Evaluation of the efficacy and safety of dienogest in the treatment of painful symptoms in patients with adenomyosis: a randomized, double-blind, multicenter, placebo-controlled study

Yutaka Osuga, M.D.,[a] Haruka Fujimoto-Okabe,[b] and Atsushi Hagino[b]

[a] Department of Obstetrics and Gynecology, Faculty of Medicine, The University of Tokyo; and [b] Clinical Development Department, Mochida Pharmaceutical Co., Ltd., Tokyo, Japan

Objective: To evaluate the efficacy and safety of dienogest (DNG), a progestational 19-norsteroid, in patients with symptomatic adenomyosis.
Design: Phase III, randomized, double-blind, multicenter, placebo-controlled study.
Setting: Clinical study sites in Japan.
Patient(s): Sixty-seven patients with adenomyosis.
Intervention(s): Patients were randomly assigned to receive DNG (2 mg/d, orally) or placebo for 16 weeks. In cases of complicated anemia, patients were treated for anemia before randomization.
Main Outcome Measure(s): The primary end point was the change from baseline to after treatment pain score, using zero- to three-point verbal rating scales that defined pain severity according to limited ability to work and need for analgesics. The visual analogue scale was used as another pain parameter.
Result(s): Decreases from baseline in the pain score and the visual analogue scale at the end of treatment were significantly more in the DNG group than in the placebo group ($P<.001$). During the treatment period, almost all of the patients treated with DNG experienced irregular uterine bleeding and one patient had mild anemia. No severe cases of anemia were observed.
Conclusion(s): These results suggest that DNG is effective and well tolerated in the treatment for painful symptoms associated with adenomyosis not complicated by severe uterine enlargement or severe anemia.
Clinical Trial Registration Number: JapicCTI-142642(en). (Fertil Steril® 2017;108:673–8. ©2017 by American Society for Reproductive Medicine.)
Key Words: Dienogest, adenomyosis, placebo-controlled study, double-blind, randomized study

Discuss: You can discuss this article with its authors and with other ASRM members at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/18486-23741

Adenomyosis is a common gynecological disease in women of reproductive age. Adenomyosis is an estrogen (E)-dependent disease characterized by the proliferation of ectopic endometrial-like tissue within the myometrium. It significantly reduces quality of life (QOL) due to severe painful symptoms such as dysmenorrhea and pelvic pain. Based on the biological similarity of adenomyosis to endometriosis, GnRH agonists, low-dose oral contraceptives (OCs), or levonorgestrel intrauterine system are primarily used according to hormonal therapies for endometriosis. However, none of them have been clearly validated for the therapeutic effect in adenomyosis, and there are no drugs indicated for adenomyosis in Japan and overseas. Therefore, an

Received January 22, 2017; revised and accepted July 12, 2017.
Y.O. is a medical expert contracted to Mochida Pharmaceutical Co., Ltd. H.F.-O. has nothing to disclose. A.H. has nothing to disclose.
Sponsored by Mochida Pharmaceutical Co., Ltd., Tokyo, Japan.
Reprint requests: Yutaka Osuga, M.D., Department of Obstetrics and Gynecology, Faculty of Medicine, The University of Tokyo, Tokyo 113-8655, Japan (E-mail: yutakaos-tky@umin.ac.jp).

Fertility and Sterility® Vol. 108, No. 4, October 2017 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2017.07.021

effective and well-tolerated option for the treatment of adenomyosis symptoms is highly desirable.

Dienogest (DNG), a progestational 19-norsteroid derivative, is a synthetic oral progestin with highly selective binding to P receptors (PR) (1). It exerts antiovulatory (2) and mild hypoestrogenic (3) effects, as well as antiproliferative activity in human endometrial cells (4). Based on this hormonal profile, DNG is used as a treatment for painful symptoms in patients with endometriosis, without causing any severe hypoestrogenic adverse effects (3, 5). It is also expected to be an effective treatment for painful symptoms associated with adenomyosis. On the other hand, irregular genital bleeding due to the progestational action of DNG on the endometrium is a well-known adverse effect in patients with endometriosis (6). It occasionally results in severe anemia in patients with adenomyosis (7).

The aim of this study was to elucidate the efficacy and safety of DNG in patients with adenomyosis with pelvic pain. Randomized controlled conditions were the goals of this study.

MATERIALS AND METHODS

Patients and Study Design

This study was a randomized, double-blind, multicenter, placebo-controlled phase III study of DNG. It was conducted between August 2014 and June 2015 at 20 clinical study sites in Japan. The protocol was approved by the institutional review boards of all of the participating sites.

Inclusion criteria were as follows: [1] aged 20 years or older; [2] regular menstrual cycles of 38 days or less; [3] adenomyosis diagnosed by imaging analysis (both magnetic resonance imaging [MRI] and transvaginal sonography) (8); and [4] pain symptoms (lower abdominal pain and/or lumbago) scoring three points or more on the verbal pain rating scale developed by Harada et al. (9, 10; Table 1) during the menstrual cycle.

Exclusion criteria were as follows: [1] endometriosis or uterine leiomyoma diagnosed by imaging analysis (both MRI and transvaginal sonography); [2] severe anemia (hemoglobin concentrations <8.0 g/dL); and [3] marked uterine enlargement (maximum dimension, >100.0 mm or myometrial thickness, >40.0 mm). In cases of mild or moderate anemia (hemoglobin levels between 8.0 and 11.0 g/dL), patients were given anemia treatment for the hemoglobin concentrations reached at least 11.0 g/dL before randomization. Written informed consent was obtained from all of the patients.

Gynecologists with ample experience of image diagnosis were selected as investigators in this study. No specific criteria for adenomyosis based on transvaginal ultrasonography and MRI were selected. Adenomyosis was diagnosed by investigators, and no central determination was made by image specialists.

TABLE 1

Grading, scoring, and definitions for components of the pain score.

Grade	Score	Definition
Pain severity score (lower abdominal pain and/or lumbago)		
None	0	None
Mild	1	Low efficiency for work and/or study
Moderate	2	Needing to rest in bed and/or loss of work
Severe	3	In bed for ≥1 da
Analgesics usage score		
None	0	None
Mild	1	Taking analgesics for 1 d
Moderate	2	Taking analgesics for 2 d
Severe	3	Taking analgesics for ≥3 d

Osuga. Dienogest in treatment of adenomyosis. Fertil Steril 2017.

Study Treatments and Measurements

Patients who met all of the inclusion criteria and did not have any of the exclusion criteria were randomly assigned by the permuted-block method in a 1:1 ratio to receive a 1-mg DNG tablet (the DNG group) or an identical placebo tablet (the placebo group) twice daily for 16 weeks, starting between the second and fifth day of the menstrual cycle. Allocation concealment was accomplished centrally by an independent organization and maintained blindness for patients, investigators, and sponsor until after all data were collected. For the duration of the study, the use of reliable contraception other than hormonal agents was required and patients were allowed to take analgesics.

Patients were assessed for their pain score, visual analogue scale (VAS), uterine size, and serum E_2 concentration at baseline menstrual cycle before randomization and every 4 weeks during the treatment period. The QOL was rated using the MOS 36-Item Short-Form Health Survey (11) at baseline and at the end of treatment (EOT: 16 weeks or when discontinued).

Laboratory hematology was measured at baseline, every 4 weeks during the treatment period, 4 weeks after EOT, and after resuming menstruation. Laboratory biochemical and urinalysis tests were conducted at baseline and every 8 weeks during the treatment period. Monitoring and auditing procedures confirmed that the clinical study was conducted in accordance with the Helsinki Declaration and Good Clinical Practice.

Efficacy and Safety End Points

The primary efficacy end point was the change in the pain score from baseline to after treatment. The other efficacy end points were the change in the pain score during the course of treatment and change in the VAS and uterine size from baseline to after treatment. Uterine size was determined based on the diameters of three angles (D1, D2, D3, in millimeters) including the maximum diameter of the uterus by transvaginal ultrasonography. The uterus was evaluated as a spheroid. The maximum diameter of the uterine corpus (from the internal cervical os to the fundus serosa) was measured for the maximum diameter of the uterus.

The primary safety end point was adverse effects (AEs). The secondary safety end point was adverse drug reactions (ADRs). The number of days and severity of genital bleeding were assessed using a patient diary form.

Statistical Analysis

The primary analysis set for the efficacy analysis was the full analysis set (FAS). Sensitivity was analyzed by comparing the