Effectiveness of combined GnRH analogue plus raloxifene administration in the treatment of uterine leiomyomas: a prospective, randomized, single-blind, placebo-controlled clinical trial

Stefano Palomba1,6, Tiziana Russo1, Francesco Orio Jr2, Libuse Tauchmanová2, Errico Zupi4, Pier Luigi Benedetti Panici5, Carmine Nappi3, Annamaria Colao2, Gaetano Lombardi2 and Fulvio Zullo1

1Department of Obstetrics & Gynecology, University ‘Magna Graecia’ of Catanzaro, Catanzaro, 2Department of Endocrinology and Experimental Oncology and 3Department of Gynecology, Obstetrics and Human Reproduction, University of Naples ‘Federico II’, Naples, 4Department of Obstetrics and Gynecology, University ‘Tor Vergata’ of Rome, and 5Department of Obstetrics and Gynecology, University of Rome ‘Campus Biomedico’, Rome, Italy

6To whom correspondence should be addressed at: Via Nicolardi 188, Napoli 80131, Italy. E-mail: stefanopalomba@tin.it

BACKGROUND: Raloxifene hydrochloride is a synthetic non-steroidal drug used for the prevention and treatment of post-menopausal osteoporosis. Pre-clinical and clinical data have shown that raloxifene may have a beneficial effect on leiomyomas. The aim of this prospective single-blind, randomized, placebo-controlled clinical trial was to evaluate the effectiveness of the addition of raloxifene to GnRH analogues on uterine, leiomyoma, and non-leiomyoma sizes, and on the occurrence of leiomyoma-related symptoms. METHODS: After randomization using a computer-generated list, 100 pre-menopausal women with symptomatic uterine leiomyomas received either leuprolide acetate depot plus raloxifene 60 mg daily (group A) or leuprolide plus placebo tablet (group B) for six cycles of 28 days. At baseline and after treatment, uterine, leiomyoma and non-leiomyoma sizes, and leiomyoma-related symptoms were evaluated for each woman. Analysis was by intention-to-treat method. RESULTS: After six cycles of treatment, a significant decrease in uterine, leiomyoma, and non-leiomyoma sizes was detected in both groups in comparison with baseline. At the same time, no significant difference in uterine and non-leiomyoma sizes was observed between the groups. Leiomyoma sizes were significantly (P < 0.05) lower in group A than in group B. No difference was observed in leiomyoma-related symptoms between groups throughout the study period. CONCLUSIONS: In women treated with GnRH analogue, the raloxifene administration induces a higher reduction of leiomyoma sizes.

Key words: add-back therapy/fibroids/GnRH analogue/leiomyomas/raloxifene

Introduction

Uterine leiomyomas are the most frequent benign tumours affecting ~25% of pre-menopausal women (Steward, 2001). These gynaecological diseases have a high economic cost, in fact one-third of hysterectomies are performed in patients referred for uterine leiomyomas (Steward, 2001).

Several medical therapies have been proposed for the treatment of uterine leiomyomas, such as gestrinone, danazol, RU486, estraprogestins, tamoxifen, analogue of somatostatin, or interferon alpha (Coutinho, 1989; Coutinho and Goncalves, 1989; Lumsden et al., 1989; Murphy et al., 1993; Kertel et al., 1994; Barbieri, 1997; Marshall et al., 1998; Friedman and Thomas, 1999; De Leo et al., 1999, 2001; Minakuchi et al., 1999; Sadan et al., 2001). GnRH analogue administration has been considered to be more effective medical therapy for uterine leiomyomas (Filicori et al., 1983; Steward, 2001).

The hypoestrogenic state induced by GnRH analogue causes climacteric-like symptoms, such as hot flushes, vaginal dryness, reduction of libido, and bone loss, which may be reduced or prevented with the administration of sex hormones (‘add-back therapy’) (Friedman et al., 1990; Adashi, 1994; Surrey, 1995; Pickersgill, 1998). Furthermore, the addition of progestins or estraprogestins at the start of the GnRH analogue administration reduces the effectiveness of the analogue on the uterine and leiomyoma size (Carr et al., 1993; Friedman et al., 1994; Nakayama et al., 1999). At present, only the addition of tibolone, a steroid compound structurally related to 19-nortestosterone derivatives, which exhibits a concomitant weak estrogenic, progestinic, and androgenic activity (Modelska and Cummings, 2002), is an effective add-back therapy for GnRH analogue treatment if administered with the analogue (Palomba et al., 1998, 1999, 2001a).
Raloxifene hydrochloride is a synthetic non-steroidal drug derived from benzothiophene and afferent to selective estrogen receptor modulators (SERM), a group of compounds that interact with estrogen receptors eliciting tissue-specific responses (Kuiper et al., 1997; Paech et al., 1997; Khovdihunkit and Shoback, 1999). It is known that raloxifene acts on the metabolism, the central nervous system, the skeleton and the cardiovascular system as an estrogenic agonist (Walsh et al., 1998; Ettenger et al., 1999; Mosca, 2001; Barrett-Connor et al., 2002), whereas it shows a weak estrogenic antagonist effect on reproductive organs, including the breast and the uterus (Cummings et al., 1999; Cohen et al., 2000; Goldstein et al., 2000).

Pre-clinical data (Black et al., 1994; Bryant et al., 1996; Fuchs-Young et al., 1996; Porter et al., 1998; Walker et al., 2000) have suggested that raloxifene may have a beneficial effect on leiomyomas. In a recent clinical study (Palomba et al., 2001b), we observed a significant reduction in leiomyoma size after 1 year of treatment with raloxifene 60 mg daily in post-menopausal women. On the contrary, the administration of raloxifene at standard and high dose, in pre-menopausal women affected by uterine leiomyomas, did not induce any reduction in uterine and leiomyoma sizes (Palomba et al., 2002a).

Based on these considerations, the present study was designed to investigate the effect of adding 60 mg raloxifene daily on both uterine and leiomyoma size, and also on leiomyoma-related symptoms in symptomatic pre-menopausal women treated with GnRH analogue.

Materials and methods

The procedures used during the study were in accordance with the guidelines of the Helsinki Declaration on human experimentation. The protocol was approved by the Local Ethics Committees. Before entering the study, the purpose of the protocol was explained to all women attending the Departments of Gynecology of the University of Catanzaro, Naples ‘Federico II’ and Rome. A written informed consent was obtained from all subjects.

Subjects

Between June 2000 and January 2001, 100 pre-menopausal women affected by symptomatic uterine leiomyomas were enrolled in the study.

Exclusion criteria were: neoplastic, metabolic, endocrine, liver, haematological and infectious diseases; active rheumatoid arthritis; history of acute or recurrent vascular thrombosis; a bone mineral density (BMD) value <1.0 SD of the mean peak BMD for sex-matched healthy young adults (~1.0 T-score) at posterior-anterior lumbar spine; a body mass index (BMI) <18 or >30 kg/m²; previous or current treatment with bisphosphonates, sodium fluoride, calcitomin, estroprogestins or anabolic steroids, corticosteroids, calcium or vitamin D, phosphate, thiazide diuretics or other drugs interfering with bone metabolism; abnormal serum levels of creatinine and parathyroid hormone (PTH). Women smoking >20 cigarettes per day and drinking more than three alcoholic beverages per day were also excluded. The presence of hypoechoic or calcified leiomyomas, or endometrial abnormalities detected at transvaginal ultrasonography (TV-USG) was also considered an exclusion criterion.

Treatment protocol

At trial entry, all subjects were randomized in single blocks into a single-blind, placebo-controlled study design using a computer-generated randomization list. The subjects were assigned to one of two groups of 50 women each. All women received leuprolide acetate depot (LAD) (Enantone; Takeda, Rome, Italy) at a dose of 3.75 mg/28 days combined with raloxifene hydrochloride (Evista; Eli Lilly, Sesto Fiorentino, Italy) at a dose of 60 mg/day p.o. (group A) or placebo tablets (1 tablet/day; group B).

The duration of the study was six cycles of 28 days each and for this period the single-blinding was maintained in the two groups. After the six cycles, the women of group A continued the treatment for another 12 cycles.

Study protocol

At the beginning of the study and after six cycles of treatment, uterine and leiomyoma sizes, the number of tumours, and endometrial thickness were measured by TV-USG. At the same time, bone metabolism was measured, and calcium intake, alcohol consumption, and physical activity were evaluated (Palomba et al., 2002b).

No dietary restriction or changes were implemented during the study. To ensure adequate calcium intake, all patients with an intake <1000 mg received daily supplements of elemental calcium in the form of an effervescent tablet composed of calcium carbonate (Cacit; Procter & Gamble, Rome, Italy) to achieve a total daily intake of ≥1000 mg.

All women agreed to use barrier contraception throughout the study. Ultrasonographic scans were performed by the same experienced operator using a Toshiba PowerVision 6000 (Toshiba Medical System, Rome, Italy) equipped with a 7.5 MHz transvaginal probe. The operator was unaware of treatment assignment. Uterine and leiomyoma sizes were evaluated measuring the three main diameters (D1, D2, D3) and applying the formula of the ellipsoid (D1×D2×D3×0.52). An arithmetic mean of the sizes was used where two leiomyomas were present. As previously described (Palomba et al., 2001b), to evaluate the effect of treatments on the non- leiomyoma tissue, the difference between uterine and leiomyoma volumes (∆ size) was calculated in each subject. The data were expressed as percentage change of baseline values. Endometrial thickness was also measured.

The subjects were instructed to maintain a personal daily diary of the severity of leiomyoma-related symptoms, such as menorrhagia, pelvic pressure and pain, urinary frequency, and constipation. The severity of symptoms was carefully recorded by each woman using a rank scale ranging from 1 to 10, with 1 being the least and 10 being the most severe (Palomba et al., 1998, 2002a). The women recorded in the diary the number of uterine vaginal bleeding episodes and of hot flushes.

The bone metabolism was evaluated measuring the BMD and the bone turnover markers. The BMD was determined by dual energy X-ray absorptiometry (Dexa QDR 1000; Hologic, Waltham, MA, USA) at posterior-anterior lumbar spine (vertebrae L1–L4) and at hip (trochanter and femoral neck) (Palomba et al., 2002b). The bone metabolism was evaluated at entry and after six cycles by determining the serum levels of osteocalcin and bone alkaline phosphatase levels, and urinary creatinine-corrected free deoxypyridinoline and pyridinol- D (Palomba et al., 2002b).

Standard clinical evaluations and laboratory analyses, including haematological, renal function and liver function tests, measurements of serum calcium and phosphate concentrations, and microscopic examinations of sediment from midstream urine specimens were performed before treatment, and after three and six cycles of treatment.

The subjects were also instructed to report in the daily diary the appearance of adverse experiences (AE). The AE were defined as
any undesirable clinical experience occurring to patients during the study, whether or not related to the drugs administered. A serious AE was defined as death, overdose, diagnosis of cancer, or any event that was life-threatening, permanently disabling or requiring hospitalization. From the time the patients received the first dose of the drugs all subjects were seen every 3 months to check the personal diary. All patient data were carefully considered to establish the severity, duration, seriousness, and a possible cause-effect relationship.

Statistical analysis
Using previous studies (Sener et al., 1996; Palomba et al., 2001b, 2002a) a sample of 30 subjects per group would be necessary to detect an effect on the size of one SD with an α value of 0.05 (two-sided) and a power 1 – δ of 0.8. Furthermore, because the primary end-point of our protocol study was lumbar spine BMD changes, the sample size studied was 50 subjects/group (Palomba et al., 2002b,c).

All data shown in this paper were analysed by intention-to-treat method.

Statistical analysis was performed using the SPSS 9.0 (SPSS Inc., Chicago, IL, USA) package. Data are expressed as mean ± SD. Analysis of the variance was used to evaluate differences between the two groups in age, BMI, BMD, parity, number of cigarettes smoked per day, endometrial thickness, uterine and leiomyoma sizes, and Δ size between groups at entry and after six cycles of treatment. Wilcoxon’s signed-rank test was used to compare parity, cigarettes smoked, alcohol consumption, calcium intake and physical activity. The proportion of women receiving calcium supplements in the two groups of treatment was compared using the χ²-test. The differences in length and severity of menstrual cycles between and within groups were compared at entry and after six cycles of treatment using analysis of variance and Wilcoxon’s signed rank tests, respectively. Fisher’s exact test was used to compare the incidence of AE between treatment groups.

Results
Demographic data
Ninety-one of the 100 enrolled patients completed the study. Patient profiles are shown in Table I. After randomization, the two groups were similar for age, parity, BMI, cigarettes smoked, calcium intake, alcohol consumption, and physical activity (Table I). The data about the effect of raloxifene addition on bone metabolism in subjects treated with GnRH analogues have been reported elsewhere (Palomba et al., 2002c).

Drop-outs
The numbers of withdrawals were similar in the two groups (five and four women in groups A and B respectively) and no drop-out was due to drug-related AE.

In group A, two women dropped out for lack of compliance to the treatment (one subject did not take only raloxifene at the second month and one GnRH analogue and raloxifene at the start), and three because of missed BMD and TV-USG examinations after 6 months (two did not perform the BMD measurements and one the TV-USG evaluation).

In group B, one woman dropped out for lack of compliance to the treatment (she did not take GnRH analogue and raloxifene at the start of the study), and three because of missed BMD examinations at the sixth month.

Uterine, leiomyoma and Δ sizes
After randomization, no difference in uterine, leiomyoma, and Δ sizes was detected between the two groups at entry (Table I). After six cycles of treatment, a significant (P < 0.05) decrease in uterine and leiomyoma size was obtained in both groups (Figure 1). No significant difference was observed in percentage of change in uterine size between groups (Figure 1). Furthermore, in group A, a significant decrease (P < 0.05) in leiomyoma size was observed between baseline and group B (Figure 1). After treatment, a significant (P < 0.05) change in Δ sizes was observed in the two groups in comparison with baseline without differences between groups (Figure 1).

Leiomyoma-related symptoms
After randomization, no significant difference in leiomyoma-related symptoms was detected between the two groups at entry (Table II). The changes in the intensity of leiomyoma-related symptoms are shown in Table II. After six cycles of treatment, a significant (P < 0.05) decrease in severity of all leiomyoma symptoms was observed in both groups in comparison with baseline. At the same time, there were no significant differences between the two groups (Table II).

In both groups, the percentage of patients with bleeding decreased constantly throughout the cycles of treatment (Figure 2). At the sixth cycle of treatment, no significant differences in percentage of women with uterine bleeding was detected between the two groups (Figure 2). In particular, 3/48 (6.3%) and 4/49 (8.3%) women were bleeding after six cycles of treatment in groups A and B respectively. In all cases the uterine bleedings had a ‘spotting’ pattern.

After randomization, no significant differences in serum haemoglobin levels (mg/l ± SD) were observed between the two groups (9.4 ± 1.2 and 9.6 ± 1.4 for groups A and B, respectively). After six cycles of treatment, a significant (P < 0.05) increase in serum haemoglobin levels (12.1 ± 1.4 and 11.9 ± 1.6 for groups A and B respectively) was observed in both groups in comparison with baseline values without significant differences between the two groups.
Table I. Characteristics of the patients at study entry

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment regimen</td>
<td>LAD 3.75 mg/28 days + raloxifene 60 mg/day</td>
<td>LAD 3.75 mg/28 days + placebo</td>
</tr>
<tr>
<td>No. of patients</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Demographic data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>49.1 ± 4.2</td>
<td>48.6 ± 3.9</td>
</tr>
<tr>
<td>Parity (no.)</td>
<td>1.8 ± 1.4</td>
<td>1.7 ± 1.3</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.8 ± 3.2</td>
<td>25.6 ± 3.6</td>
</tr>
<tr>
<td>Cigarettes smoked (no./daily)</td>
<td>6.4 ± 5.6</td>
<td>6.2 ± 5.4</td>
</tr>
<tr>
<td>Calcium intake score</td>
<td>2.5 ± 0.8</td>
<td>2.7 ± 0.9</td>
</tr>
<tr>
<td>Alcohol consumption score</td>
<td>1.1 ± 0.6</td>
<td>1.2 ± 0.7</td>
</tr>
<tr>
<td>Physical activity score</td>
<td>1.9 ± 0.9</td>
<td>2.0 ± 1.0</td>
</tr>
<tr>
<td>Ultrasonographic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uterine size (cm³)</td>
<td>473 ± 112</td>
<td>446 ± 105</td>
</tr>
<tr>
<td>Leiomyoma size (cm³)</td>
<td>197 ± 61</td>
<td>189 ± 54</td>
</tr>
<tr>
<td>Δ size (cm³)</td>
<td>259 ± 67</td>
<td>243 ± 59</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD.

a1 1 = <500 mg/day; 2 = 500–1000 mg/day; 3 = >1000 mg/day.

b1 1 = <1000 mg/day; 2 = 1000–2000 mg/day; 3 = >2000 mg/day.

c1 1 = low; 2 = moderate; 3 = high.

LAD = leuprolide acetate depot.

Table II. Leiomyoma-related symptoms in women treated with GnRH analogue plus raloxifene (group A) or placebo (group B)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (n, %)</td>
<td>6th cycle (n, %)</td>
</tr>
<tr>
<td>Menorrhagia</td>
<td>7.6 ± 1.7 (45, 100)</td>
<td>– (0, 0)a</td>
</tr>
<tr>
<td>Pelvic pressure</td>
<td>6.8 ± 1.5 (39, 86.7)</td>
<td>3.5 ± 0.8 (3, 6.7)a</td>
</tr>
<tr>
<td>Pelvic pain</td>
<td>7.0 ± 1.7 (18, 40.0)</td>
<td>3.4 ± 1.0 (2, 4.4)a</td>
</tr>
<tr>
<td>Urinary frequency</td>
<td>5.9 ± 1.6 (22, 48.9)</td>
<td>2.0 ± 0.9 (3, 6.7)a</td>
</tr>
<tr>
<td>Constipation</td>
<td>5.2 ± 1.7 (8, 17.8)</td>
<td>– (0, 0)a</td>
</tr>
</tbody>
</table>

Values are reported as mean ± SD. The number and the percentage of symptomatic women are shown in parentheses. Symptoms were graded according to severity on a 10-point scale.

aP < 0.05 versus baseline.

Vasomotor symptoms

In both groups, the mean number of hot flushes per day increased significantly (P < 0.05) after 15 days from the start of the treatment and remained constant for all six cycles of treatment. No significant differences were observed between the two groups (Figure 3).

Side-effects

Throughout the study, the two treatment schedules were generally well tolerated. The total incidence of all AE and of drug-related AE was not significantly different between the two groups. In particular, raloxifene was well tolerated and its safety profile was similar to that of placebo. No serious AE was reported during the study.

There was also no significant difference in the incidence of clinical effects and/or laboratory abnormalities between the two groups of treatment.

Discussion

Pre-clinical data have suggested that raloxifene may act on leiomyoma tissue (Black et al., 1994; Fuchs-Young et al.,
analogue plus placebo). In particular, Fuchs-Young et al. have shown an inhibition of the proliferation of rat leiomyoma cells in vitro using raloxifene hydrochloride (Fuchs-Young et al., 1996).

Data on animal models have also demonstrated that raloxifene has a dose-related capacity of blocking estrogen-induced stimulation of uterine weight gain (Bryant et al., 1996) and induces minimal effects on myometrial thickness and uterine weight in untreated ovariectomized rats as determined by histological examination of uteri (Black et al., 1994).

In guinea-pigs, a fast regression of abdominal wall estrogen-induced leiomyomas was observed after raloxifene administration (Porter et al., 1998). A more recent study in the rat (Walker et al., 2000) has confirmed that raloxifene analogue inhibits the cell proliferation in leiomyoma tissue, reducing their size and incidence by 40–60%.

Our previous clinical data (Palomba et al., 2001b) have shown that 1 year of raloxifene administration at doses of 60 mg daily significantly reduces the uterine and leiomyoma sizes in post-menopausal women. A relevant finding of this study was the selective action of raloxifene on the leiomyoma tissue. In particular, in post-menopausal women the raloxifene administration seems to induce a significant reduction of leiomyoma sizes, without any significant action on normal myometrium. No significant effect on uterine and leiomyoma sizes, furthermore, was observed after six cycles of raloxifene administration at standard and/or high doses in pre-menopausal women affected by asymptomatic uterine leiomyomas (Palomba et al., 2002a). These findings may have a 2-fold explanation. First, it is possible that the raloxifene doses were too low to reduce or revert the proliferative effect of serum estradiol in normal ovulatory women. In fact, in post-menopausal women the serum estradiol levels are ~10-fold lower in comparison with normally cycled pre-menopausal women. Second, in post-menopausal women estrogen receptors could have a different intra-tumoral pattern in terms of concentration, expression and affinity in comparison with pre-menopausal women (Brandon et al., 1995; Lessl et al., 1997).

Based on these considerations, we designed this prospective, randomized, single-blind, placebo-controlled clinical trial in order to confirm the beneficial effect of raloxifene administration on uterine leiomyomas in women with low levels of sex hormones during GnRH analogue treatment.

The main outcome measure of our study was to demonstrate the effectiveness of raloxifene administration on bone metabolism during GnRH analogue treatment. Indeed, no negative effects of GnRH analogue on BMD and bone turnover markers were observed during the administration of analogues plus raloxifene at standard doses (Palomba et al., 2002c).

Our data confirm (Carr et al., 1993; Friedman et al., 1994; Palomba et al., 1998, 1999, 2001a; Nakayama et al., 1999) that GnRH analogue administration is effective for the treatment of symptomatic uterine leiomyomas in terms of reduction in uterine and leiomyoma sizes, and of leiomyoma-related symptomatology. Raloxifene addition induced a reduction in leiomyoma dimensions, which was significantly higher than that observed after treatment with placebo. Moreover, this reduction did not lead to any significant further reduction in leiomyoma-related symptoms.

The raloxifene-related reduction in leiomyoma dimensions observed in the present study was higher and more rapid in comparison with that obtained in post-menopausal women (Palomba et al., 2001b). These data were probably due to the profound hypoestrogenism achieved after GnRH analogue administration. In both groups the decrease in leiomyoma size was higher in comparison with that obtained in ∆ size, confirming that GnRH analogue seems to act more on tumoral than on non-leiomyoma tissue as previously observed (Carr et al., 1993) using magnetic resonance imaging. In addition, after 6 months of treatment, whereas the leiomyoma size decreased more significantly in women treated with raloxifene, no significant difference was detected in non-leiomyoma size (Δ size) between groups, showing that (as is the case in pre-menopausal women during GnRH analogue administration) raloxifene acts selectively on leiomyoma tissue.

During our study period, few side-effects were detected and the raloxifene treatment was tolerated as well as the placebo. In particular, no significant difference in mean hot flushes per day and in uterine bleedings was observed between the two treatment groups.

Unfortunately, raloxifene administration did not reduce the GnRH analogue-related vasomotor symptoms. On the contrary, a significant reduction in mean number of hot flushes per day was observed when adding tibolone to GnRH analogue treatment (Palomba et al., 1998, 1999, 2001a; Di Carlo et al., 2000).

Raloxifene and tibolone are two compounds that did not induce endometrial proliferation in post-menopausal women with a high percentage of ‘non-bleeding’ cycles (Goldstein et al., 2000; Modelska and Cummings, 2002); our study confirms these data. In fact, tibolone (Palomba et al., 1998) or raloxifene addition to GnRH analogue treatment in women with uterine leiomyomas did not increase the percentage of women with uterine bleedings in comparison with analogue alone.

Figure 3. Mean number of hot flushes per day throughout the study in groups A (GnRH analogue plus raloxifene) and B (GnRH analogue plus placebo).

*P < 0.05 versus baseline.

GnRH analogue and raloxifene for the treatment of uterine leiomyomas
In conclusion, the administration of GnRH analogue plus raloxifene in pre-menopausal women with symptomatic uterine leiomyomas is effective in reducing uterine and leiomyoma size with a strong effect on leiomyoma tissue. It is possible to envisage the use of raloxifene as an ‘add-back therapy’ in women treated with GnRH analogue during the first months of treatment to preserve bone mass and to achieve the maximal reduction in leiomyoma sizes, using successively tibolone or estroprogestin addition for a long-term treatment.

Acknowledgement

We thank Dr Benito Chinea (Ibis Informatica & Idee) for assistance in statistical support.

References


Submitted on June 13, 2002; accepted on August 25, 2002