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Is Tesamorelin a safe and effective drug to treat Lipodystrophy in HIV patients?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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Abstract

Objective: The objective of this selective EBM review is to determine whether or not Tesamorelin is a safe and effective drug to treat lipodystrophy in HIV patients.

Study Design: Review of three English language primary randomized controlled trials published between 2005-2010.

Data Sources: Randomized, placebo-controlled, double-blind clinical trials comparing Tesamorelin to a visually matched placebo were found using PubMed.

Outcome(s) Measured: Each of the three clinical trials assessed the improvement of lipodystrophy (accumulation of visceral adipose tissue) in HIV patients. In addition, they noted how the improvement in lipodystrophy would impact patient's self body image and quality of life. Prior to the study, all patients received a CT scan in order to get a visceral adipose tissue baseline, this allowed researchers to note patient's percent change from baseline. Furthermore, patients also completed a self-perceived body image questionnaire. Patients rated their "belly size" comparing their current appearance to their perceived healthy look with scores from -100 (much thinner) to +100 (much bigger). Similarly, they rated their "belly image distress" from 0 (extremely upsetting and distressing) to 100 (extremely encouraging); and "belly profile" by choosing from six silhouettes scored from 0 (normal) to 5 (very dysmorphic).

Results: Three randomized-controlled trials were included in this review. Results from each study reveals that Tesamorelin (2 mg) is a safe and effective drug to treat lipodystrophy in HIV patients. Similarly, patient's self body image and quality of life also improved due to the reduction in their visceral adipose tissue. Although all three trials reported similar adverse events, for two of the trials, headache was the most common; while injection site erythema was the most common for the other trial.

Conclusion: The three randomized-controlled trials have proven that Tesamorelin is a safe and effective treatment for lipodystrophy in HIV patients. It is because of these clinical trials that Tesamorelin was approved by the FDA on November 10, 2010 and it is currently the only alternative treatment for lipodystrophy in HIV patients besides surgery or diet and exercise.

Key Words: Tesamorelin; growth hormone releasing hormone; HIV; lipodystrophy; abdominal fat accumulation

INTRODUCTION

Human Immunodeficiency Virus (HIV) is a continually growing pandemic that affects approximately 33.3 million people worldwide. HIV can affect people of all ages and is responsible for about 1.8 million deaths annually. HIV is a retrovirus that can be acquired in a number of different ways which include: sexual contact (vaginal, anal, or oral), intravenous drug use, tattoos, accidental needle sticks in the healthcare setting, or from mother to child via pregnancy and childbirth (vertical transmission). Once a person develops HIV, it can be up to 10 years or more before a person develops Acquired Immune Deficiency Syndrome (AIDS). The development of AIDS (when the CD4 count is less than 200) makes a person more likely to develop various opportunistic infections, dementia, cardiovascular disease, diabetes, and various cancers. Ultimately, patients do not die of AIDS but they instead die of the complications associated with having AIDS.¹

Unfortunately, there is no cure for HIV; however, there are several treatment options available to manage this disease and slow down the progression to AIDS. The most common regimen used to manage HIV is HAART (highly active antiretroviral therapy) which generally includes a combination of three drugs. The drug classes that may be included in the HAART combination are nucleoside or non-nucleoside reverse transcriptase inhibitors (NRTI or NNRTI), protease inhibitors (PI), entry inhibitors (includes fusion inhibitors), and integrase inhibitors. The average monthly cost of HAART ranges between \$2,100-4,700. Although these medications are extremely effective (especially when used in combination), they have a lot of adverse side effects. The most common adverse side effect is lipodystrophy and it is estimated that 14-40% of HIV patients on HAART will develop this. Of the medications included in the HAART cocktail, it has been proven that protease inhibitors put patients at greatest risk for developing lipodystrophy.²

Since the prevalence of lipodystrophy varies, it is not known how many healthcare visits occur

each year due to this problem. It is well known that patients who develop lipodystrophy are at increased risk for developing new onset hyperglycemia (5%), hypertriglyceridemia (19%), and hypercholesterolemia (24%). Furthermore, it is known that hyperlipidemia, insulin resistance, hyperinsulinemia, and hyperglycemia are features associated with HIV lipodystrophy which can consequently put HIV patients at risk for developing atherosclerosis and diabetes.²

Since lipodystrophy is a continually growing problem in the HIV community, there was a need to develop a better treatment method for this condition. Prior to the development of Tesamorelin (Egrifta), the only available treatment options were surgery and diet and exercise.² Surgical options included: liposuction and lipectomy which can cost about \$2884 nationally on average (not including anesthesia or facility fees); however, re-occurrence was very common. With diet and exercise, no specific regimen exists; however, adequate nutrition and exercise has shown modest improvement in these patients. With the above being said, Tesamorelin is being proposed as a more effective treatment option since the re-occurrence rate of the above treatment methods are rather high. Tesamorelin is to be administered as a 2mg subcutaneous injection once a day. Since the approval of Tesamorelin, the latest reported cost of Tesamorelin is approximately \$2356.80 per month.³

OBJECTIVE

The objective of this selective EBM review is to determine whether or not Tesamorelin is a safe and effective drug to treat lipodystrophy in HIV patients.

METHODS

All three clinical trials utilized for this review were selected because their population group included male and female HIV patients with lipodystrophy who were over the age of 18 years old. The intervention used for these HIV patients was 2 mg of Tesamorelin (subcutaneous injection in the abdomen) and the comparison group of HIV patients were treated with a visually matched placebo.

Outcomes measured included how effective Tesamorelin was overall at improving body composition (reduction of visceral adipose tissue) and improving self body image as well as quality of life; which are patient oriented evidence that matters. The amount of visceral adipose tissue was predetermined by a CT scan and the improvement was based on a change from the baseline amount. The remaining outcomes were based on improvement in questionnaire scores on self body image and quality of life. The types of studies that were included are randomized-controlled trials; one of the studies was double-blind and placebo-controlled while the other two studies were only double-blinded.^{4,5,6}

Information obtained for this review was found on PubMed using the following key words: Tesamorelin, growth hormone releasing hormone, HIV, lipodystrophy, and abdominal fat accumulation. All articles were published in the English language in peer-reviewed journals that were published between the years 2005-2010. All of the articles were selected based on their relevance and importance of outcomes to the patient. The three trials were included in this review because they met the following inclusion criteria: randomized-controlled trials published after 1996, articles that included patient oriented evidence that matters, and studies that were double-blinded. Other studies were excluded because they were not randomized-controlled trials and they did not include the selected patient population. The statistics in this review were reported using p-value, numbers needed to treat (NNT), relative benefit increase (RBI), and absolute benefit increase (ABI).

Table 1. Demographics of included studies. I was unable to include all of the inclusion & exclusion criteria because the list is very long so I included the most common.

Study	Type	# of pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Faultz Article ⁴ , 2010	RCT (double-blind study)	404	47.7 ± 7.5	Men & women age 18-65 w/ HIV Lipodystrophy (WC ≥ 95 cm for men & ≥ 94 cm for women or a WTH ratio ≥ 0.94 cm for men & ≥ 0.88 for women).	-Pts with a BMI ≤ 20 kg/m ² -Pts receiving estrogen w/in 6 months of the study -Pts w/ a clinical history of pituitary disease	31	Randomized to receive 2 mg of SQ Tesamorelin or Placebo
Faultz Article ⁵ , 2007	RCT (double-blind study)	412	47.3 ± 7.3	Men & women age 18-65 w/ HIV Lipodystrophy (WC ≥ 95 cm for men & ≥ 94 cm for women or a WTH ratio ≥ 0.94 cm for men & ≥ 0.88 for women).	-Pts receiving estrogen w/in 6 months of the study -Pts w/ a clinical history of pituitary disease	32	Randomized to receive 2 mg of SQ Tesamorelin or Placebo
Faultz Article ⁶ , 2005	RCT (double-blind, placebo controlled)	61	44.6	Men & women age 18-65 w/ HIV Lipodystrophy (WC ≥ 95 cm for men & ≥ 94 cm for women or a WTH ratio ≥ 0.94 cm for men & ≥ 0.88 for women).	-Pts with a BMI ≤ 20 kg/m ² -Pts w/ a prior history of DM Type I -Pts w/ prior use of GH or GH-related products w/in 6 months of the study	10	Randomized to receive 2 mg of SQ Tesamorelin or Placebo.

OUTCOMES MEASURED

Each of the three clinical trials assessed the overall improvement of body composition (visceral adipose tissue) while noting how this improvement also impacted patient's self body image and quality of life. All of the above measured outcomes are patient oriented evidence that matters. Prior to the study, all participants had their amount of visceral adipose tissue predetermined by a CT scan and improvements were noted in the amount of change from baseline. The remaining outcomes were based on improvement in baseline questionnaire scores on self body image and quality of life. The self-perceived body image questionnaire had patients rate their “belly size” comparing their current appearance to their perceived healthy look with scores from -100 (much thinner) to +100 (much bigger). Similarly, the questionnaire had patients rate their “belly image distress” from 0 (extremely upsetting and distressing) to 100 (extremely encouraging); and “belly profile” by choosing from six silhouettes scored from 0 (normal) to 5 (very dysmorphic).^{4,5}

RESULTS

The results of all three clinical trials evaluated were presented as dichotomous data in order to evaluate the improvement of lipodystrophy in HIV patients.

Faultz et al (2010) found that visceral adipose tissue decreased by -10.9% (-21 cm²) in the Tesamorelin group versus only a -0.6% (-1 cm²) in the placebo group. This data demonstrated a 17.17% RBI and a -0.103% ABI when comparing Tesamorelin to the visually-matched placebo. NNT for this study was found to be -10 with a p-value of <0.001 and a 95% CI of (-28 to -11) (Table 2). A negative NNT value in this study indicated that for every ten patients who were given Tesamorelin, there would be one fewer patient who would have a reduction in visceral adipose tissue when compared to the placebo. The p-value of <0.001 indicates that this test is statistically significant and we are 95%

confident that the true NNT for the population lies between the interval -28 and -11.⁴

Cole: Tesamorelin and Lipodystrophy 6

Faultz et al (2007) also compared Tesamorelin to a visually matched placebo. This study found that patients who received Tesamorelin had a decrease of 27.8 cm² in visceral adipose tissue while patients who received the placebo had an increase in visceral adipose tissue of 5.1 cm². The calculated RBI was 2.04% and the ABI was 0.102%. Moreover, the NNT was calculated to be 10 with a p-value of <0.001 and a 95% CI of (-40.7 to -25.0) (Table 2). A positive NNT value in this study indicates that ten patients must be treated with Tesamorelin in order for one additional patient to benefit from Tesamorelin when compared to the placebo group. The p-value of <0.001 indicates that this test is statistically significant and we are 95% confident that the true NNT for the population lies between the interval -40.7 and -25.0.⁵

The study performed by Faultz et al (2005) also compared Tesamorelin to a visually-matched placebo. This study showed that patients who received Tesamorelin had a decrease in visceral adipose tissue of -15.7% while the placebo only had a decrease of -5.4%. The RBI was calculated to be 1.91 and the ABI was -0.103. Furthermore, the NNT was calculated to be -10 with a p-value=0.03 (Table 2). No confidence interval was provided by this study. A negative NNT value in this study indicated that for every ten patients who were given Tesamorelin, there would be one fewer patient who would have a reduction in visceral adipose tissue when compared to the placebo. The p-value=0.03 indicates that this test is not statistically significant.⁶

Table 2. Efficacy of Tesamorelin on Improving Lipodystrophy (Overall Body Composition)

Study	Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Number needed to treat (NNT)	p-value	95% Confidence Interval (CI)
Faultz Article ¹ , 2010	17.17	-0.103	-10	p< 0.001	95% CI: (-28 to -11)
Faultz Article ² , 2007	2.04	0.102	10	p<0.001	95% CI: (-40.7 to -25.0)
Faultz Article ³ , 2005	1.91	-0.103	-10	p=0.03	NR

In addition to the above, two of the trials noted how reducing lipodystrophy would impact patient's self body image while the other study noted how it impacted patient's quality of life. In terms of self body image, patients were given a questionnaire prior to the study and they were asked to rate their body image distress (0 to 100), belly size (-100 to 100), and belly profile (0 to 5). Table 3a represents that values of improvement in these three areas for Faultz et al (2010) and Faultz et al (2007). The baseline questionnaire scores were not reported in either of the studies and all of these values represent an overall change from the baseline.^{4,5}

Faultz et al (2010) showed an improvement of 8.4 ± 29.0 in the Tesamorelin group versus only 5.2 ± 26.6 in the placebo group for belly image distress and the reported p-value was 0.02. Moreover, the Tesamorelin group demonstrated a 14.8 ± 27.8 improvement in belly size while patients in the placebo group had a 11.7 ± 25.2 with a p-value of 0.21. Lastly, belly profile seemed to improve in the Tesamorelin group with -0.5 ± 1.3 versus -0.3 ± 1.0 in the placebo group with a p-value of 0.08. All of the reported p-values for improving self body image for this study were deemed significant except for the p-value that represents belly size (See table 3a).⁴

Faultz et al (2007) showed similar improvements to that of Faultz et al (2010) in all areas. For belly image distress, the reported improvements were 11.6 ± 26.9 and 6.2 ± 25.8 for Tesamorelin and

placebo respectively; with a p-value of 0.03. In terms of belly size, the reported improvement scores

Cole: Tesamorelin and Lipodystrophy 8

were 35.1 ± 55.0 and 35.4 ± 55.0 for Tesamorelin and placebo respectively; with a reported p-value of 0.70. Furthermore, the study reported the improvement scores for belly profile as 0.67 ± 1.25 and 0.34 ± 1.25 for Tesamorelin and placebo respectively with a p-value of 0.03. All of the reported p-values for improving self body image in this study were concluded to be significant except for the p-value that represents belly size (See table 3a).⁵

Table 3b represents the improvements in quality of life as reported in Faultz et al (2005). The quality of life element which improved the most was social well being. The baseline score in the Tesamorelin group was 3.00 with a change of -0.34 versus a baseline score of 2.80 with a change of -0.07 in the placebo group. The reported p-value was 0.05 which indicates that this test is statistically significant.⁶

Table 3a. Efficacy of Tesamorelin on Improving Body Image

Study	Belly Image Distress	Belly Size	Belly Profile
Faultz Article ¹ , 2010	Tesamorelin: 8.4 ± 29.0 Placebo: 5.2 ± 26.6 p-value=0.02	Tesamorelin: 14.8 ± 27.8 Placebo: 11.7 ± 25.2 p-value=0.21	Tesamorelin: -0.5 ± 1.3 Placebo: -0.3 ± 1.0 p-value=0.08
Faultz Article ² , 2007	Tesamorelin: 11.6 ± 26.9 Placebo: 6.2 ± 25.8 p-value=0.03	Tesamorelin: 35.1 ± 55.0 Placebo: 35.4 ± 55.0 p-value=0.70	Tesamorelin: 0.67 ± 1.25 Placebo: 0.34 ± 1.25 p-value= 0.03

Table 3b. Efficacy of Tesamorelin on Improving Quality of Life (Social Well Being)

Study	Tesamorelin Baseline	Tesamorelin Change	Placebo Baseline	Placebo Change	p-value
Faultz Article ³ , 2005	3.00	-0.34	2.80	-0.07	0.05

Lastly, each of the three trials reported and discussed any adverse events that occurred during the study. For two of the trials, the most common reported adverse event was headache which is seen in

table 4. In Faultz et al (2007), RRI was -0.115%, ARI was -0.021%, and NNH was -48 with a p-value

Cole: Tesamorelin and Lipodystrophy 9

of 0.58 which means the test is statistically insignificant. A negative NNH in this case means that for every forty-eight patients, one more patient will report the adverse effect of headache if they received Tesamorelin (See table 4).⁵ Similarly, with Faultz et al (2005), RRI was 1.070%, ARI was 0.150%, and NNH was 7. No p-value was reported for this study. A positive NNH for this study means seven patients must be treated with Tesamorelin for one person to develop a headache. (See table 4).⁶

In Faultz et al (2010), the most common reported adverse event was injection site erythema which is seen in table 4. The RRI was 1.940%, the ARI was 0.093%, and NNH was 11 with a p-value of 0.006. A positive NNH in this case means that 11 patients must be treated with Tesamorelin for one person to experience erythema at the injection site. The p-value of 0.006 means that the test is statistically significant (See Table 4).⁴

Table 4. Adverse Events: Headache and Injection Site Erythema

Study	Adverse Event	Relative risk increase (RRI)	Absolute risk increase (ARI)	Number needed to harm (NNH)	p-value
Faultz Article ² , 2007	Headache	-0.115	-0.021	-48	p=0.58
Faultz Article ³ , 2005	Headache	1.070	0.150	7	NR
Faultz Article ¹ , 2010	Injection Site Erythema	1.940	0.093	11	p=0.006

DISCUSSION

Throughout all three clinical trials, Tesamorelin (2 mg) was proven to be an effective drug to treat lipodystrophy in HIV patients; however, Faultz et al (2005) was limited in that the sample size only included 61 patients and the study was only conducted over a 12 weeks period compared to the other studies which had a larger sample size and a longer duration.^{4,5,6} Since it's FDA approval,

Tesamorelin is only indicated to treat lipodystrophy in HIV patients. Tesamorelin is an accepted

Cole: Tesamorelin and Lipodystrophy 10

treatment option in the United States; however, several steps must be taken before a patient can be prescribed this medication. If a clinician would like their patient to take Tesamorelin, they must fill out a Statement of Medical Necessity (SMN) that is signed by the clinician and patient. This form must then be faxed to the AXIS Center which is the center that provides patient information and education about Tesamorelin. The AXIS Center offers reimbursement programs, in-home or in-office training on how to properly use Tesamorelin; as well as 24 hour customer support. A clinician can only get the SMN forms from EMD Serono (the company that makes Tesamorelin) or the AXIS center.⁷

Another problem that clinicians may run into is the cost of Tesamorelin. As stated earlier, the cost is about \$2356.80 per month which may not be covered by the patient's insurance; however there are some solutions available to address this problem. One solution is the Co-pay assistance program. This program was designed for commercially insured patients with a prescription drug benefit that covers Tesamorelin (Egrifta). And this program will cover up to \$2,400 of patients' out of pocket cost over a 12-month period. Patients must use the card for the first time in 2011 and can off-set up to \$200 of their copay or coinsurance for up to 12 uses prior to 12/31/12. Unfortunately, patients with Medicare or Medicaid or patients who live in Massachusetts may not use this program. Another solution is Patient Assisted Program (PAP) which offers free Tesamorelin to eligible patients who are under or uninsured. In order for patients to qualify for PAP, they must meet the following criteria: household income that does not exceed 600% of the Federal Poverty Level (FPL), must be diagnosed with HIV, and must be a resident of the United States. PAP is only available on a yearly basis and patients must reapply every year to receive this benefit.⁷

In addition to being an effective drug, Tesamorelin also proved to be a relatively safe drug. The most common side effect reported in two of the articles was headache while the other article reported

injection site erythema (reported in tables above). Moreover, there are some contraindications for the

Cole: Tesamorelin and Lipodystrophy 11

use of Tesamorelin which includes pregnancy (Tesamorelin is a Category X), known hypersensitivity to Tesamorelin and/or Mannitol, active malignancy (either newly diagnosed or recurrent), and disruption of the hypothalamic-pituitary axis due to hypophysectomy, hypopituitarism, pituitary tumor/surgery, head trauma, or head irradiation.⁷

CONCLUSION

Tesamorelin, a growth hormone releasing factor, was proven to be a safe and effective treatment for lipodystrophy in HIV patients. In addition, Tesamorelin overall demonstrated low numbers of treatment induced adverse events which further proves that it is a safe and effective drug. Due to these clinical trials, the FDA officially approved Tesamorelin on November 10, 2010; making it the first and only approved drug to treat lipodystrophy in HIV patients. Although the methods used in these trials were sufficient and proved that Tesamorelin can improve lipodystrophy by decreasing visceral adipose tissue; however these trials failed to demonstrate how these changes benefit patients long term with their cardiovascular health. Therefore, a future study is warranted to evaluate how reducing visceral adipose tissue improves cardiovascular health in HIV patients. Furthermore, due to the success of this drug for HIV patients, Tesamorelin is currently being studied for use in healthy adults to reduce visceral adipose tissue and to improve mild cognitive impairment.

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