Prasterone and Bone Mineral Density in Women with Systemic Lupus Erythematous

To the Editor:

We read with interest the report by Mease, et al describing improved bone mineral density (BMD) in glucocorticoid-treated women with systemic lupus erythematous, after prasterone (DHEA) therapy at 200 mg/day for one year1. Readers should be aware that DHEA doses of 200 mg/day are clearly supraphysiological. Based on our own clinical and laboratory experience with DHEA therapy, and the scientific literature, doses of DHEA greater than 50 mg/day almost always result in urinary DHEA and DHEA metabolite (androsterone and etiocholanolone) concentrations that are higher than those measured in healthy young adults.

Callies, et al reported that when DHEA 50 mg/day was given to elderly men and women, urinary excretions of DHEA and metabolites were slightly higher than in healthy young adults, while DHEA 100 mg/day resulted in clearly supraphysiological values2. A study of the effects of DHEA on prednisone pharmacokinetics and cortisol suppression in healthy women reported that serum DHEA and DHEA-S were significantly greater than endogenous levels at a dose of 200 mg/day3. The risk of adverse effects increases with increasing DHEA dose4.

In our experience, women receiving DHEA doses of 100 mg/day or higher often have elevated testosterone concentrations in serum and urine, and prominent androgenic side effects.

Some patients may need supraphysiological doses of DHEA. In these cases, monitoring of DHEA and its metabolites would be prudent. Improved BMD in older women after DHEA 50 mg/day has been reported in one study5. Followup studies comparing 50 mg doses of DHEA to the 200 mg dose should be undertaken to evaluate effects on bone density. In any case, based on our experience with thousands of patients receiving DHEA therapy, we recommend laboratory testing for any patient taking 25 mg/day or more. Twenty-four hour urinary steroid hormone profiling may be especially helpful, because it allows determination of DHEA and several downstream metabolites, including androsterone, etiocholanolone, estradiol, estrone, and testosterone.

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Dr. Mease and Dr. Schwartz reply

To the Editor:

Alexander and colleagues have queried about the rationale for the 200 mg/day dose of prasterone used in our recent study1. Our study assessing bone mineral density (BMD) was nested within a larger 381 patient study designed to assess effects of prasterone on overall lupus disease2. Women with active systemic lupus erythematous have low circulating levels of DHEA-S, which are suppressed even further by treatment with exogenous glucocorticoids3-4. The dose of prasterone, 200 mg/day, was intended to be a pharmacologic rather than a replacement dose and was based partly on earlier Stanford reports5-6, as well as our own experience with 100 mg/day in a steroid-sparing study, in which a dose response was observed between placebo and 100 and 200 mg prasterone per day7.

Acne and hirsutism have been the principal androgenic side effects observed; most reported side effects have been mild and have not led to withdrawal from treatment2.

Alexander, et al cite a French study that assessed changes in bone mineral density (BMD) in normal, healthy men and women aged 60–79 years who received 50 mg/day prasterone or placebo for up to one year8. No effects on BMD were observed in men; in women, a positive effect on BMD was observed, mostly in trabecular bone zones. However, few of the multiple comparisons reported were statistically significant, and none of the comparisons for change in BMD at the total hip was significant. Further, they did not report BMD in the lumbar spine and, importantly, these were not patients receiving glucocorticoids.

The metabolism of prasterone is complex, with both downstream androgenic and estrogenic metabolites. Additionally, prasterone may also have direct actions that do not require conversion to downstream androgens or estrogenic metabolites9-11. While measurement of various downstream metabolites is of interest, we believe the most important measurements remain those of serum testosterone, estradiol, and DHEA/DHEA-S.

Finally, it should be noted that prasterone is an investigational agent, currently in testing as a treatment for lupus. There are currently no US Food and Drug Administration-approved indications for its use.

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It was with great interest that I read the article by Kokotis, et al, which described bilateral ocular myositis occurring in a patient several years after dermatomyositis. The authors state that the diagnosis of definite DM was established based on the information referred to above. They support their statement by referring to 2 book chapters instead of referring to established diagnostic criteria.

Second, the authors do not provide solid evidence that the patient suffered from DM and ocular myositis. It cannot be concluded that the patient suffered from DM and ocular myositis. It can therefore be stated that the general rule mentioned earlier (that the occurrence of diplopia or ophthalmoplegia in a patient diagnosed with an idiopathic inflammatory myopathy is indicative of another coincidental disease) is still valid.

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fibrillation was present with heart rate of 80/min. Laboratory evaluation showed antinuclear antibodies (ANA, 1:640, homogeneous pattern), but no other autoantibodies (anti-DNA, antinuclear cytoplasmic antibodies, antiperoxidase, anti-SSA/Ro, and rheumatoid factor). The other laboratory data were normal, including creatine phosphokinase, C-reactive protein, complement, and thyroid function tests.

Orbital magnetic resonance imaging (MRI) was consistent with inflammatory myopathy of extrinsic ocular muscles. Electromyography (EMG) of arm and leg muscles showed mild involvement confined to deltoid. She refused azathioprine and began methotrexate (MTX), 7.5 mg once a week, with a slow but significant improvement. Orbital MRI was unchanged in June 2000, but by December 2000 did not show any myopathy, even though a mild exophthalmus persisted. MTX was progressively reduced and discontinued. When last seen (March 2004), she was in good health.

As far as we know, this is the second case of bilateral orbital myositis in patients with systemic inflammatory myopathy. Interestingly, our patient, like the patient described by Kokotis, et al1, developed orbital myositis several years after systemic muscle involvement, with no other symptoms than proptosis and exophthalmus, and with normal circulating muscle enzymes (Kokotis’s patient reported erythema on the back and eyelid). Several cases of orbital myositis have been reported in association with autoimmune rheumatic diseases2-4, however, although our patient had antinuclear antibodies, since there were no symptoms/signs suggesting other rheumatic diseases, since mild signs of myopathy were indeed recorded on EMG, and because the previous biopsy-based diagnosis of inflammatory polymyositis, we conclude that our patient had bilateral ocular myositis as a late complication of polymyositis.

Another interesting feature that seemed to emerge in both patients was good response to low dose MTX. Our patient was started on MTX, having refused azathioprine and because steroids were contraindicated for severe osteoporosis. Kokotis’s patient did not benefit from azathioprine or intravenous immunoglobulin, but did improve with MTX. Poor response to steroids has been recently reported in a child with idiopathic orbital myositis5.

In accord with Kokotis, et al, we conclude that ocular myositis is probably less rare than previously thought and suggest the usefulness of low dose MTX.

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REFERENCES

Dr. Kokotis replies
To the Editor:
We thank Dr. Hengstman for his comments on our article. Our patient pre-

Figure 1. Orbital MRI (T1 sequence) showing enlargement of the muscle bellies (arrow A), as well of the tendons of the orbital muscles (arrow B) in a patient who developed bilateral ocular myositis as a late complication of dermatomyositis.
sent with typical red-purple edematous erythema on the upper palpebra (skin lesion), he had myopathic-like changes on electromyography and pathologic findings compatible with inflammatory myositis in muscle biopsy, and had experienced proximal muscle weakness in the past that resolved with prednisone treatment. Therefore, he met the classification criteria for dermatomyositis (DM) according to Tanimoto, et al, as well as the proposed revised classification criteria for idiopathic inflammatory myopathies by Targoff, et al. Serum creatine kinase or aldolase levels were not measured at the time when proximal muscle weakness was clinically evident. Clearly this is not a case of severe DM, but, as we have stated, represents a mild disease form that was untreated for years. Further, the presence of orbital myositis is fully supported by his clinical condition, i.e., the presence of erythema, eyelid edema, and orbital pain, as well as by magnetic resonance image (MRI) findings. The absence of diplonia or ophthalmoplegia, which were also not present in 15% of the 52 patients with orbital myositis reviewed by Berkhoff, et al, does not exclude this diagnosis. Indeed, Siatkowski, et al observed normal function of the affected muscles in 34 of 74 patients (45%) with idiopathic orbital myositis.

Unintentionally, we failed to mention that ophthalmopathy associated with Graves’ disease was excluded on the basis of normal thyroid function and thyroid autoantibody profile, including thyrotopin receptor antibodies. Further, the MRI findings (Figure 1) disclosed not only involvement of the muscle bellies, but also enlargement of the tendons of the orbital muscles. MRI measurements of orbital tissues in thyroid-associated ophthalmopathy have shown that tendons are not affected in patients with Graves’ disease6.

Dr. Marasini and her colleagues report a second case of bilateral ocular myositis that developed 10 years after initial diagnosis of inflammatory myopathy. Their case has striking similarities to our patient, including normal levels of serum muscle enzymes and thyroid function, no diplonia or ophthalmoplegia, and a beneficial response to treatment with methotrexate.

To conclude, although we agree that the occurrence of diplonia or ophthalmoplegia in a patient diagnosed with polymyositis or DM requires a thorough differential diagnosis to exclude coincidental disease, we feel that our case report as well as the second patient described by Marasini, et al indicate that ocular myositis should not be overlooked in patients with Graves’ disease.

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of BCG vaccine, the injection technique, and the age and immune status of the vaccinated person. Disseminated BCG disease causes fever, weight loss, lymphadenopathy, severe illness, and pulmonary symptoms. Talbot, et al reported one case of disseminated BCG disease in an HIV-negative infant and reviewed another 27 cases, mostly associated with immunodeficiency, including 9 patients with acquired immunodeficiency syndrome.

In BCG infected mice, TNF-α is required for granuloma formation and mycobacterial elimination, and TNF-α messenger RNA has been detected in granulomas. Thus, BCG vaccine must be considered a potent active mycobacterium in anti-TNF-α treated patients. However, several substrains of BCG exist that may have different virulence and reactivity. Our patient did not develop any reaction to BCG vaccination. This might indicate that the BCG substrain used for inoculation had low virulence or a good safety profile. An alternative explanation might be the efficacy of the isoniazid treatment, since the BCG substrains used in France are highly sensitive to this drug. The duration of isoniazid treatment in our patient was empiric. Although BCG disseminated disease usually occurs a few months after vaccination, rarely later, caution is required before reintroducing anti-TNF-α therapy, and it is difficult to decide when the anti-TNF-α agent should be reintroduced in this situation.

In light of these observations, BCG vaccination should be avoided in patients taking TNF-α blockers. In case of accidental BCG administration, anti-tuberculosis prophylaxis is strongly recommended, the choice of anti-tuberculosis drug depending on the BCG substrain. This case also highlights the importance of education, in particular regarding vaccinations, in patients receiving anti-TNF-α therapy.

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Simultaneous Presentation of Cryptococcal Meningitis and Lupus Nephritis

To the Editor:

Infection is a significant cause of morbidity and mortality in systemic lupus erythematosus (SLE). Patients with lupus are known to be at heightened risk for common pathogens as well as opportunistic organisms. Susceptibility to infection may be attributed to underlying immune dysregulation and to immunosuppressive therapy. Clinicians caring for these patients need to be familiar with the range of potential pathogens and maintain a high index of suspicion for infection whenever new symptoms or fevers occur. Indeed, severe life-threatening infection can not only mimic but can present simultaneously with new-onset lupus, based on our recent experience.

A 30-year-old woman originally from Guatemala presented to the Johns Hopkins Hospital with acute renal failure. She was well until 2 months prior to admission, when she developed gradual onset of fatigue with intermittent diffuse abdominal discomfort and nausea. One week prior to admission, she developed diffuse myalgias and arthralgias involving the knees, hands, and wrists and pleuritic chest pain. Several days prior to admission she complained of a bitemporal headache without photophobia. Upon hospitalization, she was afebrile. She had no rash, oropharyngeal ulcers, or synovitis. Meningismus was absent; mental status and peripheral neurologic examination were unremarkable. Admission examinations included serum creatinine of 4.4 mg/dl and white blood cell (WBC) count of 2300 cells/mm³. Erythrocyte sedimentation rate was elevated at 102 mm/h. Profound hypoalbuminemia was present, with C3 24 mg/dl and C4 3 mg/dl. Antinuclear antibody titer was 1:640. Anti-double-stranded DNA titer was markedly elevated at 1:640. Chest computer tomography scan revealed pleural and pericardial effusions. Renal histopathology showed WHO class IV glomerulonephritis with numerous crescents.

Based on these findings she was diagnosed with SLE. The headache was initially attributed to lupus disease activity. Intravenous methylprednisolone was initiated at 1 gm/day for 3 consecutive days, followed by oral prednisone 60 mg/day. Given the severity of renal disease, intravenous cyclophosphamide was administered at 750 mg/m². The day after cyclophosphamide infusion, she developed fever. She continued to have a mild intermittent headache and no abnormalities detected by neurologic or funduscopic examination. Lumbar puncture revealed normal cerebrospinal fluid (CSF) protein and glucose concentrations and only 1–2 WBC/mm³, but both CSF and blood cultures grew Cryptococcus neoformans.

She was treated with a 14 day course of liposomal amphotericin, followed by a 42 day course of fluconazole, with prompt resolution of the fever and headache. Corticosteroids were gradually tapered. Subsequent blood and CSF cultures one month after diagnosis were negative for fungal growth. She did require hemodialysis at the time of discharge, but was not given additional cyclophosphamide during the hospitalization.

A large variety of organisms have been reported in association with SLE including bacteria, mycobacteria, viruses, fungi, and protozoa. Moreover, infections are reported to account for 14% of hospital admissions in affected persons. Whether susceptibility to infection is due to immunosuppressive treatment only or to the underlying disease is uncertain.

Glucocorticoid and cytotoxic drugs may suppress the immune system and heighten susceptibility to infection. Infection rates are reported to be 2–4 times higher in patients treated with compared to those treated without steroids.

Interestingly, there may be inherent immunologic abnormalities associated with lupus that also predispose to infection. Studies conducted prior to the widespread use of immunosuppressive therapies indicated an elevated
risk of infection in lupus. Further, deficiencies of complement components, which are known to predispose to development of lupus, may also lead to impaired clearance of immune complexes and microbial pathogens. Specifically, patients with lupus who possess deficient mannose-binding lectin are at higher risk for serious infection.

Cryptococcal meningitis is an uncommon complication of SLE. Most reports of cryptococcal disease in lupus describe patients who have been maintained on high levels and sustained durations of immunosuppressive therapy. Zimmermann, et al reported 2 new cases and reviewed the literature regarding 24 previous cases. Mean duration of lupus at development of cryptococcal meningitis was 3.3 years. Twenty-four of these patients were treated with corticosteroids and 10 with azathioprine. The outcome without antifungal therapy was uniformly poor, and all 5 untreated patients died. In contrast, there were 8 deaths in the 20 patients treated with amphotericin. Further, there has been one previous report of a patient who developed cryptococcal meningitis concurrent with the diagnosis of SLE and prior to initiation of immunosuppressive therapy.

Our case represents the second report of a patient diagnosed with cryptococcal meningitis simultaneously with onset of SLE. We believe the unusual presentation suggests that underlying immune defects associated with lupus contributed to their infection, since both cases became clinically apparent before receipt of prolonged immunosuppression.

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