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Long-term dienogest administration in patients with symptomatic adenomyosis

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Abstract

Aim: Adenomyosis is a common gynecological disorder that causes dysmenorrhea, hypermenorrhea and metrorrhagia. Previously, we reported that 24 weeks of dienogest treatment is highly effective for pain in symptomatic adenomyosis. Up to present, there is no report that describes treatment of adenomyosis with long-term dienogest administration for more than 2 years. In this retrospective cohort study, we investigated the course of long-term dienogest treatment in patients with symptomatic adenomyosis.

Methods: This is a retrospective cohort study. Dienogest was continuously administered at a dose of 2 mg daily for patients with symptomatic adenomyosis. The outcome of long-term administration of dienogest was investigated, and the characteristics of patients were compared between discontinued cases and long-term administration cases.

Results: Two patients were excluded from this study because of transfer to another hospital or discontinuation due to infertility treatment. Twelve of 18 patients (66.7%) received dienogest until menopause or for a period of >80 months. Four cases (22.2%) discontinued dienogest treatment because of severe metrorrhagia. In the discontinued cases because of severe metrorrhagia, the pain score for dysmenorrhea and serum CA125 level at baseline significantly elevated, and the hemoglobin level at baseline and the frequency of type 2 adenomyosis significantly decreased, compared to those with long-term use. Moreover, long-term dienogest use did not decrease the serum estradiol level.

Conclusion: Our report suggests that dienogest is tolerable for long-term use until menopause and can be an alternative treatment option in some patients, especially those with type 2 adenomyosis, to avoid hysterectomy.

Key words: adenomyosis, dienogest, gynecological disorder, menopause, metrorrhagia.

Introduction

Similar to endometriosis and uterine fibroids, uterine adenomyosis is an estrogen-dependent disease. Currently, GnRH agonists,[1–3] danazol,[4] aromatase inhibitor[5] and levonorgestrel-releasing intrauterine devices[6,7] have been used as treatments for uterine adenomyosis. Symptoms could recur when medication administration is discontinued; hence, medicines that could be safely used for a long period, that is, until menopause, are highly desirable.

Dienogest, a novel 19-nortestosterone derivative, is a synthetic oral progestin that is highly selective for progesterone receptors. Previous studies reported that dienogest is highly effective in reducing adenomyosis-related pain.[8,9] Dienogest is generally well tolerated[10]; however, massive metrorrhagia is a major reason for discontinuing treatment with dienogest.[11]

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Only one study on the long-term dienogest use for uterine adenomyosis has been conducted,[12] although some studies reported on long-term dienogest use and its effects on endometriosis.[10,13–17] Moreover, no study that describes dienogest use for >2 years has been reported. In this study, we investigated the subsequent outcome of our previously reported cases series of dienogest use for symptomatic adenomyosis. Particularly, we sought to examine whether hysterectomy could be avoided or not after long-term dienogest administration.

Methods

This was a retrospective cohort study. We examined the cases of our previous case series.[8] The inclusion criteria in our previous report were as follows: age > 20 years; regular menstrual cycles before dienogest administration; no other treatment for adenomyosis for at least 3 months before dienogest administration; adenomyosis diagnosed using magnetic resonance imaging (MRI) or ultrasonography; and dysmenorrhea, adenomyosis-associated chronic pain and/or menorrhagia. The following patients were excluded: pregnant or breast-feeding women and those with a uterine neoplasm, ovarian neoplasm, benign ovarian cyst including endometrioma, pelvic inflammatory disease or other endocrine diseases. Seventeen patients with symptomatic adenomyosis met the inclusion criteria. In this study, data of three of our previous cases with endometrioma were recovered and included in the analysis. Hence, the outcomes of a total of 20 cases were investigated using the medical records. Dienogest was continuously administered at a dose of 1 mg twice daily on days 2–5 of menstruation.

MRI was performed at baseline in all cases, which were categorized according to previously reported criteria based on the MRI exam.[18] Briefly, Kishi *et al*. described adenomyosis in the inner uterine layer without affecting the outer structures as intrinsic (type I), that in the outer uterine layer without affecting the junctional zone as extrinsic (type II), and that which solitarily occurs with no relationship to the junctional zone or serosa as intramural (type III). Adenomyosis that did not satisfy the criteria was described as indeterminate (type IV). The main study variables were as follows: the level of adenomyosis-associated chronic pain, dysmenorrhea or pain during uterine bleeding, and defecation pain or dyspareunia at baseline, assessed using the visual analog scale (VAS); blood test (levels of hemoglobin [Hb], CA-125 and E2); and the size of the uterus, assessed by sonography. The uterus was measured in the sagittal section and the long and short axes were measured. We used an ellipse formula to measure the uterus size: $\pi/4 \times$ long axis $\times$ short axis. The study protocol was approved by the Institutional Review Board of the University of Tokyo.

Statistics

Statistical analysis was performed using JMP version 12.0 (SAS Institute Inc.). A P value <0.05 was considered statistically significant.

Results

One patient was transferred to other hospitals after 79 months of uneventful continuous administration, and one case discontinued dienogest administration for desire of pregnancy (Fig. 1). These two cases were excluded from this study. The outcome of the remaining 18 cases after dienogest administration was determined. Eight cases completed dienogest administration until their menopause or perimenopause (Group A), four cases were still on dienogest treatment (Group B) and six cases discontinued dienogest use because of severe metrorrhagia (4 cases, Group C) and other adverse effects (hot flush, 1 case; depression, 1 case, Group D). In Group C, two finally underwent laparoscopic hysterectomy after GnRH agonist administration, one received a low-dose contraceptive, and one had non-steroidal anti-inflammatory drugs for pain control. In the cases of discontinuation, the mean duration of dienogest treatment was 7.0 ±3.5 (2–11) months. In Group C, dienogest was discontinued at 2–11 months; the four cases had severe anemia with Hb level < 9.5 g/dL and were included in the five cases with worsening anemia during the 24 weeks of dienogest treatment in the previous report. Dienogest was administered continuously until menopause or for >80 months in 12 of 18 cases (66.7%). One of the five cases with worsening anemia received dienogest until menopause. Table 1 shows the baseline characteristics of the 18 cases.

We measured the uterine size and CA125 level at baseline and at the final measurement before treatment completion to investigate the effect of long-term use. Long-term dienogest administration (Groups A and B) significantly decreased the size of the uterus from 38.7 ±18.7 to 26.9 ±10.9 cm^2 ($P < 0.01$); the ratio

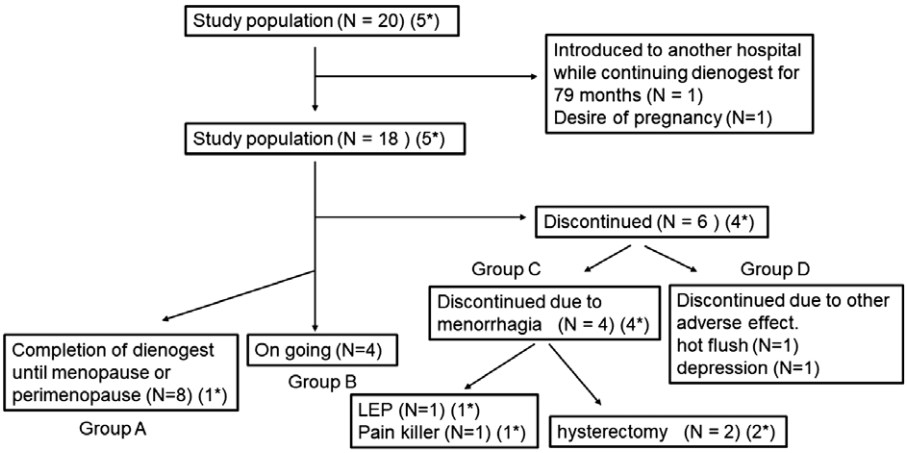

Figure 1 Flow chart of this study. The asterisk indicates the number of patients who experienced worsening anemia during 24 weeks of dienogest treatment.

was 72.6 ±17.6%. Moreover, CA125 level significantly decreased from 124.1 ±84.0 to 19.6 ±6.7 IU/mL ($P < 0.01$).

To elucidate the factors associated with severe genital bleeding with dienogest administration, we compared the cases with severe metrorrhagia (Group C) and those without (Groups A and B). The duration of dienogest administration clearly showed a significant difference between Groups A and B and Group C (64.1 and 8.0 months, respectively). In addition, as shown in Table 2, the pain score for dysmenorrhea and serum CA125 level at baseline significantly increased in Group C, and the Hb level at baseline and the frequency of type 2 adenomyosis significantly decreased. Moreover, the uterus size at baseline tended to be larger in Group C than in Groups A and B; however, the difference was not statistically significant.

Finally, we determined the serum estradiol level to evaluate the hypoestrogenic effect of dienogest. The mean serum estradiol level did not change significantly during the 5-year treatment (Fig. 2).

Discussion

In this study, 12 of 18 cases were able to continue dienogest administration until menopause or for a long period of >80 months. To our knowledge, this is the first study to describe the long-term use of dienogest in symptomatic adenomyosis. A comparison between cases with long-term dienogest administration and those with discontinued treatment due to irregular genital bleeding revealed significant differences in Hb level at baseline, pain score for dysmenorrhea at baseline, and the frequency of type 2 uterine adenomyosis. In addition, reduction in uterine size and serum CA125 level was confirmed in cases with long-term dienogest administration.

Table 1 The characteristics of patients

	Total	Group A	Group B	Group C	Group D
n	18	8	4	4	2
Gravity	1.61 ± 1.88	1.75 ± 2.12	0.75 ±0.96	2.75 ±2.22	0.50 ±0.71
Parity	0.89 ±0.83	1.00 ±0.76	0.75 ±0.96	1.25 ±0.96	0.0 ±0.0
BMI (kg/m^2)	21.0 ± 2.5	20.6 ± 1.5	21.6 ± 3.4	21.4 ± 1.1	20.9 ±2.2
Age at starting dienogest (year)	42.3 ± 5.1 (31–48)	46.1 ±2.0 (42–48)	39.5 ± 1.3 (38–41)	37.3 ±5.9 (31–44)	38.5 ±6.4 (34–43)
Age at stopping dienogest (year)	N/A	50.8 ± 2.1 (47–53)	N/A	37.5 ± 5.5 (32–44)	39.5 ± 6.4 (35–44)
Age at the final evaluation (year)	N/A		47.0 ± 1.8 (45–49)		
Administration period (month)	45.1 ± 36.1 (2–96)	52.5 ± 28.2 (8–93)	93.8 ± 7.6 (88–104)	6.5 ±3.7 (2–11)	8.0 ±4.2 (5–11)

BMI, body mass index.

Table 2 Comparison of clinical characteristic at baseline between cases with long-term use and discontinued cases due to severe bleeding

	Cases with long-term use (Groups A and B)	Discontinued cases due to bleeding (Group C)	
n	12	4	
Gravity	1.42 ± 1.83	2.75 ± 2.21	N.S.
Parity	0.92 ±0.79	1.25 ±0.96	N.S.
Age at starting dienogest	43.9 ± 3.7	37.2 ± 5.9	N.S.
Administration period (month)	66.1 ± 30.7 (8–104)	6.5 ±3.7 (2–11)	P <0.01
Basal uterine size (cm^2)	4925 ± 2387	7010 ±3204	N.S.
Baseline VAS score (dysmenorhea)	7.25 ± 1.36	9.48 ±0.50	P < 0.01
Baseline VAS score (chronic pain)	4.98 ± 2.26	5.88 ± 3.16	N.S.
Baseline VAS score (dyspareunia)	2.28 ± 2.36	4.43 ± 3.14	N.S.
Baseline VAS score (defecation pain)	1.81 ± 2.78	2.63 ± 4.46	N.S.
The presence of myoma	3 (3/12)	0 (0/4)	N.S.
Basal Hb (g/dL)	11.9 ± 1.4	9.6 ± 0.9	P < 0.01
Serum CA125 (U/mL)	122.6 ± 76.9	463.5 ± 247.1	P < 0.01
Serum CA19-9 (U/mL)	38.9 ± 26.1	103.5 ± 120.2	N.S.
Type 2 adenomyosis	9	0	P < 0.01
Adenomyosis other than type 2	3	4	

N.S., not significant; VAS, visual analog scale.

For symptomatic uterine adenomyosis, hysterectomy is the definitive treatment specifically for patients without the desire of uterine preservation. For patients who wish to preserve their uterus, medical treatment is the most favorable option given that resection of uterine adenomyosis and other treatments have not yet been established. For the management of symptomatic adenomyosis, a medication that could stop menstruation and could be used safely for a long time is highly desirable.

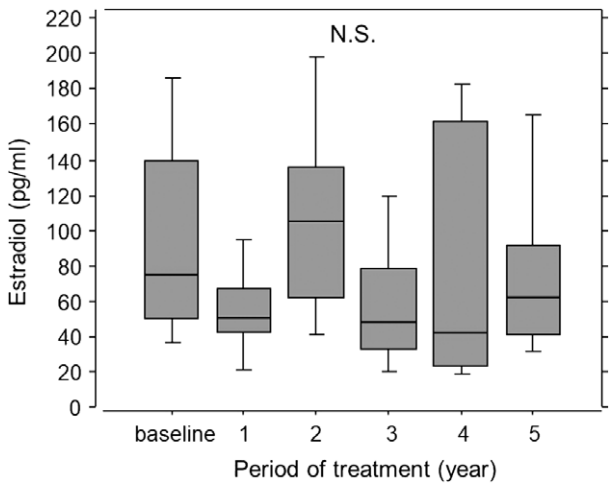

Figure 2 Serum estradiol concentration during the treatment. The center line indicates the median. The bottom and top boxes indicate the first and third quartiles, respectively. The difference was not significant.

We and other groups previously reported that dienogest is highly effective for pain associated with adenomyosis during 24 weeks[8] or 16 weeks[9] of treatment. A recent randomized, double blind, placebo-controlled study also confirmed that dienogest is effective for pain due to adenomyosis during 16 weeks.[19] Here, the pain relief effect continued after 24 weeks and lasted for a maximum of 104 months, and no patient dropped out because of pelvic pain. Recently, Osuga *et al*. also reported that 52 weeks of dienogest treatment is safe and effective for symptomatic adenomyosis.[12] In their report, remarkable pain relief effect continued up to 52 weeks of treatment. This finding indicated that dienogest still has a pain relief effect even in the long term. Furthermore, 67% of patients had dienogest treatment up to menopause and did not undergo hysterectomy; all of the patients had chosen to continue the treatment to avoid pain recurrence by discontinuing the medication. Moreover, previous reports showed that approximately 70% of patients used dienogest for >12 months,[11] which is in line with our result. Hence, dienogest is a favorable option for patients who wish to preserve their uterus.

However, 30% of patients discontinued dienogest treatment because of adverse effects, such as severe metrorrhagia, hot flush and depression. Other previous studies showed that approximately 20% of patients discontinued the treatment because of adverse effects and indicated that the majority of those adverse effects were associated with severe

uterine bleeding. Dienogest administration could lead to frequent irregular bleeding as a major side effect, which could be attributed to the breakthrough bleeding from the pseudodecidua.[20] Thus, patients with adenomyosis are more likely to discontinue dienogest treatment because of severe metrorrhagia.[11] Therefore, in patients with adenomyosis, dienogest should be administered with particular caution.

In this study, we compared the patient characteristics between the cases with long-term dienogest administration and those with discontinued treatment due to severe metrorrhagia. The Hb level at baseline, the pain score for dysmenorrhea at baseline, and the frequency of type 2 adenomyosis, which were suggested to be factors associated with dienogest treatment discontinuation, were significantly different. In a previous report, treatment continuation rate decreased in cases with Hb <12 g/dL.[11] High VAS scores may be associated with adenomyosis severity. Hence, with a significantly high VAS score for dysmenorrhea at baseline, long-term administration of dienogest may not be suitable for extremely painful uterine adenomyosis. However, type 2 adenomyosis was negatively associated with treatment discontinuation. The lesion in type 2 adenomyosis does not merge with the junctional zone of the uterus, which suggests that excessive menorrhagia may not be observed because of the intact junctional zone. By contrast, the lesion in types 1 and 4 adenomyosis has a direct connection to the thickened junctional zone. Thus, the adenomyotic lesion may directly affect the endometrium–myometrium interface, which could be the reason for the severe metrorrhagia in types 1 and 4 adenomyosis. Hence, type 2 adenomyosis may be a good therapeutic target for long-term dienogest administration. In addition, we previously reported that type 2 adenomyosis increased the difficulty of laparoscopic hysterectomy because of severe adhesion due to pelvic endometriosis.[21] Therefore, long-term dienogest administration may be beneficial to avoid difficult hysterectomy for patients with type 2 adenomyosis.

Previous studies reported a slight hypoestrogenic effect of dienogest after 52 or 65 weeks of treatment.[10,12,15] Our result was consistent with that of the previous reports, and we showed that dienogest is tolerable for long-term use. Estradiol levels in dienogest treatment, unlike those in GnRH agonist treatment, were maintained with low physiologic range and without inducing hypoestrogenic effects,[15] thereby indicating that dienogest is tolerable and preferable for long-term use.

This study has several limitations because of its retrospective nature. First, data on some essential outcomes were missing (e.g. bone mass density). Second, the number of cases is limited. We did not add more cases because this study was a long-term cohort study. A prospective study is required to further evaluate the effects of dienogest administration and to determine whether dienogest treatment is a risk factor for osteoporosis and other adverse outcomes.

In conclusion, dienogest is tolerable for long-term use in patients with symptomatic adenomyosis and can be an alternative option in some patients to avoid hysterectomy.

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Disclosure

None declared.

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