Subcutaneous injection of depot medroxyprogesterone acetate compared with leuprolide acetate in the treatment of endometriosis-associated pain

William D. Schlaff, M.D.,[a] *Sandra Ann Carson, M.D.,*[b] *Anthony Luciano, M.D.,*[c] *Doug Ross, M.D.,*[d] *and Agneta Bergqvist, M.D.*[e]

[a] University of Colorado Health Sciences Center, Aurora, Colorado; [b] Baylor College of Medicine, Houston, Texas; [c] University of Connecticut School of Medicine, New Britain, Connecticut; [d] Pfizer Inc, New York, New York; and [e] Karolinska Institute, Stockholm, Sweden

Objective: To compare the efficacy and safety of SC depot medroxyprogesterone acetate (DMPA-SC 104) with that of leuprolide acetate in treatment of endometriosis.
Design: Phase 3, multicenter, randomized, evaluator-blinded, comparator-controlled trial.
Setting: Clinical trial sites in Canada and United States.
Patient(s): Two hundred seventy-four women with surgically diagnosed endometriosis.
Intervention(s): Intramuscular injections of DMPA-SC (104 mg) or leuprolide acetate (11.25 mg), given every 3 months for 6 months, with 12 months of posttreatment follow-up.
Main Outcome Measure(s): Reduction in five endometriosis symptoms or signs (dysmenorrhea, dyspareunia, pelvic pain, pelvic tenderness, pelvic induration); change in bone mineral density (BMD), hypoestrogenic symptoms, bleeding, and weight.
Result(s): The depot medroxyprogesterone acetate given SC was statistically equivalent to leuprolide in reducing four of five endometriosis symptoms or signs at the end of treatment (month 6) and in reducing all five symptoms after 12 months' follow-up (month 18). Patients in the DMPA-SC 104 group showed significantly less BMD loss than did leuprolide patients at month 6, with scores returning to baseline at 12 months' follow-up. No statistically significant differences in median weight changes were observed between groups. Compared with leuprolide, DMPA-SC 104 was associated with fewer hypoestrogenic symptoms but more irregular bleeding.
Conclusion(s): Efficacy of DMPA-SC 104 was equivalent to that of leuprolide for reducing endometriosis-associated pain, with less impact on BMD and fewer hypoestrogenic side effects but more bleeding. (Fertil Steril® 2006;85:314–25. ©2006 by American Society for Reproductive Medicine.)

Key Words: Endometriosis, depot medroxyprogesterone acetate, leuprolide, bone mineral density, hypoestrogenic symptoms

Endometriosis is a chronic and recurrent disease that is characterized by the presence of endometrial-like tissue (glands and stroma) outside the uterine lining. Goals of treatment for patients with endometriosis include reducing symptoms, arresting the growth and activity of endometriotic lesions, and restoring normal anatomy (1–3). A number of new treatment approaches, particularly medical options, have been described in recent years.

Medroxyprogesterone acetate and other progestins have been used as therapy for endometriosis worldwide for 40 years (4). Progestins provoke marked decidualization, acyclicity, and atrophy of eutopic and ectopic endometrium (5). They also induce dose-related anovulation and amenorrhea and decrease intraperitoneal inflammation (6). Progestins usually are well tolerated and generally have limited metabolic side effects at low doses (4). In view of their safety profile and demonstrated clinical efficacy in a wide range of dosing and delivery options, progestins represent an alternative treatment option for endometriosis-associated pain.

This study investigated the use of a new, subcutaneous formulation of depot medroxyprogesterone acetate 104 mg/0.65 mL (DMPA-SC 104) as a treatment for endometriosis-related pain. This formulation offers a lower-dose alternative to the IM formulation of depot medroxyprogesterone acetate (DMPA 150 mg/mL IM), which has an established safety history that is based on 40 years of its worldwide use as a contraceptive and on more than a decade of use in the United States (7–11). The DMPA-SC 104 formulation was developed specifically for SC administration. Its composition and ratio of ingredients differs from that of the IM formulation. As such, DMPA-SC 104 is a unique formulation that cannot be compounded from the IM formulation.

The primary efficacy objective of this study was to assess the equivalence (i.e., noninferiority) of DMPA-SC 104, as compared with leuprolide acetate (2, 12, 13), in the reduction

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Reprint requests: William Schlaff, M.D., University of Colorado Health Sciences Center–AOP,1635 North Ursula Street, Mail Stop F-701, Box 6510, Aurora, Colorado 80045 (FAX: 720-848-1662; E-mail: william.schlaff@uchsc.edu).

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of endometriosis-associated pain. The primary safety objective was to evaluate differential effects of these treatments on bone mineral density (BMD) after 6 months of treatment relative to baseline and to assess BMD recovery after 12 months of post-treatment follow-up (month 18). Secondary metabolic and symptom side effects evaluated included hypoestrogenic symptoms, bleeding patterns, quality of life, and adverse events.

MATERIALS AND METHODS

Patients and Study Design

This phase 3, multicenter, randomized, evaluator-blinded, comparator-controlled clinical trial compared the efficacy and safety of DMPA-SC 104 with that of leuprolide acetate in the treatment of endometriosis. The total duration of the study was 18 months, including 6 months of active treatment (DMPA-SC 104 or leuprolide) and 12 months of follow-up, during which time neither drug was used. This study was conducted at 7 sites in Canada and at 43 sites in the United States. Institutional review board approval was obtained at all participating sites.

Patients included in this trial were premenopausal women who ranged in age from 18 to 49 years, with persistent symptoms of pain caused by endometriosis (surgically diagnosed within the previous 42 months). A patient's pain must have returned to its previous level within 30 days after a diagnostic laparoscopy or within 3 months after laparoscopy or laparotomy with surgical treatment, and it must have persisted for a minimum of 3 months.

Pain was evaluated by using the modified Biberoglu and Behrman (B and B) symptom scale, on which symptoms are rated on a scale of 0 (no discomfort) to 3 (severe symptoms) in each of five categories, namely, dysmenorrhea, dyspareunia, pelvic pain, pelvic tenderness, and induration. Patients enrolled in this trial were required to have symptoms with a total score of at least 6 (of a possible 15), including a total of at least two in the symptoms of dysmenorrhea, dyspareunia, and pelvic pain. If a patient was sexually inactive for reasons other than endometriosis, the total score must have been at least four, with scores of at least two from both dysmenorrhea and pelvic pain. Women were excluded if their baseline BMD at the lumbar spine and hip had a score that was less than 1.0 SD below the mean for peak adult bone mass. All sexually active women were advised to use nonhormonal contraception throughout the study.

Study Treatments and Assessments

Patients enrolled in this trial were randomized 1:1 to receive either DMPA-SC 104 (104 mg/0.65 mL given by SC injection) or leuprolide (11.25 mg given by IM injection). Both treatments were initiated within the first 5 days of a normal menstrual cycle at visit 1, and a second injection was given 3 months (91 ± 7 days) later, for a total duration of 6 months of active treatment.

Patients were seen for a follow-up visit on a monthly basis, at which time a pelvic examination was performed. Patient diaries were reviewed at each visit for evaluation of symptoms and bleeding patterns. Side effects or other health concerns also were elicited. After 6 months of treatment, patients then entered the follow-up phase. A patient diary, which included the endometriosis-impact information, was distributed every 3 months during the follow-up period. No bleeding pattern information was collected during follow-up. Bone mineral density was evaluated at baseline, after 6 months of treatment, and during the follow-up phase at 6 and 12 months after treatment.

In this evaluator-blinded study, the principal investigator and any designated subinvestigators and study coordinators at each center were blinded to the randomization of each patient. To maintain the blind, an independent person maintained the randomization code, received the study syringes, and administered the study medication. This individual was instructed not to reveal the randomization code or to discuss the patient's route of administration with clinical study site personnel. Patients also were instructed not to discuss the route of administration.

Study Endpoints

The primary efficacy endpoint was the reduction of pain (dysmenorrhea, dyspareunia, pelvic pain, pelvic tenderness, and induration) after 6 months of treatment compared with baseline, as measured by the modified B and B symptom scale. For each of the five categories, a positive response was defined as an improvement from baseline of at least one point on the scale.

Clinical equivalence between DMPA-SC 104 and leuprolide for the reduction of endometriosis-associated symptoms and signs was defined as statistically equivalent improvement in at least four of the five categories at end of treatment (month 6). A mean decrease of four points in the composite score (i.e., the total score of all five categories) after 6 months of treatment relative to baseline was considered clinically meaningful for each of the two treatment groups. Analysis also included changes in each symptom or sign score as well as in the composite score after 12 months of follow-up (month 18) compared with baseline.

The primary safety endpoint was the effect of treatment on BMD after 6 months of treatment relative to baseline and BMD recovery after 12 months of follow-up (month 18). Secondary endpoints included changes in hypoestrogenic symptoms as measured by the Kupperman Index and the occurrence of hot flushes, hormonal values (serum E_2, sex hormone–binding globulin, and P levels), side effects, bleeding patterns, blood pressure, body weight, and safety laboratory values. Information describing standard bleeding patterns was collected from the endometriosis-impact diaries and was analyzed by using a 90-day reference period. The number of bleeding or spotting days in each reference period was evaluated for each treatment group.

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