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Dorothy I. Shulman, Gary L. Francis, Mark R. Palmert, Erica A. Eugster and for the Lawson Wilkins Pediatric Endocrine Society Drug and Therapeutics Committee

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Use of Aromatase Inhibitors in Children and Adolescents With Disorders of Growth and Adolescent Development

Dorothy I. Shulman, MD, MD, Gary L. Francis, MD, PhD, Mark R. Palmert, MD, PhD, Erica A. Eugster, MD, for the Lawson Wilkins Pediatric Endocrine Society Drug and Therapeutics Committee

ABSTRACT

Although treatment of children and adolescents who have disorders of growth and adolescent development with aromatase inhibitors is increasingly common, data for or against their use are extremely limited. Precocious puberty, short stature, and gynecomastia are conditions for which inhibition of the enzyme aromatase might prove beneficial to reduce clinical signs of estrogenization and/or estrogen-mediated skeletal maturation. In this report, we summarize the published data regarding the use of aromatase inhibitors in these conditions, and review known and potential benefits, safety concerns, and shortcomings of the available information.

USE OF AROMATASE inhibitors (AIs) has now been reported for a wide variety of disorders that range from estrogen-responsive breast cancer and endometriosis in adult women, to peripheral precocious puberty, congenital adrenal hyperplasia (CAH), short stature, and gynecomastia in children and adolescents. The use in children and adolescents expanded after the important role of estrogen in skeletal maturation became evident in the mid-1990s after reports of 2 young adult men in their 20s, 1 with an estrogen receptor defect and the other with an inactivating mutation of the aromatase gene. Both were described as having tall stature and unfused epiphyses despite adult pubertal development. Other clinical and biochemical features included osteopenia, insulin resistance, elevated serum gonadotropin levels, oligospermia, and impaired sperm motility. In this article, we briefly review the mechanism of action of AIs, describe the currently available agents, and evaluate the published data regarding use of AIs in children and adolescents.

BACKGROUND

The value of inhibiting aromatase activity developed from the inadvertent discovery that the adrenotoxic, antiepileptic drug aminoglutethimide improved the clinical outcome for patients with breast cancer. Initially, this was attributed to aminoglutethimide-induced blockade of adrenal steroidogenesis. It was not until pioneering work by Thompson and Siiteri that aminoglutethimide was shown to block aromatase (cytochrome P450 XIX [CYP19]) activity. Since that time, numerous compounds have been shown to inhibit this important enzyme.

The aromatase enzyme is a complex formed by 2 proteins, the CYP19 and the nicotinamide-adenine dinucleotide phosphate–cytochrome P450 reductase. There is 1 copy of the CYP19 gene located on chromosome 15q21.2. Tissue-specific expression results from the interplay of 9 promoters that are differentially expressed in various tissues. The net effect of the aromatase chemical reaction is to aromatize the steroid A ring of androgen substrates resulting in estrogen formation (Fig 1). This is believed to proceed through a sequence of 3 oxygenations at the C-19 position that generate 19-hydroxy and 19,19-dihydroxy intermediates. Subsequently, C-19 and the I8,2β-hydrogens are eliminated, resulting in aromatization of the A ring. Although androgens (androstenedione and testosterone) are widely recognized as substrates for aromatase, estrogens are also substrates for aromatase, and their reactions generate catechol estrogen, 2-hydroxyestrogen, and 6α-hydroxyestrogen that may have critical roles in the induction or promotion of estrogen-responsive malignancies. Because of this, both androgens and estrogens act as competitive inhibitors of aromatase, and derivatives of both androgens and estrogens have been tested as AIs.
In general, there are 2 distinct structural classes of AIs. Type I, or the steroidal derivatives (Fig 1), are usually derived from androstenedione and irreversibly bind to the catalytic site, a hydrophobic region of the N-terminal sequence, or regions in close proximity. Type II, or the nonsteroidal inhibitors (Fig 2), are imidazole/triazole compounds or derivatives of phenobarbitone (eg, aminoglutethimide). Nonsteroidal AIs are characterized by reversible binding to the P450 portion of the aromatase enzyme.

First-generation and second-generation AIs were found to reduce aromatase activity by 90% (Table 1). The newest, third-generation inhibitors reduce aromatase activity by 97%. These third-generation non-steroidal inhibitors are triazole derivatives such as letrozole and anastrozole. They bind to the active site of P450 aromatase through interaction of a heterocyclic nitrogen that is critical for their markedly increased activity. Table 1 lists various AIs, including reputed effectiveness in aromatase inhibition and dosing. In addition to increased potency, third-generation AIs have a longer half-life (2 days) than earlier compounds, allowing once-daily oral administration. The approximate cost of letrozole (2.5 mg) and anastrozole (1 mg) is $10 a tablet.

**PERIPHERAL PRECOCIOUS PUBERTY**

Thus far, AIs have been used as primary treatment in 2 forms of peripheral precocious puberty: familial male precocious puberty (FMPP) and McCune-Albright syndrome (MAS). Although initial experience was gained with first-generation agents, recent interest has focused on the potential use of third-generation AIs, which have greater selectivity, longer half-lives, and increased potency. Progress in this area is hampered by the rarity of these 2 disorders, rendering it difficult to conduct meaningful clinical trials at a single institution. Rather, multicenter studies are usually necessary to amass a sample size that is sufficient to address questions of safety and efficacy. Fortunately, collaborative research efforts in this area have increased during recent years, which should improve our ability to provide optimal clinical care to affected patients. Contemporary information about the use of AIs in these disorders is reviewed below.

**Familial Male Precocious Puberty**

Initial reports of efficacy in the treatment of FMPP with an AI involved the first-generation drug testolactone. When combined with the antiandrogen spironolactone, response to therapy in a small group of boys with FMPP (n = 9) was greater compared with that achieved with either compound alone. After 6 months of the combined regimen, growth velocities and rates of skeletal maturation significantly decreased. In addition to beneficial effects on physical parameters, an improvement in aggressive behavior and acne were noted. In a longer term study, testolactone and spironolactone were administered to 8 patients for 2 to 4.2 years, with the addition of the gonadotropin-releasing hormone (GnRH) analog deslorelin with the onset of central puberty. Although this approach was successful in restoring prepubertal growth rates, gonadotropin concentrations, and rates of bone age advancement, no change in...

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**TABLE 1 Relative Potency of Select AIs**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dosage</th>
<th>% Aromatase Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglutethimide</td>
<td>250 mg 4 times daily</td>
<td>90.6</td>
</tr>
<tr>
<td>Testolactone</td>
<td>10 mg/kg 4 times daily</td>
<td>&lt;90.0</td>
</tr>
<tr>
<td>Formestane</td>
<td>125 mg twice daily</td>
<td>91.9</td>
</tr>
<tr>
<td>Fadrozole</td>
<td>2 mg twice daily</td>
<td>92.6</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>1 mg once daily</td>
<td>97.3</td>
</tr>
<tr>
<td>Letrozole</td>
<td>2.5 mg once daily</td>
<td>&gt;99.1</td>
</tr>
</tbody>
</table>
predicted adult height was noted at the conclusion of the
study.^

In a subsequent follow-up report, however, an
average increase in predicted adult height of 12.9 cm
was noted after 6 years of combination therapy.^

Although this was a limited data set, the paucity of other
robust treatment options and the positive results effect-
ively established spironolactone and testolactone as
first-line treatment for this disorder for many years.
With the advent of newer and more potent pharma-
ologic agents with similar mechanisms of action, attention
has now turned to potential alternatives for the treat-
ment of FMPP.^

Novel combination therapy in the form of the antiandrogen bicalutamide, combined with the
third-generation AI anastrozole has now been reported
in 2 patients with FMPP, who have been treated for 16
to 44 months. In both boys, striking reductions in
growth velocity, rate of skeletal maturation, and puber-
tal progression have been observed without adverse
events.^

Both medications require once-daily dosing,
which represents an additional superior feature over
earlier regimens. An international, prospective, multi-
center study is under way which will undoubtedly pro-
vide valuable information regarding the safety and effi-
cacy of bicalutamide and anastrozole for the treatment of
precocious puberty in boys with FMPP.

McCune-Albright Syndrome

In contrast to the generally positive results of AIs (com-
bined with antiandrogens) for the treatment of FMPP,
experience with this class of compounds in children with
MAS has been mixed. To date, limited data are available
on the use of first-, second-, and third-generation AIs for
the treatment of precocious puberty in this setting, pri-
marily in girls. An initial pilot study of short-term testo-
lactone administration involving 5 girls with MAS
seemed beneficial.^

When patients were followed for a
longer period of time, however, a distinct loss of efficacy
was noted in many after 3 years of treatment.^

Not only was there a recurrence of ovarian cysts, but also most
patients continued to have periodic vaginal bleeding.
Additional difficulties were noted with compliance, be-
cause of the 4-times-a-day dosing schedule required
when using testolactone. A trial that investigated the
second-generation AI fadrazole for the treatment of
MAS-associated precocious puberty also proved disap-
pointing.^

In addition to suboptimal efficacy, fadrazole resulted in a dosage-dependent subclinical inhibition of
cortisol and aldosterone biosynthesis, causing additional
research efforts with this drug in MAS to be aban-
doned.^

In this study, as with testolactone,^
testoster-
one and androstenedione levels were mildly elevated
above the prepubertal range, but no virilization was
observed. Until recently, only anecdotal reports regard-
ing the utility of the third-generation agents anastrozole
and letrozole for the treatment of MAS were avail-
able;^

however, data from a recently completed mul-
ticenter study in which 27 girls with MAS were treated
with anastrozole for 1 year have now been analyzed.^

Anastrozole was ineffective in halting vaginal bleeding
and other indices of precocious puberty in these patients;
no adverse events were noted. A recently published pilot
study of letrozole in 9 girls who had MAS and precocious
puberty and were treated for up to 36 months reported
a slowing of growth rate and bone age advancement and
fewer episodes of vaginal bleeding;^

however, by 24 to 36 months, increased ovarian volume and cyst enlarge-
ment were observed. One girl experienced ovarian tor-
sion. Given the latter observations, it is reasonable to
conclude that no “gold standard” currently exists for the
treatment of precocious puberty in children with MAS.^

CONGENITAL ADRENAL HYPERPLASIA

Judicious treatment of children with CAH can allow
them to reach midparental height with traditional ther-
apy (hydrocortisone and fludrocortisone).^

Poorer height outcomes tend to occur in simple virilizers who
begin treatment late or in children who are exposed to
equivalent dosages of glucocorticoids > 15 mg/m² per
day of hydrocortisone,^

or to prednisone.^

Nonetheless, the average adult height of children who are treated with conventional therapy and appropriate oversight
and compliance is approximately −1.4 SD.^

In some patients, supraphysiologic dosages of glucocorticoids are
required to suppress excess adrenal androgen secretion. Either chronic increased androgen secretion or increased
glucocorticoid exposure may adversely affect adult
height. A long-term clinical trial evaluating the addition of
the antiandrogen flutamide (10 mg/kg per day divided
twice daily) and the AI testolactone (40 mg/kg per day
divided 3 times daily), in addition to a relatively low
replacement dosage of hydrocortisone (8 mg/m² per
day) and fludrocortisone has been under way at the
National Institutes of Health since the late 1990s. An
interim report described 20 children who were ran-
donously assigned to long-term parallel groups comparing
the experimental 4-drug regimen with traditional ther-
apy (hydrocortisone 13 mg/m² per day and fludrocorti-
sone).^

After 2 years, the group that is receiving the
experimental treatment regimen had elevated blood an-
drogen levels yet had normal linear growth rate and
bone maturation. No significant long-term adverse ef-
fects were seen. This trial is still ongoing and has been
fully enrolled (32 patients) for 2 years. Patients in the
experimental group were switched from testolactone to
letrozole after May 2004. Letrozole has been very well
tolerated (D. Merke, MD, personal written communica-
tion, November 2006). Until these data are critically
assessed and published, this therapeutic regimen must
be considered experimental.

PUBERTAL GYNECOMASTIA

Gynecomastia represents a benign proliferation of the
breast glandular tissue and can be detected in up to 60%
of boys during puberty. This clinical condition is thought
to result from an imbalance of the estrogen stimulatory
effects relative to the androgen inhibitory effects at the
breast tissue level.^

Histologically, gynecomastia is charact-
erized early by ductal proliferation and the for-
mation of vascular connective tissue. If present beyond 1
year, then chronic fibrous changes may occur associated
with dilated ducts and increased stromal hyaliniza-
tion, 38-40 Whereas most pubertal gynecomastia resolves spontaneously, 25% may persist for ≥2 years.41 Antiestrogens, nonaromatizable androgens (including dihydrotestosterone), and first-generation AIs have been used to treat gynecomastia with variable success. Most reports include small numbers of patients with no control group.42-47 In 2004, Plourde et al48 reported the only randomized, placebo-controlled study performed in adolescents with pubertal gynecomastia using an AI. At the start of the study, patients had gynecomastia that was present for at least 6 months and was stable or increasing. The trial assessed breast volume ultrasonographically in boys aged 11 to 18 years before and after a 6-month trial of anastrozole 1 mg or placebo. A positive response was considered > 50% reduction in breast volume. At 6 months, anastrozole significantly increased the testosterone/estradiol ratio compared with pretreatment (166% anastrozole vs 39% placebo), but the percentage of boys with significant reduction in breast volume did not differ between groups (38% vs 31%). Breast pain decreased in both groups. In the anastrozole-treated group, estradiol levels declined 20% and gonadotropin and testosterone levels increased. Biochemical changes did not correlate with clinical response. The authors postulated that if therapy had begun earlier while breast tissue was in a more proliferative stage, then an effect of the AI may have been observed. Also, the estradiol assay used in the study was not very sensitive, and it was difficult to assess the degree of estrogen reduction. The authors suggested that in the presence of even a small amount of estrogen, gynecomastia can persist. Although a more effective enzyme blockade and earlier initiation of therapy may prove beneficial, additional randomized, controlled trials are needed to test these hypotheses before AIs can be endorsed for the treatment of adolescents with pubertal gynecomastia. Lack of sensitivity of commercial estradiol assays49 may prove to be an obstacle for effective laboratory monitoring of aromatase blockade in adolescents.

In a randomized, placebo-controlled study of 114 adult men who had prostate cancer and were treated with the antiandrogen bicalutamide, the effects of tamoxifen (20 mg/day), an antiestrogen, and anastrozole (1 mg/day) on prevention of gynecomastia were assessed. Tamoxifen significantly reduced the occurrence of gynecomastia after 48 weeks of bicalutamide treatment (10% vs 73% in placebo). The effect of anastrozole did not differ from placebo (51%).49 It may be that estrogen receptor blockers are a more effective treatment than AIs in the prevention of gynecomastia.

Gynecomastia may occur in boys with aromatase excess associated with Sertoli cell tumors in Peutz-Jeghers syndrome and in families with constitutively active mutations affecting the aromatase gene. Although reports are extremely limited, it has been suggested that gynecomastia in these conditions may be more responsive to AI therapy than is pubertal gynecomastia.50-51

**SHORT STATURE**

Children with short stature comprise a large portion of the typical pediatric endocrinologist’s practice. Current strategies for increasing adult height include growth hormone treatment alone or together with GnRH analog therapy to suppress pubertal development.54-56 These approaches are expensive and invasive (requiring injections), and GnRH analog therapy may result in potentially adverse metabolic aberrations in children whose puberty is occurring at a physiologically normal time.57-59 The emergence of AIs as a possible alternative means of delaying epiphyseal fusion and prolonging linear growth has, therefore, generated immense interest. Before widespread acceptance, it is critical to examine the existing data on use of AIs in boys with short stature with an emphasis on its limitations and the remaining questions.

The literature regarding the use of AIs for treatment of boys with short stature is limited to a small number of original studies60-65 and 2 reviews.66 The primary data from the 6 English-language articles cited in PubMed are summarized in Table 2. Taken together, these data suggest that AIs hold promise for increasing adult height in short children, apparently by maintaining growth velocity while decreasing bone age progression. Although limited to 1 report,63 the available data on near adult height indicate that gains noted during initial therapy may be (although not always fully) sustained into adulthood. Several features are common among the published reports. All of the data derive from interventions limited to male patients (1 abstract reported treatment of female patients67), and the AIs used (anastrozole and letrozole) seemed to be well tolerated. When measured, estradiol levels were substantially decreased, whereas testosterone, follicle-stimulating hormone, and luteinizing hormone levels were significantly increased in those who received treatment compared with control subjects. Presumably, the increased follicle-stimulating hormone levels were primarily responsible for the increases in testicular volume noted during initial treatment in 2 of the trials.61,64 The effects of the high testosterone levels have not been systematically evaluated, but it is important to note that these levels may be substantially elevated and can reach values far above the adult male reference range. The highest levels were reported in the trial that involved patients with constitutional delay of growth and puberty, in which mean testosterone levels reached 1416 ng/dL (49.1 nmol/L) and 1863 ng/dL (64.6 nmol/L) in the initial treatment group and in the subgroup that was followed to near-adult height, respectively.61,65 These values compare to control values of 456 ng/dL (15.6 nmol/L) and 542 ng/dL (18.8 nmol/L). Other features of the reports include some patients’ experiencing gynecomastia while receiving the AIs,61 which, along with reduced but still measurable levels of estradiol, indicates that none of the protocols likely achieved full blockade of aromatase enzyme activity. In each report, the hormonal changes that were induced by the AIs all normalized within 6 months after the discontinuation of treatment.60,61,64 Finally, growth velocity seems to have been preserved in the treatment groups despite apparent lack of estradiol-induced changes in insulin-like growth factor-1 levels during treatment.61,62
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>No. of Subjects</th>
<th>Underlying Diagnoses</th>
<th>Mean CA, y</th>
<th>Mean BA, y</th>
<th>Treatment Protocol</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faglia et al(^60), 2000</td>
<td>Case Report</td>
<td>1</td>
<td>History of central precocious puberty</td>
<td>11.0</td>
<td>16.4</td>
<td>Anastrozole 1 mg orally once daily for 36 mo</td>
<td>Gain of 6 cm over pretherapy predicted height; BA progressed only 19 mo during 36 mo</td>
</tr>
<tr>
<td>Wickman et al(^61), 2001</td>
<td>RDBPCT</td>
<td>22 (10 therapy; 12 placebo)</td>
<td>Constitutional delay</td>
<td>15.2 therapy; 15.0 placebo</td>
<td>13.1 therapy; 12.6 placebo</td>
<td>Tenanthate 1 mg/kg every 4 weeks × 6 plus letrozole 2.5 mg once daily or placebo for 12 mo</td>
<td>Mean increase in predicted adult height of 5.1 ± 3.7 cm letrozole versus placebo</td>
</tr>
<tr>
<td>Mauras et al(^62), 2004</td>
<td>Open label, controlled, not an RDBPCT</td>
<td>19 (10 therapy; 9 control)</td>
<td>Growth hormone deficiency</td>
<td>14.9 therapy; 15.1 control</td>
<td>13.2 therapy; 13.4 control</td>
<td>Growth hormone 0.3 mg/kg per wk plus anastrozole 1 mg once daily or no therapy for 12 mo</td>
<td>No difference in GV, height SDS, BA advancement, or predicted adult height in therapy versus control group</td>
</tr>
<tr>
<td>Karmazin et al(^63), 2005</td>
<td>Chart review</td>
<td>24</td>
<td>Various; 6 different diagnoses included; 15 of 24 on GH therapy, 6 of 24 on androgen therapy</td>
<td>14.0</td>
<td>Not reported</td>
<td>Letrozole 2.5 mg once daily for mean of 12.3 mo plus ongoing other therapy</td>
<td>Predicted height SDS increase 0.77 (no androgen therapy) and 1.03 (androgen therapy); BA progression decelerated; GV did not change</td>
</tr>
<tr>
<td>Hero et al(^64), 2005</td>
<td>RDBPCT</td>
<td>30 (16 therapy; 14 placebo)</td>
<td>Idiopathic short stature, including SGA</td>
<td>11.0 therapy; 11.0 placebo</td>
<td>9.1 therapy; 8.9 placebo</td>
<td>Letrozole 2.5 mg once daily or placebo for 24 mo</td>
<td>Predicted height increase 5.9 cm; height SDS for BA increase 0.7; BA progression decelerated; no difference seen in GV</td>
</tr>
<tr>
<td>Hero et al(^65), 2006</td>
<td>RDBPCT, follow-up of previous study(^2)</td>
<td>17 (9 therapy; 8 placebo), final data from 3 fewer than in previous study(^2)</td>
<td>Constitutional delay</td>
<td>15.2 therapy; 14.8 placebo</td>
<td>Delayed: 2.2 therapy; 2.3 placebo</td>
<td>Tenanthate; 1 mg/kg every 4 weeks × 6 plus letrozole 2.5 mg once daily or placebo for 12 mo (as in previous study) followed to near final height</td>
<td>Near final height closer to MPH in therapy versus placebo group, —1.3 vs. —4.8 cm; 0.6 SDS additional increase in height compared with pretherapy height in therapy group</td>
</tr>
</tbody>
</table>

CA, chronologic age; BA, bone age; RDBPCT, randomized, double-blinded, placebo-controlled trial; SDS, SD score; GV, growth velocity; SGA, small for gestational age; T, testosterone; MPH, midparental height.
Although these reports are encouraging, it is important that they be interpreted cautiously. In the combined reports, only 61 patients had been treated, and only 2 randomized, double-blinded, placebo-controlled trials had been performed. Three of the 6 original reports derive from the same research group, and 2 of those involve the same initial patients. Only 9 patients have been followed to near-adult height; there are no available data regarding adult heights from the controlled trials. Moreover, 1 of the studies involving patients with growth hormone deficiency found no change in mean predicted adult height among the patients who were treated with the AI.

The reasons for the lack of effect in this study of growth hormone–deficient boys are not clear. Theoretically, it could stem from less effective blockade of enzyme activity by anastrozole than letrozole or from too short an intervention (12 months). Alternatively, this study could be an indication that there are important limitations in the ability of AIs to increase adult height. In support of the first hypotheses is a related ongoing randomized, double-blinded, placebo-controlled trial reported thus far only in abstract form. This trial involves 52 growth hormone–deficient boys who were randomly assigned to receive growth hormone or growth hormone plus anastrozole and has thus far demonstrated an increase in predicted adult height of 2 cm in those who received the AI for 24 months. Conversely, the possibility of limitations on efficacy is supported by another abstract reporting 2 years of data from an open-label study involving 40 boys with idiopathic short stature, 20 of whom received anastrozole for 2 years. In this study, treatment seemed neither to slow skeletal maturation nor to increase predicted adult height. Similarly, it should be noted that 3 patients in 1 of the published reports experienced an increase in progression of bone age compared with chronologic age and that 1 patient in another report experienced a decrease in predicted adult height of 3.5 cm while on therapy.

Although the overall results of treatment with AIs are encouraging and their use seems to be rapidly expanding, we agree with the recommendation by several of the authors of the above-mentioned studies that endocrinologists should be cautious and that AIs should preferentially be used in carefully controlled clinical trials. More data on adult heights are needed. If AIs are shown to increase adult height, then questions that will still need to be addressed include the optimal agent and dosage, the duration of therapy, and whether the intervention is equally efficacious regardless of underlying diagnosis (eg, do patients with idiopathic short stature, constitutional delay of growth and maturation, and growth hormone deficiency all gain similarly?). What is the average and range of the gain in adult (not predicted adult) height? Are there predictors of height gain such as chronologic age or bone age at initiation of therapy? In 1 report, outcome did not depend on bone age at initiation, but the mean bone age at baseline was only 9.1 ± 2.3 years. It is not yet clear how effective the intervention would be among children with more advanced bone ages.

SAFETY ISSUES

For short stature as well as other indications, it is critical that additional safety data be obtained during subsequent clinical trials. The available short-term data are reassuring; however, long-term data are lacking, and the number of children and adolescents who are treated within trials is still small. These safety concerns are perhaps most pertinent to short stature, for which the number of youth who might be treated is large. An area of substantial concern is the potential effect on bone mineral density (BMD) of a treatment regimen that decreases estradiol concentrations. Although data are limited, BMD of lumbar vertebrae, the femoral neck, and whole body as well as markers of bone formation, such as alkaline phosphatase and osteocalcin, have been assessed in several of the published reports. The available data are reassuring and indicate that as puberty progressed, bone density increased similarly in patients who were receiving AIs and in control subjects, and 1 study even reported that volumetric, as opposed to areal, BMD of the lumbar spine increased during AI administration. Although the ability to preserve and perhaps even temporarily advance the progression of puberty in boys is an attractive feature of AIs, potential effect on spermatogenesis and sperm motility is another area of concern. This issue has not yet been fully assessed in children and adolescents who are treated with AIs, and it is imperative that normal spermatogenesis be verified in larger studies with longer follow-up. Related to other safety concerns, Hero et al reported that aromatase inhibition reduced high-density lipoprotein cholesterol and decreased relative fat mass in boys who were treated for 2 years, but no significant effects on insulin sensitivity have been observed.

Acquisition of additional data regarding bone health, reproductive function, lipid and carbohydrate metabolism, and adrenal function will be important in assessing the pros and cons of AI therapy. These additional safety data are critical to providing sufficient surveillance for relatively rare adverse effects that might influence the clinical use of these agents but have not yet been detected among the small number of patients studied to date.

CONCLUSIONS

The use of third-generation AIs will likely play an emerging role in the treatment of specific endocrine disorders in children. They are well tolerated and are available as a convenient once-daily oral dose; however, safety information regarding long-term effects of AIs on indices such as bone mineral acquisition, spermatogenesis, and exposure to supraphysiologic testosterone levels are still needed. In addition, definitive data for most indications are still lacking. AIs when combined with antiandrogens are the treatment of choice for male limited peripheral precocious puberty, and data from an ongoing clinical trial may provide additional evidence in support of the specific combination of bicalutamide with anastrozole. Use of similar combined therapy as an adjunct to traditional therapy for CAH, allowing lower glucocorticoid dosages, may prove effective to increase
adult height and prevent early virilization; results of a long-term study testing this hypothesis should be forthcoming. Efficacy of AIs in girls with MAS seems to be limited; progression of ovarian cyst formation may further curtail utility in this group of patients. Use of AIs in boys with idiopathic short stature and short stature associated with growth hormone deficiency or constitutional delay may increase adult height modestly; however, data on adult height are lacking, and there is no information identifying which children are likely to benefit most. Additional controlled studies are required before this therapy can be routinely recommended to augment adult height. There is no current evidence that third-generation AIs reduce pubertal gynecomastia; studies testing the hypothesis that benefit would derive from initiating therapy before 6 months and establishing a more effective blockade need to be performed. Thus, despite the potential promise of these agents in the treatment of selected pediatric endocrine disorders, we urge physicians to exercise caution in the use of these agents outside of controlled clinical trials.

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