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*Original Articles*

# Anti-androgenic Therapy Using Oral Spironolactone for Acne Vulgaris in Asians

Katsujiro Sato, M.D,[1] Daisuke Matsumoto, M.D,[1] Fumiko Iizuka, M.D,[1] Emiko Aiba-Kojima, M.D,[1] Asami Watanabe-Ono, M.D,[2] Hirotaka Suga, M.D,[1] Keita Inoue, M.D,[1] Koichi Gonda, M.D,[1] and Kotaro Yoshimura, M.D[1]

[1]Department of Plastic Surgery, University of Tokyo School of Medicine, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
[2]Ritz Medical Clinic, Meguro Toho Building 4F, 3-1-7, Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan

**Abstract.**
*Background:* Few studies have addressed anti-androgenic therapy using oral spironolactone for acne in Asians. Obtaining this race-specific information is important because Westerners and Asians respond differently to hormone therapy. This study aimed to examine the efficacy and safety of oral spironolactone used to treat acne in Asians.
*Methods:* Spironolactone (initial dose, 200 mg/day) was administered orally to 139 Japanese patients (116 females and 23 males) with acne. Serum laboratory data, including various hormones and electrolytes, were examined for 25 of the subjects.
*Results:* Most of the female patients who completed the 20-week regimen exhibited excellent improvement (evaluated by a photographic grading scale), although some discontinued treatment because of menstrual disturbances or other reasons. The treatment was less efficacious for the males than for the females, and because gynecomastia developed in three male patients, spironolactone treatment for males was stopped. Examination of the serum of 25 patients did not identify any toxicity associated with the treatment. Drug eruptions and edema in the lower extremities were each seen in three patients.
*Conclusion:* Oral spironolactone is effective and safe for the treatment of acne in Asian females, and can be a good option for severe, recurring, and widespread types of the condition.

**Key words:** Acne vulgaris—Anti-androgenic therapy—Contraceptive—Hormonal therapy—Oral spironolactone—Testosterone

Correspondence to K. Yoshimura M.D; *email:* yoshimura@cosmetic-medicine.jp

The treatment of acne in postadolescent females often fails [4,17]. Some patients experience severe and chronic acne, whereas others have widespread acne eruptions in locations such as the chest and back. When chronic or recurrent acne is not adequately controlled, inflammation, scars, or postinflammatory hyperpigmentation may disfigure the appearance of the patient.

Acne treatment can be divided into two approaches: (1) antisymptomatic treatment such as the use of chemical peeling, lasers, and antibiotics [20]), and (2) inhibitory treatment such as the use of oral retinoids or anti-androgen therapies (retinoids also have symptomatic effects). Systemic treatments are especially needed for severe or chronic acne, and cases in which symptoms are widespread.

Hormonal anti-androgenic treatments can inhibit sebum production and acne formation in postadolescent females, but they also can induce side effects such as menstrual irregularity. Cyproterone acetate, a synthetic progestin, was the first steroidal anti-androgen used widely used in the treatment of advanced prostatic carcinoma and severe acne. However, the drug is potentially carcinogenic, and long-term use can induce severe hepatocellular dysfunction [5,11]. Consequently, the sale of the agent was discontinued in Japan in 1999. The drug still is widely used alone or in combination with ethinyl estradiol, a contraceptive (e.g., Diane-35), for severe acne in many Western countries.

Flutamide is a nonsteroidal competitive anti-androgenic agent available for the treatment of prostate cancer, benign prostatic hyperplasia, and hirsutism. Despite its proven efficacy, the use of this agent is restricted because of its reported hepatotoxicity [19]. In addition, flutamide-induced

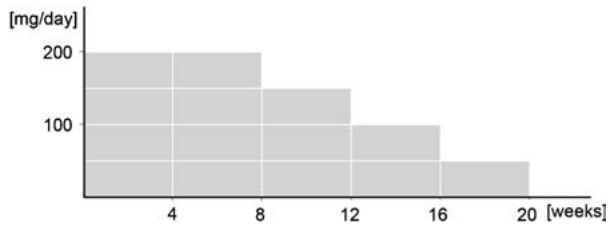


**Fig. 1.** Oral spironolactone administration protocol.

hepatotoxicity reportedly occurs more frequently among Asians than among Caucasians [16]. For this reason, monthly liver function testing is required when it is used in Japan.

Spironolactone, a well-known diuretic agent, has been used for more than 20 years as an antagonist of androgens in the treatment of acne and hirsutism [8,9]. Several randomized studies have evaluated its efficacy for the treatment of hirsutism [2,6,15,18]. Serious adverse drug-related events and discontinuation of therapy have been uncommon in spironolactone therapy [14], although gynecomastia [12] and menstrual irregularities frequently accompany high-dose use. Other side effects such as lethargy, fatigue, dizziness, and headache also have been reported [7–9,13].

Hormonal actions, serum hormone levels, and side effects of hormonal agents differ frequently among races and populations. For the Asian population, spironolactone appears to be the safest of the three aforementioned anti-androgenic agents. This study was performed to assess the therapeutic value and side effects of oral spironolactone in Japanese patients.

## Patients and Methods

Spironolactone was administered orally to 139 Japanese patients (116 females and 23 males; ages, 15–46 years; mean, 26 ± 6.8 years) with acne at the Ritz Medical Clinic. Informed consent approved by the local institutional review board was obtained from each patient or legal guardian. No other therapies for acne were permitted for the duration of the study.

A 20-week course of therapy was administered. The initial dose was 200 mg/day for the first 8 weeks. After the initial period, the doses were progressively lowered by 50 mg every 4 weeks (Fig. 1).

The effectiveness of the treatment was evaluated for 64 patients (all females) who completed the 20-week regimen. A digital camera was used to take clinical photographs before, during, and after treatment. Two experienced plastic surgeons who did not perform the treatment evaluated acne severity by examining the photos. Overall acne severity was assessed using a modified version of a scale published by Allen and Smith [1] (Table 1). Clinical improvement was graded using a 3-point scale (Table 2). A posttreatment improvement of three or more grades of acne severity was considered "excellent." We also ranked patients who showed no inflammatory lesions as "excellent."

**Table 1.** Overall inflammatory acne severity scale

| Grade | Definition |
|---|---|
| 1 | Clear, no inflammatory lesions |
| 2 | One or two inflammatory lesions |
| 3 | Three to five inflammatory lesions |
| 4 | Six to nine inflammatory lesions over a wide area of the face |
| 5 | Moderate number of inflammatory lesions, some large, over a wide area of the face, with increasing erythema |
| 6 | Papules and pustules with larger inflamed lesions over much of the face, with pronounced erythema |
| 7 | Large papules and pustules with pronounced erythema involving most of the face |

**Table 2.** Global response to treatment scale

| Description | Improvement |
|---|---|
| Excellent | Improved 3 or more grades or showed no inflammatory lesions |
| Good | Improved 1 or 2 grades |
| Poor | No change or worsened condition |

To find related adverse events, we tested the blood of 25 patients, collected before and after treatment. We examined serum levels of alanine transferase (ALT), aspartate transferase (AST), blood urea nitrogen (BUN), creatinine (Cr), sodium ($Na^+$), potassium ($K^+$), chlorine ($Cl^-$), luteinizing hormone (LH), dehydroepiandrostenedione sulfate (DHEAS), sex hormone–binding globulin (SHBG), total testosterone, and free testosterone. Not all the blood tests were performed for all the patients because of insufficient blood collected.

### *Statistical Analysis*

Data were calculated as mean ± standard error. The nonparametric Mann–Whitney *U* test was used to compare clinical and hormonal data before and after treatment.

## Results

All 64 female patients who completed the 20-week treatment regimen exhibited clinical improvement, with 34 patients (53.1%) evaluated as excellent

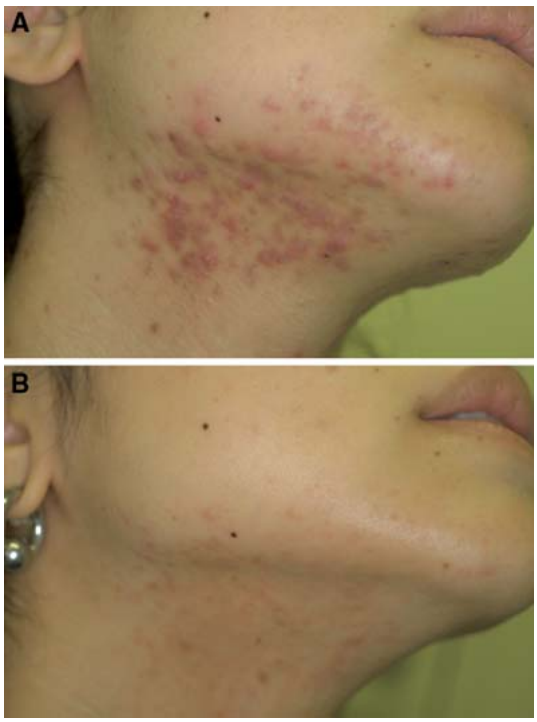


**Fig. 2.** A 27-year-old female with acne vulgaris from the jawline to the neck who did not improve with repeated alpha hydroxy acid (AHA) peeling and oral antibiotics. (**A**) Before treatment. (**B**) After 20 weeks of oral spironolactone (excellent results, fewer inflammatory spots).

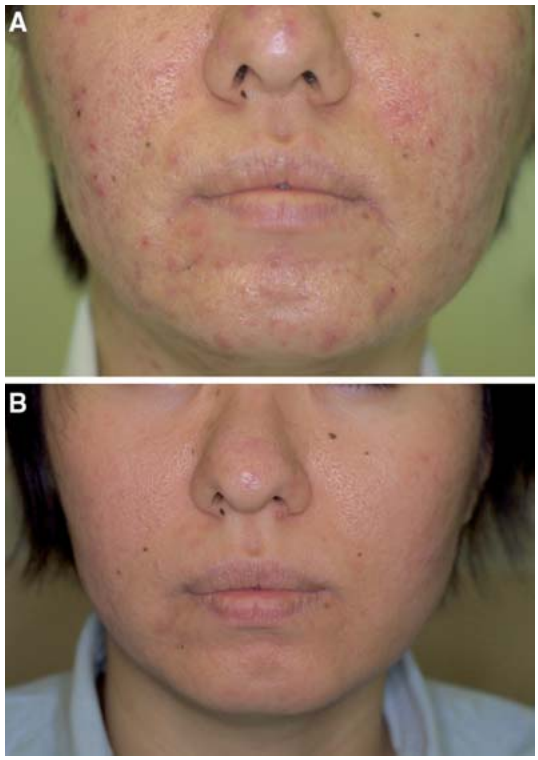


**Fig. 3.** A 31-year-old female with acne vulgaris and seborrheic dermatitis on the whole face. (**A**) Before treatment. (**B**) After 4 months of oral spironolactone (excellent results). Sebum discharge was markedly reduced, and seborrheic dermatitis and acne both improved.

(Figs. 2, 3, and 4) and 30 patients (46.9%) assessed as good. During the study, 52 of the 116 female patients dropped out for various reasons such as menstrual irregularities or reluctance to make repeated visits to the clinic, although most patients who completed the regimen also experienced menstrual irregularities.

We administered spironolactone to 23 male patients, but discontinued treatment for males when gynecomastia developed in 3 males (13%) after 4 to 8 weeks of treatment. All three of these male patients were between 19 and 21 years of age.

In terms of side effects and complications, approximately 80% of 116 female patients experienced menstrual irregularities. Five patients had no menstrual bleeding during the first 3 months of treatment, and four had severe menstrual irregularities. These nine patients were given an intramuscular injection of estrogen (estradiol benzoate 10 mg) and progesterone (hydroxyprogesterone caproate 125 mg) to induce menstrual bleeding.

Other side effects reported previously with spironolactone treatment such as lethargy, fatigue, dizziness, and headache were not observed in this trial. Changes in urinary frequency were observed occasionally (at a rate less than 10%), but these changes did not seem to reduce patient quality of life. Other side effects that occurred in only a few patients included drug-induced red papules (in 3 of 139 patients) and edema in the lower extremities (also in 3 patients). We analyzed changes in serum hormones, laboratory data, and blood levels of electrolytes resulting from oral spironolactone treatment in 25 patients (Fig. 5).

Unexpectedly, only two and four patients had high total ($>0.6$ ng/dl) and free ($>1.5$ pg/dl) testosterone levels before treatment, respectively. All the cases with high testosterone showed decreased total and free testosterone levels after treatment. On the other hand, 4 of 7 patients with low total testosterone level ($<0.2$ ng/dl) and 12 of 14 patients with low free testosterone level ($<1.0$ pg/dl) showed increased total and free testosterone levels after treatment, respectively. Thus, patients with high total or free testosterone levels tended to have lower levels after treatment, whereas total or free testosterone levels tended to rise with treatment for patients with low initial levels.

The values of LH, DHEAS, and SHBG for all the patients were within normal limits except for one case each. Indices of liver functions (ALT and AST) and those of kidney functions (BUN and Cr) were not affected by oral spironolactone. Unexpectedly, $Na^+$ and $K^+$ levels also were not affected significantly by this urinary agent. Only $Cl^-$ showed a significant decrease ($p < 0.05$) with treatment. However, almost all values were within normal limits.

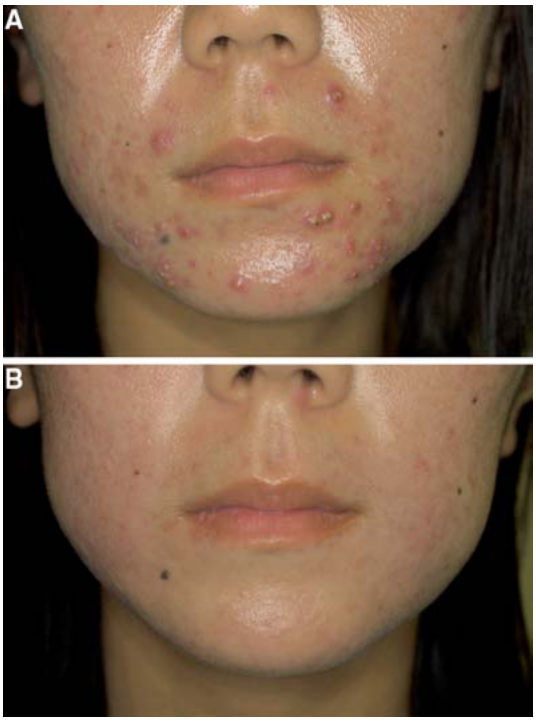


**Fig. 4.** A 28-year-old female with acne vulgaris and severe sebum discharge. (**A**) Before treatment. (**B**) After 4 months of oral spironolactone (excellent results).

## Discussion

Because acne almost always recurs, the key to successful management is to provide both preventive and curative treatment. Our results show that oral spironolactone is very effective for treating acne in Japanese females without serious side effects other than menstrual irregularities.

Although we observed no significant abnormalities in the pretreatment levels of serum and free testosterone in Japanese patients with severe acne, all the female patients in our study exhibited clinical improvement after 2 to 4 months of oral spironolactone monotherapy. Thus, our results strongly suggest that androgen signals affect acne in almost all patients, but factors other than serum hormonal levels may have a critical influence on sebum production and subsequent new acne formation. Oral contraceptives can reduce gonadotropins such as luteinizing hormone, with consequent reduction of testosterone production and serum levels of testosterone, but they cannot block androgen signals at the level of the androgen receptors (some progestins can, but much less selectively for the androgen receptor than for the progesterone receptor). Thus, this difference may be the reason why some acne patients do not respond to oral contraceptive treatments. These results also suggest that oral spironolactone may be better for treatment of acne than for use as oral contraceptives.

Acne occasionally recurred several months after the administration of oral spironolactone had ended. Gradually decreasing the spironolactone dosage can help prevent rebound and recurrence of acne after treatment. Several patients who dropped out of the study and discontinued spironolactone without tapering the dose had an immediate recurrence of acne formation.

Some patients who also suffered from concurrent seborrheic dermatitis on their faces also showed improvement after administration of oral spironolactone. This effect probably results from the inhibitory action of spironolactone on sebum production by blockage of androgen signals at the receptor level. Indeed, almost all patients reported reduced sebum discharge as soon as 2 weeks after starting treatment.

The mechanism by which oral spironolactone causes menstrual irregularities is not clearly understood. After the start of administration, the serum levels of testosterone or dehydrotestosterone may be acutely elevated because androgen receptors are competitively blocked by the drug. The excessive testosterone could then be transformed into estradiol, which can induce endometrial hyperplasia and menstrual irregularities. Gynecomastia may be induced in males for the same reason [12]. Because the three male patients with gynecomastia in this study were between 19 and 22 years of age, males in this age range may be the most susceptible to the conversion from testosterone to estradiol due to the high serum level of testosterone during this period. This study shows that male patients do not tolerate oral spironolactone well, so other therapeutic agents such as oral isoretinoin [3,10] must be considered for their treatment.

Most of the females in our trial were satisfied with their clinical results despite the menstrual irregularities because they had experienced recurrent acne for a long time and had lived stressful lives caused by disfigurement. For 9 of 64 patients (14%), a combined injection of estrogen and progesterone was performed to induce normal menstruation, which usually was observed within 10 to 14 days after the injection. Concurrent administration of contraceptives can be useful for preventing possible pregnancy during the treatment and may stabilize the menstrual periods.

Other side effects such as itching and allergic eruptions occurred in only a few patients. We observed no abnormal blood levels of electrolytes or laboratory values for ALT, AST, BUN, Cr, $Na^+$, or $K^+$ after administration of the oral spironolactone series. Only $Cl^-$ showed a significant, but minor, decrease.

In summary, this study demonstrated that oral spironolactone is quite effective for acne in Asian females, and that this therapy is a good option, especially for recurrent, severe, resistant, or widespread types of the condition, although it frequently induces menstrual irregularities. Oral spironolactone has been used extensively as a diuretic, and its safety

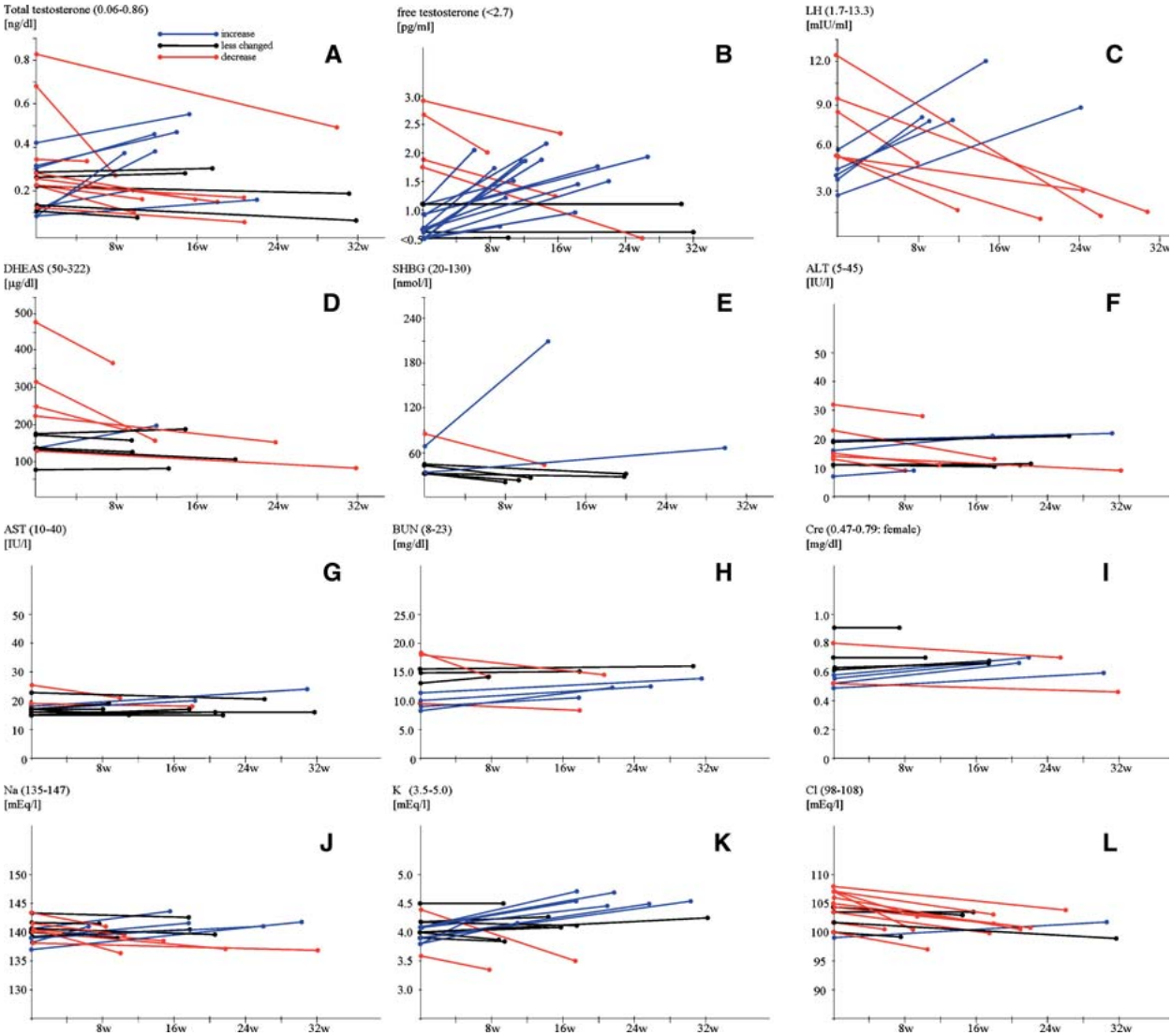


**Fig. 5.** Blood test results before and after administration of oral spironolactone. (**A**) Total testosterone. (**B**) Free testosterone. (**C**) Luteinizing hormone (LH). (**D**) Dehydroepiandrostenedione sulfate (DHEAS). (**E**) Sex hormone–binding globulin (SHBG). (**F**) Alanine transferase (ALT). (**G**) Aspartate transferase (AST). (**H**) Blood urea nitrogen (BUN). (**I**) Creatinine (Cr). (**J**) Sodium ($Na^+$). (**K**) Potassium ($K^+$). (**L**) Chlorine ($Cl^-$). Increases or decreases of more than 10% from initial values are shown as blue and red lines, respectively. Free testosterone increased significantly ($p < 0.05$) and $Cl^-$ decreased significantly ($p < 0.05$) with pretreatment, although almost all values were within normal limits. The LH, DHEAS, SHBG, ALT, AST, BUN, Cr, $Na^+$, and $K^+$ values did not change significantly with treatment.

has been established for Asian people, in contrast to two other hormonal agonists used in acne therapy (cyproterone acetate and flutamide) that cause liver dysfunction in Asians. Menstrual irregularities are common as a side effect, but a compensatory hormonal injection is available to induce menstrual regularity. Spironolactone may be regarded as an important alternative when conventional antibiotics such as doxycyclin and oral isotretinoin do not work. It cannot be administered to male patients because of a potential risk of inducing gynecomastia.

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