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Review

Leptin treatment: Facts and expectations

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ABSTRACT

Leptin has key roles in the regulation of energy balance, body weight, metabolism, and endocrine function. Leptin levels are undetectable or very low in patients with lipodystrophy, hypothalamic amenorrhea, and congenital leptin deficiency (CLD) due to mutations in the leptin gene. For these patients, leptin replacement therapy with metreleptin (a recombinant leptin analog) has improved or normalized most of their phenotypes, including normalization of endocrine axes, decrease in insulin resistance, and improvement of lipid profile and hepatic steatosis. Remarkable weight loss has been observed in patients with CLD. Due to its effects, leptin therapy has also been evaluated in conditions where leptin levels are normal or high, such as common obesity, diabetes (types 1 and 2), and Rabson–Mendenhall syndrome. A better understanding of the physiological roles of leptin may lead to the development of leptin-based therapies for other prevalent disorders such as obesity-associated nonalcoholic fatty liver disease, depression and dementia.

1. Introduction

The adipose tissue functions as an endocrine organ, where hormones with cytokine-like actions, called adipokines, are synthesized and secreted [1]. Leptin is one of the most abundant and important adipokines. The most well-known effect of leptin is to regulate body weight and energy balance [2], but it also has fundamental roles in glucose and lipid homeostasis, reproduction, immunity, inflammation, bone physiology, and tissue remodeling. In its absence, severe and potentially lethal changes in body homeostasis occur [3].

Leptin deficiency is observed in specific conditions, such as lipodystrophy syndromes, hypothalamic amenorrhea, anorexia nervosa and congenital leptin deficiency (CLD) due

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; CLD, congenital leptin deficiency; Cmax, peak serum concentration; CYP450, cytochrome P450; DXA, dual-energy X-ray absorptiometry; FGF21, fibroblast growth factor 21; FSH, follicle-stimulating hormone; GH, growth hormone; GnRH, gonadotropin-releasing hormone; HAART, highly active antiretroviral therapy; HbA1c, hemoglobin A1c; IGF-1, insulin-like factor-1; IGFBP, insulin-like growth factor-binding protein; LH, luteinizing hormone; LRT, leptin replacement therapy; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; Nf-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; SOCS3, suppressor of cytokine signaling-3; POMC, proopiomelanocortin; PTP1B, protein tyrosine phosphatase 1B; Tmax, time to the maximum concentration; TNFα, tumor necrosis factor α; TSH, thyroid stimulating hormone.

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Table 1 – Metreleptin drug facts.

Structure	146 amino acids (as in the mature human leptin), with an additional methionyl residue at the N-terminal end of the recombinant protein
Route and frequency of administration	Subcutaneous, once a day
Recommended starting dose for generalized lipodystrophy	0.06 mg/kg/day (if body weight ≤40 kg) 2.5 mg/day (males >40 kg) 5 mg/day (females >40 kg)
Maximum dose	0.13 mg/kg (if body weight ≤40 kg) 10 mg/day (if body weight >40 kg)
Cmax	4.0–4.3 hours
Tmax	4 hours (range 2–8 hours)
Volume of distribution	4–5 times plasma volume
Route of elimination	Renal
Half-life	3.8–4.7 hours
Most common adverse reactions (≥10%)	Headache, hypoglycemia, decreased weight, and abdominal pain
Contraindications	General obesity not associated with congenital leptin deficiency; hypersensitivity to metreleptin
Safety during pregnancy and nursing	Uncertain. During nursing, metreleptin therapy or nursing should be discontinued
Use in geriatric patients >65 years-old	Unclear; dose selection should be cautious, and start at the low end of the dosing range
Drug interactions	Potential to alter the formation of CYP450 enzymes

From Myalept package insert [11].
Cmax: peak serum leptin concentration.
Tmax: median time to the maximum concentration.

to mutations in the leptin gene. The clinical manifestations in these conditions may include increased insulin resistance, hyperglycemia, dyslipidemia, endocrine disruptions, and fatty liver disease. In addition, morbid obesity, impaired cognitive development, and potentially lethal T-cell hyporesponsiveness have been reported in patients with CLD [4].

The discovery of leptin in 1994 [5], and the observation that its replacement reverses morbid obesity in leptin-deficient mice [6,7] and in humans with CLD [8], led to speculation that it might be a powerful tool to treat common obesity, or to facilitate adherence to diet and avoid a decline in energy expenditure [9]. However, due to the leptin-resistant state that is observed in patients with common obesity, that was not the case. The effects of leptin replacement therapy (LRT) with recombinant human leptin have been extensively evaluated in humans with CLD, to whom LRT is the only available treatment. More recently, leptin treatment has been approved for the treatment of patients with generalized lipodystrophy [10]. Other possible therapeutic uses of leptin include the treatment of hypothalamic amenorrhea, partial forms of lipodystrophy, diabetes, neurodegenerative disorders, depression, and common obesity with relatively low levels of plasma leptin.

2. Metreleptin drug profile

The form of leptin that is currently available for human therapy is known as recombinant methionyl human leptin (metreleptin, Myalept®, Amylin Pharmaceuticals; recently acquired by Bristol-Myers Squibb, and subsequently by AstraZeneca plc), initially available as Leptin A-100 (when its patent was owned by Amgen). Metreleptin is the only pharmaceutical form of leptin, and is composed by the 146 amino acids of mature human leptin, with an additional methionyl residue at the N-terminal end of the recombinant protein. It is a nonglycosylated polypeptide with one disulfide bond between Cys-97 and Cys-147, and a molecular weight of approximately 16.15 kDa.

Myalept® has been recently approved by the FDA for the treatment of congenital or acquired generalized lipodystrophy (non-HIV-related), but not for the partial forms of the disease, for which safety and effectiveness have not been established yet. The recommended starting dose varies according to gender and body weight, to a maximum daily dose of 0.13 mg/kg if body weight ≤40 kg, and 10 mg/day if body weight >40 kg (Table 1). Metreleptin is administered once daily at the same time every day, subcutaneously [11]. Due to its short half-life, some researchers prefer to divide the dose into two subcutaneous injections, when treating patients with CLD. Patients need to be evaluated regularly, and doses, recalculated to avoid excessively rapid weight loss.

Pharmacokinetic studies have been conducted mostly on healthy individuals, and few patients with lipodystrophy (Table 1). Data indicate that renal clearance is the major route of elimination, with no apparent contribution of systemic metabolism or degradation. In the presence of anti-leptin antibodies, the clearance of metreleptin is expected to be delayed, and its biological effects, attenuated or completely neutralized [11].

The most commonly reported adverse reactions (≥10%) include headache, hypoglycemia, decreased weight, and abdominal pain. T-cell lymphoma has also been reported in patients with acquired generalized lipodystrophy being treated with metreleptin [12]. However, a causal relationship between metreleptin and the development and/or progression of lymphoma has not been established, since lymphoproliferative disorders, including lymphomas, have been reported in patients with familial partial lipodystrophy [13] and acquired generalized lipodystrophy [14] not treated with the drug. Therefore, doctors should consider the benefits and risks of treatment with metreleptin in patients with significant hematologic abnormalities and/or acquired generalized lipodystrophy. Due to the risk of hypoglycemia [12], dose

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