BSPED Recommendations for Recombinant IGF-I Therapy in Children with Severe Primary IGF-I Deficiency (SPIGFD)

HL Storr, P Sachdev, JH Davies. BSPED Growth Disorders Special Interest Group.

These guidelines were originally produced and approved by the UK IGF-I User's Group in February 2015 and revised/updated in February 2018 and April 2021 by Professor Helen Storr. The guidelines were reviewed and updated by the BSPED Growth Disorders Special Interest Group (SIG) in December 2023.

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

BSPED **Recommendations for Recombinant IGF-I Therapy in Children with Severe Insulin Resistance Syndromes** can be found here on the Guidelines page of our website.

A. Background

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

rhIGF-1 became a European Medicines Agency (EMA) licensed indication for SPIGFD in the UK in 2007 and was commissioned by NHSE in 2013.

Eligibility for treatment of SPIGFD with recombinant IGF-1 (rhIGF-1) in Europe:

- Age 2-18 years and
- Height <-3.0 SDS and
- Serum IGF-I <2.5th centile and
- GH sufficiency
- Exclusion of secondary forms of IGF-1 deficiency (e.g., malnutrition, hypopituitarism, hypothyroidism, chronic inflammatory conditions treated with steroids)

Contra-indications to therapy:

- Hypersensitivity to the active substance or excipients
- Active or suspected neoplasia
- Conditions or a medical history that increase the risk of benign or malignant neoplasia

B. Objective of rhIGF-I treatment

Improvement of adult height in children with SPIGFD.

C. Diagnosis of SPIGFD

1. Diagnosis of SPIGFD requires a low serum IGF-I (<2.5th centile) and normal or increased GH secretion
2. The diagnosis of SPIGFD does not necessarily require a GH stimulation test or an IGF-I 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 hypoplasia / fontal bossing), high baseline GH and low or undetectable serum IGF-I and/or genetic confirmation
3. In classic cases, genetic analysis of *GHR* is recommended to understand the condition and confirm the clinical diagnosis - see genetic testing (see 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, ALS and GH binding protein (GHBP) may also be useful, if available
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, need detailed endocrine evaluation of the GH-IGF-I axis including a GH stimulation test to exclude other causes of short stature
7. An IGF-I generation test (IGFGT) may also be undertaken; 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 (± IGFBP-3) before the first injection and 12 hours after the 4th injection. This will not identify partial or non-classical cases and does not give a prediction of response to rhIGF-1 or hGH therapy
8. Milder cases of SPIGFD with non-classical clinical or biochemical features occur
9. Chronic inflammatory diseases and ongoing systemic therapy with drugs such as glucocorticoids can be associated with secondary IGF-I 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

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

Baseline assessment	Standard	Optional
Enter patient on IGFD Register*	+	
Physical examination: height, weight, sitting height, pubertal stage, blood pressure, fundoscopy, tonsillar examination	+	
Formal ophthalmology review	+	
Formal ENT review		
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	+	
Parents trained in injection technique	+	
Parents trained in hypoglycaemia management	+	
Open access to local hospital arranged	+	
Local paediatrician informed of plan	+	

D. Initiating rhIGF-I therapy

1. The family should be counselled about potential benefits of therapy, informed of side effects, and provided with written information (see section F). The option of not intervening should be explored
2. Given the relative rarity of SPIGFD, rhIGF-I 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
4. Initiation of rhIGF-I therapy may require a short admission, particularly in younger children because of the potential risk of hypoglycaemia. A starting dose of rhIGF-I 0.04 mg/kg twice daily SC is recommended. The dose should be increased at regular increments to reach a maintenance dose of 0.12 mg/kg twice daily by ~2-3 months, as tolerated.
5. The recommended maximum dose of rhIGF-1 is 0.12 mg/kg given twice daily by subcutaneous injection. Long-term treatment with doses less than 0.12 mg/kg/day may lead to suboptimal growth responses. rhIGF-1 is given by an insulin syringe (U50 or U30, where 1mg=10 units). See also the dosing guide:
   https://www.medicines.org.uk/emc/product/384/rmms
   https://bnfc.nice.org.uk/drugs/mecasermin/
6. After an increase in rhIGF-I dose, it is advisable to measure capillary blood glucose (CBG) before breakfast and the evening meal (coinciding with the rhIGF-I injections) for at least 2 days. Once established on a maintenance rhIGF-1 dose, CBG would usually only be recommended if symptomatic.

7. rhIGF-I 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-I should NOT be administered.
8. Following informed consent, children on rhIGF-I therapy should be entered onto the web-based post-marketing surveillance registry:
   IncrelexRegistry@ipsen.com (ClinicalTrials.gov Identifier:NCT00903110)
   (contact: clinical.trials@ipsen.com)
9. The recommended baseline assessments that should be undertaken prior to commencing rhIGF-I therapy are shown in Table 1
10. Increlex patient and physician leaflets can be downloaded here: https://www.medicines.org.uk/emc/product/384/rmms

E. Maintenance of rhIGF-I therapy

1. Clinic visits 3-4 monthly for consultant assessment, ideally the same doctor at each visit, with more detailed annual review
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-I 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. GnRH agonist (GnRHa) therapy may be considered in pubertal children who are markedly short and have not had a sufficiently long treatment period with rhIGF-I. However,

there are limited data on its use (and outcomes) for this clinical indication and decisions regarding the use of GnRHa as an adjunct to rhIGF-1 should be individualised[1]

9. 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 nurse support as required	+	

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

F. Adverse reactions

1. Adverse reactions are generally more prevalent in the most severe cases of SPIGFD (reference to paper from the IPSEN registry (Bang et al EJE 2021)
2. rhIGF-I 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 patterns. At the start of the treatment, strenuous activities 2-3 hours following the administration of rhIGF-I 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-I 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-I should be stopped. These symptoms should resolve after discontinuing rhIGF-I. rhIGF-I can be restarted at a lower dose initially after the symptoms and signs have resolved
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-I 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). See the physician leaflet for additional information
8. Lipohypertrophy of the injection site may occur if injection sites are not alternated appropriately.
9. Cases of benign and malignant neoplasms have been observed among children and adolescents who received treatment with rhIGF-I. Do not use rhIGF-I in children or adolescents with active or suspected neoplasia or with any condition or medical history that increases the risk of benign or malignant neoplasia. Data suggest the risk of neoplasia is higher when used outside of the licensed indication or dose. https://www.gov.uk/drug-safety-update/mecasermin-increlex-risk-of-benign-and-malignant-neoplasia
10. Adverse events should be recorded within:

- The IGFD Global Registry (IncrelexRegistry@ipsen.com)
- Global AE reporting adverse.events@ipsen.com
- MHRA www.mhra.gov.uk/yellowcard
- Ipsen Medical Information department medinfo.uk-ie@ipsen.com (01753 627777)

G. Discontinuation of rhIGF-I therapy

Treatment should be discontinued if any of the following apply:

- Height velocity <2 cm/yr
- Fused epiphyses
- Poor adherence
- Unacceptable adverse effects
- Poor growth response after a year of documented good compliance

Metabolic and body composition status related to on-going severe IGF-I 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-I replacement therapy, if available.

H. Genetic Testing

GH-IGF-1 axis genes that cause SPIGFD (*GHR, STAT5B, IGF1, PAPPA2*) are included on the NHS Genomic Medicine Service R147.1 'Growth Failure in Early Childhood' panel.

Genetic testing can also be undertaken free of charge as part of the GRASP (Genetic Research Analysing Short Patients) study at the Centre for Endocrinology, Barts and the London School of Medicine and Dentistry, London. For further information please contact Professor 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 and information sheets visit the website - https://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 athttps://www.medicines.org.uk/emc/product/384/smpc orhttps://mhraproducts4853.blob.core.windows.net/docs/3c7e77f8542cb77d8fd8a99c5e3fb02d1d271bf8

- 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 or requested to medical.information.uk@ipsen.com

K. References

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