A Randomized Controlled Double-Masked Study of Transdermal Androgen in Dry Eye Patients Associated With Androgen Deficiency

SUMET SUPALASET, NAPAPORN TANANUVAT, SAIPIN PONGSATHA, WINAI CHAIDAROON, AND SOMSANGUAN AUSAYAKHUN

• PURPOSE: To evaluate the efficacy, safety, and quality of life (QOL) of transdermal androgen in treatment of dry eye patients associated with androgen deficiency.
• DESIGN: Randomized controlled trial.
• METHODS: Fifty patients with dry eye from a tertiary eye center in northern Thailand were randomized to receive transdermal androgen (AndroGel; Besins Healthcare, Brussels, Belgium) or placebo for 4 weeks. Main outcome measures were symptoms and signs of dry eye. Serum level of sex hormone and QOL questionnaires were also evaluated at the baseline and after treatment.
• RESULTS: After 4 weeks, the Ocular Surface Disease Index decreased significantly in the AndroGel group compared to the placebo (−14.36 ± 7.76 vs 0.14 ± 14.60, $P < .001$). Significant improvements of tear break-up time (7.40 ± 3.37 vs −1.14 ± 1.68 seconds, $P < .001$), corneal fluorescein staining (−0.62 ± 0.30 vs 0.19 ± 0.37, $P < .001$), and Schirmer test (6.84 ± 5.10 vs −0.48 ± 2.14 mm, $P < .001$) were observed in the AndroGel group compared to the placebo. Serum testosterone in female patients significantly increased in the AndroGel group compared to the placebo ($P < .001$), while no different change was observed in serum testosterone in male subjects and the sex hormone-binding globulin in both groups. In the AndroGel group, 20% of patients had oily skin and 4% had acne. No serious adverse effects were reported. The menopause rating score improved significantly in the AndroGel group compared to the placebo ($P < .001$), while the aging male symptoms were not different in both groups ($P = .589$).
• CONCLUSIONS: Transdermal androgen was effective in relieving symptoms and signs of dry eye as well as improving QOL in aging patients. There were no serious side effects during a short-term treatment. (Am J Ophthalmol 2019;197:136–144. © 2018 Elsevier Inc. All rights reserved.)

DRY EYE DISEASE (DED) IS A MULTIFACTORIAL DISease that has a complex etiology and pathophysiology and is classified into 2 main groups: aqueous-deficient dry eye (ADE), which has decreased lacrimal gland secretion, and evaporative dry eye (EDE), which has an unstable tear film instead of normal tear production.[1] DED becomes more frequent with age in both women and men, but women are at a higher risk of dry eye than men, suggesting that sex hormones may play a role in this condition.[2] Sex hormones, particularly androgens, have been shown to impact the structure and function of the lacrimal gland and meibomian glands, with reduced androgen levels leading to reduced tear volume, reduced tear film stability, decreased tear turnover rate, and hyperosmolarity. Moreover, androgens have been shown to have a direct effect on the tissues of the ocular surface, such as the cornea and conjunctiva, leading to altered mucin production.[3,4] Besides Sjögren syndrome, ADE is commonly found in both aging men and women with decreased androgen levels.[5,6] The association between androgen deficiency and dry eye makes androgen therapy a promising potential treatment for DED.

Previous studies demonstrated the efficacy of androgen treatment in relieving dry eye symptoms and signs related to both ADE and EDE. In animal studies, subcutaneous androgen injection stimulated the function of the exorbital lacrimal gland of the castrated rat.[7] The vesicular change of the acini of exorbital glands could be quantitated, thus employing them as an index of androgenicity. A case report of a 54-year-old male patient with severe keratoconjunctivitis sicca using transdermal testosterone 3% cream for 3 months found that the tear break-up time (TBUT) and lipid layer thickness had increased to a normal level.[8] Another uncontrolled case series showed improvement of TBUT, Schirmer test, and Ocular Surface Disease Index (OSDI) scores in patients with EDE and androgen deficiency after transdermal androgen patches.[9] This study aimed to evaluate the efficacy, safety, and quality of life (QOL) of transdermal androgen therapy in a population of patients with DED associated with androgen deficiency.

AJO.com Supplemental Material available at AJO.com.
Accepted for publication Sep 17, 2018.

From the Departments of Ophthalmology (S.S., N.T., W.C., S.A.) and Obstetrics and Gynecology (S.P.), Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand.
Inquiries to Napaporn Tananuvat, Department of Ophthalmology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; e-mail: ntananuvat@gmail.com

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2018.09.021

METHODS

THIS STUDY WAS CONDUCTED ACCORDING TO A PROTOcol approved by the Research and Ethics Committee, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand (study code: OPT-2558-03637), and Thai Clinical Trial Registry Committee (study ID 20160324001, http://www.clinicaltrials.in.th) and conformed to the ethical guidelines of the 2013 Helsinki Declaration. Written informed consent was obtained from each patient before initiation of the study. The study was performed between May 1, 2016 to October 31, 2016 at the Outpatient Department, Chiang Mai University Hospital, a tertiary eye center in northern Thailand.

• **STUDY POPULATION:** Postmenopausal women and andropausal men who also had signs and symptoms of DED were recruited for the study. Menopausal status was determined by a gynecologist (S.P.) as either natural menopause with permanent menstrual cessation of at least 12 months' duration or surgical menopause after oophorectomy. Andropausal status was defined as a serum level of testosterone lower than that of similarly aged men. The diagnosis of DED was made in the eye clinic and required symptoms owing to dry eye as well as all of the following clinical signs: TBUT < 10 seconds, positive corneal fluorescein staining, and Schirmer test with anesthesia < 10 mm.

Patients with a history of androgen or ethanol (composition of AndroGel) hypersensitivity, breast or prostate cancer, and/or skin inflammation at the applied area were excluded. Patients were excluded if they were contact lens users, used glaucoma medications and/or anti-inflammatory agents, or had other causes of dry eye, including autoimmune diseases, Sjögren syndrome, human immunodeficiency virus (HIV) infection, sarcoidosis, and/or skin disease. In addition, patients were excluded if they had initiated or altered the dose of systemic medications known to affect tear production within 30 days of enrollment and during the study period. Finally, those patients who received androgen replacement therapy within 1 year and those who could not attend a follow-up were also excluded.

• **STUDY MATERIALS AND TREATMENT:** The subjects were randomized into 2 groups according to allocation codes generated for the AndroGel and the placebo groups using the permuted block method by the randomization manager. The treatment group received androgen gel (AndroGel; Besins Healthcare, Brussels, Belgium), with 1 sachet (50 mg testosterone) applied to the lower abdomen (in an area approximately 14 cm horizontal by 7 cm vertical) on alternating days for 4 weeks. The control group received urea cream 10%, with 1 package (100 mg of urea) applied to the lower abdomen on alternating days in the same fashion as the treatment group. Each drug was placed in a container with a concealed label (Supplemental Figure 1; Supplemental Material available at AJO.com). Patients were asked to report the use of the drugs on a checklist table. Artificial tear eye drops could be used in all patients as needed and the frequency of the drops used per day was recorded.

• **OUTCOME MEASURES:** For outcome evaluation, the modified OSDI questionnaire (Thai version) was used to assess the symptoms of dry eye (scores 0–12: normal, 13–22: mild, 23–32: moderate, and 33–100: severe).[10] The Menopause Rating Scale (MRS) questionnaire, which was related to psychological, somatic, and urogenital-sexual symptoms, and the Aging Male Symptoms (AMS) questionnaire, which was related to psychological, somatic, and sexual symptoms, were used to evaluate the QOL of female and male patients, respectively. The MRS questionnaire (total scores ranged from 0 [asymptomatic] to 44 [highest degree of complaints])[11] or AMS questionnaire (scores 17–26: fine; 27–36: minor effects; 37–49: significant effects; ≥50: severe symptoms of andropause)[12] was assessed in each patient by 1 interviewer.

All patients underwent the eye examination including slit-lamp examination, lower tear meniscus height (TMH; mm), corneal fluorescein staining (CFS) using a modified Van Bijsterveld scoring system[13] (the average score was the mean of the sum of scores in 3 areas—nasal, mid, and temporal cornea—ranging from 0 [none] to 3 [maximum]), TBUT (recorded from the average of 3 times),[14] and basic tear secretion test (Schirmer test with anesthesia). Ocular protective index (OPI) was calculated from TBUT divided by the interblink interval (OPI of < 1 was considered to be risk of dry eye).[15] The blood examinations for testosterone level and sex hormone-binding globulin (SHBG) were performed to assess the sex hormone level. Apart from visual acuity and blink rate, all examinations were performed by 1 investigator (S.S.). All parameters were assessed at the baseline and 4 weeks after treatment. The detail of the evaluation of the outcome measures can be found in the Supplemental Text and Supplemental Figure 2 (Supplemental Material available at AJO.com). Any adverse effects were evaluated during the study period.

• **STATISTICAL ANALYSIS:** The demographic data and the outcome of treatment were descriptively analyzed as frequency for categorical data, mean ± standard deviation, median (range), or mean difference for continuous data. Apart from OSDI, AMS, and MRS score, the results from the right eye of each patient were used for statistical analysis. The outcome of treatment between groups was compared by Student *t* test for data with normal distribution (male serum testosterone, SHBG level, MRS, and AMS score), and Mann-Whitney *U* test for data with abnormal distribution (OSDI score, best-corrected visual acuity [BCVA], CFS, TMH, TBUT, Schirmer test, OPI, female serum testosterone, and frequency of artificial tears)

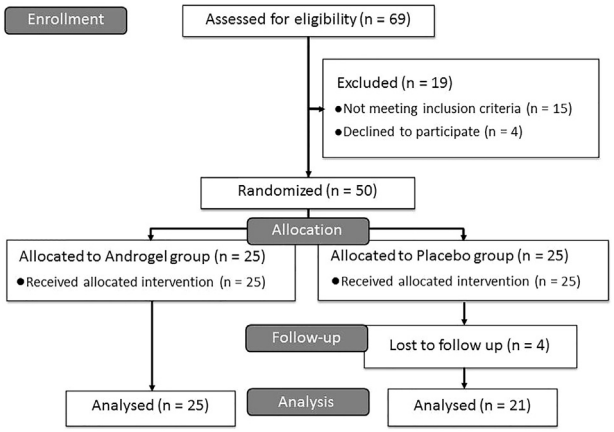

FIGURE 1. CONSORT flow diagram.

or Fisher exact test for categorical data (adverse effects).The mean differences among groups were analyzed by *t* test. The *P* value of <.05 was considered as a significant difference. The SPSS program (version 22; IBM Corp, Armonk, New York, USA) was used for data analysis.

RESULTS

SIXTY-NINE PATIENTS WERE RECRUITED IN THIS STUDY. Nineteen patients were excluded because the dry eye was caused by Sjögren syndrome (2), human immunodeficiency virus infection (1), and patients who refused (4) or could not come for a follow-up (12). Therefore, 50 patients were randomized. Four patients in the placebo group were unable to attend a follow-up. Finally, there were 25 patients and 21 patients in the AndroGel group and the placebo group, respectively (Figure 1).

• **BASELINE CHARACTERISTICS:** At the baseline, the demographic data, such as number of patients, age, sex, other associated ocular surface abnormalities (pinguecula, pterygium, or meibomian gland dysfunction), the underlying systemic diseases, and the use of systemic medications and types of artificial tears used among both groups, were not significantly different (Table 1). The baseline characteristics of the mean or median OSDI, BCVA, TMH, TBUT, OPI, Schirmer test, serum testosterone level, serum SHBG level, frequency of artificial tear administration, and AMS score were not significantly different in both groups. However, a significant intergroup difference was found in the baseline CFS and MRS score (Tables 2 and 3).

• **FOUR WEEKS AFTER TREATMENT:** The results after 4 weeks of treatment between the AndroGel group and the placebo group were compared and summarized in Tables 2–4 and Figures 2–4.

TABLE 1. Demographics and Baseline Characteristics of Dry Eye Patients Associated With Androgen Deficiency, Compared Between Patients Treated With Transdermal Androgen and Those Treated With the Placebo

Characteristics	AndroGel Group (N = 25)	Placebo Group (N = 21)	*P* Value
Female, n (%)	19 (76.0)	15 (71.4)	.988[a]
Natural menopause	17 (89.5)	12 (80.0)	.634[b]
Surgical menopause	2 (10.5)	3 (20.0)	.634[b]
Male, n (%)	6 (24.0)	6 (28.6)	.988[a]
Age, years (mean ± SD)	61.12 ± 7.09	64.24 ± 6.88	.139[c]
Pterygium, n (%)	4 (16.0)	5 (23.8)	.711[b]
Pingecula, n (%)	5 (20.0)	6 (28.6)	.740[a]
Concurrent MGD, n (%)	3 (12.0)	1 (4.8)	.614[b]
Systemic disease,[d] n (%)			
No	7 (28.0%)	6 (28.6%)	
Yes	18 (72.0%)	15 (71.4%)	.966[a]
Systemic medications,[e] n (%)			
No	11 (44.0%)	8 (38.1%)	
Yes	14 (56.0%)	13 (61.9%)	.685[a]
Artificial tears use, n (%)			
Nonpreserved	13 (52.0%)	10 (47.6%)	.767[a]
Preserved	6 (24.0%)	7 (33.3%)	.484[a]

MGD = meibomian gland dysfunction.
[a]χ^2 test.
[b]Fisher exact test.
[c]*t* test.
[d]Systemic diseases included diabetes mellitus (3), dyslipidemia (16), hypertension (8), hepatitis B (2), spondylosis (1), peptic ulcer (1), migraine (1), Graves disease (1).
[e]Systemic medications included rosuvastatin (1), atorvastatin (3), simvastatin (11), glipizide (3), amlodipine (3), losartan (4), calcium carbonate (2).

Ocular Symptoms. The median OSDI symptom scores showed a significant improvement in the AndroGel group. The median OSDI scores were 8 and 26 in the AndroGel group and the placebo group, respectively, at 4 weeks after treatment ($P = .002$) (Table 2). The AndroGel group had a significant improvement in mean OSDI score compared to the placebo group (−14.36 ± 7.76 vs 0.14 ± 14.60, $P < .001$) (Figure 2, Top left).

Best-Corrected Visual Acuity. No significant changes were observed in the BCVA in both groups after 4 weeks ($P = .112$). The mean change in BCVA was 0.02 ± 0.06 in the AndroGel group and 0.00 ± 0.00 in the placebo group ($P = .104$).

Corneal Fluorescein Staining. The median CFS score showed a significant improvement in the AndroGel group. The mean change in CFS score was significantly greater in the AndroGel compared to the placebo group (−0.62 ± 0.30 vs 0.19 ± 0.37, $P < .001$) (Figure 2, Top right).

TABLE 2. Comparison of Dry Eye Symptoms and Signs, and the Use of Lubricants Between Baseline and at 4 Weeks After Treatment in Dry Eye Patients Associated With Androgen Deficiency Treated With Transdermal Androgen and Those Treated With Placebo

	At Baseline			At 4 Weeks After Treatment		
Parameters	AndroGel (N = 25)	Placebo (N = 21)	*P* Value	Androgel (N = 25)	Placebo (N = 21)	*P* Value
OSDI scores	24 (3–63)	22 (7–76)	.501[a]	8 (1–64)	26 (0–53)	.002[a]
BCVA	0.0 (0.0–0.6)	0.0 (0.0–0.6)	.320[a]	0.0 (0.0–0.6)	0.0 (0.0–0.6)	.112[a]
CFS	0.5 (0.5–2.0)	1.0 (0.5–2.5)	.014[a]	0.0 (0.0–0.5)	1.0 (0.5–1.0)	<.001[a]
TMH, mm	0.1 (0.1–0.2)	0.1 (0.1–0.2)	.643[a]	0.2 (0.1–0.3)	0.1 (0.1–0.2)	<.001[a]
TBUT, s	5.0 (3.0–9.0)	5.0 (3.0–9.0)	.893[a]	12.0 (7.0–24.0)	4.0 (2.0–7.0)	<.001[a]
Schirmer test, mm	7.0 (0.0–9.0)	5.0 (1.0–9.0)	.634[a]	11.0 (3.0–30.0)	4.0 (1.0–12.0)	<.001[a]
OPI	1.3 (0.5–4.3)	1.3 (0.6–4.1)	.669[a]	3.3 (1.5–7.1)	0.9 (0.4–2.9)	<.001[a]
Artificial tears used, drops/day	3.0 (1.0–7.0)	2.0 (1.0–4.0)	.126[a]	2.0 (0.0–3.0)	3.0 (1.0–4.0)	.039[a]

BCVA = best-corrected visual acuity; CFS = corneal fluorescein staining; OPI = ocular protective index; OSDI = Ocular Surface Disease Index; TBUT = tear break-up time; TMH = tear meniscus height.

Data represent median (range).

[a]Mann-Whitney *U* test.

TABLE 3. Comparison of Sex Hormone Levels and Quality of Life Between Baseline and at 4 Weeks After Treatment in Dry Eye Patients Associated With Androgen Deficiency Treated With Transdermal Androgen and Those Treated With Placebo

	At Baseline			At 4 Weeks After Treatment		
Parameters	Androgel	Placebo	*P* Value	Androgel	Placebo	*P* Value
Female serum testosterone (ng/mL)[a] (n = 34)	0.07 (0.02–0.17)	0.06 (0.02–0.18)	1.000[b]	0.65 (0.03–9.85)	0.05 (0.02–0.14)	<.001[b]
Male serum testosterone (ng/mL) (n = 12)	3.59 ± 0.91	3.91 ± 0.82	.536[c]	4.17 ± 0.90	4.43 ± 2.03	.784[c]
Female serum SHBG (nMol/L) (n = 34)	70.07 ± 38.78	83.85 ± 44.42	.342[c]	64.78 ± 34.81	78.29 ± 43.07	.319[c]
Male serum SHBG (nMol/L) (n = 12)	39.11 ± 11.21	51.64 ± 17.73	.174[c]	34.53 ± 11.17	50.00 ± 24.75	.193[c]
MRS scores (n = 34)	12.7 ± 8.7	7.3 ± 5.0	.041[c]	3.7 ± 5.8	8.7 ± 6.4	<.001[c]
AMS scores (n = 12)	28.3 ± 6.9	30.8 ± 6.4	.530[c]	24.5 ± 6.8	30.3 ± 6.9	.172[c]

AMS = aging male symptoms; MRS = menopausal rating scale; SHBG = sex hormone-binding globulin.

Data represent mean ± SD unless indicated.

[a]Uses median (range) for non-normal distribution data.

[b]Mann-Whitney *U* test.

[c]*t* test.

Tear Meniscus Height. The median TMH showed a significant improvement in the AndroGel group. The median TMH was 0.2 mm and 0.1 mm in the AndroGel group and the placebo group, respectively, at 4 weeks after treatment ($P < .001$). The mean change of TMH was significantly increased in the AndroGel compared to the placebo group (0.08 ± 0.06 vs 0.00 ± 00 mm, $P < .001$).

Tear Break-up Time. The median TBUT showed a significant improvement in the AndroGel group. The median TBUT was 12 and 4 seconds in the AndroGel group and placebo group, respectively, at 4 weeks after treatment ($P < .001$) (Table 2). The mean change of TBUT was significantly increased in the AndroGel compared to the placebo group (7.40 ± 3.37 vs −1.14 ± 1.68 seconds, $P < .001$) (Figure 2, Middle left).

Basic Tear Secretion Test. The median Schirmer test with anesthesia showed a significant improvement in the AndroGel group. The median Schirmer test was 11 mm and 4 mm in the AndroGel group and placebo group, respectively, at 4 weeks after treatment ($P < .001$). The mean change in Schirmer test was significantly greater in the AndroGel compared to the placebo group

(6.84 ± 5.10 mm vs −0.48 ± 2.14 mm, $P < .001$) (Figure 2, Middle right).

Ocular Protective Index. The median OPI showed a significant improvement in the AndroGel group. The median OPI score was 3.33 and 0.94 in the AndroGel group and the placebo group, respectively, at 4 weeks after treatment ($P < .001$). The mean change of OPI score was significantly improved in the AndroGel compared to the placebo group (1.91 ± 1.32 and −0.47 ± 0.78, $P < .001$) (Figure 2, Bottom left).

Frequency of Artificial Tear Administration. The median frequency of artificial tear eye drops per day showed a significant decrease in the AndroGel group. The median frequency of artificial tear eye drops used was 2 and 3 drops per day in the AndroGel group and the placebo group, respectively, at 4 weeks after treatment ($P = .039$). The mean change of the use of artificial tears was significantly greater in the AndroGel compared to the placebo group (−1.44 ± 1.42 drops/day vs 0.00 ± 0.32 drop/day, $P < .001$) (Figure 2, Bottom right).

Serum Testosterone and Sex Hormone-Binding Globulin. After 4 weeks, serum testosterone in female patients significantly increased in the AndroGel group compared to the placebo ($P < .001$), while no significant change was observed in male patients (Table 3). The mean change of serum testosterone in female patients significantly increased in the AndroGel group compared to the placebo (1.41 ± 2.34 ng/mL vs −0.02 ± 0.05 ng/mL, $P < .001$), while there was no difference in male patients(0.58 ± 0.57 ng/mL vs 0.52 ± 1.38 ng/mL, $P = .917$) (Figure 3, Left) Neither group experienced a change in mean serum SHBG levels (decreased SHBG signifies a higher fraction of free androgens). The mean change in SHBG levels in both groups was not significantly different for either female or male patients (−5.28 ± 17.85 nMol/L vs −5.56 ± 14.80 nMol/L for female patients, $P = .784$, and −4.58 ± 2.94 nMol/L vs −1.64 ± 8.85 nMol/L for male patients, $P = .124$) (Figure 3, Right).

Impact on Quality of Life. At 4 weeks, the mean MRS score showed a significant improvement in the AndroGel compared to the placebo group ($P < .001$). The mean change in MRS scores was significantly decreased in the AndroGel group compared to the placebo group (−4.74 ± 3.12 vs 0.87 ± 3.54, $P < .001$) (Figure 4, Left), while the mean AMS score was not significantly different in both groups (24.50 ± 6.83 and 30.33 ± 6.89, $P = .172$). The mean change in AMS scores was also not significantly different between the AndroGel and the placebo groups at 4 weeks after treatment (−3.83 ± 4.96 and −0.50 ± 5.39, $P = .589$) (Figure 4, Right).

TABLE 4. Adverse Effects During 4 Weeks of Treatment in Dry Eye Patients Associated With Androgen Deficiency Treated With Transdermal Androgen and Those Treated With Placebo

Adverse Events	AndroGel (N = 25)	Placebo (N = 21)	*P* Value
Oily skin, n (%)	5 (20%)	0 (0%)	.054[a]
Acne, n (%)	1 (4%)	0 (0%)	1.000[a]

[a]Fisher exact test.

• **ADVERSE EFFECTS:** There were some adverse effects, such as oily skin and acne, in the patients treated with AndroGel. Five patients treated with AndroGel had oily skin and 1 patient had acne ($P = .054$ and $P = 1.000$) (Table 4). However, no serious adverse effect was found in both groups.

DISCUSSION

ANDROGENS ARE EXTREMELY IMPORTANT IN THE REGULATION of the ocular surface and adnexa.[3,16] Androgen receptors have been detected in the lacrimal gland, meibomian glands, and conjunctival epithelial cells.[17] Androgens have a role in the structure, gene expression, and protein synthesis of the lacrimal gland as well as the meibomian glands.[4] Animal studies show that regulation of lacrimal gland integrity and secretory function depends primarily on androgen action. Sex-related differences in androgen influence contribute to the sexual dimorphism of lacrimal gland characteristics observed in various animal species.[18] In addition, androgens may have an effect on the conjunctival goblet cells. One study found that women with dry eye owing to complete androgen insensitivity syndrome exhibited reduced MUC1 and MUC5AC protein expression in conjunctival goblet cells.[19] Androgen reduction had been found to influence autoimmune diseases such as Sjögren syndrome, resulting in inflammatory changes in the lacrimal gland, which led to ADE.[20,21] Apart from Sjögren syndrome,[22] ADE commonly occurs during menopause and aging.

Androgens are hormones produced and released into the circulation by the gonads. However, the gonads are not the major source of androgens in women, and only about 50% of androgens originate from the gonads in men. Almost all androgens in women before menopause, and close to 100% after menopause, as well as a significant percentage in men (eg, 40%–50%), are synthesized in peripheral intracrine tissue from adrenal sex steroid precursors such as dehydroepiandrosterone (DHEA), DHEA-sulfate, and androstenedione.[23,24] With advancing age, the adrenal glands produce less androgens, specifically less DHEA, which are important sources of estrogen and testosterone in elderly

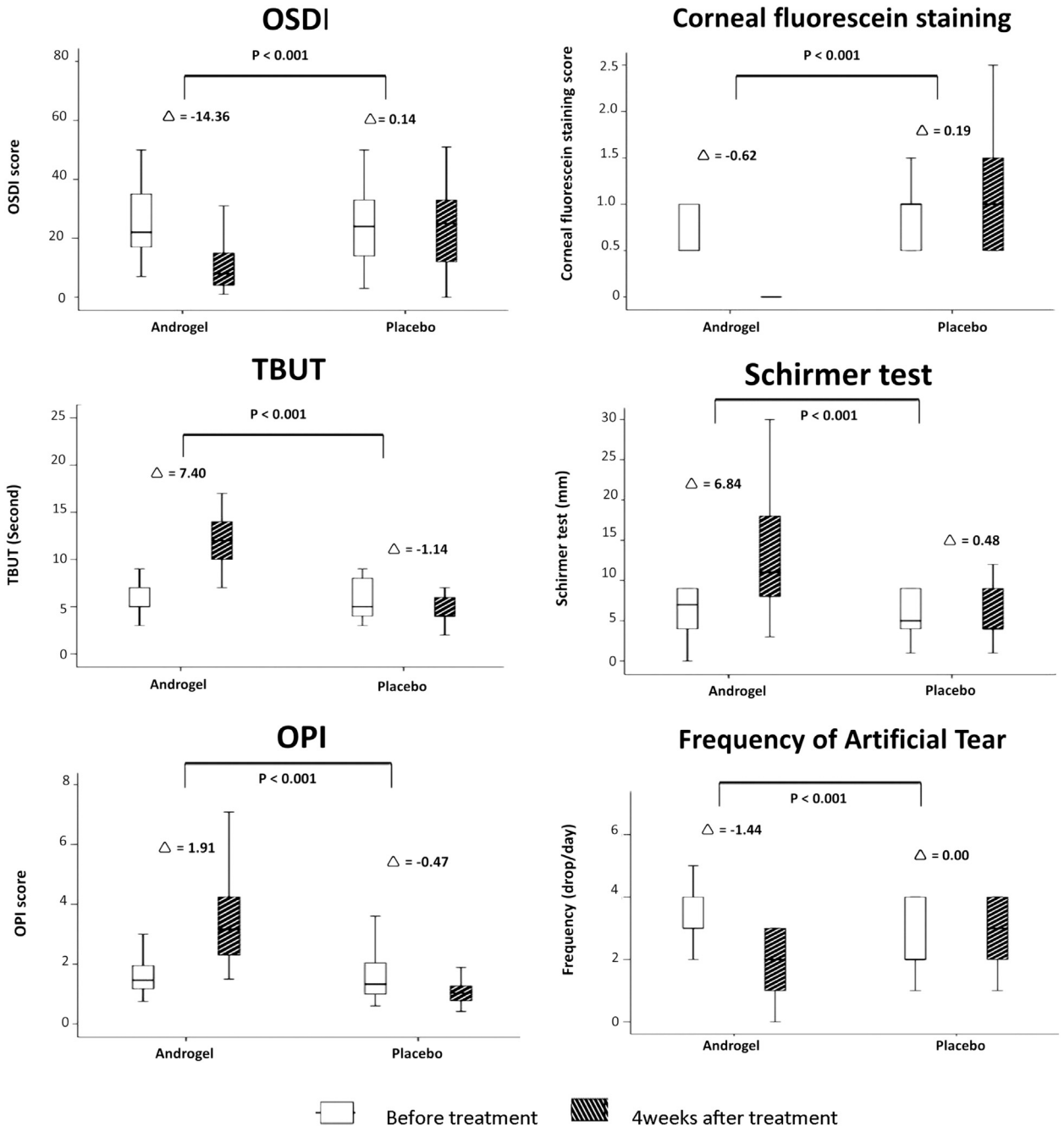

FIGURE 2. Comparison of dry eye parameters and the frequency of artificial tear administration in the AndroGel and the placebo group at baseline and at 4 weeks after treatment. (Top left) Ocular Surface Disease Index (OSDI) score. (Top right) Corneal fluorescein staining (CFS). (Middle left) Tear break-up time (TBUT). (Middle right) Schirmer test. (Bottom left) Ocular protective index (OPI) score. (Bottom right) Frequency of artificial tear administration. At 4 weeks after treatment, all parameters of the AndroGel group were significantly different compared to those of the placebo group. The mean change of all parameters showed significant improvement from the baseline in the AndroGel group compared to that of the placebo group.

women and men. Therefore, aging is associated with a gradual decline in circulating testosterone concentration in both sexes. In men, beginning around the age of 35–40 years, circulating testosterone levels decrease by approximately 1%–3% per year.[25] In women, testosterone levels decline in the fourth decade of life, and on average circulating DHEA decreases by 60% in postmenopausal women.[26]

The progressive reduction of androgens may contribute to increased risk of dry eye in these populations. Vehof and associates performed an extensive analysis of 222 serum metabolites in more than 2600 women, of whom 15.5%

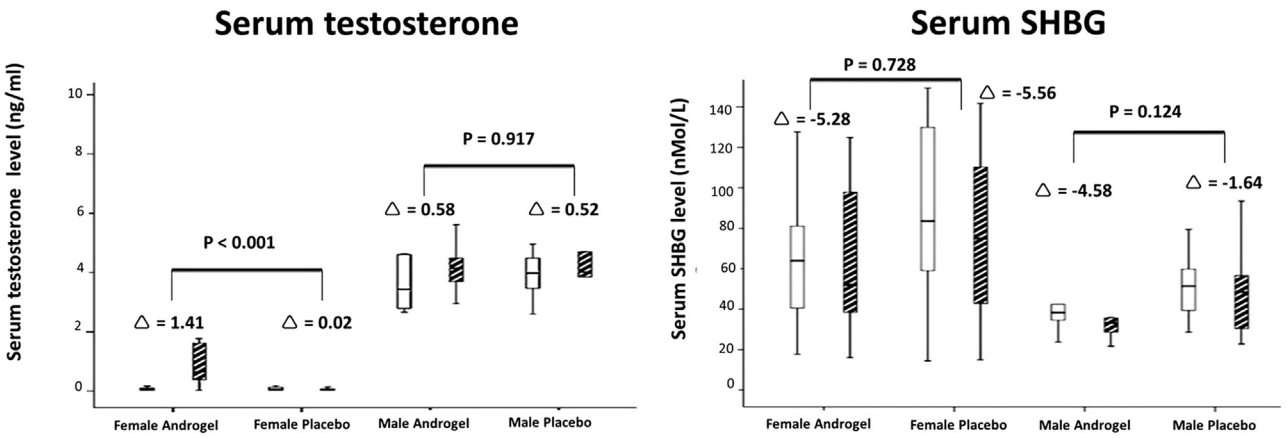

FIGURE 3. Comparison between baseline and at 4 weeks after treatment of (Left) serum testosterone and (Right) serum sex hormone-binding globulin (SHBG) level in the AndroGel and placebo groups. At 4 weeks after treatment, the mean change of serum testosterone level in female patients was significantly improved compared to that of the placebo group ($P < .001$), while that of serum testosterone level in male patients and serum SHBG level in both sexes showed no significant differences in both groups.

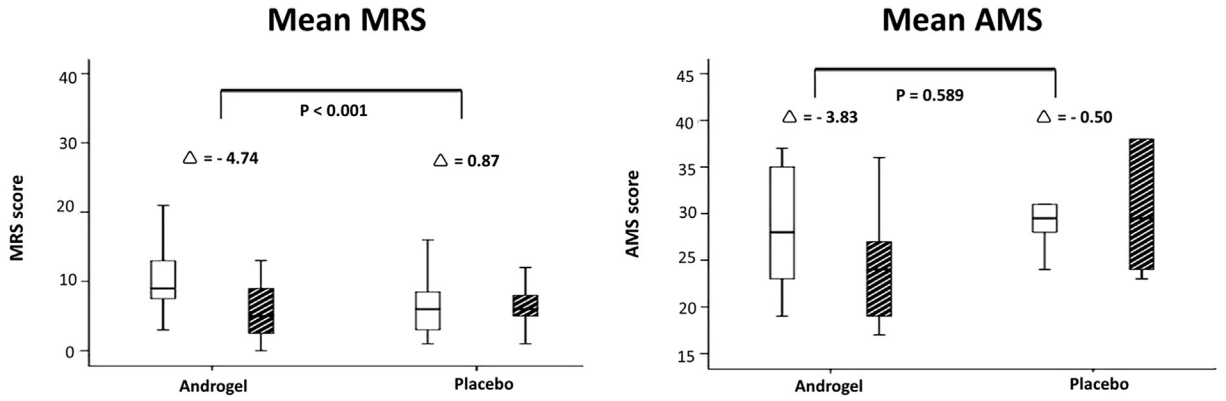

FIGURE 4. Comparison between baseline and at 4 weeks after treatment of (Left) the mean menopause rating scale (MRS) score and (Right) aging male symptoms (AMS) score in the AndroGel and placebo group. At 4 weeks after treatment, the mean change of MRS score was significantly improved compared to that of the placebo group ($P < .001$), while that of AMS score showed no significant differences in both groups ($P = .587$).

had dry eye. A highly significant association between decreased androgen level and DED was found. Androgen, and possibly epiandrosterone (a hormone with weak antigenic activity), may act as a biomarker for dry eye.[27]

Thus, androgens might be a potential treatment of dry eye disease. Among studies of androgen treatment for dry eye, animal studies have shown that testosterone treatment of castrated rats likewise stimulated the lacrimal secretory immune system.[18] The administration of testosterone to castrated rats restored the number of androgen receptors to the intact male rats, suggesting that androgens autoregulate their own binding sites.[21] In humans, Bizzarro and associates showed a therapeutic effect of oral testosterone supplement on autoimmune diseases in 5 patients with hypogonadism and Klinefelter syndrome (3 of whom had Sjögren syndrome and 2 of whom had systemic lupus erythematosus). Patients with DED and Sjögren syndrome had significantly increased Schirmer test and decreased Bijsterveld scores after 60 days of oral testosterone supplement compared to the placebo.[28] The results of a multicenter, double-masked, randomized controlled trial showed that testosterone ophthalmic solution improved the quality of meibomian gland secretions and reduced ocular discomfort in patients with meibomian gland dysfunction (Schiffman RM, et al. IOVS 2006;47. ARVO E-Abstract 5608). Topical administration with a lower dose of androgen-containing drops would be an alternate route of treatment to minimize the systemic adverse effects of hormone supplement. Recently, a randomized placebo-controlled pilot study on the effects of transdermal

testosterone and estrogen therapy in 40 postmenopausal women did not show a benefit of either testosterone, estrogen, or both testosterone and estrogen on dry eye symptoms compared to the placebo.[29]

In addition to these clinical trials, there have been some case reports and case series showing a potential benefit of androgen treatment in DED.[8,9,30] Among them, Scott and associates reported a case series of 11 postmenopausal women treated with systemic replacement with combined estrogen and methyltestosterone and found that dry eye symptoms improved in 10 of 11 patients.[30] On the other hand, some studies failed to validate the improvement of dry eye parameters after systemic supplement of DHEA in patients with Sjögren syndrome.[31,32]

The controversy of the therapeutic effects and safety of the use of hormone supplement in DED as well as the optimal route of administration was a rationale to focus on this interesting issue. This present study was designed as a pilot randomized double-masked placebo control to evaluate the efficacy, safety, and QOL of transdermal androgen in patients with DED related to sex hormone deficiency. This study demonstrated that transdermal androgen significantly improved the OSDI score, tear meniscus, TBUT, CFS, basic tear production, and OPI in aging patients with DED. The improvement of tear secretion and tear stability may be confirmed by an increase in serum testosterone levels, though the serum SHBG levels, which are correlated with levels of free androgens, were not significantly decreased. We also observed that some patients treated with transdermal androgen could stop using artificial tears during treatment. It might be possible that transdermal androgen could be used instead of artificial tears.

For safety issues, there were no serious side effects detected after using transdermal androgen. Nonetheless, the side effects of long-term use of androgen should be monitored. From the results of QOL evaluation, this study showed a significant improvement on the MRS score with transdermal androgen in aging female patients with DED, whereas the AMS score was not significantly improved among aging male patients. The findings may be owing to a small proportion of male patients in this study.

• **STUDY LIMITATIONS:** First, there were a small number of patients, of whom the majority were female, making it difficult to analyze some outcomes (such as serum hormone levels) that were different among female and male subjects. Second, the outcome measures such as symptoms and clinical tear functions (ie, TBUT and Schirmer test) may not be accurately used to diagnose or reflect the severity of dry eye. The ocular symptoms may vary among dry eye patients owing to the various levels of nerve injury in dry eye patients. The inconsistent and sometimes discordant correlation of symptoms and clinical signs of DED could be a confounding variable in clinical trials and might have an impact on the results and data interpretation. Third, the use of data from only the right eye may miss the inter-eye variability, which has been found to be correlated with increasing dry eye severity.[33] Fourth, this study may have a bias owing to the dissimilarity of the treatment and the placebo, which may not truly mask the patients. Last, the use of serum testosterone levels may not directly reflect the amount of hormone supplement. Instead, the reliable estimate of the total androgen pool is the serum concentration of conjugated dihydrotestosterone metabolites (eg, androsterone-glucuronide, androstane-3<alpha>,17<beta>-diol-glucuronide), which reflects the total intracrine production and metabolism of androgens in peripheral tissues throughout the body.[23,24]

In conclusion, transdermal androgen was effective for treatment in dry eye associated with sex hormone deficiency. Transdermal androgen could relieve dry eye symptoms and signs as well as improve QOL in aging patients with dry eye over a short-term period. Larger, placebo-controlled studies regarding the titration dose and long-term side effects of transdermal androgen therapy in patients with dry eye are required.

FUNDING/SUPPORT: THIS STUDY WAS SUPPORTED BY THE FACULTY OF MEDICINE ENDOWMENT FUND, FACULTY OF MEDICINE, Chiang Mai University, Chiang Mai, Thailand (Grant Number 091/2559). Financial Disclosures: The following authors have no financial disclosures: Sumet Supalaset, Napaporn Tananuvat, Saipin Pongsatha, Winai Chaidaroon, and Somsanguan Ausayakhun. All authors attest that they meet the current ICMJE criteria for authorship.

Other Acknowledgments: The authors thank Associated Professor Janejit Choovuthayakorn, MD (Department of Ophthalmology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand) for her kind assistance in statistical analysis.

REFERENCES

1. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II definition and classification report. *Ocul Surf* 2017;15(3):276–283.
2. Stapleton F, Alves M, Bunya VY, et al. TFOS DEWS II epidemiology report. *Ocul Surf* 2017;15(3):334–365.
3. Sullivan DA, Rocha EM, Aragona P, et al. TFOS DEWS II sex, gender, and hormones report. *Ocul Surf* 2017;15(3):284–333.
4. Knop E, Knop N, Millar T, Obata H, Sullivan DA. The international workshop on meibomian gland dysfunction: report of the subcommittee on anatomy, physiology, and pathophysiology of the meibomian gland. *Invest Ophthalmol Vis Sci* 2011;52(4):1938–1978.
5. Belanger A, Candas B, Dupont A, et al. Changes in serum concentrations of conjugated and unconjugated steroids in 40- to 80-year-old men. *J Clin Endocrinol Metab* 1994;79(4):1086–1090.

6. Metka M, Enzelsberger H, Knogler W, Schurz B, Aichmair H. Ophthalmic complaints as a climacteric symptom. *Maturitas* 1991;14(1):3–8.
7. Cavallero C, Ofner P. Relative effectiveness of various steroids in an androgen assay using the exorbital lacrimal gland of the castrated rat. II. C 19-steroids of the 5-alpha-androstane series. *Acta Endocrinol (Copenh)* 1967;55(1):131–135.
8. Worda C, Nepp J, Huber JC, Sator MO. Treatment of keratoconjunctivitis sicca with topical androgen. *Maturitas* 2001; 37(3):209–212.
9. Nanavaty MA, Long M, Malhotra R. Transdermal androgen patches in evaporative dry eye syndrome with androgen deficiency: a pilot study. *Br J Ophthalmol* 2014;98(4):567–569.
10. Walt J, Rowe M, Stern K. Evaluating the functional impact of dry eye: the Ocular Surface Disease Index. *Drug Inf J* 1997; 31(1436):b5.
11. The menopause rating scale (MRS). Berlin Center for Epidemiology and Health Research. Available at http://www.menopause-rating-scale.info/evaluation.htm. Accessed February 23, 2016.
12. The aging males' symptoms (AMS), Berlin Center for Epidemiology and Health Research. Available at http://www.issam.ch/ams.html. Accessed February 23, 2016.
13. van Bijsterveld OP. Diagnostic tests in the Sicca syndrome. *Arch Ophthalmol* 1969;82(1):10–14.
14. Lemp MA, Hamill JR Jr. Factors affecting tear film breakup in normal eyes. *Arch Ophthalmol* 1973;89(2):103–105.
15. Ousler GW 3rd, Hagberg KW, Schindelar M, Welch D, Abelson MB. The Ocular Protection Index. *Cornea* 2008; 27(5):509–513.
16. Truong S, Cole N, Stapleton F, Golebiowski B. Sex hormones and the dry eye. *Clin Exp Optom* 2014;97(4):324–336.
17. Rocha EM, Wickham LA, da Silveira LA, et al. Identification of androgen receptor protein and 5alpha-reductase mRNA in human ocular tissues. *Br J Ophthalmol* 2000;84(1):76–84.
18. Sullivan DA, Bloch KJ, Allansmith MR. Hormonal influence on the secretory immune system of the eye: androgen control of secretory component production by the rat exorbital gland. *Immunology* 1984;52(2):239–246.
19. Mantelli F, Moretti C, Micera A, Bonini S. Conjunctival mucin deficiency in complete androgen insensitivity syndrome (CAIS). *Graefes Arch Clin Exp Ophthalmol* 2007; 245(6):899–902.
20. Sullivan DA, Belanger A, Cermak JM, et al. Are women with Sjogren's syndrome androgen-deficient? *J Rheumatol* 2003; 30(11):2413–2419.
21. Rocha FJ, Wickham LA, Pena JD, et al. Influence of gender and the endocrine environment on the distribution of androgen receptors in the lacrimal gland. *J Steroid Biochem Mol Biol* 1993;46(6):737–749.
22. Sullivan DA. Sex hormones and Sjogren's syndrome. *J Rheumatol Suppl* 1997;50:17–32.
23. Labrie F. Intracrinology. *Mol Cell Endocrinol* 1991;78(3): C113–C118.
24. Labrie F, Belanger A, Cusan L, Candas B. Physiological changes in dehydroepiandrosterone are not reflected by serum levels of active androgens and estrogens but of their metabolites: intracrinology. *J Clin Endocrinol Metab* 1997;82(8): 2403–2409.
25. Feldman HA, Longcope C, Derby CA, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. *J Clin Endocrinol Metab* 2002;87(2):589–598.
26. Labrie F, Belanger A, Luu-The V, et al. DHEA and the intracrine formation of androgens and estrogens in peripheral target tissues: its role during aging. *Steroids* 1998;63(5-6): 322–328.
27. Vehof J, Hysi PG, Hammond CJ. A metabolome-wide study of dry eye disease reveals serum androgens as biomarkers. *Ophthalmology* 2017;124(4):505–511.
28. Bizzarro A, Valentini G, Di Martino G, DaPonte A, De Bellis A, Iacono G. Influence of testosterone therapy on clinical and immunological features of autoimmune diseases associated with Klinefelter's syndrome. *J Clin Endocrinol Metab* 1987;64(1):32–36.
29. Golebiowski B, Badarudin N, Eden J, et al. The effects of transdermal testosterone and oestrogen therapy on dry eye in postmenopausal women: a randomised, placebo-controlled, pilot study. *Br J Ophthalmol* 2017;101(7): 926–932.
30. Scott G, Yiu SC, Wasilewski D, Song J, Smith RE. Combined esterified estrogen and methyltestosterone treatment for dry eye syndrome in postmenopausal women. *Am J Ophthalmol* 2005;139(6):1109–1110.
31. Pillemer SR, Brennan MT, Sankar V, et al. Pilot clinical trial of dehydroepiandrosterone (DHEA) versus placebo for Sjogren's syndrome. *Arthritis Rheum* 2004;51(4):601–604.
32. Forsblad-d'Elia H, Carlsten H, Labrie F, Konttinen YT, Ohlsson C. Low serum levels of sex steroids are associated with disease characteristics in primary Sjogren's syndrome; supplementation with dehydroepiandrosterone restores the concentrations. *J Clin Endocrinol Metab* 2009;94(6): 2044–2051.
33. Lemp MA, Bron AJ, Baudouin C, et al. Tear osmolarity in the diagnosis and management of dry eye disease. *Am J Ophthalmol* 2011;151(5):792–798.e1.