A Randomized, Parallel, Comparative Study of the Efficacy and Safety of Nafarelin Versus Danazol in the Treatment of Endometriosis in Taiwan

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Background: The purpose of this study was to evaluate the efficacy and safety of nafarelin, a gonadotropin-releasing hormone (GnRH) analogue, versus danazol in the treatment of women with endometriosis in Taiwan.

Methods: Fifty-nine women with laparoscopically and pathologically confirmed endometriosis were randomized to receive nafarelin or danazol for 180 days. Efficacy was assessed from mean changes in laparoscopy score (LS) and total symptom severity score (TSSS). Adverse events (AEs) and laboratory parameters, including hematology, hepatic function, blood pressure, and lipid levels, were monitored for safety evaluations.

Results: All demographic and baseline factors, except body weight, were comparable between the 2 treatment groups. Both nafarelin and danazol satisfactorily resolved pelvic tenderness, induration, pelvic pain, dysmenorrhea and dyspareunia. No significant differences were noted in efficacy endpoints between nafarelin and danazol regarding LS and TSSS at 90 and 180 days of treatment. No significant difference was observed between the 2 groups regarding the overall incidence of AEs, except for laboratory-related AEs. However, nafarelin tended to have less impact than danazol on aspartate transaminase and alanine transaminase, and nafarelin was better tolerated than danazol regarding changes in lipid profiles. Both treatments had little or no effect on hematologic parameters.

Conclusion: Nafarelin and danazol demonstrated similar clinical efficacy, but nafarelin was associated with fewer laboratory changes and a stable lipid profile, relative to danazol. Moreover, intranasally administered nafarelin is noninvasive, and may be a more comfortable and safer alternative to slow-release injectable GnRH agonists. Based on this study, we suggest that nafarelin, like other GnRH analogues, may be a treatment of choice for Taiwanese women with endometriosis. However, direct comparative studies of nafarelin with slow-release injectable GnRH agonists are now required. [*J Chin Med Assoc* 2005;68(7):307–314]

Key Words: danazol, endometriosis, nafarelin

Introduction

Endometriosis, which affects up to 1 in 15 women of reproductive age,[1] is progressive in nature, and is characterized by symptoms such as pelvic tenderness, induration, dysmenorrhea, dyspareunia, and chronic pelvic pain. Endometriosis can also be an important factor contributing to infertility.

Combined surgery (most appropriately through laparoscopy) and medical treatment is currently considered the optimal treatment for advanced endometriosis.[2–4] Medical treatment can be classed as steroidal or nonsteroidal: danazol, a 17-α-ethinyltestosterone derivative, represents the primary steroidal intervention and has androgenic and anabolic effects; whereas gonadotropin-releasing hormone

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(GnRH) agonists, which include buserelin, goserelin, histrelin, leuprolide and nafarelin, are nonsteroidal compounds used in the treatment of endometriosis.[5] Both steroidal and nonsteroidal therapies, through hypoestrogenism and ovarian quiescence, have demonstrated efficacy in the treatment of endometriosis. Selection of a particular treatment for endometriosis depends largely on safety, tolerability, patient compliance and, of course, economic considerations.

The androgenic and anabolic effects of danazol are well known; the compound can, therefore, overcome adverse effects (AEs) secondary to hypoestrogenism and ovarian quiescence, including hot flushes, loss of bone mineral density (osteoporosis), and many other menopause-related signs and symptoms.[6] However, danazol may cause androgenic AEs such as weight gain, edema, acne, seborrhea, reduced breast size, hirsutism and, importantly, changes in lipid profile.[7–9] Increased levels of low-density lipoprotein (LDL) cholesterol and decreased levels of high-density lipoprotein (HDL) cholesterol, which have been demonstrated in previous clinical trials in danazol-treated patients, pose significant concerns regarding the risks of danazol-induced cardiovascular disease.[8,10]

Intranasal nafarelin acetate is a GnRH agonist that has proven to be similarly effective to danazol, but with superior safety and tolerability.[8,11] Nafarelin is formulated as an intranasal spray, and is absorbed into the systemic circulation with a time to peak plasma concentration (T_{max}) of 18.4 minutes, and peak plasma concentration (C_{max}) of 2.04 mg/L.[12,13] The pharmacokinetic profile and high biologic potency of nafarelin would appear to facilitate use of the compound as an effective and noninvasive treatment in the long-term management of endometriosis.[1]

This study of intranasal nafarelin 400 μg daily versus oral danazol 600 mg daily aimed to provide more information, particularly about probable equivalence of efficacy and effects on lipid profiles, in the treatment of endometriosis in Taiwanese women.

Methods

Study population

Before initiation of this randomized, parallel, comparative study, approval was granted by the independent ethics committee and institutional review board at Taipei Veterans General Hospital, Taipei, Taiwan, and by the Department of Health, Executive Yuan, Republic of China.

Fifty-nine consecutive women with a histologically proven diagnosis of endometriosis via laparoscopy entered the study. Recruitment started in January 1998 and ended in October 2000. Subjects were aged 18–48 years, and were adequately protected from pregnancy with a method other than hormonal contraception. Laparoscopy to establish a diagnosis, and the need for treatment, of endometriosis was performed within the 3 months before study participation. Laparoscopic excision of ovarian endometrioma, and lysis of severe adhesions, was also performed at this time, if necessary.

Patients who satisfied the inclusion criteria gave written informed consent before starting the trial. Exclusion criteria comprised pregnancy or breast-feeding, menopausal or postmenopausal status, use of estrogen, progesterone, or contraceptive steroids in the previous 3 months, impaired hepatic or renal function, cardiovascular disease, acquired immune deficiency syndrome or other sexually transmitted diseases.

Study protocol

All eligible patients entered the trial on the third to tenth day of their menstrual cycles and were randomized to 1 of 2 groups: intranasal nafarelin acetate (Synarel®; Searle Pharma Ltd, Chicago, IL, USA) 200 μg twice daily (2 200-μg sprays in alternating nostrils); or oral danazol (Danocrine™; Sanofi-Synthelabo Australia Pty Ltd, North Ryde, NSW, Austalia) 600 mg daily (1 200-mg tablet 3 times per day). The duration of nafarelin or danazol treatment was 180 days.

At the baseline examination on day 1, HDL-, LDL- and total-cholesterol levels, and triglycerides, were measured. Lipid levels, total symptom severity score (TSSS), and AEs were assessed on days 30, 90, 120, and at the end of treatment. Hematologic and hepatic function tests were performed at baseline and at the final study visit. Laparoscopy for efficacy evaluations was performed before and at the completion of treatment. Efficacy variables comprised the endometriosis TSSS and laparoscopic score (LS). The TSSS consists of 5 measures: pelvic tenderness and induration assessed by investigators, and pelvic pain, dysmenorrhea and dyspareunia evaluated by patients. The LS and staging used in this study were standards from the revised American Fertility Society classification of endometriosis (1985).[14]

Statistical analysis

Demographic and baseline characteristics were tabulated by descriptive statistics (Table 1), and results are described as mean ± standard deviation (SD) and medians for parametric analysis. Differences between the 2 groups were assessed by Fisher's exact test,

Table 1. Demographic and baseline characteristics*

	Nafarelin (n = 29)	Danazol (n = 30)	$p^{\dagger}$
Age, yr	34.8 ± 6.6	32.4 ± 7.2	0.242
Body weight, kg	51.2 ± 5.2	54.7 ± 6.5	0.037†
Menarche, age (yr)	13.7 ± 1.2	13.6 ± 1.4	0.975
Cycle length, d	5.4 ± 1.8	6.0 ± 2.0	0.150
Para	0.8 ± 1.1	1.0 ± 1.2	0.456
Systolic BP, mmHg	108.1 ± 8.6	106.1 ± 8.2	0.462
Diastolic BP, mmHg	72.8 ± 8.8	72.2 ± 7.5	0.896
LDL-cholesterol, mg/dL	118.5 ± 33.2	111.0 ± 25.0	0.362
HDL-cholesterol, mg/dL	55.7 ± 9.7	51.2 ± 11.3	0.105
Total cholesterol, mg/dL	190.7 ± 33.5	178.4 ± 27.7	0.125
Triglycerides, mg/dL	96.4 ± 86.8	73.4 ± 33.7	0.376
Baseline LS	28.0 ± 28.5	23.1 ± 26.4	0.395
Baseline TSSS	6.3 ± 3.2	6.1 ± 2.7	0.975
Presence of ovarian endometrioma with surgical excision, n (%)	16 (55.0)	15 (50.0)	0.863
Stage I, n (%)	5 (17.0)	8 (26.0)	0.323

*Data shown are mean ± standard deviation, except for the bottom 2 rows which are number (%) of patients; †between-group p values were calculated by the Wilcoxon rank-sum test; †$p < 0.05$.
BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; LS = laparoscopic score; TSSS = total symptom severity score.

Chi-squared test, Cochran-Mantel-Haenszel or Wilcoxon rank-sum test. Efficacy variables and laboratory parameters were analyzed using the Wilcoxon rank-sum test for between-group comparisons, and the Wilcoxon signed-rank test for within-group comparisons. Significance was set at a p value of less than 0.05 in all statistical tests.

Results

Demographic and baseline characteristics

All 59 patients were considered as the intent-to-treat population, with a similar number of patients given nafarelin (n = 29) or danazol (n = 30) (Table 1). Nafarelin recipients had a significantly lower mean body weight than danazol-treated patients (51.2 vs 54.7 kg, p = 0.037), but there were no significant differences between the 2 groups in terms of age, obstetric and medical history, and menstrual history and pattern. Six of 29 nafarelin recipients (20.7%) and 5 of 30 danazol-treated patients (16.7%) complained of infertility. In the nafarelin group, 55% of patients underwent combined extensive surgery and medical treatment, whereas 50% of patients in the danazol group did so; mean LS, TSSS and laparoscopic staging at baseline were comparable between the 2 groups.

Clinical efficacy

Forty-one of 59 patients (22 nafarelin and 19 danazol recipients) who completed 90 days' treatment, and who underwent laparoscopic examinations before and after treatment, qualified for the efficacy evaluation. In both treatment groups, improvements in TSSS from baseline to days 90 and 180 were statistically significant in almost all of the 5 items used to evaluate symptoms. In the nafarelin group, decreased levels of pelvic pain were noted at days 90 and 180, but these decreases were not statistically significant. After 180 days of nafarelin therapy, pelvic tenderness was completely resolved (62% of patients), or of only mild severity (38%). Among danazol-treated patients, 58% had complete resolution of pelvic tenderness, whereas 10.5% had moderate, and 32% mild, symptoms remaining. Regarding net change in TSSS, no significant between-group difference was noted after 90 days (–4.4 ± 2.7 [nafarelin] vs –4.1 ± 1.7 [danazol]; p = 0.901) or 180 days (–4.2 ± 2.4 vs –4.6 ± 1.7; p = 0.502) (Table 2).

The LS before treatment was similar in nafarelin versus danazol recipients (28.7 ± 25.9 vs 29.7 ± 29.5; p = 1.000). Regarding net change in LS from baseline to day 180, both treatments reduced LS (–4.2 ± 10.7 [nafarelin] vs –0.3 ± 14.6 [danazol]). This between-group difference was not statistically significant (p = 0.541); however, the decrease of 4.2 from baseline in the nafarelin group was statistically significant (p = 0.047), whereas that of 0.3 in the danazol group was not (p = 0.453). Endometriosis and adhesion components of LS revealed that the overall decrease in

Table 2. Comparison of clinical efficacy between nafarelin and danazol*

	After 90 days' treatment			After 180 days' treatment		
	Nafarelin (n = 22)	Danazol (n = 19)	$p^{\dagger}$	Nafarelin (n = 22)	Danazol (n = 19)	$p^{\dagger}$
Net change in TSSS	–4.4 ± 2.7	–4.1 ± 1.7	0.901	–4.2 ± 2.4	–4.6 ± 1.7	0.502
Pelvic tenderness	–0.9 ± 1.0	–0.7 ± 0.9	0.948	–0.9 ± 1.0	–0.7 ± 0.8	0.820
Induration	–0.5 ± 0.9	–0.4 ± 0.7	0.868	–0.5 ± 0.8	–0.7 ± 0.8	0.544
Pelvic pain	–0.3 ± 0.7	–0.5 ± 0.8	0.815	–0.2 ± 0.6	–0.5 ± 0.7	0.172
Dysmenorrhea	–2.0 ± 0.9	–2.1 ± 1.0	0.664	–2.0 ± 0.9	–2.4 ± 0.8	0.196
Dyspareunia	–0.6 ± 1.2	–0.4 ± 0.6	0.921	–0.6 ± 1.0	–0.2 ± 0.6	0.346
Net change in LS	ND	ND	ND	–4.2 ± 10.7	–0.3 ± 14.6	0.541

*Data shown are mean ± standard deviation; †between-group p values were calculated by the Wilcoxon rank-sum test.
LS = laparoscopic score; ND = no data; TSSS = total symptom severity score.

Table 3. Within- and between-group comparisons of serum lipid levels in nafarelin and danazol recipients*

	Baseline	After 90 days	After 180 days	90-day net change	180-day net change
LDL-cholesterol, mg/dL					
Nafarelin (n = 21)	117.6 ± 35.6	124.0 ± 35.4	134.0 ± 37.5†	6.6 ± 30.6	13.9 ± 21.9
Danazol (n = 23)	110.7 ± 27.0	144.0 ± 31.4†	146.1 ± 46.4§	31.5 ± 33.5	34.3 ± 47.4
p	0.267	0.089	0.382	0.026$^{\|}$	0.033
HDL-cholesterol, mg/dL					
Nafarelin (n = 21)	55.4 ± 10.5	56.7 ± 12.9	58.3 ± 9.0	1.3 ± 7.1	2.4 ± 8.2
Danazol (n = 23)	52.1 ± 12.2	29.4 ± 5.4†	31.4 ± 6.1	–21.3 ± 9.9	–20.6 ± 10.4
p	0.159	0.000	0.000	0.000$^{\|}$	0.000$^{\|}$
Total cholesterol, mg/dL					
Nafarelin (n = 21)	190.1 ± 36.1	199.8 ± 39.4	198.4 ± 38.0	8.2 ± 34.3	14.2 ± 25.3
Danazol (n = 23)	179.4 ± 29.6	181.3 ± 28.9	186.7 ± 39.0	–0.1 ± 33.2	2.4 ± 32.9
p	0.136	0.134	0.317	0.459	0.360
Triglycerides, mg/dL					
Nafarelin (n = 21)	102.0 ± 95.5	112.4 ± 152.4	75.4 ± 26.4	10.4 ± 150.5	–21.7 ± 94.0
Danazol (n = 23)	76.0 ± 36.6	67.3 ± 30.0	75.4 ± 41.6	–10.3 ± 27.0	–1.7 ± 32.4
p	0.555	0.188	0.822	0.156	0.915

*Data shown are mean ± standard deviation; within-group statistical significance (vs baseline) was calculated by the Wilcoxon signed-rank test — $^{\dagger}p = 0.015$, $^{\dagger}p < 0.001$, $^{\S}p = 0.002$; $^{\|}$between-group statistical significance was calculated by the Wilcoxon rank-sum test.
HDL = high-density lipoprotein; LDL = low-density lipoprotein.

LS after nafarelin treatment was due primarily to alleviation of endometriosis, not adhesion (data not shown). Neither nafarelin nor danazol eradicated endometriosis spots completely; therefore, none of the 13 women with stage I endometriosis was cured with nafarelin (n = 5) or danazol (n = 8). Danazol did not significantly reduce LS, or endometriosis or adhesion scores.

Lipid profile

Forty-four of 59 patients (21 nafarelin and 23 danazol recipients) who received study medication for at least 90 days, and who had serum lipid data available both before and after treatment, were included in the evaluation of lipid-profile changes (Table 3). Nafarelin versus danazol recipients had a significantly smaller increase in mean LDL-cholesterol level from baseline to days 90 and 180. However, the actual mean LDL-cholesterol level after 180 days' treatment was not significantly different between the nafarelin and danazol groups. Although danazol-treated patients tended to have an elevated LDL-cholesterol level after 90 days' treatment, there was no further significant increase in this parameter with another 90 days of treatment.

Nafarelin recipients had a relatively stable mean HDL-cholesterol level throughout the study, whereas danazol-treated patients had a clear drop in this parameter, from 52.1 mg/dL at baseline to 29.4 mg/dL at day 90 ($p < 0.001$); however, there was no further decrease in mean HDL-cholesterol level in the danazol group from day 90 to 180. Overall, 90- and 180-day net changes in mean HDL-cholesterol level revealed a small increase in nafarelin recipients and a marked decrease in danazol-treated patients; differences between the 2 treatment groups were highly statistically significant ($p < 0.001$).

Total cholesterol levels for nafarelin and danazol recipients appeared to remain relatively constant throughout the study, whereas triglyceride levels fluctuated in both treatment groups; however, none of the within- or between-group comparisons was statistically significant, thus implying that neither treatment had a marked effect on triglyceride levels.

Hematology and liver function tests

Hematologic changes associated with both treatments are shown in Table 4. White blood cell (WBC) count remained relatively constant throughout the study in the nafarelin group, but increased significantly in the danazol group. The between-group comparison of mean WBC count revealed that danazol caused a significantly ($p = 0.032$) greater increase in this parameter than nafarelin; however, this difference was unlikely to be clinically significant because all values for mean WBC count remained within the normal range.

Mean values for red blood cell (RBC) count, hemoglobin (Hb), hematocrit (Hct), and platelet count, were all within normal limits. Values for RBC count, Hb, Hct and platelet count remained relatively stable in nafarelin recipients, whereas a trend towards increased values for these parameters was noted from baseline to day 180 in danazol-treated patients. Between-group differences regarding net changes in RBC count, Hb, Hct and platelet count were statistically significant, but of little clinical relevance because all values remained within acceptable limits.

Baseline and post-treatment serum levels of alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are documented

Table 4. Within- and between-group comparisons of changes in hematologic parameters in nafarelin and danazol recipients*

	Nafarelin		Danazol		$p^{\|\|}$
	n	Mean ± SD	*n*	Mean ± SD	
WBC, cells/mm^3					
Baseline	28	5,190 ± 1,485	27	5,772 ± 1,309	
Day 180	24	5,340 ± 1,521	23	6,360 ± 1,515†	
Net change		0.4 ± 1,330		892 ± 1,468	0.032
RBC, ×10^6 cells/mm^3					
Baseline	28	4.3 ± 0.5	27	4.4 ± 0.3	
Day 180	24	4.3 ± 0.4	23	5.0 ± 0.4†	
Net change		0.1 ± 0.3		0.6 ± 0.5	0.001
Hemoglobin, g/dL					
Baseline	28	12.6 ± 1.1	27	12.2 ± 1.6	
Day 180	24	13.1 ± 1.1§	23	14.0 ± 1.5†	
Net change		0.4 ± 0.6		1.6 ± 1.3	0.000
Hematocrit, %					
Baseline	28	38.0 ± 3.6	27	37.0 ± 4.5	
Day 180	24	38.6 ± 3.2	23	41.8 ± 3.5†	
Net change		0.5 ± 2.6		4.5 ± 4.1	0.001
Platelet count, cells/mm^3					
Baseline	28	237,786 ± 60,423	27	284,815 ± 65,577	
Day 180	24	222,917 ± 50,646	23	331,652 ± 69,582†	
Net change		–5,174 ± 38,007		56,762 ± 57,850	0.001

*Data shown are mean ± standard deviation; within-group statistical significance (vs baseline) was calculated by the Wilcoxon signed-rank test — $^\dagger p = 0.009$, $^\dagger p < 0.001$, $^\S p = 0.003$; $^{\|\|}$between-group statistical significance was calculated by the Wilcoxon rank-sum test.
SD = standard deviation; RBC = red blood cell count; WBC = white blood cell count.

Table 5. Within- and between-group comparisons of hepatic function test results in nafarelin and danazol recipients*

	Nafarelin		Danazol		*p*
	n	Mean ± SD	*n*	Mean ± SD	
ALP (U/L)					
Baseline	25	55.7 ± 16.1	28	55.8 ± 14.3	
Day 180	23	70.0 ± 19.6†	20	52.1 ± 21.0	
Net change		15.0 ± 13.9		–3.1 ± 15.4	0.001‖
AST (U/L)					
Baseline	26	19.8 ± 8.4	28	16.7 ± 3.8	
Day 180	23	25.2 ± 14.5†	20	29.5 ± 12.5†	
Net change		6.4 ± 12.6		12.2 ± 13.0	0.084
ALT (U/L)					
Baseline	26	15.3 ± 12.0	28	14.7 ± 9.5	
Day 180	23	25.7 ± 20.5§	20	46.7 ± 41.1†	
Net change		11.6 ± 19.0		31.0 ± 38.8	0.028‖

*Data shown are mean ± standard deviation; within-group statistical significance (vs baseline) was calculated by the Wilcoxon signed-rank test — †$p < 0.001$, ‡$p = 0.027$, §$p = 0.012$; ‖between-group statistical significance was calculated by the Wilcoxon rank-sum test.
ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

in Table 5. Nafarelin significantly increased the mean ALP level from baseline (+25.7%, $p < 0.001$), whereas danazol had no significant effect on this parameter. Conversely, both nafarelin and danazol significantly increased mean ALT and AST levels from baseline. The magnitude of the ALT increase was significantly smaller in nafarelin than danazol recipients ($p = 0.028$), and that of the AST increase tended, not significantly, to be smaller in nafarelin than danazol recipients ($p = 0.084$). Mean baseline and post-treatment values for liver function indices were within normal ranges in the nafarelin group, and ALP and AST values in the danazol group generally returned to normal after treatment was stopped. However, after treatment withdrawal, the mean ALT level in danazol-treated patients remained above normal limits, a finding consistent with the previously documented negative impact of danazol on hepatic function.

Adverse events

A total of 592 AEs were reported: 262 in the nafarelin group and 330 in the danazol group. No significant between-group difference was noted in the overall incidence of AEs. Twenty-four of 29 patients in the nafarelin group (82.8%), and 29 of 30 patients in the danazol group (96.7%), experienced at least 1 AE. In the nafarelin group, the most frequent AEs were vaginitis and vasodilation (each with an incidence of 24.1%), followed by weight gain, leukorrhea, menstrual disorders, and chest pain (10.3%). In the danazol group, the most common AE was weight gain (40.0%), followed by acne, vaginal hemorrhage, and generalized spasm (each with an incidence of 20.0%), vaginitis (16.7%), pain and hypertonia (13.3%), and leukorrhea, menstrual disorders, asthenia, constipation, pharyngitis, abdominal pain, rash, voice alteration, and vulvovaginal disorders (10%). Significantly more patients in the nafarelin than danazol group had hot flashes (24% vs 0%, $p = 0.005$), whereas significantly fewer had weight gain (10% vs 40%, $p = 0.015$). Only patients in the danazol group experienced generalized spasm (20%).

Discussion

Steroidal therapy with danazol, because of its satisfactory clinical efficacy, has traditionally been the standard treatment for endometriosis. However, the negative impact of danazol on lipid profiles, especially the well-documented effects of increased LDL-cholesterol and reduced HDL-cholesterol concentrations, has raised concerns about the potential for increased cardiovascular risks to patients. Conversely, GnRH agonists have made possible the nonsteroidal treatment of endometriosis by medical castration. These compounds are rapidly inactivated by gastrointestinal enzymes after oral administration; therefore, alternative routes of administration, including intravenous, intramuscular, or subcutaneous injection, are required to achieve the desired therapeutic effect. The need for safer, noninvasive, and more

convenient methods for administering GnRH agonists led to the development of intranasal nafarelin.

In the current study, no statistically significant difference was noted between nafarelin and danazol regarding efficacy endpoints. Both nafarelin and danazol satisfactorily resolved pelvic tenderness, induration, pelvic pain, dysmenorrhea, and dyspareunia. Our data confirm the previous findings of Henzl and Kwei,[11] who reported that 47–57% of patients had complete symptom relief, and 38–45% had only mild symptoms, after treatment with nafarelin 400 μg per day. In our study, only nafarelin recipients experienced a statistically significant change in LS from baseline to day 180 (net score change –4.2; percent score change –14.6%; $p = 0.047$); there was no major change in LS in danazol-treated patients. These findings disagree with those of Henzl and Kwei,[11] who reported a decrease of 43–48% in LS after treatment with nafarelin 400 μg/day, and a decrease of approximately 49% after treatment with danazol 600 mg/day.

Regarding lipid-profile effects in our study, mean LDL-cholesterol level increased from 110.7 mg/dL at baseline to 146.1 mg/dL after danazol therapy; a smaller increase in this parameter (+16.4 mg/dL) was noted in nafarelin-treated patients. Danazol recipients also had a significantly lower mean HDL-cholesterol level than nafarelin-treated patients, in whom HDL-cholesterol concentrations remained relatively constant throughout the study. The negative lipid-profile effects of danazol were similar to those found in previous studies.[1,15,16] However, the lipid-profile effects of nafarelin identified in other studies,[8,10] i.e. increased HDL-cholesterol concentrations and relatively constant LDL-cholesterol concentrations, were not found in our study. Despite such discrepant results, it seems clear that nafarelin has lipid-profile effects that are superior to those of danazol; thus, it has been suggested that nafarelin may have a clinical advantage over danazol regarding the potential for lower cardiovascular risk.

In our study, a lower incidence of AEs was observed in the nafarelin than danazol group; this finding was consistent with a previous study report.[16] All AEs in our trial were mild to moderate in intensity, except for 1 allergic reaction in the nafarelin group. Hot flashes and reduced libido in nafarelin recipients were noted less frequently than in a previous trial,[11] in which up to 90% and 22% of patients experienced hot flashes and reduced libido, respectively. Bone mineral density may be reduced because of hypoestrogenism, but our study did not evaluate changes in this parameter in nafarelin and danazol recipients. Indeed, given our relatively short study duration (180 days), an evaluation of changes in bone mineral density may not have been clinically relevant. In major multinational studies comparing nafarelin with danazol, nafarelin appeared to increase ALP level and WBC count, and danazol seemed to increase ALT and AST levels, WBC count, and Hct.[1] We found similar results in this trial.

As Taiwan has a high prevalence of hepatitis, and as danazol is largely metabolized by the liver, the marked negative effects of danazol on hepatic function should be carefully considered in patients with active hepatitis. The need for further studies on the effects of danazol in patients with hepatitis may now be an important issue in Taiwan. Additional studies are also needed to directly compare the efficacy and safety of intranasal nafarelin with that of other GnRH agonists. Such studies may confirm intranasally administered nafarelin as a more comfortable, less invasive, and safer alternative to slow-release, injectable GnRH agonists, which are expensive, and which may be inappropriate for long-term treatment because of the potential for reduced bone mineral density.[6,17] Meanwhile, the current study clearly demonstrated that nafarelin and danazol were equally effective in endometriosis, although nafarelin was better tolerated regarding certain AEs, laboratory changes, and maintenance of a relatively stable lipid profile.

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