

Recombinant IGF-1 Therapy in Children with Severe Primary IGF-1 Deficiency (SPIGFD)

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Scope - To guide UK paediatric endocrinologists who are considering the use of rhIGF-1 for severe primary IGF-1 deficiency (SPIGFD).

A. Background

Primary insulin-like growth factor 1 (IGF-1) deficiency is characterised by an inadequate production of IGF-1, despite sufficient secretion of growth hormone (GH). This can lead to severe growth failure. The classical form of severe primary IGF-1 deficiency (SPIGFD) is Laron syndrome, where a genetic defect of the GH receptor gene (*GHR*) leads to GH resistance and low or undetectable IGF-1 levels. Abnormalities of the GH signal transducer and activator of transcription 5B (*STAT5B*), *IGF-1* and *PAPP-A2* genes also lead to SPIGFD and short stature.

In 2007, SPIGFD (defined as height <-3 SD, serum IGF-1 $<2.5^{\text{th}}$ centile and normal GH) became a European Medicines Agency (EMA) licensed indication for recombinant human IGF-1 therapy (rhIGF-1) in the UK.

B. Objective of rhIGF-1 treatment

Improvement of adult height in SPIGFD children.

C. Diagnosis of SPIGFD

1. Diagnosis of SPIGFD requires measurement of serum IGF-1 and the demonstration of normal or increased GH secretion.
2. The diagnosis of SPIGFD does not necessarily require a GH stimulation test or an IGF-1 generation test (IGFGT) particularly when the presentation is clearly classical i.e. positive family history, consanguineous pedigree, severe short stature, clinical features of Laron syndrome (mid-facial hyperplasia / fontal bossing), high baseline GH and low or undetectable serum IGF-1.
3. In classic cases, genetic analysis of *GHR* is recommended in order to understand the condition and confirm the clinical diagnosis - see genetic testing (**section H**).
4. In cases where a *GHR* mutation is not confirmed by genetic sequencing, genetic analysis of other candidate genes or whole exome sequencing should be considered (**see section H**). In these cases, biochemical measurements of IGFBP-3 and ALS may also be useful.

5. Pre-treatment serum samples should be stored in local clinical biochemistry departments for later analysis of the above biochemical markers.
6. Children with suspected SPIGFD and abnormal auxology / features of growth failure without classical features of SIGFD, may need detailed endocrine evaluation of the GH-IGF-1 axis including a GH stimulation test.
7. An IGF-1 generation test (IGFGT) may also be included; however, the clinical utility of this test in the diagnosis of SPIGFD has not been definitively demonstrated. A recommended protocol for the IGFT is GH 0.033 mg/kg daily x 4 with IGF-I (\pm IGFBP-3) before the first injection and 12 hours after the 4th injection.
8. Paediatric endocrinologists may encounter milder cases of SPIGFD with non-classical clinical or biochemical features.
9. Chronic inflammatory diseases and ongoing systemic therapy with drugs such as glucocorticoids can be associated with secondary IGF-1 deficiency and these conditions need to be excluded before a diagnosis of SPIGFD is made.
10. It is possible that some children with classical SPIGFD may present late as extreme short stature may be attributed to failure to thrive or familial short stature.

D. Initiating rhIGF-1 therapy

1. Contraindications to rhIGF-1 therapy include hypersensitivity to the active substance or the excipients and active or suspected neoplasia.
2. Given the relative rarity of SPIGFD, rhIGF-1 therapy should be managed by a paediatric endocrinologist with experience of treating children with complex growth disorders.
3. If the prescriber is encountering difficulties in seeking approval, the clinician can approach the Clinical Committee of the BSPED for guidance building a case for support. Initiation of rhIGF-1 therapy may require a short admission, particularly in younger children because of the potential risk of hypoglycaemia.
4. A starting dose of rhIGF-1 0.04 mg/kg twice daily SC is recommended. The dose should be increased at regular increments to reach the maintenance dose of 0.12 mg/kg twice daily by ~2-3 months, as tolerated. Long-term treatment with doses less than 0.12 mg/kg/day may lead to suboptimal growth responses. See also the dosing guide <https://www.medicines.org.uk/emc/product/384/rmms>.
5. After an increase in rhIGF-1 dose, it is advisable to measure capillary blood glucose (CBG) before breakfast and the evening meal (coinciding with the rhIGF-1 injections) for at least 2 days.
6. RhIGF-1 should be administered shortly before or after a meal or snack. If hypoglycaemia occurs with the recommended doses, despite adequate food intake, the dose should be reduced. If the patient is unable to eat for any reason, rhIGF-1 should NOT be administered.
7. Following informed consent, children on rhIGF-1 should be entered onto the web-based post-marketing surveillance registry (NCT00903110); study director Caroline Sert (clinical.trials@ipsen.com).
8. The recommended baseline assessments that should be undertaken prior to commencing rhIGF-1 therapy are shown in Table 1.
9. Increlex patient and physician leaflets can be downloaded here: <https://www.medicines.org.uk/emc/product/384/rmms>

Table 1. Recommended baseline assessment prior to commencing rhIGF-1 therapy

| Baseline assessment | Standard | Optional |
|---|-----------------|-----------------|
| Enter patient on IGFD Register* | + | |
| Physical examination: height, weight, sitting height, pubertal stage, blood pressure, fundoscopy, tonsillar examination | + | |
| Echocardiography | | + |
| Bone Age | + | |
| Photograph of the face (frontal and lateral) | + | |
| Dietary advice | + | |
| First injection as in-patient | | + |
| Fasting cholesterol (HDL, LDL and total), triglycerides | | + |
| DEXA – whole body and lumbar spine | | + |
| Arrange home care and nursing support to monitor compliance | + | |

* UK IGFD register (NCT00903110); study director Caroline Sert (clinical.trials@ipson.com).

E. Maintenance of rhIGF-1 therapy

1. Clinic visits should occur 3-4 monthly for consultant assessment, ideally seeing the same doctor at each visit, and an annual review should be performed.
2. The following targeted adverse events (TAE) should be enquired about at every clinic review and reported through the yellow card scheme AND the IGFD Registry
 - Hypoglycaemia
 - Lymphoid Hyperplasia (particularly tonsils)
 - Intracranial hypertension
 - SCFE
 - Scoliosis
 - Coarsening of facial features
 - Allergic reaction
 - Lipohypertrophy
 - Hypoacusis
 - Tachycardia
 - Overweight
 - Hyperandrogenism
 - Cardiac hypertrophy
3. More detailed assessment may be required in those cases where clinical history is positive e.g. a clinical history of sleep-disordered breathing which may require pulse oximetry monitoring and / or formal sleep studies.
4. Routine measurement of serum IGF-1 is not necessary or recommended but may be useful in those cases where adherence to therapy is questionable.
5. Hypoglycaemia is defined as capillary blood glucose testing of <3.5mmol or symptoms of hypoglycaemia.

6. Dietary advice should be considered at an early stage if there are concerns about lack of weight gain or excessive weight gain.
7. Regular specialist nursing support is necessary to check injection technique and ensure adherence.
8. Involvement of occupational therapy and clinical psychology may be needed in those cases where marked short stature persists despite rhIGF-1 therapy.
9. GnRH agonist therapy may be indicated in pubertal children who are markedly short and who have not had a sufficiently long period of treatment with rhIGF-1.
10. Treatment with rhIGF-1 should be reconsidered if after a year of documented good compliance, the patient has an increase in height velocity of <30% of baseline (pre-treatment) or a change in height SDS score of <0.3.
11. Table 2 shows the recommended testing, which should be undertaken at every clinic visit and at the annual assessment.

Table 2. Recommended testing at clinic visits and annual assessments

| | Every Visit | Annually |
|---|-------------|----------|
| Enter data on IGFD Register | + | |
| Physical examination: height, weight, sitting height, pubertal stage, blood pressure, fundoscopy, tonsillar examination | + | |
| Echocardiography, if clinically indicated* | | + |
| Bone Age | | + |
| Examination of injection sites | + | |
| Photograph of the face (frontal and lateral) | | + |
| DEXA – whole body and lumbar spine* | | + |
| Audiology* | | + |
| Monitor compliance, enlisting Ipsen nurse support as required | + | |

* These investigations are not considered standard but may provide objective data on any changes during treatment.

F. Adverse reactions

1. RhIGF-1 can have insulin-like hypoglycaemic effects. Special attention should be paid to young children, children with a history of hypoglycaemia or children with an irregular eating pattern. At the start of the treatment, strenuous activities 2 to 3 hours following the administration of rhIGF-1 should be avoided, until a well-tolerated dose is determined. The frequency of hypoglycaemia is the highest in young, severely affected children in the first month of treatment. Parents should be educated about symptoms and management of hypoglycaemia.
2. The use of rhIGF-1 has been associated with hypertrophy of the lymphoid tissue (adenoids and tonsils), notably in the first 1-2 years of treatment. An ENT specialist should be consulted if there is a medical history and / or physical examination consistent with enlarged adenoids or tonsillar hypertrophy (snoring, poor feeding pattern, apnoea, reduced hearing).
3. Intracranial hypertension, associated with papilloedema, visual changes, headache, nausea and / or vomiting have been reported. If this is diagnosed, rhIGF-1 should be stopped.

These symptoms should resolve after discontinuing rhIGF-1. RhIGF-1 can be restarted at a lower dose initially after the symptoms and signs have disappeared.

4. Rapid growth may be associated with slipped capital femoral epiphysis (SCFE; limping or pain) or progression of scoliosis.
5. Coarsening of facial features has been observed and can be documented by regular photographs.
6. Local or systemic allergic reactions may occur. In post-marketing experience, cases of hypersensitivity, urticaria, pruritis and erythema have been reported, both as systemic and / or local to the injection site. In a small number of cases, anaphylaxis requiring hospitalisation have been reported. Patients and parents should be informed of this, and if a systemic allergic reaction occurs, treatment should be interrupted and prompt medical attention should be sought.
7. Antibodies against the injected rhIGF-1 may be produced. If antibody formation is suspected, the Ipsen Medical Information Department should be contacted for antibody testing (01753 627777 or medical.information.uk@ipsen.com).
8. Lipohypertrophy of the injection site may occur if injection sites are not alternated appropriately.
9. Adverse events should be recorded within the IGF Registry (clinical.trials@ipsen.com).
10. Reporting forms and information regarding reporting to the MHRA can be found at www.yellowcard.gov.uk. Adverse events should also be reported to the Ipsen Medical Information department (01753 627777 or medical.information.uk@ipsen.com).

G. Discontinuation of rhIGF-1 therapy

Treatment should be discontinued if any of the following apply:

- Height velocity <2 cm/yr
- Fused epiphyses
- Poor adherence
- Unacceptable adverse effects

Metabolic and body composition status related to on-going severe IGF-1 deficiency should be assessed at completion of linear growth. Long-term endocrine surveillance should be continued into adult life with the possibility of recommencement of rhIGF-1 replacement therapy, if available.

H. Genetic Testing

Genetic testing for cases of suspected SIGFD can be undertaken free of charge at the Centre for Endocrinology, Barts and the London School of Medicine and Dentistry, London. For further information please contact Dr Helen Storr (h.l.storr@qmul.ac.uk). Details about the genetic testing offered, how to refer a patient and to download the relevant consent forms / information sheets visit the website - <http://www.qmul.ac.uk/grasp/>.

I. UK IGF Registry

ClinicalTrials.gov Identifier: NCT00903110. Study director Caroline Sert (contact: clinical.trials@ipsen.com).

J. Important links

- Summary of Product Characteristics for Increlex (SmPC -updated September 2017) can be found at <https://www.medicines.org.uk/emc/product/384/smpc>
- Risk minimisation materials including a dosing guide, patient leaflet and physician leaflet can be assessed from: <https://www.medicines.org.uk/emc/product/384/rmms>

K. Literature

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Conflict of interest

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