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Original Research Article

Effectiveness and safety of alcohol-free minoxidil in the management of treatment-naive patients with androgenetic alopecia

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ABSTRACT

Background: Androgenetic alopecia (AGA) is a common dermatological condition in India, with potentially adverse psychosocial consequences. Here, we assess the effectiveness and safety of an alcohol-free, procapil-based formulation of minoxidil 5% in patients with AGA.
Methods: Treatment-naïve, male patients (aged 18 to ≤45 years) with AGA were enrolled in this open-label, single-arm, non-comparative, investigator-initiated study. The change in anagen/telogen ratio (ATR), hair density, and hair shaft thickness from baseline to days 45, 90, 135 and 180, investigator and patients' global assessment for effectiveness and tolerability, and safety were assessed. A total of 53 men were enrolled.
Results: The mean (standard deviation [SD]) age of the study population was 28.3 (6.0) years. The mean (SD) ATR improvement post-treatment with minoxidil 5% was seen from day 90 (mean change: 0.4; p=0.009; 95% confidence interval [CI]: 0.1-0.7) till Day 180 (mean change: 0.4; p=0.011; 95% CI: 0.1-0.6). Improvement in hair density (p<0.01) and hair shaft thickness (p<0.01) across frontal, temporal, and occipital regions was also evident. The investigator assessment for effectiveness was 'excellent'/'good'/'satisfactory' for 90% of patients, which corroborated with patients' assessment (90%) at day 180. All the investigators and patients indicated that minoxidil had 'good' tolerability for all patients. No adverse events were reported during the study.
Conclusions: Alcohol-free minoxidil 5% was found to have a good safety profile and was efficacious in Indian male patients with AGA, with a high level of patient acceptance.

Keywords: Anagen, Androgenic alopecia, Minoxidil, Procapil, Telogen, Hair loss

INTRODUCTION

Androgenic alopecia (AGA) is the most common form of hair loss in men, characterized by frontal and vertex scalp hair loss. A genetic predisposition and racial variation in the prevalence is well recognized in patients with AGA.[1,2] AGA is expected to have a greater incidence in Asian men than is widely believed.[3] In the Indian context, a prevalence rate of 58% in men aged 30-50 years has been found,[4] with incidence gradually increasing with age.

Continuous progression of AGA can immensely influence the quality of life of subjects, particularly those with psychosocial complications such as depression, low self-esteem, altered self-image, and social avoidance.[5] An association between AGA, atheromatosis, coronary artery disease, and hypertension has also been reported in previous epidemiological studies.[6-9]

The significant pathophysiological highlights of AGA are alteration in the hair cycle development, follicular

miniaturization, and inflammation.[6,10,11] Men with alopecia have a short anagen stage and a long telogen stage, which inevitably result in very short hair that fails to emerge from the follicle, thereby causing baldness. The anagen stage diminishes with each cycle, whereas the length of the telogen stage remains steady or is extended. Eventually, the duration of the anagen stages reduces to such as extent that growing hair fails to attain adequate length to reach the surface of the skin, leaving a purge follicular pore.

Minoxidil is currently approved by the US food and drug administration for the treatment of AGA.[12] Because of its low skin permeability and poor water solubility, ethanol-based formulations of minoxidil are used to enhance its effectiveness and solubility; however, ethanol can induce skin irritation, pruritus, erythema, scaling, and dryness.[7-10] Considering that most minoxidil products available in the market are ethanol, propylene glycol, or water based, new formulations free from organic solvents are required to mitigate unfavorable effects and optimize AGA treatment.[11]

Minichek (minoxidil 5%) is an ethanol-free, hair-loss solution for which limited clinical data on hair growth effectiveness and safety are available. The current investigator-initiated study was conducted to understand the effectiveness in terms of ATR, number of hairs, and hair shaft thickness and safety of Minichek in patients diagnosed with AGA.

METHODS

Study design

This investigator-initiated, open-label, single-arm, non-comparative study was conducted between October 2018 and December 2019 at three centers in India (Kelkar nursing home, Pune; Dhadphale nursing home, Pune; and Skinovate laser and cosmetic surgery centre, Pune). Patients who met the eligibility criteria received the study solution minoxidil 5% (Minichek, Abbott healthcare Pvt Ltd) to be applied twice daily (1 mL per application) for a duration of 180 days. Patients were evaluated on day 0 (screening day/baseline) and days 45±7, 90±7, 135±7 and 180±7. The patients were advised to retain the solution on the scalp for about 4 hours before washing. A total of 53 men were enrolled.

Study population

Male patients (18 to 45 years, both inclusive) attending the outpatient department of the study centers, with a confirmed diagnosis of AGA on clinical and trichoscopic examination, were screened and enrolled in the study. Patients with a history of migraine or any dermatological disease that may have interfered with administration or assessment of study medication, patients on dermatological preparations that may have interfere with the study evaluation (finasteride or any other hormonal treatment), patients undergoing any procedures for hair enhancement and curling or straightening, patients who had participated in a clinical trial in the 30 days before enrollment, and/or patients deemed unable to complete the study by the investigator were excluded from the study.

The study protocol was approved by the institutional ethics committees of the respective study sites. The study was conducted in accordance with the national regulations, the declaration of Helsinki, and the international council for harmonization-good clinical practice (ICH-GCP) guidelines. Written informed consent was obtained from each patient before enrolment in the study. The study was registered on clinical trials registry of India (CTRI/2018/10/016214).

Study outcomes

The primary endpoint of the study was to determine the effect of minoxidil 5% treatment on change in ATR from baseline to days 45, 90, 135 and 180. The effect of treatment on the number of hairs and hair diameter from baseline to days 45, 90, 135, and 180, global assessment of effectiveness and tolerability by the investigators and patients on day 180 and safety of the treatment were also assessed. Trichoscopy was used for evaluating change in hair count and hair thickness in the frontal, temporal, and occipital areas at all time points. Global photographs were also taken to assess treatment response.

Study assessments

ATR analysis

About 0.25 cm^2 area of the scalp was shaved and the length of hair follicles in the shaved area was measured under 60× magnification. The procedure was repeated on the third or fourth day, and the images were compared to obtain ATR.

Hair density

Selected regions in the frontal, temporal, and occipital areas were evaluated by trichoscopy under 60× magnification. To calculate density, 1 to 4 terminal hair (TH) and vellus hair (VH) regions were designated/marked in the selected site and the density was calculated as number of hair strands/cm^2 at each time interval.

Hair shaft thickness analysis

Trichoscopy was used to observe hair shafts. Selected regions in the frontal, temporal, and occipital areas were identified to measure hair thickness. The procedure was repeated for 4 hair strands, and average hair thickness was assessed. Images were captured under 200× magnification at each time interval.

Visual evaluation

The photographs were taken by a trained investigator using a high-resolution digital camera, and the digital images were assessed by the expert (Figure 1 and 2).

Severity of hair loss

Severity of hair loss was also evaluated using trichoscopy at baseline and on days 45, 90, 135, and 180 and graded as mild, moderate or severe.

Statistical analysis

Discrete data were summarized using numbers (n) and percentages (%) along with 95% confidence interval (CI) for percentages. Continuous data were summarized using mean, median, range, and standard deviation (SD), along with 95% CI for the mean, wherever applicable. Statistical analysis was performed using statistical analysis system (SAS) software *(*SAS institute Inc., Cary, North Carolina, USA).

RESULTS

Patient demographics and baseline characteristics

Out of the 53 enrolled patients, 50 (94.3%) completed the study. All patients were men. Three (5.66%) subjects discontinued from the study prematurely.

The mean (SD) age of the study population was 28.3 (6.0) years. The majority of the patients (77.4%) did not report any family history of baldness (Table 1). None of the patients reported use of concomitant medications.

Effect of minoxidil on ATR

The mean (SD) ATR significantly improved from 0.5 (0.5) at baseline to 0.8 (1.0) by day 90 (95% CI: 0.6-1.1; p=0.009). At day 180, the mean (SD) ATR was 0.8 (0.9) (mean change from baseline: 0.4; 95% CI: 0.1-0.6; p=0.011). The change in ATR was not significant on day 45 (Table 2).

Effect of minoxidil on hair density and hair shaft thickness

In the frontal area, mean (SD) hair density increased from 250.1 (63.2) strands/cm^2 at baseline to 313.8 (86.7) strands/cm^2 by day 180 (mean change from baseline: 59.8

strands/cm^2; 95% CI difference: 36.7-82.9; p<0.001). The increase was significant from day 45 onwards (mean [SD]: 276.7 [80.6] strands/cm^2; 95% CI: 254.5-298.9; p=0.01). Hair density also increased in the temporal and occipital areas after treatment with minoxidil (Table 3).

Increase in hair shaft thickness was also evident from day 45 onwards. In the frontal area, the mean (SD thickness increased from baseline value of 47.3 (10.5) µm to 52.7 (9.6) µm by day 180 (mean change from baseline: 8.1 µm; 95% CI: 4.6-11.5; p<0.001). Mean (SD) hair shaft thickness also increased in the temporal and occipital regions from baseline to day 180 (Table 4).

Effect of minoxidil on hair loss severity

Out of 53 enrolled patients, 25 (47.2%), 23 (43.4%), and 5 (9.4%) had mild, moderate, and severe hair loss at baseline, respectively. By day 180, the number of patients with moderate (8 [16.0%]) and severe hair loss (2 [4.0%]) decreased and the number of patients with mild hair loss (40 [80.0%]) increased.

Global assessment of effectiveness of minoxidil

Investigators' global assessment of effectiveness of minoxidil on day180) was excellent, good, or satisfactory for 90% of patients, which corroborated with patients' assessment (90%) (Table 5).

Safety and tolerability of minoxidil

No adverse events were reported during the study. Tolerability of minoxidil was assessed as good by all patients (100%) and by investigators for all patients (100) on day180.

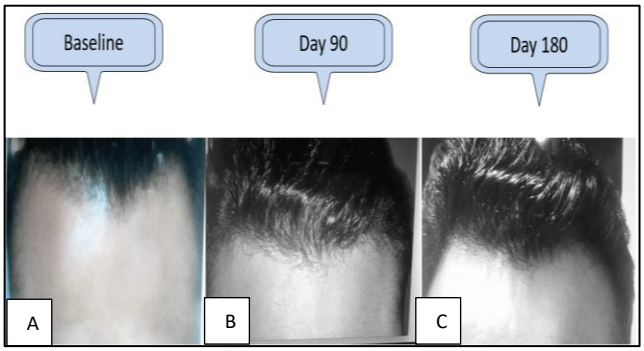

Figure 1 (A-C): View of alopecic areas before treatment; day 90 after treatment and day 180 after treatment.

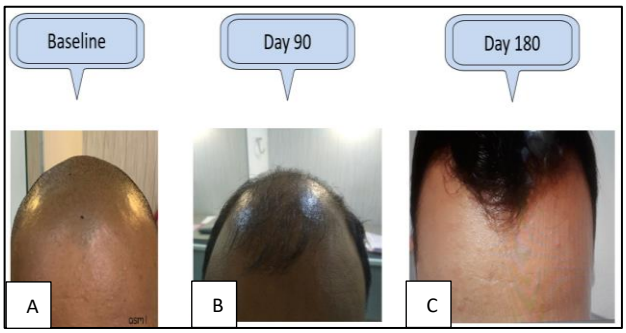

Figure 2 (A-C): View of alopecic areas before treatment; day 90 after treatment and day 180 after treatment.

Table 1: Demographics and baseline characteristics.

Parameters	Overall, (n=53)
Male sex, n (%)	53 (100)
Age (In years), mean (SD)	28.3 (6.0)
Height (cm), mean (SD)	168.8 (7.0)
Weight (kg), mean ± SD	70.3 (13.1)
Family history of baldness or AGA, n (%)	12 (22.6)
Medical history, n (%)	
AGA	50 (94.3)
Hemorrhoids	1 (1.9)
Mouth ulcers	1 (1.9)

Table 2: Change in ATR from baseline up to day 180.

ATR	Baseline, n=53	Day 45, n=50	Day 90, n=46	Day 135, n=48	Day 180, n=44
Mean (SD)	0.5 (0.5)	0.5 (0.6)	0.8 (1.0)	0.7 (0.9)	0.8 (0.9)
Mean change from baseline (95% CI)	-	0.1 (-0.1-0.3)	0.4 (0.1-0.7)	0.3 (0.0-0.6)	0.4 (0.1-0.6)
P value*	-	0.502	0.009	0.033	0.011

*Analyzed using paired 2-tailed t test for comparison between baseline and post-baseline visits.

Table 3: Change in hair density from baseline up to day 180.

Hair density (n/cm^2)	Baseline, n=53	Day 45, n=53	Day 90, n=53	Day 135, n=50	Day 180, n=50
Frontal area					
Mean (SD)	250.1 (63.2)	276.7 (80.6)	283.2 (75.8)	283.2 (70.7)	313.8 (86.7)
Mean change from baseline (95% CI)	-	26.6 (6.0-47.2)	33.0 (12.3-53.7)	29.2 (8.7-49.7)	59.8 (36.7-82.9)
P value*	-	0.01	0.002	0.006	<0.001
Temporal area					
Mean (SD)	207.9 (50.7)	221.3 (55.9)	216.7 (55.9)	253.4 (69.9)	258.6 (69.2)
Mean change from baseline (95% CI)	-	13.5 (0.6-26.3)	8.8 (-7.6-25.3)	38.0 (17.7-58.4)	43.2 (21.5-64.8)
P value*	-	0.040	0.284	<0.001	<0.001
Occipital area					
Mean (SD)	258.3 (68.5)	267.7 (68.7)	273.8 (72.0)	249.6 (62.2)	309.7 (75.4)
Mean change from baseline (95% CI)		9.4 (-9.6-28.4)	5.5 (-15.6-26.7)	28.0 (7.4-48.6)	43.1 (18.3-67.8)
P value*		0.324	0.601	0.009	0.001

*Analyzed using paired 2-tailed t test for comparison between baseline and post-baseline visits.

Table 4: Change in hair shaft thickness from baseline up to day 180.

Hair shaft thickness (µm)	Baseline, n=53	Day 45, n=53	Day 90, n=53	Day 135, n=50	Day 180, n=50
Frontal area					
Mean (SD)	44.5 (10.8)	47.3 (10.5)	55.0 (46.3)	50.2 (10.1)	52.7 (9.6)
Mean change from baseline (95% CI)	-	2.8 (-0.7-6.2)	10.5 (-2.8-23.7)	5.6 (2.3-8.9)	8.1 (4.6-11.5)
P value*	-	0.110	0.121	0.001	<0.001
Temporal area					
Mean (SD)	48.1 (10.9)	53.5 (11.1)	57.0 (23.4)	56.1 (9.1)	55.6 (8.0)
Mean change from baseline (95% CI)	-	5.4 (1.9-8.9)	8.9 (2.6–15.1)	6.8 (3.2–10.2)	6.3 (3.2-9.3)
P value*	-	0.003	0.006	<0.001	<0.001
Occipital area					
Mean (SD)	48.7 (10.7)	50.8 (8.3)	58.4 (32.1)	55.1 (8.0)	54.1 (9.3)
Mean change from baseline (95% CI)	-	2.1 (-1.2-5.3)	9.7 (0.6-18.7)	5.5 (2.2-8.8)	4.5 (1.1-7.9)
P value*	-	0.215	0.037	0.002	0.010

*Analyzed using paired 2-tailed t test for comparison between baseline and post-baseline visits.

Table 5: Summary of global assessment of effectiveness at day 180.

Proportion of patients, n (%)	Physicians' assessment, n=50	Patients' global assessment, n=50
Excellent	-	-
Very good	-	-
Good	23 (46.0)	24 (48.0)
Moderate/ satisfactory	22 (44.0)	21 (42.0)
Poor	5 (10.0)	5 (10.0)

DISCUSSION

Minoxidil, a pyridine-derivative, has been in use for the treatment of AGA for several decades. Minoxidil is a potent arteriolar vasodilator that opens potassium channels and decreases intracellular calcium, which in turn inhibits epidermal growth factor-stimulated growth of the hair root. K^+-channel activity is essential for progression to the G_1 stage of the cell cycle.[12] Malhi et al have shown that K(ATP) channel openers such as minoxidil play a role in DNA synthesis and cell proliferation.[13]

The clinical effectiveness of minoxidil has been demonstrated in several studies. A meta-analysis found that minoxidil at 2% and 5% concentrations showed mean hair density differences of 8.11 hair strands/cm^2 and 14.90 hair strands/cm^2 over placebo.[14] In a 5-year follow-up study in 31 patients with AGA who were treated with 2% or 5% minoxidil, peak hair regrowth occurred at one year though maintenance of nonvellus hair beyond that seen at baseline was also apparent. [15]In yet another study comparing the efficacy of 5% and 2 % of minoxidil, it was found that the effects of minoxidil were observed earlier in patients on minoxidil 5% and that 45% better hair growth was noted in this group relative to the 2% group.[16,17]

Ethanol enhances the poor water solubility of topical minoxidil; however, it causes severe adverse reactions such as scalp dryness, scaling, irritation, burning, pruritus, redness, and allergic contact dermatitis.[18,19] In addition, ethanol-based formulations tend to leave behind insoluble crystalline minoxidil on the scalp or skin as ethanol evaporates. This causes inefficient absorption of minoxidil through the skin.[20-22] Therefore, ethanol-free minoxidil formulations are preferred in order to minimize side effects and improve therapeutic efficacy of minoxidil.

Procapil plays a role in promoting enhanced anchorage of telogen hair in the dermis via regeneration of the root sheath, thereby slowing hair loss and improving the health of hair follicles.[23] It is a combination of three plant-derived substances that address the metabolic needs of hair follicles: 1) oleanolic acid (an inhibitor of 5α1 and 5α2 reductase enzymes), 2) apigenin (which causes vasodilation), and 3) glycyl-hystidyl-lysine peptide (a type of matrikine, which is required for pro-matrix metalloproteinase activity).[24,25] Though dermatologists believe that combining minoxidil with topical preparations such as procapil, and others may have additive effects, there is a paucity of real-world evidence on the same.[26] Hence, this study was designed to assess the effectiveness and safety of Minichek, an improvised alcohol-free, procapil based formulation of minoxidil 5%, in the management of treatment-naive patients with AGA.

Our results are consistent with the findings from other studies evaluating minoxidil treatment for AGA.[17,27-29] We observed improvements in the ATR indicating increased hair follicles in the anagen (growth) phase, decreased shedding of a hair, and improved volume and appearance post-treatment with minoxidil 5%. By day 180, ATR increased by 0.4. Further, improvement in the ATR was also associated with an increase in hair density ($p<0.001$) and hair shaft thickness ($p<0.001$). Improvised minoxidil 5% received favorable ratings for effectiveness and tolerability from investigators and patients for majority of the patients (90%) by day 180.

Though adverse events such as scalp dryness, irritation, and allergic contact dermatitis on the scalp are typically reported with minoxidil, no adverse events were observed in this study probably because the study formulation was alcohol free.[18,19,30] Given that topical treatment of AGA may necessitate prolonged usage to produce visible effects, the improvised alcohol-free, procapil based formulation represents a potentially advanced and effective approach for patients who have concerns regarding the side effects of topical minoxidil.

CONCLUSION

Overall data indicate that alcohol-free topical formulation of minoxidil 5% containing procapil significantly improved ATR ratio, increased hair density and hair shaft thickness in men with AGA. Further, there were no adverse events reported during the 180 days of study period, indicating that study formulation had good safety and tolerability profile. These study findings provide critical insights into benefits of an alcohol-free minoxidil formulation in management of AGA. Nevertheless, large-scale, controlled studies in larger patient populations are warranted to validate these findings.

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