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Commentary

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Treatment of Pediatric Growth Hormone Deficiency With Oral Secretagogues Revisited

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Growth hormone (GH) secretagogues have been explored for more than 40 years. They are small synthetic peptide and nonpeptide drugs with GH-releasing activity that can be administered by intravenous, subcutaneous, intranasal, and oral routes and have variable bioavailability [1]. LUM-201, ibutamoren, formerly MK-0677, was designed in 1995. LUM-201 and others were studied as alternative agents for GH stimulation testing, and some showed promise as diagnostic tools [1-3]. In 2017, one such agent, macimorelin, was approved by the US Food and Drug Administration as a diagnostic agent for adult GH deficiency (GHD) [4].

The orally active secretagogues were discovered during investigations of the mechanisms of endocrine changes that occur with aging [5]. Early studies of LUM-201 focused on treatment of GHD in adults and metabolic actions related to obesity [6-9].

Alternatives to daily injectable GH therapy for pediatric patients with GHD have been sought for decades. Treatment with GH-releasing hormone (GHRH) demonstrated adequate growth velocity over 1 and 4 years in the 1990s [10,11]. However, GHRH was given as twice daily subcutaneous injections, more frequent than GH. Long-acting GH currently actively pursued by several pharmaceutical companies will reduce the number of injections [12]. Intranasal GH-releasing peptide-2 spray was appealing for its less invasive form of administration but was found to have only a small effect on growth [13, 14]. Oral secretagogues are likewise attractive for the treatment of children as they are less invasive than injections and, similar to GHRH, stimulate endogenous GH secretion. More than 25 years after its discovery, LUM-201 is being revisited now for this purpose.

The studies by Bright et al and Blum et al add a new definition to the previously established diagnosis of idiopathic GHD with a moderate version [15,16]. They define moderate GHD as having insulin-like growth factor-1 (IGF-1) > 30 ng/mL although no upper limit is given and a peak GH response to stimulation >2 µg/L, which they estimate corresponds to a peak GH ≥ 5 ng/mL after ingestion of the oral secretagogue, LUM-201 [15,16]. Reanalysis of data from the Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS) from 1995 to 2015 found that in individuals with moderate GHD as previously defined the average annualized growth velocity was 8.3 cm/year and less than the rate of 9.6 cm/year in those with severe GHD, defined as peak GH to stimulation <2 µg/L [17]. Based on these results, they postulated that treatment with an oral secretagogue in those with moderate GHD would result in a reasonable growth velocity.

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Children with GHD were treated for 6 months with different daily oral LUM-201 doses after measurement of peak GH response to a single dose of LUM-201 [15]. The mean annualized growth velocity for the LUM-201 groups (6.0, 6.9 cm/year) was modestly higher than the placebo group (4.5 cm/year) but lower than the rate in those treated with GH (11.1 cm/year). Peak GH ≥ 5 ng/mL to single dose and a baseline IGF-1 concentration >30 ng/mL were found to be positive predictive enrichment markers for increased height velocity on LUM-201 treatment. Conversely, a peak GH < 5 ng/mL and a baseline IGF-1 concentration ≤30 ng/mL enriched height velocity response to GH treatment.

Several questions emerge about the potential implementation of oral secretagogues in the diagnosis and treatment of youth with GHD. Are the results of stimulation testing with a secretagogue reproducible in children, as they seem to be with macimorelin in adults? If tested again, will the results be similar enough to justify treatment? GH stimulation testing is marred by its poor reproducibility and the potential of being influenced by body mass index [18]. Peak GH response to a single dose of oral secretagogue may demonstrate the same variability and needs to be studied. The differential growth response to LUM-201 and injectable GH based on peak GH levels after stimulation contributes to the debate of peak GH cutoffs to define GH deficiency. The current cutoff of 10 ng/mL after pharmacological stimulation is most widely accepted, including by the Growth Hormone Research Society, the Pediatric Endocrine Society, and the European Society for Paediatric Endocrinology [19,20]. Cutoffs between 5 and 7 ng/mL have also been proposed [21,22].

Like the variable response to oral secretagogue reported, variable degree of GH sensitivity has been observed in children treated with GH. Prediction models to determine response to GH have included baseline IGF-1 levels and peak GH [23]. In a study by Cohen et al, subjects with GHD based on peak GH < 7 ng/mL were more responsive to GH treatment than those with peak levels of GH ≥ 7 ng/mL. GHD subjects required lower GH doses and achieved greater height gain when compared to those not deficient [20]. Comparison of the rise in IGF-1 levels on LUM-201 treatment *vs* on GH treatment was not performed. With an intact pituitary GH–IGF-1 feedback mechanisms, IGF-1 levels would be anticipated to not rise above normal ranges. Will treatment result in a feedback mediated decrease in levels of IGF-1 during long-term treatment and thus lower growth rates? Responsiveness to a longer treatment course during childhood growth in comparison to GH treatment as well as adult height outcomes will be important data before clinicians can comfortably recommend an alternative to the proven track record of injectable GH. The effects on bone age and long-term safety data still need to be studied.

The possibility of safe and effective alternatives to daily injectable GH treatment ushers in a new, exciting, and potentially challenging era in the treatment of children with growth disorders. The studies suggest that a relatively intact pituitary axis is required for GH secretagogues to be effective. Therefore, patients with normal peak GH responses to stimulation tests such as those diagnosed with idiopathic short stature may be ideal candidates for oral secretagogue treatment. Oral secretagogue treatment may be explored for children who do not have classical GHD, but rather normal variants such as constitutional growth delay, born small for gestational age, or other conditions with as yet unexplained growth failure [24]. The lower initial growth velocity, if confirmed, may hinder its use in those with limited time to achieve adequate stature. A less time-dependent population such as adults with proven GHD may form a suitable study population. In this era of personalized medicine, it would be of great interest to assess the genetic signature of individuals with severe *vs* moderate GHD and to determine the profile of those who would best respond to oral secretagogues.

Additional Information

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