Non-GH agents and novel therapeutics in the management of short stature

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Abstract

Short stature is one of the most common reasons for referral to pediatric endocrinologists. The vast majority of short children do not have growth hormone (GH) deficiency or another pathologic process that is interfering with normal growth. While GH has been approved in the US for several etiologies of non-GH deficient short stature, its high cost and need for daily injections represent barriers for many families. Alternative agents for the management of short stature include the use of gonadotropin releasing hormone analogs (GnRHas) to delay puberty, and aromatase inhibitors (AIs) in boys to postpone epiphyseal fusion. The results of studies employing GnRHas as either monotherapy or combined with GH are mixed, and there are a dearth of rigorously designed clinical trials that have followed patients to adult height. While AIs have been found to result in modest increases in adult height in some studies, important questions about their long-term safety exist. The C-type natriuretic peptide analog vosoritide is an experimental agent that is emerging as a potential treatment for a few specific conditions including achondroplasia although its efficacy in attenuating disproportionality is as yet unproven. While each of these therapeutic strategies holds promise, none are currently considered standard of care and several important questions remain. These include the impact of these interventions on quality of life as well as long-term outcomes.

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Short stature is one of the most common chief complaints that pediatric endocrinologists encounter in the clinical arena. Recombinant human growth hormone (GH) is approved in the US for several conditions of non-GH deficient short stature including idiopathic short stature (ISS), SHOX deficiency, Turner syndrome, Noonan syndrome and children born small for gestational age [1]. However, downsides of GH therapy including the high cost of treatment, need for daily injections and limited efficacy in certain situations have led to an interest in different options for the treatment of short stature. Current approaches include gonadotropin releasing hormone analogs (GnRHas) and aromatase inhibitors (AIs). Vosoritide is emerging as an additional potential treatment in a few select circumstances in which short stature is a prominent feature. A brief review of reported effectiveness and possible side effects of each of these treatment options will be highlighted.

Gonadotropin releasing hormone analogs (GnRHas):

During puberty, sex steroids are responsible for an initial increase in growth velocity followed by eventual epiphyseal fusion of long bones and ultimate attainment of final adult height (FAH). Therefore, alterations in the timing of puberty influences FAH. For example, patients with conditions such as untreated central precocious puberty (CPP) or poorly controlled congenital adrenal hyperplasia (CAH) have a compromised adult height due to early exposure of estrogen and androgens and premature closure of the growth plates. On the contrary, patients with delayed or insufficient exposure to sex steroids such as in untreated hypogonadotropic hypogonadism have prolonged linear growth and increased FAH [2]. Recognition of the importance of sex steroids in determining adult stature led to the concept of manipulating puberty in order to impact height in otherwise healthy children.

GnRHas have been the first line treatment for CPP since their development in the 1980's [2]. By suppressing gonadotropin and gonadal sex steroid secretion, and subsequently delaying bone maturation, GnRHas result in an improvement in FAH in children with CPP, with the greatest benefit seen in girls less than 6 years of age. Once the benefit of GnRHas in improving final height in children with CPP was established, the potential to use these medications to impact height outside of CPP became an area of interest. Many studies have investigated the use of GnRHas in children with non-growth hormone deficient conditions with the goal of increasing adult height [3].

A study by Khawaja et al. showed that 21 girls with normally timed puberty treated with a GnRHa reached a FAH of 151.3 ± 5.1 cm compared to a FAH of 146.8 ± 3.8 cm in 14 untreated girls ($p = 0.01$) [4]. Similar outcomes were observed in boys but the results were not statistically significant. However, it is worth noting that this was a retrospective cohort study with a small sample size. In contrast, a randomized controlled study of GnRHa monotherapy in adolescents with ISS by Yanovski et al found a modestly increased adult height compared with controls. However, an important adverse event in the treatment group was decreased accretion of bone

mineral density (mean lumbar vertebral bone mineral density at the time adult height was achieved, 1.6±1.2 SD below the population mean, vs. 0.3±1.2 SD below the population mean in the placebo group; P<0.001) leading the investigators to conclude that the risk/benefit ratio of such treatment did not justify its use [5].

Other studies have investigated combination treatment with GH and GnRHas in patients with ISS based on the reasoning that delaying bone maturation will provide more time for GH to enhance height potential. Pasquino et al. compared the effect of GH alone (n=12) vs GH + GnRHa (n=12) on FAH in girls with ISS treated for a mean duration of ~ 4.5 years. Patients who received combined treatment had a mean height gain of 10 ± 2.9 cm compared to a height gain of 6.1 ± 4.4 cm in children receiving GH alone [6]. A much larger retrospective study also compared children treated with GH to those receiving GH and a GnRHa. While FAH in both groups was similar, the predicted adult height (PAH) in the combination group was lower at the start of therapy suggesting a benefit from the addition of a GnRHa [7]. In contrast, a randomized controlled study of GH vs GH and a GnRHa found no difference in height after 2.4 years of treatment [8]. Combination therapy has also been explored in other situations of short stature such as in children who were born SGA and in those with SHOX deficiency and have demonstrated promising results [9-11].

GnRHas are extraordinarily safe with the main side effect being mild site reactions. While some studies have reported a temporary increase in BMI on treatment [12-14], others have found no such association [15]. Regardless, GnRHas are an expensive and invasive treatment and there is no convincing evidence that ending up slightly taller improves a person's quality of life [16]. The psychological consequences of postponing physiologic puberty in otherwise healthy children is unknown. The preponderance of studies investigating the effect of GnRHas on final height outcomes in children with short stature and normally timed puberty are significantly flawed since most are uncontrolled, have small sample sizes, and fail to follow patients until adult height. Due to these concerns as well as the mixed results, an international consensus statement found that the use of GnRHas to increase height beyond precocious puberty was experimental and not considered standard of care [17].

Aromatase Inhibitors (AIs)

Aromatase inhibitors (AIs) block the conversion of androgens to estrogens and are used extensively in postmenopausal women with breast cancer. Their potential role in increasing height stems from the principle that blocking estrogen biosynthesis will attenuate the effect of estrogen at the level of growth plates. This concept was illuminated in the late 1990's when 2 young adult males, one with an estrogen receptor mutation and the other with an aromatase gene mutation, were found to have tall stature and open epiphyseal growth plates despite normal virilization [18, 19]. These remarkable human examples provided proof that estrogen,

and estrogen alone, is responsible for epiphyseal fusion at the end of puberty. The availability of selective AIs and their potential use for improving FAH is intrinsically attractive due to reasonably low cost, oral administration, and little effect on pubertal development and growth velocity compared with GnRHas. Letrozole and anastrozole are third-generation AIs that reduce aromatase activity by more than 98% and have been used as off-label treatment in boys with short stature [20]. A randomized, double-blind, placebo-controlled study by Wickman et al. in 2001 randomized boys with constitutional growth delay of puberty (CGDP) to testosterone and placebo or testosterone and letrozole and found a significant delay in bone maturation in the treatment group as well as an increase in PAH by 5.1 cm ($p=0.004$) after 12 months of treatment [21]. These findings were replicated in another randomized placebo-controlled study published later by Salehpour et al. in 2010 which compared the effect of either letrozole, oxandrolone or placebo on FAH in a larger sample size of boys with CGDP. After 24 months of treatment, the study found that letrozole increased PAH with slower advancement in pubertal stage and bone mineralization compared to the oxandrolone-treated group [22]. The effect of letrozole on boys with ISS has also been investigated. A prospective, double-blind, randomized, placebo-controlled study by Hero et al. on 31 boys with ISS showed that the PAH increased by 5.9 cm ($P < 0.0001$), and that the height SD score for bone age increased by 0.7 SD score ($P < 0.0001$) in the Letrozole-treated boys compared to no changes in placebo-treated cohorts [23]. Mauras et al. also investigated the efficacy of combining GH and an AI in boys with short stature in an attempt to extend the opportunity for growth by delaying epiphyseal fusion. That study recruited 52 adolescent males with GH deficiency being treated with GH who were randomized to co-treatment with anastrozole or placebo daily for up to 36 months. The results showed that the anastrozole-treated cohort experienced a slower advancement in skeletal maturation and a net increase in PAH [24]. Another study by the same investigators randomized boys with ISS to anastrozole, GH or combination treatment with both. The combination group had gained 3.5 inches above expected at the time that near-adult height was reached compared with 2.7 inches in the GH group and 2 inches in those treated with anastrozole alone [25].

Because estrogen receptors and aromatase enzymes are expressed in different tissues, AIs may cause unwanted side effects such as changes in bone mineral density (BMD), bone turnover, lipid metabolism, insulin sensitivity and cognitive performance [26]. BMD evaluated via DEXA scans in the above-mentioned studies [21-24] increased in a similar manner and was not statistically different between the study groups by the end of these trials. This could be explained by the inhibitory effect of androgens on osteoclast activity thus reducing the extent of bone resorption as has been shown in a study by Hero et al. where bone turnover markers where reduced in letrozole-treated group compared to controls [27]. However, concerning bone morphology including vertebral wedge deformities have been described in boys with ISS previously treated with letrozole. The significance of this finding is as yet unclear and most patients have been asymptomatic thus far [27].

No adverse events related to LDL cholesterol or triglycerides in adolescent males taking AIs have been documented in randomized controlled trials [21, 22] but a minimal decrease in HDL

cholesterol in boys receiving letrozole has been reported [28]. Regarding the effect of AIs on insulin sensitivity, the results of the trials taken together show that these drugs either had no effect [23] or resulted in improved insulin sensitivity temporarily during the treatment phase [21]. One postulated explanation for improved insulin sensitivity is the inhibitory effect of AIs on estrogen-mediated insulin resistance during puberty [28, 29].

As the effect of estrogen on cognitive function, mainly verbal memory [30], is established, the impact of AIs on cognition is a reasonable question to address. Reassuringly, a selection of cognitive tests in a study by Hero et al. in boys with ISS who received AIs did not report any differences in verbal or spatial memory compared to those who received placebo [31].

Despite the suggestion of a modest increase in height in some boys treated with AIs, these drugs remain experimental [32]. It should be noted that AIs are considered contraindicated in girls with short stature due to concerns about precipitating ovarian cysts with risk of torsion. Concerns in boys include the limited number of patients treated, the modest degree of benefit and that increases in PAH have not translated into increases in FAH in some studies. Questions regarding long-term safety in terms of fertility, vertebral morphology and other outcomes remain, and more research is needed.

Vosoritide

Vasoritide is an experimental drug that has shown promising results in improving height potential in certain conditions like achondroplasia. Achondroplasia is the most common form of disproportionate short stature and is caused by an autosomal dominant mutation in the fibroblast growth factor receptor 3 (FGFR3) gene resulting in the inhibition of downstream endochondral ossification [33]. It has been shown that C-type natriuretic peptide (CNP) antagonizes FGFR3 downstream signaling by inhibiting the pathway of mitogen-activated protein kinase (MAPK) [34]. Vosoritide is a recombinant C-type natriuretic peptide analogue with a longer half-life than its endogenous form [34]. Wendt et al. have shown that daily subcutaneous administration of vosoritide promotes long-bone growth in juvenile, skeletally normal mice and monkeys and corrects the dwarfism phenotype in mice with achondroplasia [35]. Based on these promising findings, a randomized, double-blind phase 3 placebo-controlled multicenter trial by Savarirayan et al. investigated the use of vosoritide in children with achondroplasia [36]. After 52 weeks of treatment, there was an increase in annualized growth velocity in patients treated with vosoritide versus placebo of 1.57 cm/year (with a two-sided p-value of <0·0001) [36]. Although no serious adverse events related to vosoritide were noted, there were no significant improvements in the disproportionality of the upper and lower limbs either [36]. Therefore, the long term efficacy of vosoritide on limb disproportionality and its safety is still an area to be investigated. There is also interest in the use of vosoritide in other conditions including Noonan syndrome and SHOX deficiency, and studies are currently underway.

In summary, several strategies for the management of short stature beyond GH exist. Challenges in deriving firm conclusions about their safety and effectiveness include that many studies involve combination therapy and that there are a dearth of vigorously designed trials that follow children to adult height. Although GnRHas and AIs are being used in the clinical setting, the need for additional research regarding their use in the treatment of short stature is widely acknowledged. Vosoritide is a newcomer in the therapeutic armamentarium that holds promise in the treatment of specific forms of short stature, and more information about its use will be forthcoming.

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