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Comparative Efficacy of Various Treatment Regimens for Androgenetic Alopecia in Men

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Abstract

Our understanding of the aetiology of androgenetic alopecia (AGA) has substantially increased in recent years. As a result, several treatment modalities have been tried with promising results especially in early stages of AGA. However, as far as has been ascertained, there is no comprehensive study comparing the efficacy of these agents alone and in combination with each other. One hundered male patients with AGA of Hamilton grades II to IV were enrolled in an open, randomized, parallel-group study, designed to evaluate and compare the efficacy of oral finasteride (1 mg per day), topical 2% minoxidil solution and topical 2% ketoconazole shampoo alone and in combination. They were randomized into four groups. Group I (30 patients) was administered oral finasteride, Group II (36 patients) was given a combination of finasteride and topical minoxidil, Group III (24 patients) applied minoxidil alone and Group IV (10 patients) was administered finasteride with topical ketoconazole. Treatment efficacy was assessed on the basis of patient and physician assessment scores and global photographic review during the study period of one year. At the end of one year, hair growth was observed in all the groups with best results recorded with a combination of finasteride and minoxidil (Group II) followed by groups IV, I and III. Subjects receiving finasteride alone or in combination with minoxidil or ketoconazole showed statistically significant improvement ($p<0.05$) over minoxidil only recipients. No signifcant side-effects related to the drugs were observed. In conclusion, it is inferred that the therapeutic efficacy is enhanced by combining the two drugs acting on different aetiological aspects of AGA.

Key words: androgenetic alopecia; finasteride; minoxidil; ketoconazole

Introduction

Androgenetic alopecia (AGA) is an emotionally distressing and therapeutically frustrating dermatological problem characterized by patterned hair loss. It occurs as a result of progressive miniaturization of scalp hair with changes in hair cycle dynamics in genetically predisposed individuals (1). The condition is associated with significant psychosocial embarrassment and may result in severe personality dysfunction especially in individuals with excessive and premature hair loss.

Advances in the field of genetics and hair follicle biology have certainly improved our understanding of the etiopathogenesis of AGA. The role of androgens and follicular androgen receptors as the key factors in disease causation has been established (2, 3). In addition, immunoregulatory mechanisms acting synergistically with hormonal factors to potentiate follicular injury are also implicated (4).

Various treatment modalities targeted at different patho-physiological aspects of AGA have been tried independently in several western studies with promising results (5–7). However, there is a paucity of literature comparing the efficacy of these drugs

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Table 1. Drug regimens evaluated in treating AGA

Study group	Drug regimen
Group I (n=30)	1 mg oral finasteride once daily
Group II (n=36)	1 mg oral finasteride once daily + 2% minoxidil solution topical application twice a day
Group III (n=24)	2% minoxidil solution twice a day
Group IV (n=10)	1 mg oral finasteride once daily + 2% ketoconazole shampoo topical application thrice weekly

alone and in combination for treating Indian patients. Hence, the present study was undertaken to assess and compare the clinical potential of oral finasteride, topical minoxidil and topical ketoconazole alone and in combination in male patients with AGA.

Patients and Methods

Study Design

One hundred eligible male subjects with AGA of Hamilton grades II-IV were inducted into the study. They were in the age group of 18–35 years (mean 24.86 years). The majority (42%) were students. The duration of hair loss ranged from 5 months to 10 years. A positive family history was present in 68% of the cases within the second degree of consanguinity. Examination of the scalp revealed that 82% of the cases had involvement of both the fronto-parietal region and vertex; the other 18% had only fronto-parietal involvement.

After obtaining informed written consent, all the patients were subjected to a detailed medical history followed by thorough general physical, dermatological and systemic examinations. A baseline hemogram, urinalysis, liver and kidney function tests, blood sugar, chest X-ray, blood pressure recording and electrocardiogram (ECG) were performed in each case. These tests were repeated at 6 months and after completion of the study.

Exclusion criteria

Hypertensive patients (blood pressure more than 140/90 mmHg recorded on three consecutive occasions) or individuals with a history of a cardiac, hepatic, renal, endocrine or psychiatric disorder were excluded. In addition, subjects with scalp involvement in the form of seborrheic dermatitis, psoriasis or scalp infection were excluded. Patients giving history of use of investigational drugs, hair restorers or drugs that might interfere with hair growth (antihypertensives, systemic corticosteroids, cytotoxic agents, antiepileptics, broncho- and vasodilators) in the previous six months were also excluded from the study.

Study Group

The subjects were divided into four groups and assigned the drugs in a randomized manner (Table 1). Group I (30 patients) received 1 mg oral finasteride (Tab. Finpecia, Cipla Ltd., Mumbai Central®, India) daily. Group II (36 patients) received 1 mg oral finasteride daily in combination with topical application of 2% minoxidil solution (2% Mintop solution, Dr. Reddy's Laboratories Ltd.®, Hyderabad, India). They were instructed to apply 1 ml of the solution to the balding area with a calibrated dropper twice daily at 12-hour intervals. Applications were made on the dry scalp and spread with one finger-tip. Group III (24 patients) exclusively used 2% minoxidil solution twice daily, and Group IV (10 patients) received oral finasteride 1 mg daily in combination with topical 2% ketoconazole shampoo (Nizral Shampoo, Johnson and Johnson Ltd.®, India) applied thrice weekly.

Evaluation Procedure

The patients were evaluated every 3 months for one year on the following basis:

Patients' self assessment

The patients' perception of improvement in the degree of hair fall and hair growth was evaluated from the base-line on a 7 point scale. +1-mild improvement; +2-moderate improvement;

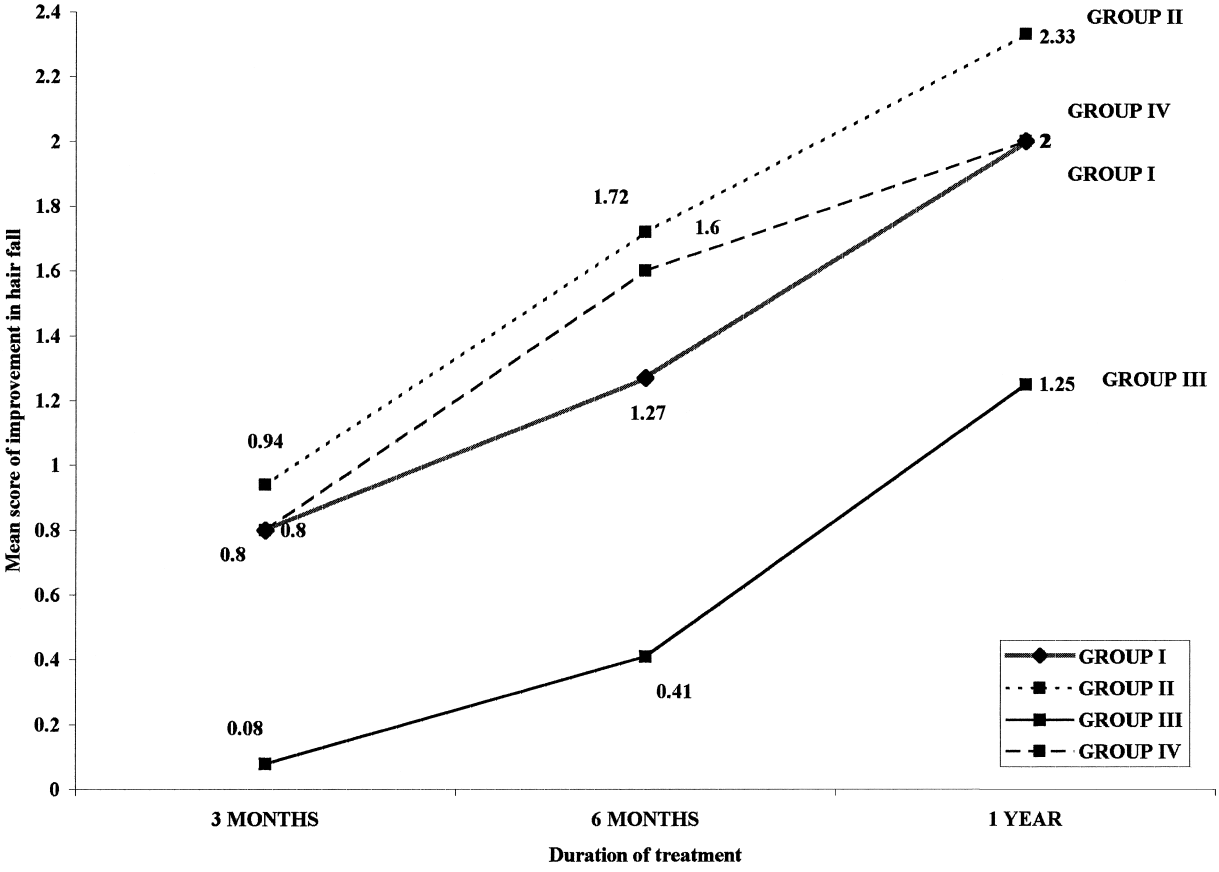

Fig. 1. Comparison of improvement in hair fall in four groups (Patients' self assessment score)

+3-excellent improvement; 0-no change; −1-mild hair fall; −2-moderate hair fall; −3-severe hair fall.

Physician's assessement

A panel of three dermatologists subjectively evaluated the degree of hair growth or hair loss from base-line on a 5 point scale. +1-mild improvement; +2-moderate improvement; +3-excellent improvement; 0-no change; −1-deterioration

Global photographic assessment

A standardized global pretreatment photograph of the anterior and mid areas of the scalp was taken in each case. Consistency was maintained with regards to the patients' positioning, photographic distance and light exposure. Before taking the photograph, the patients' hair was combed in a consistent manner so that the balding area could be optimally viewed. They were instructed to maintain the same hair style and to refrain from dyeing their hair throughout the study.

Evaluation of safety

Any medical event occurring during the course of the study was recorded with special emphasis on the vital signs, *i.e.*, pulse rate, blood pressure, weight, ECG changes, local reactions on the scalp secondary to topical applications, or sexual dysfunction including loss of libido, ejaculation disorder or impotence.

Statistical Methods

Statistical comparison among the four groups of patients was based on the scores obtained during subjective evaluation of efficacy, *i.e.* patients' self-assessment and physicians' assessment. We calculated the mean of the scores allotted by patients regarding improvement in hair fall and hair growth at 3, 6 and 12 months of follow-up. To test the statistical difference in the mean grading among the four groups,

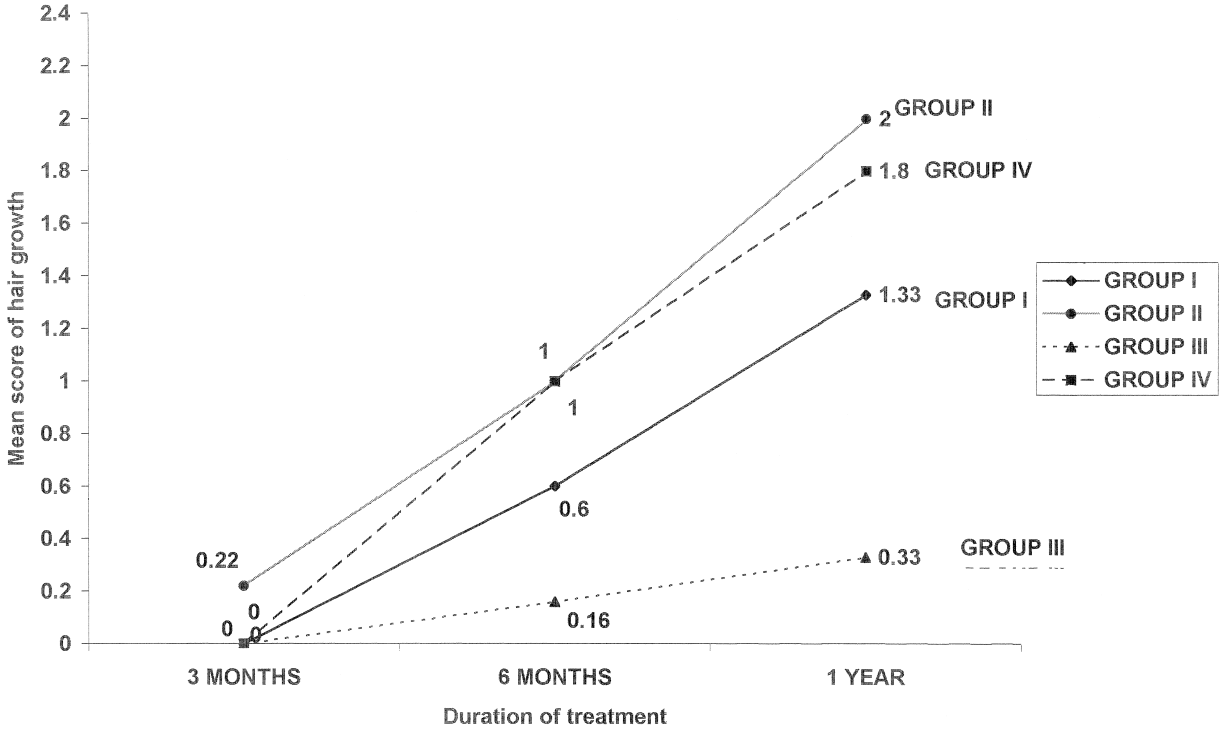

Fig. 2. Comparison of hair growth in four groups (Patients' self assessment score)

Table 2. Between-group statistical comparison of improvement in AGA after one year of treatment

Group	Statistical difference	
	Patient self-assessment (Teacher's t-test)	Physician assessment (Fischer's exact test)
I and II	p<0.005	p<0.03
I and III	p<0.001	p<0.001
II and III	p<0.001	p=0.0014
III and IV	p<0.001	p<0.001
II and IV	p<0.1	p=0.3
I and IV	p<0.1	p=1

Statistical significance (p<0.05)

Table 3. Results of physician assessment recorded at one year

Group	Physician assessment scale				
	+1	+2	+3	0	−1
Group I (n=30)	16 (53.34%)	10 (33.34%)	—	2 (6.67%)	2 (6.67%)
Group II (n=36)	10 (27.78%)	24 (66.67%)	2 (5.56%)	—	—
Group III (n=24)	8 (33.34%)	2 (8.34%)	—	12 (50%)	2 (8.34%)
Group IV (n=10)	2 (20%)	8 (80%)	—	—	—

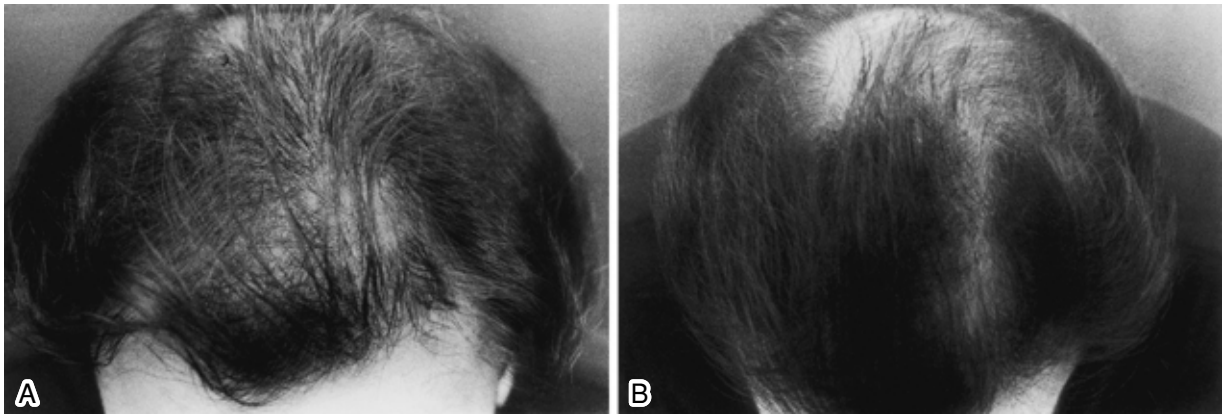

Fig. 3. Clinical photograph of a patient with AGA. (A) Before treatment, (B) After 1 year of treatment with oral finasteride showing moderate improvement (2+)

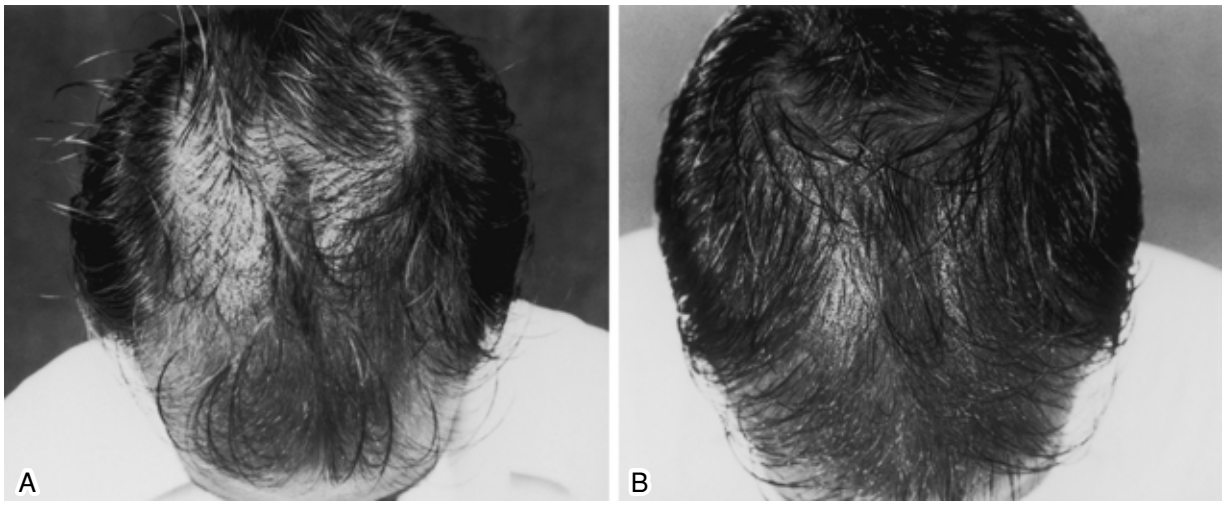

Fig. 4. Clinical photograph of a patient with AGA. (A) Before treatment, (B) After 1 year of treatment with oral finasteride +2% minoxidil showing excellent improvement (3+)

'analysis of variance' was initially employed. Further, wherever this revealed statistical significance, 'Teacher's t-test' of significance was used in order to test the difference in the mean values.

Treatment efficacy based on physicians' assessment was evaluated as the percentage of cases showing mild, moderate or excellent improvement, no change, or deterioration at the end of one year. For the purpose of statistical comparison, they were grouped into two categories: 'positive score on assessment' and 'negative score on assessment'. 'Fischers exact test' was used for pair-wise between treatment-group comparisons. All the results were considered to be significant at the 5% critical level.

Observations and Results

An increase in the mean values of the patients' self assessment score was recorded, both in terms of improvement in hair fall and hair growth in all four groups, as treatment proceeded from 3 months to one year. The highest mean values were recorded in Group II followed by groups IV, I and III respectively (Figs. 1 and 2). Statistical comparison of the mean values of scores recorded for hair growth at the end of one year re-

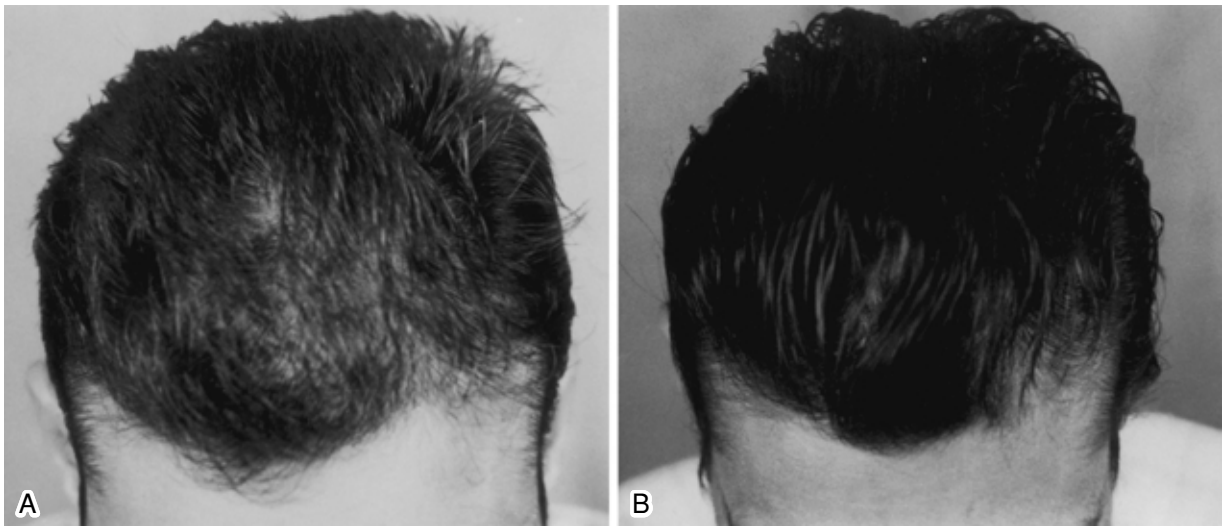

Fig. 5. Clinical photograph of a patient with AGA. (A) Before treatment, (B) After 1 year of treatment with 2% minoxidil showing mild improvement (1+)

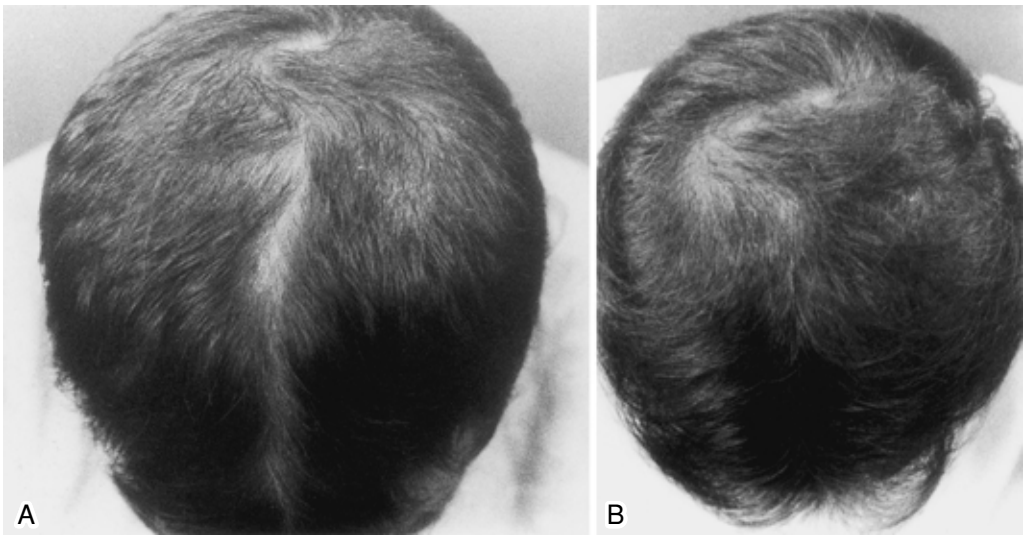

Fig. 6. Clinical photograph of a patient with AGA. (A) Before treatment, (B) After 1 year of treatment with oral finasteride +2% ketoconazole shampoo showing moderate improvement (2+)

vealed significant differences ($p<0.05$) between groups I and II ($p<0.005$), I and III ($p<0.001$), II and III ($p<0.001$) and III and IV ($p<0.001$). However, no significant difference in improvement was recorded between groups II and IV ($p<0.1$) or I and IV ($p<0.01$) (Table 2).

The results of physicians' assessment at the end of one year showed excellent improvement only in Group II in 5.56% of the cases. Moderate improvement was observed in 66.67% of cases in Group II, 33.34% of cases in Group I, 8.34% of cases in Group III and 80% of cases in Group IV. Mild improvement in hair growth was achieved in 53.34%, 27.78%, 33.34% and 20% of the patients in groups I, II, IIII and IV, respectively. However, no change in the patients' profile was recorded in 6.67% of patients in Group I and 50% of cases of Group III, while fur-

ther deterioration in AGA grading was observed in 6.67% and 8.34% of cases in Groups I and III, respectively, at the end of one year (Table 3). By employing the 'Fischer' s exact test', the difference in cure rates was found to be statistically significant ($p<0.05$), between groups I and II ($p<0.03$), II and III ($p<0.001$), III and IV ($p<0.0014$) and I and III ($p<0.001$). No significant difference was recorded between groups I and IV ($p=0.3$) and II and IV ($p=1$) (Table 2).

Post treatment photographs of the scalp were taken at 3 and 6 months and after one year of therapy; these showed clinical improvement in all four groups. The observations were comparable to the findings of patient and physician assessment scores (Figs. 3–6).

Side-Effects

No significant adverse events occurred during the follow-up period of one year. One patient (1.32%) complained of loss of libido after 3 months of finasteride administration but continued to take the drug without any further decrease in sexual function. Hypotension (blood pressure –90/60 mmHg) occurred in one patient (1.67%) on minoxidil and his ECG revealed sinus tachycardia. However, other signs of cardiac abnormality such as pedal edema, palpitations or dyspnea were not observed. No local side effects of topical applications were recorded during the study.

Discussion

AGA affects up to 30% of men below the age of 30 years and approximately 50% of men above 50 years of age (8). Western studies have shown racial differences in the incidence and pattern of hair loss in AGA, with a higher frequency noted in Indian populations (9). In a community based, cross-sectional survey conducted in Singapore, the prevalence of AGA was found to be 63%, with the highest proportion of cases observed in the Indian population (87%) as compared to the Chinese (61%) or Malay (65%) ones (10).

In our study, the majority of the patients were students with a mean age of 24.86 years. It is logical that young individuals who are extremely sensitive to cosmetic disfigurement present themselves more commonly for treatment. Moreover, younger subjects in early Hamilton stages of AGA (I to IV) are more likely to benefit from medical treatment.

A family history of AGA was present in 68% of our cases within the second degree of consanguinity. This condition is believed to be due to an autosomally dominant gene with variable penetrance, although a polygenic mode of inheritance cannot be excluded (11). A positive family history predisposes to early development and rapid progression of male-pattern baldness (12). However, no such correlation was observed in our study.

At the end of the one-year study period, the best results were observed with a combination of oral finasteride and topical minoxidil therapy (Group II). Finasteride therapy either alone (Group I) or in combination with minoxidil (Group II) or ketoconazole (Group IV) yielded significantly better results than minoxidil alone (Group III). We did not find a statistically significant difference in clinical improvement between groups II and IV, *i.e.* when finasteride was combined either with minoxidil or ketoconazole, although separately, both groups of patients showed encouraging results.

Currently, finasteride and minoxidil are the only two agents approved by the Food and Drug Administration (FDA) in the United States for the treatment of AGA (13). Finasteride was FDA approved for use in men in December of 1997 following several successful experiments on the stumptail macaque, an animal model for AGA, and a series of clinical trials in humans (14–16). Finasteride, a 4-aza steroid derivative, is a specific non-competitive inhibitor of the type II 5α-reductase enzyme, which catalyses the conversion of testosterone to dihydrotestosterone (DHT) (17). DHT binds to the androgen receptors present in the dermal papillae of the hair follicles (18,

19, 20) five times more avidly than the parent compound leading to progressive miniaturization of the hair follicles, reduction in the duration of anagen phase, and decrease in the anagen to telogen ratio. This phenomenon is reversed by finasteride. A three phase randomized, double-blind, placebo-controlled trial conducted in 1997 showed a significant clinical response in 48% of the finasteride recipients at the end of one year (15). Subsequent trials with 1 mg of the drug have demonstrated hair growth in 48–65% AGA patients after one year of treatment (5, 16, 21). In our study, hair growth occurred in 86.67% (26/30) of the finasteride recipients (Group I). Side-effects in the form of loss of libido were recorded in 1.32% of the patients, which was comparable to the incidence of 1–4.2% reported in other studies (5, 15, 16). The adverse events reported in association with finasteride are a result of its serum DHT lowering effect. A median 68.4% reduction in serum DHT levels has been observed after one year of 1 mg/day finasteride administration (22). However, there is evidence to suggest that it causes no change in the sperm counts, morphology and motility or serum levels of luterinizing and follicular-stimulating hormones, prolactin, sex hormone binding globulin, aldosterone or cortisol (17, 23, 24).

Minoxidil, an antihypertensive agent, stimulates hair growth by promoting anagen phase duration when applied topically. It resets the slope of hair loss by enhancing the incorporation of amino acids into the hair follicles, stimulating DNA synthesis in matrix cells and increasing scalp blood flow (25). Several studies have shown cosmetically acceptable hair growth in 40–60% of the cases after 1 year of treatment with topical minoxidil (26, 27). We observed hair growth in approximately 42% of the patients after 12 months of twice daily application. This effect was considerably enhanced when minoxidil was combined with finasteride. Mild to moderate hair growth occurred in 94.5% of the cases while dense growth was observed in 5.56% of patients using this combination. Recent experiments performed on the stump-tail macaque have shown the minoxidil-finasteride association to be more efficacious than either agent used alone (28). So far, this combination has not been widely tested in humans, although anecdotal reports suggest a synergistic effect (29).

Topical minoxidil has been reported to be extremely safe in clinical practice. Pharmacokinetic studies on its percutaneous absorption have shown that only 0.3–4.5% of the applied dose is systemically absorbed, which is responsible for a very low incidence of side-effects (30). No documented adverse effects such as local cutaneous reactions, irritant and allergic contact dermatitis, or cardiovascular events (25) were observed in our study other than a single episode of hypotension and reflex tachycardia.

Research work undertaken in the field of hair follicle biology has suggested immunological injury to the anagen follicles as an important patho-physiological event in AGA. Immunocompetent T-cells abutting on the infundibulum and isthmus have been observed, and the role of interleukin-1 in inducing hair loss has been postulated (4, 31). *Pityrosporon ovale*, a lipophilic yeast residing in the hair follicles, plays an important role in inducing inflammation by activating the alternate complement pathway. Topical ketoconazole has been shown to stabilize hair loss and improve hair density by reducing fungal colonization and by its direct anti-inflammatory action (32, 33). Encouraged by these findings, the therapeutic efficacy of topical ketoconazole in combination with finasteride (Group IV) was evaluated in this study. Mild to moderate hair growth occurred in all the cases after 1 year. These results were significantly better than finasteride or minoxidil used alone and comparable to those achieved by combining the two agents. The extent of improvement noted with ketoconazole regimen in our study corroborated with a report from Belgium (7), probably because *P. ovale* is found in 90–100% of subjects as normal cutaneous

flora with comparable density and incidence of skin carriage throughout the world (34). The high incidence of infections like pityriasis versicolor, pityrosporon folliculitis or seborrheic dermatitis observed in tropical conditions is due to its conversion into the pathogenic mycelial form in a warm and humid skin environment. These infections were excluded in our study before initiating treatment with ketoconazole.

The treatment modalities investigated in the present study showed encouraging results. A synergistic effect was achieved when agents with different modes of action were rationally combined. Further studies encompassing quantitative parameters such as changes in hair counts, density, and hair shaft diameters for the objective assessment of their efficacy are essential.

References

1) Curtois M, Loussouarn G, Horseau C, Grollier JF: Hair cycle and alopecia, *Skin Pharmacol,* **7**: 84–89, 1994.
2) Obana NJ, Uno H: Dermal papilla cells in macaque alopecia trigger a testosterone-dependent inhibition of follicular cell proliferation, in van Neste D, Randal VA (eds): *Hair Research in the Next Millenium,* Elsevier, Amsterdam, 1966, pp 307–310
3) Kaufman KD: Androgen metabolism as it affects hair growth in androgenetic alopecia, in Whiting DA (ed): *Update in Hair Disorders, Dermatol Clin,* **14**: 697–711, 1996.
4) Jaworsky C, Kligman AM, Murphy GF: Characterization of inflammatory infiltrates in male pattern alopecia: Implications for pathogenesis, *Br J Dermatol,* **127**: 239–246, 1992.
5) Leyden J, Dunlap F, Miller B, et al: Finasteride in the treatment of men with frontal male pattern hair loss, *J Am Acad Dermatol,* **40**: 930–937, 1999.
6) Rietschel RL, Duncan SH: Safety and efficacy of topical minoxidil in the management of androgenetic alopecia, *J Am Acad Dermatol,* **16**: 677–685, 1987.
7) Piérard-Franchimont C, De Doncker P, Cauwenberg G, et al: Ketoconazole shampoo: Effect of long-term use in androgenetic alopecia, *Dermatology,* **196**: 474–477, 1998.
8) Hamilton JB: Patterned hair loss in man: Types and incidence, *Ann NY Acad Sci,* **53**: 708–728, 1951.
9) Olsen EA: Androgenetic alopecia, in Olsen EA (ed): *Disorders of Hair Growth: Diagnosis and Treatment,* McGraw-Hill, New York, 1994, pp 257–284.
10) Tand PH, Chia HP, Cheong LL, Koh D: A community study of male androgenetic alopecia in Bishan, Singapore, *Singapore Med J,* **41**: 202–205, 2000.
11) Kuster W, Happle R: The inheritance of common baldness: to B or not to B?, *J Am Acad Dermatol,* **11**: 921–926, 1984.
12) Tosti A, Piraccini BM: Androgenetic alopecia, *Int J Dermatol,* **38** (Suppl 1): 1–7, 1999.
13) Sinclair R: Male pattern androgenetic alopecia, *Br Med J,* **317**: 865–869, 1998.
14) Rhodes L, Harper J, Uno H, et al: The effects of finasteride (Proscar) on hair growth, hair cycle stage and serum testosterone and dihydrotestosterone in adult male and female stump tail macaques (*Macaca arctoides*), *J Clin Endocrinol Metab,* **79**: 991–996, 1994.
15) Kaufman KD, Olsen EA, Whiting D, et al: Finasteride in the treatment of men with androgenetic alopecia, *J Am Acad Dermatol,* **39**: 578–589, 1998.
16) Waldstreicher J, Thiboutot D, Dunlap F, et al: The effects of finasteride in men with frontal male pattern hair loss, *Australas J Dermatol,* **38** (Suppl 2): 101–102, 1997.
17) McClellan KJ, Markham A: Finasteride: A review of its use in male pattern hair loss, *Durgs,* **57**: 111–126, 1999.
18) Hibberts NA, Howell AE, Randall VA: Balding hair follicle dermal papilla cells contain higher levels of androgen receptors than those from the non-balding scalp, *J Endocrinol,* **156**: 59–65, 1998.
19) Randall VA, Thorton MJ, Messenger AG: Cultured dermal papilla cells from androgen-dependant human hair follicles (*e.g.* beard) contain more androgen receptors than those from non-balding areas of sclap, *J Endocrinol,* **133**: 141–147, 1992.
20) Choudhry R, Hodgins MB, Van der Kwast TH, et al: Localization of androgen receptors in human skin by immunohistochemistry: Implications for the hormonal regulation of hair growth, sebaceous glands and sweat glands, *J Endocrinol,* **133**: 467–475, 1992.
21) Shapiro J, Price V: Hair regrowth, therapeutic agents, *Dermatol Clin,* **16**: 341–356, 1998.
22) Gormley GJ, Stoner E, Rittmaster RS, et al: Effects of finasteride (MK-906), a 5α-reductase inhibitor on circulating androgens in male volunteers, *J Clin Endocrinol Metab,* **70**: 1136–1141, 1990.
23) Rittmaster RS, Antonian L, New MI, et al: Effect of finasteride on adrenal steroidogenesis in men, *J Androl,* **15**: 298–301, 1994.
24) Rittmaster RS, Lemay A, Zwicker H, et al: Effect of finasteride: A 5α-reductase inhibitor on serum gonadotrophins in normal men, *J Clin En-*

docrinol Metab, **75**: 484–488, 1992.
25) Savin RC, Atton AV: Minoxidil: Update on its clinical role, *Dermatol Clin,* **11**: 55–64, 1993.
26) De Villez RL: Topical minoxidil for androgenetic alopecia: Optimizing the chance for success by appropriate patient selection, *Dermatologica,* **175** (suppl 2): 50–53, 1987.
27) Olsen EA, Weiner MS, Amara IA, et al: Five-year follow-up of men with androgenetic alopecia treated with topical minoxidil, *J Am Acad Dermatol,* **22**: 643–646, 1990.
28) Diani AR, Mulholland MJ, Shull KL, et al: Hair growth effects of oral administration of finasteride, a steroid 5α-reductase inhibitor, alone and in combination with topical minoxidil in the balding stump tail macaque, *J Clin Endocrinol Metab,* **74**: 345–350, 1992.
29) Walsh DS, Dunn CL, James WD: Improvement in androgenetic alopecia (Stage V) using topical minoxidil in a retinoid vehicle and oral finasteride, *Arch Dermatol,* **131**: 1373–1375, 1995.
30) Franz TJ: Percutaneous absorbtion of minoxidil in man, *Arch Dermatol,* **121**: 203–206, 1985.
31) Hoffman R, Happle R: Does interleukin-1 induce hair loss?, *Dermatology,* **191**: 273–275, 1995.
32) Piérard GE, Piérard-Franchimont C, Van Cutsem J, et al: Ketoconazole 2% emulsion in the treatment of seborrheic dermatitis, *Int J Dermatol,* **30**: 806–809, 1991.
33) Van Cutsem, Van Gerven F, Cauwenbergh G, et al: The antiinflammatory effects of ketoconazole, *J Am Acad Dermatol,* **25**: 257–261, 1991.
34) Schmidt A: Malassezia furfur: A fungus belonging to the physiological skin flora and its relevance in skin disorders, *Cutis,* **59**: 21–24, 1997.