

Efficacy and safety of standard versus low-dose Femarelle (DT56a) for the treatment of menopausal symptoms

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Summary

Objective: In a previous study treatment with a daily standard dose of Femarelle (644 mg/day) resulted in a significant elevation in bone mineral density (BMD) while a reduced dose resulted in a decrease in BMD. The aim of the current study was to examine the efficacy and safety of the two doses of Femarelle in the treatment of menopausal symptoms.

Materials and Methods: Eighty healthy postmenopausal women were randomly allocated to receive either the standard dose (SD) or low dose (LD) of Femarelle (644 mg/day vs 344 mg/day). A detailed medical history was taken on enrollment, followed by a physical examination, pelvic ultrasound, and sex hormone and lipid profiles. A detailed Kupperman index for each patient was completed. These measures were repeated every three months for 12 months.

Results: In both groups there was a significant reduction in the Kupperman index following 12 weeks of treatment, which was sustained throughout the 12 months of treatment ($p < 0.01$). Seventy-six percent of the patients in the SD group reported a decrease in vasomotor symptoms and seventy eight % in the LD group (NS). This decrease was sustained following 12 months of treatment. There was no change in TSH and sex hormone levels or endometrial thickness during the study period.

Conclusions: In the current study we found that menopausal symptoms were reduced similarly by LD and SD, however for the combined treatment of menopausal symptoms and osteoporosis the standard dosage of 644 mg/day of Femarelle is needed.

Key words: Femarelle; Tofupill; Menopause; Hot flashes; Menopausal.

Introduction

The accumulating data on the side-effects related to the conventional hormone replacement therapy (HRT) [1-3] intensifies the need of both health providers and patients for a safe and effective alternative for the treatment of menopausal symptoms and osteoporosis. In previous pre-clinical and clinical studies, Femarelle (DT56a) was shown to be a new potent phyto selective estrogen receptor modulator (SERM) [4, 5]. DT56a is a composition of substances and molecules derived from soy through an enzymatic production process. During this process, the prime substance is converted to a format similar to that obtained through fermentation with no change in the accompanying proteins [6, 7]. This unique process sets up a biochemical potentiation effect resulting in a more potent substance with an efficacy of 8:1 compared to the raw material. The effect of DT56a on bone and cartilage of immature or ovariectomized female rats was compared to estradiol-17 β (E₂) by measuring the changes in the specific activity of the BB isozyme of creatine kinase (CK). When administered in multiple oral doses, DT56a stimulated skeletal tissues similarly to E₂, but whereas E₂ increased CK specific activity in the uterus, DT56a did not. Thus, DT56a selectively stimulated estrogen

receptors in skeletal tissues but not in the uterus [4]. The SERM Raloxifene blocked the stimulation of CK by both DT56a and E₂ in all tissues tested pointing towards a common receptor(s) mechanism of action [4]. In ovariectomized rats fed for two months with DT56a at a dose equivalent to the standard dose, a significant increase in bone histomorphometric measurements was found compared to the placebo-fed group (submitted for publication). We have previously shown [5] that Femarelle had a positive effect on bone mineral density at a standard dose but not at a low dose. Following one year of treatment, standard-dose treatment resulted in an elevation of 3.6% density in the spine and 2% in the hip while low dose treatment resulted in a reduction of 0.6% in both sites. The conclusion of these studies is that Femarelle had a positive effect on bone mineral density at a standard dose but not at a low dose.

The aim of the present study was to compare the efficacy of the two doses of Femarelle for the relief of menopausal symptoms.

Materials and Methods

The study group included healthy postmenopausal women attending health care centers in Israel. Eligibility for participating in the study was limited to patients who had an intact uterus, no menses within the last six months, and blood hormone levels indicating menopause: follicle-stimulating hormone (FSH) > 30 mIU/ml and estradiol (E₂) < 150 pmol/l. Women with any pre-existing chronic illness, endometrial polyps or hyperplasia, and

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moderate or severe hypertension were excluded, as were habitual users of drugs or alcohol. The study was approved by the local ethics committee of the Rabin Medical Center, and all patients signed a written informed consent form after receiving a comprehensive explanation of the study.

At enrollment, a complete medical and gynecological history was obtained for each patient, and the physician completed an assessment questionnaire of the frequency-severity of menopausal symptoms (Kupperman index). All participants underwent a physical examination, gynecological and breast examination, and transvaginal ultrasonography. Laboratory tests included hormonal and lipid profiles, tests for liver and kidney function and mammography.

For the trial, externally identical SD (standard dose) and LD (low dose) capsules were placed in identical white bottles with no identifying marks apart from a serial number. The bottles were placed in front of the participants, and they were asked to choose one at random. The contents were unknown to the research team. Patients were randomized to receive the SD or LD of Femarelle (DT56a), 644 mg/day vs 344 mg/day (Se-cure Pharmaceuticals, Yavne, Israel) for 12 months. All tests and assessments done at the time of enrollment were repeated after three, six, and 12 months. Mammograms were performed at enrollment and after 12 months. Compliance and side-effects were assessed every three months. The Kupperman index was analyzed at the time of enrollment, after 12 weeks and 12 months.

Statistical analysis:

Data were analyzed by the matched paired t-test. A p value less than 0.05 was considered statistically significant.

Results

One hundred and fifteen women were enrolled in the study. At 12 months complete data was available for 80 women, 38 in the SD group and 42 in the LD. Most of the drop-out patients were at the early stage of the study and all of them withdrew from the study due to personal reasons. None of the patients enrolled in the study reported adverse effects of treatment.

In both groups the demographic characteristics were similar (Table 1). The prominent symptom in both groups was hot flushes: 36 of 38 patients in the SD group and 40 of 42 in the LD group.

In both groups treatment resulted in a significant reduction in the Kupperman index: In the SD group 16 ± 7.2 at enrollment and 9 ± 6 and 8.7 ± 7 at 12 weeks and 12 months respectively ($p < 0.01$). Similarly, in the LD group there was a significant decrease from enrollment (17 ± 8.4) to 12 weeks (10 ± 5.7) and to 12 months (8.6

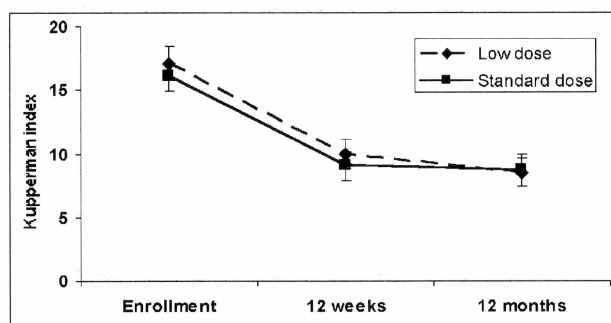


Figure 1. — The Kupperman index $\pm$ SE at enrollment, 12 weeks and 12 months. In the SD group: 16 ± 1.1 at enrollment, 9 ± 1.1 and 8.7 ± 1.26 at 12 weeks and 12 months respectively ($p < 0.01$). In the LD group: 17 ± 1.3 at enrollment, 10 ± 1.1 at 12 weeks and 8.6 ± 1.3 at 12 months ($p < 0.01$).

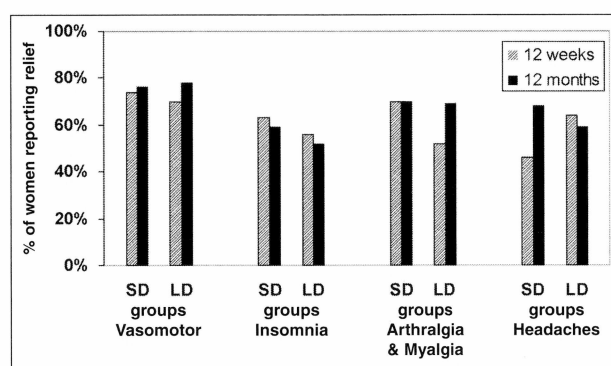


Figure 2. — Percent of patients who reported relief of major menopausal symptoms in the SD and LD groups. No statistically significant difference was found in the rate of relief between 12 weeks and 12 months of treatment in either group.

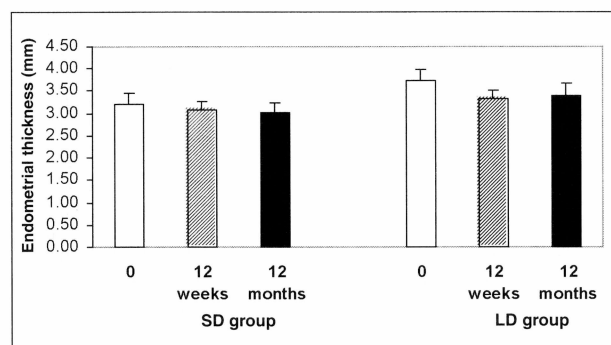


Figure 3. — Endometrial thickness at 12 weeks and 12 months in both groups (no change).

Table 1. — Demographic characteristics of the SD and LD groups.

Characteristics*	SD (n = 38)	LD (n = 42)
Age (yrs)	55.34 $\pm$ 5.62	56.21 $\pm$ 5.24
Height (cm)	160.44 $\pm$ 5.34	159.80 $\pm$ 6.51
Weight (kg)	65.13 $\pm$ 9.14	67.32 $\pm$ 11.45
BMI (kg/m ²)	25.26 $\pm$ 3.05	26.36 $\pm$ 4.61
Smokers	3 (7.9%)	5 (11.9%)

*All values are mean $\pm$ SD except smokers, where values are (%).

± 7.3) ($p < 0.01$). Following 12 weeks and 12 months of treatment, there was no statistical difference in the decline in the Kupperman index between the SD and LD groups (Figure 1).

The majority of patients in both groups reported relief of main menopausal symptoms; vasomotor: 76-78% in the SD and LD groups, respectively, headaches: 68-60%, insomnia: 59-52% and arthralgia and myalgia: 70-70% of patients reported relief. This improvement was maintained following 12 months of treatment (Figure 2). Relief of at

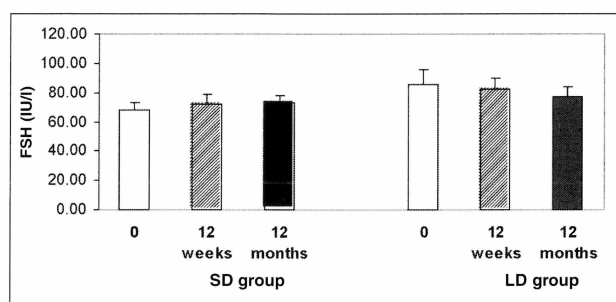


Figure 4. — FSH levels at 12 weeks and 12 months in both groups (no change).

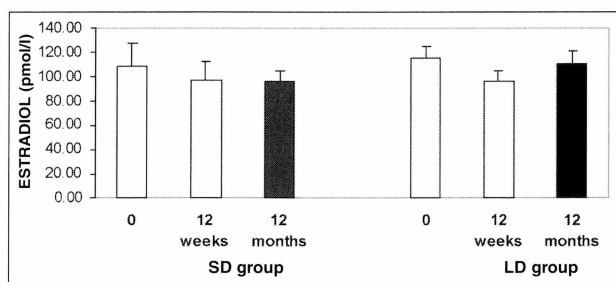


Figure 5. — E₂ levels at 12 weeks and 12 months in both groups (no change).

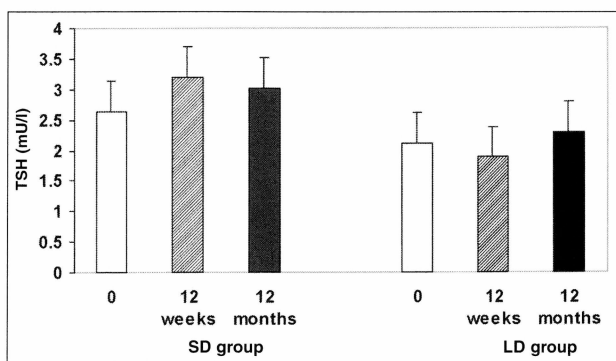


Figure 6. — TSH levels at 12 weeks and 12 months in both groups (no change).

least one symptom was achieved in 81% of the patients and sustained in 76% after 12 months in both groups.

There was no statistically significant change in endometrial thickness (Figure 3), FSH (Figure 4), E₂ (Figure 5) or TSH levels (Figure 6) from enrollment to the end of the study in either group.

Discussion

The current study showed that both standard and low dose Femarelle treatment resulted in a significant reduction in the Kupperman index.

The accumulating data on the side-effects of conventional HRT has led the scientific community into a great confusion [8-14] Recently Grodstein and colleagues tried

to clarify the divergence of the earlier positive observational studies versus the WHI-study results [9]. They concluded that: "The clearest message from these studies is that we have much to learn about women's health and hormone use". Perhaps the title of an editorial in the *Journal of Clinical Oncology* precisely describes this confusion: "Why do we still use hormone replacement therapy? Why don't we use it more?" [14] Health-care providers in general and gynecologists in particular, confront day by day the key problem of helping the menopausal patient to find a safe and effective treatment for the two main problems resulting from estrogen deficiency: menopausal symptoms and osteoporosis. The SERMs currently available may successfully treat postmenopausal osteoporosis, however they do not provide solutions for menopausal symptoms. Some SERMs even induce and worsen menopausal symptoms [15, 16].

Femarelle/DT56a is a new potent phyto-SERM. In previous preclinical and clinical studies, a positive effect of DT56a (Femarelle) was found on bone health, when given in the standard dose or equivalents of 644 mg/day. In rats, DT56a stimulated skeletal tissues similarly to E₂, but whereas E₂ increased CK specific activity in the uterus, DT56a did not [4]. In ovariectomized rats fed for two months with DT56a at the equivalent of the standard recommended dose, a significant increase was found in the trabecular bone volume and cortical width compared to the placebo-fed group (submitted for publication). In a clinical study, treatment of menopausal women with 644 mg/day of Femarelle for 12 months resulted in a substantial elevation in the BMD of the spine and the hip, compared to treatment with a low-dose regime [5]. The current study showed that both the standard and low dose treatment resulted in a significant reduction in the Kupperman index. Thus, just for the treatment of menopausal symptoms, 344 mg/day is a sufficient treatment. However this dosage does not provide protection against the development of osteoporosis since it resulted in a decrease in BMD following 12 months of treatment. We suggest that while a low dose of Femarelle is adequate to treat menopausal symptoms, the recommended dose of 644 mg/day is needed to reverse postmenopausal bone loss as well as treat menopausal symptoms.

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