# 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.

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## 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)<br><br>Age death (years)/cause of death | 14.7/unknown(recurrent sepsis and ketoacidosis) | 11.5 | 1.3/liver dysfunction; respiratory infection | 0.8 |
| 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<br><br>Therapy duration (years) | 1.9; restarted at 13.4<br><br>3.3 (2 trials) | 1.6 (IGF-1+IGFBP3 until age 8)<br><br>10 | 0.1<br><br>0.3 | 0.1<br><br>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)<br><br>Frequency | 40<br><br>once daily | 80<br><br>12 hourly | 67<br><br>12 hourly | 70<br><br>12 hourly |
| Latest rhIGF-1 dose (mcg/kg/day)<br><br>Frequency | 590<br><br>once daily | 325<br><br>8 hourly | 116<br><br>12 hourly | 150<br><br>12 hourly |
| Latest feeding<br><br>Fasting time pre IGF-1/ on rhIGF-1 | Oral<br><br>na*/12 hours | Oral/ continuous enteral overnight<br><br>2 hours/ 8 hours | Continuous parenteral<br><br>1-2 hours/1-2 hours | Bolus/continuous enteral overnight<br><br>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.

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