BRIEF REPORT

Proopiomelanocortin Deficiency Treated with a Melanocortin-4 Receptor Agonist

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SUMMARY

Patients with rare defects in the gene encoding proopiomelanocortin (*POMC*) have extreme early-onset obesity, hyperphagia, hypopigmentation, and hypocortisolism, resulting from the lack of the proopiomelanocortin-derived peptides melanocyte-stimulating hormone and corticotropin. In such patients, adrenal insufficiency must be treated with hydrocortisone early in life. No effective pharmacologic treatments have been available for the hyperphagia and obesity that characterize the condition. In this investigator-initiated, open-label study, two patients with proopiomelanocortin deficiency were treated with setmelanotide, a new melanocortin-4 receptor agonist. The patients had a sustainable reduction in hunger and substantial weight loss (51.0 kg after 42 weeks in Patient 1 and 20.5 kg after 12 weeks in Patient 2).

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Melanocyte-stimulating hormone, which is produced from proopiomelanocortin, plays a pivotal role in the regulation of satiety and energy expenditure. In the hypothalamic leptin–melanocortin signaling pathway, melanocyte-stimulating hormone transmits the anorexic effect of leptin through the melanocortin-4 receptor.[1] Patients with a mutation in the gene encoding proopiomelanocortin (*POMC*), a very rare condition, have early-onset obesity due to severe hyperphagia as a result of the lack of hypothalamic melanocyte-stimulating hormone. Furthermore, the lack of melanocyte-stimulating hormone at the melanocortin-1 receptor in melanocytes and hair follicles may lead to pale skin and red hair. In addition, affected persons have secondary hypocortisolism due to the lack of proopiomelanocortin-derived corticotropin. Therefore, in the neonatal period, they are prone to hypoglycemia, hyperbilirubinemia, and cholestasis.

The symptoms related to the lack of corticotropin can be fully reversed with hydrocortisone. In contrast, the early-onset obesity and hyperphagia can only be treated symptomatically, with very limited success.[2] Whether affected persons have increased risks of weight-related cardiovascular disease, type 2 diabetes, and other obesity-related conditions is unclear. However, the absence of older adult patients with proopiomelanocortin deficiency might point to high mortality in earlier adulthood. We now present our experience in using a melanocortin-4 receptor agonist, setmelanotide, to treat severe obesity and hyperphagia in two patients with proopiomelanocortin deficiency.

METHODS

STUDY MEDICATION

Setmelanotide, an eight-amino-acid cyclic peptide also known as RM-493, is a melanocortin-4 receptor agonist (50% effective concentration [EC_{50}], 0.27 nM).[3] Setmelanotide has been administered to more than 200 obese patients who were not known to have genetic defects. In short-term phase 1b studies, an average weight loss of approximately 1 kg per week has been observed for up to 4 weeks. Although previous melanocortin-4 receptor agonists were found to have important side effects, such as hypertension and increased erections,[4,5] setmelanotide, to date, has been associated with few, if any, signs of increased blood pressure[6] or other adverse effects. Therefore, setmelanotide potentially offers a mechanism-based treatment of the obesity in proopiomelanocortin deficiency, in effect providing a substitute for the absent melanocyte-stimulating hormone that could bind to the melanocortin-4 receptor and then activating it.

Consequently, we designed an investigator-initiated, phase 2, nonrandomized, open-label pilot study of setmelanotide (EudraCT number, 2014-002392-28; ClinicalTrials.gov number, NCT02507492) involving two adult patients with proopiomelanocortin deficiency, in cooperation with Rhythm Pharmaceuticals, which provided the study medication and regulatory support. The study was approved by an ethics committee of the federal state of Berlin (14/0344), and each patient provided written informed consent. The protocol is available with the full text of this article at NEJM.org.

PRESTUDY EVALUATION

At baseline, Patient 1 weighed 155.0 kg, and her height was 176.5 cm (body-mass index [BMI, the weight in kilograms divided by the square of the height in meters], 49.8; BMI standard-deviation score, 4.52). Patient 2 weighed 152.8 kg, and her height was 168.0 cm (BMI, 54.1; BMI standard-deviation score, 4.78). Both patients were markedly hyperphagic, as indicated by a score of 9 on a Likert hunger scale ranging from 0 (no hunger) to 10 (extreme hunger). Psychological evaluations revealed constant extreme dissatisfaction with their quality of life owing to the marked obesity.

Prestudy assessments included an oral glucose-tolerance test, a gonadotropin-releasing hormone stimulation test, measurement of serum leptin and fasting blood glucose levels, bioelectrical impedance analysis, indirect calorimetry (VMAX Encore system, CareFusion), heart-rate and blood-pressure monitoring (with frequent measurements of each during the 12 hours after the first injection and after each escalation in dose and with measurement of blood pressure at home three times daily), scoring of hunger, and dermatologic and psychological examinations. Fasting insulin levels were markedly elevated, reflecting severe insulin resistance. Other laboratory values that were measured at baseline were within normal limits, except for lipoprotein(a) in Patient 2 (Table 1). These measurements were repeated after 13 and 42 weeks of treatment in Patient 1 and after 12 weeks in Patient 2. (For a detailed description of the methods, see the Supplementary Appendix, available at NEJM.org.)

PHENOTYPES OF THE PATIENTS

In Patient 1, who was a 21-year-old woman from Germany, a compound heterozygous loss-of-function *POMC* mutation had been identified when she was 4 years of age.[7] She had received a diagnosis of adrenal insufficiency after birth. Her older brother had died at 7 months of age from liver failure that was considered to be secondary to undiagnosed hypocortisolism. Symptoms of adrenal failure had resolved in Patient 1 with hydrocortisone-replacement therapy consisting of 12.7 mg of hydrocortisone per square meter of body-surface area (35 mg per day). However, severe hyperphagia and extreme obesity had developed by the third month of life (Fig. 1A). Despite enormous efforts by the patient and her family, her weight gain could not be controlled — after any period of short-term weight loss, weight regain occurred immediately.

Her extreme obesity resulted in metabolic disturbances (e.g., hyperinsulinemia), starting in adolescence. At the time of the study, breast development had stopped at Tanner stage 2, pubic hair was absent, and she had not undergone menarche, all symptoms that are associated with leptin and leptin-receptor deficiencies.[9,10]

Patient 2 was a 26-year-old woman from France, in whom a homozygous *POMC* mutation

Table 1. Body Weight and Composition, Energy Expenditure, and Metabolic Variables during Treatment.*

Variable	Patient 1			Patient 2		Normal Value or Range
	Prestudy	13 Weeks (End of Main Study)	42 Weeks (Extension)	Prestudy	12 Weeks (End of Main Study)	
Weight						
Value (kg)	155.0	129.2	104.0	152.8	132.3	
Change from prestudy (%)		–16.6	–32.9		–13.4	
Body-mass index						
Value	49.8	41.5	33.4	54.1	46.9	
Change from prestudy		–8.3	–16.4		–7.2	
REE (kcal/24 hr)						
Value	2408	2141	1537	2124	1815	
Change from prestudy		–267	–871		–309	
REE per kg of body weight						
Value	15.5	16.6	14.8	13.9	13.7	
Change from prestudy		1.1	–0.7		–0.2	
REE per unit of lean body mass						
Value	35.1	33.0	26.7	35.7	31.8	
Change from prestudy		–2.1	–8.4		–3.9	
Lean body mass (kg)						
Value	68.7	64.8	57.5	59.6	57.0	
Change from prestudy		–3.9	–11.2		–2.6	
Fat mass (kg)						
Value	88.4	65.2	47.3	93.2	75.3	
Change from prestudy		–23.2	–41.1		–17.9	
Cholesterol (mg/dl)						
Total	166	140	134	144	112	<200
HDL	33	28	35	54	37	>45
LDL	113	86	93	83	62	<130
Triglycerides (mg/dl)	99	99	63	63	66	<200
Lipoprotein(a) (nmol/liter)	30.5	29.8	10.5	170.6	112.4	<72
Glycated hemoglobin (%)	5.0	5.0	4.5	5.4	5.1	6.0
IGF-1 (ng/ml)	50.1	91.7	42.4	51.8	32.7	114–442
Leptin (pg/ml)	45,215	16,766	3814	100,311	49,587	†
Fasting insulin (mU/liter)	26.7	8.3	4.5	9.8	3.9	3–20
Fasting glucose (mg/dl)	65	67	70	76	64	55–110
Luteinizing hormone (U/liter)						
0 min	4.4	5.3	5.7	10.1	5.3	1.5–16.6
30 min	14.8	19.0	15.6	25.3	40.3	26.4–96.3
Follicle-stimulating hormone (U/liter)						
0 min	2.0	2.2	3.0	10.1	2.7	3.9–5.7
30 min	3.0	3.4	4.0	13.9	4.9	9.3–19.7

* Body composition was assessed by means of bioelectrical impedance analysis, and energy expenditure was assessed by means of indirect calorimetry. Gonadotropin-releasing hormone stimulation tests, which were performed to analyze secretion of luteinizing hormone and follicle-stimulating hormone, showed insufficient secretion of follicle-stimulating hormone in Patient 1. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for insulin to picomoles per liter, multiply by 6.945. To convert the values for glucose to millimoles per liter, multiply by 0.05551. HDL denotes high-density lipoprotein, IGF-1 insulin-like growth factor 1, LDL low-density lipoprotein, and REE resting energy expenditure.

† The normal range for leptin varies according to body weight and pubertal stage and has not been determined for the assay used for this measurement.

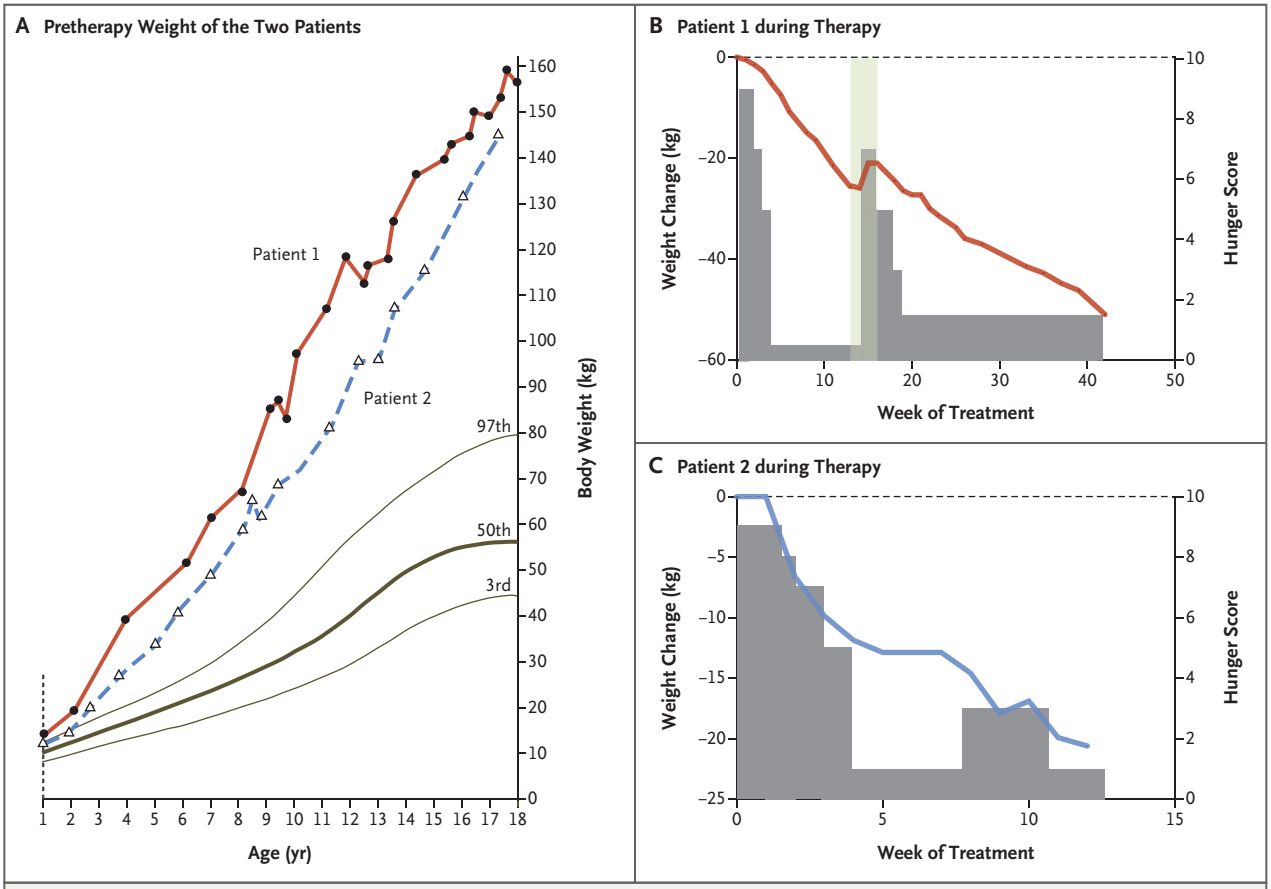

Figure 1. Pretherapy Weight and Changes in Weight and Hunger Scores during Therapy.

Panel A shows the body weight of Patient 1 and Patient 2 in the first 18 and 17 years of life, respectively, as compared with normal percentiles for girls of their age.[8] Panel B shows weight change (left scale and red line) and hunger scores (on a scale of 0 [no hunger] to 10 [extreme hunger]; right scale and gray bars) in Patient 1 during therapy. After the initial 13 weeks of treatment, Patient 1 entered a 3-week off-treatment phase (marked in green), before treatment was restarted. Data are shown to 42 weeks. Panel C shows weight change (blue line) and hunger scores (gray bars) in Patient 2 during the initial 12 weeks of therapy.

had been identified.[11] She had received hydrocortisone-replacement therapy since her first weeks of life (most recent hydrocortisone dose, 13.1 mg per square meter [35 mg per day]). Severe hyperphagia and extreme obesity had developed early in life, as in Patient 1 (Fig. 1A). An older brother had died soon after birth from hepatic insufficiency that was considered to be due to undiagnosed corticotropin insufficiency.

Both patients had been considered for bariatric surgery, because that was thought to be the only potentially effective procedure for their obesity. However, before any procedure, we considered the possibility of treatment with the newly identified melanocortin-4 receptor agonist setmelanotide. We contacted Rhythm Pharmaceuticals to provide this new peptide for an investigator-initiated clinical trial.

RESULTS

WEIGHT LOSS AND CHANGE IN HUNGER SCORES

Setmelanotide was injected subcutaneously once daily, starting at a dose of 0.25 mg in Patient 1 and 0.5 mg in Patient 2. This was followed by dose escalation in weekly increments, to 0.5 mg per day in Patient 1 and then, in both patients, to 1.0 mg and finally to 1.5 mg. At doses below 1.0 mg, the patients' weight loss was moderate, with few changes in their sensation of hunger. However, both patients reported a substantial reduction in hunger with increasing doses: the Likert hunger score decreased to 5 at a daily dose of 1.0 mg of setmelanotide, and appetite was nearly abolished at the 1.5-mg dose (Likert hunger score, 0 or 1). With this change in satiety, Patient 1 had a stable weight loss of approximately 2 kg per week at

the 1.5-mg dose, leading to a total weight loss of 25.8 kg after the initial 13 weeks of treatment (16.6% of her initial body weight; end body weight, 129.2 kg; BMI, 41.5; BMI standard-deviation score, 3.86) (Fig. 1B). Patient 2 had a similar weight reduction, with a total weight loss of 20.5 kg at 12 weeks, equivalent to 1.7 kg per week (13.4% of the initial body weight) (Fig. 1C).

Owing to regulatory obligations (available toxicology data for only 3 months' duration), the treatment in Patient 1 was stopped after 13 weeks. Soon thereafter, she reported markedly increased hunger (Likert hunger score, 7) and regained some weight (4.8 kg). The patient then had an episode of anger and dejection, which she believed was connected to the reversal in her clinical course. For that reason, setmelanotide was restarted (after 3 weeks of nonuse). Immediately after reinitiating setmelanotide (at a dose of 1.0 mg for 4 weeks and 1.5 mg thereafter), hunger decreased and weight loss resumed. During this second treatment phase, Patient 1 lost 1 to 2 kg per week, ultimately losing 51.0 kg after 42 weeks of treatment (32.9% of her initial body weight). At that point, her BMI was 33.4 (BMI standard-deviation score, 2.93).

METABOLISM

Blood glucose values in both patients remained in the normal range (fasting and after glucose challenge) during the study. Prestudy elevated insulin levels, which signified marked insulin resistance, decreased substantially with setmelanotide treatment (Fig. 2A, and Fig. S2 in the Supplementary Appendix). Total resting energy expenditure declined after weight loss. However, resting energy expenditure per unit of lean body mass was only mildly reduced (Table 1). The reduction in body weight was mainly due to loss of body fat, which was accompanied by a substantial decrease in serum leptin levels (Table 1).

BLOOD PRESSURE

Blood pressure was carefully assessed, because an increase in blood pressure had previously been observed with other melanocortin-4 receptor agonists.[4,12,13] However, blood pressure did not increase during any dose escalation in either patient. In Patient 1, the systolic and diastolic blood pressure, as well as heart rate, were reduced during the extension phase after weight loss, a finding of clinical significance (Fig. 2B, 2C, and 2D).

PUBERTAL DEVELOPMENT

Patients with proopiomelanocortin deficiency appear to have impaired secretion of follicle-stimulating hormone, as do patients with leptin deficiency.[14] After 13 weeks as well as after 42 weeks of treatment in Patient 1 and after 12 weeks in Patient 2, standard gonadotropin-releasing hormone stimulation tests and clinical examinations showed no signs of progression of pubertal development (Table 1).

SAFETY AND ADVERSE EVENTS

Both patients reported dry mouth, though infrequently, and mild pain and induration at the injection site for a few hours after injection during the first few days of treatment. Skin nevi that were present before drug administration and general skin color darkened considerably over time, and the hair color of both patients gradually changed from red to dark brown, suggesting that setmelanotide may also act at the closely related melanocortin-1 receptor (Figs. S1 and S2 in the Supplementary Appendix). Safety laboratory values remained stable (Table 1). We observed no serious adverse events, and neither patient discontinued treatment owing to adverse events, which included mild episodes of fatigue, sadness, or emptiness. (A detailed description of adverse events is provided in Table S1 in the Supplementary Appendix.)

DISCUSSION

We describe a mechanism-based therapy for hyperphagia and obesity in two patients with proopiomelanocortin deficiency. Such therapy is based on the use of an agonist that substitutes for the lack of melanocyte-stimulating hormone binding at its receptor and thus replaces the missing melanocyte-stimulating hormone activity in the hypothalamic leptin–melanocortin pathway.[7] Setmelanotide appeared to completely reverse hyperphagia, leading to impressive weight loss and normalization of insulin resistance. More important, both patients reported a dramatic improvement in their quality of life after the initiation of setmelanotide therapy. Moreover, the substantial and ongoing reduction in body weight was similar to the changes observed after leptin administration in patients with leptin deficiency. The current study treated two of the three known adult patients with proopiomelanocortin deficiency.[7,11] On the basis of the

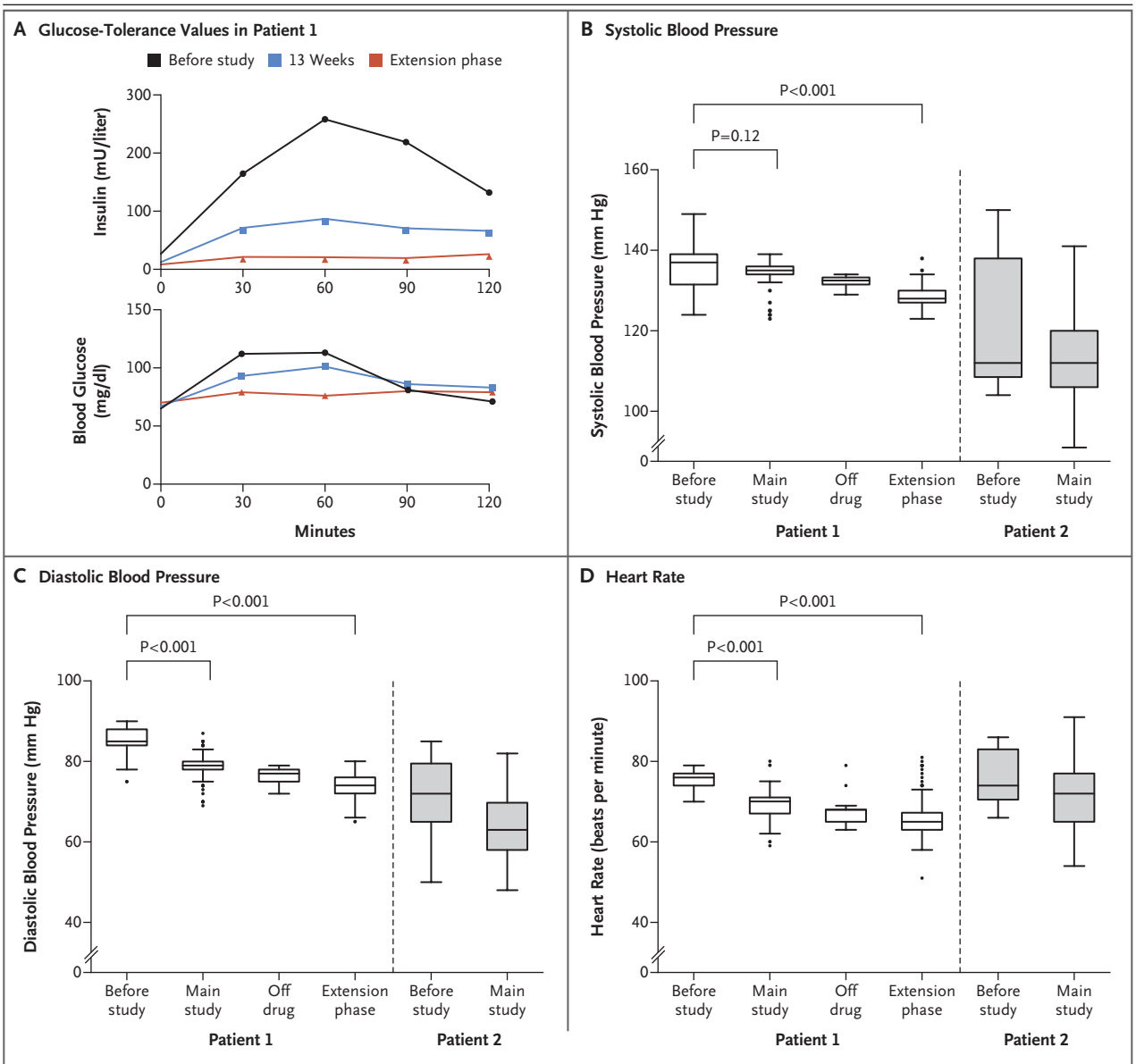

Figure 2. Metabolic Variables, Blood Pressure, and Heart Rate during Therapy.

Oral glucose-tolerance testing (Panel A) was performed in Patient 1 before the initiation of the study (black line), after 13 weeks (blue line), and during the extension phase (red line). Blood sugar levels were relatively stable in all tests; however, insulin sensitivity improved significantly and normalized during the course of setmelanotide therapy. Blood pressure was measured three times per day by the patients and over a period of 12 hours after the start of therapy and after each dose escalation. Shown are systolic blood pressure (Panel B), diastolic blood pressure (Panel C), and the heart rate (Panel D) before the study (135 individual measurements), during the main study (279 individual measurements), during the reversibility off-treatment phase (39 individual measurements), and during the extension phase (302 individual measurements) in Patient 1 and before the study (20 individual measurements) and during the first study part (75 individual measurements) in Patient 2. In the box plots, the horizontal line inside each box indicates the median, the top and bottom of the box indicate the interquartile range, the I bars indicate the 5th and 95th percentiles, and the squares indicate outliers.

current data, it appears feasible to consider the use of setmelanotide as a treatment option in children and adolescents with proopiomelanocortin deficiency.[10,15-17]

This open-label, uncontrolled, pilot phase 2 study has obvious limitations, because only two patients were treated. Nevertheless, the use of setmelanotide allowed these patients to lose substantial weight, and neither patient had been able to lose a clinically important amount of

weight before this treatment. Moreover, there was a clear dose–response relationship with respect to both hunger and weight loss during dose escalation. In addition, during the off-treatment phase in Patient 1, hunger and weight gain returned almost immediately and were reversed after the resumption of treatment.

The efficacy of setmelanotide to reduce body weight in the two patients suggests that this melanocortin-4 receptor agonist might be effective in the treatment of other monogenic defects of the hypothalamic leptin–melanocortin pathway, such as leptin-receptor deficiency and PCSK1 deficiency, for which no effective pharmacologic therapy is available. We speculate that patients with other rare genetic defects that are related to reduced proopiomelanocortin activity, such as obese persons with epigenetic variations in *POMC*[18] and patients affected by the Prader–Willi syndrome,[19] might also have a response to treatment with setmelanotide.

Both patients described here had very high leptin levels before treatment, suggesting leptin resistance. In patients with proopiomelanocortin deficiency, the leptin signal is probably not properly transduced into anorexigenic responses, given the lack of melanocyte-stimulating hormone. Setmelanotide substitutes for melanocyte-stimulating hormone and binds at its receptor, thus overcoming leptin resistance. On the basis of the observation that obese patients without known genetic abnormalities have severe leptin resistance and regain weight owing to a post-dieting increase in appetite, we speculate that setmelanotide may also be effective in nongenetic forms of obesity.

In conclusion, open-label treatment with setmelanotide, a melanocortin-4 receptor agonist, in two patients with proopiomelanocortin deficiency led to a reduction in hunger and substantial and sustained weight loss.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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REFERENCES

1. Farooqi IS, O'Rahilly S. Mutations in ligands and receptors of the leptin-melanocortin pathway that lead to obesity. Nat Clin Pract Endocrinol Metab 2008;4:569-77.
2. Farooqi S, O'Rahilly S. Genetics of obesity in humans. Endocr Rev 2006;27:710-8.
3. Chen KY, Muniyappa R, Abel BS, et al. RM-493, a melanocortin-4 receptor (MC4R) agonist, increases resting energy expenditure in obese individuals. J Clin Endocrinol Metab 2015;100:1639-45.
4. Greenfield JR, Miller JW, Keogh JM, et al. Modulation of blood pressure by central melanocortinergic pathways. N Engl J Med 2009;360:44-52.
5. Molinoff PB, Shadiack AM, Earle D, Diamond LE, Quon CY. PT-141: a melanocortin agonist for the treatment of sexual dysfunction. Ann N Y Acad Sci 2003;994:96-102.
6. Gottesdiener KHC, Van der Ploeg L, Fiedorek F, Hylan M, Louis W, Lasseter K. Analysis of the synthetic peptide setmelanotide (RM-493), a melanocortin-4 receptor (MC4R) agonist, on cardiovascular parameters in three phase1b/2a studies. Presented at ObesityWeek 2015, Los Angeles, November 2–6, 2015.
7. Krude H, Biebermann H, Luck W, Horn R, Brabant G, Grüters A. Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. Nat Genet 1998;19:155-7.
8. Kromeyer-Hauschild K, Wabitsch M, Kunze D, et al. Perzentile für den Body-mass-Index für das Kindes- und Jugendalter unter Heranziehung verschiedener deutscher Stichproben. Monatsschrift Kinderheilkunde 2001;149:807-18.
9. Farooqi IS, Jebb SA, Langmack G, et al. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. N Engl J Med 1999;341:879-84.
10. Clément K, Vaisse C, Lahlou N, et al. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature 1998;392:398-401.
11. Clément K, Dubern B, Mencarelli M, et al. Unexpected endocrine features and normal pigmentation in a young adult patient carrying a novel homozygous mutation in the POMC gene. J Clin Endocrinol Metab 2008;93:4955-62.
12. Kuo JJ, da Silva AA, Tallam LS, Hall JE. Role of adrenergic activity in pressor responses to chronic melanocortin receptor activation. Hypertension 2004;43:370-5.
13. Ni XP, Butler AA, Cone RD, Humphreys MH. Central receptors mediating the cardiovascular actions of melanocyte stimulating hormones. J Hypertens 2006;24:2239-46.
14. Montague CT, Farooqi IS, Whitehead JP, et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature 1997;387:903-8.
15. Farooqi IS, Drop S, Clements A, et al. Heterozygosity for a POMC-null mutation and increased obesity risk in humans. Diabetes 2006;55:2549-53.
16. Mendiratta MS, Yang Y, Balazs AE, et al. Early onset obesity and adrenal insufficiency associated with a homozygous POMC mutation. Int J Pediatr Endocrinol 2011;2011:5.
17. Samuels ME, Gallo-Payet N, Pinard S, et al. Bioinactive ACTH causing glucocorticoid deficiency. J Clin Endocrinol Metab 2013;98:736-42.
18. Kuehnen P, Mischke M, Wiegand S, et al. An Alu element-associated hypermethylation variant of the POMC gene is associated with childhood obesity. PLoS Genet 2012;8(3):e1002543.
19. Mercer RE, Michaelson SD, Chee MJ, Atallah TA, Wevrick R, Colmers WF. Magel2 is required for leptin-mediated depolarization of POMC neurons in the hypothalamic arcuate nucleus in mice. PLoS Genet 2013;9(1):e1003207.