GH therapy in children with Prader-Willi syndrome

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Introduction

- Prader-Willi syndrome affects approximately 1 in 10,000 to 1 in 30,000 people[1]

➢ Prader-Willi Syndrome is caused by lack of expression of genes on the paternally inherited chromosome 15q11.2-q13 region[2]

➢ There are three main genetic subtypes in Prader-Willi Syndrome:

1. Paternal 15q11-q13 deletion (65–75% of cases)
2. Maternal uniparental disomy 15 (20–30% of cases)
3. Imprinting defect (1–3% of cases)

- Reduced GH secretion, low peak GH response to stimulation, decreased spontaneous GH secretion and low serum IGF-I levels have been documented in Prader-Willi syndrome[1]

1. Aycan Z, et al. *J Clin Res Pediatr Endocrinol.* 2014;6(2):62–67.
2. Angulo MA, et al. *J Endocrinol Invest.* 2015;38(12):1249–1263.

GH, growth hormone; IGF-I, insulin-like growth factor I.

Clinical presentation

- Prader-Willi syndrome is a spectrum disorder; symptoms can range from mild to severe and may change throughout the patient's lifetime[1,2]

Clinical symptoms in neonates include:[2]

- Hypotonia
- Lethargy
- Feeding difficulties
- Thick saliva
- Increased head/chest circumference ratio
- Small genitalia

Clinical symptoms in older children include:[2]

- Obesity
- Developmental delay
- Short stature and/or decreased growth velocity
- Dysmorphic features
  - A narrow bifrontal diameter, almond-shaped palpebral fissures, a thin upper lip with a down-turned mouth, small hands and feet, straight borders of ulnar side of hands and of inner legs

1. Gunay-Aygun M, et al. *Pediatrics*. 2001;108:e92–96.
2. Angulo MA, et al. *J Endocrinol Invest.*. 2015;38(12):1249–1263.

Diagnosis

- Clinical diagnostic criteria established by consensus in 1993 were modified in 2001 to help identify appropriate patients for DNA testing[1]

Clinical criteria to prompt DNA testing for Prader-Willi Syndrome[1,2]

Age at Assessment	Features Sufficient to Prompt DNA Testing
Birth to 2 years	1. Hypotonia with poor suck
2–6 years	1. Hypotonia with history of poor suck 2. Global developmental delay 3. Short stature and/or decreased growth velocity 4. Hypogenitalism/hypogonadism
6–12 years	1. History of hypotonia with poor suck (hypotonia often persists) 2. Global developmental delay 3. Excessive eating (hyperphagia; obsession with food) with central obesity if uncontrolled 4. Hypogenitalism/hypogonadism
13 years through adulthood	1. Cognitive impairment; usually mild mental retardation 2. Excessive eating (hyperphagia; obsession with food) with 3. central obesity if uncontrolled 4. Hypothalamic hypogonadism and/or typical behavior problems (including temper tantrums and obsessive-compulsive features) 5. Short stature; small hands and feet

1. Gunay-Aygun M, et al. *Pediatrics*. 2001;108:e92–96.
2. Angulo MA, et al. J Endocrinol Invest.. 2015;38(12):1249–1263.

GH treatment in children with Prader Willi syndrome

- In children with PWS, human GH can help with height, weight, body mass, strength, and agility, and also may help with cognitive development.
- In addition, reports on the use of a low dose of human GH in the adult PWS population have shown positive results in the areas of bone-strengthening and the promotion of leaner muscle mass and greater energy.
- Before 1990, there were no scientific studies to show the use of human GH to be a good idea for children born with Prader-Willi syndrome.
- Even if a doctor prescribed GH, the family's health insurance plan might refuse to cover the cost because it was considered an "experimental" treatment in children with PWS.
- In June 2000, the FDA approved an application from Pharmacia Corporation (since acquired by Pfizer), the makers of Genotropin® brand recombinant growth hormone, to market and promote its product for the treatment of growth failure due to Prader-Willi syndrome.

GH treatment in children with Prader Willi syndrome

- There is no longer any doubt that growth hormone treatment can improve the health and quality of life of children with PWS.
- Although human GH treatments do not decrease appetite, these therapies together with early intervention have helped to create a whole new generation of children with PWS who are taller, slimmer, more active and alert, and who are living much longer and healthier lives.
- The questions that remain are largely individual ones:
  - how early to consider treatment?
  - when there are good reasons to stop treatment or not to use GH in a particular child?
    - Signs for upper airway obstruction, sleep apnoea, or respiratory infections should be assessed carefully!!
    - Scoliosis in PWS!

Treatment

- rhGH therapy in Prader-Willi syndrome has been used by the medical community and advocated by parental support groups since its approval in the United States in 2000 and in Europe in 2001[1]

➢ Consensus group recommendations for the use of rhGH in children and adult patients with Prader-Willi syndrome include:

rhGH treatment should be considered for patients with genetically confirmed PWS in conjunction with dietary, environmental, and lifestyle interventions

Cognitive impairment should not be a barrier to treatment, and informed consent/assent should include benefit/risk information

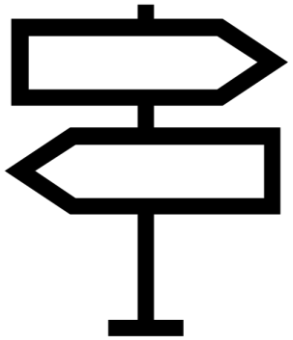
Exclusion criteria should include severe obesity, uncontrolled diabetes mellitus, untreated severe obstructive sleep apnoea, active cancer, or psychosis

Clinical outcome priorities should vary depending upon age and the presence of physical, mental, and social disability, and treatment should be continued for as long as demonstrated benefits outweigh the risks

1. Deal CL, et al. *J Clin Endocrinol Metab*. 2013:98(6):E1072–1087.

rhGH, recombinant growth hormone.

Evidence for efficacy for rhGH[1]

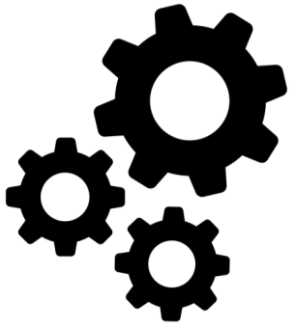


Objective

- To evaluate the response to rhGH treatment and adverse events in children with Prader–Willi syndrome from KIGS, the Pfizer International Growth Database

Method

- Patients treated with GH for at least six or seven days per week and at least one year of growth data available were included in the analysis
- 328 children were treated for one year and 161 children were treated for two years with GH



1. Craig ME, et al. *Clin Endocrinol (Oxf).* 2006;65(2):178–185.

rhGH, recombinant growth hormone.

Evidence for efficacy for rhGH

Results

- Height SDS increased significantly during treatment; the response was greater in pre-pubertal (−0·7vs.−1·8 pre-treatment) than in pubertal children (−1·5 vs.−1·8)

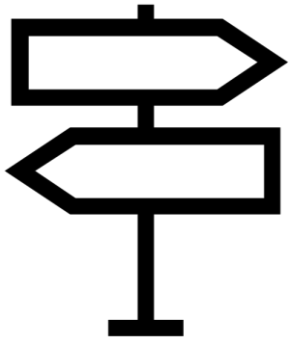
- Predictors of first-year height velocity in multiple regression analysis were:
  - GH dose
  - Body weight (positively correlated)
  - Height SDS minus mid-parental height SDS
  - Chronological age (negatively correlated)

Conclusions: Short-term growth improved in response to conventional doses of GH in children with Prader-Willi syndrome

1. Craig ME, et al. *Clin Endocrinol (Oxf).* 2006;65(2):178–185.

rhGH, recombinant growth hormone;
SDS, standard deviation score.

Evidence for efficacy for rhGH

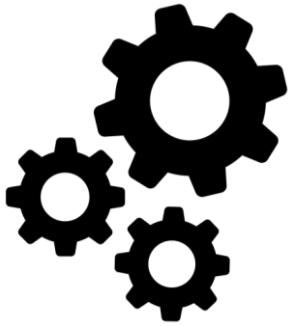


Objective

- To assess the effects of growth hormone (Genotropin®) treatment in patients with Prader-Willi syndrome: experience from KIGS (Pfizer International Growth Database)

Method

- This study followed a cohort of 22 genetically verified patients with Prader-Willi syndrome from the start of GH treatment in the KIGS database at the median age of 6.9 years (4.9–11.3) to near-adult height at 18.1 years (16.4–21.2)



1. Lindgren AC, et al. *Horm Res.* 2008;70(3):182–187.

BMI, body mass index; LBM, lean body mass; rhGH, recombinant growth hormone.

Evidence for efficacy for rhGH

Results

- Patients were treated with a median GH dose of 0.03 mg/kg/day (0.02–0.03) for a median duration of 10.2 years (6.9–11.5)

	Median Height SDS	BMI SDS	LBM SDS
At start	–1.6 SDS (–3.5 to –0.3)	1.7 SDS (0.8–3.3)	–2.6 SDS (–4.0 to –0.9)
Year 1	–0.4 SDS (–2.3 to 1.5)	1.0 SDS (0.2–2.5)*	–1.4 SDS (–2.6 to 0.1)*

- All patients reached near-adult height within mid-parental height median –0.5 SDS (–1.4 to 0.7) and 0.9 SDS (0.1–1.9) for girls and boys, respectively
- No serious side effects were reported when the caloric intake was controlled to maintain an appropriate bodyweight

Conclusions: GH treatment in children with Prader-Willi syndrome normalizes adult height and improves body composition

*p<0.05 compared with start.

1. Lindgren AC, et al. *Horm Res.* 2008;70(3):182–187.

BMI, body mass index; LBM, lean body mass; rhGH, recombinant growth hormone; SDS, standard deviation score.

Summary

- Genotropin® indications include Turner syndrome, chronic renal insufficiency, and Prader-Willi syndrome
- The use of rhGH can improve outcomes in patients with these conditions

rhGH, recombinant human growth hormone

Rh-GH: Special warnings & precautions for use Prader-Willi syndrome

BEFORE TREATMENT

- Treatment should always be in combination with a calorie-restricted diet
  - Patients should also have effective weight control before and during GH treatment
- Signs for upper airway obstruction, sleep apnoea, or respiratory infections should be assessed
  - If pathological findings are observed, the child should be referred to an ENT specialist for treatment and resolution of the respiratory disorder prior to initiating GH treatment
- Fatalities associated with the use of GH in patients with PWS have been reported in those who had ≥1 of the following risk factors:
  - Severe obesity (weight / height exceeding 200%)
  - History of respiratory impairment or sleep apnoea
  - Unidentified respiratory infection

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ENT, ear, nose and throat;
GH, growth hormone;
PWS, Prader-Willi syndrome

Rh-GH Adverse events in children Prader-Willi syndrome

System organ class	Common (≥1/100 to <1/10)	Frequency not known*
Neoplasms benign, malignant, and unspecified (including cysts and polyps)		Leukemia†
Metabolism and nutrition disorders		Type 2 diabetes mellitus
Nervous system disorders	Paresthesia* Benign intracranial hypertension	
Musculoskeletal and connective tissue disorders	Arthralgia* Myalgia*	Musculoskeletal stiffness*
General disorders and administration-site conditions	Edema peripheral*	Injection-site reactions (transient)
Investigations		Blood cortisol decreased

*Cannot be estimated from available data;
† Reported in growth hormone deficient children treated with somatropin, but the incidence appears to be similar to that in children without growth hormone deficiency.

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Rh-GH : Special warnings & precautions for use Prader-Willi syndrome

DURING TREATMENT

- All patients should have effective weight control
- If patients show signs of upper airway obstruction (including onset of, or increased, snoring), treatment should be interrupted, and an ENT assessment performed
  - All patients with PWS should be monitored if sleep apnoea is suspected
- Patients should be monitored for signs of respiratory infections, which should be diagnosed as early as possible and treated aggressively
- Scoliosis is common in patients with PWS. Scoliosis may progress in any child during rapid growth
  - Signs of scoliosis should be monitored during treatment

- Experience with prolonged treatment in adults and in patients with PWS is limited

Genotropin SPC. Saudi Arabia. V4 September 2014.

ENT, ear, nose and throat;
PWS, Prader-Willi syndrome

Thank You