Ipriflavone in the Treatment of Postmenopausal Osteoporosis
A Randomized Controlled Trial

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STUDIES OF IPRIFLAVONE, A SYNTHETIC isoflavone derivative, have suggested that it inhibits bone resorption and stimulates osteoblast activity in vitro in cell cultures1,2 and in vivo in experimental models of osteoporosis.3 For example, ipriflavone was demonstrated to inhibit 45Ca release from fetal long-bone cultures, both spontaneously and after stimulation with parathyroid hormone,1 and to inhibit resorption pits induced by osteoclast activity.2 Incubation of rat osteosarcoma cells (cell-line UMR 106-a) with ipriflavone resulted in increased release of alkaline phosphatase into the media.4 Furthermore, ipriflavone has been shown to inhibit bone loss in osteoporotic rats (induced by corticosteroids).3 These encouraging results led to a number of clinical trials to test the efficacy on bone mass in various populations. This inhibition of bone loss in these populations was typically mirrored by a reduction in the concentration of biochemical markers of bone metabolism.5 In postmenopausal women, data on the efficacy and safety of ipriflavone for prevention of postmenopausal bone loss are conflicting.

Objectives To investigate the effect of oral ipriflavone on prevention of postmenopausal bone loss and to assess the safety profile of long-term treatment with ipriflavone in postmenopausal osteoporotic women.

Design and Setting Prospective, randomized, double-blind, placebo-controlled, 4-year study conducted in 4 centers in Belgium, Denmark, and Italy from August 1994 to July 1998.

Participants Four hundred seventy-four postmenopausal white women, aged 45 to 75 years, with bone mineral densities (BMDs) of less than 0.86 g/cm².

Interventions Patients were randomly assigned to receive ipriflavone, 200 mg 3 times per day (n = 234), or placebo (n = 240); all received 500 mg/d of calcium.

Main Outcome Measures Efficacy measures included spine, hip, and forearm BMD and biochemical markers of bone resorption (urinary hydroxyproline corrected for creatinine and urinary CrossLaps [Osteometer Biotech, Herlev, Denmark] corrected for creatinine), assessed every 6 months. Laboratory safety measures and adverse events were recorded every 3 months.

Results Based on intent-to-treat analysis, after 36 months of treatment, the annual percentage change from baseline in BMD of the lumbar spine for ipriflavone vs placebo (0.1% [95% confidence interval {CI}, −7.9% to 8.1%] vs 0.8% [95% CI, −9.1% to 10.7%]; P = .14), or in any of the other sites measured, did not differ significantly between groups. The response in biochemical markers was also similar between groups (eg, for hydroxyproline corrected for creatinine, 20.13 mg/g [95% CI, 18.85-21.41 mg/g] vs 20.67 mg/g [95% CI, 19.41-21.92 mg/g]; P = .96); urinary CrossLaps corrected for creatinine, 268 mg/mol (95% CI, 249-288 mg/mol) vs 268 mg/mol (95% CI, 254-282 mg/mol); P = .81. The number of women with new vertebral fracture was identical or nearly so in the 2 groups at all time points. Lymphocyte concentrations decreased significantly (500/µL (0.5 × 10⁹/L)) in women treated with ipriflavone. Thirty-one women (13.2%) in the ipriflavone group developed subclinical lymphocytopenia, of whom 29 developed it during ipriflavone treatment. Of these, 15 (52%) of 29 had recovered spontaneously by 1 year and 22 (81%) of 29 by 2 years.

Conclusions Our data indicate that ipriflavone does not prevent bone loss or affect biochemical markers of bone metabolism. Additionally, ipriflavone induces lymphocytopenia in a significant number of women.

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women, data on the efficacy of ipriflavone on the prevention of bone loss are conflicting. Nevertheless, most studies have shown that ipriflavone (typical dosage, 600 mg/d) is able to prevent bone loss, and some data have even suggested that ipriflavone may increase bone mass in postmenopausal women. However, reports of lymphocytopenia in women taking ipriflavone have generated some concerns regarding the safety of ipriflavone.

Ipriflavone is marketed and easily available as an over-the-counter product in several countries (i.e., Ostovone in the United States, Osten in Japan, Ossteochin in Hungary, and Osteofix and Iprosten in Italy). We report the results from a large, randomized, double-blind, placebo-controlled, 3-year clinical study, designed to investigate the efficacy and safety of ipriflavone on bone density, biochemical markers of bone turnover, and fracture rate in postmenopausal women with osteoporosis.

METHODS

Subjects

Four hundred seventy-four white women between the ages of 45 and 75 years, with a natural menopause at least 1 year before entering the study, with low bone mass defined as a bone mineral density (BMD) of the lumbar spine (L2-L4) below 0.86 g/cm², as determined by the QDR 1000 (Hologic Inc, Waltham, Mass), corresponding to at least 2 SDs below the premenopausal mean value were included in the study. No women with a body mass index lower than 30 kg/m² were enrolled. Protocol exclusion criteria were (1) any x-ray film that documented previous vertebral fracture, substantial scoliosis, osteoarthrosis, or spinal secondary osteoporosis, or bone-related diseases; (2) significant concomitant disease or medical history that could interfere with the study; (3) alcohol abuse; (4) medication such as sex steroids, bisphosphonates, calcitonin, fluoride, glucocorticoids within 12 months prior to randomization, or any ipriflavone intake in the month prior to randomization. In addition, at the time of inclusion, participants were taking no medication known to affect bone metabolism. Women participating in the study were identified by advertisements and via the national registration office (Denmark only).

Ethical Aspects

The study was approved by the local ethics committees and health authorities in all 3 countries recruiting participants to the study (Belgium, Denmark, and Italy). The study was conducted in accordance with the Helsinki Declaration, and all participants were informed about the study and gave written informed consent before entering the study.

Settings

The study was conducted at 4 European centers. The 2 Belgian centers recruited 205 and 52 subjects, the Danish center recruited 197, and the Italian center recruited 20 subjects. Details about the study design have been published elsewhere.

Study Treatment Groups

Women were randomly assigned in blocks (assigned to each center) to either ipriflavone (200 mg 3 times a day) or placebo administered orally in connection with meals in a double-blind fashion. Tablets (ipriflavone or placebo) were all identical in appearance, shape, color, smell, taste, and weight. All participants received a concomitant calcium supplementation of 500 mg/d.

Individual participant treatment code envelopes were provided to the investigator by the sponsor prior to allocation. The lead investigator kept the treatment code envelopes in a locked, secure storage facility. Unblinding of the individual treatment codes occurred upon completion of the study by all subjects.

End Points

Bone Mineral Density. Lumbar spine (L2-L4), total hip, and distal radius BMD was determined by dual-energy radiograph absorptiometry (QDR 1000). Calibration was performed with a phantom before measurement at each skeletal site on a daily basis. The BMD was determined every 6 months throughout the 3 years. An internal quality assurance control was set up at the Danish center for the BMD measurements, as previously described. For women who dropped out of the study, the last BMD observation was carried forward.

Biochemical Markers of Bone Turnover. Bone formation was determined by serum alkaline phosphatase automatic analyzer (Cobas Mira Plus, Roche Diagnostic Systems, Basel, Switzerland). Bone resorption was evaluated by fasting urinary hydroxyproline corrected for creatinine by spectrophotometry (UV-160 A), as described previously. In addition, bone metabolism was evaluated by serum calcium, serum phosphorus, and urinary excretion of calcium corrected for creatinine (Cobas Mira Plus). In the Danish subpopulation, we also measured urinary CrossLaps (Osteometer Biotech A/S, Herlev, Denmark) corrected for urinary creatinine as determined by enzyme-linked immunosorbent assay. Biochemical markers were assessed at baseline and every 6 months throughout the study. All analyses were performed when the study was completed.

Incident Nontraumatic Vertebral Fractures. The incidence of nontraumatic vertebral fractures was evaluated as a secondary end point. Lateral radiography of the thoracic and lumbar spine was performed according to a standardized acquisition procedure, and assessed in a central facility. The x-ray film examination was performed at baseline (unless this had been done less than a year prior to entry in the study) and again after years 1, 2, and 3. The x-ray films were evaluated by a radiologist blinded to treatment. A fracture was defined as a 20% or greater reduction of the anterior, middle, or posterior height of a vertebra at the level of T4-L4. The total number of incident spinal fractures and the number of women with incident fractures were then calculated for each group.

Measurement of Ipriflavone-Circulating Metabolites in the Plasma. Ipriflavone and its active plasma metabolites M-III and M-V were analyzed by hydrolysis followed by a sp-
specific high-performance liquid chromatography with UV detection. Calibration curves were linear over the studied concentration range of 20 to 4000 ng/mL. The lower limit of the calibration curves was taken as the limit of quantitation of the method. The extraction recovery determined at 3 concentration levels was higher than 80%, the precision of the method ranged between 2% and 9%, and the accuracy between 90% and 113%.  

Safety Determinations

Laboratory Safety Parameters. Routine blood samples were collected after 12 hours of fasting at baseline (prior to randomization) and semianually during the course of the study. Hematology (including erythrocytes, leukocytes, differential count, hematocrit, hemoglobin, and platelets) was determined using the Sysmex (Toa Medical Electronics, Surrey, England), biochemistry (including glucose, serum urea nitrogen, aspartate transaminase, alanine transaminase, γ-glutamyltransferase, lactic dehydrogenase, alkaline phosphatase, total bilirubin, total cholesterol, triglycerides, total amount of protein, albumin, creatinine, sodium, potassium, chloride, thyrotropin [baseline], and vitamin D3 [baseline]) were determined using the Cobas Mira Plus. Microscopic examination was performed if abnormal dipstick results were obtained.

Physical Examination. A complete physical examination of each participant was performed every 3 months. Adverse Events. Every 3 months, adverse events were recorded. An adverse event was defined as any adverse change from the baseline clinical or laboratory condition and classified by body system or preferred term. Relationship of the adverse events to the study drug was evaluated.

Table 1. Demographic Data*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ipriflavone (n = 234)</th>
<th>Placebo (n = 240)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>63.2 (6.2)</td>
<td>63.4 (6.2)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>159.2 (6.5)</td>
<td>160.0 (6.6)</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>62.8 (8.7)</td>
<td>63.2 (9.0)</td>
</tr>
<tr>
<td>Bone mineral density, g/cm²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spine†</td>
<td>0.76 (0.08)</td>
<td>0.76 (0.07)</td>
</tr>
<tr>
<td>Hip‡</td>
<td>0.74 (0.09)</td>
<td>0.74 (0.10)</td>
</tr>
<tr>
<td>Follicle-stimulating hormone, miU/mL</td>
<td>87 (28)</td>
<td>83 (36)</td>
</tr>
<tr>
<td>Lymphocyte count, ×10⁹/L</td>
<td>1.92 (0.56)</td>
<td>1.91 (0.59)</td>
</tr>
</tbody>
</table>

| No. (%)                       |                       |                   |
| Surgical menopause            | 35 (15)               | 48 (20)           |
| Family history of osteoporosis| 44 (19)               | 50 (21)           |
| Smokers                       | 50 (21.4)             | 63 (26.4)         |

| Daily calcium intake          |                       |                   |
| Low (~800 mg/d)               | 101 (43.2)            | 106 (44.2)        |
| Normal (800-1500 mg/d)        | 100 (42.9)            | 106 (44.2)        |
| High (~1500 mg/d)             | 30 (12.8)             | 24 (10.0)         |
| None                          | 3 (1.3)               | 4 (1.7)           |

| Physical exercise (walking)   |                       |                   |
| Low (~1 h/d)                  | 124 (53.0)            | 124 (51.7)        |
| Moderate (1 h/d)              | 90 (38.5)             | 104 (43.3)        |
| Intense (~1 h/d or other      | 19 (8.1)              | 11 (4.6)          |
| physical activity)            |                       |                   |
| None                          | 1 (0.4)               | 1 (0.4)           |

*There was no significant difference between the groups for any variable tested.
†Mean T score for ipriflavone is −2.69; placebo, −2.86.
‡Mean T score for ipriflavone is −1.97; placebo, −1.99.

Compliance

An account was made for each participant concerning study drugs dispensed and returned at each visit. Plasma levels of ipriflavone and its metabolites were determined after the first, second, and third year.

Statistical Analysis

The data presented are based on intent-to-treat analysis. Baseline parameters and changes in end points at various time points (during the 3-year treatment period) were compared by using the t test. Changes over time in the vertebral morphometry parameters (height ratios) were analyzed in the timeinterval baseline (3 years) by repeated measures analysis of variance with baseline values and center included as covariates. The number of fractures after 1, 2, and 3 years of treatment was evaluated using 1-sided Fisher exact test. Similarly, changes over time in BMD and biochemical markers of bone turnover were analyzed in the same time interval by repeated measures analysis of variance. The SAS statistical software (SAS Institute Inc, Cary, NC) was used for the statistical analysis, and P<.05 was regarded as statistically significant.

Sample size calculation was based on a mean (SD) annual decrease in spinal BMD of approximately 1% (6%) in placebo-treated women, which gives a power of just over 97% (240 placebo-treated women and P = .05). The actual SD in the study was 3% per year for both groups. Conversely, to detect a 1% difference in spinal BMD with at least 90% power would require a study size of about 1300 subjects.

RESULTS

Population

Table 1 depicts the baseline characteristics for the 2 groups. None had a prevalent spine fracture in either group at the time of randomization. At baseline, 339 of the total population (71.6%) had a spinal T score of less than −2.5 SD. Figure 1 illustrates the progress of patients throughout the study. A total of 292 women completed the study: 132...
in the ipriflavone group, and 160 in the placebo group.

**Efficacy Parameters**

The data on efficacy presented are for intent-to-treat. Data for validated completers were essentially identical to the intent-to-treat analysis (data available upon request). Figure 2 shows the change in BMD (mean [90% confidence interval {CI}]) in the 2 groups during the course of the study.

After 36 months of treatment, there was no statistically significant difference between annual percentage change from baseline in BMD of the lumbar spine (ipriflavone vs placebo, 0.1% [95% CI, −.7.9% to 8.1%] vs 0.8% [95% CI, −9.1% to 10.7%]; P = .14); or in any of the other sites between the 2 groups. The response in the excretion of hydroxyproline corrected for creatinine was also similar between groups (ipriflavone vs placebo, 20.13 mg/g [95% CI, 18.85-21.41 mg/g] vs 20.67 mg/g [95% CI, 19.41-21.92 mg/g]; P = .96) and in the excretion of CrossLaps corrected for creatinine was 268 mg/mol (95% CI, 249-288 mg/mol) vs 268 mg/mol (95% CI, 254-282 mg/mol); P = .81. The lymphocyte concentration decreased significantly in women treated with ipriflavone and 29 women developed subclinical lymphocytopenia (<500/µL [<0.5 × 10²/µL]) during ipriflavone treatment. Of these, 52% had recovered spontaneously by 1 year and 81% by 2 years. The development in spine BMD (Figure 2A), hip BMD (Figure 2B), or arm BMD (Figure 2C) between the 2 groups was similar at all time points. Figure 3 shows the changes in serum alkaline (Figure 3A), in urinary hydroxyproline corrected for creatinine (Figure 3B), and in urinary CrossLaps corrected for creatinine (Figure 3C). We found no statistically significant difference between the 2 treatment groups for any of the biochemical markers of either bone formation or bone resorption. There was no statistically significant difference between the 2 groups regarding incidental vertebral fractures or the number of subjects with an incident vertebral fracture after 1, 2, or 3 years of treatment (Table 2). In the ipriflavone group, the plasma ipriflavone concentration (mean [SEM]) was 93 (10) ng/mL after 1 year, 107 (20) ng/mL after 2 years, and 64 (16) ng/mL after 3 years of treatment. The concentration of the active metabolite M-V was 1001 (58) ng/mL after 1 year, 1115 (95) ng/mL after 2 years, and 886 (95) ng/mL after 3 years and similar values were found for the other metabolite M-III (916 [425], 3900 [1695], and 1233 [671] ng/mL, respectively). The values for the placebo group regarding...
plasma concentrations of ipriflavone and its metabolites were not detectable.

**Safety Parameters**

Table 3 and Table 4 summarize the number of adverse events reported in the study for the 2 groups. The most important adverse event in this study was lymphocytopenia (total lymphocyte concentration <500/µL). The mean lymphocyte percentage fraction of lymphocytes relative to the total white blood cell count in the entire ipriflavone group decreased significantly from about 33% (1900/µL [1.9 x 10^9/L]) to about 27% (1400/µL [1.4 x 10^9/L]) (P <.001) (Figure 4). This decrease had occurred after 6 months and remained stable throughout the treatment period. In 31 of the subjects treated with ipriflavone (13.2%), the concentration of circulating lymphocytes decreased significantly below 500/µL during the treatment period (this study did not discriminate between lymphocyte subpopulations). Of the 31 women with low lymphocyte counts, 29 developed them during the course of the study, while 2 had lymphocytopenia at 36 months. Of the 29 with low lymphocyte concentrations, 15 (52%) had recovered to normal values within 12 months and 22 (81%) in 24 months after discontinuation of ipriflavone. All cases of lymphocytopenia were subclinical (ie, clinically asymptomatic). There were no significant changes between the groups in any other clinical or laboratory parameter investigated (data not shown). One patient (3%) had lymphocytopenia once before the baseline counts. The cut-off point was when the absolute lymphocyte count was below 500/µL. Five of the lymphocytopenic women (16%) are still considered to be lymphocytopenic women (16%) at the point when the absolute lymphocyte count was below 500/µL. Five of the lymphocytopenic women (16%) are still being monitored.

No statistically significant differences in overall treatment and in calcium compliance were found between the 2 groups. During the 4-year study period, the number compliant (≥75%) and noncompliant (<75%) were 130 (55.6%) vs 18 (7.7%) for ipriflavone, respectively, and 153 (63.8%) vs 21 (8.8%) for placebo, respectively. Data were missing for 86 (36.8%) for ipriflavone and 66 (27.5%) for placebo.

**COMMENT**

Ipriflavone (7-isopropoxy-isoflavone) is a synthetic daidzein derivative of natural isoflavone, the natural compound daidzein is its metabolite M-II, thought to have a positive effect on health similarly to other isoflavones, such as genistein. Several in vitro studies have suggested that ipriflavone (typically 200 mg orally 3 times per day) inhibits bone resorption and increases bone formation, believed to be the mechanism by which ipriflavone may prevent bone loss in postmenopausal women.

However, the present study did not confirm the previous findings on bone metabolism in terms of biochemical markers of bone turnover, BMD, or fracture rates.

There may be several potential explanations for the present lack of efficacy of ipriflavone observed in this study. First, it could be speculated that the dosage used in this study was not correct, or at least suboptimal. Second, it is relevant to question whether the statistical power of the study was sufficient to detect statistically significant differences between the ipriflavone group and the placebo group for the end points evaluated. And third, it could be ques-
tioned if the study population studied was too old, or had too little bone mass.

With respect to the dosage issue, the tablets used in this study each contained 200 mg of ipriflavone, and were given 3 times a day with a meal. This regimen has typically been used in previous clinical studies. Measurements of the physiologically active ipriflavone metabolites M-III and M-V in plasma during the course of the study showed values that were comparable with those obtained in positive studies, indicating that the dosage of ipriflavone presumably was clinically sufficient. Therefore, it seems unlikely that the dosage of ipriflavone used in the present study should have been insufficient.

Concerning the second question of statistical power, the size of this study population was large enough to detect a statistically significant change in both bone turnover parameters and in bone mass. Although only 292 individuals were valid completers, we found no effect on any of these parameters. The methods used are all generally accepted, indicating that the results are reliable in terms of bone mass and biochemical markers.

One previous study found that in early postmenopausal women, urinary deoxypyridinoline did not decrease more in a group receiving ipriflavone and calcium compared with a group receiving calcium only. Deoxypyridinoline has been demonstrated to correlate highly and significantly to CrossLaps, the resorption marker used in a subpopulation of our study. Despite this, in the study cited, ipriflavone prevented bone loss compared with calcium alone and the difference (approximately −2%) was significantly different. Other studies have shown that ipriflavone decreases bone resorption and prevents bone loss compared with placebo. In the current study, the values of urinary excretion of CrossLaps were in the same range as found in other postmenopausal women with low bone mass treated with calcium. The different results when comparing our study with previous studies showing a bone-preserving effect of ipriflavone may in part be due to the fact that our study population was older than in most of these other controlled studies. We also found no effects on the fracture incidence (primary end point) in the ipriflavone-treated women. However, our study did not have sufficient power to detect an effect of ipriflavone on fracture incidence. So far, no studies on ipriflavone have been sufficiently powered to study fracture incidence in relation to ipriflavone. Recent fracture studies performed (eg, of bisphosphonates or raloxifene) have enrolled several hundred, or even thousands, of patients. Thus, with regard to the surrogate end points bone mass and the markers of bone resorption, of which CrossLaps is known to be both specific and sensitive, we consistently found no difference from placebo.

Therefore, it remains to be considered if we looked at the right study population. Studies of early and later postmenopausal women and of women with senile osteoporosis have reported positive results with ipriflavone (ie, ipriflavone may prevent postmenopausal bone loss). The population considered in the current study was postmenopausal women with established osteoporosis but no prevalent vertebral fractures, and therefore a positive result in terms of bone mass should be able to be detected. Theoretically, our population could have been too osteoporotic and this might explain the lack of effect of ipriflavone in these women, but we observed not even a tendency toward an effect in ipriflavone-treated women compared with placebo. Furthermore, other interventions to increase BMD are effective in this population. Another factor may be that the women in this study came from various parts of Europe, and geographic differences within subpopulations may be important because of differences in behavioral, nutritional, and environmental factors influencing bone mass, which were not controlled in this study. However, the study was randomized and conducted in accordance with Good Clinical Practice guidelines. Evaluation of efficacy and safety parameters was performed with the investigators being unaware of treatment groups. Therefore, we conclude that the reason for a lack of effect probably is not in the design of the study, nor in the quality of data obtained in positive studies, indicating that the dosage of ipriflavone presumably was clinically sufficient. Therefore, it seems unlikely that the dosage of ipriflavone used in the present study should have been insufficient.

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the study, its conduct, and surrogate end points, nor is it related to dosage or compliance issues of the drug, and we exclude having considered the wrong end points or the wrong population. The most obvious explanation is that ipriflavone does not have a significant effect on the factors evaluated in this population. We observed that women treated with ipriflavone had a significant decrease in lymphocyte concentrations from about 33% to about 27%, whereas women treated with placebo did not. The decrease occurred after 6 months of treatment and the lymphocyte concentration thereafter remained stable. A number of the ipriflavone-treated women developed lymphocytopenia (<500/µL). The lymphocyte subpopulations CD4 and CD8 were not determined in this study, and thus it is unknown if these subpopulations were affected equally. However, this effect of ipriflavone has previously been reported, albeit in a smaller sample.18 In the current trial, this adverse laboratory condition returned to normal within 24 months in 81% of the patients, whereas the remaining 19% were followed up at regular intervals until the lymphocyte count returned to normal.

Ipriflavone-treated women with lymphocytopenia withdrawn from the study also were regularly monitored even after the termination of the study, and some (16%) are still being followed up after the termination of the study, and some (16%) are still being followed up in the safety study until normalization. However, no statistically significant difference in opportunistic infections, neoplastic events, or other adverse effects was found between the ipriflavone and placebo groups and the lymphocyteopenic and nonlymphocyteopenic, ipriflavone-treated women. Hence, all causes of lymphocytopenia observed were subclinical (ie, all subjects remained clinically healthy). The importance of the lymphocytopenia observed in association with ipriflavone in terms of health remains unknown.22,23

In conclusion, the present large randomized, double-blind, placebo-controlled study failed to find any effect of ipriflavone on calcium metabolism in women with postmenopausal osteoporosis, but indicated that some women treated with ipriflavone may develop subclinical lymphocytopenia that may take more than 24 months to resolve. On the basis of our results, the relative benefit-risk ratio of ipriflavone appears low when compared with the alternative antosteoporotic drugs available. Its use in treatment is not supported by these data.

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