

ORIGINAL

## Efficacy of a combined alendronate and calcitriol agent (Maxmarvil<sup>®</sup>) in Korean postmenopausal women with early breast cancer receiving aromatase inhibitor: a double-blind, randomized, placebo-controlled study

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**Abstract.** The use of aromatase inhibitor (AI) in postmenopausal women with hormone receptor (HR)-positive early breast cancer (EBC) produces a deleterious effect on bone mass and an increase in fractures. Several studies using intravenous bisphosphonates have shown effective management of AI-induced bone loss. To determine whether a lower dosage in oral form combined with calcitriol can effectively manage AI-induced bone loss, we performed a randomized, double-blind, prospective, placebo-controlled 24-week trial with a combination of alendronate and 0.5- $\mu$ g of calcitriol daily to HR-positive EBC patients. A total of 98 Korean postmenopausal women with HR-positive EBC who received daily AI, calcium and vitamin D were randomly assigned to 5-mg of alendronate and 0.5- $\mu$ g of calcitriol (Maxmarvil<sup>®</sup>) or placebo groups. The bone mineral density (BMD) and turnover markers were measured. At week 24, the difference in lumbar BMD between the groups was 3.0% ( $p < 0.005$ ). The increase in C-telopeptide after 24 weeks was significantly less in the Maxmarvil group compared to that in the placebo group ( $35.2 \pm 17.5\%$  vs.  $109.8 \pm 28.6\%$ ,  $p < 0.05$ ). Our study demonstrates that a combination of 5-mg alendronate and 0.5- $\mu$ g calcitriol is effective to prevent bone loss due to AI in Korean postmenopausal women with EBC.

**Key words:** Aromatase inhibitor, Alendronate, Calcitriol, Combinative agent, Osteoporosis

**LONG-TERM** survival of women with early breast cancer (EBC) has been improved by advances in adjuvant therapy, especially the use of aromatase inhibitors (AI) for hormone receptor (HR)-positive EBC in postmenopausal women [1-3]. AIs suppress the peripheral conversion of androgen to estrogen, resulting in significant estrogen deficiency. Accordingly, accelerated bone loss due to the absence of estrogen leads to a lower bone density and increased fracture risk [4].

The current preferred treatment of AI-induced bone loss is bisphosphonates to stop further loss of bone mineral density (BMD) and to prevent fractures [5]. The Zometa-Femara Adjuvant Synergy Trials (Z-FAST/

ZO-FAST) have shown that immediate zoledronic acid in a 4 mg biannual infusion in patients treated with letrozole significantly improved bone mass even with normal BMD at baseline [6, 7]. Administration of oral bisphosphonate at the usual dosage used for postmenopausal osteoporosis, such as weekly 35 mg risedronate in the SABRE trial [8] and monthly 150 mg ibandronate in the ARIBON trial [9], were effective in maintaining bone health in women treated with anastrozole. In the SABRE trial, bone loss was prevented only in groups administered with risedronate, while the patients who did not receive risedronate lost bone whether in low or moderate risk of fractures [8].

Calcitriol (1,25-dihydroxyvitamin D<sub>3</sub>) is an active metabolite of vitamin D that exerts an anticancer effect on breast cancer cells and inhibits the expression of aromatase *in vitro* and *in vivo* [10]. In addition, the combination of calcitriol with an AI also results in enhanced

Submitted Jul. 31, 2012; Accepted Sep. 18, 2012 as EJ12-0283

Released online in J-STAGE as advance publication Oct. 13, 2012

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tumor inhibition [11].

We have previously shown that the combinative alendronate (5 mg) and calcitriol (0.5 µg) agent (Maxmarvil<sup>®</sup>, Yuyu Co., Seoul, Korea) is quite effective in maintaining bone mass in Asian osteoporotic postmenopausal women, even though the daily dosage of alendronate approved by the USA Food and Drug Administration is 10 mg [12]. The primary goal of the present study was to evaluate the effects of the combined administration of low-dose alendronate and calcitriol on BMD in postmenopausal women with HR-positive EBC who received daily AI, calcium and vitamin D.

## Materials and Methods

### Study design

This randomized, placebo-controlled, double-blind 24-week study was performed at a single hospital. Maxmarvil<sup>®</sup>, which is manufactured by the pharmaceutical company Yuyu Co., has an international patent from the World Intellectual Property Organization. Assignments to the Maxmarvil or placebo group were made using a list of randomly allocated treatment codes. Each patient received either a tablet of Maxmarvil or a dummy tablet in the early morning with a glass of water after an overnight fast. They were instructed to remain upright for at least 30 min before the first food intake of the day. Every patient also received daily 500 mg elementary calcium with 400 IU cholecalciferol. Treatment was continued for 24 weeks.

### Ethical issues

Permission to execute this clinical trial was granted by the institutional review board committee of Severance Hospital. Prior to the start of this study, written informed consent was obtained from all subjects after they had been provided with sufficient information about the study and related matters. This study followed the rights, safety and wellbeing of the subjects consistent with the ethical principles laid down in the Declaration of Helsinki.

### Study participants

The 98 patients enrolled in this study were randomly placed into one of the two treatment groups. The patients were selected according to the following criteria: HR-positive EBC treated with appropriate surgical treatment, Eastern Cooperative Oncology Group (ECOG) Performance status less than 2, postmenopausal, and

newly treated with any of the third-generation AIs, either anastrozole or letrozole. However, patients with the following conditions were excluded: clinical and/or radiological evidence of distant metastasis, previous use of intravenous or oral bisphosphonate, any selective estrogen receptor modulator or systemic corticosteroid within 12 months, continuous use of drugs affecting bone metabolism, use of drugs affecting the musculoskeletal system within 12 weeks of the study (estrogen, progesterone, calcitonin, fluoride, calcitriol, calcitonin, mithramycin, gallium nitrate), esophageal stricture or achalasia and hypersensitivity to alendronate or calcitriol, hypocalcemia or hypercalcemia, scheduled for surgery, or judged to be inappropriate as clinical test subjects.

### BMD and fracture risk assessment

The measurements were conducted using central dual X-ray absorptiometry (DXA, Hologic QDR 4500A, Waltham, U.S.A.). The L1-L4 spine and the total hip with the femoral neck were evaluated at baseline and after 24 weeks of treatment. The average precision error was less than 1.1%. To detect any fracture in the spine, vertebral fracture assessment (VFA) by DXA was performed. Existence of any fragility fracture was questioned to each participant. However, the fracture was not detected in any of the subjects. Fracture risk assessment was calculated using FRAX<sup>®</sup> in the <http://www.shef.ac.uk/FRAX/tool> for South Korea.

### Biochemical analysis

In all patients, routine chemical data were collected every 12 weeks. The serum levels of osteocalcin (OCN) (ELISA; CIS Biointernational, Filsur Yvetter, France, intra-coefficient variance (CV) 3.9%, inter-CV 7.6%) and serum C-telopeptide (CTX) (Ostex International, Seattle, WA, USA, intra-CV 10.0%, inter-CV 7.0%) were also measured before and after treatment. Intact parathyroid hormone (PTH, IRMA; Biosource, Belgium, intra-CV 2.8%, inter-CV 3.2%) and 25(OH)D (D3-RIA-CT, Belgium, intra-CV 3.3%, inter-CV 5.2%) were assayed before treatment initiation. Subjective symptoms related to adverse effects were also monitored by noting complaints at each visit. An overall safety assessment was made by the principal investigator considering laboratory data and adverse effects.

### Statistical analysis

For the estimation of the number of subjects, the dif-

ference of percent change in LS BMD between two study groups, the primary endpoint, was set as 3% with 5% of standard deviation according to our previous study [12]. To obtain 80% statistical power with a two-sided alpha value of 0.05, the needed number of subjects per group was 44. Considering 10% dropout, total number of subjects was calculated as 98. The baseline characteristics and homogeneity of patient backgrounds between the two treatment groups were compared using Student's *t*-test and the Chi-square test. The differences between the two groups in mean baseline values for each item were also examined using Student's *t*-test. The percent change differences in BMD and bone turnover markers between the groups were analyzed with Student's *t*-test. The incidences of adverse effects and abnormal changes in clinical laboratory data were examined and compared between the two treatment groups using the Chi-square test. The data are expressed as the mean  $\pm$  SD. *P* values less than 0.05 were considered statistically significant. All results are shown based on per-protocol analyses and were not different from the intent-to-treat analyses.

## Results

### Baseline clinical characteristics

Two hundred nineteen postmenopausal women with HR-positive EBC were enrolled, with a final total of 98 women randomized to the actual clinical trial (Fig. 1). Baseline characteristics and demographic data were similar between the two groups including the period after menopause, subclasses of AIs, and percentage of exposure to previous chemotherapy, biochemical profiles, baseline BMD at all sites and FRAX score (Table 1, no significant statistical differ-

ences between the two groups).

### Treatment effect on BMD

Fig. 2 shows the percentage changes in lumbar and total hip BMD during the 24-week treatment period compared with baseline values. Lumbar BMD significantly decreased by  $3.5 \pm 0.6\%$  24 weeks after the initiation of AI in the placebo group, while it was well maintained in the Maxmarvil group (Fig. 2A). The difference in lumbar BMD was about 3.0% between two groups ( $p < 0.05$ ). Sub-group analysis was performed according to the duration of menopause since there were 20 women who had begun menopause within the year. The loss of lumbar BMD was much more significant in the recently menopausal patients by  $-7.4 \pm 1.8\%$ , while Maxmarvil effectively prevented further bone loss ( $p < 0.05$ , data not shown). However, there were no significant differences in the BMD of any hip region including the total hip and femur neck (Fig. 2B).

### Biochemical Changes

Fig. 3A (CTX) and 3B (OCN) show the data for the changes in serum bone turnover markers of the subjects (shown as Maxmarvil vs. Placebo). Serum CTX in the placebo group was markedly higher 24 weeks after the initiation of AI treatment, as was OCN. The difference in the changes in CTX between the Maxmarvil and Placebo groups were also significant (72.4%,  $p < 0.05$ ). The increase in OCN in the Maxmarvil group tended to be smaller than that in the Placebo group (29.0%,  $p = 0.08$ ). Changes in serum calcium and phosphate were assessed in both groups but no significant differences were noted (Table 2).

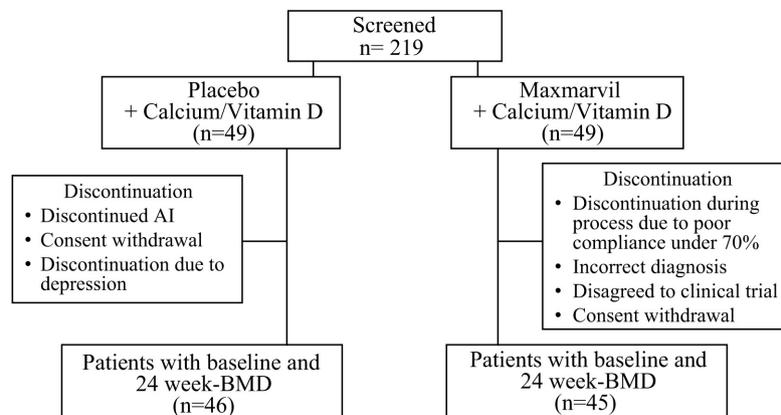
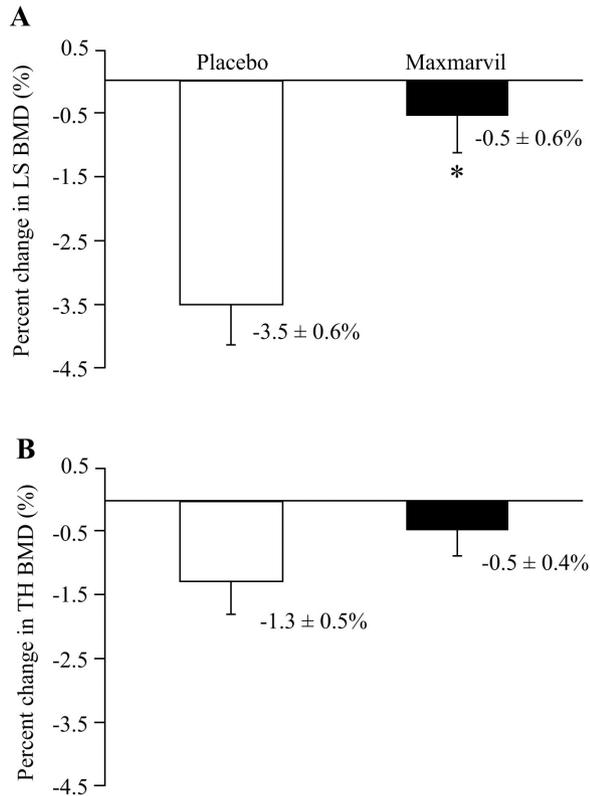


Fig. 1 Outcome of the randomization process in this study

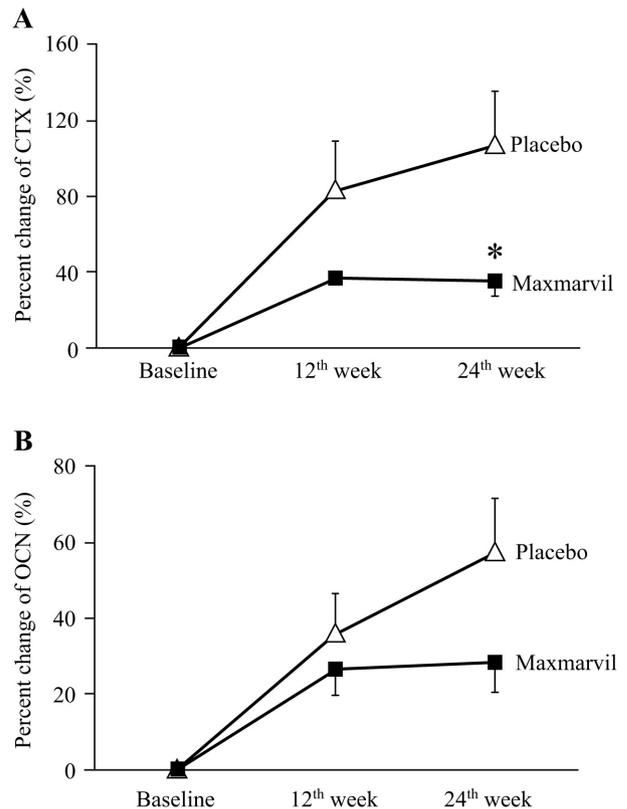
**Table 1** Clinical characteristics of participants

Characteristic	Placebo (n=49)	Maxmarvil (n=49)
Age (years)	58.5 ± 1.1	57.1 ± 1.0
Years since menopause (years)	8.5 ± 1.1	7.0 ± 1.0
Height (cm)	153.9 ± 5.3	155.9 ± 5.0
Weight (kg)	57.8 ± 7.7	58.6 ± 7.7
Class of AI (Letrozole:Anastrozole)	18 : 31	21 : 28
Previous chemotherapy (%)	53.1	46.9
BMD at L1-L4 (g/cm <sup>2</sup> )	0.871 ± 0.016	0.876 ± 0.022
T-score at L1-L4	-1.1 ± 0.14	-1.1 ± 0.19
BMD at the total hip (g/cm <sup>2</sup> )	0.770 ± 0.013	0.805 ± 0.016
T-score at the total hip	-0.7 ± 0.11	-0.4 ± 0.14
10 year probability of major osteoporotic fracture (%)	5.0 ± 2.1	4.4 ± 2.0
10 year probability of hip fracture (%)	1.0 ± 1.2	0.7 ± 1.1
Serum calcium (mg/dL)	9.2 ± 0.07	9.2 ± 0.06
Serum phosphorous (mg/dL)	3.9 ± 0.09	3.9 ± 0.07
25(OH)D (nmol/L)	42.3 ± 2.6	35.0 ± 2.5
Intact PTH (pg/mL)	26.2 ± 1.75	22.6 ± 1.32
OCN (ng/mL)	21.4 ± 1.38	22.6 ± 1.32
CTX (ng/mL)	0.34 ± 0.03	0.42 ± 0.83

\* No significant statistical difference between two groups.



**Fig. 2** A. Changes in lumbar BMD during the 24-week treatment (\**p* < 0.05, Maxmarvil vs. Placebo, by Student's *t*-test). B. Changes in total hip BMD during the 24-week treatment (*p* = NS, Maxmarvil vs. Placebo, by Student's *t*-test).



**Fig. 3** A. Changes in CTX during the 24-week treatment (\**p* < 0.05, Maxmarvil vs. Placebo, by Student's *t*-test). B. Changes in OCN during the 24-week treatment (*p* = 0.08, Maxmarvil vs. Placebo, by Student's *t*-test).

**Table 2** Changes in calcium and phosphate during 24-week treatment

Week	Placebo		Maxmarvil		<i>p</i> value between groups*	
	0	24	0	24	0	24
Serum Ca (mg/dL)	9.2 ± 0.5	9.4 ± 0.5	9.2 ± 0.4	9.5 ± 0.3	NS	NS
Serum P (mg/dL)	3.9 ± 0.6	4.1 ± 0.4	3.9 ± 0.5	4.0 ± 0.5	NS	NS

Mean ± SD; NS, Not significant; \**p* value by Student's *t*-test

### Adverse events

Safety analyses were performed in the 98 subjects (Maxmarvil, 49; Placebo, 49). Adverse events were evaluated based on the occurrence of clinical symptoms and biochemical data. The incidence of adverse effects did not differ significantly between the two groups. In the placebo group, one patient had trigeminal neuralgia and one had a fever, both of which subsided, and they continued the study without any problem. In the Maxmarvil group, there was one patient with hemoptysis and one with epigastric pain, but none of the patients had to drop-out of the study since these complaints disappeared without drug cessation.

### Discussion

Oral treatment with the newly combined agents alendronate (5 mg) and calcitriol (0.5 µg) administered over a short duration of 24 weeks was quite effective in preventing loss of lumbar BMD and repressing high bone turnover in HR-positive EBC patients treated with AI.

As potent inhibitors of estradiol production, AIs are prescribed in both the adjuvant and metastatic treatment of breast cancer patients with HR-positivity. Due to the estrogen deficiency, significant bone loss occurs both in patients with normal BMD or osteopenia and in those with osteoporosis [8]. The third generation AIs, anastrozole and letrozole, have been shown to decrease bone mass as well as increase the incidence of fracture compared to tamoxifen in postmenopausal women with EBC [13]. Meanwhile, a racial difference has been reported in that there was a much lower degree of bone loss with AI in Japanese postmenopausal breast cancer patients, 1.3% and 2.8% at 1 and 2 years, respectively [14]. However, there was significant bone loss as early as 24 weeks in Korean postmenopausal breast cancer patients treated with AI.

As in postmenopausal osteoporosis management, bisphosphonates are the preferred treatment against AI-induced bone loss related to high bone turnover. Several clinical trials using intravenous or oral bisphosphonates have revealed the efficacy of these agents in

maintaining or increasing BMD in AI-induced bone loss [6, 8, 9]. Administration of intravenous zoledronic acid effectively increased both lumbar and hip BMD in postmenopausal women with EBC with a baseline T-score higher than -2.0 [6]. However, the dosage used in this study was 4 mg twice a year, which is much more than the yearly 5 mg infusion typically used for the osteoporosis patients. Other studies using oral bisphosphonates at the dose and schedule used in postmenopausal osteoporosis, 35 mg weekly risedronate or 150 mg monthly ibandronate, were also effective for AI-induced bone loss [8, 9].

Recently, there have been considerable concerns associated with bisphosphonate use such as osteonecrosis of the jaw and atypical fractures [15, 16]. The incidences of these adverse effects are generally related to the dosage and duration of bisphosphonate use. Therefore, in a 5-year treatment involving AI-induced bone loss regardless of baseline BMD, the maintenance of good bone health involves not only increasing the bone mass but rather preventing any loss with minimal risk of side effects. We have previously shown that, rather than the general dosage of alendronate of 10 mg daily or 70 mg weekly, the use of a lower dosage of alendronate, 5 mg, combined with 0.5 µg of calcitriol effectively results in a 2.4% increase in lumbar BMD over a short 6-month period in Korean postmenopausal women with osteoporosis [12]. In the present study, the differences between the groups in the lumbar spine BMD was 3.0% ( $p < 0.005$ ) due to more loss in the placebo group, while the Maxmarvil group maintained bone mass. The degree of increase in CTX was significantly lower in the Maxmarvil group than in the Placebo group, by 72.4% ( $p < 0.05$ ).

Calcitriol is an active metabolite of vitamin D which controls the calcium and phosphate homeostasis mainly by regulating intestinal absorption. It is worthwhile to consider the extra-skeletal effect of calcitriol in the breast cancer setting. Calcitriol is known to exert an anticancer effect on breast cancer cells as well as to inhibit the expression of aromatase *in vitro* and *in vivo* [10]. In addition, combining calcitriol with AIs

also results in enhanced tumor inhibition [11]. This makes calcitriol a favorable choice for combination with alendronate considering the status of our patients with respect to the recurrence of breast cancer.

Our study only demonstrates the changes in BMD and bone markers. Therefore, the results from our study are not sufficient to address the efficacy of Maxmarvil in fracture reduction. By combining calcitriol with Maxmarvil, hypercalciuria might become a concern, but the degree of hypercalciuria has been shown to be significantly less with concomitant use

of alendronate [12]. Moreover, the overall safety of Maxmarvil was similar to that of the placebo. There were only a few incidents regarding gastrointestinal discomfort or fever. The actual drop-out rate was not different between the groups.

In conclusion, combining a low dose of alendronate with calcitriol seems to be reasonable and helpful for HR-positive EBC patients who are treated with an AI, regardless of baseline BMD or exposure to chemotherapy.

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