Off-Label Drug Uses

Recombinant Human Growth Hormone: HIV-Related Lipodystrophy

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This *Hospital Pharmacy* feature is extracted from *Off-Label Drug Facts*, a publication available from Wolters Kluwer Health. *Off-Label Drug Facts* is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature enables the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. References direct the reader to the full literature for more comprehensive information before patient care decisions are made. Direct questions or comments regarding *Off-Label Drug Uses* to jgeneral@ku.edu.

BACKGROUND

HIV-related lipodystrophy, a syndrome that occurs in HIV-infected patients treated with protease inhibitors, is characterized by excess accumulation of visceral fat, peripheral fat atrophy, dyslipidemia, and insulin resistance. In obese non-HIV-infected patients, reduced growth hormone secretion has been associated with abnormal fat distribution. In addition, some HIV-infected patients with lipodystrophy and increased trunk fat have had documented growth hormone deficiencies. Thus, the use of growth hormone for the treatment of HIV-related lipodystrophy has been suggested to improve body fat distribution.¹

PATIENT POPULATION

Adult patients with HIV lipodystrophy with trunk enlargement during antiretroviral therapy.

DOSAGE AND DURATION

Recombinant human growth hormone has been administered in several regimens with wide ranges of dosing. Optimal dosing has not been established.

- Initial dose: 2 mcg/kg/day increased to a maximum dose of 6 mcg/kg/day (mean dose, 3.7 mcg/kg/day or 0.33 mg/day) for 18 months²
- Induction (weeks 1-12): 4 mg daily; maintenance (weeks 12-36): 2 mg every other day³
- 4 mg daily or every other day for 12 to 24 weeks⁴

RESULTS

Recombinant human growth hormone has been studied in controlled and noncontrolled trials enrolling over 500 patients and has demonstrated significant reductions in visceral adipose tissue (VAT) and subcutaneous fat tissue (SAT) but not lean body mass (LBM).²⁻⁸

Systematic Review

A systematic review evaluated the effects growth hormone axis drugs compared to placebo on VAT, SAT, and LBM in patients with HIV-related lipodystrophy. Inclusion criteria involved randomized placebo-controlled trials (RCTs) with patients with HIV-related lipodystrophy who received growth hormone (GH), growth hormone releasing hormone (GHRH), or tesamorelin or insulin-like growth factor-1 (IGF-1) and assessing at least one primary outcome (eg, VAT, SAT, or LBM). Ten double-blinded RCTs including 1,511 patients were reviewed. The duration of therapy interventions ranged from 12 to 26 weeks, with the majority of studies evaluating growth hormone.⁶ When compared to placebo, the summary effects for growth hormone demonstrated significant reductions in VAT (weighted mean difference [WMD], -32.61 cm²; 95% CI, -41.82 to -23.40 cm²; $P < .001$) and SAT (WMD, -16.02 cm²; 95% CI, -24.08 to -7.97 cm²; $P < .001$) but not LBM (WMD, 1.51 kg; 95% CI, -0.22 to 3.24 kg; $P = .09$). Overall GH axis drugs

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significantly increased fasting plasma glucose (WMD, 2.88 mg/dL; 95% CI, 1.10 to 4.65 mg/dL; $P = .001$), decreasing waist circumference (WMD, -1.61 cm; 95% CI, -2.33 to -0.89 cm; $P < .001$), decreasing extremity fat (WMD, -0.25 kg; 95% CI, -0.49 to 0.01 kg; $P = .04$), and decreasing triglycerides (WMD, -25.37 mg/dL; 95% CI, -46.84 to -3.89 mg/dL; $P = .02$). Although the overall rate of all moderate-to-severe adverse events was not significantly different between GH axis drugs when compared with placebo (relative risk [RR], 1.09; 95% CI, 0.92 to 1.29; $P = .32$), the number of cases of arthralgia (RR, 1.49; 95% CI, 1.17–1.89; $P = .001$) and edema (RR, 3.95; 95% CI, 1.73 to 9.00; $P = .001$) were higher in the GH axis drug arm.⁹

Controlled Trials

In a double-blind, placebo-controlled trial, 56 HIV patients with abdominal fat accumulation and reduced GH secretion (peak GH < 7.5 ng/mL) were randomly assigned to receive either subcutaneous recombinant growth hormone (r-hGH) or placebo for 18 months. Initial doses were 2 mcg/kg/daily and increased to a maximum of 6 mcg/kg/daily (mean dose, 0.33 mg daily). Primary outcome was change in body fat composition as measured by VAT assessment and change in fat distribution (trunk to extremity fat). A total of 48 patients completed the study. VAT decreased significantly in the r-hGH group compared with placebo (treatment effect, -19 cm²; 95% CI, -38 to -0.5 cm²; $P = .049$), corresponding to -8.5% and -1.6% changes, respectively. The trunk to lower extremity fat ratio (treatment effect, -0.4; 95% CI, -0.6 to -0.2; $P < .001$) and trunk fat (treatment effect, -0.8 kg; 95% CI, -1.5 to -0.04 kg; $P = .04$) decreased in the r-hGH group compared to placebo. Adverse events were not significantly increased in the r-hGH group (23% vs 28%). Triglycerides decreased (treatment effect, 7 mg/dL; $P = .002$), whereas total cholesterol and high-density lipoprotein cholesterol (HDL-C) were unchanged compared to placebo.²

In a double-blind, placebo-controlled multicenter trial, 326 patients with HIV-associated adipose redistribution syndrome were randomized to receive r-hGH (4 mg daily) or placebo for 12 weeks. At week 12, patients receiving r-hGH were re-randomized to receive r-hGH (maintenance, 2 mg every other day) or placebo for 24 weeks (to week 36). Patients initially treated with placebo were switched to r-hGH (4 mg daily) at weeks 24 through 36. During the induction period (baseline to week 12), absolute mean changes in intent-to-treat (ITT) population

for VAT area were -32.6 cm² and 0.5 cm² in the r-hGH and placebo groups, respectively. During this period, mean changes were significantly greater in the r-hGH group for abdominal SAT, limb fat, and total fat. Of those who lost VAT during the induction phase (weeks 1-12) and received maintenance dosing, approximately 40.3% gained back greater than 50% of their loss, which was significantly less than those in the placebo group and fit the criteria for efficacy in the maintenance phase. Patients in the maintenance group also sustained losses in trunk fat but not losses in subcutaneous fat in the abdomen or limbs. During the induction phase, the patients receiving r-hGH experienced significant mean absolute and percent reductions in total cholesterol, non-HDL-C, and low-density lipoprotein cholesterol (LDL-C) and increases in HDL-C and the HDL:LDL ratio. Patients in the placebo group only had significant mean decreases in LDL-C. The authors concluded that patients with HIV-associated adipose redistribution syndrome had greater relative losses of VAT and trunk fat than of subcutaneous fat.³

SAFETY

This is a limited safety profile. Refer to package labeling for complete prescribing information (eg, Warnings/Precautions, Adverse Reactions, Drug Interactions).

Adverse events attributed to growth hormone in controlled trials have included paresthesias, carpal tunnel syndrome, arthralgias, swelling, hyperglycemia, malignancy, and hypertension, although incidences did not significantly differ from those found with placebo in some studies^{2,3} and were significantly higher in others.⁴

THERAPY CONSIDERATIONS

Recombinant human growth hormone has been studied in controlled and noncontrolled trials, demonstrating significant reductions in VAT, and SAT but not LBM. Dosage regimens vary and optimal dosing has not been established for this indication.

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