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The Effect of Combined Estrogen and Progesterone Hormone Replacement Therapy on Disease Activity in Systemic Lupus Erythematosus: A Randomized Trial

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Background: **There is concern that exogenous female hormones may worsen disease activity in women with systemic lupus erythematosus (SLE).**

Objective: **To evaluate the effect of hormone replacement therapy (HRT) on disease activity in postmenopausal women with SLE.**

Design: **Randomized, double-blind, placebo-controlled noninferiority trial conducted from March 1996 to June 2002.**

Setting: **16 university-affiliated rheumatology clinics or practices in 11 U.S. states.**

Patients: **351 menopausal patients (mean age, 50 years) with inactive (81.5%) or stable-active (18.5%) SLE.**

Interventions: **12 months of treatment with active drug (0.625 mg of conjugated estrogen daily, plus 5 mg of medroxyprogesterone for 12 days per month) or placebo. The 12-month follow-up rate was 82% for the HRT group and 87% for the placebo group.**

Measurements: **The primary end point was occurrence of a severe flare as defined by Safety of Estrogens in Lupus Erythematosus, National Assessment–Systemic Lupus Erythematosus Disease Activity Index composite.**

Results: **Severe flare was rare in both treatment groups: The 12-month severe flare rate was 0.081 for the HRT group and 0.049 for the placebo group, yielding an estimated difference of 0.033 ($P = 0.23$). The upper limit of the 1-sided 95% CI for the treatment difference was 0.078, within the prespecified margin of 9% for noninferiority. Mild to moderate flares were significantly increased in the HRT group: 1.14 flares/person-year for HRT and 0.86 flare/person-year for placebo (relative risk, 1.34; $P = 0.01$). The probability of any type of flare by 12 months was 0.64 for the HRT group and 0.51 for the placebo group ($P = 0.01$). In the HRT group, there were 1 death, 1 stroke, 2 cases of deep venous thrombosis, and 1 case of thrombosis in an arteriovenous graft; in the placebo group, 1 patient developed deep venous thrombosis.**

Limitations: **Findings are not generalizable to women with high-titer anticardiolipin antibodies, lupus anticoagulant, or previous thrombosis.**

Conclusions: **Adding a short course of HRT is associated with a small risk for increasing the natural flare rate of lupus. Most of these flares are mild to moderate. The benefits of HRT can be balanced against the risk for flare because HRT did not significantly increase the risk for severe flare compared with placebo.**

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This trial is registered as NCT00000419 on http://clinicaltrials.gov.

Since systemic lupus erythematosus (SLE) exhibits a female bias, disease activity may be sex-determined or hormonally regulated. Exogenous estrogens are generally not prescribed for women with SLE because of the widely held view that these medications can activate disease. Concern is based on the 10-fold greater incidence of SLE in women than men (1), disease onset after menarche and before menopause, skewing of estrone metabolism toward more feminizing 16-hydroxylated metabolites (2, 3), exacerbation of murine lupus by estrogens (4), anecdotes of disease flares during exogenous hormone therapy (5–13), a retrospective study in patients with preexisting renal disease (14), and the ability of estrogens to augment murine B-cell survival and autoreactivity (15). However, health issues specific to women warrant attention and need to be confronted in patients with SLE. Although long-term HRT is not currently recommended, short-term salutary effects include treatment of hot flashes and vaginal dryness. Because of premature ovarian failure secondary to cyclophosphamide treatment, some women with SLE may require longer exposures to HRT. A further consideration is increased risk for osteoporosis after exposure to glucocorticoids or secondary to the disease itself.

Although the levels of circulating 17β-estradiol reached during HRT are about one fifth of peak menstrual

See also:

Print

Editors' Notes 954
Editorial comment. 1014
Summary for Patients. I-22

Web-Only

Appendix
Appendix Table
Conversion of figures and tables into slides

Context

Clinicians sometimes avoid hormone replacement therapy (HRT) in women with systemic lupus erythematosus (SLE) because they think estrogens activate the disease.

Contribution

In this multicenter, double-blind trial, 351 menopausal patients with SLE were randomly assigned to HRT or placebo for 12 months. Severe flares were infrequent in both groups, and were not significantly increased in women taking HRT. Women taking HRT had more mild to moderate flares than did those taking placebo (1.14 flares vs. 0.86 flare/person-year). Four women taking HRT and 1 taking placebo had thromboembolic events.

Implications

Hormone replacement therapy given for 1 year does not significantly increase the risk for severe flare but does increase the risk for mild to moderate flares in menopausal women with SLE.

–The Editors

cycle levels (16) and HRT has roughly one fourth to one fifth the estrogenic potency of current "low-dose" oral contraceptives, the added "estrogen load" over barely detectable postmenopausal levels might induce or exacerbate SLE. While definitive studies in mice regarding the role of sex hormones in disease phenotype may be feasible, to date no compelling data for or against a detrimental effect of estrogen in patients with SLE are available. Sanchez-Guerrero and colleagues (17) identified a modestly increased relative risk (2.1 [95% CI, 1.1 to 4.0]; $P = 0.011$) for the development of SLE in a "naive" cohort of nurses exposed to HRT. Meier and colleagues (18), using the United Kingdom–based General Practice Research Database (41 patients with SLE; 34 patients with discoid lupus; and 295 age-, sex-, and practice-matched controls), reported a significantly increased risk for SLE or discoid lupus among current users exposed for 2 or more years (odds ratio, 2.8). With respect to established SLE, Arden and colleagues' retrospective study (19) reported no increase in flare rate in 30 patients taking HRT compared with 30 age-matched patients who never used HRT. These results are similar to those observed in 2 other retrospective studies (20, 21). In a limited prospective study, Mok and colleagues (22) found no significant difference in flare rate between HRT and placebo groups. Finally, Sanchez-Guerrero and colleagues (23) reported no differences in flare rates in 106 postmenopausal Mexican women with SLE randomly assigned to HRT or placebo for 24 months.

Informed decisions on the use of HRT in women with SLE require prospective studies in large numbers of patients. Accordingly, the Safety of Estrogens in Lupus Erythematosus, National Assessment (SELENA) trial—which comprised 2 separate randomized, placebo-controlled, multicenter studies (HRT vs. placebo, reported here, and oral contraceptives vs. placebo, forthcoming)—was initiated. The HRT-SELENA trial sought to determine the effect of conjugated estrogens and cyclic progestins on disease activity in postmenopausal women with SLE. The study was designed as a noninferiority trial to establish that HRT is not inferior to placebo with respect to risk for a severe flare.

METHODS

Definition of Disease Activity and Flare

Investigators from 5 centers that constituted the core SELENA group, authors of a previous retrospective study (20), met before recruitment to revise the definitions of the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (24) instrument itself, so that the organ system descriptors would include ongoing activity (in addition to new and recurrent activity). Specifically, rash, alopecia, and oral ulcers are scored if they are ongoing, not just recurrent, in order to capture persistent activity. Hematuria identified by urinalysis was not counted on the SELENA–SLEDAI instrument if attributed to menstrual bleeding.

The SELENA–SLEDAI composite (25) comprised 3 elements: 1) the SELENA–SLEDAI instrument; 2) new or worse activity, medication changes, and hospitalizations not captured in the instrument (b, c, and d in the following paragraphs); and 3) the physician's score on the global assessment visual analogue scale.

Mild to moderate flares were defined as 1 or more of the following: a) greater than 3-point change in SELENA–SLEDAI instrument score, with total score of 12 or less; b) new or worsening discoid, photosensitive, or other rash attributable to lupus (including lupus profundus, cutaneous vasculitis, or bullous lupus), nasopharyngeal ulcers, pleuritis, pericarditis, arthritis, or fever not attributable to infection; c) increase in prednisone dosage but not to greater than 0.5 mg/kg of body weight per day; d) initiation of therapy with either hydroxychloroquine or nonsteroidal anti-inflammatory drugs, without an increase in prednisone dosage; and e) change in the physician's global assessment score of 1.0 or more but remaining 2.5 or less.

Severe flares were defined as 1 or more of the following: a) SELENA–SLEDAI instrument score greater than 12; b) new or worsening central nervous system involvement, vasculitis, glomerulonephritis, myositis, thrombocytopenia (platelet count $<60 \times 10^9$ cells/L), or hemolytic anemia (hemoglobin level <70 g/L or decrease in hemoglobin level >30 g/L over a 2-week period), each requiring doubling of corticosteroid dosage to a final dosage greater than 0.5 mg/kg per day or acute hospitalization; c) any manifestation requiring an increase in dosage of prednisone or equivalent drug to greater than 0.5 mg/kg per day, or initiation of therapy with cyclophosphamide, azathioprine, mycophenolate mofetil, or methotrexate; d) hospitalization for lupus activity; and e) change in physician's global assessment score from baseline to greater than 2.5.

The SELENA investigators agreed upon these definitions for reliably discriminating severe flares from mild to moderate flares. Symptoms attributed to menopause, such as hot flashes, fatigue, and irritability, did not overlap with the definitions of flares. The core investigators then tested these new definitions (the SELENA–SLEDAI composite) by using patient scenarios from the Hopkins Lupus Cohort (26).

Study Sample

Patients entered this multicenter, randomized, double-blind, placebo-controlled trial between March 1996 and June 2002 (when the enrollment target was met). In total, 351 patients with SLE were enrolled from 16 participating clinical sites (see **Appendix Table**, available at www.annals.org). Institutional review boards of all participating sites approved the protocol and consent forms before initiation of the study, and informed consent was obtained from all patients before enrollment. Throughout the study, all institutional review boards were notified of adverse events occurring at all sites.

At entry, all patients fulfilled at least 4 of the American College of Rheumatology (ACR) criteria for the classification of SLE (27) and had serum follicle-stimulating hormone levels greater than 40 mIU, follicle-stimulating hormone levels above the range for premenopausal women in a given laboratory, or amenorrhea for 6 months (among patients >50 years of age). Patients were stratified as having either inactive disease (a SELENA–SLEDAI instrument score that was 4 or less and had remained stable or improved in the previous 3 months; prednisone dosage that was 0.5 mg/kg per day or less and had not increased in the previous 3 months) or stable-active disease (a SELENA–SLEDAI instrument score that ranged from 5 to 12 and had remained stable or improved in the previous 3 months; prednisone dosage that was 0.5 mg/kg per day or less and had not increased in the previous 3 weeks). Additional immunosuppressive drugs (cyclophosphamide, azathioprine, methotrexate, and mycophenolate mofetil) were permitted if the dose had been stable for 2 months preceding enrollment.

Exclusion criteria were uncontrolled high blood pressure requiring frequent change in medication or the finding of a diastolic blood pressure greater than 95 mm Hg or systolic blood pressure greater than 145 mm Hg on 3 separate determinations; history of spontaneous superficial or deep venous thrombosis, arterial thrombosis, or pulmonary embolus; presence of high-titer anticardiolipin antibodies (>40 IgG phospholipid [GPL] units/mL, >40 IgM phospholipid [MPL] units/mL, or >50 IgA phospholipid [APL] units/mL) or demonstration of lupus anticoagulant; history of gynecologic or breast cancer; history of myocardial infarction; hepatic dysfunction or liver tumors; uncontrolled diabetes; congenital hyperlipidemia; migraines associated with neurologic sequelae; or unexplained vaginal bleeding.

Randomization and Treatment

Patients were randomly assigned in a 1:1 ratio to receive either 0.625 mg of conjugated estrogen (Premarin, Wyeth-Ayerst Pharmaceuticals, St. David's, Pennsylvania) daily plus an additional pill containing 5 mg of medroxyprogesterone (Provera, Wyeth-Ayerst Pharmaceuticals) for days 1 to 12 of the month or biologically inert placebo identical in appearance, dosage schedule, and packaging to the active regimen. The randomization scheme, generated by the study statistician, was stratified by study site and severity of disease (stable-active vs. inactive). Permuted blocks with variable block size (2 through 8) were used within each stratum for treatment assignments. The list of treatment assignments was forwarded to the pharmacist at the Hospital for Joint Diseases, New York, New York, who then allocated treatments to patients in a blinded fashion.

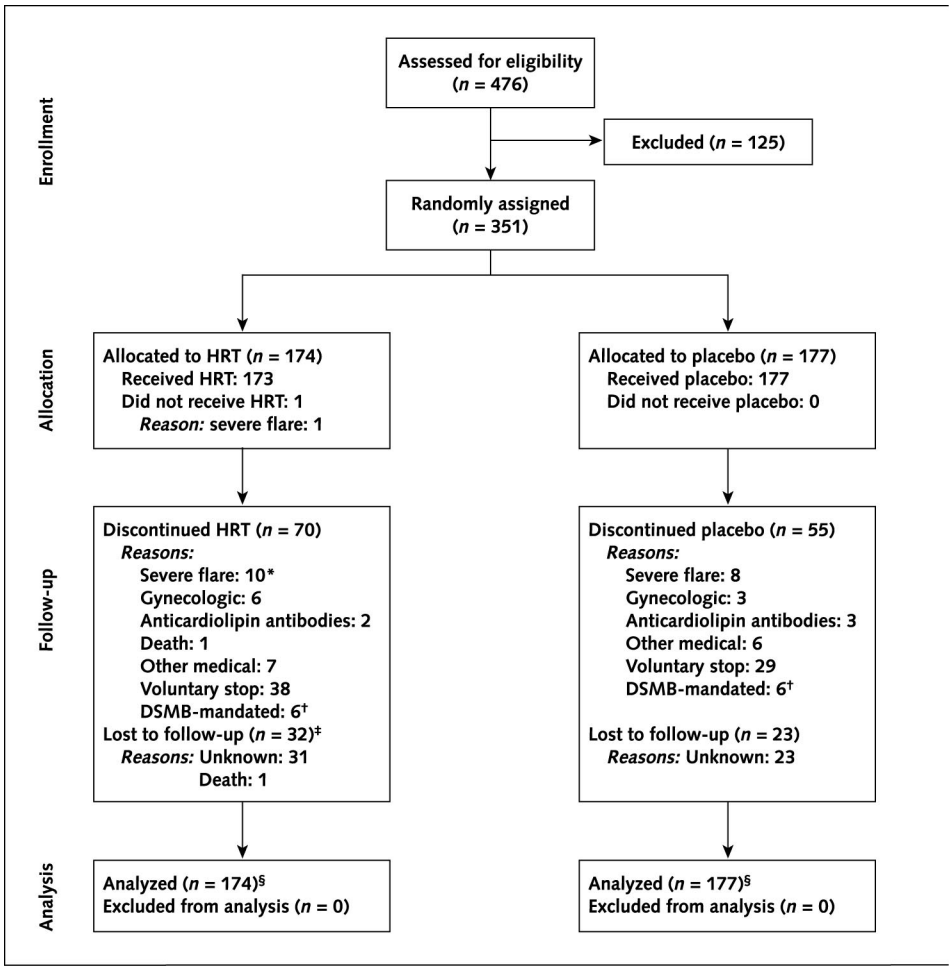
Enrollment and Follow-up Visits

At screening, a detailed history and physical examination were performed. Mammography must have been done within 1 year before enrollment. Laboratory tests included complete blood count; liver function tests (as part of a routine metabolic panel); lipid profile, including total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol; urinalysis (dipstick and microscopic examination); and 24-hour urine collection for measurement of creatinine clearance and protein excretion. Serologic profiles included measurement of antinuclear antibodies assayed by a HEp-2 cell line (BioRad Laboratories, Redmond, Washington), anti–double-stranded DNA antibodies determined by enzyme-linked immunosorbent assay (ELISA) (Diamedix, Miami, Florida), and C3/C4 determined by nephelometry (Dade Behring, Marburg, Germany) at the Hospital for Joint Diseases Clinical Immunology Laboratory; lupus anticoagulant by dilute Russell viper venom time test with confirmatory mixing studies at Johns Hopkins University, Baltimore, Maryland; and anticardiolipin antibodies by ELISA (standard β_2-glycoprotein I–dependent assay) at the Hospital for Special Surgery, New York, New York. Patients were seen at screening and qualifying visits, contacted 2 weeks after entry, and then seen at 1, 2, 3, 6, 9, and 12 months after entry (8 visits total).

Outcomes and adverse effects were ascertained at follow-up visits according to a history of current symptoms and medications, complete physical examination, and laboratory testing. Specific effects related to HRT were ascertained via a questionnaire designed by the study gynecologist. All information was recorded on case report forms. Adverse events were not rated as expected or unexpected but rather as attributable or not attributable to HRT.

The trial was prematurely terminated in August 2002 after the Women's Health Initiative (WHI) report of statistically increased risk for breast cancer, stroke, and cardiovascular disease in women taking HRT (28). However, all 351 patients were already enrolled. Twelve patients had

Figure 1. **Flow diagram of the hormone replacement therapy (*HRT*) portion of the Safety of Estrogens in Lupus Erythematosus, National Assessment (SELENA) trial.**



*Thirteen patients in the HRT group had a severe flare: Ten discontinued HRT because of severe flare, 1 had a flare after allocation but before taking the drug, 2 had a flare after discontinuing therapy with the drug (1 patient discontinued therapy because of medical reasons, and 1 discontinued voluntarily). †In consideration of the results of the Women's Health Initiative trial (28), the SELENA Data and Safety Monitoring Board (*DSMB*) mandated discontinuation of therapy with the study drug in September 2002. ‡Losses to follow-up are a subset of patients who discontinued therapy with the drug. §All patients were included in the intention-to-treat analysis according to the length of follow-up completed by each. A per protocol analysis to evaluate the primary end point (severe flare) was also performed; this analysis included only patients who completed 12 months of medication or who stopped taking medication because of severe flare and completed 12 months of follow-up (113 patients in the HRT group and 130 in the placebo group).

not completed the trial and were asked to discontinue therapy with the study medications, 8 of these 12 patients were followed for the full 12 months, and all were included in the intention-to-treat analysis (see **Figure 1** for flow diagram of the trial).

End Points

The primary end point was occurrence of a severe flare, and secondary end points were mild to moderate flares, as defined by the SELENA–SLEDAI composite.

Blinding

An estimated 80% of women taking sequential HRT will have regular withdrawal bleeding or spotting (29). To maintain blinding, patients were told that there were 2 formulations and that neither they nor their physicians would know which formulation they received. All patients were told they might experience bleeding. In the interest of safety, patients were asked to report the quantity of bleeding so that excess bleeding could be immediately reported to the consulting gynecologist. This information was obtained by a member of the site team other than the principal investigator and was maintained in a folder separate from the patient's study chart. The principal investigator filling out the SELENA–SLEDAI at each site was not aware of this information, and patients were specifically informed at the time of enrollment that they should not discuss information on bleeding with the principal investigator.

At each follow-up visit, patients filled out a form asking whether they were taking HRT or placebo. Physicians were asked whether they believed the patient was taking HRT or placebo or whether they simply did not know.

Table 1. **Baseline Characteristics of Study Patients by Treatment Group***

Characteristic	Hormone Replacement Therapy Group	Placebo Group
Mean age (range), *y*	50.6 (32–80)	49.5 (27–72)
Active disease, %	18	19
Mean SELENA–SLEDAI instrument score (range)	2.57 (0–12)	2.40 (0–12)
History of renal disorder, %	41	40
Low complement level, %	22	15
Increased DNA binding, %	27	24
Prednisone use, %	54	59
Mean prednisone dosage (range), *mg/d*	4.62 (0–60)	5.13 (0–30)

* SELENA–SLEDAI = Safety of Estrogens in Lupus Erythematosus, National Assessment–Systemic Lupus Erythematosus Disease Activity Index.

Physicians were blinded to patient responses, and vice versa. On the basis of the final response for patient and physician before study completion or stopping of therapy with medication, 71% of patients in the HRT group accurately guessed that they were taking active drug (presumably because cyclic bleeding occurred), but only 56% of those in the placebo group guessed correctly. However, the study physician guessed correctly less than 20% of the time, supporting maintenance of blinding.

Reliability and Validation Studies of the SELENA–SLEDAI Composite

Throughout the study, investigators tested the SELENA–SLEDAI flare definitions using actual case report forms from the trial as "paper patients." These exercises demonstrated a high intraclass coefficient (0.89) for the SELENA-SLEDAI composite.

Statistical Analysis

To evaluate the safety of HRT over a 12-month period in postmenopausal women with SLE, we designed a noninferiority trial with occurrence of severe flare as the primary end point. The rationale for adopting the noninferiority design was its ability to show that HRT did not increase the risk for severe flare by more than a prespecified maximum clinically acceptable margin compared with placebo. The SELENA investigators determined a priori the margin of noninferiority to be a 9% absolute difference in the 12-month rates of severe flare.

The margin was formulated in terms of a difference in event rates as opposed to a relative risk, since the former approach was more clinically interpretable given the low expected severe flare rate in the placebo group.

The criterion for establishing the safety of HRT with respect to the primary end point was that the upper bound of the 1-sided 95% CI for the between-group difference (HRT − placebo) in severe flare rates had to be less than 9%. If this criterion were satisfied, one could conclude that HRT does not increase the risk for severe flare by more than 9% compared with placebo. A total sample size of 350 patients was determined to yield 95% power to conclude that HRT is not inferior to placebo with use of a 1-sided 95% CI, a noninferiority margin of 9%, and a 6% severe flare rate in both treatment groups.

The distributions of the time to first occurrence of a severe flare for the placebo and HRT groups were estimated by using the Kaplan–Meier method. The difference in the 12-month severe flare rates between treatment groups was computed from the difference of the corresponding Kaplan–Meier estimates. Confidence limits on the true difference were based on the Greenwood formula for the standard errors.

We used the Cox proportional hazards model to estimate relative risk for severe flare and corresponding CIs. We adjusted for disease stratum and other baseline characteristics by including the relevant covariates. Since adjusted results did not differ from the unadjusted results, we report only the latter. Times to first occurrences of mild to moderate flares and flares of any type (mild to moderate or severe) were analyzed by using similar approaches. We evaluated recurrent events by using the method of Wei, Lin, and Weissfeld (30). The SELENA–SLEDAI instrument score was analyzed by computing the change from baseline at each follow-up visit and comparing the magnitude of the changes between treatment groups by using the 2-sample *t*-test. Mixed-effects linear models were also fitted to the repeated measures of the SELENA–SLEDAI instrument score, with treatment group, time, and baseline SELENA–SLEDAI instrument score as the fixed effects and the patient as the random effect. We used the intention-to-treat approach for all analyses. *P* values are 2-sided and are based on the standard null hypothesis of no treatment difference.

The computational software was SAS, version 8.2 (SAS Institute, Inc., Cary, North Carolina).

Role of the Funding Source

The funding source, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication. The funding source, in consultation with the SELENA Data and Safety Monitoring Board, decided to terminate this study in view of the WHI results (28).

RESULTS

Baseline Data and Treatment

One hundred seventy-four patients were randomly assigned to the active HRT group, and 177 were assigned to

Table 2. **Severe Flares by Treatment Group: Specific Clinical Manifestations**

Type of Manifestation	Manifestations, *n*
Hormone replacement therapy group	
Nephritis	3
Central nervous system manifestations plus nephritis	1
Multisystem flare	2
Vasculitis	2
Cranial neuropathy	1
Lupus enterocolitis	1
Severe arthritis	1
Fever	1
Severe rash	1
Placebo group	
Nephritis	4
Peripheral neuropathy	1
Episcleritis	1
Bronchiolitis obliterans with organizing pneumonia	1
Thrombocytopenia	1

the placebo group. **Table 1** summarizes clinical characteristics of the study sample at enrollment. For 81.5% of the patients randomly assigned to HRT or placebo, the disease stratum at entry was inactive. Ethnicity of the study sample was similar for both HRT and placebo groups: 39% and 31% white patients, 37% and 38% African-American patients, 5% and 7% Asian-American patients, 18% and 20% Hispanic patients, and 2% and 4% other ethnicities, respectively (total is 101% because of rounding).

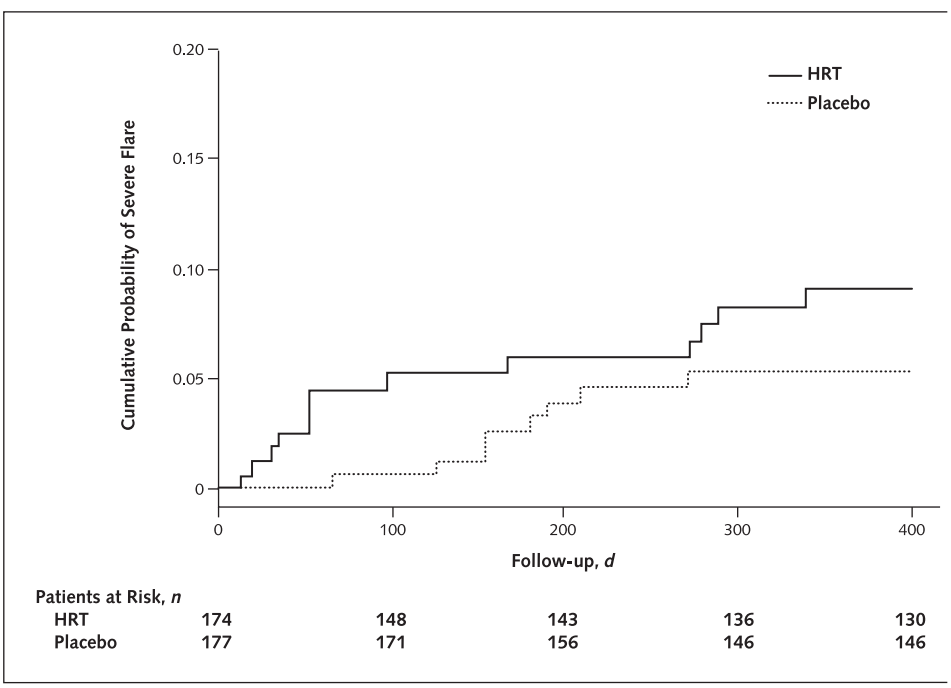
The 12-month nonadherence rate was 35% for the HRT group and 27% for the placebo group ($P = 0.08$). Patients considered nonadherent were those who terminated the study early for any reason other than severe flare. The 12-month rate of loss to follow-up was 18% for the HRT group and 13% for the placebo group ($P = 0.21$). Persons lost to follow-up were nonadherent patients who were not followed for the full 12 months (**Figure 1**).

Primary Outcome

Severe flare was infrequent in both groups: Thirteen (7.5%) of the 174 patients in the HRT group and 8 (4.5%) of the 177 in the placebo group experienced a severe flare (for specific clinical manifestations, see **Table 2**). The 12-month severe flare rate estimated from the Kaplan–Meier approach was 0.081 for the HRT group (95% CI, 0.039 to 0.12) and 0.049 for the placebo group (CI, 0.016 to 0.082). The difference in the 12-month severe flare rate between groups was 0.033 ($P = 0.23$). The upper limit of the 1-sided 95% CI for the true difference was 0.078. This implies that the data are consistent with an absolute difference in severe flare rates up to 7.8%, which is less than the prespecified 9% margin of noninferiority.

Figure 2 provides a Kaplan–Meier estimate for the cumulative probability of severe flare. The estimated relative risk (HRT/placebo) of severe flare from the Cox proportional hazards model was 1.75 (CI, 0.73 to 4.22; $P = 0.21$). Of note, 3 of the 13 severe flares in the HRT group occurred when patients were not actually taking the drug: One patient voluntarily stopped taking the study drug at 3 months and experienced a severe flare 5 months later; a second patient reached a medical stopping point (abnormal

Figure 2. **Kaplan–Meier estimates of the cumulative probability of severe flare for patients in the hormone replacement therapy (*HRT*) and placebo groups.**



The difference between treatment groups in the 12-month severe flare rate is 0.033 ($P = 0.23$).

Table 3. **Mean Change in SELENA–SLEDAI (Safety of Estrogens in Lupus Erythematosus, National Assessment–Systemic Lupus Erythematosus Disease Activity Index) Instrument Score from Baseline, by Treatment Group and Month of Follow-up**

Month	Hormone Replacement Therapy Group		Placebo Group		*P* Value
	Patients, *n*	Mean Change	Patients, *n*	Mean Change	
1	160	−0.11, SD 2.3	170	−0.05, SD 2.1	0.81
2	151	−0.33, SD 2.4	164	−0.34, SD 2.5	0.97
3	160	−0.10, SD 2.9	169	−0.45, SD 2.3	0.23
6	150	−0.23, SD 2.5	160	−0.28, SD 2.6	0.87
9	144	0.19, SD 3.0	155	−0.29, SD 2.7	0.14
12	140	0.11, SD 3.0	154	−0.12, SD 2.7	0.49

liver function test results) at 3 months and had a severe flare 8 months later; and a third patient experienced a severe flare after qualifying for the study and being randomly assigned to the HRT group, but before actually taking the study drug.

A per protocol analysis that excluded nonadherent patients was also performed to evaluate the primary end point. The sample for this analysis comprised 113 HRT recipients and 130 placebo recipients. The estimated 12-month severe flare rate based on the per protocol analysis was 0.089 for the HRT group (CI, 0.036 to 0.14) and 0.062 for the placebo group (CI, 0.020 to 0.10). The difference in the 12-month severe flare rate between groups was 0.027 ($P = 0.43$), and the upper limit of the 1-sided 95% CI for the true difference was 0.083, less than the prespecified 9% margin of noninferiority. Therefore, the per protocol analysis is consistent with the intention-to-treat finding that HRT is noninferior to placebo with respect to severe flare.

In both treatment groups, patients who entered the trial with stable-active disease had a greater risk for severe flare than those with inactive disease at enrollment. The estimated relative risk, adjusted for treatment, was 2.87 (CI, 1.19 to 6.92; $P = 0.02$). A history of renal disorder was also associated with increased risk for severe flare after adjustment for treatment group (relative risk, 2.2 [CI, 0.92 to 5.38]; $P = 0.07$).

Secondary Outcomes

Mild to moderate flares were more frequent than severe flares in both treatment groups: 102 (59%) patients in the HRT group and 88 (50%) patients in the placebo group had 1 or more mild to moderate flares. The incidence rate of mild to moderate flares was significantly greater in the HRT group than in the placebo group: 1.14 flares/person-year for HRT and 0.86 flare/person-year for placebo (relative risk, 1.34 [CI, 1.07 to 1.66]; $P = 0.01$).

The probability of having at least 1 flare of any type (mild to moderate or severe) during the 12-month follow-up period was 64% for the HRT group and 51% for the placebo group, resulting in a treatment difference of 0.13 (upper limit of 1-sided 95% CI, 0.22; $P = 0.01$). The estimated relative risk from the Cox proportional hazards model based on time to first flare of any type was 1.37 (CI, 1.04 to 1.82; $P = 0.03$). When multiple occurrences of flares of any type were included in the analysis, the overall incidence rate was 1.25 flares/person-years for HRT and 0.93 flare/person-year for placebo ($P = 0.006$). According to the approach of Wei, Lin, and Weissfeld (30), the estimate of the common relative risk (HRT/placebo) across multiple flares was 1.39 (CI, 1.05 to 1.83; $P = 0.02$), similar to the results based only on first flare.

The mean change in SELENA–SLEDAI instrument score did not significantly differ between groups at all follow-up visits (**Table 3**) and was less than 1 for each group throughout the 12 months of the study. A mixed-effects linear model was also fitted to the change in SELENA–SLEDAI instrument score, with treatment group, time, and baseline SELENA–SLEDAI instrument score as the fixed effects and patient as the random effect ($P = 0.12$ for the HRT group vs. the placebo group).

Serious Adverse Events

Serious adverse events (summarized in **Table 4**) were rare in the overall cohort ($P = 0.12$ for the HRT group vs. the placebo group).

DISCUSSION

Understanding the benefits and risks for exogenous estrogens is an important consideration in the care of women with SLE. The SELENA trial is the largest prospective study to provide evidence-based information. Moreover, this trial is likely to have a major impact on the

Table 4. **Serious Adverse Events by Treatment Group**

Type of Adverse Event	Adverse Events, *n*
Hormone replacement therapy group	
Death	1
Stroke	1
Deep venous thrombosis	2
Thrombosis of arteriovenous graft	1
Placebo group	
Deep venous thrombosis (occurred during follow-up after patient stopped taking placebo because of severe renal flare)	1

success of future multicenter SLE trials by emphasizing the need for validation of site investigators in use of the instrument that defines flare. Validation is necessary to assure uniform agreement in the assignment of outcome measures, especially for diseases as heterogeneous as SLE. Our conclusions are relevant to physicians caring for patients, basic researchers considering biological effects of estrogens, and clinical trialists. First, the use of HRT (conjugated estrogen/cyclic medroxyprogesterone) does not result in a statistically significant increased risk for severe flares in women with SLE. Second, HRT is associated with a significantly increased rate and number of mild to moderate flares. Third, the mean change in SELENA–SLEDAI instrument score did not significantly differ between groups across all 12 months of analysis.

Overall, the number of severe flares in the treatment and placebo groups was low; this finding is not unexpected given published experience in menopausal women with SLE (22). However, it was reassuring that in this prospective study HRT did not significantly increase the rate of severe flares, since the SELENA investigators considered this to be the most clinically meaningful outcome before the initiation of the study.

With regard to the 20% increase in mild to moderate flares, clinical significance must be interpreted by the treating physician who weighs each individual's risks and benefits. One implication of the data is that a specific subset of patients with SLE will experience an adverse effect of exogenous estrogens based on a biological predisposition. Murine data suggest that an estrogen-mediated breakdown in B-cell tolerance is genetically determined (31). Women with SLE may also differ with respect to estrogen effects on B cells. In the future, it may be possible to identify the subset of women with SLE in whom estrogen administration poses no threat (from the perspective of lupus activity).

Three retrospective studies differed from the SELENA trial because they did not separately evaluate mild to moderate and severe flares (19–21). In the limited prospective study of patients with SLE (11 patients in the HRT group and 23 in the placebo group) by Mok and colleagues (22), flare rate did not differ significantly between groups (estrogen exposure was lower than in the SELENA trial: 0.625 mg of conjugated estrogen given for only 21 days per month). In their prospective evaluation of a regimen identical to that used in the SELENA trial, Sanchez-Guerrero and colleagues (23) reported no increase in flare during HRT ($n = 52$) or during receipt of placebo ($n = 54$).

Among the undisputed health benefits of HRT are relief of vasomotor flushes, atrophic vaginitis, and urethritis and prevention or retardation of postmenopausal and steroid-induced osteoporosis. Particularly in young women with SLE and premature ovarian failure, symptoms related to a decrease in hormone levels can be a source of serious emotional and physical dysfunction. Because symptoms such as hot flashes are often most severe in the perimenopausal period, the relief of symptoms and the brevity of treatment may offset the cardiovascular risks discussed below. Osteoporosis is a particularly relevant consideration in SLE given the frequent use of glucocorticoids. Ramsey-Goldman and colleagues (32) ascertained the incidence of fractures and associated risk factors by self-report in a retrospective group of 702 women with SLE followed for 5951 person-years. Fractures occurred in 12.3% of the patients, a nearly 5-fold increase compared with women in the general U.S. population. Recent evidence suggests that limited HRT administration in the early postmenopausal years may offer long-lasting benefits for the prevention of postmenopausal bone loss and osteoporotic fracture (33).

With regard to benefit, it is clear that a major paradigm shift has followed the reporting of results from the prospective Heart and Estrogen/progestin Replacement Study (HERS) (34, 35) and the WHI trial (28, 36). These studies statistically negated the prevailing dogma, based on earlier observational trials (37–39), that HRT with estrogens is cardioprotective. Contrary to expected results, the WHI trial revealed a significantly higher number of strokes and myocardial infarctions in women randomly assigned to HRT, particularly in year 1. Note that the SELENA trial excluded women with evidence of hypercoagulability by using antiphospholipid assays, and evaluated cyclic medroxyprogesterone rather than the continuous progesterone used in the WHI trial. Nonetheless, the increased number of adverse cardiovascular events with HRT in the WHI trial is important because accumulating data support an increased susceptibility to atherosclerosis in SLE (40–44). However, the cause of this increased susceptibility is not fully defined and may be intrinsic to the biology of SLE, as well as traditional risk factors. Once risk factors are defined, a decision to use HRT may be made accordingly. It should also be noted that, by design, the WHI sample was underpowered to show cardioprotection of women starting HRT during the menopausal transition (45). This might be the situation in a lupus population in which patients are followed closely and perimenopause would be readily identified. Thus, observational studies demonstrating cardioprotection in such women remain the only applicable clinical guide to this issue.

In the HRT-SELENA trial, 4 thrombotic events occurred in the HRT group and 1 occurred in the placebo group, but this difference did not reach statistical significance. Of note, patients with high-titer anticardiolipin antibodies, lupus anticoagulant, or previous thrombosis were excluded from the SELENA trial. In Arden and colleagues' retrospective study (19), only 1 thromboembolic event occurred among 30 patients taking HRT (5 weeks after discontinuation of HRT), even though 7 patients had documented antiphospholipid antibodies.

In addition to the scientific results of the HRT-SELENA trial, this study set a precedent for the design of multicenter clinical trials in SLE. The need for unambiguous scoring of instruments was continually emphasized during this trial and was initially addressed by the provi-

sion of detailed guidelines on scoring the SELENA–SLEDAI instrument and subsequently by 3 validation studies. The observational, longitudinal LUMINA (LUpus in Minority Populations: NAture vs. Nurture) cohort study conducted a similar validation exercise (46). The SELENA trial demonstrates that the measurement of flares by a composite index may lead to a different conclusion than that obtained from the measurement of absolute disease activity (as assessed by a change in SELENA–SLEDAI instrument score alone).

In summary, while the pendulum has swung away from long-term use of HRT in menopausal women, this does not reduce the importance of establishing the clinical safety of exogenous estrogens in women with SLE. That HRT use did not significantly increase the risk for a severe flare in patients with SLE should reassure physicians considering this approach, with the caveat that these results are not generalizable to women with high-titer anticardiolipin antibodies, lupus anticoagulant, or previous thrombosis. Certainly, short-term HRT has indications for alleviating vasomotor symptoms, especially in patients with premature ovarian failure due to chemotherapy. While there are alternatives to estrogens for preventing and treating osteoporosis, HRT may be justified in some situations. The increased risk for mild to moderate flares in patients taking HRT needs to be considered on an individual basis. Future studies should be conducted to address the biological mechanism for this effect.

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Appendix Table. **Participating Clinical Sites and Enrollment in the Hormone Replacement Therapy Trial of the Safety of Estrogens in Lupus Erythematosus, National Assessment**

Clinical Site	Hormone Replacement Therapy Group, *n (%)*	Placebo Group, *n (%)*	Total, *n (%)*
Johns Hopkins University School of Medicine, Baltimore, Maryland	36 (21)	37 (21)	73 (21)
Hospital for Joint Diseases/Bellevue/New York University School of Medicine, New York, New York	37 (21)	34 (19)	71 (20)
University of California, Los Angeles, Los Angeles, California	31 (18)	32 (18)	63 (18)
St. Luke's-Roosevelt Hospital Center, New York, New York	19 (11)	20 (11)	39 (11)
Hospital for Special Surgery, New York, New York	12 (7)	14 (8)	26 (7)
University of Pittsburgh, Pittsburgh, Pennsylvania	8 (5)	9 (5)	17 (5)
University of Alabama at Birmingham, Birmingham, Alabama	8 (5)	8 (5)	16 (5)
University of North Carolina at Chapel Hill, Chapel Hill, North Carolina	5 (3)	7 (4)	12 (3)
Louisiana State University Health Sciences Center, Shreveport, Louisiana	6 (3)	5 (3)	11 (3)
Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, New York	3 (2)	3 (2)	6 (2)
University of Pennsylvania, Philadelphia, Pennsylvania	3 (2)	2 (1)	5 (1)
University of Michigan, Ann Arbor, Michigan	2 (1)	2 (1)	4 (1)
Rheumatology Associates of Long Island, Port Jefferson Station, New York	3 (2)	0	3 (<1)
Medical College of Wisconsin, Milwaukee, Wisconsin	0	2 (1)	2 (<1)
Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma	1 (<1)	1 (<1)	2 (<1)
University of Texas–Houston, Houston, Texas	0	1 (<1)	1 (<1)
Total	174	177	351

Appendix: Participating Clinical Sites and Personnel

Hospital for Joint Diseases and Bellevue Hospital at New York University School of Medicine, New York, New York. *Personnel:* Jill P. Buyon, MD; Anca Dinu Askanase, MD, MPH; H. Michael Belmont, MD; Frederick Licciardi, MD; and Ping Louie, MS.

Montefiore Medical Center at Albert Einstein College of Medicine, New York, New York. *Personnel:* Jane Wachs, MD.

Johns Hopkins Hospital, Baltimore, Maryland. *Personnel:* Michelle A. Petri, MD, MPH; Courtland Robinson, MD; Lisa Sigler, MA; and Michael Fillius.

Hospital for Special Surgery, New York, New York. *Personnel:* Lisa Sammaritano, MD; Michael Lockshin, MD; and Victoria Kaplan.

Louisiana State University Health Sciences Center, Shreveport, Louisiana. *Personnel:* Michelene Hearth-Holmes, MD; Lea Green, RN; and Rose Brouillette, MD.

Medical College of Wisconsin, Milwaukee, Wisconsin. *Personnel:* Mary Cronin, MD, and Jovanka Zrnic, RN.

Oklahoma Medical Research Foundation, Oklahoma City, Oklahoma. *Personnel:* Joan T. Merrill, MD; Judith James, MD; Bobbie Lee, LPN; and Fredonna Shelton.

Rheumatology Associates of Long Island, Port Jefferson Station, New York. *Personnel:* Mark Tan, MD, and Diana Kaell.

St. Luke's-Roosevelt Hospital Center, New York, New York. *Personnel:* Joan T. Merrill, MD; Ranit Shriky; and Angelique Shriky.

The University of Alabama at Birmingham, Birmingham, Alabama. *Personnel:* Graciela S. Alarcón, MD, MPH, and Martha L. Sanchez, MD, MPH.

University of California, Los Angeles, Los Angeles, California. *Personnel:* Kenneth C. Kalunian, MD; Bevra H. Hahn, MD; Jennifer Grossman, MD; Andrea Rapkin, MD; and Weiling Chen.

University of Michigan, Ann Arbor, Michigan. *Personnel:* W. Joseph McCune, MD; Cosmas J.M. Van De Ven, MD; Gregory Christman, MD; and Barbara Gilson, RN.

University of North Carolina at Chapel Hill, Chapel Hill, North Carolina. *Personnel:* Mary Anne Dooley, MD, MPH; William Meyer, MD; and Brenda Meier, RN.

University of Pennsylvania, Philadelphia, Pennsylvania. *Personnel:* Joan Von Feldt, MD; Kurt Barnhart, MD; and Louise Loh, RN.

University of Pittsburgh, Pittsburgh, Pennsylvania. *Personnel:* Susan Manzi, MD, MPH, and Jackie Lapina, RN.

University of Texas, Houston, Texas. *Personnel:* Alan Friedman, MD, and Nai-Hui Chiu, RN.