

# Managing the Child with Severe Primary Insulin-Like Growth Factor-1 Deficiency (IGFD): IGFD Diagnosis and Management

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**Abstract** Growth failure associated with severe primary insulin-like growth factor 1 (IGF-1) deficiency (SPIGFD), a condition defined as basal IGF-1 standard deviation score (SDS) less than or equal to  $-3$  and height SDS less than or equal to  $-3$  in a child with normal or elevated levels of growth hormone, can be successfully treated with the recombinant human IGF-1 mecasermin. In this review, we describe the most safe and effective way to use mecasermin in the treatment of patients with SPIGFD, including how to initiate dosing, key side effects, and how to monitor treatment. Finally, mention of how to reinstate therapy is made, given the recent drug shortage with mecasermin.

## Key Points

It is important to achieve a stable therapeutic dose, ideally within 1 month, as both first-year growth and long-term outcomes are best at doses  $\geq 0.1$  mg/kg/dose given twice daily.

Extensive family discussions are needed to emphasize the importance of compliance and monitoring for side effects.

Doses should be adjusted for weight gain at regular intervals as growth progresses.

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## 1 Introduction

Many genes and environmental factors affect post-natal growth; however, the growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis is one of the most important [1, 2]. IGF-1 is a 70-amino acid peptide hormone and growth factor that is structurally homologous to proinsulin. Its metabolic actions leading to growth and other anabolic effects include insulin-like actions such as stimulation of glucose uptake, glycogen synthesis, amino acid transport, and an increase in net protein synthesis [3]. In normal individuals, IGF-1 circulates as part of a ternary complex with a molecular weight of 150 kDa. The complex consists of IGF-1 itself, an acid-labile subunit (ALS), and a protein that binds IGF-1 (IGFBP-3). Serum levels of both ALS and IGFBP-3 are also dependent on the presence of normal GH secretion [4]. The half-life of the 150 kDa complex is approximately 18–20 h [5], while that of free IGF-1 is approximately 4 h [6].

In normal children, GH is the major regulator of circulating IGF-1. Because GH provocative testing is complex, many physicians begin the evaluation of a short child by measuring serum IGF-1 and IGFBP-3, and evaluate GH production only in those with low IGF-1 levels. However, there are instances where the information provided by the IGF-1 and GH tests is discordant. That is, a child with normal or high GH secretion may have low IGF-1 levels. Rosenfeld [7] proposed the term ‘primary IGF deficiency’ to describe these patients, and ‘secondary IGF deficiency’ to describe children with low IGF-1 levels due to GH deficiency. This definition is consistent with other endocrine systems consisting of a trophic and peripherally active hormone [8]. A comprehensive recent review of IGF-1 deficiency (IGFD) by Savage is also available [9].

In an analysis of the pivotal study for mecasermin, Chernausek et al. [10] showed that treatment with recombinant human IGF-1 (rhIGF-1) was effective in promoting growth in children with severe primary IGFD (SPIGFD) due to GH insensitivity. IGF-1, Increlex<sup>®</sup> (mecasermin [rDNA origin]) manufactured by Ipsen Biopharmaceuticals, Inc., has marketing authorization by the US FDA and the European Medicines Agency (EMA) for the treatment of children with SPIGFD, and by the FDA for the treatment of children with GH gene deletion who have developed neutralizing antibodies to recombinant GH. There are some differences in the SPIGFD definition in the US versus Europe based on the level of circulating IGF-1 (less than or equal to  $-3$  standard deviation score [SDS] in the US and  $<2.5$ th percentile for age and gender in the EU); both require the height SDS to be less than or equal to  $-3$ , GH to be sufficient and, in the EU, the label specifically requires the exclusion of secondary forms of IGFD.

## 2 Diagnosis of Severe Primary Insulin-Like Growth Factor 1 (IGF-1) Deficiency

Early recognition of growth disorders can come from several sources and is often a result of parental concern. Ideally, a growth chart maintained by the primary care physician provides a record of the pattern of growth, which can determine the need for further evaluation by a pediatric endocrinologist. Learning how to accurately measure children and adolescents is beyond the scope of this review, but includes removing shoes, correct positioning of the child, and correctly plotting their heights and weights on a gender-appropriate growth chart. This is critical to early recognition of a growth disorder. Careful assessment of growth velocity should also be done. Initial evaluation includes taking a full medical history, including family and

perinatal history. A nutritional history is important because malnutrition can be associated with low levels of IGF-1 in the presence of normal or increased GH secretion [11]. Laboratory testing consists of screening studies, including markers of liver and kidney function, electrolytes, complete blood count (CBC), sedimentation rate, urinalysis, celiac disease screen, cortisol level, thyroid function evaluation, IGF-1 and IGFBP-3 levels, and chromosome analysis. An x-ray (bone age) of the left hand and wrist should be taken and an estimation compared to chronological age will be determined to allow assessment of the window of opportunity for growth—the ‘younger’ or more delayed the bone maturation, the more growth potential a child has, although a bone age determination does not reveal the cause of the growth disorder.

IGF-1 and IGFBP-3 measurements are part of the initial evaluation to help diagnose SPIGFD. If IGF-1 is low, GH stimulation testing should be done. If there is evidence of GH deficiency (secondary IGF-1 deficiency), an magnetic resonance image (MRI) of the brain, with attention to the pituitary-hypothalamic area, is indicated to consider structural abnormalities in the region (i.e. craniopharyngioma, optic glioma, sarcoidosis, hypophysitis, hemorrhage, or infarct, etc.). Normal GH secretion in the presence of low IGF-1 suggests primary IGF-1 deficiency. If a diagnosis of SPIGFD is confirmed, IGF-1 replacement therapy should be initiated with mecasermin [6].

Children treated with GH who have a poor response to treatment, defined as a suboptimal growth response [12] and a failure to increase IGF-1 levels, should be re-evaluated to determine if they meet the diagnostic criteria for SPIGFD (i.e. height and IGF-1 less than or equal to  $-3$  SDS, normal GH secretion, after poor compliance with scheduled GH injections has been ruled out). In cases where compliance is a question, the recombinant human GH (rhGH) should be administered by a reliable source.

## 3 The IGF-1 Generation Test

The principle behind the design of the IGF-1 Generation Test (IGFGT) was that repeated injections of human GH induce measurable increases in IGF-1, IGFBP-3 and ALS secretion. However, in GH-deficient patients, the degree of IGF-1 response did not convincingly predict the growth response to GH therapy [13]. Because of this, the IGFGT is primarily a research tool. Performing the IGFGT is not necessary to make a diagnosis of SPIGFD, nor should it be required to begin mecasermin replacement; meeting the less than or equal to  $-3$  height and IGF-1 SDS criteria in the setting of normal-to-high GH is sufficient to make the diagnosis of SPIGFD.

## 4 Treatment

### 4.1 IGF-1 (Mecasermin rDNA) Administration

Once a diagnosis of SPIGFD has been made, it is important to begin treatment with mecasermin as soon as possible. Growth rates are highest during the first year of treatment [6], and both first-year catch-up growth and long-term outcomes, such as adult height, are better when therapy is initiated in younger children at an appropriate dose [10, 14]. Treatment with mecasermin involves twice-daily injections [6], ideally over a period of years to maximize adult height, and compliance is crucial to achieve both optimal growth outcomes and safety. In our practices, treatment therefore begins with extensive family discussions.

### 4.2 Side Effects

Patients and caregivers must be familiar with all the risks and benefits of treatment, especially with regard to common side effects of mecasermin, including symptoms of hypoglycemia. The most common side effects of mecasermin therapy are listed below [6].

- *Hypoglycemia* is often present before treatment in patients with SPIGFD, particularly young children with the phenotype of Laron syndrome [15]. Treatment with mecasermin may exacerbate this, especially during the early stages of therapy. Information about the occurrence of hypoglycemia should be sought even before beginning mecasermin. The dose of mecasermin should be increased more slowly in children with a prior history of hypoglycemia. Younger patients, who may have difficulty articulating symptoms, should be monitored carefully during the treatment initiation phase. Hypoglycemic episodes are minimized through adequate carbohydrate (or caloric) intake along with each injection and by avoiding overdose; we advise administration within 20 min of a meal or snack [6], and provide training in dose calculation and delivery.
- *Injection site reactions* may be avoided or minimized by alternation of injection site among the upper arm, thigh, buttock, and abdomen, and by the following techniques: avoiding the use of ultra-short needles; removing mecasermin from the refrigerator at least 20 min before injecting; and cleaning the site using soap and water instead of alcohol.
- *Lymphoid tissue overgrowth* may occur, including enlarged tonsils/adenoids (which may require tonsillectomy), snoring, and middle-ear effusion (which occasionally requires tympanostomy tube placement).
- *Headaches* While some headaches may be associated with normal childhood illnesses, we advise parents to

report any prolonged, unusual headaches to their healthcare professional as soon as possible in order to allow the child to be evaluated for possible intracranial hypertension.

- *Craniofacial growth, sometimes with coarsening of facial features*, may occur during treatment with IGF-1. The results appear to soften with time, especially after completion of linear growth and subsequent discontinuation of mecasermin. [10, 14] This coarsening is due to soft tissue growth and does not represent bony overgrowth, such as is seen in acromegaly [14].

Obesity is well-recognized in pubertal and adult patients with untreated Laron syndrome, and the relationship of obesity to mecasermin treatment is not clear [16].

### 4.3 Dose of Mecasermin

The FDA-approved initial dosing is from 0.04 to 0.08 mg/kg/dose twice daily given for at least 1 week [6]. If the initial dose is well-tolerated, the dose is increased by 0.04 mg/kg/dose, up to a maximum of 0.12 mg/kg/dose. It is important to achieve a stable therapeutic dose as quickly as possible (ideally within 1 month), as both first-year growth and long-term outcomes are best at doses  $\geq 0.1$  mg/kg/dose given twice daily [10]. Younger children, especially those with a history of hypoglycemia, are generally started at a dose in the lower bound of the starting range (e.g. 0.04 mg/kg/dose) and the dose is increased more slowly. Once a stable dose in the efficacious range is achieved, it is important to monitor the patient's weight to make sure they do not outgrow their dose. That is, as the patient gains weight, it is critical to also adjust the dose so the patient remains in the most effective dose range. Also, if mecasermin treatment is interrupted for an extended period (e.g. due to a drug shortage), the patients should be reassessed to determine their need for resumption of mecasermin therapy, and if the patients still have growth potential, mecasermin dose escalation should likely be undertaken similar to when the drug was originally initiated. Data on this scenario are limited, and judgment of the treating physician is critical. For those children who experienced hypoglycemia or other drug-related adverse events while on mecasermin, we would recommend repeating the schedule of sequential dose increases that was followed originally when they reinstate the drug.

### 4.4 Monitoring Treatment

Determination of IGF-1 levels during mecasermin treatment is of limited value [6] and we do not recommend measuring them as part of routine care. They can be of value when compliance with prescribed injections is a

concern (administering an observed injection in the office followed by a serum IGF-1 level 2 h later would be helpful in this situation).

#### 4.5 Duration of Treatment

Treatment should continue until the epiphyses fuse and full growth potential has been achieved. During the course of treatment we monitor patients at regular intervals to check both the progress of growth and occurrence of side effects. Treatment efficacy is assessed through careful monitoring of the growth chart and patient examination. As noted above, substantial catch-up growth may occur with early achievement of a stable therapeutic dose. To maintain efficacy, the dose of mecasestermin should be adjusted for weight gain at regular intervals as growth progresses. Treating physicians should be aware that the typical growth response to mecasestermin in SPIGFD is not as robust as the response to GH in patients with GH deficiency.

#### 4.6 Use of Gonadotropin-Releasing Hormone Analogues to Delay Puberty

There have been no randomized controlled studies of this question. Some children in the mecasestermin pivotal study (described by both Chernausk et al. [10] and Backeljauw et al. [14]) did receive these agents. There was no statistically significant difference in adult height between those who were treated with gonadotropin-releasing hormone (GnRH) analogues and those who were not, although it is biologically plausible that combination therapy of mecasestermin with GnRH analogues may improve height in SPIGFD patients if the GnRH analogues are started at the onset of puberty [14]. In our opinion, the best way to avoid the issue of puberty leading to truncation of height gain is to begin mecasestermin treatment as early as possible, with the caveat that the safety and effectiveness of mecasestermin treatment has not been established in pediatric patients below the age of 2 years.

### 5 Conclusion

This article illustrates how the diagnosis of patients with SPIGFD is determined and how this condition can be effectively treated with mecasestermin. It is very important to have careful discussions with the family prior to treatment initiation to discuss the necessity of being compliant over the long-term course of therapy, and to educate the family about potential adverse effects. It is also critical when initiating therapy to promptly escalate the dose to the efficacious range  $>0.1$  mg/kg/dose given twice daily, as symptoms allow, and to adjust the dose over time to

account for increases in weight as the patient grows. Finally, for patients who had to stop mecasestermin as a result of the drug shortage, consideration should be given to re-initiating the original dose escalation scheme when the drug is resumed.

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