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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/m^2·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 ($P \leq 0.01$) and bone age advance ($P \leq 0.004$) 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 ($P \leq 0.05$) 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)**

PRECOCIOUS PUBERTY and vaginal bleeding are often the presenting signs in young girls affected with the rare condition, McCune-Albright syndrome [MAS: the triad of precocious puberty and other forms of endocrine hyperfunction, cafe-au-lait pigment, and the bone disease, polyostotic fibrous dysplasia (PFD; OM 174800)]. MAS is a sporadic disorder associated with postzygotic activating missense mutations (Cys or His $\rightarrow$ Arg^{201}) in the gene for the α-subunit of the stimulatory G protein that regulates cell function by coupling hormone and other receptors to adenylyl cyclase (1). The mutations in MAS are often found in affected tissues, including the ovaries and bone lesions, and are sometimes also found in peripheral lymphocytes (2). The precocious puberty in MAS is caused by estrogen production from large ovarian cysts. In most girls, ovarian cyst formation appears to be independent of gonadotropin action; the gonadotropin levels are often low or in the prepubertal range; thus, the precocious puberty is gonadotropin independent and typically does not initially respond to treatment with the long-acting GnRH agonists (3). Surgical cystectomy or ovariectomy is almost always ineffective in girls with MAS because cysts usually develop in the remaining ovarian tissue (4). Adult stature in MAS patients with precocious puberty is often markedly decreased due to the combined factors of early fusion of the epiphyseal growth regions in the long bones (a result of elevated sex steroid levels) together with the deformities and fractures of the long bones caused by the PFD (5).

In MAS patients, the PFD exhibits a broad spectrum of severity, ranging from the presence of isolated lesions in the skull and/or extremities to involvement of the entire skeleton. In PFD, areas of normal bone and bone marrow are replaced by haphazardly distributed regions of fibrous tissue intermingled by irregular trabeculae of woven bone (6) resulting in skull and facial deformity, limb asymmetry, fractures, and general disability. The condition is usually progressive over time, with enlargement of lesions and involvement of additional bones; the incidence of fractures is greatest in childhood, between the age of 6 and 10 yr (7). The PFD is often associated with increased serum and urine levels of bone biomarkers (indices of bone metabolism) such as serum alkaline phosphatase (AP), serum osteocalcin (OC), and 24-h urinary levels of hydroxyproline (OHP), *N*-telopep-

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Abbreviations: AP, Alkaline phosphatase; BA/CA, bone age advance; ΔBA/ΔCA, change in bone age *vs.* change in chronological age; dPYR, deoxypyridinoline; E, estradiol; MAS, McCune-Albright syndrome; MOV, mean ovarian volume; NTX, *N*-telopeptides; OC, serum osteocalcin; OHP, hydroxyproline; PFD, polyostotic fibrous dysplasia; PYR, pyridinoline; SDS, SD score; TmP/GFR, tubular maximum reabsorption of phosphate relative to glomerular filtration rate.

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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 lesional 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 studied 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 group of girls with MAS (13).

A recent 12-month trial of the estrogen antagonist tamoxifen in 25 girls with MAS yielded promising initial results, with decreased mean rates of linear growth, bone age advance (BA/CA), and vaginal bleeding (14). However, no information is available at the present time regarding tamoxifen's effectiveness beyond 12 months of therapy, and the finding of an increase in average uterine volumes during treatment raises concerns that tamoxifen may have adverse effects on the endometrial stroma.

The potent, long-lasting aromatase inhibitor letrozole (Femara; Novartis Pharmaceuticals, East Hanover, NJ) is now 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/m^2) 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 SD scores (SDS). Seven girls had areas of cafe-au-lait pigment. 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. ^{99}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

Patient	CA (yr)	BA (yr) (BA/CA)	Height (cm) (SDS)[a]	Growth (cm/yr) (SDS)[a]	Pubertal stage Br/PH	Café-au-lait pigment	Bone disease[b]	Menses	Previous Tx for puberty
1	4.3	8.3 (1.9)	99.5 (−0.8)	13.2 (+5.0)	IV/I	Yes	++	Yes	None
2	5.8	11.0 (1.9)	128.2 (+2.7)	9.9 (+3.8)	IV/II	Yes	+++	Yes	Testolactone
3	4.8	8.3 (1.7)	108.4 (+0.4)	10.8 (+4.0)	IV/I	Yes	+	Yes	R ovariectomy
4	5.9	8.8 (1.5)	119.8 (+1.1)	9.3 (+3.2)	IV/IV	Yes	+	Yes	None
5	6.1	8.8 (1.4)	120.1 (+0.9)	10.6 (+4.6)	IV/III	Yes	No	No	None
6	3.5	5.0 (1.4)	103.0 (+1.5)	11.0 (+2.7)	IV/I	Yes	+++	Yes	None
7	4.8	10 (2.1)	116.8 (+2.4)	8.5 (+1.5)	IV/III	Yes	No	Yes	None
8	3.3	6.8 (2.1)	105.0 (+2.3)	11.8 (+2.6)	IV/III	No	+	Yes	R ovarian cystectomy
9	8.1	12.0 (1.5)	132.5 (+0.7)	6.3 (+0.6)	II/II	No	No	No	None

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

[a] SDS, compared with normal girls of comparable chronological age.

[b] +, 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/m^2·d during d 1–7 of treatment. The dose was increased to 1.0 mg/m^2·d on d 8–14 and to 1.5 mg/m^2·d on d 15–21. There was an option to increase the dose to 2 mg/m^2/d during therapy if a patient had progressive BA/CA, elevated serum estradiol (E) levels, or increased ovarian cyst volume while on 1.5 mg/m^2·d. 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 uteri. 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 (ΔBA/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

	Before	During	After
MOV (ml)	5.3 ± 5.7	1.4 ± 1.0[a]	4.3 ± 4.3
ΔBA/ΔCA	1.6 ± 0.3	1.5 ± 0.3[a]	1.4 ± 0.3
Growth rate (SDS)[b]	2.8 ± 1.4	−1.2 ± 1.0	2.5 ± 3.5
Serum AP (U/liter)	361 ± 72	275 ± 68[a]	301 ± 69
OC (μg/liter)	75 ± 23	54 ± 45	30 ± 3
Urine OHP (μg/mg creatinine)	231 ± 51	147 ± 46[a]	179 ± 39
NTX (nmol/mmol creatinine)	835 ± 227	570 ± 220	652 ± 181
dPYR (nmol/mmol creatinine)	73 ± 13	65 ± 27	75 ± 20
PYR (nmol/mmol creatinine)	306 ± 45	263 ± 96	305 ± 54

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.

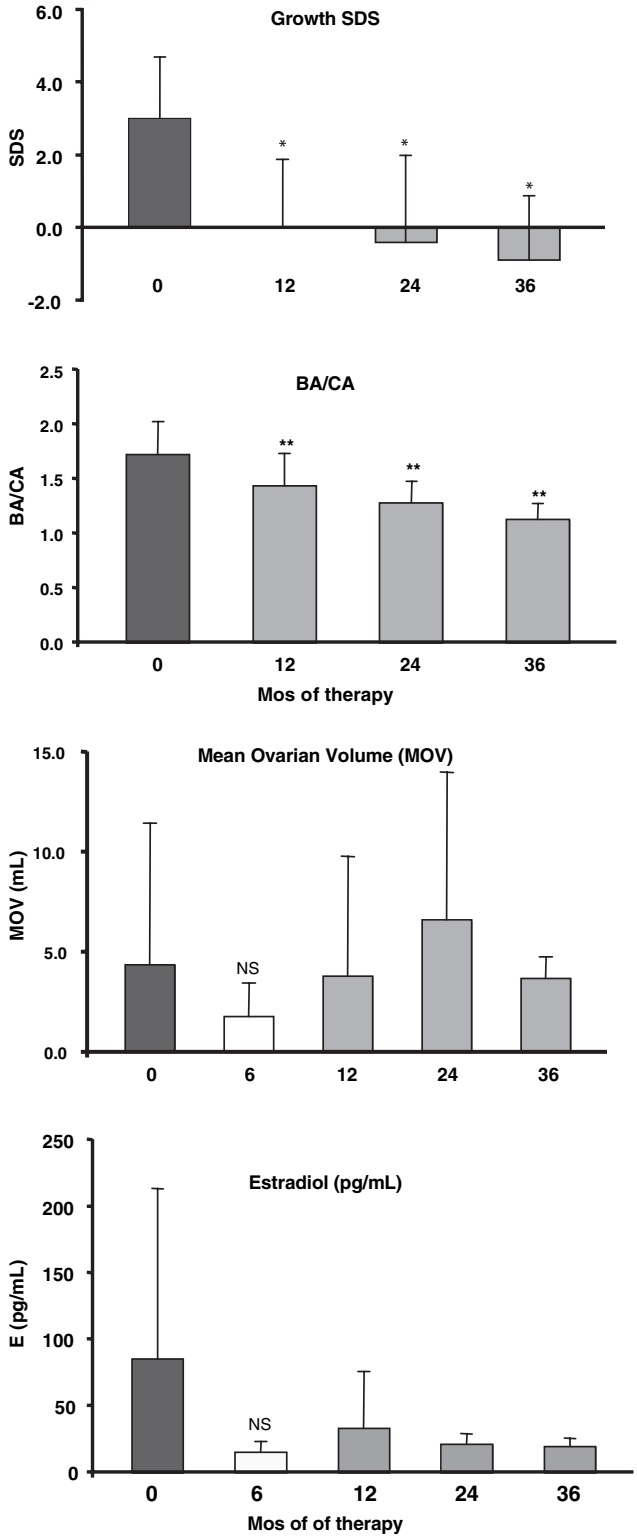

FIG. 1. Mean ± SD growth rate SDS, BA/CA, MOV, and serum E in girls with MAS before treatment 0 months (nine patients) and at 6, 12 (nine patients), 24 (7 patients), and 36 (five patients) months (Mos) of letrozole therapy. *, $P \leq 0.01$; **, $P \leq 0.004$.

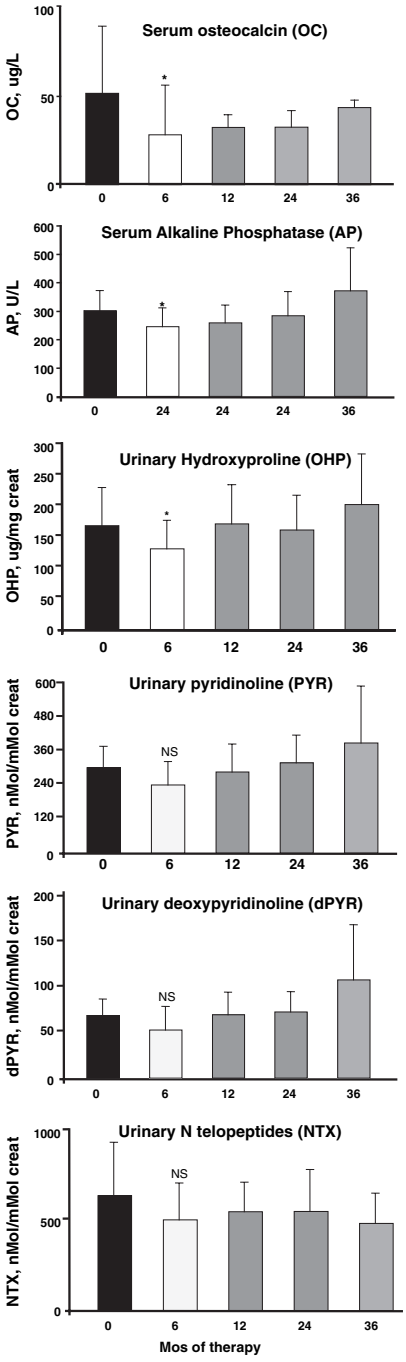

FIG. 2. Mean ± SD serum OC, AP, and 24 h urinary OHP, PYR, dPYR, and NTX in girls with MAS before treatment 0 months (nine patients) and at 12 (nine patients), 24 (seven patients), and 36 (five patients) months (Mos) of letrozole therapy. *, $P \leq 0.05$ (normal ranges in prepubertal children: OC, 40.2–108 ng/ml; AP, 115–303 μg/liter; OHP, 100–150 μg/mg creatinine; PYR, 158–441 nmol/mmol creatinine; dPYR, 31–112 nmol/mmol creatinine; NTP, 576-1763 nmol/mmol creatinine).

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, 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 continued to have vaginal bleeding, although less frequently than before therapy, were not lower (3 h, 167 nmol/liter; 24 h, 158 nmol/liter) than those in the other three girls, who had stopped bleeding while on treatment.

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 3 and 6 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/m^2·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/m^2·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 95 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 PFD 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

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 fibrodysplastic 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/m^2·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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References

1. **Weinstein LS, Shenker A, Gejman PV, Merino MJ, Friedman E, Speigel AM** 1991 Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. N Engl J Med 325:1688–1695
2. **Lumbroso S, Paris F, Sultan C** 2004 Activating Gsα mutations: analysis of 113 patients with signs of McCune-Albright syndrome—a European collaborative study. J Clin Endocrinol Metab 89:2107–2113
3. **Foster CM, Comite F, Pescovitz OH, Ross JL, Loriaux DL, Cutler Jr GB** 1984 Variable response to a long-acting agonist of luteinizing hormone releasing hormone in girls with McCune-Albright syndrome. J Clin Endocrinol Metab 59:801–805
4. **Feuillan PP, Jones J, Cutler Jr GB** 1998, Long-term testolactone therapy for precocious puberty in girls with the McCune-Albright syndrome. J Clin Endocrinol Metab 77:647–651
5. **Akintoye SO, Chebli C, Booher S, Feuillan P, Kushner H, Leroith D, Cherman N, Biance P, Wientroub S, Robey P, Collins M** 2002 Characterization of *gsp*-mediated growth hormone excess in the context of McCune-Albright syndrome. J Clin Endocrinol Metab 87:5104–5112
6. **Riminucci M, Liu B, Corsi A, Shenker A, Speigel AM, Robey PG** 1999 The histopathology of fibrous dysplasia of bone in patients with activating mutations of the Gsα gene: site-specific patterns and recurrent histologic hallmarks. J Pathol 187:249–258
7. **Leet AI, Chebli C, Kushner H, Chen C, Kelly M, Brillante B, Robey PG, Bianco P, Wientroub S, Collins MT** 2004 Fracture incidence in polyostotic fibrous dysplasia and the McCune-Albright syndrome. J Bone Miner Res 19:571–577
8. **Isaia GC, Lala R, Defillipi C, Matarazzo P, Andreo M, Roggia C, Priolo G, deSanctis C** 2002 Bone turnover in children and adolescents with McCune-

Albright syndrome treated with pamidronate for bone fibrous dysplasia. Calcif Tiss Int 71:121–128
9. **Collins MT, Kushner H, Reynolds JC, Chebli C, Kelly MH, Gupta A, Brillante B, Leet AI, Riminucci M, Robey PG, Bianco P, Wientroub S, Chen C** 2005 An instrument to measure skeletal burden and predict functional outcome in fibrous dysplasia of bone. J Bone Miner Res 20:219–226
10. **Collins MT, Chebli C, Jones J, Kushner H, Consugar M, Rinaldo P, Wientroub S, Bianco P, Robey PG** 2001 Renal phosphate wasting in fibrous dysplasia of bone is part of a generalized renal tubular dysfunction similar to that seen in tumor-induced osteomalacia. J Bone Miner Res 16:806–813
11. **Kaplan FS, Fallon MD, Boden SD, Schmidt R, Senior M, Haddad JG** 1988 Estrogen receptors in bone in a patient with polyostotic fibrous dysplasia (McCune-Albright syndrome). N Engl J Med 319:421–425
12. **Osada H, Sakamoto R, Seki K, Sekiya S** 2005 Accelerated bone turnover in pregnant women with McCune-Albright syndrome. Gynecol Obstet Invest 60:102–107
13. **Nunez SB, Calis K, Cutler Jr GB, Jones J, Feuillan, PP** 2003 Lack of efficacy of fadrozole in treating precocious puberty in girls with the McCune-Albright syndrome. J Clin Endocrinol Metab 88:5730–5733
14. **Eugster EA, Rubin SD, Reiter EO, Plourde P, Jou H-C, Pescovitz OH, and the McCune-Albright Study Group** 2003 Tamoxifen treatment for precocious puberty in McCune-Albright syndrome: a multicenter trial. J Pediatr 143:60–66
15. **Bhatnagar AS, Hausler A, Schieweck K, Lang M, Bowman R** 1990 Highly selective inhibition of estrogen biosynthesis by CGS 20267, a new, nonsteroidal aromatase inhibitor. J Steroid Biochem Mol Biol 37:1021–1027
16. **Novartis Pharmaceuticals Corp.** 2006 Femara: adverse reactions. Physicians' Desk Reference. Montvale, NJ: Thomson PDR (www.femara.com/pdf/FemaraPPI.pdf)
17. **Corsi A, Collins MT, Riminucci M, Howell PG, Boyde A, Robey PG, Bianco P** 2003 Osteomalacic and hyperparathyroid changes in fibrous dysplasia of bone: core biopsy studies and clinical correlations. J Bone Mineral Res 18: 1235–1246
18. **Sample WF, Lippe BM, Gypes MT** 1977 Grey scale ultrasonography of the normal female pelvis. Radiology 125:477–483
19. **Greulich WW, Pyle SI** 1950 Radiographic atlas of skeletal development of the hand and wrist. 2nd ed. Stanford, CA: Stanford University Press
20. **Walton RJ, Bijvoet OLM** 1977 A simple slide rule method for the assessment of renal tubular reabsorption of phosphate in man. Clin Chim Acta 81:273–276
21. **Marfil F, Pineau V, Sioufi A, Godbillon J** 1996 High-performance liquid chromatography of the aromatase inhibitor letrozole, and its metabolite in biological fluids with automated liquid-solid extraction and fluorescence detection. J Chromatog 683:251–258
22. **Pfister CU, Martoni A, Zamagni C, Lelli G, DeBraud F, Souppart C, Duval M, Hornberger U** 2001 Effect of age and single versus multiple dose pharmacokinetics of letrozole (Femara) in breast cancer patients. Biopharm Drug Dispos 22:191–197
23. **Levine MA** 2003 Biochemical markers of bone metabolism: application to understanding bone remodeling in children and adolescents. J Pediatr Endocrinol Metab 16:661–672
24. **Van Coeverden SCCM, Netelenbos JC, de Ridder CM, Roos JC, Popp-Snidjers C, Delemarre-van de Waal HA** 2002 Bone metabolism markers and bone mass in healthy pubertal boys and girls. Clin Endocrinol (Oxf) 57:107–116
25. **Blumsohn A, Hannon RA, Wrate R, Barton J, Al-Dehaimi AW, Colwell A, Eastell R** 1994 Biochemical markers of bone turnover in girls during puberty. Clin Endocrinol (Oxf) 40:663–670
26. **Pfeffer S, Molina E, Feuillan P, Simon T** 1990 McCune-Albright syndrome: the patterns of scintigraphic abnormalities. J Nucl Med 31:1474–1478
27. **Akintoye SO, Kelly MH, Brillante B, Cherman N, Turner S, Butman JA, Robey PG, Collins MT** 2006 Pegvisomant for the treatment of *gsp*-mediated growth hormone excess in patients with McCune-Albright syndrome. J Clin Endocrinol Metab 91:2960–2966
28. **Al-Fadhli R, Sylvestre C, Buckett W, Tan SL, Tulandi T** 2006 A randomized trial of superovulation with two different doses of letrozole. Fertil Steril 85: 161–164
29. **deZiegler D** 2003 The dawning of the non-cancer uses of aromatase inhibitors in gynaecology. Hum Rep 18:1598–1602

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