear, however, is that the health risks and emotional distress caused by these body shape changes are severe enough to discourage some people from adhering to their treatment regimen, or from starting antiretroviral therapy at all. That’s one reason why HIV treatment advocates have been rooting for a safe and effective drug to treat lipodystrophy—and why the approval of tesamorelin is good news.

SHRINKING VAT WITH GROWTH HORMONE

Experimental treatments for lipohypertrophy have focused largely on growth hormone products. Growth hormone is a chemical produced by the pituitary gland, located at the base of the brain. It stimulates gluconeogenesis—production of glucose by the liver—and also prompts the liver to secrete a protein called “insulin-like growth factor-1” (IGF-1). The production of this protein stimulates growth during childhood and continues to promote cell growth throughout the body in adulthood. Growth hormone is therefore critical for maintaining muscle and bone mass, and it also affects fat distribution in the body.

HIV positive men with VAT have been reported to have lower levels of growth hormone than HIV negative men or positive men without abdominal fat accumulation. Numerous studies have linked growth hormone levels with decreases in VAT.

One growth hormone product, called somatropin and marketed as Serostim, is FDA-approved for treatment of AIDS wasting (defined as loss of 10% of body weight, along with other symptoms), and has been used off-label to reduce VAT without simultaneously decreasing subcutaneous fat. While the treatment was found to be effective in clinical trials, side effects (including swelling, limb pain, and elevated blood glucose) are problematic for some individuals, and the drug has not been approved to specifically treat abdominal fat accumulation.

TESAMORELIN IN THE PIPELINE

Tesamorelin, developed by the Canadian pharmaceutical company Theratechnologies and referred to in research studies as TH9507, is a growth hormone product—specifically, a growth hormone–releasing factor analog. Tesamorelin is not exactly growth hormone; rather, it stimulates the pituitary gland to secrete growth hormone.

A Phase II study of tesamorelin, described in the August 12, 2005, issue of the journal *AIDS*, enrolled 61 patients in three groups: placebo or 1 mg or 2 mg tesamorelin injected once daily. Visceral fat decreased by nearly 16% in the 2-mg treatment group (without a decrease in limb fat), and lean body mass increased in the tesamorelin groups compared with the placebo group. Cholesterol and triglyceride levels also went down in the treatment group. The treatment was found to be generally well tolerated, with no effect on blood glucose levels.

Subsequently, a Phase III study described at the 2007 Conference on Retroviruses and Opportunistic Infections and subsequently published in the *New England Journal of Medicine* examined the effect of tesamorelin on HIV-associated abdominal fat accumulation. In a press conference, investigator Steven Grinspoon, MD, of Harvard Medical School's Division of Nutrition stressed the need for treat-

ments to decrease VAT as a way of reducing cardiovascular disease risk for people living with HIV.

In this larger study, 412 participants were randomized in to receive 2 mg tesamorelin or placebo once daily. At 26 weeks, a 15.2% reduction in VAT was seen in the tesamorelin group, compared with a 5% increase in VAT in the placebo group. Waist circumference decreased by three centimeters on average in the tesamorelin group—approximately one pants size, said Dr. Grinspoon.

Lipid profiles also improved in the treatment group, and the researchers reported no increase in glucose levels. Adverse events included headaches and arthralgias (joint pain) in more than 10% of participants in both groups, and swelling in the limbs, muscle aches, and allergic rashes were slightly more common in the treatment group.

More recently, in the March 1, 2010, issue of *JAIDS*, Julian Falutz, MD, of McGill University School of Medicine and colleagues described results from a 12-month Phase III safety and efficacy study of tesamorelin for reduction of VAT.

A total of 404 HIV positive participants on HAART and with excess abdominal fat were enrolled in the two-phase study. In the primary efficacy phase (the first six months), individuals were randomly assigned to receive either tesamorelin (2 mg injected subcutaneously once daily) or a placebo injection. In the extension phase (months 6–12), participants who originally received tesamorelin were re-randomized to either continue on tesamorelin (at the same dose) or switch to placebo. Those who were initially randomized to the placebo group were started on tesamorelin.

The results were encouraging: VAT decreased by 10.9% (a loss of 21 cm²) in the tesamorelin group compared with only 0.6% (a reduction of 1 cm²) in the placebo group in the first six months. In participants who continued on tesamorelin for 12 months, VAT declined by approximately 18%. IGF-1 levels also increased significantly.

MEASURING BELLY FAT

Three imaging techniques, *computed tomography (CT)*, *magnetic resonance imaging (MRI)*, and *dual-energy X-ray absorptiometry (DEXA) scanning*, are non-invasive methods commonly used to measure belly fat and accurately distinguish between subcutaneous fat and visceral adipose tissue.

Waist circumference (how big a person is around the middle) is a lower-tech method of assessing abdominal fat. The National Cholesterol Education Program defines “central obesity” as a waist circumference above 88 cm (just under 35 inches) for women and 102 cm (roughly 40 inches) for men.

Waist-to-hip ratio (WHR) compares waist circumference to the circumference of the hips. A higher WHR gives the body an “apple” shape, with a bigger middle and narrower hips, whereas a “pear-shaped” body carries more weight in the hips than around the middle. High WHR is linked to cardiovascular disease risk.

Trunk fat, waist circumference, and waist-to-hip ratio—further measures of abdominal fat accumulation that are predictors of cardiovascular disease—improved in the tesamorelin group, with no loss of subcutaneous fat in the abdomen and no limb fat reduction. As described at the 50th Interscience Conference on Antimicrobial Agents and Chemotherapy, held in Boston in September 2010, study participants were asked to rate their “belly appearance distress”; this measure improved significantly, as did physician’s ratings of belly profile, in the tesamorelin groups compared with those receiving placebo.

Importantly, the researchers observed, “these benefits occurred without any significant increases in glucose or insulin levels, a major concern for any strategy to augment [growth hormone] secretion in the HIV population.”

The investigators reported that tesamorelin was well tolerated, although more adverse events were experienced by the tesamorelin-treated participants than by those on placebo. Adverse events were similar to those seen in earlier studies, with injection site reactions (including redness and itching) topping the list for both tesamorelin and placebo recipients—although they occurred more frequently with tesamorelin.

One frequent criticism of clinical trials of new drugs is that the study sample fails to represent the larger population of people who need the treatments most; not every person who will want to use tesamorelin is white, male, and free of hepatitis, for example. In an effort to address this common shortcoming, Monica Zoltowska, PhD, from Theratechnologies and colleagues performed a sub-group analysis using data from the two Phase III trials of tesamorelin. They examined the growth hormone product’s safety and efficacy among trial participants grouped by age, sex, race/ethnicity, use of anti-HIV drugs, HIV viral load, and whether they also had hepatitis B or C.

At 26 weeks, the researchers reported, the effect of tesamorelin on VAT in the five sub-groups was consistent with that seen across the broader sample of participants in the two studies. No important differences in adverse events were detected throughout the full 52-week study. These data suggest that tesamorelin “reduces VAT in different sub-populations of HIV-infected patients with lipohypertrophy, without any clinically meaningful differences in long-term safety,” the researchers concluded.

FURTHER QUESTIONS

On May 27, 2010, the FDA advisory committee charged with reviewing the data on tesamorelin unanimously recommended that the agency approve the treatment for marketing. Nearly six months later, the FDA approved

tesamorelin “for the treatment of excess abdominal fat in HIV-infected patients with lipodystrophy,” as stated in Theratechnologies’ November 11 press release. The drug will be marketed in the United States under the brand name Egrifta by EMD Serono, Inc., an affiliate of the major pharmaceutical company Merck.

While the approval of tesamorelin is a welcome development, some concerns remain about the drug’s safety and long-term effects. At the May 27 advisory committee meeting, Graziella Soulban, MD, director of clinical research at Theratechnologies, reported that the tesamorelin-receiving study groups experienced higher rates of pre-diabetes and diabetes than did those taking placebo during the first 26 weeks, although those rates declined by week 52. Study participants who entered the trial with pre-diabetes also ran the risk of developing diabetes during the studies, suggesting that tesamorelin may not be appropriate for people with this (unfortunately common) condition.

A possible safety concern with tesamorelin and other growth hormone products used in the setting of HIV care is that elevated IGF-1 may promote the formation of tumors. Increased IGF-1 levels are an indicator that tesamorelin is working, but this effect must be balanced against the already higher risk of cancers in HIV positive people (see “A Glass Half Full: Cancer Risk for People Living with HIV,” page 30). According to Soulban, however, increased IGF-1 levels were not associated with higher risk of cancer in the Phase III trials.

Further studies are also warranted to more closely examine tesamorelin’s safety and efficacy in women. Although men made up the majority of participants in the tesamorelin trials, women are extremely likely to use the treatment if it is approved. In fact, as reported by Massimo Galli, MD, of the Institute of Infectious and Tropical Diseases at the University of Milan and colleagues, HIV positive women are more likely than HIV positive men to have fat accumulation, including excess VAT. This makes it important to better understand whether the drug affects women’s bodies differently. In addition, tesamorelin is contraindicated for use by pregnant or breastfeeding mothers, as changes in growth hormone secretion may be harmful to the developing fetus or infant.

Other lingering—and important—questions concern the need for long-term treatment. Tesamorelin’s VAT-reducing effect apparently ends once treatment is stopped; as Falutz noted in a 2010 article, “the initial improvements over six months in VAT were rapidly lost in those switching from tesamorelin to placebo.” Will life-long treatment therefore be necessary—and will it be safe and affordable? And will the fact that tesamorelin must be injected deter people from using it long-term?

For one trial participant, at least, injecting the drug daily was not a challenge: “Adhering to this medication regimen was easy,” said Lisa Hamilton during the open public hearing at the FDA advisory committee meeting. “Given the opportunity, I would stay on tesamorelin for life.” The treatment “improved my quality of life so much, and the physical and psychological burdens [of lipohypertrophy] were lifted.”

WHAT'S NEXT?

HIV treatment advocates asked the FDA to approve tesamorelin, but with some important conditions. “We strongly urge against reviewing, approving, or labeling Egrifta as a cosmetic treatment,” said long-time treatment advocate Jeff Berry in an eloquent appeal at the advisory panel meeting. Berry likened lipodystrophy treatment to reconstructive surgery for women who have had mastectomies: both have benefits that go far beyond the merely “cosmetic.”

Hamilton described to the committee how her abdominal fat has returned since the tesamorelin trial ended, making it once again difficult to bend over and perform normal activities of daily life and causing her much anxiety: “Since I’ve been off the tesamorelin and the abnormal fat accumulations of the abdomen returned, my fears regarding heart attack, hypertension, and stroke have returned”

Clearly, treatment for abdominal fat accumulation isn’t just about trimming down a protruding belly. Lipodystrophy, said Berry, “is conspicuous and stigmatizing, an overt sign of HIV infection and illness, and according to the collected data and countless anecdotal reports, significantly affects psychological well-being, quality of life, willingness to commence antiretroviral therapy in light of lipodystrophy fears, and adherence levels among those on antiretroviral therapy.”

No drug or treatment is perfect for everyone, of course, and advocates will need help ensure affordable access. That said, tesamorelin has the potential to improve physical health, antiretroviral treatment adherence, and overall well-being for many people living with HIV, and its approval is a welcome development in HIV care.

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