Metreleptin treatment of non-HIV lipodystrophy syndromes.

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Abbreviations:

AGL: acquired generalized lipodystrophy, ALAT: alanine aminotransferase, ALP: Alkaline phosphatase, ASAT: aspartate aminotransferase, AgRP: Agouti Related Protein, CGL: congenital generalized lipodystrophy, FPLD: Familial partial lipodystrophy, FSH: Follicle Stimulating Hormone, GGT: gamma glutamyl transpeptidase, GL: Generalized Lipodystrophy, GLP-1 : Glucagon-like peptide 1, HbA1c: glycated hemoglobin, HDLc: High Density Lipoprotein cholesterol, HIV: Human Immunodeficiency Virus, LH: luteinizing hormone, LMNA: *Lamin A*, LDLc: Low Density Lipoprotein cholesterol, LPL: Lipoprotein Lipase, LS: lipodystrophic syndromes, NPY : Neuropeptide Y, PCOS: Polycystic ovary syndrome, PL: Partial Lipodystrophy, PPARG: *Peroxisome proliferator-activated receptor gamma*, SGLT2 : Sodium-Glucose Co-transporter 2, TG: Triglycerides,

BMD

Abstract

Lipodystrophy syndromes (LS) constitute a group of rare diseases of the adipose tissue, characterized by a complete or selective deficiency of the fat mass. These disorders are associated with important insulin resistance, cardiovascular and metabolic comorbidities that impact patient's survival and quality of life. Management is challenging and includes diet, physical activity, and specific pharmacological treatment of LS-associated comorbidities. Because of a common pathophysiology involving decreased concentration of the adipokine leptin, efforts have been made to develop therapeutic strategies with leptin replacement therapy. Metreleptin, a recombinant human leptin analogue, has been proposed in hypoleptinemic patients since the beginning of 2000's. The treatment leads to an improvement in metabolic parameters, more important in generalized than in partial LS forms. In this review, the current knowledge about the development of the drug, its outcomes in the treatment of lipodystrophic patients as well as the peculiarities of its use will be presented.

Introduction

Lipodystrophy syndromes (LS) represent a heterogeneous group of rare diseases of the adipose tissue. They are characterized by a complete or partial lack of adipose tissue associated or not with hypertrophy of fat depots in other locations of the body. As mentioned in this issue by Sorkina et al. and Araujo et al., LS can be generalized (GL) or partial (PL), sporadic or inherited, with a neonatal or adult-onset (1,2). Because of the absence of adipose tissue in certain areas, lipids are stored in other organs such as muscles and liver; therefore LS are associated with marked insulin resistance, high prevalence of diabetes, dyslipidemia, cardiovascular and metabolic complications such as non-alcoholic steato-hepatitis (3) and Akinci et al. in this issue). They are also regularly associated with altered production of adipokines, i.e. cytokines produced by the adipose tissue, such as leptin, adiponectin or interleukin-6 which are less secreted. We will describe in this review the clinical results observed in LS with metreleptin, a recombinant form of leptin. The HIV-related LS syndromes are excluded from this review.

Leptin: discovery, physiological roles.

Leptin was first discovered in 1994 by the group of J. Friedman, studying the *ob/ob* obese mouse (4). This murine model presented leptin deficiency and treatment of mice with metreleptin was the first treatment of a leptin deficiency associated-obesity (5). Leptin is an adipokine, i.e a hormone produced within the adipose tissue. The level of leptin production is correlated with the amount of fat tissue mass, in a circadian rhythm, and seem to be more influenced by subcutaneous than visceral adipose tissue (6–8). Its half-life is estimated to ~25 min in humans (9). Furthermore, leptin secretion is influenced by nutritional status, and decreases during starvation (10). This adipokine exerts its effect via binding on the leptin receptor (ObR) expressed on multiple tissues (including multiple brain areas, hypothalamus,

liver, muscle, adipocyte, heart, immune cells…) and subsequently activate the JAK-STAT pathway (11). Thereby, on receptors expressed in the central nervous system, mainly in ventro-median hypothalamus, leptin leads to a decrease of appetite and food intake via inhibition of orexigenic peptides (AgRP, NPY)-producing neurons and activation of anorexigenic peptides (POMC)-producing neurons. It can thus be considered as an "energy thermostat" (figure 1): in condition with food available in abundance and a sufficient adipose mass, leptin concentration will rise in order to limit "non-necessary" nutriment ingestion (12). As a corollary, leptin physiologically inhibits insulin secretion and lipogenesis (13–15). In case of starvation, leptin levels fall, which leads to metabolic and neuroendocrine adaptations, including decreased production of thyroid and sexual hormones, in order to limit the energy expenditure from an evolutionary point of view (10,16). Recombinant leptin decreases satiety in lipodystrophic patients, modifies body weight and composition, and ameliorates glucose and lipid parameters. It is the reason why the drug was also tested in patients with common obesity (17). Indeed, the amount of weight loss was modest, notably compared with other drugs like GLP1-receptor agonists (18,19). Moreover, the dose of drug necessary to observe those effects was significantly higher than in lipodystrophic patients, limiting its development in this indication. The well-established explanation of these poor results is the naturally higher leptin concentrations in obese versus lean patients leading to a leptin-resistance state (20). Indeed, signaling pathways downstream leptin receptors are saturable, at ~30-50ng/ml leptin concentrations (21,22).

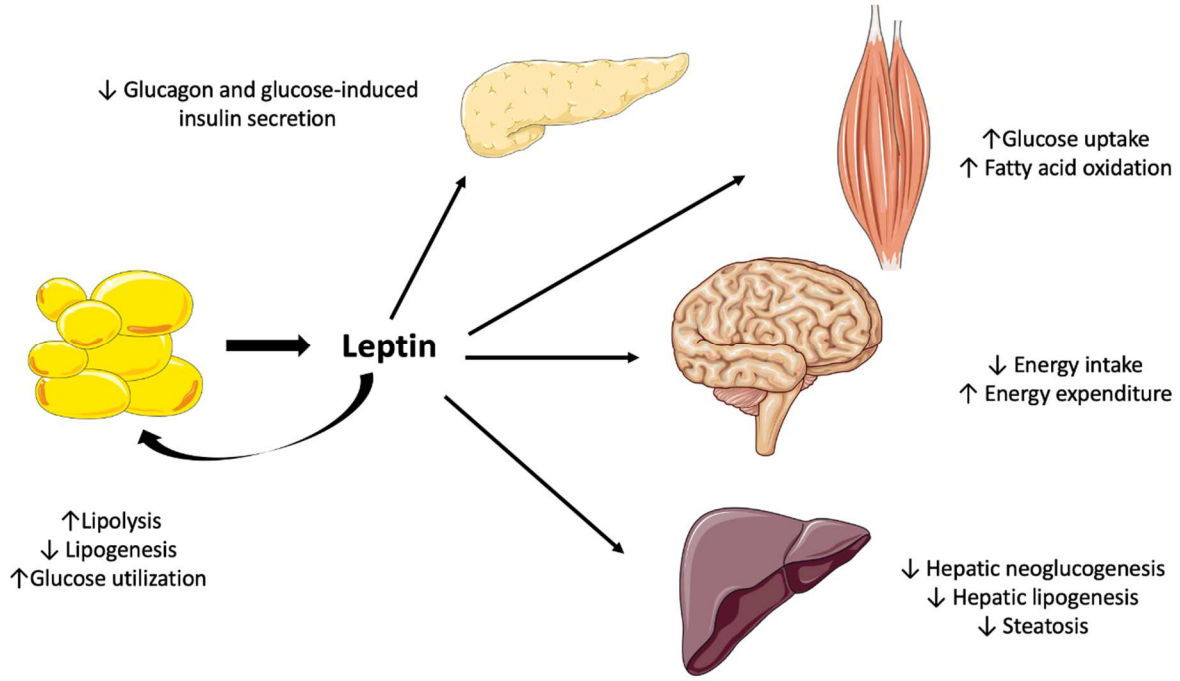

Figure 1: Metabolic effects of leptin. Adapted from (23)

Role of recombinant leptin in management of lipodystrophy syndromes,

Management of LS include diet, physical activity, associated with specific pharmacological treatment of LS-associated comorbidities in a multidisciplinary team (3). It is challenging and should aim to increase patients' survival, reduced compared to the general population, especially in case of GL, because of the evolution of liver and kidney comorbidities, also cardiovascular outcome (median lifespan 51 years old)(24). Noticeably, an heterogeneity in term of prognosis regarding the etiology of LS, has been suggested with *LMNA*-mutated progeroid- patients presenting the worse outcomes, mainly due to cardiovascular complications (3,25). Given the common pathophysiology of those diseases, associated with variable defect in leptin production, great interest has been shown in recombinant leptin replacement therapy.

The interest for this pharmacological approach began at the end of 1990's, with studies showing that recombinant leptin improved insulin resistance and metabolic parameters in mice models of LS (26). In 2002, the first clinical results were published in 8 patients

93 presenting GL and one patient with partial lipodystrophy (PL) who exhibited a significant
94 improvement in both glucose and triglycerides levels (27).
95
96 **Effects of metreleptin on diabetes and glucose metabolism.**
97 Leptin replacement therapy leads to an improvement of hyperglycemia in diabetic
98 lipodystrophic patients (table 1). Indeed, HbA1c and fasting plasma glucose levels decreased
99 quickly after a few months of treatment, by about 1.5% and > 0.4 g/l respectively (27–30)
100 (Table1). There is no known escape to treatment, but real-life studies are not available yet as
101 well as long-term studies (10 years). Neutralizing antibodies decreasing the treatment
102 effectiveness may occur and the respect of diet remains very important for the treatment
103 effectiveness. Efficacy has been demonstrated in both GL and PL, with better diabetes results
104 in GL, about 2% in HbA1c decrease *vs.* 1% in PL (31–36). Leptin levels before treatment
105 initiation doesn't seem to influence metabolic outcomes in Dunnigan syndrome, and data
106 aren't available in others LS (37). Note, nevertheless, that the treatment was made available
107 only in patients with leptin levels grossly below 15 ng/ml. Regarding genetic status, it seems
108 that recombinant leptin is effective in both patients with *LMNA* and *PPARG* variants;
109 however reduction in HbA1c levels were higher in *PPARG* patients (38).
110 The improvement of glycemic parameters seems related to an improvement of both insulin
111 sensitivity and glucose-induced insulin secretion, studied with hyperinsulinemic clamps and
112 glucose infusion respectively (28,31,39). The insulin sensitivity improvement observed with
113 metreleptin was independent of food intake (40). This led to a decrease in daily insulin dose
114 and even insulin discontinuation in some patients.
115
116 **Effects of metreleptin on dyslipidemia and lipid metabolism.**

Mechanisms of improvement in lipid profiles with metreleptin treatment are now well studied (table 1). The hormone is known to decrease *de novo* hepatic lipogenesis, reducing hepatic and serum concentration of triglycerides (TG) (15,41). This is thought to be mediated by increased insulin sensitivity, decrease in fasting insulin secretion and an improvement in glycemic control. In clinical trials and retrospective series using metreleptin, the mean percentage decrease of TG is ~30-35%, with, still there, better results observed in GL than in PL (~60% vs 20% respectively) (42) (Table1). Reduction in TG levels are higher in *PPARG* than in *LMNA*-mutated patients (38).

Some works have studied the metabolism of triglycerides, notably their clearance by lipoprotein lipase (LPL). The latter is affected in LS patients due to increased levels of LPL inhibitors, notably apo CII, apo CIII, and ANGPTL3, 8 but no 4 (43–45). Metreleptin treatment is associated with a decrease in these LPL inhibitors; however, results are discordant regarding apo CIII. Interestingly, a decrease in triglyceride levels should be associated with an inverse increase in HDLc concentration, as known in metabolic syndromes. However, the low HDL- cholesterol levels of LS patients were not modified with metreleptin treatment in several studies, except one that showed a mild increase in HDLc from 0.28g/l to 0.32g/l after 12 months of metreleptin in a population of 7 GL and 6 PL patients (46,47). LDL-cholesterol levels are usually not elevated in LS, frequently < 1g/l, and metreleptin further decreases LDLc levels, in correlation with concomitant decrease in PCSK9 concentrations (48,49). Finally, a recent work explored lipid profiles of 17 LS patients (5GL, 12 PL) and found a proatherogenic lipid profile, improved after 6 months of metreleptin treatment (50).

Reference	Ref (38)		Ref (59)	Ref (61)	Ref (33)	Ref (34)
Inclusion criteria	LMNA or PPARγ Mutations, leptin < 12 (W) or < 8ng/ml (M), diabetes and/or fasting insulin > 30 µU/ml and/or Tg > 2 g/l		Severe LS, leptin <5 (W) or < 4 ng/ml (M), metabolic disorder (hyperTG and/or diabetes)	LS, replacement included hypoleptinemia (< 12 ng/ml), metabolic abnormalities such as hyperTG and/or diabetes	non-HIV related LS, age > 14, leptin < 4 (W) ou < 3 ng/ml (M), diabetes and/or fasting insulin > 30 µg/ml and/or TG > 2 g/l,	
LS Type	FPLD (PPAR γ mutation)	FPLD (LMNA mutation)	2 FPLD, 4 CGL, 4 AGL	15 GL, 12 PL	GL (21 AL 45GL)	PL
Metreleptin dose	0,08 to 0,16 mg/kg/day	0,08 to 0,16 mg/kg/day		between 0,06 and 0,24 mg/kg/day	5mg	8,4mg
Treatment duration (months) [min-max]	13 [11-15]	13 [6-20]	6,6 [14-18]	15 [4-68]	62,5	48 months
Number of patients	7	22	10	27	66	41
Median Age	30,8 ± 12,1	37,3 ± 15,2	40 ± 5	29 ± 3	15,0 (1,0–68,0)	34,0 (10,0, 64,0)
Sex ratio M:W			02:08	06:21	15:51	01:40
Leptin concentration (ng/dl) (±DS)	6,3 ± 3,8	5,5 ± 2,5	1,4 ± 0,3	2,72 ± 0,5	1,3 [1]	6,4 [3,5]
Anthropometric parameters (Baseline -> evolution on metreleptin)						
Weight (kg)	64 ± 13 -> 65 ± 14 (ns)	70 ± 13 -> 68 ± 13				
BMI (kg/m2)	24,4 ± 2,2 -> 25,2 ± 2,5 (ns)	25,7 ± 3,4 -> 24,9 ± 3,4				
Glucidic parameters (Baseline -> evolution on metreleptin)						
HbA1c (%)	9,2 ± 2,3 -> 7,7 ± 2,4	7,8 ± 2,1 -> 7,3 ± 1,7	8,5 ± 0,3 -> 6,7 ± 0,4	7,9 ± 0,4 -> 6,3 ± 0,2	8,6 -> 6,4	7,9 -> 7,4%
Fasting Blood Glucose (g/l)	1,77 ± 0,97 -> 1,58 ± 0,81 (ns)	1,80 ± 0,89 -> 1,24 ± 0,49	2,2 ± 0,27 -> 1,44 ± 0,13	1,78 ± 0,15 -> 1,17 ± 0,9	1,85 -> 1,27	1,81 -> 1,47
Fasting Blood Insulin (mUI/l)	70 (27-144) -> 76 (27-105) (ns)	15 (11-42) -> 18 (9-56)	46,4 ± 13 -> 24,8 ± 7,4			
Insulin Daily Dose (UI/d)	3,8 (2,7-4,3) -> 2 (1,6-3)	1,7 (1,3-4,4) -> 1,2 (0,9-2,3)				
Lipid parameters (Baseline -> evolution on metreleptin)						
TG (g/l)	13,77 (2,78-55,77) -> 6,8 (2,96-7,83) (ns)	3,32 (1,98-5,62) -> 2,93 (1,48-4,06)	12,06 ± 5,9 -> 2,26 ± 0,57	9,52 ± 2,91 -> 3,03 ± 0,65	14 -> 3,98	13,89 -> 5,3
HDLc (g/l)	0,27 ± 0,05 -> 0,25 ± 0,05 (ns)	0,34 ± 0,1 -> 0,35 ± 0,1 (ns)				
LDLc (g/l)	0,60 ± 0,14 -> 0,88 ± 0,58 (ns)	0,98 ± 0,31 -> 1,03 ± 0,35 (ns)				
CT (g/l)	3,21 (1,55-4,15) -> 2,02 (1,4-2,09)	2,05 (1,53-2,43) -> 1,75 (1,61-2,18) (ns)				
Liver parameters (Baseline -> evolution on metreleptin)						
ASAT (U/l)	25 (18-37) -> 26 (17-40) (ns)	25 (19-30) -> 21 (18-27) (ns)	47 ± 11 -> 22 ± 2	66 ± 11 -> 35 ± 5	112,5 -> 59,4	38,4 -> 35,8 (ns)
ALAT (U/l)	36 (20-46) -> 29 (23-52) (ns)	29 (23-47) -> 29 (19-44) (ns)		99 ± 19 -> 53 ± 12	75,3 -> 51,5 (ns)	54,8 -> 59,9 (ns)
GGT (U/l)			54 ±13 -> 24 ± 4			
ALP (U/l)						
Steatosis proportion (%) (Evaluated on MRI)			31 ± 7 -> 11 ± 6			
Histological steatosis score (/4)			1,7 ± 0,4 -> 0,4 ± 0,2	0,75± 0,2 -> 0,37 ± 0,2 (ns)		
Histological NASH Activity Score			5,3 ± 0,8 -> 2,1 ± 0,4	4,3 -> 2,4		
Liver Volume (cc)					3357,7 -> 2585,4	2624,6 -> 2169,0

Reference	Ref (28)	Ref (63)		Ref (56)	
Inclusion criteria	Acquired or genetic LS (except HIV-related) diabetes, leptin < 6 ng/ml	non-HIV related LS, age > 6 months, leptin < 12 (W) ou < 8 ng/ml (M), diabetes and/or fasting insulin > 30 µU/ml and/or TG > 2 g/l,		non-HIV related LS, age > 14, leptin < 4 (W) ou < 3 ng/ml (M), diabetes and/or fasting insulin > 30 µg/ml and/or TG > 2 g/l,	
LS Type	11 FPLD, 5 CGL	48 CGL, 10 AGL, 6 Atypical progeria	42 FPLD	68 GL (20AL 48 GL)	44 PL (6AP 38 FPLD)
Metreleptin dose	0,10 mg/kg/day ± 0,02				
Treatment duration (months) [min-max]	12	23,6 (17,3-24,9)	23,6 (17,3-24,9)	Analysis after 1yo of treatment	Analysis after 1yo of treatment
Number of patients	16	73	42	68	44
Median Age	39,2 ± 4	16 (12-21)	35 (19-46)	17,5 [11,4]	34,6 [15,2]
Sex ratio M:W		17:56	02:40		
Leptin concentration (ng/dl) (±DS)	2,7 ± 0,5	1,1 (0,8-1,8)	6,2 (3,9-9,4)	1,3 [1]	6,4 [3,5]
Anthropometric parameters (Baseline -> evolution on metreleptin)					
Weight (kg)					
BMI (kg/m2)	23,9 ± 0,7 -> 22,6 ± 0,8				
Glucidic parameters (Baseline -> evolution on metreleptin)					
HbA1c (%)	8,5 ± 0,4 -> 7,5 ± 0,3	8,6 ± 2,4 -> 6,2 ± 1,6	8,1 ± 2,1 -> 7,4 ± 1,7	8,7	8
Fasting Blood Glucose (g/l)	1,35 ± 0,09 -> 1,26 ± 0,14 (ns)	1,88 ± 0,83 -> 1,16 ± 0,43	1,73 ± 0,82 -> 1,37 ± 0,63		
Fasting Blood Insulin (mUI/l)	37,3 ± 11,7 -> 54,8 ± 18,1 (ns)				
Insulin Daily Dose (UI/d)		225 (100-420) -> 0 (0-30)	181 (98-280) -> 150 (70-232) (ns)		
Lipid parameters (Baseline -> evolution on metreleptin)					
TG (g/l)	4,04 ± 0,79 -> 2,98 ± 0,79	4,41 (2,30-11,64) -> 1,71 (0,87-3,37)	4,22 (2,34-9,10) -> 3,24 (2-4,81) (ns)	5,45 [2,20–12,51]	512,5 [2,44–8,41]
HDLc (g/l)	0,27 ± 0,02 -> 0,31 ± 0,02 (ns)				
LDLc (g/l)	0,97 ± 0,12 -> 0,78 ± 0,01 (ns)				
CT (g/l)					
Liver parameters (Baseline -> evolution on metreleptin)					
ASAT (U/l)	47,8 ± 8,5 -> 32,4 ± 2,9			56% with increased baseline TGO -> 79% of them with > 20% reduction	23% with increased baseline TGO -> 50% of them with > 20% reduction
ALAT (U/l)	70,9 ± 17,2 -> 49,4 ± 6,9 (ns)			66% with increased baseline TGP -> 91% of them with > 20% reduction	27% with increased baseline TGP -> 58% of them with > 20% reduction
GGT (U/l)	84,9 ± 21,7 -> 57,6 ± 19,9				
ALP (U/l)					
Steatosis proportion (%) (Evaluated on MRI)					
Histological steatosis score (/4)					
Histological NASH Activity Score					
Liver Volume (cc)					
Kidney parameters (Baseline -> evolution on metreleptin)					
Urinary albumin excretion	297,5 (166,5) -> 83,4mg/l (55,9) (ns)	244mg/24h [31,978] -> 58mg/24h [16,96]	18mg/24h [7,9,79] -> 36 mg/24h [9,101] (ns)	50% with elevated baseline 24-hour protein excretion -> 68% of them with > 20% reduction	27% with elevated baseline 24-hour protein excretion -> 33% of them with > 20% reduction
estimated Glomerular Filtration Rate (ml/min/1,73m2)		143 [112,169] -> 141[129,160] (ns)	105 [85,129] -> 108 [94,127] (ns)		

Table 1: Effect of metreleptin on diabetes, dyslipidemia, liver, and kidney diseases in LS

ASAT: aspartate aminotransferase, ALAT: alanine aminotransferase, GGT: gamma glutamyl transpeptidase, ALP: Alkaline phosphatase, AGL: acquired generalized lipodystrophy, CGL: congenital generalized lipodystrophy, FPLD: Familial partial lipodystrophy,

Effects of metreleptin on hypertension & cardiovascular outcome

The potential beneficial effects of metreleptin on cardiovascular outcome are in major part due to the improvement of risk factors such as dyslipidemia or diabetes. The direct impact of the drug on cardiovascular function is still unknown (51,52). In mouse model, metreleptin could improve endothelial function per se, but this result needs to be investigated in human settings, notably in *LMNA*-mutated patients that can present severe heart failure (53,54). No clear impact of the drug on hypertension had been shown (55), until a recent study demonstrating a significant improvement of blood pressure on a series of 112 LS patients

whom 54% had hypertension at baseline (56). After 1 year of treatment with metreleptin, 59% improved their level of blood pressure (> 20mm Hg reduction of systolic blood pressure and/or > 10mm Hg reduction of diastolic blood pressure) , including 77% of GL and 35% of PL patients. Nevertheless, the number of anti-hypertensive drugs and their evolution during metreleptin treatment were not documented, furthermore multivariate analysis wasn't performed.

Effects of metreleptin on liver and steatosis.

Steatosis, nonalcoholic steato-hepatitis (NASH) and subsequent metabolic cirrhosis are extremely frequent in LS patients, and contribute to its severity. Indeed, steato-hepatitis is present in up to 85-95% of cases in histological series. In this condition, metreleptin has been shown to reduce liver enzymes and GGT levels in several works (28,57–59). The NIH group also found an improvement of the proportion of steatosis and NASH activity score based on MRI and liver biopsies (59–61)(table1). A reduction of liver volume from 3209cc to 2391cc in MRI was also observed on a 10- patients study (8GL and 2 PL) after 12 months of metreleptin treatment (30). Liver fat content also decreased from 31% to 11%. Nevertheless, no improvement was shown in the two patients with PL. Indeed, the improvement of liver dysfunction is mostly observed in GL. In PL patients, long-term use of metreleptin improved the liver volume but did not significantly modify the hepatic enzymes, which were however generally modestly elevated (34). Case of hepatocellular carcinoma have rarely been reported, and liver-specific mortality is more frequently related to complications of cirrhosis (62–64).

Effects of metreleptin on kidney function in LS

Patients with lipodystrophy present increased frequency of proteinuria and glomerular renal disease, with causal mechanisms still unclear, potentially linked to diabetes duration (3,65).

The effect of metreleptin on renal function was studied on a series of 115 LS patients from the US (table 1). Seventy-three patients had GL, with a median age of 18yo; 78% were diabetic with a median diabetes duration of 4.5yo; 80% had elevated urinary protein excretion > 150mg/24h) without impairment of glomerular filtration rate. These series also included 42 PL patients with a median age of 35yo; 83% were diabetic with a median diabetes duration of 1yo; 61% had elevated urinary protein excretion without alteration of glomerular filtration rate. Treatment with recombinant leptin was shown to significantly improve proteinuria in GL (> ~20% reduction in 24-hour protein excretion after one year of treatment), without changes in estimated glomerular filtration rate (66,67) (Table 1). There was no modification in albuminuria regarding PL, but these patients presented mild albuminuria.

Effects of metreleptin on bone

Few data are available on the impact of metreleptin on bone mass in LS. In hypoleptinemic women presenting hypothalamic amenorrhea, long-term metreleptin therapy was shown to increase bone mineral density (BMD) (68). However, there was no influence on BMD in GL, probably because these patients present increased bone mass content in comparison with normal population without over-risk to develop osteopenia or osteoporosis (69,70). Furthermore, duration of treatment was relatively short (~2 years) and long-term effects of metreleptin on bone tissue are not known yet.

Effects of metreleptin on weight, eating behavior & quality of life

As expected, treatment with recombinant leptin leads to an improvement of satiety and less caloric and more satiating meals (71). This result is negatively correlated with ghrelin concentration. Interestingly, there is no escape and the satiating effects were durable and sustained, with change in neural networks regulating eating behavior (72,73). Therefore,

patients generally present a decrease in weight in the first months of treatment, which then stabilizes. The weight loss affects both fat and lean body mass (70)(Table1). It is sometimes a cause of treatment discontinuation.

Furthermore, the improvement in LS-associated comorbidities leads to an increased health self-perception and an improvement in quality of life, however not normalized as compared with healthy subjects. Therefore, even if 80% of patients are satisfied with the treatment, the efficacy was evaluated at 66% by the patients themselves, and 55% for ease and comfort of use, sometimes leading to treatment discontinuation (56,74).

Effects of metreleptin on reproductive functions

Lipodystrophic women frequently harbor hyperandrogenism, polycystic ovaries, and hypogonadotropic hypogonadism. In those conditions, metreleptin was effective in restoring menstruations, probably because of an improvement in both insulin sensitivity and LH pulsatility (75–77)(Table 2). It doesn't seem to influence the polycystic ovarian pattern. A significant effect of metreleptin on gonadotropins concentrations is observed on short cycles of treatments. There is, however, no modification on the long-term (76,77). Note, however, that the first study mentioned was performed in a mixed population of GL and PL patients whereas the second one studied GL patients only. Total testosterone was however significantly decreased with metreleptin in female, and increased in male (76).

Reference	Ref (73)	Ref (74)
LS Type	5GL 7PL	14 GL
Metreleptin dose	5mg/d for naive patients 4,0 ± 0,5 mg/d for patients on treatment	0,03 mg/kg/d for females under 18 years and 0,04 mg/kg/d for adult females
Treatment duration	14 days	12 months
Number of patients	12	14
Median Age	31 ± 13 years	from 12 to 40yo
Sex ratio H:F	4H:8F	4H:10F
Leptin concentration (ng/dl)	7,8±11,5	1,3 ± 0,1
Anthropometric parameters (baseline)		
Weight (kg)	70 ± 19	
BMI (kg/m2)		22 ± 0,9
Reproductive parameters (off metreleptin -> evolution on metreleptin)		
Normal menstrual function	0/8	1/10 -> 9/10 (+1 patient with hysterectomy)
Ovarian Ultrasound		PCOS features in all patients -> no evolution
Total Testosterone (ng/dl)	507 ± 286 -> 360 ± 174	92 ± 30 -> 54,8 ± 8,8
LH (U/L)	4,97 ± 3,10 -> 3,17 ± 1,32	6,4 ± 1,9 -> 6,7 ± 1,5 (ns)
FSH (U/L)	5,99 ± 6,18 4,40 ± 3,91	5,2 ± 0,7 -> 5 ± 0,6 (ns)
Estradiol (pg/dl)	73,8 ± 36,4 -> 29,4 ± 24,4	44,5 ± 10 -> 73,9 ± 25 (ns)

Table 2: Effect of metreleptin on reproductive parameters

LH: luteinizing hormone, FSH: Follicle Stimulating Hormone, PCOS: Polycystic ovary syndrome

Effects of metreleptin on LS-associated autoimmune diseases

Auto-immune diseases can be associated with LS, and patients treated with metreleptin in these conditions are reported on table 3 (78). Metreleptin was shown to reverse lipodystrophic features in two cases of acquired PL after hematopoietic stem cell transplantation : In the first patient, HbA1c and triglyceride levels returned to normal ranges with metreleptin treatment; the second one presented initially normal blood glucose and severe hypertriglyceridemia (around 10 g/L which improved with metreleptin (79)). Two patients with type 1 diabetes associated with acquired GL improved their glucose and triglyceride levels with metreleptin treatment (80). However, metreleptin does not seem to modify the natural history of the autoimmune disease as shown in patients with juvenile dermatomyositis, Grave's disease or auto-immune hepatitis (81). Also, recent data obtained from a patient presenting acquired GL and combined Crohn's disease suggested that metreleptin could exacerbate digestive

240 inflammation in a TNF α dependent manner; however other results are discordant and do not
241 argue for impairment of pro-inflammatory cytokines with metreleptin treatment(82,83).

Reference	Ref (76)		Ref (77)		Ref (78)		
	Patient 1	Patient 2	Patient 1	Patient 2	Patient 1	Patient 2	Patient 3
Autoimmune disorder(s)	Graft vs Host Disease	Graft vs Host Disease	Type 1 Diabetes	Type 1 Diabetes	Juvenile dermatomoysitis	Graves' disease; GAD-65 antibody	Autoimmune hepatitis and urticaria
LS Type	PL	PL	GL	GL	GL	GL	GL
Metreleptin dose	0,04 mg/kg/day	0,08 mg/kg/day					
Metreleptin duration	Unknown	Unknown	36 months	14 months	72 months	45 months	48 months
Age	28yo	40yo	8yo	6yo	7yo	9yo	8yo
Pretreatment leptin concentration (ng/dl)	6,5	3,5	1,09	3,95	< 0,7	< 0,7	< 0,7
Anthropometric parameters (baseline -> evolution on metreleptin)							
Weight (kg)	42,6	37,9	59,1 -> 52	31 -> 32,8			
BMI (kg/m2)	16,9	17,1	21,7 -> 19,1	15,4 -> 15,6	14,6	23	18,6
Glucose parameters (baseline -> evolution on metreleptin)							
HbA1c (%)	8,7% -> normalization	5,30%	10,7 -> 8,4	10,6 -> 7,3	9,3 -> 8,6	10,2-> 4,5	5,5-> 4,8
Fasting Plasma Glucose (g/l)	2,32		1,79 -> 2,67	2,98 -> 2,53			
Lipid parameters (baseline -> evolution on metreleptin)							
TG (g/l)	9,68 -> normalization	9,68 -> improvement	2,82 -> 0,86	29,8 -> 4,41	10,6-> 3,9	1,84 -> 0,50	0,35-> 0,11
HDLc (g/l)	0,4	0,4	0,21 -> 0,23	0,2 -> 0,11			
LDLc (g/l)			0,18 -> 0,62	1,65 -> 0,38			
Hepatic parameters (baseline -> evolution on metreleptin)							
ASAT (UI/l)	21	38					
ALAT (UI/l)	19	13			20 -> 23	145-> 20	208 -> 60
(UI/l)	32	241			27 -> 36	259 -> 19	419 -> 89
Steato hepatitis ?	Yes	Yes -> improvement			Yes	Yes	Yes
Liver volume (cc)			2291,47 -> 1719	4291 -> 3174			

242

243 **Table 3: Effect of metreleptin on autoimmune-associated LS.**

244

245 **Indications and use of metreleptin**

246 Currently metreleptin can be used in the following indications:

247 - in Europe as an adjunct to diet as a replacement therapy to treat the complications of
248 leptin deficiency in LS patients
249 (https://www.ema.europa.eu/en/medicines/human/EPAR/myalepta):

250 - with confirmed congenital generalized LD or acquired generalized LD in
251 adults and children 2 years of age and above

252 - with confirmed familial partial LD or acquired partial LD, in adults and
253 children 12 years of age and above for whom standard treatments have failed to achieve
254 adequate metabolic control

255 -in the USA, metreleptin is indicated as an adjunct to diet as replacement therapy to
256 treat the complications of leptin deficiency in patients with congenital or acquired generalized

lipodystrophy (FDA Summary Review for Regulatory Action - Metreleptin: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125390Orig1s000SumR.pdf)

- in Asia, in generalized and acquired lipodystrophic syndrome (https://www.shionogi.com/content/dam/shionogi/seu/news/pdf/2013/25032013.pdf)

There is no contraindication to metreleptin treatment except in case of known allergy to excipient. Administration is performed by daily subcutaneous injection, with initial drug dose of 2.5mg/day in men and 5mg per day in women, > 40kgs respectively. Subsequent drug dosage adaptation can be performed up to 10mg per day according to metabolic response, i.e decrease in HbA1c and/or insulin dose and/or triglyceride levels. Special attention should be paid to ponderal evolution on treatment, and excessive weight loss must lead to dose reduction. There is no target concentration recommended. No dose adjustment is required in case of kidney or liver insufficiency. Recombinant metreleptin is not recommended during pregnancy and breast feeding; however guidelines proposed by the Endocrine society recommend that “clinicians may consider continuing metreleptin if withdrawal would harm the mother and fetus “ (84). Furthermore some pregnancy has been reported on treatment, without abnormality (85).

Metreleptin can be used in pediatric population with similar profiles of effectiveness and safety, which is particularly interesting because those young patients already present metabolic comorbidities (86,87). Not surprisingly an uninterrupted treatment is preferrable to intermittent administration of leptin that can lead to worsening metabolic characteristics (88). Indeed, due to the short half-life of leptin, an interruption in treatment will probably quickly lead to a hypoleptinemic state with consequence on food intake and the increase of insulin resistance that will worsen the phenotype.

Side effects and safety of metreleptin

Regarding side effect, injection site reactions can be observed in 1 to 10% of treated patients. Adherence is excellent or acceptable in the majority of treated patients. However data from the French LS compassionate program revealed that 25% of treated patients presented a poor adherence with metreleptin, correlated with their global satisfaction with treatment and effectiveness, but also to discomfort related to its use (74). Hypoglycemia can be frequently observed, especially at initiation of treatment and should lead to a decrease of daily insulin dose. Rare cases of peripheral T-cell lymphoma have been reported, but the link with metreleptin is not well documented because of the increased risk of lipodystrophy patients, especially those with acquired generalized forms, to develop hemopathies (89).

Antibodies directed against recombinant leptin have been observed in a large proportion of treated patients (85-90%), and antibodies can be detected as early as a few months after treatment introduction (90,91). The neutralizing capacities of these antibodies are not largely assessed. These antibodies could spontaneously decrease over time even if treatment is continued but seems to be associated with a progressively worsening of the metabolic control. As recently suggested, in this situation, a treatment by the MC4R agonist setmelanotide could be an alternative (57).

Limitations and perspectives for metreleptin in LS

Although interesting and currently used as a standard of care in LS patients, it must be noted that there is no randomized clinical trial to compare the long-term efficacy of metreleptin in this rare disease, nor any evaluating metreleptin versus specific pharmacological optimization of LS-associated comorbidities. Furthermore, blood leptin concentration under treatment is not documented and could explain poor clinical benefit in some patients. As mentioned previously, quality of life and adherence to metreleptin are not perfect and could lead to treatment discontinuation (71). Finally data are emerging on the potential interest of other

treatments for LS patients, such as SGLT2 inhibitors or GLP-1 receptor agonists, and the evaluation of the positioning and/or association of these drugs with metreleptin would be of interest (92–95).

Conclusions

Metreleptin is the only drug specifically approved for lipodystrophy syndromes. It improves parameters (diabetes, dyslipidemia), and a reduction in mortality with metreleptin treatment was recently shown as compared with a non-treated cohort (24). Metreleptin seems to improve quality of life. As previously mentioned, LS are a heterogenous group of diseases and there are several differences regarding the generalized or partial forms. Indeed, the latter is thought to induce less important metabolic effects than in generalized forms, however still significant. The treatment appears to be safe and can be used in both pediatric and adult' populations. These results must nevertheless be considered with caution given the small number of patients treated and the absence of randomized clinical trials. Future studies are necessary to evaluate the interest of other treatments in LS patients.

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