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Novel approaches to short stature therapy

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Besides growth hormone, several pharmaceutical products have been investigated for efficacy and safety in increasing short term growth or adult height. Short-term treatment with testosterone esters in boys with constitutional delay of growth and puberty is efficacious in generating secondary sex characteristics and growth acceleration. The addition of oxandrolone to growth hormone (GH) in Turner syndrome has an additive effect on adult height gain. Treatment with GnRH analogs is the established treatment of central precocious puberty, and its addition to GH therapy appears effective in increasing adult height in GH deficient children, and possibly short children born SGA or with SHOX deficiency, who are still short at pubertal onset. Aromatase inhibitors appear effective in several rare disorders, but their value in increasing adult height in early pubertal boys with GH deficiency or idiopathic short stature is uncertain. A trial with a C-natriuretic peptide analog offers hope for children with achondroplasia.

Introduction

The main treatment option for short stature is growth hormone (GH), but manipulation of sex steroid exposure can also affect growth. Remarkably, administration of sex steroids as well as drugs to decrease their effect have been used, and this will be the main topic of this review (search strategy available on request). For further reading, the reader is referred to previous general reviews (for example [1–3]) and specific reviews on androgens [4], oxandrolone (Ox) in Turner syndrome [5], GnRH analogs (GnRHas) [6],

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and aromatase inhibitors (AIs) [7]. A recent development is that studies on the role of the C-natriuretic peptide (CNP)-NPR2 axis in the pathophysiology of achondroplasia have suggested a possible treatment for this condition. None of the medications discussed in this review are registered for the treatment of a growth disorder.

Sex steroids and analogs

Testosterone esters

Testosterone esters have been used for several decades in boys with constitutional delay of growth and puberty (CDGP) to increase height velocity and generate secondary sex characteristics [4,8], and are usually administered i.m. in a monthly dose of 50–100 mg. At this dosage, there is no negative effect on adult height (AH) [9,10]. In most cases, this treatment is only needed for 3–6 months because in the meantime endogenous androgen production will have become sufficient.The oral preparation testosterone undecanoate (40 mg/day) can also be used, although its effect is considered more variable than of i.m. administration; it appears equally effective as Ox [11]. No data are available for newer cutaneous forms of androgens, for example gels or patches.

Anabolic steroids

Oxandrolone in idiopathic short stature

In an effort to increase the anabolic actions and decrease the virilizing actions of testosterone, testosterone analogs (anabolic steroids) were synthesized, of which Ox has been investigated best. This compound is not aromatized, and does not inhibit endogenous testosterone production if administered in appropriate dosage. Ox has been used for several groups of children in a catabolic state, for example, severely burned children and children with cystic fibrosis or Duchenne muscular dystrophy. Presently, Ox is only available in the USA.

In short prepubertal children, Ox, in a dosage of 1.25–5.0 mg p.o., increases height velocity as well as bone maturation, and probably has no effect on AH [11–13]. Given the lack of effect on AH, scarcity of scientific data and difficulties to obtain the product (at least in Europe) we believe that there is no place for Ox in the management of idiopathic short stature (ISS).

Oxandrolone in Turner syndrome

After several reports on partially controlled studies in the early 1990s, in 2010–2011 the results were published of three placebo-controlled studies in which GH plus Ox was compared with GH alone in girls with Turner syndrome [14–16]. In a recent review [5] the joint investigators concluded that the addition of Ox to GH starting at an age between 8 and 16 yr leads to an increase in height velocity and a modest increase of AH, on average 2.3–4.6 cm, equivalent to a 25–50% increase in comparison with GH alone. The additional costs of this medication is more than outweighed by the shorter duration of GH treatment if Ox is added. Side effects include voice deepening, transient delay of breast development, and a decrease of HDL-cholesterol, but these are mild and rare if the dosage is lower than 0.06 mg/kg/d. In a follow-up study in young adults who had participated in the Dutch study, no new long-term adverse events were noted [17]. Therefore, adjunctive treatment with Ox at a dosage of 0.03–0.05 mg/kg/d from the age of 8–10 years onwards can be considered if a girl is severely short for age; if very short AH is anticipated; or if growth rate is modest despite good compliance with GH [5]. Besides effects on growth, Ox may also be associated with a small decrease in frequency of severe arithmetic learning disability [18], and an improved working memory [19].

Estrogens

Since estrogens are believed to have more effect on bone maturation than on growth, clinicians have tended to postpone estrogen substitution in girls with Turner syndrome, and in fact a late start of estrogens (14 versus 12 years) was associated with a greater AH [15,20]. However, a late start of estrogen substitution