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Therapeutic indications and metabolic effects of metreleptin in patients with lipodystrophy syndromes: Real-life experience from a national reference network

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Abstract

Aim: 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, at 1 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, the median (interquartile range [IQR]) patient age was 29.3 (16.6-47.6) years, body mass index was 23.8 (21.2-25.7) kg/m^2 and serum leptin was 3.2 (1.0-4.9) ng/mL, 94% of patients had diabetes (66% insulin-treated), 53% had hypertension and 87% had dyslipidaemia. Metreleptin therapy, administered for a median (IQR) of 31.7 (14.2-76.0) months, was ongoing in 77% of patients at the latest follow-up. In patients with GLD, glycated haemoglobin (HbA1c) and fasting triglyceride levels significantly decreased from baseline to 1 year of metreleptin treatment, from 8.4 (6.5-9.9)% [68 (48-85) mmol/mol] to 6.8 (5.6-7.4)% [51(38-57) mmol/mol], and 3.6 (1.7-8.5) mmol/L to 2.2 (1.1-3.7) mmol/L, respectively ($P < 0.001$), with sustained efficacy thereafter. In patients with PLD, HbA1c was not significantly modified (7.7 [7.1-9.1]% [61 (54-76) mmol/mol] at baseline vs. 7.7 [7.4-9.5]% [61(57-80) mmol/mol] at 1 year), and the decrease in fasting triglycerides (from 3.3 [1.9-9.9] mmol/L to 2.5 [1.6-5.3] mmol/L; $P < 0.01$) was not confirmed at the latest assessment (5.2 [2.2-11.3] mmol/L). However, among PLD patients, at 1 year, 61% were responders regarding glucose homeostasis, with lower baseline leptin levels compared to nonresponders, and 61% were responders regarding triglyceridaemia. Liver enzymes significantly decreased only in the GLD group.

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

1 | INTRODUCTION

Lipodystrophy (LD) syndromes 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, namely, glucose tolerance abnormalities, hypertriglyceridaemia, liver steatosis, atherosclerotic events, and ovarian hyperandrogenism in females.[1] LD syndromes are probably largely underdiagnosed, as illustrated by their estimated prevalence, initially reported at 1.3-4.7 cases per million,[2] but recently re-evaluated at 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 analogue, is efficient in reducing hyperphagia and improving insulin sensitivity, glycated haemoglobin (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 after 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, for patients with partial forms of

lipodystrophy (partial 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 the United States, and was given European Medicines Agency (EMA) marketing authorization in 2018 for the treatment of metabolic complications associated with leptin deficiency in patients with LD. 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 to lead to adequate metabolic control.[22] The French National Health Authority (HAS) followed the favourable opinion of the EMA, but recommended a multidisciplinary decision from the French Reference Centre 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 was to describe the characteristics of patients with LD treated with metreleptin therapy in France, and to evaluate treatment efficacy, in a real-life setting.

2 | PATIENTS AND METHODS

2.1 | Study design

This multicentre retrospective observational cohort study included all patients with LD who started metreleptin therapy in France between 2009 and 2020. Data collection was coordinated by the PRISIS National Reference Centre, 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.

2.2 | Patients

Forty-seven patients with genetic or acquired PLD or GLD, in the absence of human immunodeficiency virus (HIV) infection, were included. Twenty-seven patients (14 with GLD and 13 with PLD) entered a programme of compassionate metreleptin therapy, approved by the HAS, from 2009 to 2017.[24] The 20 remaining patients (14 with GLD and six 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, that is, 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]

3 | METHODS

Patients' records were reviewed using structured data collection forms. The following variables 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):

i. Sex, weight, body mass index (BMI), ongoing treatments (lipid-lowering and antidiabetic drugs), daily insulin dose and daily metreleptin dose
ii. HbA1c, liver enzymes (aspartate aminotransferase [ASAT], alanine aminotransferase [ALAT], gamma glutamyl transferase [GGT]), total cholesterol, 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 LD, subtype of LD (GLD or PLD, genetic or acquired), gene pathogenic variant when applicable, presence of hypertension, dyslipidaemia and/or diabetes, age at diagnosis of diabetes when applicable, and pretreatment serum leptin level, measured by ELISA (Quantikine; R&D Systems, Minneapolis, MN, USA). Fat mass percentage was evaluated with dual energy X-ray absorptiometry.

Diabetes was defined by an HbA1c concentration ≥6.5% (≥48 mmol/mol) 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 antihypertensive treatment. In children below the age of 16 years, 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] Dyslipidaemia 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 during metreleptin treatment.

A favourable effect of metreleptin on glucose control was defined, in patients with diabetes at baseline, as a ≥0.5-point (pt) 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 favourable 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 glucagon-like peptide-1 (GLP-1) receptor agonists. In these patients, we compared the metabolic results of the latest visit while on metreleptin therapy to those of GLP-1 analogue therapy thereafter.

3.1 | Statistical analysis

Results are reported as median and interquartile range (IQR; 25th percentile-75th percentile) for quantitative variables, and as number

and percentage for qualitative variables. In patients under the age of 18 years, 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-squared tests of independence were used for qualitative variables. Correlation analyses were conducted using Spearman nonparametric tests. Descriptive and comparative statistical analyses were performed using GraphPad Prism (Windows version 9.0, GraphPad Software, San Diego, California). Two-sided *P* values ≤0.05 were taken to indicate statistical significance.

4 | RESULTS

4.1 | Baseline characteristics

4.1.1 | General characteristics of patients with LD initiating metreleptin therapy in France

Patients' baseline characteristics are shown in Table 1. Among the 47 patients initiating metreleptin therapy in France, 28 had GLD and 19 had PLD. Women represented 75% of the whole cohort, and 95% of the PLD group. Patients with GLD were diagnosed with LD earlier, and were younger at metreleptin initiation, than patients with PLD.

Most patients were diagnosed with a genetic form of LD (83%). The genes and variants involved are provided in Table S1, including *AGPAT2* biallelic pathogenic variants in eight patients (congenital GLD type 1), and *LMNA* p.Arg482 heterozygous substitutions in 12 patients (Dunnigan familial PLD). Three patients presented with autoimmune GLD. In five patients, the aetiology of LD was unknown.

4.1.2 | Metabolic variables at baseline

As expected, leptin level and fat mass were correlated ($r = 0.64$, $P < 0.001$), and patients with GLD had lower leptin levels and lower fat mass than those with PLD. There was no significant difference between the GLD and PLD groups concerning the prevalence of diabetes, hypertension or dyslipidaemia at metreleptin initiation (Table 1). However, diabetes was 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 were treated with metformin and 66% with insulin, with a high median daily insulin dose (2.0 U/kg/d), in keeping with LD-associated insulin resistance. The median HbA1c level was 8.1% (65 mmol/mol), and was not different between the GLD and PLD groups ($P = 0.78$). Most patients had increased albuminuria (median value 21.3 mg/L), with higher levels associated with GLD than PLD (median 72.5 vs. 11.5 mg/L, respectively; $P = 0.05$). Transaminases are frequently high, especially ALAT in patients with GLD, with no significant differences between groups. A majority of patients were on lipid-lowering drugs at metreleptin initiation (60%), especially patients with PLD (95%). Serum fasting triglycerides were increased in both the GLD and PLD groups (median 3.6 mmol/L) and HDL cholesterol was low (median 0.8 mmol/L), but LDL cholesterol was not increased (median 2.3 mmol/L).

4.2 | Response to metreleptin treatment

The median (IQR) metreleptin treatment duration was 31.7 (14.2-76.0) months. Patients with GLD were treated with a lower metreleptin dose (adjusted to weight) than patients with PLD (Table S2). In five metreleptin-treated patients, all with GLD, the last metabolic profile was measured before the 1-year treatment data point: three patients chose to interrupt their treatment, which they considered as burdensome, after 2.5 ($n = 2$) or 4.1 months. Data were missing for one patient after 6 months. In one patient, metreleptin was withdrawn after 1 month following an allergic reaction. Since the evolutions of their HbA1c and triglyceride levels at the latest assessment while on metreleptin therapy were not significantly different from those collected in patients with GLD after 12 ± 3 months of metreleptin treatment, data from these five patients were included in the "short-term response" group.

We first analysed the metreleptin response in all patients with LD (Table S3). After short-term metreleptin therapy, LD patients lost weight, and had improved fasting triglyceride and HbA1c levels, while their insulin requirements decreased. These effects were maintained in the long term. Total cholesterol and liver enzymes also decreased rapidly following metreleptin therapy, but were no longer different from pretreatment levels in the long term. Finally, albuminuria did not significantly change in the long term versus baseline (median values 33.5 vs. 21.3 mg/L, mean values 354 vs. 345 mg/L; $P = 0.94$).

4.2.1 | Response to metreleptin in patients with GLD

Metreleptin response was different in GLD patients as compared to PLD patients. Weight and BMI significantly decreased after short-term metreleptin therapy in adults and children with GLD. Thereafter, BMI was not significantly modified in adult patients, whereas children showed a slight, but significant, improvement of weight *Z* score during long-term metreleptin therapy, which remained significantly lower, however, than baseline levels (Table 2).

Glucose homeostasis improved in GLD patients receiving metreleptin therapy. Indeed, the median HbA1c level significantly decreased from baseline to short-term follow-up (8.4%, 68 mmol/mol to 6.8%, 51 mmol/mol; $P < 0.0001$), allowing five patients to stop insulin therapy, while others significantly decreased their daily insulin doses (Table 2, Figure 1A,B). At long-term follow-up, we did not observe a significant rebound in the median HbA1c level. Fasting triglyceride levels improved significantly, from a median value of 3.6 mmol/L at baseline to 2.2 and 1.9 mmol/L at short-term and

TABLE 1 Patient characteristics at metreleptin initiation

	Whole group of metreleptin-treated patients, n = 47	GLD, n = 28	PLD, n = 19	*P* (GLD vs. PLD groups)
General characteristics				
Women, n/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 LD, 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 LD, n/n (%)				
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 aged <18 years	0.8 (−0.4;1.1) (n = 15)	0.8 (−0.4;1.1) (n = 15)	—	NA
BMI in patients aged >18 years, kg/m^2	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, n/n (%)	44/47 (94)	25/28 (89)	19/19 (100)	0.26
Hypertension, n/n (%)	25/47 (53)	13/28 (46)	12/19 (63)	0.37
Dyslipidaemia, n/n (%)	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/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, %, mmol/mol	8.1 (7.1-9.9), 65 (54-85)	8.4 (6.5-9.9), 68 (48-85)	7.7 (7.1-9.1), 61 (54-76)	0.78
Lipids				
Patients on lipid-lowering drugs, n/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 variables				
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**

Notes: 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% (≥48 mmol/mol) or antidiabetic treatment. Hypertension is defined by systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or antihypertensive treatment. Dyslipidaemia 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.
P values are obtained from Wilcoxon tests for quantitative variables and from chi-squared tests for qualitative variables. The significant *p* values are in bold.
Abbreviations: Abbreviations: ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; BMI, body mass index; GGT, gamma glutamyl transferase; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LD, lipodystrophy; LDL, low-density lipoprotein; N, normal values.
NA, nonapplicable.

long-term follow-ups, respectively (*P* < 0.001 and <0.01 vs. baseline; Table 2, Figure 1C,D**)**. Total cholesterol followed a similar trajectory during metreleptin treatment, towards a significant decrease at short-term follow-up, with stable values thereafter. The short-term effect of metreleptin on liver transaminases and albuminuria was not maintained in the long term. The use of lipid-lowering therapy and

TABLE 2 Anthropometric and metabolic characteristics 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 (*Z* score)						
<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**
BMI, 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, %, mmol/mol	8.4 (6.5-9.9), 68 (48-85)	6.8 (5.6-7.4), 51 (38-57) (n = 23)	6.9 (5.5-8.7), 52 (37-72)	**<0.0001**	**<0.01**	0.33
Patients on insulin, n/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/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

Notes: 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 % (≥48 mmol/mol) or antidiabetic treatment. Hypertension is defined by systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or antihypertensive treatment. Dyslipidaemia 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. *P* values are obtained from Wilcoxon tests for quantitative variables and from chi-squared tests for qualitative variables.

The significant *p* values are in bold.

Abbreviations: Abbreviations: ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; BMI, body mass index; GGT, gamma glutamyl transferase; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N, normal values.

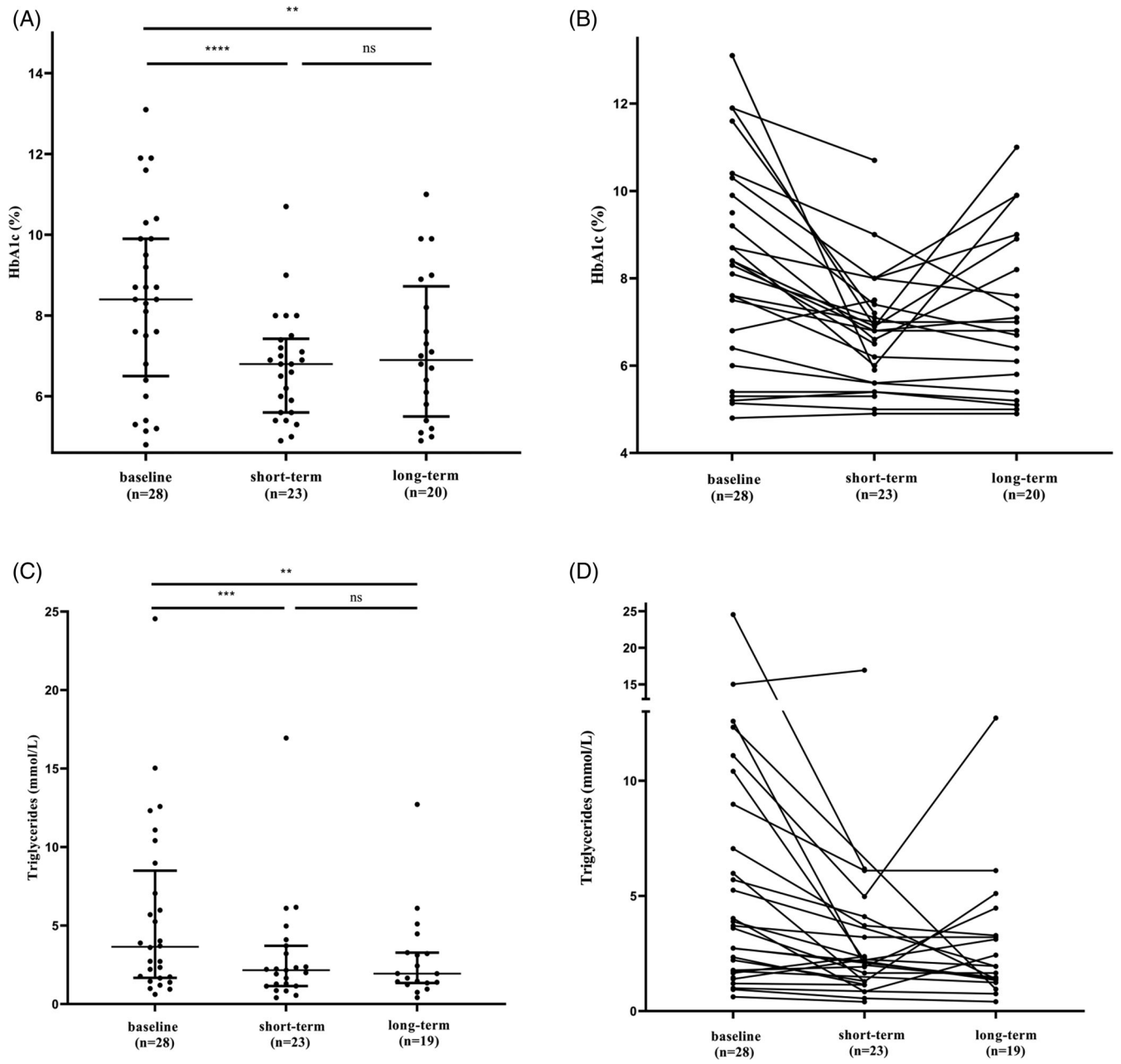

FIGURE 1 Glycated haemoglobin (HbA1c) (A, B) and triglycerides (C, D) during metreleptin treatment in patients with generalized lipodystrophy at baseline, and short- and long-term follow-ups. ns, nonsignificant. $^{**}P < 0.01$. $^{***}P < 0.001$. $^{****}P < 0.0001$. Individual values are depicted as dots. Left panel: horizontal lines show median values and interquartile ranges

antidiabetics other than insulin was not significantly modified during the treatment period in patients with GLD (Table 2). Only one patient, with GLD, was able to discontinue antidiabetic treatment (metformin) after 6 months on metreleptin, with HbA1c remaining <6% (42 mmol/mol) at the last follow-up (at 30 months of metreleptin treatment). Regarding dyslipidaemia, only one patient, also with GLD, stopped 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.

4.2.2 | Response to metreleptin in patients with PLD

Patients with PLD (n = 19) also experienced sustainable weight loss while on metreleptin therapy (median BMI 24.8 kg/m^2 at baseline, 23.9 kg/m^2 at short-term follow-up [$P = 0.03$], then 23.5 kg/m^2 at long-term follow-up [$P = 0.02$ compared to baseline]; Table 3). However, in patients with PLD, median (IQR) HbA1c values (7.7 [7.1-9.1]%, 61 [54-76] mmol/mol) did not significantly improve with metreleptin therapy, either in the short term (7.7 [7.4-9.5]%, 61 [57-

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						
BMI, 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,%, mmol/mol	7.7 (7.1-9.1), 61 (54-76)	7.7 (7.4-9.5), 61 (57-80) (n = 18)	8.0 (7.6-8.5), 64 (60-69)	0.45	0.73	0.29
Patients treated with insulin, n/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/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 variables						
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

Notes: 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% (≥48 mmol/mol) or antidiabetic treatment. Hypertension is defined by systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or antihypertensive treatment. Dyslipidaemia 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. *P* values are obtained from Wilcoxon tests for quantitative variables and from chi-squared tests for qualitative variables.
The significant *p* values are in bold.
Abbreviations: Abbreviations: ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase; BMI, body mass index; GGT, gamma glutamyl transferase; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N, normal values.

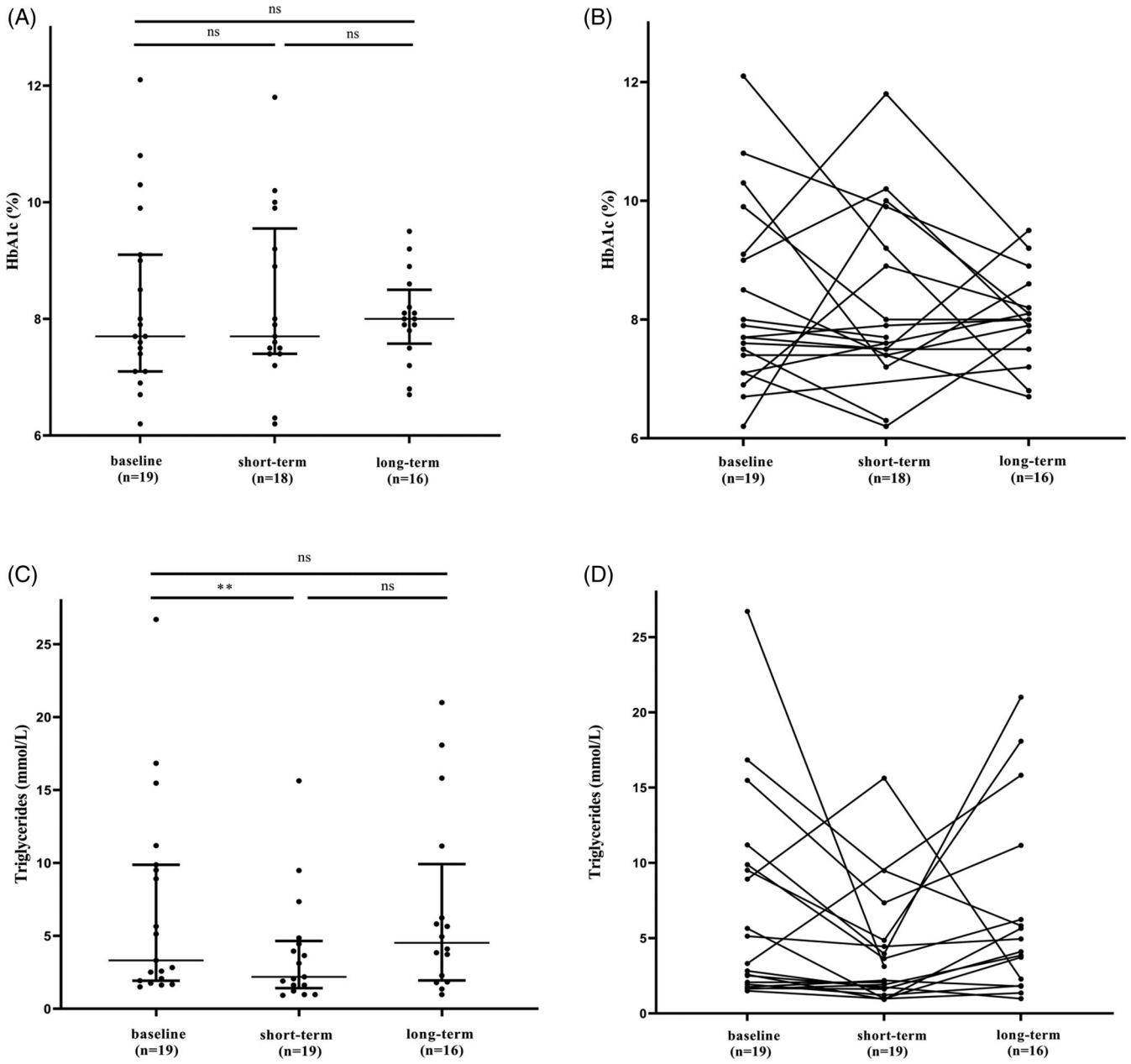

FIGURE 2 Glycated haemoglobin (HbA1c) (A, B) and triglycerides (C, D) during metreleptin treatment in patients with partial lipodystrophy at baseline, and short- and long-term follow-ups. ns, nonsignificant. $^{**}P < 0.01$. Individual values are depicted as dots. Left panel: horizontal lines show median values and interquartile ranges

80] mmol/mol) or the long term (8.0 [7.6-8.5]%, 64 [60-69]); Table 3, Figure 2A,B). Insulin therapy and other antidiabetic treatments were not significantly modified. No patient discontinued antidiabetic treatment during metreleptin therapy. Serum fasting triglycerides significantly decreased after short-term metreleptin treatment (from 3.3 [1.9-9.9] mmol/L to 2.5 [1.6-5.3] mmol/L; $P < 0.01$) but returned to baseline levels afterwards (5.2 [2.2-11.3] mmol/L; $P = 0.94$ compared to baseline) (Table 3, Figure 2C,D). A large majority of patients with PLD were treated with lipid-lowering drugs during metreleptin therapy. No patient discontinued lipid-lowering or antihypertensive treatments during metreleptin therapy. We did not observe any significant changes in liver enzymes or in albuminuria values during metreleptin therapy.

4.3 | Predictive factors of metreleptin therapy efficacy in PLD patients

Since patients with PLD demonstrated a highly variable metabolic response to metreleptin, we sought to determine which factor(s) could predict treatment efficacy (Figure S1). Data on glucose and triglyceride control were available for 18 PLD patients (follow-up data were missing for one patient).

All patients with PLD had diabetes at metreleptin initiation. Regarding glucose homeostasis, criteria previously used to define a favourable effect of metreleptin[24] allowed us to identify 11 patients (61%) as responders following short-term metreleptin treatment.

Responders and non-responders did not differ in terms of age at treatment initiation, age at diagnosis of LD or age at diagnosis of diabetes, nor in daily insulin dose, fat mass percentage or changes in weight/BMI on metreleptin therapy. However, responders had lower leptin levels compared to nonresponders (median [IQR] 3.9 [3.3-4.4] ng/mL vs. 8.0 [3.4-8.7] ng/mL; $P = 0.05$). Among patients with PLD treated with insulin (n = 11), only four (36%) were responders when evaluated in the short term, whereas the proportion of responders was 100% in patients with PLD-associated diabetes not treated with insulin therapy (n = 7; $P = 0.01$). Regarding the effect of metreleptin therapy on triglyceride levels, 11 patients with PLD (61%) could be defined as responders (Figure S1). Comparison of the responder and non-responder groups did 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%) were classified as responders to metreleptin (Figure S1).

Diker-Cohen et al have previously proposed that baseline HbA1c levels >8% (>64 mmol/mol), triglyceride levels >5.6 mmol/L and serum leptin levels <4 ng/mL could be predictive factors for improvement of glucose and triglycerides after metreleptin therapy 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 was the only one who did not respond to metreleptin treatment, regarding either glucose homeostasis or triglyceride levels. All the other patients were classified as responders to metreleptin for either glucose and/or triglyceride control.

4.4 | 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; Table S2). One patient with an autoimmune form of GLD developed neutralizing anti-metreleptin autoantibodies and had concomitantly worse metabolic values after 45 months of treatment. One patient developed skin allergy to metreleptin, leading to treatment interruption after 1 month of treatment.

4.5 | Metabolic changes in patients switched from metreleptin to GLP-1 receptor agonist therapy during follow-up

Seven lipodystrophy patients (three with GLD and four with PLD) were switched from metreleptin to GLP-1 receptor agonist therapy. They received metreleptin for a median (IQR) of 77 (34-87) months, then GLP-1 analogues, namely, dulaglutide for five patients and liraglutide for two patients, for 20 (6-23) months. GLP-1 analogues were used with antidiabetic doses (1.5 mg/week for dulaglutide and 1.8 mg/d for liraglutide). We did not observe any significant difference between BMI ($P = 0.44$), HbA1c levels ($P = 0.30$), fasting triglyceride levels ($P = 0.81$) or albuminuria ($P = 0.16$) after metreleptin or GLP-1 receptor agonist therapy in those patients (Table S4). However, considering only the three patients with GLD, all were treated only transiently with GLP-1 analogues, for 3, 6 and 20 months, and all were restarted with metreleptin thereafter. Indeed, HbA1c increased in all three patients (by 0.8, 0.5 and 0.1pt, respectively), and triglycerides increased in two out of three patients during GLP-1 analogue treatment. The four patients with PLD were treated with metreleptin for between 18.5 and 85.0 months, then switched to GLP-1 analogues, and none of these patients restarted metreleptin thereafter. Their median HbA1c values were 7.7% (61 mmol/mol) on metreleptin then 7.9% (63 mmol/mol) on GLP-1 analogues. The median serum triglyceride level in these patients was 6.3 mmol/L on metreleptin then 2.2 mmol/L on GLP-1 analogues.

5 | DISCUSSION

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

Importantly, the study confirms that metreleptin treatment is efficient, in a sustainable manner, in reducing hyperglycaemia and hypertriglyceridaemia in patients with GLD. Conversely, the 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 through 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 HAS,[23] serum leptin <4 ng/mL, HbA1c >8% (64 mmol/mol) 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 treatment programmes before marketing authorization, which could explain why patients with PLD had lower median HbA1c (7.7[7.1-9.1]%, 61 [54-76] mmol/mol) and triglyceride values (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, the two groups had comparable metabolic markers at baseline, even though patients with PLD had a 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] In the

present study, in patients with PLD, BMI and fasting triglycerides, but not HbA1c, albuminuria or liver enzymes, significantly improved in the short term with metreleptin therapy, in line with previous observations.[18,20,33,34] The decrease in triglyceride levels was in the same range as that recently reported in 36 patients with PLD included in clinical trials (−28.7%).[13] In that same study, HbA1c decreased by a mean of −0.61 pt in patients with PLD, compared to −2.16 pt 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 the 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. Similarly, in clinical trials including patients with PLD, insulin therapy at baseline was associated with a smaller decrease in HbA1c after 1 year of 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 β-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 β-cell function only.[13] Furthermore, patients with PLD were older than patients with GLD, and older age has been suggested to beassociated with decreased β-cell mass.

In our study, patients with PLD showing a favourable response to metreleptin with regard to glucose homeostasis had lower serum leptin levels than nonresponders. 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 sensitivities of the leptin assays currently available.[28] Nevertheless, baseline serum leptin level, assessed by the same assay, could be an important criterion for the indication of metreleptin therapy, as observed in the present study. We failed to identify other predictive factors for metreleptin efficacy. Larger patient sample sizes, as reached through international rare diseases registries,[38] could help us to understand the role of factors such as LD aetiologies, the genotypes involved or the 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 achieve a favourable 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 reported, one patient with autoimmune GLD developed anti-metreleptin antibodies, leading to secondary inefficacy of metreleptin, and one patient had allergy to metreleptin.[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-1 receptor agonists after cessation of metreleptin therapy. Due to the effects of GLP-1 receptor 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-1 receptor agonists following metreleptin therapy in a real-life setting. Importantly, metreleptin was restarted in all three patients with GLD who were switched on GLP-1 receptor agonists, due to deterioration of glucose and triglycerides values. These data should be considered with caution in this very low number of patients, whose adherence to the medication was not monitored. It will certainly be useful to compare metreleptin and GLP-1 receptor agonist treatments in a larger cohort of patients. Similarly, the efficacy of sodium-glucose cotransporter-2 (SGLT2) inhibitors with regard to the 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 LD 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 (SGLT2 inhibitors were approved in April 2020). We did not have access to data on adherence to treatment, which is a potential 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 centres within our National Rare Disease Reference network.

The results of our observational study show 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 in this therapeutic decision. Metreleptin treatment should be regularly re-evaluated and stopped if inefficient. In addition, patients with LD may require greater educational support. Studies in larger cohorts and double-blind randomized controlled trials are needed to better evaluate the metabolic efficacy of metreleptin treatment in PLD, and to define the predictive factors of response.

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CONFLICTS OF INTEREST

Camille Vatier, Corinne Vigouroux and Marie-Christine Vantyghem report meeting fees from Aegerion Pharmaceuticals. Héléna Mosbah reports educational fees from Amryt.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14726.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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