Letrozole Treatment of Precocious Puberty in Girls with the McCune-Albright Syndrome: A Pilot Study

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Context: Girls with McCune-Albright syndrome (MAS) and related disorders have gonadotropin-independent precocious puberty due to estrogen secretion from ovarian cysts. Their puberty does not respond to GnRH agonist therapy, and short-acting aromatase inhibitors have had limited effectiveness.

Objective: Our objective was to assess the effectiveness of the potent, third-generation aromatase inhibitor letrozole in decreasing pubertal progression in girls with MAS and to assess the response of indices of bone turnover associated with the patients’ polyostotic fibrous dysplasia.

Design: Subjects were evaluated at baseline and every 6 months for 12–36 months while on treatment with letrozole 1.5–2.0 mg/m²·d.

Setting: This was an open-label therapeutic trial at a single clinical center.

Patients: Patients included nine girls aged 3–8 yr with MAS and/or gonadotropin-independent puberty.

Main Outcome Measures: Measures included rates of linear growth, bone age advance, mean ovarian volume, estradiol, episodes of vaginal bleeding, and levels of the indices of bone metabolism: serum osteocalcin, alkaline phosphatase, urinary hydroxyproline, pyridinoline, deoxypyridinoline, and N-telopeptides.

Results: Girls had decreased rates of growth (P ≤ 0.01) and bone age advance (P = 0.004) and cessation or slowing in their rates of bleeding over 12–36 months of therapy. Mean ovarian volume, estradiol, and indices of bone metabolism fell after 6 months (P ≤ 0.05) but tended to rise by 24–36 months. Uterine volumes did not change. One girl had a ruptured ovarian cyst after 2 yr of treatment.

Conclusions: This preliminary study suggests that letrozole may be effective therapy in some girls with MAS and/or gonadotropin-independent precocious puberty. Possible adverse effects include ovarian enlargement and cyst formation. (J Clin Endocrinol Metab 92: 2100–2106, 2007)
tides (NTX), pyridinoline (PYR), and deoxypyridinoline (dPYR) (8). The levels of biomarkers often correlate with the extent and severity of skeletal involvement and with the degree of impairment of physical function in MAS (9). Patients may also exhibit renal phosphate wasting with a decrease in the renal tubular maximum reabsorption of phosphate relative to glomerular filtration rate (TmP/GFR). This may result in low levels of serum phosphate (10), with hypophosphatemic rickets and lesion osteomalacia that may exacerbate the deformities of the bone disease.

It is not known whether exposure to elevated levels of sex steroids directly affects the progression of bone lesions in MAS patients. Estrogen receptors have been identified in a bone lesion from a pregnant woman with MAS (11), and increased levels of bone biomarkers have been observed during pregnancy in MAS patients (12), suggesting that estrogens or other intrapartum growth factors could stimulate lesion growth. In addition, we observed that girls who present with vaginal bleeding and precocious puberty at a very early age (<1–2 yr) often have severe, progressive, disabling fibrous dysplasia as well, although it is also possible that this reflects the presence of a higher concentration of mutated cells in the ovaries, bones, and other organs of severely affected subjects.

Establishing a safe, effective, long-term treatment for the precocious puberty in girls with MAS, and in girls with isolated gonadotropin-independent precocious puberty without the other signs of MAS, has been a challenge. Trials have used drugs that block the biosynthesis of estrogens, such as the aromatase inhibitors, and estrogen antagonists. Our own early studies demonstrated that the short-acting aromatase inhibitor testolactone was partially effective therapy initially but that puberty resumed in many girls after 2–4 yr of treatment (4). Conversely, our studies of the second generation, nonsteroidal aromatase inhibitor fadrozole, used together with a GnRH agonist, demonstrated no benefit in a generation, nonsteroidal aromatase inhibitor fadrozole, used for the treatment of estrogen-dependent malignancies such as breast cancer. Letrozole reportedly suppresses estrogen levels by more than 95% in postmenopausal women and is usually administered at a dose of 2.5 mg (~1.5 mg/m²) per day. It has not been associated with clinical evidence of impaired biosynthesis of aldosterone or cortisol (15). Side effects in adult women have reportedly included musculoskeletal discomfort (22%) and nausea (15%) (16).

Here we report the results of a study designed to assess the effectiveness of letrozole in treating the precocious puberty in girls with MAS and learn whether treatment would affect the serum and urine levels of the indices of bone metabolism that reflect the activity of PFD (17).

**Subjects and Methods**

**Subjects (Table 1)**

The subjects were nine girls with gonadotropin-independent precocious puberty who had initially presented at ages 1.3–6.0 yr with breast development, vaginal bleeding or discharge, and suppressed levels of LH and FSH. All girls had advanced BA and 8 had significantly increased growth rate SDS scores (SDS). Seven girls had areas of cafe-au-lait pigmentation. No girl had the thyroid abnormalities (suppressed TSH, elevated T3 or thyroid inhomogeneity on ultrasound) characteristic of many patients with MAS, and none had a history of adrenal hyperfunction. Serum phosphate levels were normal for age (4.5–5.6 mg/dl) in all girls. Technetium bone scans and/or skeletal survey revealed asymmetrical areas of increased uptake and ground glass lucencies in

**TABLE 1. Clinical characteristics of nine girls with MAS at the start of letrozole therapy**

<table>
<thead>
<tr>
<th>Patient</th>
<th>CA (yr)</th>
<th>BA (yr)</th>
<th>Height (cm)</th>
<th>Growth (cm/yr)</th>
<th>Pubertal stage</th>
<th>Bone disease</th>
<th>Menses</th>
<th>Previous Tx for precocious puberty</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>SDS</td>
<td>SDS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>4.3</td>
<td>8.3</td>
<td>99.5 (1.9)</td>
<td>+0.8 (5.0)</td>
<td>IV/I</td>
<td>Yes</td>
<td>++</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>5.8</td>
<td>11.0</td>
<td>128.2 (1.9)</td>
<td>+2.7 (3.8)</td>
<td>IV/II</td>
<td>Yes</td>
<td>++++</td>
<td>Testolactone</td>
</tr>
<tr>
<td>3</td>
<td>4.8</td>
<td>8.5</td>
<td>108.4 (1.7)</td>
<td>+0.4 (4.0)</td>
<td>IV/I</td>
<td>Yes</td>
<td>+</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>5.9</td>
<td>8.8</td>
<td>119.8 (1.5)</td>
<td>+1.1 (3.2)</td>
<td>IV/IV</td>
<td>Yes</td>
<td>+</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>6.1</td>
<td>8.8</td>
<td>120.1 (1.4)</td>
<td>+0.9 (4.6)</td>
<td>IV/III</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>3.5</td>
<td>8.5</td>
<td>103.0 (1.4)</td>
<td>+1.5 (2.7)</td>
<td>IV/I</td>
<td>Yes</td>
<td>+ + +</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>4.8</td>
<td>10</td>
<td>116.8 (2.1)</td>
<td>+2.4 (1.5)</td>
<td>IV/III</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>3.3</td>
<td>8.5</td>
<td>105.0 (2.1)</td>
<td>+2.3 (2.6)</td>
<td>IV/III</td>
<td>No</td>
<td>+</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>8.1</td>
<td>12.0</td>
<td>132.5 (1.5)</td>
<td>+0.7 (0.6)</td>
<td>II/II</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

CA, Chronological age; BA, bone age; Tx, treatment; R, right.

* SDS, compared with normal girls of comparable chronological age.

**+**, mild absence of facial asymmetry, limb length discrepancy or gait abnormality; **+,** moderate, facial or skull asymmetry, limb length discrepancy, no fracture or surgery; **+++,** marked, as in moderate but impaired mobility, fracture, previous surgery.
the skull and/or extremities in 5 girls, indicating the presence of active PFD. Patient 2 had sustained a fracture of the right femur at age 3.8 yr and also had a moderate scoliosis (37°) at the start of therapy. Patient 2 had also been treated with testolactone, 40 mg/kg/d, with inadequate response. Her testolactone was discontinued 6 months before initiating letrozole. Patient 6 had a fracture of the left femur at 3 yr, that was treated with an intramedullary rod. Patient 3 had undergone right ovariectomy at age 1.3 yr, and patient 8, a right ovarian cystectomy at age 2.0 yr; pubertal development and vaginal bleeding recurred in both these girls. Patient 9 had gonadotropin-independent puberty and bleeding at age 6 yr, but had no other skin or bone signs of MAS.

**Methods**

**Protocol.** After a 3- to 6-month baseline period, letrozole was initiated orally at a dose of 0.5 mg/m² during 1-7 of treatment. The dose was increased to 1.0 mg/m² on d 8-14 and to 1.5 mg/m² on d 15-21. There was an option to increase the dose to 2 mg/m² during therapy if a patient had progressive BA/CA, elevated serum estradiol (E) levels, or increased ovarian cyst volume while on 1.5 mg/m². The dose was divided twice a day (every 12 h) to decrease the possibility of gastric discomfort.

At the start of the study, to confirm the effectiveness and the safety of letrozole, the first four subjects (patients 1-4) were treated for 6 months, followed by a 6-month withdrawal period (Table 2). These subjects were evaluated every 3 months during the on- and off-treatment periods. On the last day of the 6-month on-treatment period, serum levels of letrozole were measured at 0, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, and 24 h after the final, morning dose of drug.

In these four subjects, letrozole was restarted after the 6-month off-treatment period when girls exhibited recurrent signs and symptoms of puberty (vaginal bleeding, breast development, and/or bone age progression).

Because the safety and apparent effectiveness of letrozole had been confirmed by the initial studies in patients 1-4, patients 5-9 were given uninterrupted therapy for periods of 12-36 months. These patients were evaluated every 6 months. In patients 1-4, the 12-, 24-, and 36-month data were obtained from the periods of continuous, uninterrupted letrozole therapy that was begun after the completion of the initial 6 months on/6 months off periods. Patients 1, 3, and 4 received 36 months, and patient 2 received 12 months of uninterrupted treatment.

The patients’ mean ovarian volume (MOV), E, LH, and FSH and indices of bone turnover values are presented at baseline (before treatment); 6 months after the start of treatment; and after 12, 24, and 36 months of uninterrupted treatment. The linear growth and BA/CA values are presented after 12, 24, and 36 months of uninterrupted treatment.

**Growth, ovarian volume, skeletal maturation**

Height was determined at 0900 h as the average of three measurements on a stadiometer. Growth rate (centimeters per year) was expressed as sd units (SDS), compared with normal girls of comparable age. Ovarian volumes were calculated using pelvic ultrasonography according to the formula: volume = length × width × thickness × 0.52 (18) The MOV denotes the mean of the volume of the right and left ovaries. When one ovary was absent, the MOV was the volume of the remaining ovary. Uterine length was estimated from the craniocaudal dimensions of the uter. Bone age was determined according to the method of Greulich and Pyle (19); all bone ages were read by a single investigator (S.H.) who was blinded to treatment status. Frequency and duration of vaginal bleeding were obtained from parental diaries and recorded as days per episodes of bleeding in each 6-month period.

**Serum and urinary assays**

Blood samples were collected at 0900 h after an overnight fast. Urine measurements were performed on aliquots from 24-h collections collected coincidentally with serum. Commercial immunoassay kits were used to measure levels of E (Diagnostic Products Corp., Los Angeles, CA), LH, and FSH (Abbott Laboratories, Abbott Park, IL) and OC (immunoradiometric assay; Nichols Institute Diagnostics, San Clemente, CA). Urinary OHP and PYR-dPYR were measured using a commercial HPLC, and urinary NTX were measured using a commercial immunoassay (Mayo Medical Laboratories, Rochester, MN).

Renal phosphate handling (TmP/GFR) was measured with aliquots from 24-h urine collections as previously described using an adaptation of the nomogram of Walton and Bijvoet (20).

Serum concentrations of letrozole were measured by HPLC after extraction using previously described methods (21). The detection limit of the assay was 1.4 nmol/liter and the interassay coefficient of variation was 9.8%.

An Institutional Review Board at the National Institutes of Health approved the protocol, and informed consent was obtained from a parent.

**Results**

**Initial 6-month trial (patients 1-4; Table 2)**

During the 6 months on treatment, the mean ± sd MOV, change in bone age vs. change in chronological age (ABA/ΔCA), and growth velocity SDS were decreased, compared with before treatment. E fell during therapy (213 vs. < 20 pg/ml) in patient 2, the only subject with detectable serum E at the start of therapy. During the 6 months off letrozole, the mean MOV, ΔBA/ΔCA, and growth SDS increased in all girls.

Patients 3 and 4 had no vaginal bleeding during treatment, patient 1 had a single episode 1 month after starting treatment, and patient 2 continued to bleed but at a decreased frequency. Patients 1 and 4 had a decrease in breast stage, and patients 2 and 3 had a decrease in pubic hair stage after 6 months of treatment.

**Table 2.** Response to 6-month trial of letrozole therapy in four girls with precocious puberty and polyostotic fibrous dysplasia of bone due to MAS

<table>
<thead>
<tr>
<th></th>
<th>Before</th>
<th>During</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOV (ml)</td>
<td>5.3 ± 5.7</td>
<td>1.4 ± 1.0b</td>
<td>4.3 ± 4.3</td>
</tr>
<tr>
<td>ΔBA/ΔCA</td>
<td>1.6 ± 0.3</td>
<td>1.5 ± 0.3a</td>
<td>1.4 ± 0.3</td>
</tr>
<tr>
<td>Growth rate (SDS)</td>
<td>2.8 ± 1.4</td>
<td>−1.2 ± 1.0</td>
<td>2.5 ± 3.5</td>
</tr>
<tr>
<td>Serum AP (U/liter)</td>
<td>361 ± 72</td>
<td>275 ± 68a</td>
<td>301 ± 69</td>
</tr>
<tr>
<td>OC (μg/liter)</td>
<td>75 ± 23</td>
<td>54 ± 45</td>
<td>30 ± 3</td>
</tr>
<tr>
<td>Urine OHP (μg/mg creatinine)</td>
<td>251 ± 51</td>
<td>147 ± 46b</td>
<td>179 ± 39</td>
</tr>
<tr>
<td>NTX (nmol/mmol creatinine)</td>
<td>835 ± 227</td>
<td>570 ± 220</td>
<td>652 ± 181</td>
</tr>
<tr>
<td>dPYR (nmol/mmol creatinine)</td>
<td>73 ± 13</td>
<td>65 ± 27</td>
<td>75 ± 20</td>
</tr>
<tr>
<td>PYR (nmol/mmol creatinine)</td>
<td>306 ± 45</td>
<td>263 ± 96</td>
<td>305 ± 54</td>
</tr>
</tbody>
</table>

Results are the mean ± SD of observations at −3 and 0 month prior to treatment (before), +3 and +6 months during treatment (during), and +9 and +12 months after discontinuation of treatment (after). To convert E to picomoles per liter, multiply by 3.671; to convert OC to nanomoles per liter, multiply by 0.17; to convert OHP to millimoles per millimole creatinine, multiply by 0.86.

a P < 0.05, compared with before treatment.

b SDS, compared with normal girls of comparable age.
During the 6 months of letrozole treatment, there were significant decreases in the mean ± sd levels of the serum markers of bone formation AP and OC (P < 0.05, compared with before treatment). There were also decreases in the urinary marker of bone resorption OHP (P < 0.05, compared with before treatment) and decreasing trends in the mean levels of NTX, dPYR, and PYR, although these latter changes were not statistically significant. During the 6 months off therapy, the urinary indices of bone turnover rose toward pretreatment levels.

The mean ± sd TmP/GFR was within the previously reported normal range [3.5–7.3 mg per 100 ml for children 2–15 yr (10)] at baseline and did not change during letrozole treatment (before treatment, 4.8 ± 0.4; during treatment, 4.4 ± 0.4 mg per 100 ml). The serum phosphate levels, random serum cortisol, and plasma renin activity levels remained normal in all girls throughout the study. Letrozole was restarted in subjects 1–4 after completion of the 6-month off-treatment period and was continued without interruption for 12–48 months. The clinical and laboratory values during long-term treatment in these subjects (see below) is from observations obtained after 12, 24, and 36 months of uninterrupted letrozole.

Long-term studies

Growth and pubertal changes (Fig. 1). The subjects’ mean ± sd BA/CA and growth velocity SDS were significantly decreased after 12, 24, and 36 months of treatment, compared with before therapy. The mean serum E and MOV fell markedly at 6 months but tended to increase toward baseline levels by 12 and 24 months; however, these changes did not achieve statistical significance due to marked variability in parameter values. Notably, at 24 months, the mean MOV tended to be higher than before the start of therapy due to an increase in ovarian cyst volumes in some girls. The patients’ mean baseline LH remained at or less than the assay detection limit (1.0 mIU/ml) both before and at all time points during treatment. The mean baseline FSH was low before treatment but tended to rise during therapy (1.5 ± 1.3, 2.2 ± 1.6, 2.4 ± 1.9, 1.9 ± 1.2, and 3.0 ± 2.5 mIU/ml before and at 6, 12, 24, and 36 months, respectively).

Uterine size did not change significantly during letrozole treatment (mean ± sd craniocaudal uterine length was 4.3 ± 0.9, 3.8 ± 0.8, 4.6 ± 1.4, 4.8 ± 1.0, and 4.3 ± 0.4 cm at 0, 6, 12, 24, and 36 months, respectively).

Vaginal bleeding and pubertal staging

Of the girls who had vaginal bleeding before therapy, patients 4–9 had no more bleeding. Patients 1–3 had a decrease in frequency (patient 2) or one episode of spotting per year (patients 1 and 3) during the 12–36 months of letrozole treatment. Pubertal stages of breasts and pubic hair stabilized (II–IV and I–IV, respectively, before therapy vs. II–V and I–V after 12–36 months of letrozole).

Indices of bone turnover (Fig. 2)

The mean serum OC and AP and the mean OHP fell after 6 months of treatment but rose at 12 and 24 months toward the pretreatment levels. Levels of NTX, PYR, and dPYR also tended to decrease at 6 months, but these changes were not statistically significant.
which is consistent with the long half-life (~2 d) previously reported for adult subjects. However, the levels in our patients were only 25–67% of the steady-state levels in adult women ages 52–76 yr (mean 467 ± 52 nmol/liter) who were treated for 8 wk at a dose of 2.5 mg/d (22).

Serum levels in patient 2, who had been treated with letrozole for 8 wk, were lower (3 h, 167 nmol/liter; 24 h, 158 nmol/liter) than those in the other three girls, who had stopped bleeding before therapy.

Adverse effects during treatment

Patient 1 complained of nonspecific discomfort in the hands and feet during the first 1–2 months of treatment; this resolved spontaneously. Patients 2, 5, 6, and 7 reported transient episodes of abdominal pain, nausea, and vomiting associated with viral syndromes; these episodes also resolved spontaneously. Patient 4 had a mild elevation of total serum bilirubin (1.1–1.4 mg/dl) during and after discontinuation of letrozole, which was restarted at a reduced dose (1.0 mg/m²/d) as a precautionary measure.

Patient 7 developed acute abdominal pain and vomiting after 28 months of letrozole treatment and 4 months after her dose had been increased to 2 mg/m²/d due to ovarian enlargement. A right-sided hemorrhagic ovarian cyst was identified, with evidence of ovarian torsion. The cyst was removed via laparoscopic surgery. Letrozole was discontinued immediately. A GnRH stimulation test performed at a subsequent evaluation in the study clinic indicated that her gonadotropins had entered the range of central puberty (baseline and 120 min LH and FSH: 5 and 42 and 3 and 21 mIU/ml, respectively); hence, she was started on GnRH agonist treatment with good response.

Two patients with more advanced PFD had progression of their bone disorder during therapy: In patient 2, a thoracolumbar scoliosis progressed (37° → 42°) over the 12 months of treatment, and patient 6 sustained increased leg asymmetry and fractures of the humerus and fifth finger after 18 months of treatment. These are expected complications of FFD in MAS children.

Discussion

This pilot study of nine girls with MAS indicates that letrozole can be effective treatment for girls with gonadotropin-independent precocious puberty. Our patients had decreased rates of growth and bone maturation and cessation or slowing of menses during therapy. However, although there was a significant decrease in ovarian volumes over the first 6 months, the mean MOV tended to increase over the first and second years of treatment, and cysts redeveloped in some girls.

Because MAS is a rare disorder and because data from an untreated control group of subjects were not available, we designed the study so that each girl would serve as her own control. In subjects 1–4, 6-month baseline data were compared with 6 months on letrozole treatment and 6 months off treatment. Subjects 5–9 were given uninterrupted letrozole, and the results compared with baseline data for each subject. Because the number of subjects was small in this preliminary

Serum letrozole levels

Letrozole was detectable in serum in patients 1–4 at all time points between 0 and 24 h after the final am dose of drug. Mean ± sd serum levels were 188 ± 107 (range 104–296) at 3 h and 178 ± 53 (range 148–257) nmol/liter at 24 h,
study and the experimental design not optimal, a larger number of subjects must be enrolled and treatment continued for a longer time to confirm the effectiveness of letrozole treatment on precocious puberty in girls with MAS and similar disorders and establish its long-term effects on indices of bone metabolism.

We found that serum concentrations of letrozole in our patients were only 25–67% of the mean steady-state plasma levels previously reported in older, postmenopausal women who were given comparable doses. It is possible that our young subjects had a more rapid drug clearance rate, but because we did not measure serum metabolites or urine concentrations and serum concentrations beyond 24 h, we are not able to better characterize the pharmacokinetic disposition of letrozole in our patients. Although the individual patients’ levels exhibited variability over the period of sampling, our finding that mean levels declined by only 5% over 24 h indicates that a single, daily dosing schedule would be appropriate for young children. We found that letrozole concentrations in the patients who stopped menstruating entirely, and thus appeared to respond better to treatment, were not higher than in the two who had some persistence of menstrual bleeding.

In normal girls, markers of osteoblastic bone formation (serum OC and AP) and bone and collagen resorption (urinary OHP, PYR, and dPYR) increase as girls progress from pubertal stages Tanner I to III and then decline to adult levels by Tanner stages IV and V. Levels of these biomarkers tend to parallel the rates of linear growth that accompany the advent of puberty (23–25). Bone biomarker levels are often markedly increased in patients with fibrous dysplasia (8, 26, 27) and can fall after treatments that slow rates of bone turnover. We observed a decrease both in markers of bone formation and bone resorption after the first 6 months of letrozole treatment. We propose that this could have been an initial response to the decreased estrogen levels and a slowing of puberty in these patients, although we are not able to rule out a direct suppressive effect of letrozole on the activity of osteoblast/osteoclast units. However, bone biomarker levels in our subjects returned to pretreatment levels after 12–36 months of letrozole, suggesting that a decrease in E levels may not have long-term suppressive effects on the activity and growth of fibrous dysplastic lesions. An additional factor is that the small group of subjects in this pilot study presented with a relatively mild form of PFD; none had extensive, severe skeletal involvement, rickets, hypophosphatemia, or the markedly elevated levels of bone biomarkers that may be observed in MAS subjects. Continuing studies that include a greater number of girls with extensive PFD lesions may reveal whether the use of potent aromatase inhibitors can modify the progression of the bone disease.

Notably, one of our girls developed a large, unilateral ovarian cyst with ovarian torsion that necessitated surgical intervention. It is not certain that letrozole was directly responsible for this event because ovarian cyst formation is a known complication of MAS in both pediatric and adult females. In this patient’s case, several factors may have contributed to the severity of ovarian cyst enlargement: her subsequent increased gonadotropin responses after GnRH stimulation indicated that she had rapidly developed gonadotropin-dependent puberty during her third year of letrozole therapy between her study evaluations. This may have been related to her increased letrozole dose (2 mg/m²·d). Studies in adults have shown that higher doses of letrozole (2.5–5.0 mg/d) and anastrozole are effective adjunctive treatments in the stimulation of gonadotropin release and follicle enlargement and in inducing ovulation in women undergoing fertility treatments (28, 29).

We were not able to determine the underlying cause of the hand/foot discomfort in patient 1. Her laboratory studies were unremarkable, and neither the bone scan nor x-ray studies revealed significant fibrous dysplasia at these sites. This finding may reflect the musculoskeletal complaints reported by adult women treated with letrozole.

This preliminary study indicates that letrozole can be an effective initial treatment for girls with gonadotropin-independent precocious puberty, and may also offer an alternative therapy for girls who fail to respond to blockers of estrogen action such as tamoxifen. A greater number of subjects and longer periods of treatment are needed before the safety and effectiveness of letrozole can be confirmed. Importantly, the present study indicates that ovarian enlargement and recurrent cyst formation may occur during therapy, particularly in girls receiving higher doses of drug. Patients should be observed at intervals of 3–6 months during treatment and gonadotropin levels measured to rule out the onset of central puberty.

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