Outcomes in patients with lipodystrophy receiving treatment with metreleptin via the National Severe Insulin Resistance Service at Addenbrookes Hospital, Cambridge

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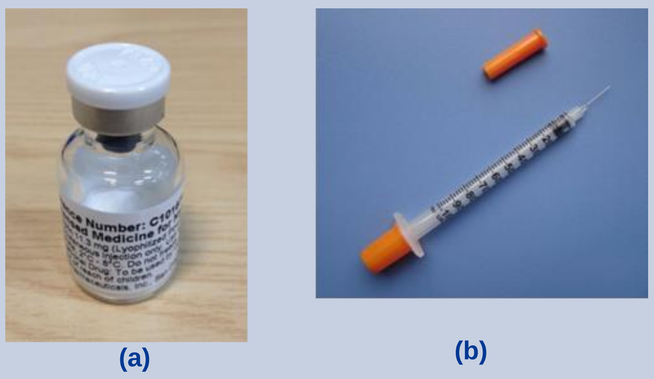
Abstract

Lipodystrophy is a rare condition characterized by complete or partial loss of subcutaneous adipose tissue. Lipodystrophy is associated with severe insulin resistance, diabetes, hypertriglyceridaemia, pancreatitis and non-alcoholic fatty liver disease. The mainstay of treatment is a low fat, energy-restricted diet. Deficiency of the appetite-regulating hormone leptin causes difficulty in adherence to dietary restrictions. Metreleptin replacement therapy has been available for several years to lipodystrophy patients attending the National Severe Insulin Resistance (NSIR) Service via a compassionate use programme run by Amryt Pharmaceuticals. NICE has recently approved NHS funding for a subgroup of patients with lipodystrophy and leptin deficiency. We describe outcomes in 25 lipodystrophy patients treated with metreleptin in addition to diet and standard medical therapies.

Background

The National Severe Insulin Resistance (NSIR) Service was established in 2011 with funding from NHS England to provide diagnosis and multi-disciplinary care of adults and children with severe insulin resistance and/or lipodystrophy. Metreleptin (Myalepta, Amryt) has a UK marketing authorisation as a replacement therapy to treat the complications of leptin deficiency in patients with lipodystrophy. Metreleptin is administered daily by subcutaneous injection. It is supplied as a powder which is reconstituted with water for injection. The starting daily dose is 2.5 mg and 5 mg for men and women weighing over 40 kg respectively. Dose adjustments can be made up to a maximum daily dose of 10 mg. It is delivered to the patient by the homecare company, Polarspeed. The most common adverse events in clinical trials included weight loss, hypoglycaemia, fatigue, injection site reactions, neutralising antibodies, decreased appetite, nausea, headache, abdominal pain, menorrhagia and alopecia. In the UK metreleptin can currently only be prescribed by the NSIR service.



(a) (b)

Figure 1 : a) Metreleptin in vial in powdered form b)syringe/needle used for s/c injection

NICE criteria for metreleptin therapy 2021

1.1 Metreleptin is recommended as an option for treating the complications of leptin deficiency in lipodystrophy for people who are 2 years and over and have generalised lipodystrophy.

1.2 Metreleptin is recommended as an option for treating the complications of leptin deficiency in lipodystrophy for people who are 12 years and over, have partial lipodystrophy, and do not have adequate metabolic control despite having standard treatments. It is only recommended if they have an HbA1c level above 7.5%, or fasting triglycerides above 5.0 mmol/litre, or both.

1.3 This recommendation is not intended to affect treatment with metreleptin that was started in the NHS before this guidance was published.

Methods

A retrospective analysis was performed comparing fasting metabolic variables before starting metreleptin therapy to results at the patient's most recent clinic visit. Inclusion criteria included a clinical diagnosis of lipodystrophy, metreleptin therapy and at least two attendances at the NSIR outpatient clinic.

Patient demographics

25 patients were included, 21 are female, median age 31 years (range 1-54). 7 patients have congenital generalized lipodystrophy, 3 acquired generalized lipodystrophy, 14 familial partial lipodystrophy (12 *LMNA* and 2 *PPARG* mutation) and 1 acquired partial lipodystrophy.

Results

The patients were followed up for median 8.3 years (range 2.5-9.3). Median baseline HbA1c was 71.5mmol/mol (IQR 50.2,83.8), and fasting triglycerides were 3.4mmol/l (IQR 1.4,4.4mmol/l), compared with HbA1c 64.0mmol/mol (IQR 44.0,69.0) and fasting triglycerides 3.1mmol/l (IQR 1.7,6.1) at the most recent visit. Most patients reported a significant reduction in hyperphagia with metreleptin which improved quality of life. Three patients have died since commencing metreleptin therapy, one has had a liver transplant and one a renal transplant

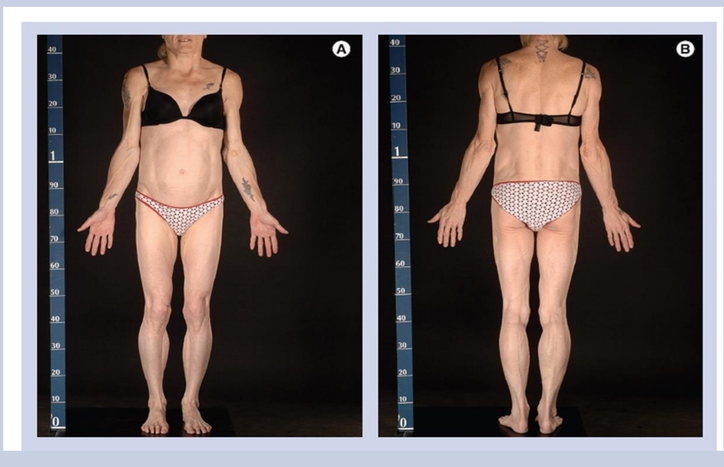


Figure 2 : 51 year old female with acquired generalised lipodystrophy. Note absence of subcutaneous fat. (Many thanks to the patient who consented for her photograph to be included in this poster to raise awareness of lipodystrophy)

Discussion

Overall, patients with lipodystrophy treated with metreleptin therapy attending the NSIR service have shown a modest improvement in metabolic control which has been maintained over several years. The baseline age, metabolic status and response of individual patients in this cohort varied widely. Variations in response to therapy may be partly dependent on compliance. The metabolic criteria for starting metreleptin therapy in patients with partial lipodystrophy recently stipulated by NICE are now more severe than for patients who participated in the patient access programme which was in place before NHS funding was approved. Early involvement of specialised multi-disciplinary teams with regular follow up and monitoring of metabolic control is important for patients with lipodystrophy to help optimise interventions and reduce long term complications. Combinations of various pharmacological regimes with lifestyle interventions are necessary. Close interaction is required between patients and health care teams to individualise plans accounting for a patient's diagnosis, psychology and lifestyle.

Conclusion

Patients with lipodystrophy and leptin deficiency attending the NSIR service, treated with metreleptin, reported a reduction in hyperphagia. There was also a sustained improvement in metabolic status in most patients. Morbidity and mortality rates in this patient group remain high. The availability of NHS funding will enable earlier access to metreleptin therapy and secures continuing therapy in patients already prescribed metreleptin, both of which may improve long term outcomes.

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