

Recombinant human insulin-like growth factor-1 treatment in patients with insulin receptor mutations resulting in Donohue syndrome: a 10-year experience in a tertiary centre.

N Improda¹, H Katugampola¹, P Shah¹, H Gordon¹, R Amin¹, CJ Peters¹, RK Semple³, MT Dattani^{1,2}

Great Ormond Street Hospital for Children
NHS Foundation Trust

¹Genetics & Genomic Medicine Programme, UCL Institute of Child Health, UK;
²The London Centre for Paediatric Endocrinology & Diabetes, Great Ormond Street Hospital for Children NHS Foundation Trust, UK;
³University of Cambridge Wellcome Trust-MRC Institute of Metabolic Science, Cambridge, UK



BACKGROUND

Donohue syndrome is the most severe form of insulin-resistance due to autosomal recessive mutations in the insulin receptor gene. Previous reports demonstrate a role for recombinant human IGF-1 (rhIGF-1), however optimal treatment strategy remains unclear.

CASE SERIES

- Four males with genetically confirmed DS treated with bolus rhIGF-1 for a period ranging from 0.3 to 10 years (see Table 1).
- ✓ All the patients had no IGF-1 response on an IGF-1 generation test.
- ✓ No long-term side effects of rhIGF-1 were reported.

Table 1

Patient	1	2	3	4
Current age (years)		11.5		0.8
Age death (years)/cause of death	14.7/unknown(recurrent sepsis and ketoacidosis)		1.3/liver dysfunction; respiratory infection	
Mutation	p.R1092Q (tyrosine kinase domain)	paternal c.576C>G, p.I119M and maternal c.3334C>T, p.R1039X	p.G84Q (alpha subunit)	c.1924T>C, p.W642R
Age (years) commencement rhIGF-1	1.9; restarted at 13.4	1.6 (IGF-1+IGFBP3 until age 8)	0.1	0.1
Therapy duration (years)	3.3 (2 trials)	10	0.3	0.5
Height/weight SDS pre-rhIGF-1	-7.1/ -5.48	-1.96/-2.36	-2.1/-5	-7/-5.45
HbA1c (%) pre-rhIGF-1	18.7	4.9	na*	5.9
Starting rhIGF-1 dose (mcg/kg/day)	40	80	67	70
Frequency	once daily	12 hourly	12 hourly	12 hourly
Latest rhIGF-1 dose (mcg/kg/day)	590	325	116	150
Frequency	once daily	8 hourly	12 hourly	12 hourly
Latest feeding	Oral	Oral/ continuous enteral overnight	Continuous parenteral	Bolus/continuous enteral overnight
Fasting time pre IGF-1/ on rhIGF-1	na*/12 hours	2 hours/ 8 hours	1-2 hours/1-2 hours	2 hours/2 hours
Latest Height/Weight SDS	-7.1/-4.2	-2.89/-1.7	na*/-4.95	-7.19/-5.12
Latest HbA1c (%) on rh-IGF-1	11.5	6.7	na*	5.2
Latest daily mean glucose (mmol/L)	24.3	9.7	5.7	9.2

*na – not available

CONCLUSIONS

- High dose rhIGF-1 is safe and can mitigate metabolic abnormalities in patients with Donohue Syndrome.
- We report survival into adolescence in a patient with no severe comorbidities, in whom the fast tolerance dramatically improved on rhIGF-1 and long-term growth was relatively preserved.
- Although a twice daily regimen is the most frequently reported, 8 hourly administration may be required to optimise metabolic control, as demonstrated in Patient 2.

