

# Menopause Management in Women with Systemic Lupus Erythematosus

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Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder that preferentially affects women.<sup>1</sup> Although the incidence of SLE peaks during the reproductive years, this disease can be diagnosed at any time during a woman's life. Cytotoxic agents used to treat SLE may induce premature menopause,<sup>2</sup> and some patients with SLE may experience immune-mediated premature ovarian failure.<sup>3</sup> Because of the broad age range at onset, the premature menopause in some, and the improved prognosis and increased life expectancy for patients with SLE, many women with SLE will become menopausal. Unfortunately, limited data on appropriate treatment of menopause-related symptoms and the coexisting morbidities of osteoporosis and cardiovascular disease in SLE patients make this issue a particularly challenging one for physicians.

This article addresses the issues that clinicians face in managing SLE in patients experiencing menopause, and pays particular attention to the management of menopausal symptoms, and issues related to hormone therapy (HT) and associated comorbidities that particularly affect SLE patients,

including osteoporosis and the increased risk of cardiovascular disease.

## The Menopause-SLE Dilemma

SLE is a multisystem disorder that can affect the musculoskeletal, renal, central nervous, cardiovascular and hematologic systems. Most of

the morbidity and mortality associated with SLE is due to renal disease, coronary artery disease and infection. When SLE occurs after the onset of menopause, renal disease is not as common, although there is an increased incidence of vascular arterial events.<sup>4</sup> Some studies suggest that there may be a mild decrease in disease activity after menopause.<sup>5</sup>

SLE itself can cause symptoms that are similar to those seen during menopause (Table 1). For example, women with SLE can have sleep disturbances and fatigue. Sjögren's syndrome, which can be seen in association with SLE, can cause mucosal dryness, including vaginal dryness and associated dyspareunia.<sup>6</sup> Patients with SLE likewise complain of cognitive impairments and slowed thought processes—which also can be menopause-related symptoms. One of the challenges for practitioners caring for SLE patients during menopause is to assess whether the symptoms a patient is experiencing are due to underlying SLE or to menopause. In general, knowledge about the patient's prior history of SLE symptoms and serologic status

can be helpful in sorting through this issue.

Patients with SLE tend to have similar symptoms during subsequent SLE flares. Thus, a woman who experiences fatigue and cognitive impairment as part of her SLE flares—and complains of these symptoms during menopause—may be having a flare of her underlying disease. Biomarkers of disease activity (such as leukopenia or lymphopenia), increases in anti-double-stranded deoxyribonucleic acid (anti-ds DNA) antibodies, decreased levels of complement, elevated erythrocyte sedimentation rate and elevated C-reactive protein suggest a disease flare rather than menopausal symptoms (Table 2).

### Postmenopausal HT and SLE

The disproportionate female-to-male ratio in SLE patients (9:1)

**There are few controlled studies on postmenopausal HT in patients with SLE because the common wisdom has been to avoid using estrogens in these patients.**

during the childbearing years implies that SLE is hormonally mediated.<sup>1</sup> In lupus-prone mice, the administration of exogenous estrogens worsens disease, while treating these mice with androgens can im-

prove outcome.<sup>7</sup> As a result, practitioners have, for many years, avoided the use of postmenopausal HT in women with SLE, fearing that such treatment would exacerbate SLE symptoms. This poses a therapeutic dilemma, since postmenopausal HT can reduce the symptoms of menopause, including hot flashes and atrophic vaginitis, and help prevent osteoporosis. The latter is particularly relevant in SLE patients, as they are more prone to the development of osteopenia and osteoporosis.

There are few controlled studies on postmenopausal HT in patients with SLE because the common wisdom has been to avoid using estrogens in these patients. In a double-blind, placebo-controlled study by Sanchez-Guerrero and colleagues,<sup>8</sup> the effect of HT on disease activity in 106 postmenopausal women was assessed when 52 patients were randomized to treatment with estrogen plus medroxyprogesterone acetate (MPA) and 54 were randomized to receive placebo. There was no difference seen in the number of mild/severe flares in each group; however, three thrombotic events occurred in those receiving HT versus one thrombotic event in the placebo arm.

In a retrospective study by Buyon and colleagues,<sup>9</sup> 94 postmenopausal SLE patients from five medical centers were surveyed. Fifty-five of the 94 women (59%) reported that they had taken estrogen at some time, and 48 of these women started the estrogen after the diagnosis of SLE was made. Eight percent of the patients who had taken estrogen flared. One

**Table 1.**  
**Symptoms that Co-exist in a Systemic Lupus Erythematosus Flare and Menopause**

- Sleep disturbances
- Fatigue
- Vaginal dryness
- Headaches

**Table 2.**  
**Laboratory Abnormalities that Suggest a Flare of Systemic Lupus Erythematosus**

- Leukopenia and lymphopenia
- Decreased platelet count
- Increased titer of anti-double-stranded DNA antibodies
- Decreased complement
- Elevated erythrocyte sedimentation rate
- Increased C-reactive protein

patient with antiphospholipid antibodies had a cerebral vascular accident. The authors concluded that estrogen therapy (ET) in postmenopausal women with SLE was reasonably well tolerated.

The most definitive study to date has been the HT arm of the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) trial.<sup>10</sup> This was a randomized, placebo-controlled, multicenter study in postmenopausal women with SLE, in which the impact on disease activity of combination estrogen/MPA therapy was compared with placebo. Subjects were excluded if they had uncontrolled high blood pressure, a history of spontaneous superficial or deep vein thrombosis (DVT), a history of arterial thrombosis or pulmonary embolus, high-titer anticardiolipin antibodies, a lupus anticoagulant, a history of gynecologic or breast cancer, a history of myocardial infarction, hepatic dysfunction or liver tumors, uncontrolled diabetes, congenital hyperlipidemia, migraines with neurologic sequelae, and/or unexplained vaginal bleeding. The trial randomized 174 women with SLE to receive 0.625mg/d of conjugated estrogens and 5 mg of MPA on days 1-12 of the month in the HT arm, and 177 women with SLE to receive a biologically inert placebo. At entry, 81.5% of the patients in both arms of the study had inactive disease; the remainder had stable-active disease. Although there was a high unexplained non-adherence rate (35% in the study group and 27% in the placebo group) and the study lasted only 12 months, it is the largest randomized study to

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date that addresses the issue of postmenopausal HT in women with SLE.

Severe flares were rare, occurring in 13 of the 174 subjects in the HT arm (three while not taking HT) and eight of the 177 women in the placebo group (not statistically significant). Women with SLE who entered the trial with stable-active disease or renal disease had an increased incidence of flares even after adjustment for therapy. The incidence rate of mild to moderate flares was significantly greater in the HT group than in the placebo group: 1.14 flares/person-year for those receiving HT and 0.86 flares/person-year for those receiving placebo (relative risk, 1.34;  $P = 0.01$ ). Serious adverse events included one death, one stroke and three thrombotic events in the study group, and one thrombotic event in the placebo group. While HT may have a modest impact on the incidence of mild and moderate flares, there does not appear to be an increased rate of severe flares.

Similarly, the oral contraceptive arm of the SELENA trial showed no increase in the flare rate in premenopausal women who received oral contraceptives.<sup>11</sup>

The SELENA trial did not measure the impact of HT on menopausal symptoms in patients with SLE; rather, it addressed the risk of lupus flare with this treatment. So we cannot conclude from this study whether HT is of benefit to lupus patients. The subjects in the SELENA trial were carefully selected and there were multiple exclusion criteria. Women with the conditions that comprised those exclusion criteria (previously discussed)—uncontrolled high blood pressure, a history of spontaneous superficial or DVT, arterial thrombosis, pulmonary embolus, history of gynecologic or breast cancer, history of myocardial infarction, hepatic dysfunction or liver tumors, uncontrolled diabetes, congenital hyperlipidemia, migraines with neurologic sequelae, and/or unexplained vaginal bleeding—should avoid HT. Four of 174 subjects in the arm of the SELENA trial versus one of 177 subjects in the placebo arm experienced a clotting event. Although this finding did not reach statistical significance, and subjects with antiphospholipid antibodies were excluded from the trial, it suggests that HT may increase the risk of clots and other hypercoagulable manifestations in women with SLE. Therefore, SLE patients with a history of thrombosis, anticardiolipin antibodies and/or a lupus anticoagulant or other thrombophilic states should likewise avoid HT. In addition, SLE itself may put patients at

additional risk for atherosclerosis, so patients should be carefully screened for traditional cardiovascular disease risk factors such as hypertension, diabetes, hyperlipidemia, smoking history and family history of coronary artery disease prior to initiating HT.

Finally, the SLE patients with stable-active disease or renal disease at study entry had increased flare rates during the study regardless of which treatment arm they were in; however, it has been suggested that these patients should probably avoid HT as well.<sup>12</sup> For menopausal women with mild to moderate SLE without these above-mentioned risk factors, the decision to use or not use HT should be made according to the recommendations put forth by The North American Menopause Society,<sup>13</sup> with the caveat that the benefits of postmenopausal HT, especially in the early menopausal period, must be weighed against the increased risk of mild/moderate flares, and that treatment should be short-term, using the lowest possible dose of estrogen.

There are few specific data that address the issue of whether selective estrogen-receptor modulators (SERMs) are safe for use in SLE patients. In one study by Mok et al<sup>14</sup> examining raloxifene use for the treatment of osteoporosis, this drug appeared to be well tolerated, although the study was not powered to detect an increase in flare rates. Like traditional HT, SERMs carry an increased risk of clotting.<sup>15</sup>

### Nonhormonal Menopause Treatments and SLE

Women with vasomotor instability

**C**urrently, there are no guidelines that specifically address the issue of when to screen postmenopausal SLE patients for osteoporosis.

during menopause can have hot flashes and associated sleep disturbances. Selective serotonin reuptake inhibitors (SSRIs) can be beneficial in these patients.<sup>16</sup> There is no evidence to suggest that these medications exacerbate SLE. It is unclear whether soy products can be used, as animal studies have shown that exogenous soy can exacerbate disease in lupus-prone mice.<sup>17</sup> Vaginal moisturizing agents and lubricants can be used in patients with vaginal dryness; in particular, in those with co-existing Sjögren's syndrome.<sup>18</sup>

### Osteoporosis and SLE

Osteoporosis and its associated fractures are leading causes of morbidity during menopause.<sup>19</sup> Peak bone density occurs at about age 30, after which bone loss occurs. Women with SLE are at particular risk for osteopenia and osteoporosis. Lower bone mineral densities (BMD) at both the spine and the hip have been reported in women with SLE.<sup>20</sup> While traditional risk factors for osteoporosis, such as female sex, low body weight, Cau-

casian or Asian ethnicity, smoking, low vitamin D and excessive alcohol use, play a role in the development of osteoporosis in women with SLE, other risk factors directly related to SLE and its treatment contribute as well. These risk factors include disease activity and medications (in particular, glucocorticoids), and sun avoidance, which may cause vitamin D deficiency. In addition, decreased physical activity from arthritis, myopathy and renal disease can contribute to an increased risk of osteoporosis.

In one study from England,<sup>21</sup> 242 patients with SLE were assessed for reduced bone density and risk factors for fracture. This study was not limited to postmenopausal women, and the median age of study subjects was 39.9 years. Fifty-one percent of these patients had reduced BMD, while 10% were osteoporotic. Fragility fractures occurred in 9% of patients. In this study, glucocorticoid exposure and non-Afro-Caribbean ethnicity were associated with decreased bone density. In a cohort of Chinese women with SLE, 48% were found to have osteoporosis and 33% were found to have osteopenia of the spine.<sup>22</sup>

*Osteoporosis screening.* Currently, there are no guidelines that specifically address the issue of when to screen postmenopausal SLE patients for osteoporosis. For the majority of postmenopausal women with SLE it seems prudent to perform a baseline BMD measurement prior to the recommended age of 65. In particular, those patients with traditional osteoporotic

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risk factors other than Caucasian ethnicity, those with premature menopause and osteoporotic risk factors,<sup>20</sup> and patients who are on or who are going to receive long-term glucocorticoid therapy (longer than 6 months) should have baseline BMD testing.<sup>23</sup> I also recommend obtaining baseline BMD measurements in postmenopausal SLE patients with a prior history of long-term glucocorticoid use. Screening of the hip as well as the spine is prudent given the proclivity of bone thinning at both sites. For patients with documented osteopenia or osteoporosis who are receiving therapy to prevent further bone loss, it seems advisable to follow the American College of Rheumatology guidelines on the treatment of glucocorticoid-induced osteoporosis,<sup>23</sup> and to perform follow-up BMD measurements on an annual basis. There are no clear recommendations for follow-up BMD assessment in postmenopausal SLE patients with normal baseline BMD values.

*Osteoporosis prevention and treatment.* Behavioral modifications, such as cigarette smoking cessation and reducing alcohol intake, are the first steps toward decreasing osteoporosis risk. Some data suggest that aerobic exercise three times per week may help prevent bone loss in SLE patients who are taking glucocorticoids.<sup>24</sup> Postmenopausal women with SLE should ingest 1,000-1,500 mg/day of calcium and 400-800 IU/day of vitamin D.<sup>23</sup> Postmenopausal SLE

**B**ehavioral modifications, such as cigarette smoking cessation and reducing alcohol intake, are the first steps toward decreasing osteoporosis risk.

patients who are either initiating glucocorticoids for more than 3 months at daily doses of 5 mg or higher, or those who are receiving long-term glucocorticoid therapy should receive bisphosphonates in conjunction with calcium and vitamin D supplementation.<sup>23</sup> Hydroxychloroquine, often a mainstay of therapy for patients with SLE, may be associated with a higher BMD of the spine and the hip and, therefore, may also be beneficial.<sup>25</sup>

Transdermal ET given as 50 µg of transdermal 17 beta-estradiol for 1 year was shown to prevent bone loss in postmenopausal women with SLE with no associated increase in disease flares.<sup>26</sup> SERMs may help in preventing or treating osteoporosis in postmenopausal women with SLE. In one study of postmenopausal Chinese women with SLE,<sup>14</sup> 16 patients were randomly assigned to receive raloxifene (60 mg/day) plus elemental calcium (1,200 mg/day), or elemental calcium alone (n = 17). All patients were receiving low-

dose prednisolone and there was no difference in baseline BMD values, age or body mass index. BMD studies done after 12 months of receiving raloxifene plus calcium or calcium alone showed a decrease in the BMD of both the femoral neck and the lumbar spine in the control group, but not in the patients who were receiving raloxifene. Although the authors reported that there were no major flares in either group, the study was not powered to detect a difference in flare rate between the two groups. This pilot study demonstrates that in a small group of postmenopausal Chinese women, raloxifene decreased the rate of bone density loss when compared with controls, and did not appear to increase the risk of a disease flare.

The bisphosphonates alendronate and risedronate are approved by the FDA for the treatment of osteoporosis and glucocorticoid-induced osteoporosis. Both of these drugs have been shown to increase bone density and reduce the risk of fracture.<sup>27,28</sup> Pamidronate and zoledronic acid are intravenous bisphosphonates that have been used off-label for the treatment of osteoporosis.<sup>29,30</sup> Parathyroid hormone can also be used in the treatment of osteoporosis.<sup>31</sup> Calcitonin, although not as effective as the bisphosphonates, may be used to treat osteoporosis, particularly in patients who are unable to tolerate bisphosphonate therapy.<sup>32</sup>

In conclusion, postmenopausal patients with SLE should be carefully monitored for osteoporosis, and in many situations early BMD testing is recommended. Adequate calcium and vitamin D is recommended for all patients. For those

patients with low bone densities, SERMs, bisphosphonates, calcitonin and newer agents are appropriate therapies. According to the recommendations put forth by the American College of Rheumatology,<sup>23</sup> patients who will be on prednisone therapy for more than 3 months at a dose greater than 5 mg/day should be placed on a bisphosphonate.

## Postmenopausal women with SLE should be carefully screened for risk factors for coronary artery disease.

### Cardiovascular Disease and SLE

For years, prevention of coronary artery disease was a major impetus for the use of postmenopausal HT. The Heart and Estrogen/progestin Replacement Study (HERS) changed that practice. HERS showed that use of combined estrogen-progestin in postmenopausal women did not reduce but rather appeared to increase the risk of coronary artery disease,<sup>33</sup> a major cause of morbidity and mortality in patients with SLE.<sup>34-36</sup> Lupus patients may present with nonspecific complaints in the setting of active coronary artery disease, so clinicians ought to have a high index of suspicion for symptoms attributable to cardiovascular disease in these patients. While traditional risk factors for cardiovascular disease certainly play a role, there also appears to be a separate disease-specific risk factor for SLE.<sup>37</sup>

Postmenopausal women with SLE should be carefully screened for risk factors for coronary artery disease. Modifiable risk factors, such as smoking, poorly controlled diabetes, hypertension and hypercholesterolemia, should be aggressively managed. Screening for elevated levels of homocysteine should also be performed, as this modifiable risk factor may also be more prevalent in SLE patients.<sup>38</sup>

### Summary and Conclusions

Menopause management is a challenge for all clinicians. Women with SLE present additional concerns for practitioners. Not only do the symptoms of SLE—such as fatigue, vaginal dryness and cognitive impairment—mimic those seen during menopause, but menopause treatment regimens in women with SLE must also be weighed against the risk of causing a disease flare. For patients with SLE who do not have evidence of, or risk factors for, coronary artery disease,

breast cancer or uterine cancer, and who do not have antiphospholipid antibodies or other thrombophilic conditions, short-term HT may provide relief from menopause symptoms and may have a modest impact on the occurrence of disease flares. Other treatments may also provide relief from hot flashes and fatigue (SSRIs), and vaginal dryness (vaginal lubricants). Most SLE patients should be taking calcium and vitamin D supplements, and should

be screened rigorously for osteopenia and osteoporosis. In patients with evidence of osteopenia or osteoporosis, or in those who are contemplating or using long-term glucocorticoid therapy, aggressive osteoporosis treatment should be employed. Finally, practitioners should be cognizant that SLE patients are

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particularly prone to coronary artery disease, and risk factor reduction should be actively pursued. ■

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**This article includes discussion of off-label use of medication.**

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