

SR-16234, a Novel Selective Estrogen Receptor Modulator for Pain Symptoms with Endometriosis: An Open-label Clinical Trial

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ABSTRACT

Background SR-16234 is a selective estrogen receptor modulator (SERM) structurally different from approved SERM and has been reported to have estrogen receptor (ER) α antagonistic activity and strong affinity with a weak partial agonistic activity to ER β receptor. SR-16234 showed strong inhibitory effects on transplanted endometrial cysts in the endometriosis model of rat and mouse. In this clinical trial, efficacy and safety of SR-16234 have been evaluated in endometriosis patients.

Methods This trial was an open-label single arm clinical trial. Ten patients with dysmenorrhea and pelvic pain associated with endometriosis and adenomyosis were enrolled in this trial, and received 40 mg of SR-16234 once daily for 12 weeks. The primary endpoint was the visual analogue scale (VAS) of pelvic pain. The secondary endpoints included dysmenorrhea score, pelvic pain score, objective observations (stiffness of Douglas' pouch, limitation of uterine movement, size of ovarian chocolate cysts, thickness of endometrium, and serum CA125 concentration) and safety.

Results After oral administration of SR-16234 40 mg for 12 weeks, there were statistically significant decreases in pelvic pain VAS, total pelvic pain score, total dysmenorrhea score, stiffness of Douglas' pouch, limitation of uterine movement compared with the baseline values.

Conclusion The present trial suggested that a selective estrogen receptor modulator could be used for treatment of pain associated with endometriosis for the first time.

Key words estrogen receptor; endometriosis; selective estrogen receptor modulator; pelvic pain; open clinical trial

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Abbreviations: AE, adverse effect; BMD, bone mineral density; E2, estradiol; ER, estrogen receptor; GnRH; gonadotropin releasing hormone; GPR30, G protein coupled estrogen receptor; SERM, selective estrogen receptor modulator; VAS, visual analogue scale

Endometriosis is a chronic and recurrent gynecological disease affecting 10% of reproductive age women. As it has been considered as an estrogen dependent disease, modalities to suppress endogenous estrogen levels have been widely utilized. Gonadotropin releasing hormone (GnRH) agonist has been a representative agent which can induce hypoestrogenic state and reduce pain symptoms and endometriosis lesions.¹ In addition, efficacy of aromatase inhibitors has been reported and is now used as an off label indication in menopausal patients.^{2,3}

Estrogen receptor antagonist or so called SERM including tamoxifen and fluvestrant have already established clinical efficacy for estrogen receptor positive breast cancer. Several SERMs have been evaluated in animal models of endometriosis, including raloxifene,^{4,5} LY-2066948,⁶ TZE-5323⁷ and bazedoxifene,⁸ and efficacies on the regression of endometriotic lesions have been reported. So far, however, efficacy of SERM has not been reported in endometriosis patients.

Tamoxifen, the first generation of SERM for treatment of breast cancer, induced endometriosis in post-menopausal breast cancer patients.^{9,10} Raloxifene used for postoperative patients with endometriosis showed a significantly shortened time for the return of chronic pelvic pain.¹¹ Partial agonistic activity of those SERMs to ER α is suggested as a potential reason to be detrimental for endometriosis.

SR-16234 is a SERM structurally different from the SERMs mentioned above and has been reported to have ER α antagonistic activity and strong affinity with a weak partial agonistic activity to ER β receptor.^{12,13} Efficacy of this compound for breast cancer has been evaluated.^{14,15} We have confirmed inhibitory effects on transplanted endometrial cysts in the endometriosis model of rat and mouse (unpublished data). In this clinical trial, efficacy and safety of SR-16234 have been evaluated in endometriosis patients.

MATERIALS AND METHODS

Patient Selection

Patient inclusion criteria included women of 20 years

Table 1. Pelvic pain score: Grading and scoring of symptoms and requirement of analgesics

	Grade	Symptom	Score
Pelvic pain	No	None	0
	Slight	Some disturbances to daily work (school work/house keeping)	1
	Moderate	Disturbances to daily work (school work/house keeping) or need rest in bed	2
	Severe	Staying in bed unable to work/to do house keeping	3
Use of analgesic	No	No usage of analgesics	0
	Slight	Usage of analgesics in one day due to pelvic pain other than during menstruation from the time of menstruation one month previous	1
	Moderate	Usage of analgesics for 2–6 days due to pelvic pain other than during menstruation from the time of menstruation of one month previous	2
	Severe	Usage of analgesics for more than 7 days due to pelvic pain other than during menstruation from the time of menstruation one month previous	3

Total pelvic pain score is the sum of 1) pelvic pain score and 2) use of analgesic score.

and older with regular menstrual cycle who have symptomatic endometriosis or adenomyosis. Usage of progestins, oral contraceptives, GnRH agonists, testosterone derivatives, FSH antagonist, aromatase inhibitors, and other drugs that might effect the secretion of sex hormones, and fixation with alcohol through the vagina, laparotomy, laparoscopic therapy or examinations were prohibited throughout the 12 weeks of the period from initiation to completion of SR-16234 administration. All patients provided written, informed consent prior to trial initiation.

Study Design

This was an open-label trial in 10 patients with endometriosis performed at two investigational sites (a university hospital, a general hospital) in Japan. Patients received SR-16234 40mg once daily for 12 weeks, and then follow-up was performed for 4 weeks. Treatment began on the second day of the menstrual cycle. SR-16234 was prepared as a 40mg capsule. The use of analgesic agents was allowed, but other hormonal treatments for pain or vaginal bleeding were prohibited.

The primary endpoint was the VAS of pelvic pain, the secondary endpoints included dysmenorrhea score,

Table 2. Dysmenorrhea score: Grading and scoring of symptoms and requirement of analgesics

	Grade	Symptom	Score
Dysmenorrhea	No	None	0
	Slight	Some disturbances to daily work (school work/house keeping)	1
	Moderate	Disturbances to daily work (school work/house keeping) or need rest in bed	2
	Severe	Staying in bed unable to work/to do house keeping	3
Use of analgesic	No	No usage of analgesics	0
	Slight	Usage of analgesics in one day at menstruation	1
	Moderate	Usage of analgesics for 2–6 days at menstruation	2
	Severe	Usage of analgesics for more than 7 days at menstruation	3

Total dysmenorrhea score is the sum of 1) dysmenorrhea score and 2) use of analgesic score.

pelvic pain score, objective observations (stiffness of Douglas' pouch, limitation of uterine movement, size of ovarian chocolate cysts, and thickness of endometrium) and safety.

The final protocol was approved by the ethics review committees of each hospital. This clinical trial was registered with the UMIN Clinical Trials Registry (UMIN000019193), and was conducted in accordance with the ethical principles established in the Declaration of Helsinki and consistent with Ethical Guidelines for Clinical Research.

Patient Monitoring

During the 6 weeks of screening period before initiating administration, each patient underwent a pre-recruitment evaluation, consisting of a general medical and gynecologic history, physical and pelvic examination, clinical evaluation of signs and symptoms, VAS of pelvic pain, pelvic pain score (Table 1), dysmenorrhea score (Table 2), use of analgesics, objective observations (stiffness of Douglas' pouch, limitation of uterine movement (Table 3), size of ovarian chocolate cysts, and thickness of endometrium), clinical laboratory assessments, vital signs and 12 lead ECG. Laboratory assessments include hematology test (white blood cells, platelet, red blood cells, hemoglobin, and hematocrit), biochemical test (total protein, albumin, GOT, GPT, r-GTP, Al-P, LDH, total bilirubin, total cholesterol, high density lipoprotein-cholesterol, TG, BUN, Creatinine, Ca, Fe, P, Na, K, and Cl) and urinalysis. At this period, eligibility

Table 3. Evaluation method of stiffness of Douglas' pouch and limitation of uterine movement

		Severity
Stiffness of Douglas' pouch	0	None: no finding
	1	Very slight: the degree to which the induration is smaller than the size of the little finger tip
	2	Slight: the degree to which the induration is about the same size as the little finger tip
	3	Moderate: intermediate degree between "Slight" and "Severe"
	4	Severe: complete closure of Douglas' pouch and no resilience
Limitation of uterine movement	0	None: no finding
	1	Very slight: the degree to which there is a slight, hardly recognizable limitation of uterine flexibility
	2	Slight: the degree to which there is a clear limitation of uterine flexibility
	3	Moderate: the degree to which there is a definite, strong, yet not complete limitation of uterine flexibility
	4	Severe: complete limitation of uterine movement flexibility

for enrollment into the trial was determined, and SR-16234 was prescribed. VAS of pelvic pain, pelvic pain score, dysmenorrhea score, use of analgesics, objective observations (stiffness of Douglas' pouch, limitation of uterine movement, size of ovarian chocolate cysts, and thickness of endometrium) were evaluated at 4, 8 and 12 weeks. Safety assessments were performed throughout the trial.

Statistical Analysis

The mean changes of the VAS of pelvic pain, total pelvic pain score, total dysmenorrhea score, pelvic pain score, dysmenorrhea score, score of analgesic use for pelvic pain, score of analgesic use for dysmenorrhea, stiffness of Douglas' pouch, limitation of uterine flexibility and thickness of endometrium from baseline were evaluated at 4, 8, 12 weeks after administration of SR-16234.

The changes of the outcome variables were analyzed with the paired *t*-test. All of the statistical tests were 2-sided with an α level of 0.05 and were performed using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

Ten patients were enrolled in this clinical trial and all patients completed the trial until follow-up period. The

Table 4. Demographic data of the patients

Number of patients	
Endometriosis	9
Adenomyosis	1
Age (Years)	
Average	39.6
SD	3.66
Minimum	34
Maximum	46
Age of the first menstruation (Years)	
Average	12.9
SD	3.7
Minimum	11
Maximum	23
Present menstruation	
Yes	10 (100%)
Menstruation cycle	
Normal	10 (100%)
Menstrual cycle (Days)	
Average	29.4
SD	4.14
Duration of menstruation (Days)	
Average	6.5
SD	1.18
Volume of menstruation	
Small	0
Moderate	3 (30%)
Large	7 (70%)
Number of pregnancy	
0	2 (20%)
1	2 (20%)
2	5 (50%)
3	1 (10%)
Number of delivery	
0	4 (40%)
1	1 (10%)
2	5 (50%)
Method of diagnosis	
Histological	0
Clinical	10 (100%)
Surgery	
Yes	1 (10%)
No	9 (90%)
Prior therapy	
Yes	5 (50%)
No	5 (50%)
Complication	
Yes	1 (10%)
No	9 (90%)

demographic data of those patients are summarized in Table 4.

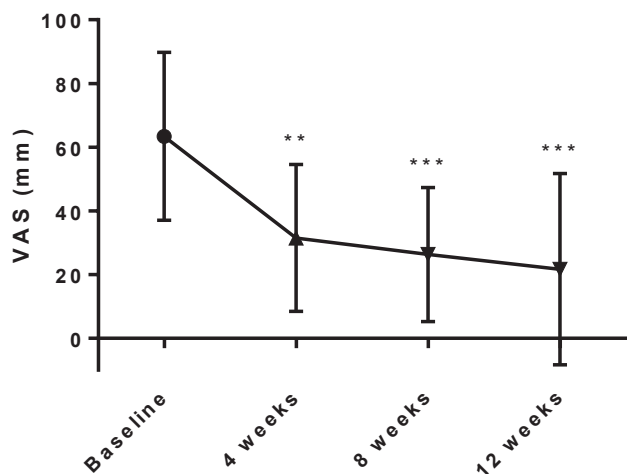


Fig. 1. Effects of SR-16234 on pelvic pain VAS in endometriosis patients. Differences in the changes of VAS were analyzed with the paired *t*-test. Data are represented as mean \pm standard deviation. ($n = 10$, ** $P < 0.01$, *** $P < 0.001$) VAS, visual analogue scale.

Changes in pelvic pain VAS

Changes in the mean pelvic pain VAS as the primary endpoint at baseline and 4, 8, 12 weeks after initiation of treatment of SR-16234 are shown in Fig. 1. VAS of pelvic pain significantly decreased at 4, 8 and 12 weeks compared with the baseline.

Changes in total pelvic pain score and total dysmenorrhea score

Changes in the mean total pelvic pain score and total dysmenorrhea score at baseline and 4, 8, 12 weeks after initiation of treatment of SR-16234 are shown in Fig. 2, 3, respectively. Total pelvic pain score and total dysmenorrhea score significantly decreased throughout the treatment period compared with the baseline. Pelvic pain score, score of analgesic use for pelvic pain, total dysmenorrhea score and score of analgesic use for dysmenorrhea that consist of total score also significantly decreased throughout the treatment period compared with the baseline (Data not shown).

Effects of SR-16234 on stiffness of Douglas' pouch, limitation of uterine movement, endometrium thickness, and size of chocolate cyst

Douglas' pouch stiffness and limitation of uterine movement were analyzed in nine patients, and the mean severity of Douglas' pouch stiffness and limitation of uterine movement decreased after treatment. (3.44 and 3.44 at baseline, 2.44 and 2.55 at 12 weeks, respectively). Endometrial thickness was evaluated in 8 patients, and mean endometrial thickness at 12 weeks (6.87 mm)

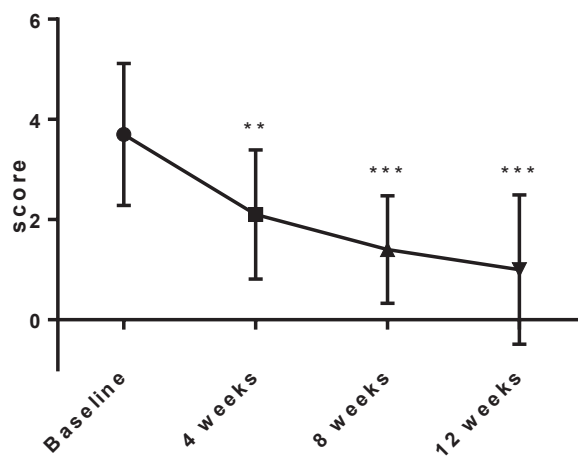


Fig. 2. Effects of SR-16234 on total pelvic pain score in endometriosis patients. Differences in the changes of score were analyzed with the paired *t*-test. Data are represented as mean \pm standard deviation. ($n = 10$, ** $P < 0.01$, *** $P < 0.001$)

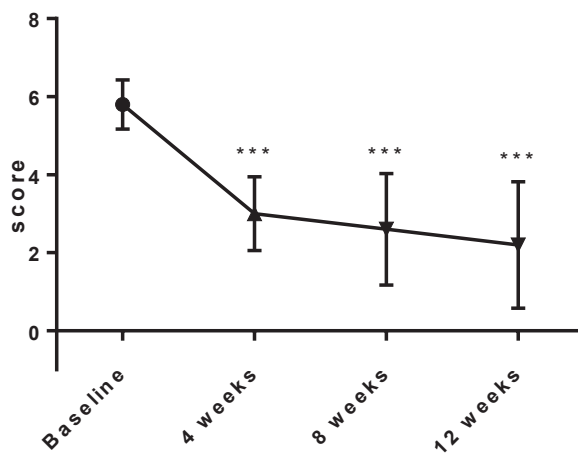


Fig. 3. Effects of SR-16234 on total dysmenorrhea score in endometriosis patients. Differences in the changes of score were analyzed with the paired *t*-test. Data are represented as mean \pm standard deviation. ($n = 10$, *** $P < 0.001$)

was less than that of baseline (9.75 mm). Effect of SR-16234 administration on the size of chocolate cyst was evaluated in one patient. A chocolate cyst with volume of 13,305 mm³ was decreased to 4,521 mm³ at 4 weeks and 1,914 mm³ at 8 weeks, respectively and disappeared at 12 weeks.

Adverse events

Three patients reported adverse events in this clinical trial including contusion of the right leg and hemorrhage subcutaneous of the right leg (1), nausea (1) and common wart (1) but none of these conditions were found to have any relation to SR-16234 usage. No serious adverse

events were reported in this trial. There were no clinically significant changes in clinical laboratory assessments (hematology, biochemical and urinalysis), vital signs and 12 lead ECG (data not shown).

DISCUSSION

Endometriosis is often manifested by pain symptoms, such as dysmenorrhea, pelvic pain, and dyspareunia. Current therapeutic options include conservative surgery and medical treatment with oral contraceptives, GnRH agonist, danazol, and progestins.¹⁶⁻¹⁸

Surgical therapy for endometriosis continues to be the primary therapeutic measure and a Cochrane meta-analysis of 5 randomized controlled studies evaluating laparoscopic treatment of endometriosis compared with diagnostic laparoscopy without treatment reported that pain was significantly improved in the treatment group. However, recurrence rate after surgical therapy is high and may be associated with significant complication rates. In addition, in the case of ovarian endometriosis, there is concern about the risk of ovarian damage and impaired ovarian reserve.¹⁹

Medical treatment of pain associated with endometriosis is generally effective with little difference in efficacy observed among the different types of agents used; however, the adverse event profiles of the various drug regimens markedly differ.^{1, 3, 20, 21}

As endometriosis is considered an estrogen dependent disease, induction of a hypoestrogenic condition is one major active mechanism using established medical agents. GnRH agonist is one representative inducer of the hypoestrogenic condition. Although strong efficacy of GnRH agonist is well known for controlling pain symptoms of endometriosis, hypoestrogenic side effects including hot flashes, vaginal dryness, emotional lability, loss of libido, and significant loss in bone mineral density (BMD) are problematic. Reduction of BMD may not be recovered until a few years after completion of the treatment. Due to these concerns, administration period of GnRH agonist is basically limited to less than 6 months.^{20, 21}

Endometriotic implants express a high level of aromatase and generate their own estrogen, which can maintain their viability and growth.²² As aromatase inhibitors inhibit local estrogen production in endometriotic implants, its efficacy for endometriosis has been evaluated.²³ A systematic review of eight studies showed that aromatase inhibitors combined with progestogens, oral contraceptives, or GnRH agonists had reduced mean pain scores and lesion size and improved QOL. However, monotherapy with aromatase inhibitor administered to reproductive age women will cause increased

FSH levels and subsequent superovulation which may result in ovarian cyst development due to the initial FSH rise.²⁴ Other concerns about prolonged aromatase inhibitor therapy are many, including associated bone loss secondary to hypoestrogenism.²⁴

Due to the estrogen dependent nature of endometriosis, SERMs have been proposed for the treatment of endometriosis.²⁵ However, no SERMs have been reported to be effective in the treatment of endometriosis.³ SERM is an acronymic term for a group of drugs that selectively modulate estrogen receptor. Tamoxifen is a first generation SERM used for the treatment of breast cancer. Usage of tamoxifen as an alternative modality in the treatment of endometriosis, especially for women desiring to conceive, was expected. However, after wide spread use of tamoxifen for breast cancer, occurrences of endometriosis was reported in postmenopausal patients who had been taking tamoxifen for treatment of breast cancer. And it had been suggested that long term tamoxifen users are more likely to have endometrial hyperplasia, endometrial polyps, and/or endometrial cancer.^{9, 10}

As these effects of tamoxifen were considered to be derived from its estrogen receptor agonistic activity, other SERMs that have more selective estrogenic activity were evaluated. Raloxifene has been used for the treatment of postmenopausal osteoporosis. In a randomized clinical trial in biopsy proven endometriosis with chronic pelvic pain, the raloxifene group experienced significant pain and had secondary surgery statistically significantly sooner than the placebo group. This truncated trial concluded that raloxifene statistically significantly shortened the time of return to chronic pelvic pain.¹¹

The mechanism of failure of raloxifene was not well explained in that publication. It may depend on the agonistic activity of raloxifene to the G protein coupled estrogen receptor (GPR30). While many effects of estrogen are mediated by its action at its nuclear estrogen receptors, ER α and ER β , novel estrogen receptor GPR30 and peripheral administration of GPR30 agonists or estradiol (E2) produces mechanical hyperalgesia within minutes after injection.²⁶ Locally injected raloxifene close to the endometrial implant in the rat model of endometriosis also induced mechanical hyperalgesia at a comparable dose with E2.⁴

Bazedoxifene reduced the size of endometrial lesions with experimental evidence of an antiproliferative effect in mouse and rat models.⁸ In addition bazedoxifene was shown to decrease proliferating cell nuclear antigen and estrogen receptor expression in the endometrium of treated animals compared with controls. However, the effectiveness of bazedoxifene on endometriosis in humans has not been published.

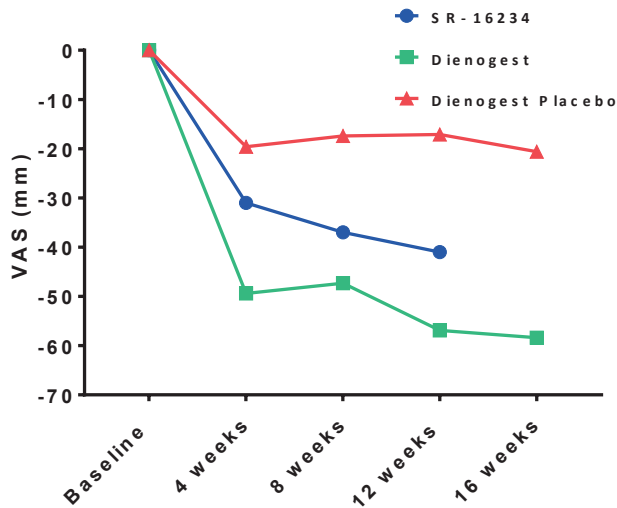


Fig. 4. Effects of SR-16234 and dienogest on pelvic pain score (VAS) in endometriosis patients. Data of dienogest and placebo were derived from common technical document (CTD).

The data of the present clinical trial suggests that SR-16234 may alleviate dysmenorrhea and pelvic pain of endometriosis at 40 mg daily dosage by oral administration. As no other SERMs have shown such clinical efficacies in endometriosis, SR-16234 may be the first SERM with reported efficacy for this disease condition. The mechanism action of SR-16234 for endometriosis is not well clarified. Other SERMs have some levels of partial agonistic activity to ER α and that may be the reason for resistance occurring in treatment for breast cancer and could be effective in increasing bone mineral density in osteoporosis patients. Compared with 1st or 2nd generation SERMs including tamoxifene, raloxifene or bazedoxifene, SR-16234 seems to be a purer ER α antagonist and that may be one of the reasons it is effective for endometriosis related pain. Its strong affinity to both ER α and ER β might be important. Bulun et al suggest that deficient methylation of the ER β promoter results in pathological overexpression of ER β in endometriotic stromal cells, high levels of ER β suppress ER α expression and a high ER β to ER α ratio in endometriotic stromal cells is associated with suppressed progesterone receptor and increased cyclooxygenase-2 levels contributing to progesterone resistance and inflammation.²³

As the affinity of SR-16234 to ER β is 10 to 100 times stronger than other SERMs that have been used for treatment of breast cancer or osteoporosis. In endometriotic tissues where high estrogen content and high ER β expression, SR-16234 may induce ER β activation to inhibit growth of endometriotic tissue, inflammatory

cytokines, COXs expression, and ER β receptor resistance.

In terms of efficacy of drugs for pain associated with endometriosis, we compared changes in pelvic pain score of SR-16234 and dienogest (data for dienogest and placebo derived from the CTD of dienogest) (Fig. 4). SR-16234 had stronger effects than the placebo, but changes in pelvic pain VAS was more profound with dienogest, suggesting potential utility of SR-16234 in pain management of endometriosis. Further large scale and placebo compared clinical trials in the future are necessary for confirmation.

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