

Zoladex (Goserelin Acetate Implant) in the Treatment of Endometriosis: A Randomized Comparison With Danazol

JOHN A. ROCK, MD, JOSEPH A. TRUGLIA, MD, RICHARD J. CAPLAN, PhD, AND THE ZOLADEX ENDOMETRIOSIS STUDY GROUP*

Objective: To compare the efficacy, endocrine effects, and safety of Zoladex (goserelin acetate) and danazol in the treatment of premenopausal women with endometriosis in a multicenter, randomized, open study.

Methods: Three hundred fifteen patients with stages I-IV endometriosis (revised American Fertility Society [AFS] classification) were treated with Zoladex, 3.6 mg every 28 days by subcutaneous injection, or danazol, 400 mg orally twice daily for 24 weeks. Efficacy was assessed by determination of pelvic signs and symptoms scores and revised AFS endometriosis scores. Endocrine effects were determined by measurements of hormone levels. Safety was evaluated by

physical examination, laboratory indices, occurrence of adverse events, and bone mineral density changes.

Results: Both treatments significantly ($P < .0001$) reduced mean subjective signs and symptoms scores both during and after therapy. The mean percent reduction in the revised AFS endometriosis score after 24 weeks of treatment was 53% for Zoladex and 33% for danazol, and reduction in the endometrial implants score was 56% for Zoladex and 46% for danazol. Serum estradiol levels decreased to the postmenopausal range in the Zoladex group and to the early follicular phase range in the danazol group. Hypoestrogenic effects occurred more frequently with Zoladex, whereas androgenic side effects were more common with danazol. There was a higher percentage of withdrawals due to adverse events with danazol than with Zoladex. Mean bone mineral density decreased from baseline by 5.4% in the Zoladex group and increased by 1.0% in the danazol group at the end of treatment.

Conclusion: Zoladex is as well tolerated and as effective as danazol in the treatment of premenopausal women with endometriosis. (*Obstet Gynecol* 1993;82:198-205)

From the Department of Gynecology and Obstetrics, Emory University School of Medicine, Atlanta, Georgia; the Department of Gynecology and Obstetrics, The Johns Hopkins University School of Medicine, Baltimore, Maryland; and ICI Pharmaceuticals Group, a business unit of Zeneca Inc., Wilmington, Delaware.

* Members of The Zoladex Endometriosis Study Group: E. James Aiman, MD, Medical College of Wisconsin, Milwaukee, Wisconsin; David H. Barad, MD, and Michael A. Feinman, MD, Albert Einstein College of Medicine, Dobbs Ferry, New York; George Betz, MD, Kaiser Medical Center, Denver, Colorado; W. Paul Dmowski, MD, Elmhurst, Illinois; Phillip C. Galle, MD, Southern Illinois University School of Medicine, Springfield, Illinois; Alvin F. Goldfarb, MD, Philadelphia, Pennsylvania; Robert Hemmings, MD, Royal Victoria Hospital, Montreal, Quebec, Canada; Ekkehard Kemmann, MD, University of Medicine and Dentistry of New Jersey, New Brunswick, New Jersey; Andre Lemay, MD, PhD, and Rodolphe Maheux, MD, Hospital St. Francois d'Assise, Quebec City, Quebec, Canada; L. Russell Malinak, MD, Houston, Texas; George Maroulis, MD, Tampa, Florida; Kamran Moghissi, MD, and Kenneth Ginsburg, MD, Hutzel Hospital, Detroit, Michigan; Eldon Schriock, MD, and Sandra Carson, MD, University Physicians Foundation, Memphis, Tennessee; Professor Robert W. Shaw and K. Geraldine McSweeney, MD, The Royal Free Hospital, London, England; Melvin Taymor, MD, Brookline, Massachusetts; Dan Tulchinsky, MD, The Malden Hospital, Malden, Massachusetts; A. Albert Yuzpe, MD, University Hospital, London, Ontario, Canada; and Richard A. Frank, MD, PhD, Wilmington, Delaware.

Supported in part by a grant from ICI Pharmaceuticals Group, a business unit of Zeneca, Inc., Wilmington, Delaware.

Editor's note: Dr. Rock, in addition to receiving research grant support from ICI Pharmaceutical Group, has also served as a paid consultant to the same organization. Drs. Truglia and Caplan are full-time employees of ICI Pharmaceuticals Group.

Endometriosis, a common gynecologic condition affecting 2.5-15% of women of reproductive age,¹ depends on cyclical ovarian steroids, especially estradiol (E2), and is associated with debilitating symptoms.² The primary sequelae of endometriosis include pelvic pain and endometrial implants,³ as well as dysmenorrhea and dyspareunia.⁴ The relationship between endometriosis and infertility is well accepted and documented.⁵ The goals of therapy include relief of symptoms, resolution of existing lesions, and prevention of new lesions.²

Among the currently available treatment approaches for endometriosis, only extirpative therapy offers the possibility of a permanent cure.⁶ Although various therapies have provided clinical benefit, danazol, which has androgenic and anabolic properties, has

been used most widely. However, because of the troublesome side effects associated with danazol, the search for effective and safe alternatives has continued.⁷

The ability of GnRH agonists to produce amenorrhea and anovulation by inducing hypoestrogenism through down-regulation of pituitary GnRH receptors has led to their use in the treatment of endometriosis. Given by injection, infusion, or via the nasal mucosa, GnRH agonists have demonstrated efficacy at least equivalent to that of danazol in the treatment of endometriosis in premenopausal women.^{2,8-10}

Recent studies have focused on Zoladex (goserelin acetate implant; ICI Pharmaceuticals, Wilmington, DE), a newer, potent synthetic GnRH agonist. Clinical studies have shown that this agent, in a biodegradable, sustained-release, subcutaneous implant formulation, effectively suppresses serum concentrations of E2 to postmenopausal levels within 2 weeks,¹¹ reduces the size of endometrial implants, decreases the revised American Fertility Society (AFS) score (an indicator of the degree of endometriosis),¹² and improves the subjective symptoms associated with endometriosis.¹³ In addition, this implant formulation has proven to be convenient for the patient because it requires administration only once a month.

This report compares the efficacy and safety of Zoladex implant and oral danazol in premenopausal women with endometriosis in a randomized, open study conducted at 17 centers. Danazol (Danocrine; Winthrop Laboratories, New York, NY) was chosen for comparison because it is approved for the treatment of endometriosis and is commonly used in clinical practice.

Materials and Methods

Three hundred fifteen premenopausal women, 20-42 years of age, with stages I-IV endometriosis (revised AFS classification) confirmed by laparoscopy or laparotomy were randomized into a multicenter, open parallel study. The revised AFS score had to be 2 or more for active peritoneal and ovarian implants to be included. Other inclusion criteria required symptomatic (total pelvic symptom score 3 or more) or asymptomatic disease, with or without infertility. All subjects gave written informed consent.

The women were randomized in a 2:1 ratio (208 Zoladex:107 danazol, to gain more experience with the new Zoladex treatment) to receive 24 weeks of therapy. A 3.6-mg dose of Zoladex was administered subcutaneously as an implant into the anterior abdominal wall every 28 days beginning on day 2 or 3 of the menstrual cycle; dose adjustment was not permitted.

The initial danazol dose of 400 mg orally twice daily could be adjusted to 200 mg thrice daily, 200 mg twice daily, or followed by any one of these three regimens if clinically indicated. Therapy with danazol was initiated on day 2 or 3 after the commencement of menstruation.

During treatment the patients were evaluated every 4 weeks; afterward they were followed for 48 weeks at 8-week intervals. Before initiating therapy, the subjects were examined and questioned regarding symptoms, and then had laparoscopy or laparotomy. To assess efficacy, post-treatment laparoscopy or laparotomy was performed between study weeks 23-25 by the same physician who performed the pre-therapy procedure (with occasional exception).

Pelvic symptoms (dysmenorrhea, dyspareunia, pelvic pain) and signs (pelvic induration, pelvic tenderness) were graded as: 0, absent; 1, mild; 2, moderate; or 3, severe. The patients were classified as symptomatic or asymptomatic based on the total pelvic symptom score, obtained by adding the scores for each of the three symptoms. A symptomatic patient was defined as having a total pelvic symptom score of 3 or more. In symptomatic patients, the scores for each of the three symptoms and the two physical signs, determined by physical examination using uniform guidelines, were summed to yield a total subjective score, which was used to compare treatment groups.

At each visit, the women were questioned about the presence or absence of recognized pharmacologic effects of therapy. Blood and urine samples were obtained for a variety of hematologic, biochemical, and endocrinologic assessments before, during, and after therapy. Dual-photon absorptiometry was used at three study centers to determine the effect of treatment on bone mineral density in the lumbar spine at the L2-L4 level.

All tests for statistical significance were two-tailed. All randomized subjects were included in the overall analysis of treatment outcome. The proportion of responders was analyzed using logistic regression, with the pre-treatment total revised AFS score as a covariate. In addition to the overall analysis of treatment outcome, analysis of covariance was performed on the change in score from pre-treatment to post-treatment using the pre-treatment score as a covariate for total, total adhesions, and total implants revised AFS scores. The total subjective score and total pelvic symptoms score were analyzed using analysis of covariance at each visit for the change in score from pre-treatment to post-treatment. Safety data were reported for all subjects by treatment received. Percent change from pre-treatment in bone mineral density measurements was calculated for each time point. Unless specified, obser-

Table 1. Baseline Characteristics of Randomized Subjects

	Zoladex (n = 208)	Danazol (n = 107)
Subjective characteristics		
Symptomatic	134 (64.4%)	67 (62.6%)
Asymptomatic	74 (35.6%)	40 (37.4%)
Objective characteristics		
R-AFS stage I	32 (15.4%)	26 (24.3%)
R-AFS stage II	81 (38.9%)	38 (35.5%)
R-AFS stage III	88 (42.3%)	36 (33.6%)
R-AFS stage IV	7 (3.4%)	7 (6.5%)

R-AFS = revised American Fertility Society endometriosis classification.

variations of changes reported were not found to be statistically significant; often this was because of insufficient statistical power to assess adequately the comparison in question.

Results

Table 1 presents the baseline characteristics for the 315 patients. The means for age and weight were 30.4 years and 59.9 kg for the Zoladex group and 29.7 years and 60.9 kg for the danazol group. About one-third of the women in each study group had received prior treatment for endometriosis.

The protocol stated that subjects with stage IV endometriosis were to be excluded from the trial. The rationale for this exclusion was based on general knowledge that many of the anatomical characteristics associated with stage IV endometriosis would show little or no physical response to hormonal therapy alone. However, some investigators believed that sig-

nificant components of stage IV endometriosis could benefit from treatment and enrolled 14 such subjects into the trial.

"Treatment success" was defined as a 50% or greater reduction in the revised AFS score from the pre-treatment value. All randomized subjects, including the stage IV subjects, were included in the analysis of treatment success. However, regardless of outcome, the 14 stage IV patients were included in this analysis as treatment failures. Further, analysis unexpectedly revealed that the stage IV subjects did respond to hormonal therapy, as detailed below. As "protocol violators," these subjects were not included in the analysis of change in the revised AFS score or subjective score.

Both Zoladex (Figure 1) and danazol (Figure 2) treatments significantly ($P < .0001$) reduced the mean total subjective symptoms scores during and after therapy. There were no statistically significant differences between therapies during treatment or follow-up, except at 16 weeks after therapy (week 40). Total subjective scores were lower among danazol-treated women at week 40 ($P < .05$). The basis for this exception is not apparent.

Both therapies effected a marked and clinically significant ($P < .0001$) reduction in total pelvic symptoms scores, which was maintained throughout the treatment and post-treatment periods. Differences between the therapies were not statistically significant, except at week 40 as noted above.

Overall, treatment was successful (50% or more decrease in the revised AFS score versus pre-treatment) in 121 of the patients (58.2%) treated with Zoladex, compared with 44 (41.1%) treated with dan-

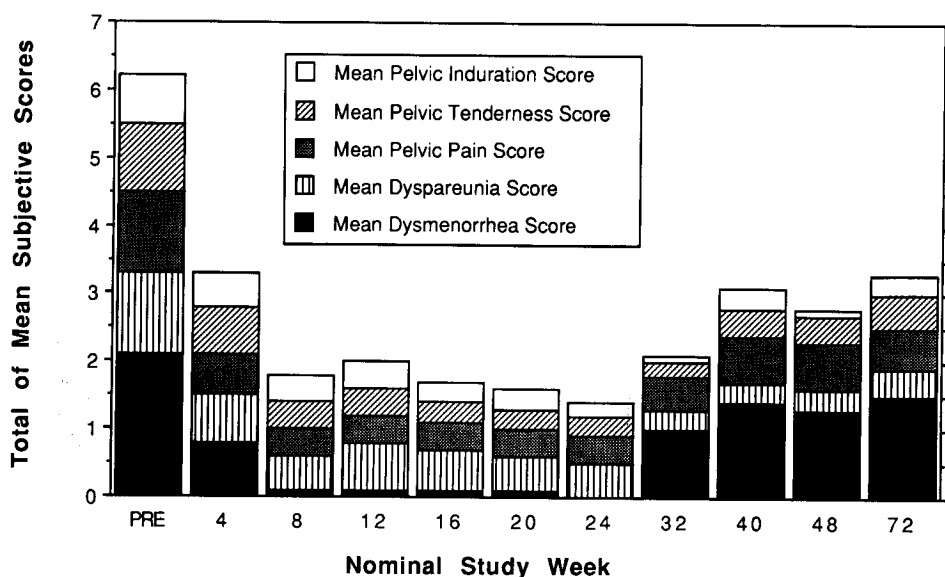
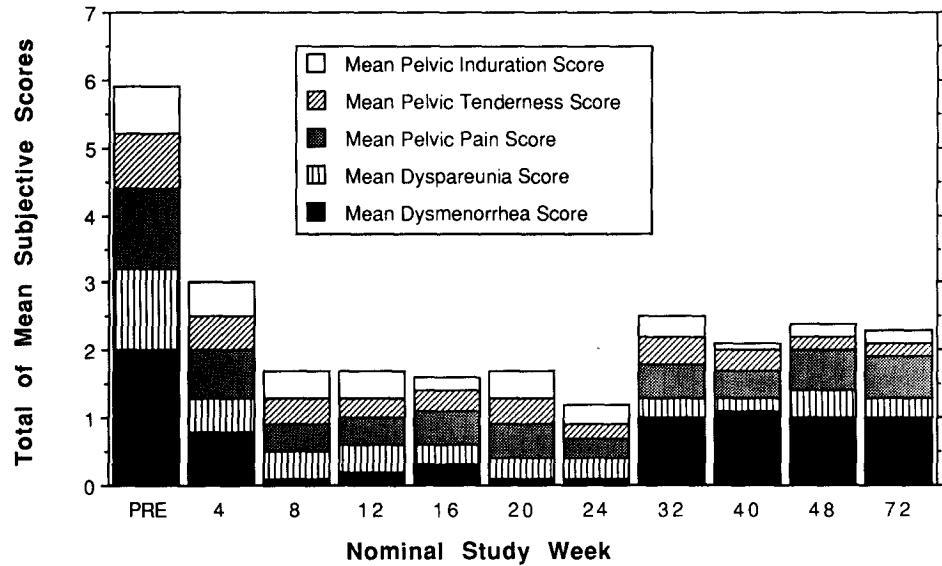


Figure 1. Mean subjective symptoms scores during and after treatment with Zoladex implant.

Figure 2. Mean subjective symptoms scores during and after treatment with danazol.



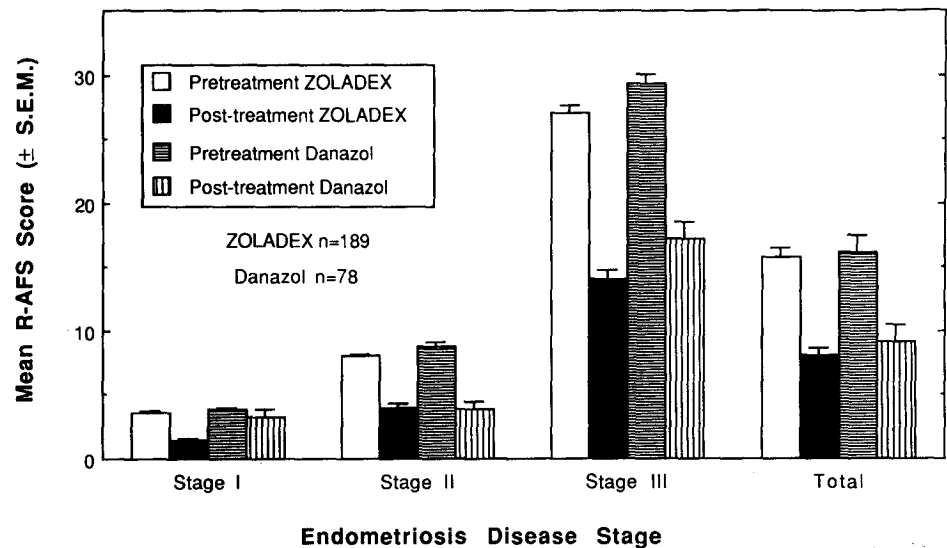
azol after 24 weeks of therapy. The odds ratio for successful response favored Zoladex by a factor of 2.3 ($P = .003$; 95% confidence interval [CI] 1.3–3.9). When the patients with stage IV disease were evaluated for response instead of being defined as treatment failures, the proportion of treatment successes was significantly ($P = .01$) higher among Zoladex-treated women (122, 58.7%) than in those treated with danazol (47, 43.9%).

Figure 3 shows the mean revised AFS scores before and after treatment. There was no significant between-group difference in mean percent reduction in the scores. The mean percent reduction in the total score following 24 weeks of treatment was 53% for the Zoladex group, compared with 33% for the danazol-treated patients. The mean percent reductions in the

implant scores were 56 and 46% for the Zoladex and danazol groups, respectively. The mean percent reductions in the adhesion scores were 19 and 18%, respectively.

As shown in Figure 4, Zoladex therapy induced a rapid fall in mean serum E2 levels to concentrations consistent with the postmenopausal state (below 73 pmol/L), whereas on average, danazol maintained serum E2 levels in the early follicular phase range (below 367.1 pmol/L). The suppressive effect of Zoladex on serum E2 levels was significantly greater than that of danazol ($P = .0001$). Progesterone levels remained in the low follicular phase range (0.3–4.8 nmol/L) throughout the treatment period in both study groups. In all patients throughout the study, LH and FSH concentrations were suppressed to follicular phase

Figure 3. Mean revised American Fertility Society (R-AFS) scores before and after treatment with Zoladex and danazol. SEM = standard error of the mean.



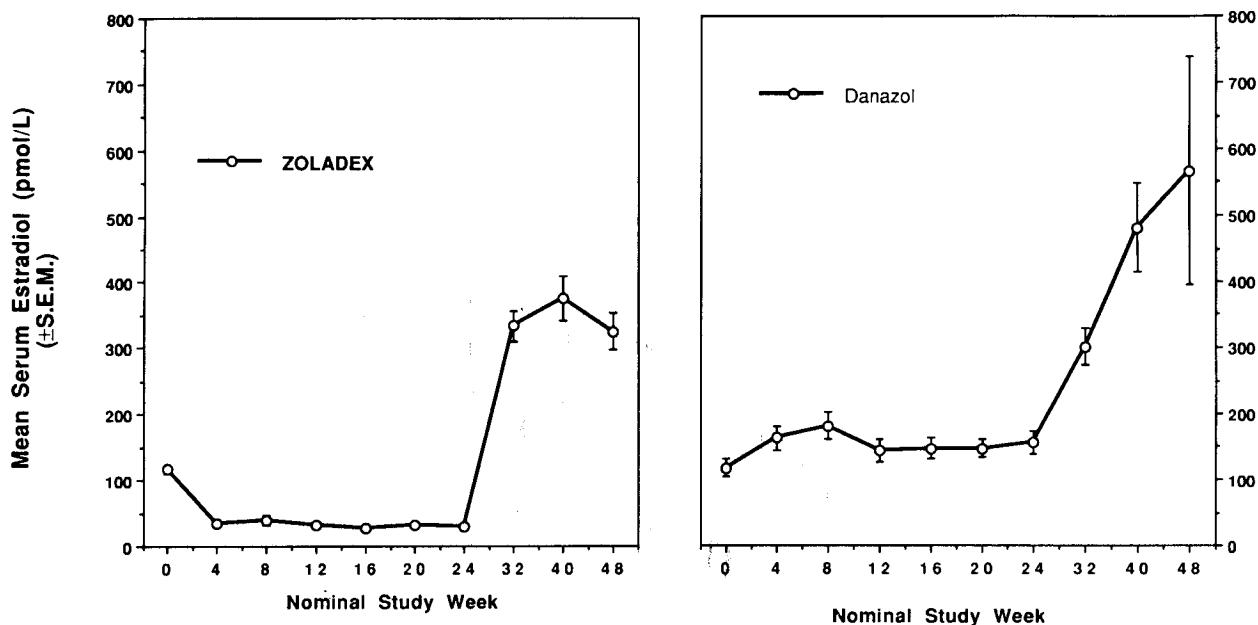


Figure 4. Mean serum estradiol levels during and after treatment. SEM = standard error of the mean.

levels. At week 4 of therapy, those treated with Zoladex had a larger decline in mean LH and FSH levels versus pre-treatment than did those in the danazol group ($P < .0001$), suggesting that danazol does not have a profound effect on gonadotropin secretion. In both treatment groups, LH and FSH levels approached or exceeded pre-treatment levels within 8 weeks after therapy completion.

By study week 8, 185 patients in the Zoladex group (88.9%) and 63 danazol subjects (58.8%) became amenorrheic (defined as no bleeding or no more than 2 days of spotting per month). For the Zoladex group, the median time to return of menses was 48 days from the last injection (4 weeks after completion of therapy), compared with 46 days following the last administration of danazol.

All patients receiving treatment, regardless of inclusion in the efficacy analysis, were included in the safety analyses. During treatment, 15 patients (7.2%) in the Zoladex group and 18 (16.8%) in the danazol group withdrew from the study. Six (2.9%) assigned to Zoladex therapy and 13 (12.1%) to danazol withdrew because of adverse events. The most common reason for withdrawal after treatment was for ovulation induction therapy.

The most frequent adverse experiences reported were those expected based on the pharmacologic action of each drug (Figure 5). A local reaction, such as mild erythema at the injection site, was noted in 3% of Zoladex administrations (42 of 1218 implants); no woman withdrew because of a local reaction. Zoladex-treated patients reported a higher incidence of hypo-

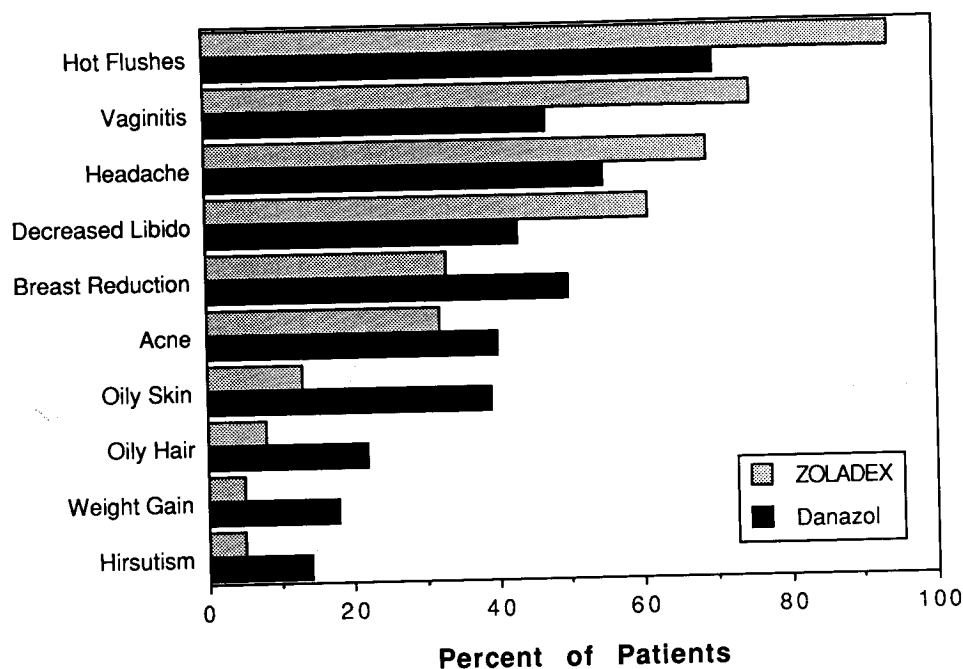
estrogenic effects, such as hot flushes, vaginal dryness, headache, and decreased libido; danazol-treated patients reported a higher incidence of androgenic effects, such as acne, oily skin or hair, weight gain, and hirsutism. In addition, clinically significant increases in weight, as defined by the investigator for that subject, were reported in 17.2% of danazol-treated women and in 12.2% of those treated with Zoladex.

Bone mineral density assessments were performed before and after therapy in 58 patients. The mean percent losses following 12 and 24 weeks of Zoladex therapy were 3.6% ($n = 37$; 95% CI -5.0 to -2.2) and 5.4% ($n = 38$; 95% CI -7.2 to -3.6), respectively (Figure 6). After treatment, the losses in Zoladex-treated subjects were 3.3% ($n = 27$; 95% CI -5.7 to -0.9) and 7.6% ($n = 11$; 95% CI -12.5 to -2.7) at weeks 48 and 72, respectively. Danazol-treated women showed a mean percent loss in bone mineral density at week 12 of 0.4% ($n = 17$; 95% CI -2.9 to $+2.1$) and a mean percent increase of 1.0% ($n = 17$; 95% CI -1.4 to $+3.4$) at week 24. There were also post-treatment losses of 1.5% ($n = 9$; 95% CI -4.8 to $+1.9$) at week 48 and 1.5% ($n = 9$; 95% CI -3.4 to $+0.5$) at week 72 in danazol-treated patients. As evidenced by the wide variation, follow-up data were insufficient to determine accurately the degree of reversibility of bone mineral density loss.

Discussion

Medical management of endometriosis has included the use of danazol and progestogens, with or without

Figure 5. The most commonly reported adverse experiences during treatment.



estrogens.⁵ The introduction of GnRH agonists has expanded the physician's choices for effective therapy for endometriosis.^{8,14} Patients are more tolerant of the symptoms of medical menopause due to GnRH agonists (eg, hot flushes and vaginal dryness) than they are of those associated with danazol (eg, acne, weight gain).¹⁵ In this comparative trial, Zoladex was better tolerated than danazol, as evidenced by fewer patient withdrawals due to adverse events (3 versus 12%, respectively).

As a potent GnRH agonist, Zoladex provides rapid and complete suppression of E2. The subcutaneous

route of administration provides a more consistent biologic efficacy profile than daily intranasal administration,¹⁶ and the implant formulation provides a convenient (once a month), effective dosing regimen.

Whereas some investigators have suggested that patients with endometriosis are not at additional risk of bone loss,¹⁷ others have documented losses in cortical and trabecular bone similar to those reported in perimenopausal women.¹⁸ Of concern, therefore, is the possibility that prolonged use of GnRH agonists may lead to clinically significant bone loss.¹⁹ In this study, treatment with Zoladex resulted in a mean bone

Figure 6. Mean percent changes in bone mineral density following Zoladex or danazol treatment. SEM = standard error of the mean.

