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Corinne Vigouroux, Héléna Mosbah, Camille Vatier

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Original article

Leptin replacement therapy in the management of lipodystrophy syndromes

Traitement substitutif par la leptine pour la prise en charge des syndromes lipodystrophiques

Corinne Vigouroux[a,b,*], Héléna Mosbah[b,c,d], Camille Vatier[a,b]

[a] *Service d'endocrinologie, diabétologie et endocrinologie de la reproduction, centre national de référence des pathologies rares de l'insulino-secrétion et de l'insulino-sensibilité (PRISIS), hôpital Saint-Antoine, Assistance publique–Hôpitaux de Paris, Paris, France*
[b] *Centre de recherche Saint-Antoine, institut hospitalo-universitaire de cardio-métabolisme et nutrition (ICAN), Sorbonne université, Inserm UMR_S 938, Paris, France*
[c] *Service endocrinologie, diabétologie, nutrition, centre de compétence PRISIS, CHU La Milétrie, Poitiers, France*
[d] *Université Paris Cité, ECEVE UMR 1123, Inserm, Paris, France*

INFO ARTICLE

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ABSTRACT

Lipodystrophy syndromes are rare diseases of genetic or acquired origin, characterized by quantitative and qualitative defects in adipose tissue. The metabolic consequences of lipodystrophy syndromes, such as insulin resistant diabetes, hypertriglyceridemia and hepatic steatosis, are frequently very difficult to treat, resulting in significant risks of acute and/or chronic complications and of decreased quality of life. The production of leptin by lipodystrophic adipose tissue is decreased, more severely in generalized forms of lipodystrophy, where adipose tissue is absent from almost all body fat depots, than in partial forms of the disease, where lipoatrophy affects only some parts of the body and can be associated with increased body fat in other anatomical regions. Several lines of evidence in preclinical and clinical models have shown that leptin replacement therapy could improve the metabolic complications of lipodystrophy syndromes. Metreleptin, a recombinant leptin analogue, was approved as an orphan drug to treat the metabolic complications of leptin deficiency in patients with generalized lipodystrophy in the USA or with either generalized or partial lipodystrophy in Japan and Europe. In this brief review, we will discuss the benefits and limitations of this therapy, and the new expectations arising from the recent development of a therapeutic monoclonal antibody able to activate the leptin receptor.

RÉSUMÉ

Les syndromes lipodystrophiques sont des maladies rares d'origine génétique ou acquise, caractérisées par des altérations quantitatives et qualitatives du tissu adipeux. Les conséquences métaboliques des syndromes lipodystrophiques, telles que le diabète insulinorésistant, l'hypertriglycéridémie et la stéatose hépatique, sont fréquemment de traitement difficile, pouvant mener à des complications aiguës et/ou chroniques, et à une diminution de la qualité de vie. La production de leptine par le tissu adipeux lipodystrophique est diminuée, plus sévèrement dans les formes généralisées de la maladie, dans lesquelles le tissu adipeux est presque totalement absent, que dans les formes partielles, dans lesquelles la lipoatrophie n'affecte que certaines régions du corps, et peut s'accompagner de lipohypertrophie dans d'autres localisations anatomiques. Un nombre significatif d'études, précliniques chez l'animal et dans des modèles cellulaires, et cliniques chez l'Homme, ont montré que le traitement substitutif par la leptine pouvait améliorer les complications métaboliques des syndromes lipodystrophiques. La métréleptine, un analogue recombinant de la leptine, a été approuvé en tant que médicament orphelin pour traiter les complications métaboliques du déficit en leptine chez les patients atteints de lipodystrophie généralisée aux États-Unis, ou de lipodystrophie généralisée ou partielle au Japon et en Europe. Dans cette brève revue,

* Corresponding author: Faculté de Santé Sorbonne université, 27, rue Chaligny, 75571 Paris cedex 12, France.
Adresse e-mail : corinne.vigouroux@inserm.fr (C. Vigouroux).

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nous discuterons des bénéfices et des limitations de cette thérapie, et des espoirs issus du développement récent d'un anticorps monoclonal thérapeutique capable d'activer le récepteur de la leptine.

1. Adipose tissue is an endocrine organ that produces leptin

Adipose tissue, in addition to its well-known effects on whole-body energy regulation, was recognized as an endocrine organ in 1994 when Jeffrey Friedman et al discovered that leptin, produced by adipose tissue, is a major hormone involved in the regulation of central satiety signals [1]. Since then, a huge number of adipokines has been shown to be secreted by adipose tissue, exerting pleiotropic actions on diverse signaling pathways [2]. The circulating levels of leptin are proportional to the amount of body fat, and also depend on age, sex, and the nutritional status. Subcutaneous adipocytes express higher levels of leptin than visceral adipocytes. Effects of leptin are initiated by its binding to leptin receptors and activation of JAK2-STAT3 signal transduction pathways. Leptin interacts with several neuronal pathways in the hypothalamus to promote satiety, and influences the mesolimbic dopaminergic system to regulate the hedonic aspects of feeding. By acting in the central nervous system leptin also regulates energy expenditure and several neuroendocrine hormonal responses, contributing, among others, to the regulation of reproductive functions [3,4]. Leptin is also expressed in non-adipose tissue, including the placenta, stomach, mammary gland, ovary and testes, and leptin gene receptors are largely expressed in peripheral tissues, where leptin exerts pleiotropic effects, in particular to regulate metabolic functions, bone homeostasis, as well as innate and adaptive immunity [4–6].

2. Leptin and obesity

Biallelic loss-of-function mutations in the *LEP* gene encoding leptin represent a very rare cause of extremely severe obesity, which strongly benefits from leptin replacement therapy [7]. However, the vast majority of clinical forms of obesity in humans are associated with high levels of circulating leptin, defining a state of "leptin resistance" which counteracts the effects of leptin on satiety and the regulation of weight. In line, clinical trials using leptin as a treatment for obesity in the general population gave disappointing results [8]. Although this could initially appear as counter-intuitive, recent studies suggest that the management of obesity should include partial reduction in circulating levels of leptin to increase leptin sensitization and action, and allow weight loss [9].

3. Leptin and lipoatrophy

Physiologically, a decrease in the amount of white adipose tissue is accompanied by a decreased production of leptin, which contributes to the homeostasis of body weight by enhancing food intake. Conversely, in anorexia nervosa, the sustained low levels of circulating leptin related to the chronic undernutrition state could contribute to the vicious circle of psychological and behavioral adaptation to starvation [10], illustrating the complex pathophysiological relationships between leptin secretion and action. Lipodystrophic diseases are rare diseases of genetic or acquired origin due to quantitative and qualitative defects in adipose tissue leading to insulin resistance-associated metabolic alterations, including glucose tolerance abnormalities, hypertriglyceridemia, hepatic steatosis and ovarian dysfunction [11]. Lipodystrophy is associated with hypoleptinemia, which parallels the extent of fat loss and/or dysfunction: circulating leptin levels vary between extremely low values in generalized forms of the diseases where almost all body fat depots are absent, to low-to-normal values in partial forms of the disease, where lipoatrophy spares some parts of the body [12].

4. Lipodystrophic mice and the proof-of-concept of leptin replacement therapy in lipodystrophy

The proof-of-concept of the potential interest of leptin replacement therapy in lipodystrophic diseases arose from preclinical studies in murine models of the disease. Transgenic mice rendered lipoatrophic following inactivation of adipogenic transcription factors recapitulate the metabolic complications of human lipodystrophy, showing the major involvement of the lack of fat in the pathophysiology of the disease [13,14]. This was further confirmed by genetic studies in humans, pointing to primary alterations of differentiation and/or structural or functional properties of adipose tissue as major determinants of the disease [11]. Importantly, surgical transplantation of adipose tissue is able to reverse insulin resistance and associated metabolic disturbances in lipodystrophic mice [15]. It was further shown that the main pathophysiological basis of insulin resistance-associated with lipodystrophy is the altered partitioning of fat between adipose tissue, unable to store excess energy as triglycerides, and muscle and liver, which conversely accumulate lipids, leading to insulin signaling defects [16]. Although surgical transplantation of adipose tissue from wild-type mice restores insulin action in muscle and liver by decreasing lipotoxicity, it is not the case when adipose tissue lacking leptin, issued from ob/ob mice, is transplanted [17]. Leptin is able to protect non-adipose tissues from ectopic lipid deposition [18], and both transgenic overexpression, and exogenous administration of leptin were shown to improve insulin sensitivity in lipodystrophic mice, independently of its effects on food intake [19,20].

5. Metreleptin therapy for human lipodystrophy

After only three years since the first proof-of-concept of leptin therapy in lipodystrophic mice, a clinical trial of leptin therapy was carried out by Elif Arioglu-Oral et al. in nine patients with lipodystrophy and severe hypoleptinemia, showing major improvements in glucose and triglyceride levels as well as in liver volume [21]. Metreleptin, the only leptin analogue available for human therapy, was subsequently used in patients with lipodystrophy in several studies; however only open-labelled clinical trials have been completed to date. Briefly, metreleptin was shown to alleviate lipotoxicity-induced insulin resistance, reduce hyperphagia associated with leptin deficiency, improve glucose tolerance abnormalities, insulin secretion, dyslipidemia and liver steatosis, as well as quality of life in patients with lipodystrophy [22–29]. An improved activity of the hypothalamic-pituitary-gonadal axis has been observed, without any acceleration of puberty, in children with lipodystrophy treated with metreleptin [30,31]. In a nonrandomized, crossover trial, Brown et al. showed that metabolic effects of metreleptin are, at least in part, independent of food intake in patients with lipodystrophy [32]. Metreleptin was approved as an orphan drug to treat the metabolic complications of leptin deficiency in patients with either generalized or partial lipodystrophy

in Japan and Europe (in 2013 and 2018, respectively), or with generalized lipodystrophy only (in the USA, 2014).

6. Limitations and questions raised by metreleptin therapy in human lipodystrophy

Although consistent data are in favor of positive effects of metreleptin therapy in generalized forms of lipodystrophy, its metabolic benefit seem more variable in patients with partial forms of the disease. Several studies have shown that the initial severity of leptin deficiency and/or of metabolic complications could influence the efficiency of metreleptin in patients with partial lipodystrophy [33–38]. Based on the real-life experience of our French rare disease reference network, we observed that, from baseline to one-year therapy, metreleptin significantly decreased HbA1c and fasting triglycerides, from 8.4 [6.5–9.9] to 6.8 [5.6–7.4] % (median [interquartile ranges]), and 3.6 [1.7–8.5] to 2.2 [1.1–3.7] mmol/L, respectively, in 28 patients with generalized lipodystrophy, with a sustained efficacy thereafter. However, HbA1c and triglycerides were not significantly modified under treatment in the group of 19 patients with partial lipodystrophy treated with metreleptin, and liver enzymes only significantly decreased in the group of patients with generalized lipodystrophy. Interestingly, patients with partial lipodystrophy who responded to metreleptin in terms of HbA1c had lower baseline leptin levels than non-responders [39].

Other issues regarding the use of metreleptin are the fact that the treatment is very expensive, and that patients' compliance to therapy could be decreased. Indeed, metreleptin therapy is administered as a daily subcutaneous injection, but prefilled devices are not currently available, implying to reconstitute the therapeutic powder in water for injection, which is reported by patients as an important practical constraint [28]. It should also be explained to patients that metreleptin does not restore adipose tissue from lipoatrophic areas.

Metreleptin treatment is generally very well tolerated, given that other antidiabetic treatments are adequately adapted to avoid hypoglycemia. However, very frequently, metreleptin therapy induces the development of circulating antimetreleptin antibodies. In rare cases, antimetreleptin antibodies could display neutralizing capacities, and could reduce the biological activity of both exogenous and endogenous leptin [40,41]. Very rare cases of lymphoma have been reported in patients with autoimmune forms of generalized lipoatrophy treated with metreleptin, but this could more likely be linked to the natural history of the disease rather than to the treatment [42].

In Europe, metreleptin can be prescribed by hospital endocrinologists or pediatricians, as an adjunction to diet in patients with generalized lipodystrophy older than 2 years old, and in patients with partial lipodystrophy of at least 12 years of age, when metabolic complications of the disease are not controlled by standard treatment. In France, the National Heath Authority (HAS) recommends the indication of metreleptin therapy to be validated and regularly re-evaluated during multidisciplinary consultation meetings of the PRISIS Rare Disease network, and the initial blood leptin level to be documented. In the USA, when the diagnosis of generalized lipoatrophy is confirmed, metreleptin therapy can be initiated without restriction regarding age or severity of metabolic complications. Metreleptin is not recommended during pregnancy, although negative signals have not been reported to our knowledge, and the exacerbation of insulin resistance and hypertriglyceridemia during pregnancy could lead to major therapeutic challenges in patients with lipodystrophy [43,44].

7. Current clinical studies using metreleptin or leptin receptor agonists in human lipodystrophy

Several ongoing clinical trials will probably give further important data regarding the use of metreleptin in lipodystrophy. In particular, the first double-blind, placebo-controlled, randomized study of metreleptin in partial lipodystrophy is currently ongoing in the USA (ClinicalTrials.gov ID NCT05164341), where metreleptin is not approved in this indication. The Metreleptin Effectiveness And Safety Registry (MEASuRE), a post-authorization prospective study, could also bring real-life additional data in patients treated with metreleptin in routine clinical practice in the USA and European Union (ClinicalTrials.gov ID NCT02325674) [45]. Preliminary results of a single-center retrospective analysis of 65 patients with congenital and acquired generalized lipodystrophy treated with metreleptin prior versus after the development of significant metabolic complications were recently presented by R.J. Brown and collaborators [46]. Better age-adjusted metabolic control over time for diabetes, hypertriglyceridemia, and proteinuria were observed in patients treated early in the course of the disease, whereas decreased endogenous insulin secretion could be associated with reduced responses to metreleptin. Although this should be confirmed by other studies, these results are in favor of an early initiation of metreleptin therapy in generalized lipodystrophy.

A therapeutic leptin receptor agonist monoclonal antibody has been developed (mibavademab, REGN4461), which activates the human leptin receptor in the absence or presence of leptin. Promising results have been obtained in using mibavademab in a preclinical model of lipodystrophy, and during a compassionate therapy in a patient presenting an atypical form of partial lipodystrophy with undetectable leptin concentrations and neutralizing antibodies to metreleptin [47]. A phase I study in humans, which showed that mibavademab was well-tolerated by healthy volunteers, support the development of mibavademab as a therapeutic option for conditions associated with leptin deficiency[48]. Patients with generalized lipodystrophy and familial partial lipodystrophy have been recruited for randomized, double-blind, placebo-controlled phase 2 therapeutic trials of mibavademab (NCT04159415 and NCT05088460, respectively).

8. Conclusion

The orphan drug metreleptin is the only specific therapy for lipodystrophic syndromes to date. It represents an important adjunction or even alternative to standard therapy in generalized forms of the disease, but the indication of metreleptin therapy in partial forms of lipodystrophy needs to be further evaluated. Ongoing clinical trials of metreleptin, and of leptin receptor agonists, will bring important data to further clarify the effects of enhancing leptin signaling for the treatment of lipodystrophy.

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Disclosure of interest

Camille Vatier and Corinne Vigouroux are, or were, investigators in the Regeneron REGN4461-PLD-20100 and Amryt APL-22 therapeutic trials. Camille Vatier, Héléna Mosbah and Corinne Vigouroux have spoken at conferences held by the pharmaceutical companies Abbott, Advanz Pharma, Amryt, AstraZeneca, Lilly, Novartis, Novo Nordisk, Sanofi (for C. Vatier), Amryt (for H. Mosbah) and Amryt, Sanofi, Ipsen and Lilly (for C. Vigouroux).

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