

## Current and Emerging Lupus Treatments

*Based on a presentation by Daniel Wallace, MD*

### **Presentation Summary**

New developments in the treatment of lupus have been lacking until recently. It is hoped that new immunomodulating therapies, including a synthetic form of dehydroepiandrosterone (prasterone), will help reduce the need for steroid treatment among patients with mild-to-moderate disease, thereby reducing the morbidity and cost associated with steroid-related side effects. In addition, newer treatments for more severe systemic lupus erythematosus appear to be on the horizon, the most promising of which include biologic agents. Meanwhile, several improvements have been made to traditional therapies that may also benefit patients.

**T**here have been no new treatments developed during the past 4 decades for systemic lupus erythematosus (SLE), a complex, chronic, multisystem disease that targets young women and men, leaving rheumatologists at a disadvantage when managing these patients. The current management of lupus results in a 70% 20-year survival, a figure that has not changed in more than 20 years. This is largely because of the comorbidities associated with the use of chronic corticosteroid therapy such as hypertension, hyperlipidemia, diabetes, and atherosclerotic heart disease, which additionally alter a lupus patient's quality of life.

Current medical therapies can often be augmented with physical measures and patient education. Physical measures may include advising the use of broad-spec-

trum sunscreens to lessen the effects of photosensitivity, the use of moist heat such as saunas to alleviate arthritis symptoms, exercise and vitamin supplementation to help prevent osteoporosis, low-fat diets to lessen detrimental cardiovascular effects, fatigue management, and coping strategies.

Patients should also be educated as to the possible long-term damage and organ disease associated with both the disease and the currently available treatments, and the potential hereditary nature of SLE should be discussed.

### **Current Treatment**

Available medical therapy for moderate-to-severe SLE include the use of topical nonfluorinated steroids for cutaneous facial manifestations, nonsteroidal anti-inflammatory drugs (NSAIDs), antimalarials, and steroids accompanied by steroid-sparing agents for those patients with organ-threatening disease.

**NSAIDs.** Although there are no NSAIDs specifically approved for use in SLE, the majority of patients take NSAIDs daily to alleviate fever, headache, pleurisy, pericarditis, myalgias, and arthralgias associated with the disease process. Nevertheless, none of these agents alter the outcome of lupus, dosing is problematic with renal involvement, and many individuals have difficulty tolerating their gastrointestinal side effects.

New, topical compounded gel formulations of ketoprofen and diclofenac may help patients with minor arthralgias avoid the risk of gastric toxicity associated with

traditional NSAIDs.<sup>1,2</sup> In addition, the cyclooxygenase-2 (COX-2) antagonists may reduce gastric injury in patients requiring chronic NSAID therapy. In a recent study we conducted, celecoxib was well tolerated in SLE patients, was not associated with disease flares, and was as effective as traditional NSAIDs.<sup>3</sup> COX-2-specific drugs, such as celecoxib and rofecoxib, may be associated with hypercoagulability, *especially* in patients with antiphospholipid antibodies. As with other NSAIDs, they may worsen hypertension and edema, although this appears to happen more often with rofecoxib.<sup>4</sup>

**Antimalarials.** Hydroxychloroquine is the most commonly used antimalarial in SLE and is effective for cutaneous manifestations, arthritis, pleurisy, serositis, malaise, and lethargy. These drugs are not immunosuppressive and have limited usefulness in organ-threatening disease.

They work by interfering with antigen processing, which is a critical pH-dependent component in autoimmune disease. By raising the pH of cells, there is less receptor surface area available for macrophage cell-mediated cytokine signaling. They also block prostaglandin, lower lipid levels, interfere with platelet aggregation, induce apoptosis, and have antiproliferative effects.<sup>5</sup>

In nonorgan-threatening disease, the use of hydroxychloroquine is associated with significantly fewer flares during 6 months of treatment compared with placebo. In addition, the risk of developing organ-threatening disease is reduced from 23% to 4%, making this a disease-modifying treatment, or one that alters the outcome of the disease.<sup>6</sup>

**Steroids.** For organ-threatening SLE, steroids are used in doses of 1 mg/kg/day and for nonorgan-threatening disease in doses of 5 to 15 mg daily. Prednisone is most commonly used, but hydrocortisone may be used for acute flares because of speed of action. Dexamethasone may be better for central nervous system lupus because it crosses the blood-brain barrier more easily.<sup>7</sup> As mentioned earlier, the

use of corticosteroids is fraught with complications. An ongoing requirement of more than 10 mg of prednisone a day should suggest to the treating physician that it is important to consider adding a steroid-sparing agent.

Steroid-sparing therapy consists of cyclophosphamide for organ-threatening lupus, azathioprine for moderate disease, and methotrexate for synovitis. Renal involvement leads to dialysis in a majority of patients without steroid-sparing therapy. In a National Institutes of Health study of 111 lupus nephritis (organ damage) patients observed for 15 years, intravenous cyclophosphamide significantly reduced renal scarring associated with prednisone therapy. Low-dose oral azathioprine plus cyclophosphamide and oral cyclophosphamide also reduced the incidence of end-stage renal disease. Azathioprine alone was not protective.<sup>8</sup> However, azathioprine may be useful in hepatic lupus.<sup>9</sup>

Newer steroids have been developed in hopes of reducing side effects. Deflazacort, available in more than 30 countries, has shown mixed results, in that it may diminish the rate of bone loss but has less predictable efficacy compared with prednisone.<sup>10</sup> One promising new oral steroid available in Canada, budesonide, appears as effective as prednisone in Crohn's disease with potentially less gastric and bone toxicity.<sup>11</sup>

### New Developments

A better understanding of the pathogenesis of SLE has led to a variety of investigations of potential new treatments. New immunomodulators including prasterone, biologic agents, vaccines, stem cell transplantation, and immunoablative therapies are all under investigation and may provide future benefits for SLE patients. A few of these potential treatments have emerged as the most promising for availability in the near future.

### Prasterone, Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is a naturally occurring, mildly androgenic hormone secreted by the adrenal gland

which has been found to be at low levels in SLE patients.<sup>12,13</sup> DHEA mainly increases interleukin-2 and also increases production of interferon gamma and other interleukins.<sup>14</sup> Early studies showed that it can be steroid sparing in lupus patients.<sup>15-17</sup>

Although available over the counter for nearly 50 years, DHEA has been previously unregulated by the Food and Drug Administration (FDA). However, prasterone, a synthetic DHEA that will be standardized for quality and dosage, is under FDA review for its use in women with mild-to-moderate SLE disease activity. Prasterone would be the first new agent approved for these patients in decades. It will be a good choice for patients taking low-dose steroids who are not having an adequate response to NSAIDs and anti-malarials. Reducing steroid use in SLE patients without organ-threatening disease is essential in terms of reducing long-term morbidity.

**Prasterone Trials.** There have been several clinical trials involving the use of prasterone in SLE patients during the past 10 years. One of the most pivotal involved 196 women receiving 10 to 30 mg of prednisone daily. They were randomized to receive either 100- or 200-mg prasterone daily or placebo for 7 to 9 months. The researchers found that among patients receiving the 200-mg dose of prasterone, 61% were able to reduce their prednisone dose to the normal physiologic range. The difference between 200-mg prasterone and placebo was statistically significant.<sup>18</sup>

In a second important trial, 381 women with mild-to-moderate SLE being maintained on 10-mg prednisone daily or less were given either prasterone or placebo for 12 months. The Systemic Lupus Activity Measure (SLAM) and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) were required to remain stable during the study and fatigue had to be stable or improved on the visual analog scale (VAS) for patients to be classified as responders.

Prasterone patients were significantly more likely to be responders and experienced fewer disease flares and improved

disease activity indices during the study period and their VAS scores improved.<sup>19</sup> Postmenopausal women in this study taking prasterone showed bone mineral density improvement similar to that seen in women taking bisphosphonates.<sup>20</sup> Although prasterone did not change complement or double-stranded deoxyribonucleic acid (dsDNA) measurements, patients felt better (as determined by VAS scores). Prasterone was well tolerated and side effects were mild, consisting mainly of acne and hirsutism in <5% of patients.

A third double-blind, randomized, controlled trial involved 119 women who received either 200-mg prasterone daily or placebo for 6 months. Changes in SLAM, SLEDAI, and VAS scores were used as primary endpoints. Only 18% of patients in the prasterone group experienced disease flares during the study period compared with 34% of those taking placebo. In addition, the researchers noted these improvements with prasterone were observed within the first 3 months of treatment.<sup>21</sup>

Overall, patients in these trials receiving prasterone showed a response rate from 10% to 20% greater than did those taking placebo. Also, researchers noted that prasterone reduced the number of flares and reduced disease activity for patients with both chronic SLE and those with periods of quiescence (ie, remission).

**Other Prasterone Effects.** Data from these studies also show that, although prasterone is metabolized to estradiol as well as testosterone and postmenopausal women taking the drug may achieve estradiol levels similar to those expected with hormone replacement therapy (HRT), no increase in breast cancer was observed in these patients. Because long-term follow-up in postmenopausal women taking prasterone has not yet been done, these patients will require the same monitoring given to those taking HRT.

A reduction in high-density lipoprotein (HDL) cholesterol was also observed with prasterone but this may be a result of a change in reverse cholesterol transport, which may be protective against atherosclerosis. Long-term follow-up will also be

needed to determine the effects of this HDL cholesterol reduction in SLE patients.

### Other Emerging Treatments

**LPJ-394.** LPJ-394 is a biologic agent, currently in phase III clinical trials, designed to reduce anti-dsDNA antibody production in patients with lupus-related organ involvement. In one early safety study, a single intravenous dose of LPJ-394 significantly lowered anti-dsDNA values.<sup>22</sup>

A more recent, 76-week multicenter trial including 211 SLE patients with renal disease was designed to determine whether treatment with LPJ-394 delayed renal flares, reduced anti-dsDNA antibody concentration, and reduced the need for steroid and cyclophosphamide usage among patients. Researchers found that patients randomized to receive the drug experienced benefit in terms of improved renal function, increased time to renal flare, and decreased SLE symptoms.<sup>23</sup>

So far, LPJ-394 appears to be well tolerated. The agent is not immunogenic or antigenic. A further double-blind, randomized, placebo-controlled safety and efficacy trial is under way.

**Mycophenolate Mofetil.** This immunosuppressive agent is approved for use in the prevention of renal and cardiac allograft rejection but recent studies show it may be of significant benefit to patients with lupus nephritis. The largest trial involved 42 patients with diffuse proliferative lupus nephritis treated for 1 year with prednisone and mycophenolate mofetil. Results indicated that this regimen was as effective in stabilizing renal function as a prednisone and oral cyclophosphamide combination given for 6 months followed by prednisone and azathioprine for another 6 months.<sup>24</sup>

**Leflunomide.** This pyrimidine synthesis inhibitor is an immunomodulatory agent approved for rheumatoid arthritis. A pilot study and open-label study have been conducted in SLE patients. Although steroid use was reduced in some patients

receiving leflunomide, it was increased in others. However, symptom improvement and lower SLEDAI scores appear to be reduced and the drug seems to be well tolerated. Larger, placebo-controlled trials are needed to determine efficacy in mild-to-moderate SLE patients.<sup>25,26</sup>

### ... DISCUSSION HIGHLIGHTS ...

**Dr. Abu-Samrah:** Did the patients receiving prasterone in the clinical trials complain of the androgen effects of acne and hirsutism?

**Dr. Petri:** There was some acne and on rare occasions, hirsutism. The acne was generally manageable with topical metronidazole and there were very rarely study withdrawals because of these side effects. Also, patients already taking prednisone often experience acne and hirsutism as well.

One problem that physicians may face is that SLE patients may be tempted to use over-the-counter DHEA supplements, which are not regulated and may be contaminated with other hormones. Furthermore, only the 200-mg dose of prasterone has been shown to be effective, and supplemental products do not guarantee accurate dosing. Adequate monitoring of patients using supplemental over-the-counter DHEA will also be lacking.

**Mr. Hardesty:** How do prasterone and other agents fit in to the management of patients with mild SLE symptoms? What would be the goal?

**Dr. Petri:** I think we will eventually have a cocktail of immunomodulators, which are not immunosuppressive. For example, mild-to-moderate SLE patients may take prasterone and hydroxychloroquine, with bromocriptine in some cases. The goal would be to eliminate the use of steroids in these patients. If the patient develops a major flare, pulsed-dose steroids can be used short term. The vast majority of lupus patients may be maintained on this regimen and significant cost savings could

be realized through the reduction in steroid side effects.

The development of biologics and new forms of treatment for severe, life-threatening forms of SLE will still be needed, however.

**Dr. Clarke:** Is prasterone something that can be continued as background medication during a flare or major organ involvement requiring prednisone therapy?

**Dr. Petri:** Yes. For those who flare, this medication can be continued as background medication during the flare. Prasterone is very much like hydroxychloroquine in that many patients will do fine.

**Dr. Clarke:** Is prasterone exclusively for female patients or may it be used in men with SLE?

**Dr. Petri:** Unfortunately there have been no studies of prasterone in men with SLE. There is some concern about how men respond to androgens and whether this would affect their endogenous testosterone levels, causing them to drop. There is a safety study under way using prasterone in men but currently, approval is being sought for women only.

**Dr. Abu-Samrah:** Are there any pharmacoeconomic studies with prasterone that would show that the addition of this medication to managed care formularies is truly cost effective?

**Dr. Petri:** There is not a formal pharmacoeconomic analysis for any of the prasterone studies completed. However, in one of the clinical trials, not only were there fewer flares among patients taking prasterone, but there were fewer hospitalizations resulting from flares and the reduction was quite compelling.<sup>21</sup>

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