

Modulation of Hormones in the Treatment of Lupus

Based on a presentation by Sara E. Walker, MD, MACP

Presentation Summary

The etiologic enigma of systemic lupus erythematosus (SLE) has so far precluded a fully integrated approach to understanding and managing the disease. As new findings continue to uncover relationships between the endocrine system and the besieged immune system in lupus patients, however, researchers have an opportunity to rethink the direction of their investigative efforts. A successful approach to development of long-awaited new treatments may well include modulation of specific hormones. The peptide hormone prolactin may be associated with SLE disease activity. The dopamine agonist bromocriptine, which inhibits pituitary secretion of prolactin, has been shown in a variety of small animal and human trials to reduce disease activity in SLE. Continued research may show that it can be an attractive alternative or adjacent therapy in cases where hydroxychloroquine is contraindicated.

The search for increasingly effective and safer treatments for systemic lupus erythematosus (SLE) is hampered by unanswered questions concerning its etiology and the causes of disease flares. There is promise, however, in emerging discoveries such as the relationship between the endocrine and immune systems. Various findings point to a clear relevance of hormonal factors that need to be further explored.

Estrogens and Testosterone

Women are the primary targets of SLE, especially during the years between puberty and menopause. Estrogen is stimulatory with regard to SLE, whereas

testosterone is protective. In F1 hybrid New Zealand black X New Zealand white mice spontaneously afflicted by severe lupus, the females become ill and die earlier than the males. All of the female mice die with severe lupus glomerulonephritis. This is true of the males as well; however, 25% of males also develop a lymphoma. Estrogen is associated with increased morbidity in these mice. Testosterone had a beneficial effect in females, even when given after development of severe renal disease.¹

In humans, estrogen metabolism has been shown to be abnormal in lupus. Specifically, estriol and 16-alpha hydroxyestrone are increased, but 17-beta estradiol is normal. Flares may be associated with certain points in the menstrual cycle and are more frequent during pregnancy. Ovulation induction and in vitro fertilization, where estradiol levels are greatly increased, have been associated with de novo lupus, SLE deaths, and severe flares.²⁻⁵

After menopause, when flares tend to subside and the number of new cases drops, hormone replacement therapy (HRT) may spur flares and even de novo SLE; these hypotheses are currently being tested. We do know that in the framework of the Nurses' Health Study,⁶ 45 of 120,000 women self-reported lupus diagnoses, and postmenopausal HRT increased the risk of developing lupus 1.8- to 2.5-fold; further, the risk was dependent on treatment duration.

Androgen levels tend to be very low in women with active lupus. At the same time, male sufferers have shown evidence

of increased estradiol levels, low hydroxyestrone and estrone levels, and not uncommonly, hypoandrogenism with elevated levels of luteinizing hormone and low testosterone.² In the New Zealand mice mentioned above, testosterone treatment proved beneficial. The attenuated androgen nandrolone, which produces masculinizing effects, showed clear benefit, whereas danazol was not beneficial.²

Testosterone treatment of 2 human Klinefelter syndrome patients resulted in lupus going into remission.⁷ Danazol in humans with mildly active disease was associated with decreased antidouble-stranded DNA, increased platelets, and raised serum complement.⁸ A study of 19-nortestosterone, however, found no effectiveness in women and disease flares in men.⁹

Anti-estrogen agents to control SLE have been used in several studies. In one trial of 11 patients with stable disease who were given tamoxifen, none improved and 2 patients' conditions deteriorated.¹⁰

Prolactin

Prolactin, a peptide hormone necessary for production of milk in mammals, is produced in various systems of the body in addition to the anterior pituitary. It is also related to the immune system; lymphocytes produce it and employ it as an endogenous growth factor. Prolactin, by its function, is thought to be a cytokine. It stimulates production of interferon (IFN) γ and IFN regulatory factor 1. Of 10 studies, 8 have shown that a significant number of lupus patients (approximately 20%) have above-normal levels of this hormone in circulation.¹¹

Bromocriptine, a dopamine agonist, prevents secretion of prolactin by the anterior pituitary. It inhibits antibody formation and cell-mediated immunity. Various specific immune effects, including inhibition of cell proliferation, immunoglobulin production, and early T-cell activation, have been demonstrated in laboratory and animal testing.¹¹

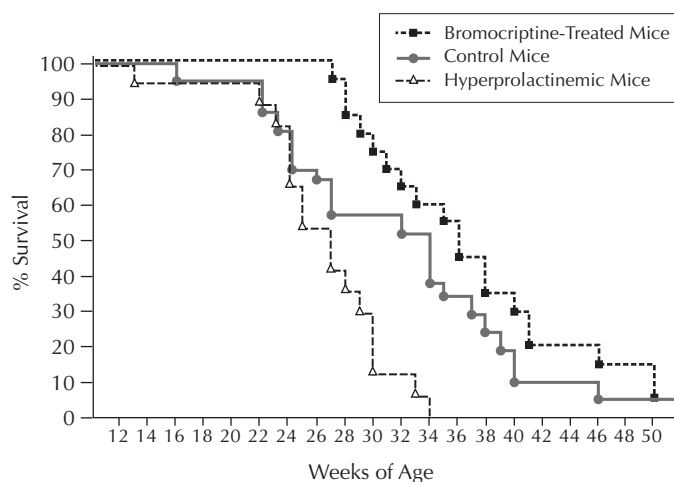
In the New Zealand mice, induction of pseudopregnancy was associated with

prolonged surges of prolactin and acceleration of lupus.¹² Inducing hyperprolactinemia in the mice (eg, via pituitary gland transplants) also exacerbated their lupus. Administration of bromocriptine reduced prolactin levels and suppressed lupus flares (Figure 1).¹³

Another study that manipulated relative levels of both estrogen and prolactin in mice found that high prolactin levels were more predictive of lupus activity.¹⁴ Keeping in mind the fact that estrogen stimulates pituitary production of prolactin in rodents, this finding sheds new light on the numerous animal studies showing a correlation between treatment with estrogen and increased severity of lupus activity. It is possible that estrogen increases production of prolactin and the high levels of prolactin lead to stimulation of lupus.

A number of SLE patients (we have found 20 in the United States) have been shown to have prolactinomas. It will be worth investigating how many previously identified hyperprolactinemic lupus

Figure 1. Survival Curves for Bromocriptine-Treated, Control, and Hyperprolactinemic Mice



Source: McMurray RW, Keisler D, Kanuckel K, Izui S, Walker SE. Prolactin influences autoimmune disease activity in the female B/W mouse. *J Immunol* 1991;147:3780-3787. Reprinted with permission.

patients have a coexisting prolactinoma. One lupus patient with a small prolactinoma had been treated with the steroid prednisone and refused further such treatment and then was treated with bromocriptine.¹⁵ During her first month on bromocriptine alone she experienced a flare, but after 3 months of treatment the disease was less active. Another young woman with a prolactinoma and SLE was treated successfully with bromocriptine. SLE disease flares correlated with high prolactin levels during the treatment period.¹⁶

In an open-label study we performed at our institution, we gave maintenance doses of bromocriptine to 7 patients with mildly active, carefully identified lupus, the goal being to reduce their serum prolactin level to 3 ng/mL. After 6 months of treatment, the patients' Systemic Lupus

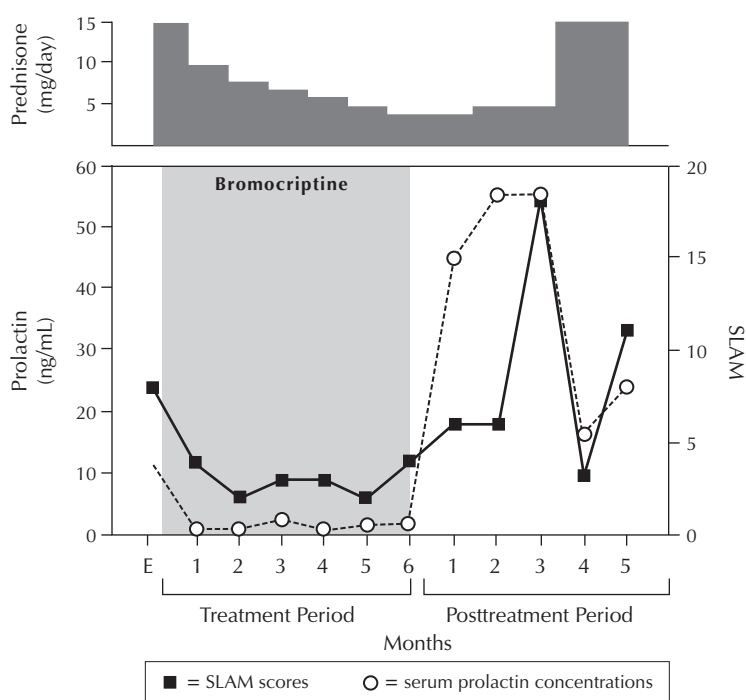
Activity Measure (SLAM) and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores had decreased substantially. All had increased disease activity upon stopping treatment; several had unexpected flares.¹⁷

Figure 2 illustrates a patient who had active SLE before treatment. Squares indicate SLAM scores, and circles indicate serum prolactin concentrations. Disease activity improved during treatment. Rebound hyperprolactinemia was observed 1 month after prolactin was stopped. Two months later, the patient had a severe lupus flare that was managed by giving an increased dose of prednisone.¹⁷

In addition, a double-blind study of 66 patients in Mexico with active or inactive disease also found reduced frequency of flares after 2 to 17 months of treatment with bromocriptine versus placebo.¹⁸

Finally, in our most recent, blinded study, 24 patients with mild, active, nonorgan-threatening disease were randomized to bromocriptine or hydroxychloroquine. Both groups experienced significant improvement in SLAM and SLEDAI scores after 1 year, and almost all bromocriptine patients chose to continue it for a second year.¹⁹

Figure 2. Serial Prolactin Levels and SLAM Assessments in an SLE Patient Before, During, and After Bromocriptine Therapy



Conclusion

In light of these various hormonal-immune system interactions, we must rethink our "separate systems" approach to SLE. Patients must be treated and counseled in a way that minimizes disease flares, with particular attention paid to planning pregnancy and extreme caution exercised with women who request ovulation induction and in vitro fertilization.

New potential treatments for SLE include bromocriptine, which has been discussed here, and prasterone, which will be discussed in detail by Dr. Wallace in his presentation.

REFERENCES

SLAM = Systemic Lupus Activity Measure; SLE = systemic lupus erythematosus.
Source: McMurray RW, Weidensaul D, Allen SH, Walker SE. Efficacy of bromocriptine in an open label therapeutic trial for systemic lupus erythematosus. *J Rheumatol* 1995;22:2084-2091. Reprinted with permission.

1. Hahn BH. Animal models of systemic lupus erythematosus. In: Wallace DJ, Hahn BH, eds. *Dubois' Lupus Erythematosus*. 5th ed. Baltimore, MD: Williams & Wilkins; 1997:339-380.

2. **Walker SE.** The importance of sex hormones in lupus. In: Wallace DJ, Hahn BH, ed. *Dubois' Lupus Erythematosus*. 5th ed. Baltimore, MD: Williams & Wilkins; 1997:311-322.
3. **Ben-Chetrit A, Ben-Chetrit E.** Systemic lupus erythematosus induced by ovulation induction treatment. *Arthritis Rheum* 1994;37:1614-1617.
4. **Casoli P, Tumiati B, La Sala G.** Fatal exacerbation of systemic lupus erythematosus after induction of ovulation. *J Rheumatol* 1997;24:1639-1640.
5. **Guballa N, Sammaritano L, Schwartzman S, Buyon J, Lockshin MD.** Ovulation induction and in vitro fertilization in systemic lupus erythematosus and antiphospholipid syndrome. *Arthritis Rheum* 2000;43:550-556.
6. **Liang MH, Karlson EW.** Female hormone therapy and the risk of developing or exacerbating systemic lupus erythematosus or rheumatoid arthritis. *Proc Assoc Am Physicians* 1996;108:25-28.
7. **Bizzarro A, Valentini G, Di Martino G, Daponte A, De Bellis A, Igcono G.** Influence of testosterone therapy on clinical and immunological features of autoimmune diseases associated with Klinefelter's syndrome. *J Clin Endocrinol Metabol* 1987;64:32-36.
8. **Agnello V, Pariser K, Gell J, Gelfand J, Turksoy RN.** Preliminary observations on danazol therapy of systemic lupus erythematosus: Effects on DNA antibodies, thrombocytopenia and complement. *J Rheumatol* 1983;10:682-687.
9. **Lahita RG, Cheng CY, Monder C, Bardin CW.** Experience with 19-nortestosterone in the therapy of systemic lupus erythematosus: Worsened disease after treatment with 19-nortestosterone in men and lack of improvement in women. *J Rheumatol* 1992;19:547-555.
10. **Sturgess AD, Evans DTP, Mackay IR, Rigler A.** Effects of the oestrogen antagonist tamoxifen on disease indices in systemic lupus erythematosus. *J Clin Lab Immunol* 1984;13:11-14.
11. **Walker SE, Jacobseon JD.** Roles of prolactin and gonadotropin-releasing hormone in rheumatic diseases. *Rheum Dis Clin North Am* 2000;26:713-736.
12. **McMurray RW, Keisler D, Izu S, Walker SE.** Effects of parturition, suckling and pseudopregnancy on variables of disease activity in the B/W mouse model of systemic lupus erythematosus. *J Rheumatol* 1993;20:1143-1151.
13. **McMurray RW, Keisler D, Kanuckel K, Izui S, Walker SE.** Prolactin influences autoimmune disease activity in the female B/W mouse. *J Immunol* 1991;147:3780-3787.
14. **Elbourne KB, Keisler D, McMurray RW.** Differential effects of estrogen and prolactin on autoimmune disease in the NZBWZWF1 mouse model of systemic lupus erythematosus. *Lupus* 1998;7:420-427.
15. **McMurray RW, Allen SH, Braun AL, Rodriguez F, Walker SE.** Longstanding hyperprolactinemia associated with systemic lupus erythematosus: Possible harmful stimulation of an autoimmune disease. *J Rheumatol* 1994;21:843-850.
16. **Funauchi M, Ikoma S, Enomoto H, et al.** Prolactin modulates the disease activity of systemic lupus erythematosus accompanied by prolactinoma. *Clin Exp Rheumatol* 1998;16:479-482.
17. **McMurray RW, Weidensaul D, Allen SH, Walker SE.** Efficacy of bromocriptine in an open label therapeutic trial for systemic lupus erythematosus. *J Rheumatol* 1995;22:2084-2091.
18. **Alvarez-Nemegyei J, Cobarrubias-Cobos A, Escalante-Triay F, Sosa-Munoz J, Miranda JM, Jara LJ.** Bromocriptine in systemic lupus erythematosus: A double-blind, randomized, placebo-controlled study. *Lupus* 1998;7:414-419.
19. **Walker SE, Reddy GH, Miller D, et al.** Treatment of active systemic lupus erythematosus (SLE) with one prolactin (PRL) lowering drug, bromocriptine (BC): comparison with hydroxychloroquine (HC) in a randomized, blinded one-year study. *Arthritis Rheum* 1999;42:S282 (abstract).

Because Dr. Walker's presentation immediately preceded Dr. Wallace's presentation, there are no Discussion Highlights for this article.