



Tesamorelin-A New Hope For Lipodystrophy In HIV Patients

Mangala Lahkar, Pradumna Pathak

Lipodystrophy in HIV patients, a condition in which excess fat develops in different areas of the body, most notably around the liver, stomach, and other abdominal organs (visceral body fat). Excess visceral fat accumulation may contribute to other health problems as well as reducing quality of life. Tesamorelin is approved to induce and maintain a reduction of excess visceral abdominal fat in HIV infected patients with lipodystrophy (1). Earlier our HIV patients rarely had lived long enough to develop those issues, and that perhaps we were finally getting somewhere with the limited advances we had made up to that point. In 1995, with the emergence of HAART, reports began fairly early on emerging signs of lipodystrophy assumed early on to be related to protease inhibitors. The prevalence of these syndromes in the HIV positive population is somewhere between 20% and 80%, depending on the study and population referred to (2). In one study, the prevalence of lipodystrophy was found to be 34% and the prevalence becomes 69.6% in those receiving HAART for > 72 weeks (3). There is also a great deal of evidence implicating anti retroviral therapy and certain agents in particular appear to play a causative role in the lipodystrophy syndromes. It may be, in reality, that a great deal of this complication emerged not simply as a complication of therapy, but due to increased survival allowing chronic effects of HIV infection, other than immunodeficiency, to exert significant pathologic effects (2).

Mechanism of Action: Tesamorelin has a highly specific effect on the pituitary to increase endogenous growth hormone release. Growth hormone is known to be directly antagonistic to insulin. In contrast tesamorelin improves visceral adipose tissue but is neutral to glucose. One potential hypothesis is that there is some mild aggravation of insulin action, as a result of increased pituitary growth hormone secretion, but of a degree that

is counterbalanced by the improvement in visceral adipose tissue, so that net effect is neutral. It is also possible that concomitant use of insulin antagonistic antiretroviral drugs counters the improvement in glucose that would ordinarily be expected with reductions in VAT among HIV-infected patients (4).

Pharmacokinetics: After repeated dosing of 2 mg tesamorelin for 14 days, C_{max} was achieved at mean times to maximum plasma concentration (T_{max}) of 0.15 hours in healthy volunteers and 0.16 hours in HIV-infected patients. The apparent mean terminal elimination (T_{1/2el}) after repeated 2-mg doses was 26 minutes in healthy participants and 38 minutes in HIV-infected patients. Overall, estimates of the apparent T_{1/2el} phase were highly variable. On the basis of the dose-adjusted area under curve (AUC) ratios after subcutaneous and intravenous administration, the absolute bioavailability of tesamorelin was estimated to be less than 4%. In summary, tesamorelin pharmacokinetic may be characterized as rapid with a low bioavailability and high variability among individuals, and it does not appear to differ between healthy volunteers and HIV-infected patients receiving anti retroviral therapy (5).

Clinical Trials : The evaluation of safety and efficacy of tesamorelin in HIV-infected patients with abdominal fat accumulation is being studied by various clinical trials around the globe. But a very few of these trials are published in peer reviewed journals. In one trial involving 404 HIV- infected patients with excess abdominal fat for a duration of 12 month, tesamorelin 2mg subcutaneous daily was compared with placebo. Visceral adipose tissue (VAT) decreased by 10.9% in tesamorelin group vs. 0.6% in placebo in 6-months efficacy phase; trunk fat, waist circumference and waist-hip ratio also improved, with no change in limb or abdominal subcutaneous fat. Insulin-like growth factor-I (IGF-I) increased, but there was no change in glucose parameters. Tesamorelin reduces visceral adipose tissue by approximately 18% in patients

From the Department of Pharmacology, Gauhati Medical College Hospital, Guwahati-781032- India

Correspondence to :Dr Mangala Lahkar, Professor Department of Pharmacology, Gauhati Medical College Hospital, Guwahati-781032 India



continuing the drug for 12 months in the same trial (4). In another trial involving 412 patients with HIV who had an accumulation of abdominal fat, VAT decreased by 15.2% in the tesamorelin group and increased by 5.0% in the placebo group; the levels of triglycerides decreased, levels of total cholesterol and HDL cholesterol also improved significantly in the tesamorelin group. Levels of IGF-I increased by 81.0% in the tesamorelin group and decreased by 5.0% in the placebo group (6).

Adverse Effects: Treatment with tesamorelin was generally well tolerated in above mentioned clinical trials. Injection site erythemas along with arthralgia are most commonly reported adverse effects. Few of the other important adverse effects are-injection site pruritus and bruising, diarrhea, pain in extremity (4,7,8).

Current Status: Tesamorelin was approved in November 2010 by US FDA to treat HIV infected patients with lipodystrophy. It is currently prescribed in a once daily subcutaneous injection. The US FDA approved the drug based on results of two clinical trials involving 816 HIV-infected patients with lipodystrophy and excess abdominal fat. In both studies patients treated with tesamorelin experienced greatest reductions in abdominal fat as compared with placebo. Some patients reported improvement in their self-image (7).

Drug Interactions: In drug-drug interaction studies, tesamorelin was co administered with simvastatin (a CYP3A-substrate) or ritonavir (a CYP3A-inhibitor). Overall results showed that the effect of tesamorelin on CYP3A activity appears to be minimal, indicating that these drugs may be co-administered with tesamorelin without a change in their dosing regimen (5).

Limitations: The short-term results from the tesamorelin studies did not address the risk of cardiovascular disease (1).

Caution: The effect of tesamorelin on visceral adipose tissue (VAT) is not sustained with discontinuation of therapy. Patients in the Phase III trials who were switched from tesamorelin to placebo after 26 weeks demonstrated a re-accumulation of VAT to near baseline levels. Chronic therapy therefore appears to be necessary to maintain the reductions in VAT, with potential exposure to long-term side effects of GH and IGF-1 stimulation. Despite the fact that GHRH administration is expected to preserve more physiologic GH secretory pulsatility and IGF-1 feedback inhibition, results from the clinical trials presented above show that patients are not free from IGF-1 related adverse events: compared with placebo, tesamorelin recipients were more likely to have an IGF-1 level above

the upper limit of normal and more likely to develop diabetes (9).

Conclusion: Tesamorelin is a new drug for lipodystrophy in HIV-infected patients and is the first FDA approved drug of such kind. It is a growth hormone releasing factor drug. The trials have involved a few hundreds of patients only and large scale trials will show its entire safety and efficacy profile. It can be a useful treatment in lipodystrophy in HIV-infected patient taking HAART. However, more studies are needed to evaluate its indirect contribution in improving patient's compliance to antiretroviral therapy. Tesamorelin is developed by Montreal based Theratechnologies Inc. in the brand name of Egrifta (Tesamorelin for injection) and marketed in US by EMD Sernø.

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