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Short running title: Metreleptin for lipodystrophy in a real-life setting

Abstract

Aims: To describe baseline characteristics and follow-up data in patients with lipodystrophy syndromes treated with metreleptin in a national reference network, in a real-life setting.

Patients and Methods: Clinical and metabolic data from patients receiving metreleptin in France were retrospectively collected, at baseline, one year and at the latest follow-up during treatment.

Results: Forty-seven patients with lipodystrophy including generalized lipodystrophy (GLD, n=28) and partial lipodystrophy (PLD, n=19) received metreleptin over the last decade. At baseline, age was 29.3 [16.6-47.6] (years, median [interquartile range]); BMI 23.8 kg/m^2 [21.2-25.7]; serum leptin 3.2 [1.0-4.9] ng/mL); 94% of patients had diabetes (66% insulin-treated), 53% hypertension, and 87% dyslipidemia. Metreleptin therapy, administered during 31.7 [14.2-76.0] months, was ongoing in 77% of patients at the latest follow-up. In patients with GLD, HbA1c (%) and fasting triglycerides (mmol/L) significantly decreased from baseline to one year-metreleptin treatment, from 8.4 [6.5-9.9] to 6.8 [5.6-7.4], and 3.6 [1.7-8.5] to 2.2 [1.1-3.7] respectively (p<0.001), with a sustained efficacy thereafter. In patients with PLD, HbA1c (%) was not significantly modified from 7.7 [7.1-9.1] at baseline vs 7.7 [7.4-9.5] at one-year), and the decrease in fasting triglycerides (mmol/L), from 3.3 [1.9-9.9] to 2.5 [1.6-5.3], p<0.01) was not confirmed at the latest assessment (5.2 [2.2-11.3]). However, among PLD patients, at one-year, 61 % were responders regarding glucose homeostasis, with lower baseline leptin levels compared to non-responders, and 61% were responders regarding triglyceridemia. Liver enzymes significantly decreased only in the GLD group.

Conclusions: In this real-life setting study, metabolic outcomes are improved under metreleptin therapy in patients with GLD. The therapeutic indication of metreleptin needs to be clarified in patients with PLD.

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Introduction

Lipodystrophy syndromes (LD) are rare diseases of acquired or genetic origin characterized by a generalized or partial loss of adipose tissue and subsequent risk of severe metabolic complications associated with insulin resistance, i.e. glucose tolerance abnormalities, hypertriglyceridemia, liver steatosis, atherosclerotic events, and ovarian hyperandrogenism in females (1). LD are probably largely underdiagnosed, as illustrated by their estimated prevalence, initially reported at 1.3 to 4.7 cases per million (2), but recently re-evaluated at rather 1 in 20 000 (3,4).

Leptin deficiency has been shown to contribute to ectopic fat storage that drives the metabolic complications in LD (5–8). Several open-label prospective studies have demonstrated that replacement therapy with metreleptin, a recombinant leptin analog, is efficient in reducing hyperphagia and improving insulin sensitivity, HbA1c, triglycerides, and hepatic steatosis, in patients with generalized lipodystrophy (GLD) (8–13). Improvement in health self-perception, quality of life, and morphotype-associated stigmatization, were also reported on leptin-replacement therapy (14–16). However, to date, the therapeutic efficacy of metreleptin has not been studied in prospective placebo-controlled trials (7). In addition, concerning patients with partial forms of lipodystrophy (PLD), the metabolic effects of metreleptin seem variable and could depend on the initial severity of leptin deficiency and/or metabolic complications (13,17–21).

Metreleptin is approved as an orphan drug in Japan and USA, and obtained a European Marketing Authorization (EMA) in 2018 for the treatment of metabolic complications associated with leptin deficiency in patients with lipodystrophy. Metreleptin treatment is authorized in Europe, as an adjunct to diet, in adults and children with GLD, from 2 years onwards, and in patients with PLD from 12 years onwards, for whom conventional treatments failed in achieving adequate metabolic control (22). The French National Health Authority (HAS) followed the favorable opinion of the EMA, but recommended a multi-disciplinary decision from the French Reference Center for Rare Diseases of Insulin Secretion and Insulin Sensitivity (PRISIS) network for the validation of the metreleptin therapy option (23).

The aim of this observational study is to describe the characteristics of patients with lipodystrophy treated with metreleptin therapy in France, and to evaluate treatment efficacy, in a real-life setting.

Patients and Methods

Study Design

This multicenter retrospective observational cohort study included all patients with lipodystrophy who started metreleptin therapy in France between 2009 and 2020. Data collection was coordinated by the PRISIS National Reference Center, Endocrinology Department, Saint-Antoine Hospital, Paris. Patients' files were included in the CEMARA National Rare Disease Database (French data protection agency CNIL # 909474). The study followed the principles of the Declaration of Helsinki and all patients gave their informed consent for data collection.

Patients

Forty-seven patients with genetic or acquired, partial or generalized lipodystrophy, in the absence of Human Immunodeficiency Virus (HIV) infection, were included. Twenty-seven patients (14 with GLD and 13 with PLD) entered a compassionate program of metreleptin therapy approved by HAS from 2009 to 2017 (24). The 20 remaining patients (14 with GLD and 6 with PLD) received metreleptin therapy following EMA authorization in 2018. The proportion of patients with GLD or PLD did not significantly differ according to the time of metreleptin initiation, i.e. before or after 2018 (p=0.24). Metreleptin was administered as a daily subcutaneous injection and dose adjustments were based on patients' response and tolerance as recommended (1).

Methods

Patients' records were reviewed using structured data collection forms. The following parameters were collected at baseline (*before metreleptin treatment*), after 12±3 months of metreleptin therapy (*short-term response*) and at the latest visit on metreleptin therapy, ≥15 months of treatment (*long-term response*):

- Sex, weight, Body Mass Index (BMI), ongoing treatments (lipid lowering and antidiabetic drugs), daily insulin dose and daily metreleptin dose

- HbA1c, liver enzymes (aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), gammaglutamyl transferase (GGT), total, High Density Lipoprotein (HDL)-, and Low Density Lipoprotein (LDL)-cholesterol, fasting triglycerides, creatinine, and albuminuria

At baseline, additional parameters were recorded including age at diagnosis of lipodystrophy (LD), subtype of LD (generalized GLD or partial PLD, genetic or acquired), gene pathogenic variant when applicable, presence of hypertension, dyslipidemia and/or diabetes, age at diagnosis of diabetes when applicable, and pretreatment serum leptin level, measured by ELISA (Quantikine, R&D Systems). Fat mass percentage was evaluated with Dual energy X-ray absorptiometry (DEXA).

Diabetes was defined by a glycated hemoglobin (HbA1c) ≥ 6.5 % or at least one antidiabetic treatment. In adults, hypertension was defined by systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg or at least one anti-hypertensive treatment. In children below the age of 16, hypertension was defined as SBP and/or DBP persistently superior to the 95th percentile for sex, age and height measured on at least three separate occasions (25). Dyslipidemia was defined by serum fasting triglycerides ≥ 1.7 mmol/L, LDL-cholesterol ≥ 4.88 mmol/L, HDL-cholesterol ≤ 1.03 mmol/L (men) or ≤ 1.28 mmol/L (women) or at least one lipid-lowering therapy.

We also collected and reviewed serious adverse events that occurred under metreleptin treatment.

A favorable effect of metreleptin on glucose control was defined, in patients with diabetes at baseline, as a ≥ 0.5-point decrease in HbA1c, or HbA1c stability with a decrease of more than 50% in total daily

insulin, or discontinuation of at least one antidiabetic class between baseline and short-term metreleptin therapy (24). A favorable effect of metreleptin on triglycerides was defined, in patients with serum fasting triglycerides ≥ 1.7 mmol/L at baseline, as serum triglyceride levels < 1.7 mmol/L, or as a decrease of more than 30% in serum triglycerides between baseline and short-term metreleptin therapy (8,9,17,19,26–28).

During follow-up, seven patients were switched from metreleptin to GLP-1R (Glucagon-like peptide-1 receptor) agonists. In these patients, we compared the metabolic results of the latest visit while on metreleptin therapy to those on GLP-1 analog therapy thereafter.

Statistical analysis

Results are reported as median and interquartile ranges [25^e percentile-75^e percentile] for quantitative variables, and as number and percentage for qualitative variables. In patients under the age of 18, weight-standard deviation scores are expressed as Z-scores. Comparisons between two groups were conducted by unpaired Mann–Whitney U-test, and between more than two groups by Wilcoxon signed-rank test. Chi-square test of independence was used for qualitative variables. Correlation analyses used Spearman non-parametric test. Descriptive and comparative statistical analyses were performed using GraphPad Prism (Windows version 9.0, GraphPad Software, San Diego, CA, USA). Two-sided P values ≤ 0.05 are considered statistically significant.

Results

Baseline characteristics

General characteristics of patients with LD initiating a metreleptin therapy in France

Patients' baseline characteristics are shown in **Table 1**. Among the forty-seven patients initiating a metreleptin therapy in France, 28 have GLD and 19 PLD. Women represent 75% of the whole cohort, and 95% of the PLD group. Patients with GLD are diagnosed with LD earlier, and are younger at metreleptin initiation, than patients with PLD.

Most patients were diagnosed with a genetic form of LD (83%). Genes and variants involved are provided in **Supplemental Table 1**, including *AGPAT2* biallelic pathogenic variants in 8 patients (Congenital Generalized Lipodystrophy type 1), and *LMNA* p.Arg482 heterozygous substitutions in 12 patients (Dunnigan Familial Partial Lipodystrophy). Three patients present with autoimmune GLD. In five patients, the etiology of LD is unknown.

Metabolic parameters at baseline **(Table 1)**

As expected, leptin level and fat mass are correlated (r=0.64, p<0.001), and patients with GLD have lower leptin levels and lower fat mass than those with PLD. There is no significant difference between the GLD and PLD groups concerning the prevalence of diabetes, hypertension and dyslipidemia at metreleptin initiation. However, diabetes is diagnosed earlier in patients with GLD than in those with PLD (median age 13.0 *vs* 21.0 years, p<0.001). Seventy-nine percent of patients with diabetes are treated with metformin and 66% with insulin, with a high median daily insulin dose (median 2.0 U/kg/day), in keeping with LD-associated insulin resistance. Median HbA1c is 8.1 %, not different in the GLD and PLD groups (p=0.78). Most patients have increased albuminuria (median value 21.3 mg/L), with higher levels associated with GLD vs PLD (median 72.5 vs 11.5 mg/L respectively, p=0.05). Transaminases are frequently high, especially ALAT in patients with GLD, without any significant differences between groups. A majority of patients are on lipid-lowering drugs at metreleptin initiation (60%), especially patients with PLD (95%). Serum fasting triglycerides are increased in both GLD and

PLD groups (median 3.6 mmol/L) and HDL-cholesterol is low (median 0.8 mmol/L), but LDL cholesterol is not increased (median 2.3 mmol/L).

Response to metreleptin treatment

The median metreleptin treatment duration is 31.7 [IQR: 14.2-76.0] months. Patients with GLD are treated with a lower metreleptin dose (adjusted to weight) than patients with PLD **(Supplemental Table 2)**. In five metreleptin-treated patients, all with GLD, the last metabolic profile has been measured before the one year-treatment data point: three patients chose to interrupt their treatment, considered as burdensome, after 2.5 (n=2) or 4.1 months. Data are missing for one patient after 6 months. In one patient, metreleptin was withdrawn after one month following an allergic reaction. Since evolution of their HbA1c and triglyceride levels at the latest assessment under metreleptin therapy is not significantly different from those collected in patients with GLD after 12±3 months of metreleptin treatment, data from these five patients are included in the "short-term response" group.

We first analyzed the metreleptin response in all patients with LD **(Supplemental Table 3)**. At short-term under metreleptin therapy, LD patients loose weight, and improve fasting triglyceride and HbA1c levels while their insulin requirements decrease. These effects are maintained in the long term. Total cholesterol and liver enzymes also decrease rapidly following metreleptin therapy, but are no longer different from pretreatment levels on the long term. Finally, albuminuria does not significantly change at long-term versus baseline (median values 33.5 vs 21.3mg/L, mean values 354 vs 345 mg/L, p=0.94).

Response to metreleptin in patients with GLD

Metreleptin response is different in GLD patients as compared to PLD patients. Weight and BMI significantly decrease after short-term metreleptin therapy in adults and children with GLD. Thereafter, BMI is not significantly modified in adult patients, whereas children showed a slight, but

significant, improvement of weight Z score during long-term metreleptin therapy, which however remained significantly lower than baseline levels **(Table 2)**.

Glucose homeostasis improves in GLD patients under metreleptin therapy. Indeed, median HbA1c significantly decreases from baseline to short-term (median 8.4 to 6.8%, p<0.0001), allowing five patients to stop insulin therapy, while others significantly decrease their daily insulin doses **(Table 2, Figure 1A and 1B)**. At long-term, we did not observe a significant rebound in the median HbA1c. Fasting triglycerides improve significantly, from a median value of 3.6 mmol/L at baseline to 2.2 and 1.9 mmol/L after short-term and long-term respectively, p<0.001 and <0.01 vs baseline **(Table 2, Figure 1C and 1D).** Total cholesterol follows a similar trajectory during metreleptin treatment, towards a significant decrease at short-term, with stable values therafter. The short-term effect of metreleptin on liver transaminases and albuminuria is not maintained in the long term. The use of lipid-lowering therapy and antidiabetics other than insulin is not significantly modified during the treatment period in patients with GLD **(Table 2)**. Only one patient, with GLD, was able to discontinue its antidiabetic treatment (metformin) after 6 months on metreleptin, with HbA1c remaining <6% at the last follow-up (at 30 months of metreleptin treatment). Regarding dyslipidemia, only one patient, also with GLD, stopped its lipid-lowering therapy after 5 months of metreleptin, and maintained normal lipid levels after 40 months of metreleptin therapy. No patient discontinued any antihypertensive treatment.

Response to metreleptin in patients with PLD

Patients with PLD (n=19) also display a sustainable weight loss under metreleptin therapy (median BMI of 24.8 at baseline, 23.9 at short-term (p=0.03), then 23.5 at long-term (p=0.02 compared to baseline) **(Table 3).** However, in patients with PLD, median HbA1c values (7.7% [7.1-9.1]) do not significantly improve under metreleptin therapy, neither in the short-term (7.7 [7.4-9.5]), nor in the long-term (8.0 [7.6-8.5]) **(Table 3, Figure 2A and 2B).** Insulin therapy and other antidiabetic treatments are not significantly modified. No patient discontinued antidiabetic treatment during metreleptin therapy. Serum fasting triglycerides significantly decrease after short-term metreleptin treatment (from 3.3

[1.9-9.9] mmol/L to 2.5[1.6-5.3], p<0.01) but return to baseline levels afterwards (5.2 [2.2-11.3] mmol/L, p=0.94 compared to baseline) **(Table 3, Figure 2C and 2D)**. A large majority of patients with PLD is treated with lipid-lowering drugs during metreleptin therapy. No patient discontinued lipid-lowering or antihypertensive treatments during metreleptin therapy. We do not observe any significant changes in liver enzymes nor in albuminuria values during metreleptin therapy.

Predictive factors of metreleptin therapy efficacy in PLD patients (**Supplemental Figure 1**)

Since patients with PLD demonstrate a highly variable metabolic response to metreleptin, we sought to determine which factor(s) could predict treatment efficacy. Values regarding glucose and triglycerides control are available for 18 PLD patients (follow-up data missing for one patient).

All patients with PLD had diabetes at metreleptin initiation. Regarding glucose homeostasis, previously used criteria to define a favorable effect of metreleptin (24) allow us to identify 11 patients (61%) as responders following short-term metreleptin treatment. Responders and non-responders do not differ in terms of age at treatment initiation, age at diagnosis of lipodystrophy and age at diagnosis of diabetes, nor in daily insulin dose, fat mass percentage or changes in weight/BMI upon metreleptin therapy. However, responders have lower leptin levels compared to non-responders (median [IQR]: 3.9 [3.3-4.4] vs 8.0 [3.4-8.7], p=0.05). Among patients with PLD treated with insulin (n=11), only 4 (36%) are responders when evaluated in the short-term, whereas the proportion of responders is 100% in patients with PLD-associated diabetes not treated with insulin therapy (n=7) (p=0.01). Regarding the effect of metreleptin therapy on triglycerides levels, 11 patients with PLD (61%) can be defined as responders (**Supplemental Figure 1**). Comparison of the responder and non-responder groups do not reveal any differences in any of the factors studied above.

When combining the study of both glucose and triglycerides levels, only seven patients with PLD (39%) are classified as responders to metreleptin (**Supplemental Figure 1**).

Diker-Cohen et al have previously proposed that baseline HbA1c > 8%, triglycerides > 5.6 mmol/L and serum leptin < 4 ng/mL could be predictive factors for improvement of glucose and triglycerides under

metreleptin in patients with PLD (17). Nine patients with PLD met those criteria, including four patients with FPLD3 due to *PPARG* pathogenic variants, three patients with FPLD2 due to p.(Arg482) *LMNA* variant, one patient with FPLD4 due to *PLIN1* pathogenic variant, and one patient with an unknown genetic cause. Among them, the patient with FPLD4 is the only one that does not respond to metreleptin treatment, neither regarding glucose homeostasis nor triglycerides levels. All the other patients are classified as responders to metreleptin for either glucose and/or triglyceride control.

Adverse events

Four patients with LD died during metreleptin therapy, from cardiovascular events (n=2, cardiomyopathy with heart failure or stroke), hepatic insufficiency (n=1), or metastatic pancreatic cancer (n=1) **(Supplemental Table 2)**. One patient, with an autoimmune form of GLD, developed neutralizing anti-metreleptin autoantibodies and concomitantly worsened her metabolic parameters after 45 months of treatment. One patient developed skin allergy to metreleptin leading to treatment interruption after one month of treatment.

Metabolic changes in patients switched from metreleptin to GLP-1R agonists therapy during follow-up

Seven lipodystrophy patients (3 with GLD and 4 with PLD) were switched from metreleptin to GLP-1R agonist therapy. They received metreleptin for 77 [34-87] months (median [interquartile range]), then GLP-1 analogs, i.e. dulaglutide for five patients, and liraglutide for two patients, for 20 [6-23] months. GLP-1 analogs were used with antidiabetic doses (1.5mg/week for dulaglutide and 1.8 mg/day for liraglutide). We do not identify any significant difference between BMI (p=0.44), HbA1c (p=0.30), fasting triglycerides (p=0.81) and albuminuria (p=0.16) after metreleptin or GLP-1R agonist therapy in those patients **(Supplemental Table 4)**. However, considering only the three patients with GLD, all were treated only transiently with GLP-1 analogs, for 3, 6 and 20 months, and all were restarted with metreleptin thereafter. Indeed, HbA1c increases in all of them (by 0.8, 0.5 and 0.1 %, respectively), and triglycerides increase in 2 out of 3 patients during GLP-1 analog treatment. Concerning the four

patients with PLD, they were treated with metreleptin between 18.5 and 85.0 months, then switched to GLP-1 analogs, and none of them restarted metreleptin thereafter. Their median HbA1c values were 7.7% on metreleptin then 7.9% on GLP-1 analogs. Their median values of serum triglycerides were 6.3 mmol/L on metreleptin then 2.2 mmol/L on GLP-1 analogs.

Discussion

This study included the largest cohort of patients with LD initiating a metreleptin therapy in a real-life setting. It provides an overview of i) characteristics of patients with lipodystrophy treated with metreleptin therapy in France ii) the metabolic effects of short and long-term metreleptin therapy in patients with GLD or PLD.

Importantly, it confirms that metreleptin treatment is efficient, in a sustainable manner, in reducing hyperglycemia and hypertriglyceridemia in patients with GLD. Conversely, metabolic efficacy of metreleptin in patients with PLD was highly variable, and did not reach statistical significance when considering the whole PLD group.

Lipodystrophy syndromes are rare diseases whose metabolic complications are difficult to treat due to the severe insulin resistance linked to adipose tissue failure. Although the orphan drug metreleptin does not aim to replace adipose tissue, it was shown to alleviate ectopic lipid storage by central and peripheral effects improving satiety and insulin sensitivity (11,29–32). Following the international guidelines published in 2016 (1), and the recommendations of the French National Health Authority (23), serum leptin<4 ng/mL, HbA1c>8% and/or triglycerides> 5.6 mmol/L are widely used prerequisites for metreleptin prescription in France (1,17). However, metreleptin was previously used in France through compassionate programs before marketing authorization, which could explain why patients with PLD had lower median values of HbA1c (7.7% [7.1-9.1]) and triglycerides (3.3 mmol/L [1.9-9.9]) at metreleptin initiation.

Not surprisingly, in comparison to patients with PLD, whose disease manifests predominantly during late childhood or puberty, patients with GLD, mainly affected by congenital forms of the disease, were younger at metreleptin initiation. However, both groups had comparable metabolic markers at baseline, even though patients with PLD had higher BMI, fat mass and endogenous leptin levels than those with GLD.

Metreleptin was previously reported to be less efficient in patients with PLD compared to those with GLD (10,13,17,33). Herein, in patients with PLD, BMI and fasting triglycerides, but not HbA1c, albuminuria or liver enzymes, significantly improved at short-term under metreleptin therapy, in line with previous observations (18,20,33,34). The decrease in triglycerides was in the same range than that recently reported in 36 patients with PLD included in clinical trials (-28.7%) (13). In that same study, HbA1c decreased by a mean -0.61% in patients with PLD, compared to -2.16% in patients with GLD (n=59). In other studies, HbA1c did not improve during metreleptin therapy in patients with PLD (20,34). Heterogeneous causes of PLD, and small numbers of patients included, might explain these discrepancies. Moreover, in patients with chronic metabolic complications, treatments are generally less effective in real-life studies than in clinical trials (10,35). Interestingly, PLD patients with inadequate metabolic control (diabetes and/or triglycerides) were mostly responders to metreleptin treatment, as previously reported (17,36,37).

In our study, insulin treatment at baseline was predictive of a poorer response to metreleptin therapy on HbA1c in patients with PLD. In line, in clinical trials including patients with PLD, insulin therapy at baseline was associated with a smaller decrease in HbA1c at one-year metreleptin therapy, although HbA1c was higher at metreleptin initiation (13). However, in patients with GLD, responders to metreleptin were more frequently insulin users (9). As proposed by Adamski et al (13), insulin use may be an indicator of beta-cell failure in PLD, whereas it may be an indicator of more severe insulin resistance in GLD. A hypothesis could be that metreleptin might improve HbA1c in patients with preserved beta cell function only (13). Besides, patients with PLD were older than patients with GLD, which can be associated with more beta-cell dysfunction.

In our study, patients with PLD showing a favorable response to metreleptin on glucose homeostasis had lower serum leptin levels than non-responders. This was reported in some, but not all previous studies (17,34). The endogenous serum leptin cut-off point to predict metreleptin response in patients with LD is still debated, partly due to the different sensitivity of the leptin assays currently available

(28). Nevertheless, the baseline serum leptin level, assessed by the same assay, could be an important criterion for the indication of metreleptin therapy, as observed here. We failed to identify other predictive factors for metreleptin efficacy. Larger effectives of patients, as reached through international rare diseases registries (38) could help to understand the role of factors such as LD etiologies, genotypes involved, or specificities of body composition, on metreleptin response.

Interestingly, patients with GLD had a better response to metreleptin than those with PLD, whereas their metreleptin doses, corrected for weight, were lower. As patients with GLD had lower baseline leptin levels, we could have expected higher doses of metreleptin to get a favorable response. The need to increase the metreleptin dose in patients with PLD is an indirect sign of lower efficacy, which might be related to a state of relative "leptin-resistance".

Adverse events were rare during metreleptin therapy. As previously described, we report the development of anti-metreleptin autoantibodies in a patient with auto-immune GLD, leading to secondary inefficacy of metreleptin, and allergy to metreleptin in one patient (1,39). Deaths observed during follow-up were not considered to be related to metreleptin treatment, but rather to disease progression and severity. Three patients stopped metreleptin because of excessive constraints. This lack of compliance may result, at least in part, from the need to reconstitute the product from powder extemporaneously and to perform daily subcutaneous injections without pre-filled devices (15).

Seven patients were switched to GLP-1R agonists after cessation of metreleptin therapy. Due to the effects of GLP1-R agonists on fat mass and insulin resistance (40,41), metabolic improvements of diabetes, serum triglycerides and/or hepatic steatosis, could have been expected, as reported in a few case reports (42,43). Nevertheless, we did not observe any additional metabolic benefit of GLP-1R agonists following metreleptin therapy in a real-life setting. Importantly, metreleptin was restarted in all three patients with GLD who were switched on GLP-1R agonists, due to deterioration of glucose and triglycerides values. These data have to be considered with caution in this very low number of patients, who were not controlled for compliance. It will certainly be useful to compare metreleptin and GLP-

1R agonist treatments in a larger cohort of patients. Similarly, efficacy of SGLT2-inhibitors (iSGLT2) on metabolic complications associated with LD has been described in two case reports only (44,45), and more data are needed regarding the use of this therapeutic drug class in lipodystrophy syndromes.

Our study has some limitations, such as its retrospective setting. As it was conducted during an extended period (2009-2020) over which antidiabetic drugs have evolved, this could have biased some outcomes. However, in France, no new antidiabetic drugs were marketed between 2009 and 2020 (iSGLT2 were approved in April 2020). We did not have access to data about treatment's compliance, which represents a potentially confounding factor. Heterogeneity in the medical management of patients could have occurred, but this risk should be minor due to the close interactions of clinical centers within our National Rare Disease Reference network.

The results of our observational study point out that metreleptin treatment is efficient in patients with GLD. However, as highlighted by published guidelines (1,23), it should be given only to selected patients with PLD. Our study suggests that leptin levels, measured with the same assay, should be taken into account for this therapeutic decision. Metreleptin treatment should be regularly reevaluated and stopped if inefficient. Patients with LD also may require stronger educational support. Studies on larger effectives and double-blind randomized controlled trials are needed to better evaluate the metabolic efficacy of metreleptin treatment in PLD, and to define predictive factors of response.

Conflicts of interest

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Legends to figures :

Figure 1: HbA1c (A,B) and triglycerides (C,D) during metreleptin treatment in patients with generalized lipodystrophy (GLD) at baseline, short-term and long-term.

ns: non-significant. **: $p < 0.01$. ***: $p < 0.001$. ****: $p < 0.0001$. Individual values are depicted as dots. Left panel: horizontal lines show median values and interquartile ranges.

Figure 2: HbA1c (A,B) and triglycerides (C,D) during metreleptin treatment in patients with partial lipodystrophy (PLD) at baseline, short-term and long-term.

ns: non-significant. **: $p < 0.01$. Individual values are depicted as dots. Left panel: horizontal lines show median values and interquartile ranges.

Tables :

Table 1: Patients' parameters at metreleptin initiation

	Whole group of metreleptin-treated patients (n=47)	Generalized lipodystrophy (GLD, n=28)	Partial lipodystrophy (PLD, n=19)	p (Generalized vs partial lipodystrophy groups)
General characteristics				
Women : n (%)	35/47 (75%)	17/28 (61%)	18/19 (95%)	**0.01**
Age (years)	29.3 [16.6-47.6]	17.7 [14.4-29.7]	44.8 [31.3-51.0]	**<0.01**
Age at diagnosis of lipodystrophy (years)	11.8 [1.8-25.0] (n=46)	4.0 [0.0-12.0] (n=27)	21.0 [16.0-45.0]	**<0.001**
Cause of lipodystrophy				
Genetic (%)	39/47 (83%)	21/28 (75%)	18/19 (95%)	0.12
Autoimmune (%)	3/47 (6%)	3/28 (11%)		
Unknown (%)	5/47 (11%)	4/28 (14%)	1/19 (5%)	0.64
Anthropometry				
Weight (Z-score) *in patients < 18 years*	0.8 [-0.4;1.1] (n=15)	0.8 [-0.4;1.1] (n=15)	-	NA
Body Mass Index *in patients > 18 years (kg/m²)*	23.8 [21.2-25.7] (n=32)	21.1 [19.3-23.1] (n=13)	24.8 [23.1-26.0]	**<0.001**
Fat Mass (%)	15.2 [9.8-21.4] (n=34)	10.1 [7.4-12.3] (n=18)	17.9 [16.0-22.5]	**<0.001**
Metabolic features				
Pretreatment leptin serum level (ng/mL)	3.2 [1.0-4.9] (n=42)	1.7 [0.4-3.3] (n=24)	4.1 [3.4-5.7] (n=18)	**<0.01**
Diabetes (%)	44/47 (94%)	25/28 (89%)	19/19 (100%)	0.26
Hypertension (%)	25/47 (53%)	13/28 (46%)	12/19 (63%)	0.37
Dyslipidemia (%)	41/47 (87%)	23/28 (82%)	18/19 (95%)	0.38
Age at diagnosis of diabetes (years)	17.5 [11.6-24.5] (n=44)	13.0 [9.0-20.0] (n=25)	21.0 [16.0-37.0]	**<0.001**
Patients treated with insulin: n (% of patients with diabetes)	29/44 (66%)	17/25 (68%)	12/19 (63%)	>0.99
Daily insulin dose (U/kg)	2.0 [0.9-3.5] (n=28)	1.3 [0.8-3.5] (n=16)	2.7 [1.1-3.7] (n=12)	0.64
HbA1c at metreleptin initiation (%)	8.1 [7.1-9.9]	8.4 [6.5-9.9]	7.7 [7.1-9.1]	0.78
Lipids				

Patients on lipid-lowering drug: n, (%)	28/47 (60%)	10/28 (36%)	18/19 (95%)	**<0.001**
Total cholesterol (mmol/L)	4.6 [3.9-5.7] (n=46)	4.6 [3.9-4.9]	4.6 [3.9-6.5] (n=18)	0.61
Serum triglycerides (mmol/L)	3.6 [1.8-9.6]	3.6 [1.7-8.5]	3.3 [1.9-9.9]	0.48
LDL-cholesterol (mmol/L)	2.3 [1.8-2.8] (n=29)	2.3 [1.5-3.1] (n=17)	2.3 [1.8-2.8] (n=12)	0.96
HDL-cholesterol (mmol/L)	0.8 [0.5-1.0] (n=46)	0.8 [0.5-1.0]	0.8 [0.5-0.8] (n=18)	0.33
Liver enzymes				
ASAT (IU/L) (N: 6-35)	31.0 [24.0-44.0] (n=43)	31.0 [24.5-49.5] (n=25)	30.5 [20.8-39.5] (n=18)	0.42
ALAT (IU/L) (N: 8-43)	42.0 [24.8-66.0] (n=46)	57.0 [24.0-81.0] (n=27)	39.0 [25.0-59.0]	0.29
GGT (IU/L) (N: 6-45)	45.0 [29.0-72.0] (n=43)	42.5 [27.5-65.8] (n=24)	61.0 [32.0-84.0]	0.32
Kidney parameters				
Serum creatinine (µmol/L)	55.5 [45.0-68.3] (n=44)	48.0 [35.0-61.5] (n=25)	64.0 [54.0-70.0]	**<0.01**
Albuminuria (mg/L)	21.3 [7.9-277.3] (n=40)	72.5 [13.3-488.0] (n=22)	11.5 [4.0-69.1] (n=18)	**0.05**

Results are expressed as median [25% percentile-75% percentile] for quantitative variables and as number (n) and percentage (%) for qualitative variables. Results are from all patients unless specified (n). Diabetes is defined by HbA1c ≥ 6.5 % or antidiabetic treatment. Hypertension is defined by systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or anti-hypertensive treatment. Dyslipidemia is defined by serum triglycerides ≥ 1.7 mmol/L, LDL cholesterol ≥ 4.88 mmol/L, HDL cholesterol ≤ 1.03 mmol/L (men) or ≤ 1.28 mmol/L (women) or lipid-lowering therapy. NA : Non-Applicable; N: normal values. p values are obtained from Wilcoxon tests for quantitative variables and from chi-square tests for qualitative variables.

Table 2: Anthropometric and metabolic parameters during metreleptin therapy in patients with generalized lipodystrophy (n=28)

	At baseline (before metreleptin initiation) (n=28)	Short-term response (n=28)	Long-term response (n=20)	p baseline vs short-term response	p baseline vs long-term response	p short-term vs long-term response
Anthropometrics						
Weight (Zscore) < 18 years (n=15)	0.8 [-0.4;1.1]	0.4 [-1.7;1.2]	0.5 [-1.2;1.1] (n=9)	**<0.01**	**0.02**	**0.03**
Body Mass Index (kg/m^2) > 18 years (n=13)	21.1 [19.3-23.1]	19.1 [18.5-22.2]	19.0 [18.0-22.2] (n=8)	**<0.01**	**0.05**	0.78
Glucose homeostasis						
HbA1c (%)	8.4 [6.5-9.9]	6.8 [5.6-7.4] (n=23)	6.9 [5.5-8.7]	**<0.0001**	**<0.01**	0.33
Patients on insulin: n (% of patients with diabetes)	17/25 (68%)	12/25 (46%)	10/20 (50%)	0.41	0.56	>0.99
Daily insulin dose according to weight (IU/kg)	1.3 [0.8-3.5] (n=16)	1.0 [0.4-2.4] (n=11)	1.1 [0.5-3.7] (n=9)	**<0.01**	0.69	0.50
Number of antidiabetic therapeutic classes used (except insulin)	1.0 [0.0-1.0]	1.0 [0.0-1.0]	1.0 [1.0-1.0]	>0.99	0.34	0.18
Lipids						
Serum triglycerides (mmol/L)	3.6 [1.7-8.5]	2.2 [1.1-3.7] (n=23)	1.9 [1.3-3.3] (n=19)	**<0.001**	**<0.01**	0.57
Total cholesterol (mmol/L)	4.6 [3.9-4.9]	3.5 [3.6-4.3] (n=23)	3.8 [3.5-4.5] (n=15)	**0.02**	**<0.01**	0.68
LDL-cholesterol (mmol/L)	2.3 [1.5-3.1] (n=17)	2.2 [1.9-2.4] (n=18)	2.2 [1.7-2.6] (n=18)	0.80	0.68	0.71
HDL-cholesterol (mmol/L)	0.8 [0.5-1.0]	0.8 [0.6-0.9] (n=23)	0.8 [0.7-1.1] (n=17)	0.47	0.06	0.95
Patients on lipid-lowering drugs: n (%)	10/28 (36%)	8/20 (44%)	7/17 (41%)	0.77	0.76	>0.99
Liver enzymes						
ASAT (IU/L) (N 6-35)	31.0 [24.5-49.5] (n=25)	27.0 [22.0-33.0] (n=19)	32.5 [24.7-65.7] (n=18)	**<0.01**	0.12	0.23
ALAT (IU/L) (N 8-43)	57.0 [24.0-81.0] (n=27)	27.0 [20.0-57.0] (n=19)	51.5 [23.5-82.5] (n=18)	**<0.01**	0.26	0.44
GGT (IU/L) (N 6-45)	42.5 [27.5-65.8] (n=24)	32.5 [17.2-62.0] (n=16)	42.0 [22.0-65.7]	0.15	0.29	0.11
Kidney parameters						
Serum creatinine (µmol/L)	48.0 [35.0-61.5] (n=25)	57.5 [38.0-87.0] (n=16)	53.0 [50.0-97.0] (n=11)	0.15	0.31	0.95
Albuminuria (mg/L)	72.5 [13.3-488.0] (n=22)	42.1 [19.9-81.7] (n=16)	54.0 [20.0-94.5] (n=13)	**0.01**	0.73	0.16

Results are expressed as median [25% percentile-75% percentile] for quantitative variables and as number (n) and percentage (%) for qualitative variables. Results are from all patients unless specified (n). Diabetes is defined by HbA1c ≥ 6.5 % or antidiabetic treatment. Hypertension is defined by systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or anti-hypertensive treatment. Dyslipidemia is defined by serum triglycerides ≥ 1.7 mmol/L, LDL cholesterol ≥ 4.88 mmol/L, HDL cholesterol ≤ 1.03 mmol/L (men) or ≤ 1.28 mmol/L (women) or lipid-lowering therapy. N: normal values. p values are obtained from Wilcoxon tests for quantitative variables and from chi-square tests for qualitative variables.

Table 3: Anthropometric and metabolic parameters during metreleptin therapy in patients with partial lipodystrophy (n=19)

	At baseline (before metreleptin initiation) (n=19)	Short-term response (n=19)	Long-term response (n=16)	p baseline *vs* short term response	p baseline *vs* long term response	p short term *vs* long term response
Anthropometrics						
Body Mass Index (kg/m^2) > 18 years	24.8 [23.1-26.0]	23.9 [22.1-25.7] (n=17)	23.5 [21.5-25.9]	**0.03**	**0.02**	0.37
Glucose homeostasis						
HbA1c (%)	7.7 [7.1-9.1]	7.7 [7.4-9.5] (n=18)	8.0 [7.6-8.5]	0.45	0.73	0.29
Patients treated with insulin: n (% of patients with diabetes)	12/19 (63%)	12/19 (63%)	11/16 (48%)	>0.99	>0.99	>0.99
Daily insulin dose according to weight (IU/kg)	2.7 [1.1-3.7] (n=12)	1.0 [0.8-3.1] (n=9)	1.8 [0.8-4.0] (n=11)	0.13	0.38	0.38
Number of antidiabetic therapeutic classes used (except insulin)	2.0 [1.0-2.0]	1.0 [1.0-2.0]	1.5 [1.0-2.7]	0.12	>0.99	0.19
Lipids						
Serum triglycerides (mmol/L)	3.3 [1.9-9.9]	2.5 [1.6-5.3]	5.2 [2.2-11.3]	**<0.01**	0.94	0.08
Total cholesterol (mmol/L)	4.6 [3.9-6.5] (n=18)	3.8 [3.4-5.5] (n=14)	4.9 [3.9-5.5] (n=12)	0.51	0.85	0.30
LDL-cholesterol (mmol/L)	2.3 [1.8-2.8] (n=12)	2.0 [1.6-2.6] (n=11)	1.9 [1.5-3.8] (n=10)	0.76	>0.99	**0.03**
HDL-cholesterol (mmol/L)	0.8 [0.5-0.8] (n=18)	0.9 [0.8-0.9] (n=14)	0.8 [0.4-1.0] (n=15)	**0.05**	0.80	>0.99
Patients treated with lipid-lowering drugs: n (%)	18/19 (95%)	13/14 (93%)	14/14 (100%)	>0.99	>0.99	>0.99
Liver enzymes						
ASAT (IU/L) (N 6-35)	30.5 [20.8-39.5] (n=18)	30.5 [21.0-37.0] (n=12)	31.5 [24.2-54.0] (n=12)	0.45	0.78	0.58
ALAT (IU/L) (N 8-43)	39.0 [25.0-59.0]	35.5 [24.5-70.2] (n=14)	46.0 [30.5-64.7] (n=12)	0.66	0.42	0.28
GGT (IU/L) (N 6-45)	61.0 [32.0-84.0]	48.0 [25.0-81.0] (n=15)	46.0 [23.0-74.0] (n=11)	0.41	0.94	0.39
Kidney parameters						
Serum creatinine (µmol/L)	64.0 [54.0-70.0]	58.0 [54.0-68.0] (n=15)	70.0 [60.0-93.0] (n=15)	0.41	0.15	**0.03**
Albuminuria (mg/L)	11.5 [4.0-69.1] (n=18)	16.8 [12.2-72.0] (n=14)	24.0 [11.0-143.7] (n=15)	0.59	0.81	0.07

Results are expressed as median [25% percentile-75% percentile] for quantitative variables and as number (n) and percentage (%) for qualitative variables. Results are from all patients unless specified (n). Diabetes is defined by HbA1c ≥ 6.5 % or antidiabetic treatment. Hypertension is defined by systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or anti-hypertensive treatment. Dyslipidemia is defined by serum triglycerides ≥ 1.7 mmol/L, LDL cholesterol ≥ 4.88 mmol/L, HDL cholesterol ≤ 1.03 mmol/L (men) or ≤ 1.28 mmol/L (women) or lipid-lowering therapy. N: normal values. p values are obtained from Wilcoxon tests for quantitative variables and from chi-square tests for qualitative variables.
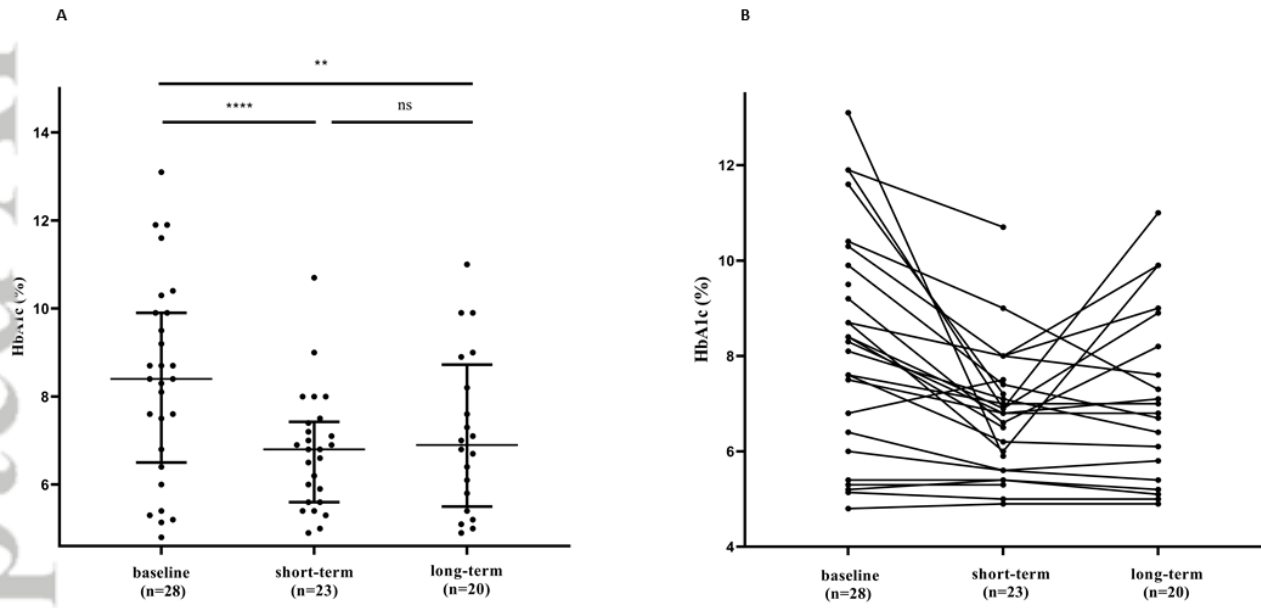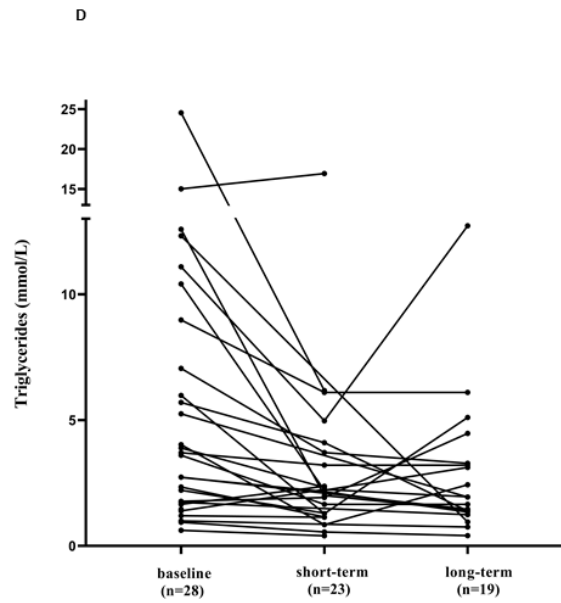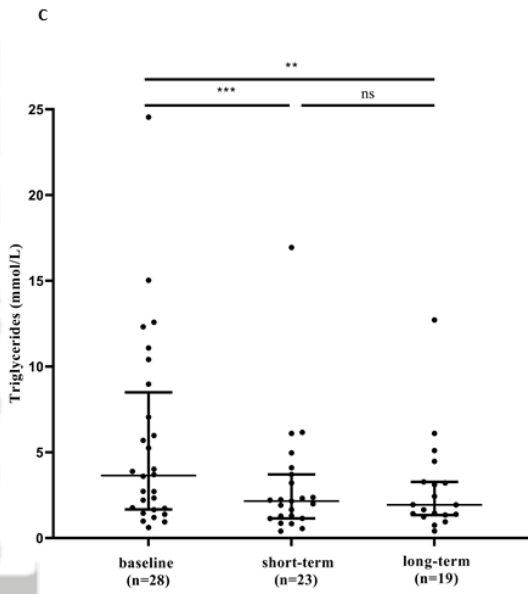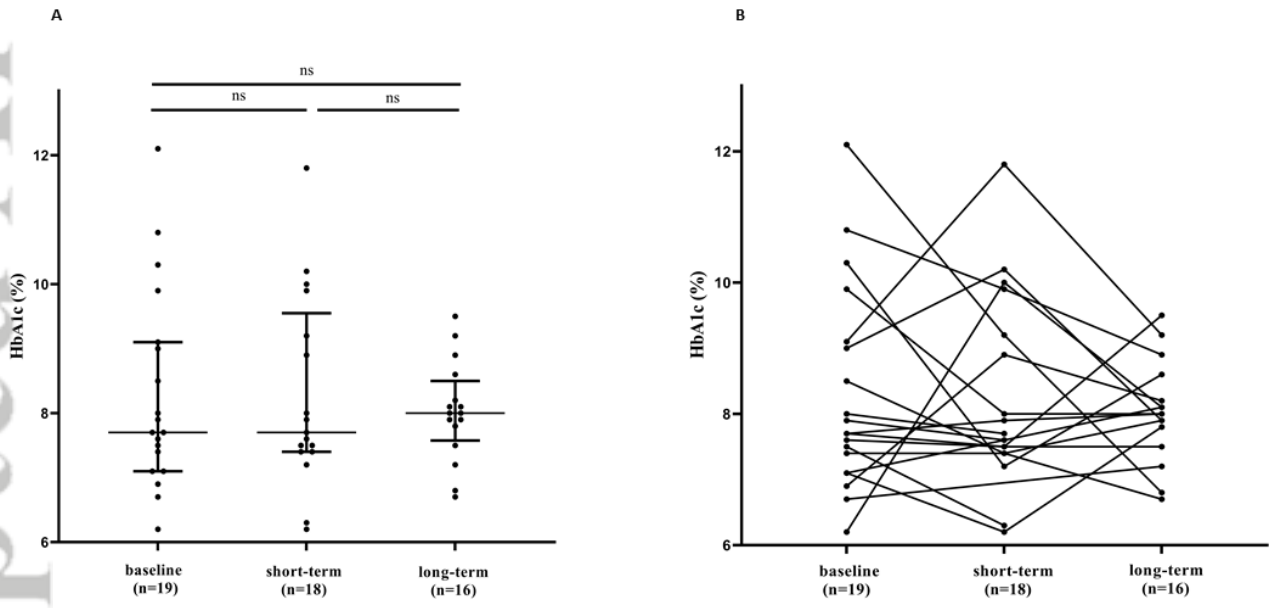
Figure 1

A

B

Figure 1

C

D

Figure 2

Figure 2