Maintenance therapy with dienogest following gonadotropin-releasing hormone agonist treatment for endometriosis-associated pelvic pain

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ABSTRACT

Objective: To examine whether long-term administration of dienogest following gonadotropin-releasing hormone agonist (GnRH-a) therapy would prolong the relief of pelvic pain while reducing the amount of irregular uterine bleeding.

Study design: This was a prospective, non-randomized clinical trial. Among the patients suffering from chronic pelvic pain associated with recurrent endometriosis, Group G (n = 38) received GnRH-a for 4–6 months and then dienogest (1 mg/day) for 12 months. The dose of dienogest was increased to 1.5 or 2 mg/day when a patient had uncontrollable uterine bleeding (n = 15 [39%]). Group D (n = 33) received only dienogest (2 mg/day) for 12 months. Pelvic pain was assessed using a visual analog scale (VAS). Uterine bleeding was semi-quantified using a pictorial blood loss assessment chart (PBAC).

Results: In Group G, GnRH-a significantly reduced the VAS score for pelvic pain, and alleviation was maintained during the 12-month therapy with dienogest. There was no significant difference in pain reduction between Group G and Group D. The PBAC score during the first 6 months on dienogest was significantly smaller in Group G than in Group D. The PBAC score during the first 6 months on dienogest was significantly smaller in Group G than in Group D.

Conclusion: Treatment with a GnRH-a followed by long-term dienogest therapy maintains the relief of endometriosis-associated pelvic pain achieved with GnRH-a therapy for at least 12 months. This regimen reduces the amount of irregular uterine bleeding that often occurs during the early phase of dienogest therapy.

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1. Introduction

Endometriosis is characterized by the presence of endometrium-like lesions outside the uterine cavity. It is an estrogen-dependent disease that occurs in 10% of women of reproductive age and regresses after the menopause or ovariectomy. The main symptoms are pelvic pain, including dysmenorrhea, chronic pelvic pain and deep dyspareunia, and infertility [1]. Gonadotropin-releasing hormone agonist (GnRH-a) is currently one of the most widely used medical therapies for endometriosis. Long-term use of GnRH-a, however, is associated with hypo-estrogenic side effects and a substantial reduction in bone mineral density. Consequently, the therapeutic use of GnRH-a is limited to a maximum of 6 months [2]. Pelvic pain often recurs after completion of GnRH-a treatment, however, with a median interval until recurrence of pain of 6.1 months [3]. We have shown that long-term administration of a tapering dose of danazol or mid/low doses of oral contraceptives after the end of GnRH-a therapy maintain the relief of endometriosis-associated pelvic pain achieved by GnRH-a therapy for at least 12 months [4].

Dienogest, a 19-nortestosterone derivative, is a fourth-generation progestin with potent oral progestational activity without any systemic androgenic activity [5–7]. Dienogest directly suppresses the proliferation of stromal [8] and immortalized epithelial cells [9] derived from human endometrium. Dienogest also suppresses the proliferation [10] and the secretion of IL-8 from endometriotic stromal cells [11]. Dienogest exerts a potent effect in relieving endometriosis-associated pelvic pain [12], and clinical trials showed that while dienogest and GnRH-a were equally effective, the adverse effects caused by the hypo-estrogenic state were less in the dienogest group [13–15]. Dienogest, however, is frequently associated with irregular uterine bleeding, a common adverse effect of progestins [14,15]. We therefore examined whether long-term administration of dienogest following GnRH-a therapy would prolong the relief of pelvic pain while reducing the amount of irregular uterine bleeding.

2. Materials and methods

Patients diagnosed with endometriosis after laparoscopic surgery who suffered recurrent endometriosis-related pelvic pain

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were selected to receive the treatment regimen. Patients who sought treatment at the Department of Obstetrics and Gynecology, Kyoto Prefectural University of Medicine between January 2008 and March 2010 were enrolled for this study. The study protocol was approved by the institutional review board, and informed consent was obtained from each patient. No patient had undergone surgery or received endocrine therapy including GnRH-a, danazol, or estrogen–progestin combination therapy for at least 6 months before enrollment into the study. Patients were excluded if their diagnoses included uterine neoplasm, ovarian neoplasms, pelvic inflammation, other endocrine disease, or contraindications to estrogens or progestins. Staging of endometriosis was done according to the revised American Society for Reproductive Medicine classification system [16]. Deep infiltrating endometriosis was defined as the presence of histologically confirmed peritoneal endometriosis penetrating >5 mm under the peritoneal surface [17].

Patients were administered GnRH-a [buserelin acetate (Sprecur MP® 1.8 mg, Mochida Pharmaceutical Co., Tokyo, Japan) or leuprorelin acetate (Leuplin® 1.88 mg, Takeda Pharmaceutical Co., Osaka, Japan)] subcutaneously once a month for 4–6 months starting from Day 1 to 5 of the menstrual cycle. The patients were then prescribed 1 mg/day of dienogest (Dinagest®, Mochida Pharmaceutical Co.) for 12 months starting 1 month after the last GnRH-a injection (Group G). The dose of dienogest was increased to 1.5 mg (1 mg/day and 2 mg/day, alternatively) or 2 mg/day when a patient had uncontrollable uterine bleeding. Group D received only 2 mg/day of dienogest for 12 months starting from Day 1 to 5 of the menstrual cycle without other preceding endocrine therapy.

Patients underwent clinical evaluations every 1–2 months that included assessment of pain severity, uterine bleeding pattern and side effects, gynecological examination, vaginal ultrasonography, and blood tests. Each patient was requested by the physician to grade the severity of dysmenorrhea, non-menstrual pelvic pain, and dyspareunia using a 10.0 cm visual analog scale (VAS). Blood loss was assessed employing a pictorial blood loss assessment chart (PBAC) [18]. Briefly, patients were instructed to record the number of sanitary pads and tampons used. The scores were assigned depending on the degree of soiling as 1, 5, and 10 for tampons, and 1, 5, and 20 for pads. Small and large clots scored 1 and 5, respectively. Serum concentrations of CA-125 were measured using an immunoradiometric assay kit as described previously [19]. Endometriomas were diagnosed based upon transvaginal sonographic findings [20] where diameter was ≥5 mm under the peritoneal surface.

The clinical characteristics of the patients were compared using Student’s t-test or χ2 test. Differences in VAS score, serum CA-125 level and diameter of the endometrioma between the two groups were analyzed employing Mann–Whitney test and those during each treatment were analyzed using Kruskal–Wallis test, followed by multiple comparisons using the non-parametric Dunn’s test. Differences in PBAC scores were analyzed using Wilcoxon test for comparison between the first and the second 6 months in Group D and using Mann–Whitney test for other comparisons. Differences in BMD were analyzed using Student’s t-test. Data are expressed as the mean ± SD or as the median with interquartile range. The level of statistical significance was set at P < 0.05. All analyses were performed with Statflex version 5.0 software (Artech, Osaka, Japan).

3. Results

Of the 78 women enrolled into our study, six discontinued dienogest treatment because of a change in their treatment strategy: In Group G, two patients were operated again and two returned to GnRH-a therapy due to treatment inefficacy; in Group D, one patient was switched to GnRH-a therapy and another was switched to low-dose danazol therapy due to uncontrollable uterine bleeding. One patient dropped out of the study because of failure to attend check-up appointments. Thus, 71 patients (38 for Group G and 33 for Group D) were eligible and subjected to further evaluation. The baseline clinical characteristics of the women are shown in Table 1. There were no significant differences in physical structure, infertility status or severity of endometriosis between the two groups.

Fig. 1 shows the change in VAS score for dysmenorrhea (Fig. 1A), non-menstrual pelvic pain (Fig. 1B), and dyspareunia (Fig. 1C), serum CA-125 level (Fig. 1D), and diameter of endometrioma (Fig. 1E) in Groups G and D. There was no significant difference in each original value between Groups G and D. In Group G, treatment with a GnRH-a for 4–6 months reduced the VAS score for dysmenorrhea (P < 0.001), non-menstrual pelvic pain (P < 0.01), and dyspareunia (P < 0.05). The reduction of VAS score was sustained during subsequent dienogest therapy for 6 and 12 months. In Group D, treatment with dienogest for 6 and 12 months significantly reduced the VAS score for the three types of pain. The reduction was equivalent to that obtained in Group G at 6 and 12 months (Fig. 1A–C).

Serum CA-125 concentrations were significantly reduced after GnRH-a therapy and the reduction was sustained during the subsequent dienogest therapy (P < 0.01). No recurrent increase of serum CA-125 was observed during the period on dienogest. By contrast, in Group D the reduction in serum CA-125 was gentile compared to that observed in Group G and a significant reduction was obtained after 12 months on dienogest (P < 0.05) (Fig. 1D). In both Groups G and D, the diameter of the ovarian endometrioma tended to decrease during dienogest therapy and a significant reduction was observed after 12 months (P < 0.05) (Fig. 1E).

The PBAC score during the first 6 months on dienogest was significantly lower in Group G than in Group D (P < 0.01). In Group D, however, the PBAC score during the second 6 months was significantly reduced to a level equivalent to that in Group G (P < 0.01) (Fig. 2). In Group G, 23 out of 38 (61%) patients received 1 mg/day dienogest for 12 months (Subgroup 1 mg D), whereas the remaining 15 (39%) patients were given an increased dose of 1.5 or 2 mg/day due to uncontrollable uterine bleeding after the initial dose of 1 mg/day dienogest (Subgroup 1–2 mg D). Naturally, during the first 6 months on dienogest, the PBAC score in Subgroup 1–2 mg D was significantly higher than that in Subgroup 1 mg D (P < 0.05). Even after the dose was increased to 1.5 or 2 mg/day, the PBAC score in Subgroup 1–2 mg D was still higher than that in Subgroup 1 mg D (P < 0.05), but no patient withdrew from treatment. We could not find any factor, such as concomitant adenomyosis, that could have caused uncontrollable bleeding in patients of Subgroup 1–2 mg D. In comparison between Subgroup
In this study we demonstrated that a regimen consisting of GnRH-a followed by long-term therapy with dienogest maintained the relief of endometriosis-associated pelvic pain (dysmenorrhea, non-menstrual pelvic pain and dyspareunia) achieved with GnRH-a therapy for at least 12 months, and prevented recurrence. This regimen reduced the amount of irregular uterine bleeding that frequently occurred during dienogest treatment.

In a previous report we described a regimen that provided long-term relief of endometriosis-associated pain with less adverse effects [4]. That regimen consisted of GnRH-a followed by a tapering dose of danazol or mid/low doses of oral contraceptives [4]. Yet there remained some problems such as the androgenic and anabolic adverse effects of danazol [21] and the fact that treatment with contraceptives includes periodical withdrawal bleeding in the treatment schedule [22].

In 2008, dienogest was first launched in the Japanese market for the treatment of endometriosis. Clinical trials showed the efficacy of dienogest was equivalent to that of GnRH-a. In a prospective, multicenter, randomized study, patients with laparoscopically diagnosed endometriosis were treated with 2 mg/day dienogest or 3.75 mg/month triptorelin, a GnRH-a, for 16 weeks. A second laparoscopy showed that dienogest and triptorelin had equivalent efficacy in maintaining rAFS score and VAS score [13]. In a phase III randomized, double-blind controlled trial performed in Japan, dienogest at a dose of 2 mg/day for 24 weeks demonstrated equivalent efficacy in alleviating endometriosis compared with intranasal buserelin acetate [14]. A European multicenter open-label trial also showed that the efficacy of treatment with dienogest at a dose of 2 mg/day for 24 weeks was equivalent to that of treatment with 3.75 mg/month of depot leuprolide acetate in relieving pelvic pain associated with endometriosis [15]. These trials demonstrated that a 24-week treatment with dienogest caused little reduction of lumbar BMD (−1.0% ± 2.3% and +0.25% ± 2.77%, respectively), suggesting the safety of long-term use of dienogest [14,15]. These trials also showed a lower frequency of hot flushes and less decrease in serum estradiol with dienogest as compared with GnRH-a [14,15]. The findings suggested that dienogest could be used for long-term treatment of endometriosis. There were frequent episodes of uterine bleeding, however, in the initial period of treatment with dienogest [14,15]. The uterine bleeding caused by dienogest is thought to be due to breakthrough bleeding from pseudodecidua and an inevitable effect of progestational agents [23].

1 mg D and 1–2 mg D in Group G we found no significant difference in relieving pain, serum CA-125 level or size of endometrioma.

After 12 months’ treatment with dienogest, the mean BMD of the lumbar spine (L2–L4) was 1.028 ± 0.150 g/cm² in Group G and 0.958 ± 0.042 g/cm² in Group D with no significant difference between the two groups.
For Group G we set a dose of 1 mg/day dienogest following GnRH-a therapy, although the dose used in the clinical trials was 2 mg/day. Our primary purpose was to maintain during dienogest therapy the pain relief achieved with a GnRH-a pain relief for at least 12 months. However, because there were no published data at the start of our study showing the safety of 2 mg/day for longer than 24 weeks, we adopted a lower dose of dienogest. Our regimen provided equal or superior efficacy in relieving pain compared to our previous regimens [4], although simple comparison was not possible. There was only a little reduction of lumbar BMD after treatment with dienogest for 12 months.

We expected that the endometrial thinning induced by GnRH-a [24] would reduce the incidence of breakthrough bleeding during dienogest therapy. As expected, our regimen reduced the overall amount of irregular uterine bleeding. However, while 60% of women in Group G could be maintained with 1 mg/day dienogest for the whole treatment period with sufficient suppression of pain and tolerable uterine bleeding, the remaining 40% of women were compelled to increase the dose to 1.5 or 2 mg/day due to uncontrollable uterine bleeding despite sufficient suppression of pain. The patients who showed a small amount of bleeding during the first 6 months did not experience uncontrollable bleeding during the second 6 months. On the other hand, the patients who showed a high incidence of bleeding episodes in the early phase of treatment experienced persistent irregular bleeding even after the dose of dienogest had been increased, suggesting that the initial control of uterine bleeding is of great importance. Nevertheless, our patients did not present any factor, such as concomitant adenomyosis or subtle fibroma, that would predict the occurrence of subsequent uterine bleeding. As a very recent study demonstrated the safety of 52-week dienogest therapy with little reduction of lumbar BMD (−1.7 ± 2.2%) [25], the initial dose of 2 mg/day would be an option to be tested in the future.

The interpretation of the present results is limited by the relatively small number of subjects and the open-label design. Therefore, data obtained from subjects were analyzed with a unified protocol without a stratified analysis, according to the severity of pain. In Group G, however, the suppression of three types of pain and other variables was comparable to that in the maintenance therapy reported previously [4].

In conclusion, the present study demonstrated that maintenance therapy with dienogest was a practical and efficient treatment regimen that maintained the relief of endometriosis-associated pelvic pain achieved with GnRH-a therapy, for at least 12 months. In addition, this method significantly reduced the amount of irregular uterine bleeding in the initial period of treatment. Further large-scale studies will be necessary to confirm these findings.

Conflict of interest

None.

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