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REVIEW

Efficacy of dienogest in improving pain in women with endometriosis: a 12-month single-center experience

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Abstract
Purpose Dienogest has recently been marketed as a medical treatment for endometriosis. Given the recent introduction on the market of Dienogest, little data are available regarding its effectiveness in routine clinical practice.
Methods The study is an observational, single-center, cohort study. Eligible was women with a surgical diagnosis of endometriosis dating back <24 months or a clinical/instrumental diagnosis of endometriosis and endometriosis-associated pelvic pain score of at least 40 mm on a 100-mm visual analog scale (VAS) at start of treatment and who had been taking Dienogest 2 mg once daily treatment at the time of study entry for no more than 30 days, consecutively observed between September 2013 to September 2014. In accordance with routine practice, women came back for clinical assessment and evaluation of pain after 1 (V1), 3 (V2), and 12 (V3) months.
Results A total of 132 women were enrolled in the study. A total of 21 of the enrolled patients were released from the study during follow-up due to adverse effects. The mean pelvic pain VAS score at baseline was 8.9 (SD 1.3). The corresponding values were 6.7 (SD 3.2) and 5.7 (SD 3.7) for dyspareunia and dyschezia. The mean VAS scores progressively and significantly decreased to 0.9 (SD 1.6) for pelvic pain, 1.4 (SD 2.1) for dyspareunia and 0.2 (SD 0.9) for dyschezia, respectively, 12 months after start of treatment.
Conclusion This study confirms that in routine clinical practice, Dienogest 2 mg is an effective and well-tolerated treatment for endometriosis-related pain in women with endometriosis.

Keywords Endometriosis · Dienogest · Pain · Dyspareunia

Introduction

Dienogest, a semisynthetic 19-nortestosterone derivative progestin, has recently been marketed as a medical treatment for endometriosis.

Randomized controlled trials have documented its efficacy on pain in women with endometriosis at different stages of the disease [8, 15, 18, 19].

Along this line, a systematic review has recently identified nine randomized trials. In these studies, Dienogest 2 mg/day was superior to placebo in reducing pelvic pain (VAS value: 27.4 versus 15.1 mm, $P < 0.0001$). The extended therapy with dienogest 2 mg/day also showed an improvement in pelvic pain after 24–52 weeks (VAS value vs basal value: −22.5 and −28.4 mm, respectively) with tolerable side effects. These latter findings, however, were based on a limited number of subjects [1].

More recently, real-life experiences have confirmed the data derived from randomized trials [11, 23]. For example, in a study conducted by Luisi et al. [11] and including 142 women with painful endometrioma or deep endometriosis, the mean VAS score progressively and significantly

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decreased from 8.0 mm (SD 1.7 mm) to 5.9 mm (SD 2.6) after 3 months of treatment.

However, given the recent introduction on the market of Dienogest, little data are available on its effectiveness in routine clinical practice.

This observational study aims to document the long-term efficacy of Dienogest 2 mg in the treatment of pain in women with endometriosis consecutively observed and treated for 12 months in a single institution in routine clinical practice.

Methods

The study is an observational, single-center, cohort study aimed at evaluating the 12-month effect of Dienogest in the treatment of pelvic pain in women with endometriosis.

Eligible for the study was women: aged 18 years or more; -not seeking pregnancy; with a surgical diagnosis of endometriosis dating back no more than 24 months; with a clinical/instrumental diagnosis of endometriosis; an endometriosis-associated pelvic pain score of at least 40 mm on a 100-mm visual analog scale (VAS) at start of treatment; and who had been taking Dienogest treatment at the time of study entry for no more than 30 days, consecutively observed at the date of recruitment, from September 2013 to September 2014.

All patients were treated at our center for diagnosis and treatment of endometriosis with dedicated physicians, psychologists, and nurses. For the duration of the study, each patient had access to a telephone number for urgent calls and an email address to send any request for help, clarification, or medical advice.

Non-surgical diagnoses were based on ultrasonographic criteria in patients with ovarian endometriomas [13]; on visual inspection of the posterior fornix and biopsy of vaginal lesions in women with rectovaginal endometriosis [21, 22]; on ultrasonographic criteria [16]; on physical signs at rectovaginal examination and ultrasonographic criteria [3] in those with deep lesions infiltrating the Douglas pouch and parametria; and on ultrasonographic criteria [7], double contrast barium enema, and rectosigmoidoscopy/colonoscopy findings in women with full-thickness bowel lesions.

Patients were excluded in case of obstructive uropathy or symptomatic bowel stenosis; evidence of complex adnexal cysts or an ovarian endometrioma with a diameter greater than 4 cm at vaginal ultrasonography; the typical contraindications to progestins; an allergy to components of the study medications; and pelvic varices or genital malformations identified at previous surgery.

Dienogest was administered orally at a dose of 2 mg once daily for 12 months.

At study entry visit, general characteristic, clinical information was collected.

Women were also requested to assess endometriosis-related pelvic pain, dyspareunia in sexually active women, and dyschezia using the VAS scale.

According to routine practice, women came back for clinical assessment and evaluation of pain after 1 (V1), 3(V2), and 12 (V3) months.

At each visit, the patient was asked about the regular intake of Dienogest 2 mg and any clinical symptoms or adverse events (including bleeding). The patients who reported vaginal bleeding while taking the drug were advised according to the following scheme: For the first 7 days of bleeding, no treatment. After the first 7 days, in the case of persistent bleeding, they were advised to take two (one in the morning and once at night) up to 7 days. In the case of persistent bleeding, they were advised to suspend for 7 days and then resume treatment with one tablet a day according to the standard protocol. This scheme, dubbed the "three sevens", gave the patients a reassuring and efficient protocol management of bleeding.

In the case of discontinuation of Dienogest 2 mg treatment, the reason for discontinuation was collected reported in clinical charts (Fig. 1).

In consideration of the observational design, the study did not foresee any examination.

AEs were documented at all study visits and continued according to the Medical Dictionary for Regulatory Activities Primary System Organ Class.

The study was approved by the Institutional Review Committee.

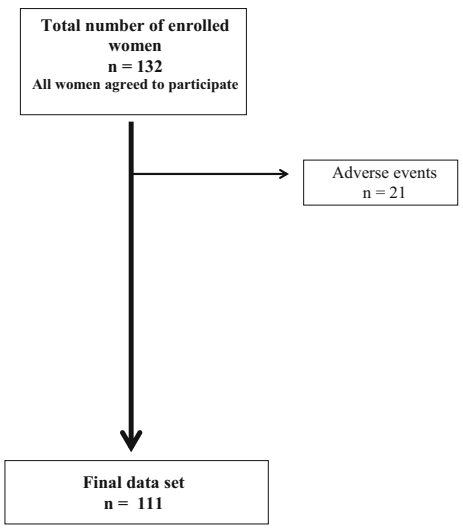

Fig. 1 Flow chart of the study

Sample size

We included 100 patients. With such a sample size, we are able to identify a change in the average value of VAS of 0.8 or greater (minimum reduction deemed significant from the clinical point of view), with a DS of the response equal to 2 [15], and considering the usual levels of alpha 0.05 beta 0:20 and a possible dropout rate of about 15%.

Statistical analysis

Descriptive statistics—mean (standard deviation, SD), median (interquartile range, IQR), and frequency (%)—were used to describe the study population.

Baseline-V3 differences in the VAS score were computed. Statistical significance of changes from baseline was evaluated by paired *t* test.

Results

A total of 132 women were enrolled in the study. 21 of the patients enrolled were released from the study during follow-up after the occurrence of one or more adverse events and in accordance with the woman's preference. In particular, spotting was observed in ten cases, mood alterations in eight cases, mastodynia in two cases, hot flashes in six cases, weight gain in six cases, vaginal dryness in four cases, and a decrease in libido in eight cases.

A total of 111 women completed the study.

Baseline characteristics of these patients are presented in Table 1. Their mean age was 33.6 (7.7; 16–47) years. A total of 59 cases (53.2%) had surgical diagnosis of endometriosis, and 52 (46.8%) had clinical/ultrasound diagnosis. 29 (26.1%) women had a family history of endometriosis.

Their mean weight was 59.5 kg (SD 7.71) at start, 62.7 kg (SD 8.1) at V3.

According to entry criteria, all women reported pelvic pain with a VAS value >4. A total of 106 women reported dyspareunia and 89 dyschezia.

Table 2 shows the VAS values of pelvic pain, dyspareunia, and dyschezia at visits 0, 1, 2, and 3.

Table 2 VAS values for pelvic pain, dyspareunia, and dyschezia at study entry and V1, V2, and V3

	Mean	SD	Median	Q1	Q3
Pelvic pain (No. 111)					
Baseline	8.9	*1.3*	9	*8*	*10*
V1	2.4	*2.6*	2	*0*	*4*
V2	1.1	*1.8*	0	*0*	*2*
V3	0.8	*1.6*	0	*0*	*1*
Dyspareunia (No. 106)					
Baseline	6.7	*3.2*	7	*6*	*9*
V1	2.8	*2.7*	3	*0*	*4.5*
V2	1.4	*2.3*	0	*0*	*2*
V3	1.4	*2.1*	0	*0*	*3*
Dyschezia (No. 89)					
Baseline	5.7	*3.7*	7	*2*	*9*
V1	1.2	*1.9*	0	*0*	*2*
V2	0.5	*1.2*	0	*0*	*0*
V3	0.2	*0.9*	0	*0*	*0*

The mean pelvic pain VAS score at baseline was 8.9 (SD 1.3). The corresponding values were 6.7 (SD 3.2) and 5.7 (SD 3.7) for dyspareunia and dyschezia. The mean VAS scores progressively and significantly decreased to 0.9 (SD 1.6) for pelvic pain, 1.4 (SD 2.1) for dyspareunia, and 0.2 (SD 0.9) for dyschezia, respectively, 12 months after start of treatment.

Similar findings emerged when we considered the median values for the analysis.

We analyzed the pelvic pain VAS values at V0 and V3 in strata of selected covariates. The baseline values were largely similar in strata of age, type of diagnosis, baseline VAS value, and family history. Likewise, changes from baseline were largely similar in the considered strata (Table 3).

A total of 66 women (59.4%) experienced at least one AE and 28 (25.2%) more than one. The most frequent AE was bleeding (47 patients, 42.3%), followed by weight gain (19 women, 17.1%), depression (18, 16.2%), reduced sexual desire (9, 8.1%), breast tenderness (9, 8.1%), headache (4, 3.6%), and vaginal dryness (4, 3.6%).

Table 1 Characteristics of study subjects (no = 111)

Characteristic	Mean (SD, range) or no (%)
Age (years)	33.9 (7.8; 18–47)
BMI (kg/m^2)	22.8 (2.7; 17.9–30.1)
Family history of endometriosis (first degree relatives)	29 (26.1)
Surgical diagnosis	59 (53.2)
Clinical diagnosis	52 (46.8)

Table 3 Median VAS at V0 and V3 and change from baseline in pelvic pain, in strata of selected covariates

	No.	V0 (IQR)	V3 (IQR)	Change from baseline (IQR)	*P*
Total series	111	9 (8, 10)	0 (0, 1)	−9 (−10, −7)	<0.0001
Surgical diagnosis	59	9 (8, 10)	0 (0, 2)	−8 (−9, −6)	<0.0001
Clinical diagnosis	52	9 (8, 10)	0 (0, 0)	−9 (−10, −7.5)	<0.0001
Pain VAS <8 at baseline	19	7 (6, 7)	1 (0, 3)	−6 (−7, −4)	<0.0001
Pain VAS ≥8 at baseline	92	10 (9, 10)	0 (0, 0)	−9 (−10, −8)	<0.0001
Age <35	52	9 (8, 10)	0 (0, 2)	−8 (−10, −6.5)	<0.0001
Age ≥35	59	9 (8, 10)	0 (0, 1)	−9 (−10, −7)	<0.0001
Family history Yes	29	9 (8, 10)	0 (0, 1)	−8 (−10, −7)	<0.0001
Family history No	82	9 (8, 10)	0 (0, 1)	−8 (−10, −7)	<0.0001

Discussion

The general findings of this observational study confirm the effect of Dienogest 2 mg in the treatment of endometriosis-related pelvic pain. In particular, this study shows that the effect of Dienogest 2 mg persists 12 months after start of treatment.

An effective and safe medical management of endometriosis is a relevant clinical objective, in consideration of the rate of pain recurrence after surgery.

Randomized clinical trials and clinical series have consistently shown that Dienogest is effective in the treatment of pain-related endometriosis [6, 11, 15, 18, 19, 25, 26].

Momoeda et al. [12] evaluated the use of dienogest 2 mg/day for 52 weeks in 135 women. A reduction in VAS score for pelvic pain was noted after 24 and 52 weeks of treatment (-22.5 ± 32.1 and -28.4 ± 29.9 mm, respectively). Similar results were reported by Petraglia et al. [15] in an extension study which has analyzed the effect of treatment with dienogest 2 mg for 53 weeks.

Our series confirms the efficacy in routine practice of dienogest 2 mg in the treatment of painful endometriosis. Furthermore, in this study, more than half of the patients that did not have surgical confirmation, but were only diagnosed with endometriosis clinically and by ultrasound, found that their pain was controlled equally as well as those patients who had a surgical diagnosis. These data confirm the possibility, quoted in the literature [2, 9, 10, 17] several times, of prescribing first-line medical treatment with progestins based on a clinical diagnosis without the need for surgical confirmation.

The safety analysis of the study indicated a profile of dienogest 2 mg in routine clinical practice that is largely consistent with data from randomized clinical studies. The rate of AE causing treatment interruption in our study was 15,9% (21 out of 132) and about 60% of women (59.4%), who completed the study experienced at least one AE, and 25% more than one.

In the 6-month study conducted by Luisi et al. [11], in routine practice, the dropout rate was 4%. In the 52-week Momoeda et al.'s [12] study, all patients experienced some side effects and about 8% of patients stopped the treatment due to AE. Furthermore, the AEs observed in our experience are largely similar to those reported in the Momoeda et al.'s study [12]. In that study, in fact, vaginal bleeding was the most commonly reported AE.

Potential limitations of this study should be considered. First, this is an observational study. No control group was foreseen. Thus, this study can not show if dienogest is superior to other available in market such as oral contraceptives or gonadotropin-releasing hormone agonists [4, 14, 20, 24].

The scope of this study was to analyze the long-term efficacy and safety of dienogest treatment: the observational design was chosen to evaluate them in routine clinical practice.

We have not considered separately the symptom dysmenorrhea. However, in most of patients, menstrual pain is almost abolished as a consequence of the amenorrhea induced by the dienogest since the first month of therapy [23]. Thus, it is not possible to evaluate the effect of treatment on dysmenorrhea. We have considered as pelvic pain each pain not related to sexual activity or defecation.

Furthermore, this is an observational study of limited numbers, but in any case, we had adequate statistical power to identify the expected difference in the VAS score.

The side effect profile was collected in the routine clinical practice and not systematically studied. Finally, as any observational study, this clinical experience has a huge risk of bias. However, we have included consecutively observe patients and the lost to follow-up rate was limited. Another limitations is the fact that we have not consider among the confounding factors that can influence patient's experience of pain any pre- and post-treatment anxiety and depression scales such as HADS score that has been showed to be associated with pain [5].

We have not taken into account the pharmacoeconomic aspects of the treatment with dienogest. The lack of a control group is a main limitation for this specific analysis. The cost of treatment should, however, always be considered in routine clinical practice, but it is extremely related to the different health and reimbursement systems and the

results of cost analysis are not easily generalizable to different countries.

In conclusion, this prospective study confirms that, in routine clinical practice, Dienogest 2 mg is an effective and well-tolerated treatment for endometriosis-related pain in women with endometriosis in the long term.

Author contribution statement AM: project development. DI: data collection or management and manuscript writing/editing. FP: data analysis. WA: manuscript writing/editing. AM: manuscript writing/editing. LG: manuscript writing/editing. LA: project development.

Compliance with ethical standards

Conflict of interest FP received fee by Bayer SpA for participation to Editorial Board. The other authors declare that they are no conflict of interest. All authors have full control of all primary data and that they agree to allow the Journal to review their data if requested.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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