HORMONAL MODULATION IN SYSTEMIC LUPUS ERYTHEMATOSUS

Preliminary Clinical and Hormonal Results with Cyproterone Acetate

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We prospectively studied the effects of hormonal modulation using the antigonadotropic drug, cyproterone acetate (CA), in 7 female patients who had moderately active systemic lupus erythematosus. CA was taken orally at a mean daily dose of 50 mg for 21–33 months by 6 patients (9 months by the seventh patient) without any side effects. The number of clinical lupus exacerbations during CA treatment was lower than that during the corresponding pretreatment period (15 of 170 patient-months versus 27 of 156 patient-months; $P < 0.05$), despite a reduction in the daily maintenance dose of corticosteroids or antimalarial drugs. Mean plasma testosterone levels were low initially and remained unchanged (0.66 ± 0.31 to 0.59 ± 0.23 nmoles/liter), whereas plasma estradiol decreased markedly (from 0.6 ± 0 38 to 0.11 ± 0.03 nmoles/liter), resulting in a significant reduction in the estradiol:testosterone ratio (from 1.19 ± 0.68 to 0.23 ± 0.12) and in the plasma concentration of the sex hormone–binding protein. Thus, cyproterone acetate induced improvement in clinical lupus activity in parallel with the expected lower estradiol:testosterone balance.

The predominance of females among patients with systemic lupus erythematosus (SLE) and the frequent exacerbation of the disease during pregnancy (1) or following oral contraceptive therapy (2) highly suggest that sex hormones influence disease activity. Animal studies have clearly demonstrated the deleterious effects of estrogens and the favorable effects of androgens on the course of murine lupus (3,4). Moreover, recent hormonal studies showed increased production of estrogenic metabolites in female SLE patients (5), and we observed low plasma androgen levels in women in remission or with active SLE (6), a finding recently confirmed by Labita et al (7).

Such concordant experimental and clinical data led to consideration of a therapeutic use of sex hormones (hormonal modulation), in an attempt to achieve a higher androgen:estrogen balance in female SLE patients. Weak androgens with anabolic properties, such as nandrolone decanoate or danazol, were used in a few trials. However, the former was ineffective (8), and while the latter induced clinical improvement (9), it was at the expense of a high incidence of side effects, as was observed in our own unpublished preliminary studies.

We therefore attempted evaluation of another means of hormonal modulation by using cyproterone acetate, a synthetic hydroxyprogesterone derivative first known as a progestogen, which possesses antigonadotropic properties, and thus, in female subjects suppresses ovulation, depresses ovarian estrogen secretion (10–12), thereby acting as an oral contraceptive. Moreover, this molecule is devoid of anabolic

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Table 1. Clinical characteristics, previous treatments, and existing therapy at the start of cyproterone acetate (CA) treatment in 7 female systemic lupus erythematosus patients*

Patient	Age	Clinical features	Anti-DNA titer (%)†	Antinuclear antibody (ANA) titer†	Previous treatment	Existing therapy	Duration taking CA (months)
1	40	Oral and vulvar ulcers, arthritis, diplopia, psychosis, proteinuria, positive skin biopsy	43	1:100	CS, AMD	Pred, 15 mg/day	33
2‡	46	Skin rash, oral ulcers, arthritis, Raynaud's phenomenon, photosensitivity, fever, positive skin biopsy	39	1:1,000	CS, CY	Pred, 25 mg/day	31
3	23	Skin rash, oral ulcers, arthritis, photosensitivity, positive ANA	15	1:100	AMD	HCQ, 400 mg/day	26
4	23	Skin rash, arthritis, photosensitivity, positive ANA	17	1:1,000	AMD	HCQ, 800 mg/day	25
5	41	Discoid rash, oral ulcers, Raynaud's phenomenon, arthritis, false-positive VDRL, lupus anticoagulant	22	1:100	AMD	HCQ, 400 mg/day	24
6	34	Skin rash, arthritis, seizures, diffuse proliferative nephritis, lupus anticoagulant	72	1:1,000	CS, AMD	Pred, 25 mg/day	21
7	20	Skin rash, arthritis, positive ANA, focal proliferative nephritis	76	1:1,000	CS	Pred, 20 mg/day	9

* CS = corticosteroids; AMD = antimalarial drugs; Pred = prednisone; CY = cyclophosphamide; HCQ = hydroxychloroquine.
† Maximum observed value.
‡ Patient 2 was amenorrheic; all other patients had regular menses.

effects and possesses antiandrogenic (mainly at skin level) and synandrogenic (on liver and kidney) properties (13–16), the latter appearing to be of potential interest for female SLE patients.

In an open preliminary trial, cyproterone acetate (CA) was administered to 7 female patients with moderately active SLE, who had been fully informed concerning the trial. Since a beneficial effect of CA on SLE activity was conjectural, the trial was confined to patients whose disease activity was mild or moderate and who did not require more than 25 mg prednisone per day to control SLE activity. In each patient, we prospectively evaluated long-term clinical effects and tolerance of the drug, as well as modifications induced in the hormonal milieu.

PATIENTS AND METHODS

Patients. Seven female patients (mean age 32.4 years, range 20–46) who satisfied the American Rheumatism Association criteria for SLE (17) volunteered to enter the trial. In each patient, SLE was mildly clinically active when the hormonal treatment was started. Clinical characteristics of the disease, previous treatments, and existing therapy are reported in Table 1. SLE had initially been severe in 4 patients (with diffuse or focal proliferative nephritis in 2

patients), who previously received high-dose corticosteroid (CS) therapy; patient 2 was also treated with cyclophosphamide.

At the time of entry into the study, 4 patients were receiving a maintenance dose of 15–25 mg/day of prednisone; 2 of them were also receiving antimalarial drugs. In the other 3 patients, who never received CS and were treated only with antimalarial drugs, the disease was less severe, marked only by cutaneous and articular manifestations. None of the patients had taken oral contraceptive or progestational treatment for at least 2 months before the start of the trial.

All patients but 1, who had persistent amenorrhea following previous cyclophosphamide therapy, had regular menstrual cycles. Hepatic enzyme, glucose, total cholesterol, and triglyceride levels were within normal ranges in all patients. Plasma creatinine levels were below 110 μmoles/liter (1.2 mg/dl) in every patient.

Oral cyproterone acetate was used at a daily dose of 50 mg, continuously in 3 patients (patients 1, 2, and 7) who became amenorrheic while taking the drug, and discontinuously (from day 5 to day 25 of each menstrual cycle) in the other 4 patients (patients 3–6) who wished to continue menstruation.

Because contraception was not assuredly effective before the second or third month of treatment with CA (10,11), patients were advised against pregnancy, and gynecologic surveillance was performed monthly during the first 3 months, and at 3-month intervals thereafter.

Disease activity was evaluated clinically every 3 months following initiation of treatment, together with determination of laboratory parameters including anti-DNA titer by the Farr technique, serum C3 and C4 complement levels, hemoglobin, platelet and white blood cell counts, liver enzymes, total cholesterol, and triglycerides. SLE flares were clinically defined as the onset (or exacerbation) of cutaneous, articular, or visceral manifestations of SLE. They were considered major when they led to an increase of CS treatment of twice (or more) the existing daily dose, or to initiation (or reinstitution) of CS therapy. The number and the severity of flares were recorded during the CA treatment period and during the corresponding pretreatment period in all patients. The average daily doses of CS and/or of antimalarial drugs were compared in each patient during the same periods.

Plasma and urine sex hormone concentrations were assessed prior to initiation of hormonal treatment and every 3 months thereafter. Radioimmunoassay was used to measure plasma concentrations of testosterone, estradiol, follicle-stimulating hormone (FSH), luteinizing hormone (LH), sex hormone–binding protein (SHBP) (18), and 24-hour urinary excretion of testosterone glucuronide and 5-α-androstene-3α,17β-diol (Adiol) (6).

Statistical methods. Comparison between clinical and laboratory data before and during hormonal treatment was made by the Wilcoxon nonparametric paired test.

RESULTS

The total duration of hormonal treatment in the 7 patients is reported in Table 1. By the end of August 1984, 6 patients had been taking CA a mean total duration of 27 months (21–33 months), while patient 7 had been treated for 9 months. All but 1 patient (patient 6) are still receiving CA treatment.

No significant side effects were reported by any of our patients. In particular, we observed neither any significant rise in total cholesterol, triglyceride, or hepatic enzyme levels (Table 2), nor significant modification in white cell or platelet count or hemoglobin level (Table 3). There were no reports of weight gain, hair loss, vaginal dryness, or reduced libido.

The number of clinical exacerbations of SLE was lower during CA treatment than during the corresponding pretreatment period. During 156 patient-months before treatment, 27 lupus flares were observed (7 of them severe enough to justify increases in CS dosage), whereas only 15 flares (2 of them leading to increase or reinstitution of CS) were observed during 170 patient-months with CA treatment ($P < 0.05$, Wilcoxon test). However, in 1 patient, who

Table 2. Plasma lipid and liver enzyme levels in 7 female systemic lupus erythematosus patients before/during cyproterone acetate treatment*

Patient	Cholesterol (mmoles/liter)	Triglycerides (mmoles/liter)	ALT (nKat/liter)	AST (nKat/liter)	Alk. Ph. (nKat/liter)
1	4.0/3.7	1.0/0.85	310/330	240/185	920/800
2	5.8/5.6	0.85/0.80	340/240	360/295	925/815
3	3.2/3.3	0.60/0.65	170/165	150/170	710/680
4	3.1/3.2	0.75/0.75	310/150	340/225	560/685
5	3.8/3.6	0.75/0.65	450/230	430/300	830/950
6	4.5/5.1	0.45/0.60	420/295	350/310	320/470
7	3.7/4.0	1.10/1.30	160/175	170/195	655/750
Mean ± SD†	4.0 ± 0.9/4.1 ± 0.9	0.78 ± 0.22/0.80 ± 0.22	308 ± 111/226 ± 68	291 ± 105/240 ± 60	702 ± 216/735 ± 148

* ALT = alanine aminotransferase (normal range: 130–450); AST = aspartate aminotransferase (normal range 80–750); Alk. Ph. = alkaline phosphatase (normal range 500–1,500).

† P values all not significant, during treatment versus before treatment.

Table 3. Immunologic and hematologic data on 7 female systemic lupus erythematosus patients at start/at end of cyproterone acetate treatment

Patient	Anti-DNA titer (%)	C3 (mg/dl)*	C4 (mg/dl)*	Hemoglobin (gm/dl)	White blood cells ($\times 10^3$/mm^3)	Platelets ($\times 10^3$/mm^3)
1	19/12	100/90	25/20	11.8/11.9	7.4/7.1	280/307
2	13/13	150/145	30/50	13.3/12.9	5.4/4.2	275/273
3	15/14	85/100	30/35	14.0/13.8	5.9/6.2	265/250
4	14/17	85/75	15/15	14.6/13.6	6.9/5.7	206/223
5	18/21	100/115	15/25	14.9/15.3	5.5/8.2	301/329
6†	17/62	65/45	25/10	15.1/13.1	5.2/3.6	368/325
7	25/22	90/85	25/15	14.7/14.0	7.3/5.0	337/266
Mean ± SD‡	17.2 ± 4.0/16.5 ± 4.2§	96 ± 26/101 ± 25§	23 ± 6/26 ± 13§	14.0 ± 1.2/13.5 ± 1.1	6.2 ± 0.9/5.7 ± 1.6	290 ± 52/281 ± 39

* Normal value: C3 >70 mg/dl; C4 >15 mg/dl.
† Lupus flare starting at end of followup.
‡ P values all not significant, end of treatment versus start of treatment.
§ Excluding end of treatment data on patient 6.

initially had a severe form of SLE with proliferative glomerulonephritis and seizures and who had been treated with high-dose CS 6 months prior to institution of CA therapy, a severe flare with the nephrotic syndrome and diffuse proliferative glomerulonephritis, diagnosed by repeat kidney biopsy, developed after 21 months of CA treatment, when the maintenance dose of CS had been reduced from 25 to 15 mg/day. With this exception, all of the other 6 patients experienced subjective improvement or stable clinical remission despite lowering of the maintenance doses of CS or antimalarial drugs. The most striking effect was a marked decrease in the frequency and severity of oral ulcerations in 3 patients. This was especially apparent in patient 1, who had frequent and incapacitating buccal and vulvar ulcerations during a disease course of otherwise mild severity. Patient 2, who experienced frequent mouth ulcers, also had marked improvement with CA therapy and, interestingly, developed 2 minor flares manifested by oral ulcerations following unadvised 15-day breaks in hormonal therapy, which reversed after reintroduction of CA.

In the CS-treated patients, the daily dose of prednisone needed to control disease activity was lower during CA treatment than during the corresponding 24-month pretreatment period (mean 13.4 versus 20.3 mg/day). Similarly, in the patients treated with antimalarial drugs, the mean daily maintenance dose of hydroxychloroquine was reduced from 400 mg to 220 mg.

There was no significant difference between the values before treatment and those at the end of the study period for anti-DNA titers or for C3 and C4 complement component levels (with the exception of patient 6, who developed a rise in DNA titer and a drop in C3 and C4 levels concomitant with SLE exacerbation) (Table 3).

Plasma levels of testosterone, estradiol, and SHBP, and the estradiol:testosterone ratio, before and 6–12 months after the start of hormonal treatment, are listed in Table 4. Before initiation of hormonal treatment, mean ± SD plasma testosterone concentrations (0.66 ± 0.31 nmoles/liter), were markedly lower in our study patients than those in healthy women

Table 4. Plasma sex hormone levels in 7 female systemic lupus erythematosus patients before/during cyproterone acetate treatment

Patient	Testosterone (nmoles/liter)	Estradiol (nmoles/liter)	Sex hormone–binding protein (nmoles/liter)*	Estradiol:testosterone
1	0.62/0.69	0.36/0.13	48/15	0.58/0.19
2	0.59/0.52	0.37/0.13	40/19	0.62/0.25
3	0.76/0.62	1.37/0.08	63/NA	1.80/0.13
4	1.21/1.01	0.96/0.06	39/28	0.79/0.06
5	0.83/0.45	0.46/0.17	57/31	0.55/0.38
6	0.10/0.17	0.24/0.07	32/33	2.40/0.41
7	0.55/0.69	0.88/0.15	54/27	1.60/0.22
Mean ± SD	0.66 ± 0.31/0.59 ± 0.23	0.66 ± 0.38/0.11 ± 0.03†	47.5 ± 10.2/25.5 ± 6.9†	1.19 ± 0.68/0.23 ± 0.12‡

* NA = not available.
† $P < 0.05$, during treatment versus before treatment.
‡ $P < 0.02$, during treatment versus before treatment.

(1.15 ± 0.50 nmoles/liter), whereas mean plasma estradiol concentrations (0.66 ± 0.38 nmoles/liter) were in the normal range for the menstrual cycle (60 ± 10 and 160 ± 80 nmoles/liter in the follicular and the luteal phase, respectively). The mean ± SD estradiol:testosterone ratio (1.19 ± 0.68) was markedly higher in our patients than that in healthy women (normal 0.19–0.52), whereas mean SHBP concentrations (47.5 ± 10.2 nmoles/liter) were not significantly different from the values observed in healthy women (60 ± 9 nmoles/liter). Testosterone glucuronide excretion was 20.5 ± 4.9 nmoles/day, i.e., near the lower limit of values observed in healthy women (39 ± 24 nmoles/day). Adiol excretion was 149 ± 91 nmoles/day, similar to the normal value (150 ± 80).

During CA treatment, plasma FSH and LH levels significantly decreased. Excluding the post-cyclophosphamide menopausal patient, the mean ± SD value of FSH declined from 6.2 ± 1.8 to 3.2 ± 0.9 mIU/ml, and the mean value of LH declined from 3.2 ± 1.8 to 1.3 ± 0.4 mIU/ml ($P < 0.05$ for both). Mean plasma testosterone concentrations remained unchanged (0.59 ± 0.23 nmoles/liter). In contrast, plasma estradiol concentrations markedly decreased in every patient (0.11 ± 0.03 nmoles/liter, $P < 0.05$). Plasma estradiol concentrations declined after 3 months and remained in the same range or declined even further throughout the whole treatment period. Estradiol:testosterone ratio significantly decreased to 0.23 ± 0.12 ($P < 0.02$), and SHBP levels fell to 25 ± 7 nmoles/liter ($P < 0.05$), a value similar to that observed in healthy male subjects (29 ± 12 nmoles/liter).

Urinary androgen excretion remained essentially unchanged under CA treatment. Daily excretion was 24.3 ± 6.8 nmoles for testosterone glucuronide and 125 ± 60 nmoles for Adiol.

DISCUSSION

Experimental and clinical evidence indicated that sex hormones modulate the expression of autoimmunity in both murine and human systemic lupus erythematosus. In New Zealand black/New Zealand white (NZB/NZW) F_1 mice, females develop lupus nephritis more rapidly and die earlier than do males. Castrated males have a female pattern of survival, whereas androgen-treated females, either intact or castrated, exhibit longer survival than control females (3,4). In humans, the predominance of reproductive age females who have SLE (19) and the frequent exacerbation of lupus activity following oral contraceptive therapy with estrogen-containing preparations (2) indicate an unfavorable effect of endogenous or exogenous estrogens. A disordered pattern of estrogen metabolism has been found in both male and female SLE patients, resulting in excessive formation of 16-α-hydroxylated metabolites which retain estrogenic potency (5). Recently, Lahita and coworkers (7) reported an excessive level of testosterone oxidation at the C17 level in female SLE patients compared with normal women.

Plasma androgen levels were found to be normal in male SLE patients (20). However, we observed a significant reduction in all plasma androgen levels in female SLE patients, either in the acute phase of the disease prior to any corticosteroid therapy or after therapeutic remission (6). Low plasma testosterone levels in women with SLE were recently confirmed by others (7).

Such concordant findings led to consideration of a therapeutic use of androgens (or of antiestrogens) in human systemic lupus erythematosus. In view of their potential undesirable effects, testosterone or dihydrotestosterone could hardly be suggested for use by female patients. Thus, the few therapeutic trials published to date utilized weak androgens. Nandrolone (19-nortestosterone) decanoate, although effective in NZB/NZW mice (21), had no demonstrable clinical effect on 8 female SLE patients (8). Danazol, which was revealed to be ineffective in murine lupus (22), gave clinical improvement in 7 women who had mildly active SLE (9) and in 2 patients who had premenstrual exacerbations of SLE (23). However, the use of this drug is associated with a high incidence of side effects such as a rise in hepatic enzymes, skin

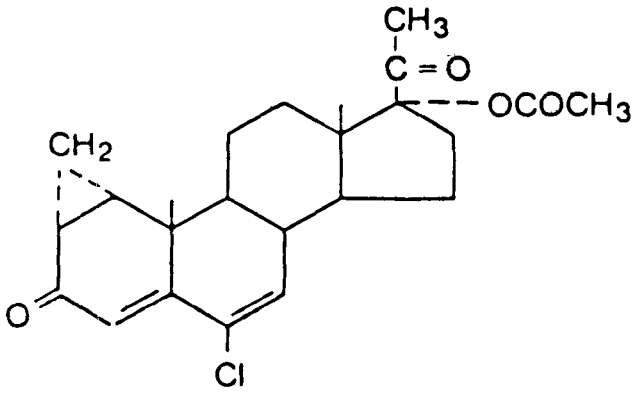

Figure 1. Structural formula of cyproterone acetate.

rash, weight gain, acne, or myalgia, which led to its discontinuance in about one-third of our patients (24).

This prompted us to evaluate the clinical and hormonal effects of another antigonadotropic molecule, cyproterone acetate, of which long-term tolerance had been established during extensive use for treatment of acne or hirsutism in otherwise normal women (11,12,16,25). CA is a synthetic hydroxyprogesterone derivative, first known as a progestagen, which was demonstrated to also possess antigonadotropic properties and peripheral antiandrogenic effects. The structural formula is shown in Figure 1. CA is widely used as an antiandrogen both in women suffering from acne or hirsutism (10–12) and in men with prostatic carcinoma (26,27). Therefore, the use of this "antiandrogenic" drug in female SLE patients, whose plasma androgen levels are already decreased (6,7), to achieve a lower estrogen:androgen balance, may at first glance appear to be paradoxical.

The rationale for use of CA for hormonal modulation in female SLE patients is primarily based on the antigonadotropic properties of the molecule, which are well established (10,11,16), and secondarily, on its synandrogenic properties (13,14). As an antigonadotropic agent, CA depresses gonadotropin secretion and thus, in females, depresses ovarian estrogen production (10,11). It affords contraception, since the daily dose needed to suppress ovulation in women is <1 mg (10). This effect is fully reversible and normal gestation may occur after withdrawal of the drug. CA accumulates in adipose tissue, and at a daily dose ≥ 50 mg, significant amounts of CA are released for 8–15 days after the drug is stopped, thus justifying possible discontinuous administration (10).

Healthy women treated with CA for hirsutism exhibit a marked fall in plasma gonadotropin and estradiol (to about 25% of the initial level) together with a lesser decrease in plasma testosterone level (to about 50% of the initial value) (11,12). In our patients, we observed a decrease in plasma gonadrotropins and a constant and marked fall in plasma estradiol, but we observed only an insignificant decrease in plasma testosterone, which already was low in all patients. Thus, the expected alteration of the hormonal milieu toward a lower estrogen/androgen balance was obtained, reflected by a significant decrease in the plasma estradiol:testosterone ratio and in the sex hormone–binding protein, the latter being considered one of the best markers of estrogen/androgen balance.

On the other hand, antiandrogenic effects of CA were of no consequence (or benefit) in our patients. In female subjects, CA acts by competing with androgen receptors of skin sebaceous glands which are androgen-dependent (10,28). This effect is the rationale of the CA treatment of acne and/or hirsutism in women, and it may explain the lack of undesirable side effects such as virilization or acne in our SLE patients treated with CA. The synandrogenic properties of CA are expressed on other target organs such as kidneys and liver (14,15), and their clinical significance in female subjects is not clearly established.

Evidence exists that CA induces in animals a particular form of intersexuality, with feminization of male fetuses when a pregnant mother received CA during the period of sexual differentiation (10). Danazol induces a virilization of female fetuses when a pregnant mother is given the drug during the same period (29). Thus, female patients treated with CA should be warned of this potential risk and should receive precise counseling on contraception. Close clinical surveillance is needed during the first 3 months of treatment since, in our experience, effective contraception is not fully achieved before the second or even the third month of CA treatment (11,23). Any gestation starting while the patient is taking CA should require therapeutic interruption. However, such a complication was not observed in any of our patients.

It may be of importance to mention that antigonadotropic drugs such as CA (and danazol, as well) should not be used in male SLE patients. In males, the antigonadotropic effect of CA induces a marked decrease in plasma testosterone concentration due to a direct inhibitory effect on the Leydig cells (10,26). In addition, CA acts as an antiandrogen in displacing 5-α-dihydrotestosterone from the specific cytosolic receptor in the prostate (30). Both effects are the rationale for the use of CA in the treatment of prostatic carcinoma (26,27). In male SLE patients, CA should induce a marked fall in plasma testosterone level which could potentially provoke an exacerbation of lupus disease. As a matter of fact, danazol, another antigonadrotropic drug (although possessing androgenic properties), was recently reported to unmask latent SLE in a male patient treated for angioneurotic edema (31).

Because the beneficial effects of CA were only potential, we selected for entry in our preliminary open trial only female SLE patients with mildly active lupus disease, thus excluding patients who needed more than 25 mg/day of prednisone to control disease activity. Since it is well known that spontaneous unpredictable flares occur in SLE, we planned a treatment duration of at least 24 months. By the end of

August 1984, most of our patients had been treated for 2 years or more and none had to interrupt the CA therapy. Comparison with the corresponding 2-year pretreatment period showed a reduction in the number and severity of lupus flares, despite the fact that the mean daily dose of corticosteroids or antimalarial drugs had been reduced. With the exception of 1 patient who initially had a severe form of lupus disease, all 6 other patients whose lupus disease initially was less severe received lower maintenance doses of CS or antimalarial drugs with no modification in serologic parameters (anti-DNA titer, C3, and C4 serum component levels). Of special interest was the marked improvement observed in 3 women who had oral ulcerations (associated with painful vulvar ulcerations in 1). Such an effect of hormonal modulation had not been previously reported.

However, in the absence of a control group, it cannot be excluded that the favorable course observed in most of our patients only reflects the natural course of the disease, as lupus flares frequently tend to decrease with time. Moreover, no beneficial effect was observed in a patient who initially had a severe form of SLE. Thus, with our present state of knowledge, we cannot recommend the use of CA in active forms of SLE.

Of special interest was the lack of toxicity of the drug. Clinically, there was no weight gain, acne, or virilization, nor loss of libido or asthenia. Blood counts were unaffected, and liver function, as well as blood lipid levels, were unchanged, as previously observed in healthy women treated with CA for hirsutism (11,24). Since CA affords effective contraception without adverse effects on blood lipid levels and possibly provides a protective effect against SLE exacerbation, it should be recommended as the best oral contraception currently available in female patients with quiescent or moderately active SLE.

In conclusion, our preliminary data indicate that in female patients, cyproterone acetate induces the expected modification in the hormonal milieu toward a lower estrogen/androgen balance, together with effective contraception and without clinical side effects in long-term administration. The true efficacy of the drug in preventing subsequent exacerbations of lupus disease remains to be demonstrated by appropriately controlled prospective trials.

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