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Long-term use of dienogest for the treatment of endometriosis

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Abstract

Aim: To investigate the safety and efficacy of 52 weeks of dienogest treatment in patients with endometriosis.

Methods: One hundred and thirty-five patients with endometriosis received 2 mg of dienogest orally each day for 52 weeks. Adverse drug reactions and bone density were evaluated. Global improvement was assessed based on the changes in severity categories of five subjective symptoms during non-menstruation (lower abdominal pain, lumbago, dyschezia, dyspareunia, and pain on vaginal examination) and two objective findings (induration involving the pouch of Douglas and limited uterine mobility).

Results: The most common adverse drug reactions included metrorrhagia (71.9%), headaches (18.5%), and constipation (10.4%). No clinically significant changes were noted in the incidence or severity of reactions associated with the course of the treatment period (52 weeks). Changes from the baseline bone mineral density of the lumbar spine measured by dual-energy X-ray absorptiometry were $-1.6 \pm 2.4\%$ and $-1.7 \pm 2.2\%$ (mean $\pm$ standard deviation) at 24 and 52 weeks, respectively, which were statistically significant decreases; however, there was no cumulative decrease. The proportions of patients assessed as marked or moderate improvement in terms of global improvement were 72.5% (95/131 cases) at 24 weeks and 90.6% (106/117 cases) at 52 weeks.

Conclusion: The long-term effect of dienogest on bone mineral density was slight, whereas the efficacy increased cumulatively.

Key words: dienogest, endometriosis, long-term administration, progestin, safety.

Introduction

Endometriosis, affecting 6 to 10% of females of reproductive age,[1] markedly reduces quality of life (QOL) owing to symptoms of pain, such as lower abdominal pain and lumbago,[2] with frequent recurrences of symptoms after discontinuation of medications or conservative therapies.[3,4] Currently, gonadotropin releasing hormone (Gn-RH) agonists and danazol are primarily used to treat endometriosis in Japan, both of which have been shown to have high therapeutic effects.[5] However, bone mineral loss is an adverse drug reaction associated with Gn-RH agonists; thus, the treatment period is generally limited to 6 months. The standard treatment period for danazol is 4 months because of impaired hepatic function associated with the drug, as well as the increased risk of thrombosis. There is, therefore, a need for new therapeutic drugs that are well-tolerated and have efficacy against endometriosis through long-term therapeutic use.

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Dienogest, a novel 19-nortestosterone derivative, is a progestin that is highly selective for progesterone receptors.[6] Because dienogest exhibits antiovulatory activity,[7] antiproliferative action on endometrial cells,[8] and inhibitory effects on cytokine production of endometriotic cells,[9] it is expected to have a therapeutic effect against endometriosis. The drug has been investigated in terms of its efficacy and safety in patients with endometriosis in Europe and Japan.[10–12]

The purpose of the present study was to investigate the safety and efficacy of 52 weeks of administration of dienogest for the treatment of endometriosis.

Methods

Study design and patients

This was a non-randomized, long-term treatment, multicenter study conducted at 18 study centers in Japan. The validity of the study was reviewed and approved by the institutional review boards of all of the centers involved in the study.

Inclusion criteria were as follows: (i) ≥20 years of age; (ii) regular menstrual cycles; (iii) endometriosis diagnosed by laparotomy, laparoscopy, or imaging analysis (combination of magnetic resonance imaging and ultrasonography) of endometriotic ovarian chocolate cysts; (iv) simultaneous presence of subjective symptoms during menstruation (at least one of the following: lower abdominal pain, lumbago, dyschezia, nausea, and headaches), subjective symptoms during non-menstruation (at least one of the following: lower abdominal pain, lumbago, dyschezia, dyspareunia, and pain on vaginal examination), and objective findings (at least one of the following: induration involving the pouch of Douglas and limited uterine mobility).

Exclusion criteria were as follows: (i) pregnant or nursing; (ii) undiagnosed abnormal genital bleeding; (iii) class 3 or more on Pap smear within 3 months prior to enrollment; (iv) a history of hypersensitivity or severe adverse drug reactions to steroid hormones; (v) use of Gn-RH agonists, testosterone derivatives, progestins, estrogens, estrogen antagonists, or aromatase inhibitors within 16 weeks prior to enrollment; (vi) having undergone surgical therapy or surgical examination for endometriosis within a menstrual cycle prior to the start of administration with dienogest; (vii) history or complications of thrombosis, embolism, depression, complications of malignancy, or serious cardiac, hepatic, renal, hematologic, or endocrine diseases; (viii) participation in another clinical trial within 4 months prior to enrollment; or (ix) deemed unsuitable for study entry by the investigators.

Written informed consent was obtained from all of the patients.

Study treatments and measurements

Dienogest was given in oral doses (1 mg twice daily), starting on the 2nd to the 5th day of menstruation.

The patients had physical examinations every 4 weeks from the start of treatment until the end of treatment (EOT: 52 weeks or when discontinued), 4 weeks after the EOT, and after resuming menstruation. Throughout the term of the study, the use of reliable contraception other than a hormonal method was required. Any concomitant use of hormonal agents affecting endometriosis was prohibited in the study, whereas analgesics were permitted to manage persistent painful symptoms.

The primary endpoint was the safety evaluation of adverse drug reactions (ADR). To support the evaluation, we examined adverse events, bodyweight, laboratory values, and bone metabolism marker levels (serum bone-derived alkaline phosphatase, serum osteocalcin, urine pyridinoline, urine deoxypyridinoline, and urine type I collagen cross-linked N-telopeptide) at baseline, every 8 weeks after the start of treatment, at the EOT, and 4 weeks after the EOT. Moreover, the intensity of genital bleeding (five categories: none, spotting, breakthrough, menstrual, and more than menstrual) were recorded daily in a diary by each patient. The intensity and length of predosing and post-EOT menstruation were also determined by interview. Bone density was measured at baseline, after 24 weeks of treatment, and at the EOT. In the subgroup comprised of the patients enrolled in the study centers equipped with dual-energy X-ray absorptiometry (DXA, QDR-4500; Hologic, Bedford, MA, USA), bone mineral density (BMD) of the lumbar spine (L2-L4) was measured. In the other centers, the bone density was measured by the methods available (e.g. quantitative computed tomography, quantitative ultrasound, or microdensitometry).

For the evaluation of efficacy, the severity of each of the five subjective symptoms during non-menstruation and the two objective findings was classified according to five stages (none, slight, mild, moderate, and severe) at baseline and every 4 weeks after the start of treatment. With these parameters, global improvement was evaluated by a predetermined sequence, as follows: (i) each improvement in the five subjective symptoms

during non-menstruation and two objective findings were scored (2: improved markedly, 1: improved, 0: unchanged, and –2: worsened) based on the change in the stage of severity from baseline to each examination point during the 52 weeks of the treatment period; (ii) the mean score of the five symptoms during non-menstruation was classified into four ranks of overall improvement (≥1.5: marked, <1.5 ≥0.5: moderate, and <0.5 ≥0: unchanged, <0: worsened); and the mean score of the two objective findings was classified in the same manner as above; and (iii) the global improvement was assessed according to five ranks (marked, moderate, slight, unchanged, and worsened) by pairing the overall improvement in the subjective symptoms and the overall improvement in objective findings according to a predetermined matrix algorithm. In addition, lower abdominal pain and lumbago during non-menstruation were assessed by the patients who used a Visual Analog Scale (VAS) at baseline, every 8 weeks after the start of treatment, and at the EOT. The subjective symptoms during menstruation were evaluated in the same manner as above at baseline and at the time menstruation resumed after EOT. Furthermore, serum cancer antigen 125 (CA125), estradiol concentrations, and the size of ovarian chocolate cysts measured by ultrasonography were examined at baseline, every 8 weeks after the start of treatment, and at the EOT. QOL was rated using the MOS 36-Item Short-Form Health Survey[13,14] at baseline, at 24 weeks of treatment, and at the EOT. Patient satisfaction with treatment as determined by interview was classified into four categories (certainly willing to use again, prefer to use again, hesitate to use again, and never willing to use again) at 24 weeks of treatment and at the EOT.

The study was monitored and audited by the sponsor to ensure compliance with the Declaration of Helsinki and good clinical practice.

Statistical analysis

The patients who took dienogest at least once were evaluated for safety and efficacy. The percentage change in BMD from baseline to 24 and 52 weeks of treatment were analyzed using a *t*-test (two-sided, significance level of 5%). The proportion of patients assessed as marked or moderate in terms of global and overall improvement were calculated. The mean changes in the VAS from baseline to each examination point were calculated. The proportion of patients with chocolate cysts in ovaries exhibiting shrinkage of ≥25% was calculated.

Results

One hundred and thirty-eight patients were enrolled between May and November 2004. One hundred and thirty five patients were given dienogest at least once and were assessed for both safety and efficacy. Of the 135 cases, 19 discontinued the study (18 during the treatment period and three during the post-treatment observation period; two patients were counted twice). Of the 18 discontinuations during the treatment period, 10 were due to adverse events (of which seven were ADR), two were consent withdrawals for personal reasons, and eight were due to other reasons. The mean ± standard deviation (SD) of the length of the treatment period was 341.5 ± 59.3 days. The mean age of the 135 patients was 34.1 ± 6.4 years (range, 21–47 years); the mean weight was 51.8 ± 6.6 kg (range, 39.0–78.0 kg). The Beecham classification was stage 2, 3, and 4 in 60, 62, and 13 cases, respectively.

Safety

The incidence of adverse events throughout the entire study period was 100% (135/135 cases), and the incidence of ADR was 88.9% (120/135 cases). Serious adverse events occurred in three cases (ulcerative colitis, colonic polyps, and splenic injury); however, none of the serious adverse events were causally related to dienogest. One case of night sweats was assessed as a severe ADR.

The primary ADR consisted of metrorrhagia (71.9%), headaches (18.5%), and constipation (10.4%; Table 1). The severity of metrorrhagia was mild in 82 cases, but moderate in 15 cases. Two of the discontinuations and 11 washouts were due to metrorrhagia. Ninety-six of the 97 cases of metrorrhagia resolved during treatment or within 2 months after the EOT. One case resolved with Kaufmann treatment on day 226 after the EOT. Anemia-related ADR believed to be associated with metrorrhagia existed in four of 97 cases (three of which showed abnormal laboratory test results), but none of these patients discontinued the study. The incidence of metrorrhagia from the start to 24 weeks of treatment was not significantly different from that after 24 weeks of treatment (Table 1).

One hundred and thirty four of 135 patients experienced genital bleeding once or more during the treatment period. The median number of days of genital bleeding per 28 days of treatment period was a maximum of 21 days at 5–8 weeks, nine days at 21–24 weeks, and two days at 49–52 weeks of treatment, indicating a decrease in tendency to bleed as the

Table 1 Adverse drug reactions reported frequently (≥5%) by women in the study of long-term use of dienogest for the treatment of endometriosis

Adverse drug reaction	Observation period		
	Entire period *n* (%)	≤Week 24 *n* (%)	>Week 24† *n* (%)
Metrorrhagia	97 (71.9)	94 (69.6)	79 (58.5)
Headache	25 (18.5)	15 (11.1)	18 (13.3)
Constipation	14 (10.4)	13 (9.6)	9 (6.7)
Nausea	13 (9.6)	10 (7.4)	5 (3.7)
Hot flushes	12 (8.9)	9 (6.7)	6 (4.4)
Hypermenorrhea	12 (8.9)	1 (0.7)	11 (8.1)
Weight gain	11 (8.1)	5 (3.7)	11 (8.1)
Dizziness	8 (5.9)	7 (5.2)	6 (4.4)
Breast discomfort	8 (5.9)	7 (5.2)	2 (1.5)
Malaise	8 (5.9)	5 (3.7)	6 (4.4)
Decreased bone density	8 (5.9)	2 (1.5)	8 (5.9)
Palpitations	7 (5.2)	4 (3.0)	5 (3.7)
Contact dermatitis	7 (5.2)	5 (3.7)	4 (3.0)

†Values include events continuing from before 24 weeks of treatment.

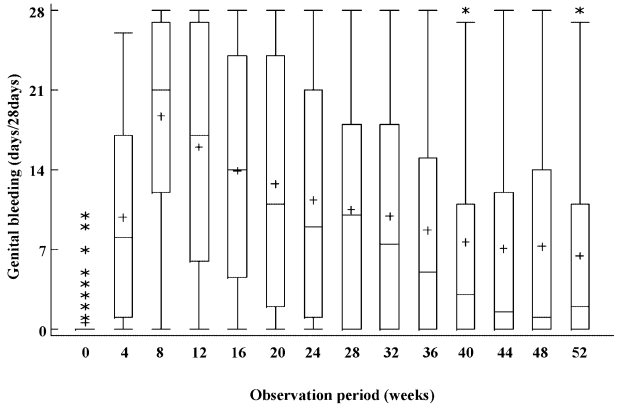

Figure 1 Profile of the number of days with genital bleeding experienced in every 28-day segment of the total observation period after the start of treatment with dienogest. +, mean; – (horizontal lines in boxes), median; top ends of boxes (top hinges), 75% quartile point; bottom ends of boxes (bottom hinges), 25% quartile point; *Outliers (more than 1.5 times the hinge distribution from top hinge).

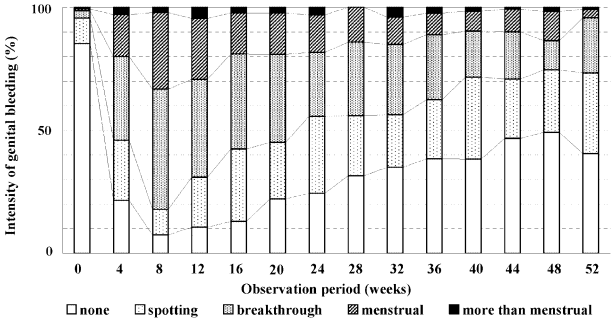

Figure 2 Profiles of the intensity of genital bleeding. The highest intensity of genital bleeding in every 28-day segment of the total observation period after the start of treatment with dienogest is shown.

treatment period was extended (Fig. 1). The proportion of patients with no genital bleeding during 28 days of treatment period was 7.4% (10/135 cases) at 5–8 weeks, 24.4% (32/131 cases) at 21–24 weeks, and 40.5% (47/116 cases) at 49–52 weeks of treatment, indicating a tendency for an increase in the proportion of patients with no genital bleeding as the treatment period was extended (Fig. 2).

The severity of headache and constipation was mild for most cases except for three and two moderate cases, respectively. One patient with moderate constipation discontinued the study. All of the cases with the reactions resolved during treatment or after EOT with the exception that no follow-up examination was possible in one case of mild constipation. The incidence of headache or constipation during the initial 24 weeks of treatment was not significantly different from that after 24 weeks of treatment (Table 1).

There were eight cases of decreased bone density as an ADR. Of these cases, five were measured at the lumbar spine by DXA, two at the forearm by quantitative computed tomography, and one at the right calcaneus by quantitative ultrasound. In one moderate case, the bone density at baseline was at a low level (0.805 g/cm^2), which had decreased to 0.746 g/cm^2 (–7.3% from the baseline), resulting in discontinuation. No

Table 2 Percentage change in lumbar bone mineral density of women in the study of long-term use of dienogest for the treatment of endometriosis

Observation period	*n*†	Mean ± SD	Maximum	Minimum
Baseline to 24 weeks*	42	−1.6 ± 2.4	2.5	−7.9
24 weeks to 52 weeks**	34	−0.2 ± 1.9	5.2	−3.6
Baseline to 52 weeks***	34	−1.7 ± 2.2	3.1	−6.1

P-values for differences (*t*-test): **P* = 0.0001, ***P* = 0.5895, ****P* < 0.0001. †Number of cases for which data were available during the observation period.

follow-up examination was possible in one of the eight cases, but five cases had resolved or were resolving after the EOT, and the remaining two cases showed no further marked decrease in bone density. Bone density decreased in two cases during the initial 24 weeks and in six cases after 24 weeks of treatment (Table 1), but a review of the individual bone density levels of the seven cases in which treatment was continued to 52 weeks revealed further decreases in bone density in four cases and increases in three cases at 52 weeks of treatment compared with 24 weeks, indicating no consistent changes. Forty-three patients were eligible for BMD analysis at the DXA-equipped study centers. The BMD at baseline was 1.024 ± 0.121 g/cm^2. The change in BMD was −1.6 ± 2.4% and −1.7 ± 2.2% from baseline to 24 and 52 weeks of treatment, respectively, both of which were statistically significant (Table 2). The difference in the BMD change from 24 to 52 weeks of treatment was −0.2 ± 1.9%, which was not statistically significant (Table 2), with no cumulative decrease in BMD up to 52 weeks of treatment. Of the five markers of bone metabolism, serum osteocalcin was found to increase over time after the start of treatment compared with the baseline level, but this was a slight change within the reference range.

Resumption of menses after the EOT was confirmed in all 132 cases (three patients of the 135 were excluded as they had withdrawn from post-treatment observation). The number of days from the EOT to the first day of menstruation was 29.9 ± 11.8 days, and menstruation was confirmed within 2 months after the EOT in 97.0% (128/132 cases) of the patients. In the longest case, the 1st day of menstruation was 122 days after the EOT, and this was considered to be an ADR of oligomenorrhea.

The abnormal changes in laboratory tests were assessed as ADR in 10.4% (14/135 cases) of the patients, but treatment with dienogest could be continued. The means and medians of all clinical laboratory parameters were within the normal ranges through the entire study period.

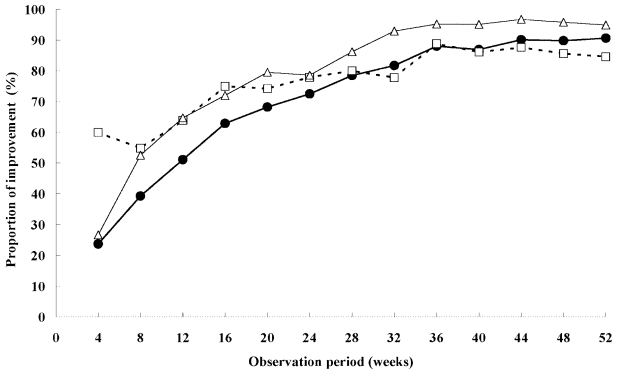

Figure 3 Changes over time in the proportion of cases assessed as marked or moderate global improvement, overall improvement of subjective symptoms during non-menstruation and overall improvement of objective findings. (●) global improvement; (□) overall improvement of subjective symptoms during non-menstruation; and (△) overall improvement of objective findings.

Efficacy

The proportion of patients with a global improvement (marked or moderate) was 72.5% (95/131 cases) at 24 weeks and 90.6% (106/117 cases) at 52 weeks of treatment. Likewise, both the proportions of patients with marked or moderate overall improvement of subjective symptoms during non-menstruation and overall improvement of objective findings increased as the treatment period was extended, with the increases persisting after 24 weeks of treatment (Fig. 3). The proportion of patients with marked or moderate overall improvement of subjective symptoms during menstruation was 65.9% (89/135 cases) at the resumed menstruation after the EOT.

The change in the VAS for lower abdominal pain from baseline to 24 and 52 weeks of treatment was −22.5 ± 32.1 mm and −28.4 ± 29.9 mm, respectively. In the case of lumbago, the changes in the VAS were −16.5 ± 28.4 mm and −19.8 ± 28.2 mm, respectively (Fig. 4). The extent of the decrease in VAS for both

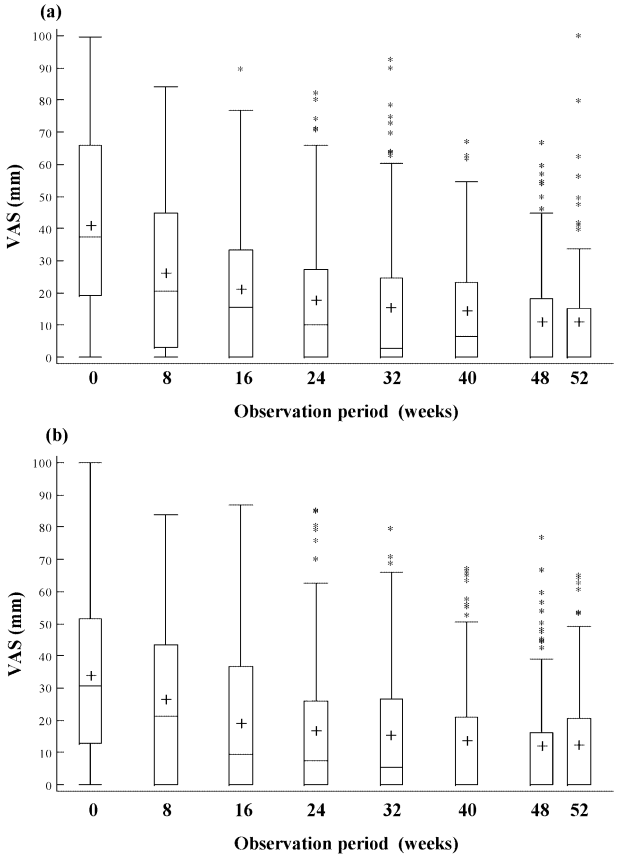

Figure 4 Changes in the Visual Analog Scale (VAS) for lower abdominal pain (a) and lumbago (b) during the treatment period. +, mean; – (horizontal lines in boxes), median; top ends of boxes (top hinges), 75% quartile point; bottom ends of boxes (bottom hinges), 25% quartile point; *Outliers (more than 1.5 times the hinge distribution from top hinge).

parameters was large in the cases that showed amelioration in the global improvement (data not shown). The proportion of patients with chocolate cysts in the ovaries exhibiting shrinkage of 25% or more was 76.9% (83/108 cases) and 84.7% (83/98 cases) at 24 and 52 weeks of treatment, respectively.

The QOL score showed a typical change in the bodily pain subscale among the eight Short-Form 36-Item Health Survey (SF-36) subscales. The score was 46.50 ± 19.51 at baseline, 70.15 ± 20.73 at 24 weeks, and 74.67 ± 21.62 at 52 weeks of treatment, thus indicating an improvement of 23.57 ± 22.37 at 24 weeks and 27.37 ± 28.64 at 52 weeks of treatment, as compared with the baseline score.

Table 3 shows the results of the review of patient satisfaction with dienogest treatment. In the patient responding "never willing to use again", the reason was "persistent genital bleeding, poor condition". This patient discontinued the treatment due to moderate menorrhagia on day 57 of treatment.

The mean serum CA125 concentrations at baseline, during treatment, and 4 weeks after the EOT were 62.3 U/mL, 29.1–43.2 U/mL (minimum-to-maximum), and 45.4 U/mL, respectively. Also, the mean serum estradiol concentrations were 92.8 pg/mL, 28.8–37.2 pg/mL (minimum-to-maximum), and 86.5 pg/mL, respectively.

Discussion

The intended outcome of the treatment of endometriosis is a continuous long-term suppression of endometriotic pathologic activity or development of lesions, as well as the alleviation of symptoms and improvement of the patient's QOL. There is, thus, the need for a therapeutic drug that can be used for the long-term treatment of endometriosis.

The safety and efficacy of dienogest during 52 weeks of long-term administration were studied in the present trial. Only 5.2% patients (7/135 cases) discontinued because of ADR, and virtually all adverse events were of mild severity, all of which resolved or were resolving after the EOT, with the exception of some withdrawn cases. One severe case of an ADR (night sweats) was observed, but this emerged after the EOT and resolved with symptomatic treatment. The incidence of ADR during the observation period after 24 weeks of treatment was not significantly different from that before 24 weeks. In addition, the number of days until the first menstrual cycle after the EOT was 29.9 ± 11.8 days. In a 24-week study of treatment with dienogest as compared with intranasal buserelin acetate in Japan, the number of days until the first menstrual cycle was 28.9 ± 8.8 days in the dienogest group and 48.6 ± 19.2 days in the intranasal buserelin acetate group (unpubl. observation). Because the inhibition of ovarian function by dienogest is believed to be mild compared with buserelin acetate, the fact that the number of days until the first menstruation after treatment with dienogest in the present study was the same as in the 24-week study shows that the inhibition of ovarian function after 52 weeks of treatment was still weaker than after 24 weeks of buserelin acetate. Based on the above, we conclude that there should be no problems associated with prolongation of the dienogest treatment period.

Table 3 Patient satisfaction with long-term dienogest for the treatment of endometriosis

Time	Satisfaction category†			
	1 *n* (%)	2 *n* (%)	3 *n* (%)	4 *n* (%)
Week 24 (*n* = 131)	53 (40.5)	77 (58.8)	1 (0.8)	0 (0.0)
Week 52 (*n* = 114)	49 (43.0)	62 (54.4)	3 (2.6)	0 (0.0)
End of treatment (n = 132‡)	51 (38.6)	70 (50.3)	6 (6.1)	1 (0.8)

†1 = Certainly willing to use again; 2 = Prefer to use again; 3 = Hesitate to use again; 4 = Never willing to use again. ‡Values includes two cases that could not be evaluated.

Metrorrhagia was an ADR of particularly high incidence during the dienogest treatment period, but based on the collated results for genital bleeding in all patients, the prolonged treatment period was accompanied by a decrease in the number of days and intensity of bleeding. Some cases underwent washout because of metrorrhagia, but two cases were discontinued because of metrorrhagia. In three cases, metrorrhagia resulted in anemia-related ADR according to the laboratory results, but these patients did not withdraw from the study. Genital bleeding with dienogest was reported to originate from breakthrough bleeding in the pseudodecidua due to the progestational effect of the drug,[15] and resolved in all patients after the EOT. The above results reveal the tolerability of genital bleeding during long-term treatment with dienogest.

It was previously reported that treatment with danazol was accompanied by a high incidence of ADR, such as abnormal hepatic function, weight gain, and acne.[4] In the present study, 3% of the patients (4/135 cases) had increased γ-glutamyl transferase levels, 2.2% (3/135 cases) had increased alanine aminotransferase levels, and 2.2% (3/135 cases) had increased aspartate aminotransferase levels. Weight gain occurred in 8.1% (11/135 cases) and acne occurred in 3% (4/135 cases). Because virtually all of the ADR were determined to be of mild severity, with no discontinuations, and clinically significant problems were concluded to have resolved during or after administration, the factors limiting the treatment period of danazol were not considered to be a significant problem in the long-term administration of dienogest.

The BMD change with dienogest was $-1.6 \pm 2.4\%$ and $-1.7 \pm 2.2\%$ at 24 and 52 weeks of treatment, respectively, both of which changes were statistically significant; but the difference in the BMD change from 24 to 52 weeks was $-0.2 \pm 1.9\%$, revealing no cumulative decrease in BMD up to 52 weeks of treatment. Furthermore, in terms of decreased bone density regarded as an ADR, prolonging the dienogest treatment period was not considered to result in a systematically cumulative decrease in bone density. The study on markers of bone metabolism revealed no change in markers of bone metabolism, except a slight increase only in serum osteocalcin, a marker of bone formation. As the annual rate of change in spinal bone density for ordinary pre-menopausal Japanese females is reportedly $-0.35 \pm 3.10\%$ (191 cases),[16] the decrease in bone density occurring in 52 weeks of treatment with dienogest may be considered mild and not significantly greater than that in the natural course. One reason why the decrease in bone density with dienogest was less than that with Gn-RH agonists may be that the serum estradiol concentration during treatment with dienogest was, on average, 28.8–37.2 pg/mL (minimum-to-maximum), which is at or over the level in menopause. Also, in terms of the profile of markers of bone metabolism during treatment with Gn-RH agonists, the increase in markers of bone resorption is far greater than that in markers of bone formation;[17] whereas only a mild increase in markers of bone formation was observed with dienogest. As a result, dienogest is a drug that is less likely to result in a cumulative decrease in bone density with long-term treatment.

On the efficacy examination, prolonging the treatment period of dienogest resulted in higher proportions of marked or moderate global improvement, overall improvement of subjective symptoms during non-menstruation and overall improvement of objective findings. These effects were also confirmed by the patients' evaluations based on VAS and QOL. Specifically, the bodily pain score in QOL after 52 weeks of treatment was nearly identical to the reference value (74.4) for Japanese women.[18] The sufficient improvement in endometriosis, as well as the good tolerability to long-term treatment, would be reasons for the

indicated willingness to use dienogest again by >90% of the patients.

In conclusion, as no ADR limiting the treatment period were found during long-term treatment with dienogest, and as an even longer treatment period would be anticipated to afford further improvement, dienogest may become a drug of first choice for the long-term hormonal therapy of endometriosis.

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