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ORIGINAL PAPERS

Combined treatment with oral finasteride and topical minoxidil in male androgenetic alopecia: a randomized and comparative study in Chinese patients

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ABSTRACT: Finasteride at 1 mg/day and 5% topical minoxidil are effective in male androgenetic alopecia (MAGA). However, studies describing their effects in Chinese individuals are scarce. 450 Chinese MAGA patients were randomly assigned to receive finasteride (n = 160), minoxidil (n = 130) and combined medication (n = 160) for 12 months. The patients returned to the clinic every 3 months for efficacy evaluation. And efficacy was evaluated in 428 men at treatment end, including 154, 122, and 152 in the finasteride, 5% minoxidil, and combination groups, respectively. All groups showed similar baseline characteristics, including age at enrollment, and duration and severity of alopecia ($p > 0.05$). At 12 months, 80.5, 59, and 94.1% men treated with finasteride, 5% minoxidil and the combination therapy showed improvement, respectively. Adverse reactions were rare (finasteride, 1.8%; minoxidil, 6.1%), and disappeared right after drug withdrawal. In conclusion, finasteride is superior to 5% minoxidil, while the combined medication showed the best efficacy.

KEYWORDS: androgenetic alopecia, finasteride, minoxidil

Introduction

Androgenetic alopecia (AGA) is the most common hair loss disorder in men, characterized by nonscarring progressive miniaturization of hair follicles with a pattern of distribution in the scalp of genetically predisposed individuals. Male androgenetic alopecia (MAGA) typically presents as a gradual recession of the frontotemporal hairline and thinning over the vertex; the modified Norwood–Hamilton scale is the most common used standard for measuring the severity of alopecia. (1) According to epidemiological investigations (2,3), the prevalence of AGA in Chinese men is 19.9–21.3%.

Dihydrotestosterone (DHT), a potent androgen produced from testosterone by 5α-reductase, is believed to be pathogenic in MAGA (4). Finasteride, approved by the U.S. Food and Drug

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Administration (FDA) in 1997, is an androgen modifier that specifically inhibits type II 5α-reductase, which primarily localizes in the innermost layer of the outer root sheath, inner root sheath, and infundibular region of the hair follicle (5). Additionally, dose-ranging studies suggested that finasteride at 1mg/day is the optimal dose for the treatment of MAGA (6).

Topical minoxidil solution, another medication approved by FDA, is a biological response modifier. Although the mechanism by which minoxidil stimulates hair growth still remains unclear, researchers have found that minoxidil increases anagen/telogen ratios as well as the follicle size (7).

The latest guidelines (8,9) recommend oral finasteride at 1 mg/day and topical 5% minoxidil to be used as first-line topical treatment for men. However, studies assessing the efficacy of finasteride and minoxidil combination are scarce, especially in Chinese MAGA. Therefore, we aimed to compare the efficacy of monotherapy and combination therapy of finasteride and 5% minoxidil.

Patients and Methods

Patients

Four hundred fifty Chinese male subjects aged 18–50 years were enrolled in this study. They were diagnosed with type II—VI AGA based on the pattern of hair loss according to the modified Norwood–Hamilton scale. The study was performed at the Department of Dermatology of Huashan Hospital, Fudan University, from March 2011 to February 2014. No patient showed evidence of systemic illnesses such as cardiovascular, endocrine, hepatic or renal diseases, and other alopecia disorders including alopecia areata, telogen effluvium, or hair loss caused by trauma or radiotherapy. They also had no history of drugs that might affect hair growth (cytotoxic agents, proandrogenic, steroids, minoxidil, finasteride, etc.) within a year. The study protocol was approved by the ethics committee of Huashan Hospital affiliated to Fudan University, Shanghai, China. Informed consent was obtained from each participant before the trial.

Treatment methods

This was a 12-month, randomized, open-label, comparative trial. The subjects were assigned to the three groups by the random number table method, to receive oral finasteride (Propecia, Merck & Co, Inc., Kenilworth, NJ) (1 mg/day, $n = 160$), topical 5% minoxidil (Mandi, Wanma Pharm, China) (twice daily with a total dose of 2 ml/day, $n = 130$), and combined medication ($n = 160$).

Global photographic evaluation

Patients returned to the clinic every 3 months after the initial visit throughout the trial for efficacy and safety assessment. At each visit, standardized global photographs were acquired with a digital camera (D70, Nicon Corp., Japan) of the vertex and anterior/mid scalp regions, and frontal/temporal hair lines. The camera parameters were fixed, and patients needed to maintain the same posture by a support bracket when photographed. Additionally, subjects were requested to keep the same hair style throughout the trial. Two dermatologists who were blinded to treatment evaluated the efficacy based on a standardized 7-point rating scale: −3 = greatly decreased (71–100% decrease from baseline), −2 = moderately decreased (41–70% decrease from baseline), −1 = slightly decreased (1–40% decrease from baseline), 0 = no change, 1 = slightly increased (1–40% increase from baseline), 2 = moderately increased (41–70% increase from baseline), 3 = greatly increased (71–100% increase from baseline).

Safety evaluation

Safety evaluation was based on patients' complaints of adverse events, and those receiving finasteride were asked to take hepatic function tests every 3 months, as this compound undergoes extensive hepatic metabolism; in addition, a few patients treated with finasteride at our clinic have shown increased levels of hepatic enzymes.

Statistical Analysis

Statistical analysis was carried out with SPSS 16.0 (SPSS, Chicago, IL). Rates were compared by χ^2 test. Rating scores were analyzed by the Kruskal–Wallis and Mann–Whitney U tests. Demographic data were compared by Student's t test. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

Efficacy was evaluated in 428 patients, including 154, 122, and 152 treated with finasteride, minoxidil, and the combined medication. A total

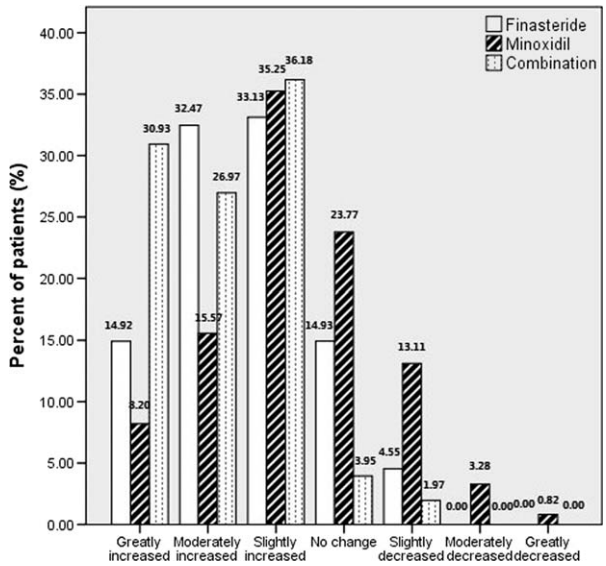

FIG. 1. Clinical assessment based on a standardized 7-point scale at treatment end.

of 22 individuals interrupted treatment due to adverse effects (16/22) and failure to return to the clinic at the required time points (6/22), and were excluded. The three treatment groups were well balanced in patient number and age at first visit, as well as duration of alopecia and hair loss severity ($p > 0.05$).

Efficacy assessment

Hair growth in patients treated with finasteride, 5% minoxidil and the combined treatment significantly increased with time ($p < 0.01$). At 12 months, 80.5, 59, and 94.1% men treated with finasteride, 5% minoxidil and the combination therapy showed improvement, respectively.

Hair growth rate in the finasteride group at month 3 was similar to that of minoxidil treated individuals (finasteride: 39.0% vs. minoxidil: 38.5%, $p > 0.05$), and reduced compared with the combination group (54.6%, $p < 0.01$). At months 6, 9, and 12, the patients taking finasteride showed a more pronounced improvement compared with those applying minoxidil ($p < 0.01$); the efficacy of the combined treatment remained the best ($p < 0.01$). The rating scores of global photographic evaluation are shown in FIG. 1. FIG. 2 exhibits the changes in hair growth from baseline by means of global photographic assessment.

Efficacy-related factors evaluation

Specific scalp regions. In the finasteride group, the improvement of vertex and anterior/mid regions was more pronounced than that of frontal/temporal hairline ($p < 0.001$). However, in the minoxidil and combination group, no relation was found between efficacy and scalp regions ($p > 0.05$).

Severity of hair loss. In all the treatment groups, patients with moderate alopecia (grade III vertex to IV) seemed to respond better, but there was no statistically significant difference ($p > 0.05$) (Table 1).

Age at therapy beginning. Men <40 years old treated with finasteride showed better results ($p < 0.05$). However, no correlation was found between age and efficacy in the minoxidil and combination groups ($p > 0.05$).

Safety evaluation. Adverse reactions were observed in 6 (1.8%) patients taking finasteride (including those with combined treatment): decreased libido ($n = 3$, 0.9%), erectile dysfunction ($n = 1$, 0.3%), testicular pain ($n = 1$, 0.3%), and impairment of hepatic function ($n = 1$, 0.3%). Most of them were mild, and patients recovered within a few weeks after drug withdrawal.

The most frequent side effect in patients administered 5% minoxidil was contact dermatitis ($n = 16$, 5.5%), and mainly presented as pruritus, burning, scaling and even rashes. Most of the symptoms were mild and endurable; only 6 (2.1%) patients discontinued the trial. Other side effects included headache ($n = 1$, 0.3%) and other body hair increase ($n = 1$, 0.3%). All the side effects disappeared soon after medication withdrawal.

Discussion

This was an open, randomized and comparative study aiming to compare the efficacy of oral finasteride and/or topical minoxidil in MAGA after12 months treatment. Oral finasteride at 1 mg/day yielded better outcome than topical 5% minoxidil used twice/day, in accordance with previous researches (10,11). The combined medication took effect faster, and was superior to monotherapies during the whole course of treatment. Moreover, longer duration of treatment resulted in better effect.

Patients treated with finasteride had more hair growth in vertex and anterior/mid scalp regions than in frontal and temporal hairlines ($p < 0.05$), corroborating the findings reported by Olsen

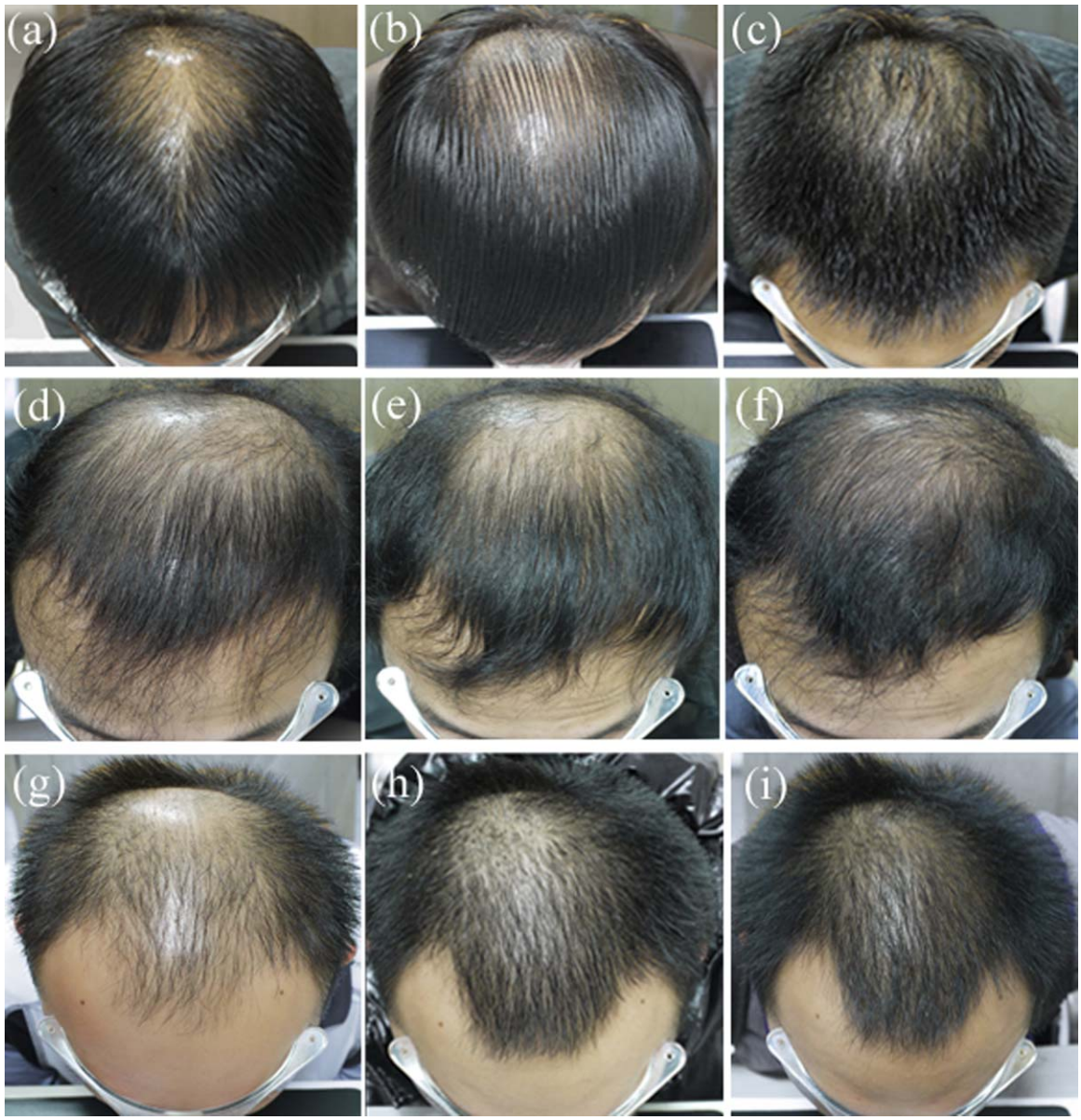

FIG. 2. (a)–(c). A 23-year-old man treated with finasteride at 1mg/day. (a) Baseline (grade IV based on modified Norwood–Hamilton scale); (b) slightly increased at month 6; (c) moderately increased at month 12. (d)–(f). A 29-year-old man treated with 5% minoxidil. (d) Baseline (grade V based on modified Norwood–Hamilton scale); (e) slightly increased at month 6; (f) moderately increased at month 12. (g)–(i). A 31-year-old man treated with combined medication. (g) Baseline (grade VI based on modified Norwood–Hamilton scale); (h) moderately increased at month 6; and (i) greatly increased at month 12.

et al. (12). Those receiving 5% minoxidil and combination therapy also presented similar trend, although no statistical significance was found ($p > 0.05$). This can be explained by severer miniaturization of hair follicles in frontal and temporal hairlines, as most patients usually first have fronto-temporal recessions.

In the finasteride group, younger men improved better ($p < 0.05$), which might be due to higher levels of DHT in younger patients (13). Those treated with 5% minoxidil and combination therapy showed a similar trend but also without significant relationship ($p > 0.05$). Fibrosis of scalp hair follicles usually increases with age or duration of AGA, which may also explain the greater efficacy observed in younger men (14).

No correlation was found between efficacy and hair loss severity ($p > 0.05$), yet patients with moderate alopecia (grade III vertex to IV) seemed to obtain better outcome. One reason is that patients with severer AGA might not respond as well as those with less severe hair

Table 1. Efficacy in hair growth at month 12 based on different types of MAGA [*n* (%)]

	II-III*	III vertex*	IV*	V-VI*
Finasteride	$N = 21$	$N = 69$	$N = 40$	$N = 24$
Age (mean ± SD, years)	26.8 ± 4.5	28.6 ± 3.4	29.42 ± 5.9	31.2 ± 5.1
Effective rate	17(81.0)	57(82.6)	33(82.5)	17(70.8)
Minoxidil	$N = 17$	$N = 55$	$N = 33$	$N = 17$
Age (mean ± SD, years)	25.1 ± 4.3	27.9 ± 4.4	30.6 ± 5.2	33.6 ± 7.8
Effective rate	8(47.1)	34(61.2)	20(60.6)	10(58.8)
Combined	$N = 22$	$N = 60$	$N = 40$	$N = 30$
Age (mean ± SD, years)	26.2 ± 4.5	28.6 ± 5.5	29.4 ± 6.9	33.4 ± 6.8
Effective rate	19(86.4)	59(98.3)	39(97.5)	26(86.7)

*According to the modified Norwood–Hamilton scale
SD = standard deviation.

loss; in addition, under global photographic assessment, relatively severer patients usually present more visible improvement.

A1-year phase III clinical studies of finasteride (15) involving 1879 MAGA patients reported that treatment-related adverse events occur in similar number of 1 mg/day finasteride recipients compared with the placebo group (7.7 vs. 7.0%); meanwhile, more patients treated with finasteride complained of sexual adverse events (3.8 vs. 2.1%, $p = 0.041$), including decreased libido (1.8 vs. 1.3%), ejaculation disorders (1.2 vs. 0.7%) and erectile dysfunction (1.3 vs. 0.7%).Previous studies have shown that sexual side effects occur in less than 2% patients in a 5-year study, similar to the placebo group, both at 1 and 5 years (16). Another 1-year controlled study of 1 mg/day finasteride involving 1553 men also reported similar rates of sexual adverse events (4.2 vs. 2.2%, $p = 0.030$), including decreased libido (1.9 vs. 1.3%), decreased ejaculate volume (1.0 vs. 0.4%) and erectile dysfunction (1.4 vs. 0.9%);17.5% (7/40)MAGA patients showed adverse events during1-year treatment with finasteride and 15% (6/40) of them suffered from loss of libido (11). The incidence of drug-related adverse events in this study was 1.8% in men receiving finasteride, with sexual adverse experiences representing 1.5%, including decreased libido ($n = 3$, 0.9%), erectile dysfunction ($n = 1$, 0.3%) and testicular pain ($n = 1$, 0.3%). Besides, increased alanine amino transferase (ALT) levels were reported in 1.5% of finasteride treated patients compared with 0.8% of placebo recipients (15); the incidence of hepatic dysfunction in this study turned out to be 0.3%. The difference in occurrence of adverse events between this study and previous reports might be a result of individual variation and sample size as well. Conversely, adverse events occurred in 6.1% men utilizing 5% minoxidil in this study, with contact dermatitis representing 5.5%, similar to an incidence of 4–6% obtained for 12 months of treatment in previous reports (8,11). Most reactions were mild and patients recovered quickly after drug withdrawal.

In conclusion, oral finasteride at 1 mg/day and topical 5% minoxidil used twice/day were well tolerated and effective in the treatment of MAGA, and their combination displayed greater advantages. Further research should be conducted to evaluate the long-term efficacy and safety of the combined medication, with a larger number of subjects and efficacy-related factors.

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Conflict of interest

No conflict of interest.

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