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Therapeutics

The effects of minoxidil, 1% pyrithione zinc and a combination of both on hair density: a randomized controlled trial

R.S.BERGER, J.L.FU,* K.A.SMILES,† C.B.TURNER,† B.M.SCHNELL,† K.M.WERCHOWSKI† AND K.M.LAMMERS†

Hill Top Research, Inc., East Brunswick, NJ, U.S.A.
**Reed Hartman Research Center, Cincinnati, OH, U.S.A.*
†The Procter & Gamble Company, Sharon Woods Technical Center, 11511 Reed Hartman Highway, Cincinnati, OH 45241, U.S.A.

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Summary

Background Recent studies of antidandruff shampoos or tonics containing antifungal or antibacterial agents produced effects suggestive of a potential hair growth benefit.

Objectives The purpose of this 6-month, 200-patient, randomized, investigator-blinded, parallel-group clinical study was to assess the hair growth benefits of a 1% pyrithione zinc shampoo. The efficacy of a 1% pyrithione zinc shampoo (used daily), was compared with that of a 5% minoxidil topical solution (applied twice daily), a placebo shampoo and a combination of the 1% pyrithione zinc shampoo and the 5% minoxidil topical solution.

Methods Two hundred healthy men between the ages of 18 and 49 years (inclusive) exhibiting Hamilton–Norwood type III vertex or type IV baldness were enrolled. Total hair counts, the primary efficacy measure, were obtained using fibre-optic microscopy and a computer-assisted, manual hair count method. Secondary measures of efficacy included assessments of hair diameter, as well as patient and investigator global assessments of improvement in hair growth. These were based on photographs of the scalp using both midline and vertex views.

Results Hair count results showed a significant ($P < 0{\cdot}05$) net increase in total visible hair counts for the 1% pyrithione zinc shampoo, the 5% minoxidil topical solution, and the combination treatment groups relative to the placebo shampoo after 9 weeks of treatment. The relative increase in hair count for the 1% pyrithione zinc shampoo was slightly less than half that for the minoxidil topical solution and was essentially maintained throughout the 26-week treatment period. No advantage was seen in using both the 5% minoxidil topical solution and the 1% pyrithione zinc shampoo. A small increase in hair diameter was observed for the minoxidil-containing treatment groups at week 17. Assessments of global improvements by the patients and investigator generally showed the benefit of 5% minoxidil. The benefit of the 1% pyrithione zinc shampoo used alone tended ($P < 0{\cdot}1$) to be apparent only to the investigator.

Conclusions Hair count results show a modest and sustained improvement in hair growth with daily use of a 1% pyrithione zinc shampoo over a 26-week treatment period.

Key words: male pattern baldness, microscopy, minoxidil, pyrithione zinc, randomized controlled trial

Androgenetic alopecia, or male pattern baldness, affects approximately 50% of adult males.[1,2] The molecular aspects of androgenetic alopecia are complex and not completely understood. A genetic predisposition and the influence of androgens have been well established.

Recent studies of antidandruff shampoos or tonics containing antifungal or antibacterial agents showed results suggestive of a potential hair growth benefit.[3,4]

Correspondence: Kenneth A.Smiles.
E-mail: smiles.ka@pg.com

The objective of the present clinical study was to assess directly the hair growth benefits of a 1% pyrithione zinc shampoo. Pyrithione zinc is known to have antimicrobial properties[5] and is used as an effective antidandruff treatment.[6] A 5% minoxidil topical solution was selected as the positive control.

The primary efficacy measure was an assessment of hair count using fibre-optic microscopy and a computer-assisted, manual hair count method. In addition, the hair diameter was evaluated over the treatment period using fibre-optic microscopy and an automated image analysis method. Perception data of overall improvement were obtained by visual inspection of global photographs by the patients and the investigator.

Patients and methods

Patient selection

Two hundred healthy men between the ages of 18 and 49 years (inclusive) exhibiting type III vertex or type IV androgenetic alopecia, according to the Hamilton–Norwood classification,[2,7] were included in this 6-month study. Patients with other skin diseases of the scalp, including severe seborrhoeic dermatitis, psoriasis, lichenoid eruption, tinea capitis, or other scalp infections or infestations, were excluded. Patients with a history of alopecia areata, totalis, universalis or other hair loss disorders other than androgenetic alopecia were also excluded. None of the patients had used products known to influence hair growth in the past 6 months prior to the study, nor had taken or were taking medications known to induce hypotrichosis or hypertrichosis.

Clinical study design

This randomized, investigator-blinded, parallel-group study was conducted simultaneously at two clinical sites (Hill Top Research Inc., East Brunswick, NJ, U.S.A and Reed Hartman Research Center, Cincinnati, OH, U.S.A). Patients were recruited between 28 April 1999 and 25 May 1999. The study period was between 1 June 1999 and 26 January 2000.

The treatment group sizes were determined on the basis that at least 40 patients in each treatment group would complete the study. The completing base size of 40 per treatment group was projected to provide an 80% power for detecting significant differences in hair counts between each of the three active treatment groups vs. the shampoo placebo with $P < 0{\cdot}05$ (two-sided), assuming that the same difference would be observed in this study as the difference between 2% minoxidil topical solution and placebo observed in a previous pilot study after 9 weeks of treatment (internal communication).

The study was approved by the Hilltop Research Institutional Review Board. All patients gave written informed consent prior to participating.

During the initial visit, four groups of 50 patients (total of 200, with 100 at each of the two clinical sites) were randomly assigned to one of four treatment groups after being stratified by baldness type. The treatment groups were: (i) 1% pyrithione zinc shampoo; (ii) 5% minoxidil topical solution + placebo shampoo; (iii) placebo shampoo; and (iv) a combination of the 1% pyrithione zinc shampoo and the 5% minoxidil topical solution. Patients using a shampoo product were instructed to use it at least daily for the duration of the study. Those using the minoxidil topical solution were instructed to apply 1 mL to balding areas of the scalp twice daily with the supplied dropper at approximately 12-h intervals. Patients were asked to avoid sun exposure to their head during the course of the study.

Products tested

The 1% pyrithione zinc shampoo was the commercially available Head & Shoulders® shampoo, fine/oily version (The Procter & Gamble Company, Cincinnati, OH, U.S.A). The Head & Shoulders shampoo evaluated here contained pyrithione zinc in the small platelet form having an average particle size of approximately 2·5 μm diameter. The placebo shampoo was identical except for the absence of pyrithione zinc. The shampoo products were blind labelled and were packaged in 16-ounce white bottles.

The 5% minoxidil topical solution was Rogaine®, extra strength version (The Upjohn Company, Kalamazoo, MI, U.S.A) in the marketed 2-ounce bottle, but relabelled to hide its identity. Product usage and compliance were monitored for each patient by reviewing patient diaries and weighing the returned test products at each scheduled visit (weeks 4, 9, 13, 17 and 26).

Clinical evaluations

Treatment efficacy was assessed at baseline and treatment weeks 9, 17 and 26. Total hair counts were assessed by collecting fibre-optic microscope images at

a tattooed vertex transitional scalp site. Total visible hair counts were obtained from digitized macrographs using a computer-assisted, manual hair count method. Evaluations of hair diameter were obtained from the same digitized macrographs and were analysed using a computer-automated image analysis method. Global photographs were taken of the midline area and posterior vertex area of the scalp at the same time-points. More detailed descriptions of the methods used are given in the sections that follow.

Fibre-optic microscopy

Microscopic images were obtained using a Hi-Scope® fibre-optic, remote head microscope, Model KH-2400R (Hirox Company, Ltd, Tokyo, Japan). The imaging unit contained a high-resolution charged couple device camera, a halogen lighting source and a fibre-optic cable. The fibre-optic probe, Model MX20Z (Hirox Company, Ltd) was used with the $\times 25$ magnification lens. A dome and cap were added to the imaging system in order to achieve the proper magnification and uniform lighting across the field of view. Magnified images were captured and digitized using a Windows-based computer system, which included a TCi Ultra II frame grabber (Coreco Inc., St Laurent, Québec, Canada). Optimas 6·2 software (Media Cybernetics, Silver Spring, MD, U.S.A) was used to obtain analogue signals from the frame grabber and to convert them to digital format, to acquire, manipulate and store images, and to control image brightness and contrast. Standards were used to ensure that brightness, contrast, magnification and colour remained consistent throughout the study. Custom software was used to create a user interface for image capture, blending, storage and recall.

Acquisition of fibre-optic macrographs

At the baseline visit, each patient was tattooed at the vertex transitional scalp site. Patients were evaluated to assure that they presented sufficient hair-to-scalp colour contrast to enable accurate hair counting. The tattoo served as a reference point for placement of the fibre-optic probe at the baseline evaluation and for repositioning the probe at the identical position for subsequent treatment evaluations. Prior to each evaluation, hair within several cm^2 around the tattoo was clipped to approximately 1 mm in length and a drop of water was placed on the scalp site to minimize light scattering due to scalp flakes and scalp texture. The fibre-optic probe was then placed against the scalp and a digital image of the visible hairs was captured and saved.

At postbaseline visits, the fibre-optic probe was repositioned to achieve registration with the baseline image. This was accomplished by lining up the treatment period image over the baseline image on the monitor screen. The tattoos were positioned over each other at the bottom centre of the image, and the fibre-optic head was moved to align the hair follicle openings in a process called blending. This resulted in near perfect registration of the baseline image with the subsequent images taken at weeks 9, 17 and 26.

Computer-assisted, manual hair count method

The total number of visible hairs in the digitized images was counted by trained and qualified expert counters. Digitized images were displayed on a computer monitor and each visible hair in the image was marked with an X. The software computed the total number of hairs in the image as the number of Xs marked by the expert counter.

Two expert counters were qualified based on the total visible hair counts obtained from a series of 15 standard images. Each counter determined the total hair count for the entire series in duplicate. The mean hair count results for each image by each counter were compared with those of an expert and with those of the other counter. To qualify, the intercounter reliability, as indicated by the intraclass correlation coefficient[8] (ICC), was required to be $= 0{\cdot}95$. The duplicate counts were compared with each other to assess the intra-counter reliability, which was then considered acceptable if the ICC was $= 0{\cdot}98$. After the final visit, reproducibility was checked from counts of the same set of 15 standard images at the beginning, the middle and the end of the counting period.

Automated image analysis method

An image analysis algorithm was used to measure the hair diameter from the digital micrographs. The algorithm automatically carried out several steps to isolate and characterize hairs in each digital image. First, the algorithm performed a local background levelling function and enhancement of the red component in the colour image. Automatic thresholding of the colour image was performed to obtain a binary image (black and white) of the hairs on the background. The algorithm then identified hairs as continuous black lines and broke the lines into individual hairs at branch points and points of high curvature.

Next, the algorithm eliminated very short objects and retained the remaining objects as 'hairs'. In the final step, the algorithm measured and recorded position and diameter (width) of each detected hair.

Acquisition and assessments of global photographs

Global photographs of the midline area and posterior vertex area of the scalp were obtained at baseline and at treatment weeks 9, 17 and 26 using the Canfield photographic system.[9] In each case, the baseline photograph was paired with the corresponding post-treatment photograph. Patients and the investigator were asked to compare the two photographs. Both the investigator and the patients were blinded as to which was the baseline photo and the week in which the post-treatment photo was taken. The order of viewing the photographic pairs was randomized according to a randomization scheme prepared by the statistician. Each pair was viewed at intervals of at least 5 min apart to minimize the possibility of the patients or the investigator recognizing the baseline photograph.

Patients and the investigator rated the global photographs based on a nine-point scale from -4 to $+4$, with a positive number indicating that the post-treatment photograph was perceived to have more hair, and a negative number indicating that the post-treatment photograph was perceived to have less hair. No difference was assigned a value of 0.

Statistical analysis

An analysis of variance was performed on the total number of visible hairs, hair diameter values and age at baseline, to assess overall balance across treatment groups. χ^2 and Fisher's exact tests were used to assess comparability with respect to baldness type, race, years of balding, age when balding began, and skin type. All patients who were randomized to a treatment group and received at least one dose were included in the analysis (intent-to-treat analysis). For those patients with missing observations, the last available observation was carried forward.

Changes in the number of visible hairs and hair diameter at weeks 9, 17 and 26 were obtained by subtracting the baseline value from the total value for each treatment group. For each time-point, an analysis of covariance was performed on the change in the number of visible hairs and hair diameter, with the baseline value as the covariate. The study site and the stratification variable used in the randomization (i.e. baldness type) were accounted for in the analysis. A factor for treatment-by–clinical site interaction was considered and retained in the statistical model when found significant at $\alpha = 0{\cdot}05$. Two-sided tests of significance for treatment differences were conducted at the experiment-wise error rate of 5%, adjusting for multiple comparisons according to Hochberg's procedure.[10]

In the analysis of patients' and investigator's perception of changes in the balding condition from the global photographs, the positive scores (1–4) were combined to indicate improvement. Scores of 0 and negative values (-1 to -4) were combined to indicate no improvement. The variable with two categories (improvement vs. no improvement) was analysed using the Cochran–Mantel–Haenszel test. Treatment differences were adjusted for baldness type and clinical site. Two-sided tests of significance for treatment differences were conducted at the experiment-wise error rate of 5%, adjusting for multiple comparisons according to Hochberg's procedure.[10]

Results

A total of 22 of the 200 patients enrolled did not complete the study, 14 for reasons unrelated to the treatments (Table 1). Significantly more patients in the minoxidil treatment groups dropped out of the study early ($P = 0{\cdot}004$) than patients from the other groups. This was associated with the relative lack of local tolerance. There were no protocol deviations from the investigational plan of the study.

The mean age of the patients in this study was 40 years. Patients were predominantly (97%) caucasian. The majority of patients (62·5%) presented with type III vertex baldness at the baseline visit. The remainder had type IV. About half (44·5%) reported losing hair for less than 10 years. For almost half (47·5%), balding began in their late 20s or earlier. Most (87·5%) of the patients had Fitzpatrick skin type III or IV.[11] No significant treatment differences were found between the treatment groups in any of the demographic variables or baseline values. Similar analyses were conducted across clinical sites. No significant differences were found between the two clinical sites except for baldness type ($P = 0{\cdot}028$). One site had significantly more patients with type III vertex baldness than the other site (70% vs. 55%).

Statistical modelling of the total number of visible hairs from the baseline visit showed that baldness type had a significant effect on the total number of visible hairs measured ($P < 0{\cdot}005$). As expected, men with

Table 1. Patient participation flowchart

Baldness type	Treatment 1 5% minoxidil + 1% PTZ[a]	Treatment 2 5% minoxidil + placebo shampoo	Treatment 3 1% PTZ[a]	Treatment 4 placebo shampoo	Total
Type III vertex	32	32	30	31	125
Type IV	18	18	20	19	75
Total entered	50	50	50	50	200
Total completed	40	41	49	48	178
Number dropped for local intolerance	4	3	0	1	8
Number dropped for non-study reasons	6	6	1	1	14
Total analysed[b]	50	50	50	50	200

[a]PTZ, pyrithione zinc shampoo; [b]last observation carried forward.

type III vertex baldness had significantly higher hair counts at the vertex transitional scalp site (least square mean = 145·25) than men with type IV baldness (least square mean = 130·20).

Statistical modelling of the change in total number of visible hairs at weeks 9, 17 and 26 showed that baseline hair count was a significant factor in explaining the variation in the change in total number of hairs, so that the baseline hair counts were used as a covariate in subsequent analyses.

Table 2 shows the change in total visible hair count cm^{-2} for each treatment group after adjustment for baseline hair counts. After 9 weeks of treatment, both treatment groups that applied the 5% minoxidil topical solution showed a significant ($P < 0·01$) net increase in total visible hair counts, relative to the placebo shampoo group. This increase in total hair counts was maintained over the 26 weeks of treatment for those patients using the 5% minoxidil topical solution + placebo shampoo. However, for patients using the combination of 5% minoxidil topical solution and 1% pyrithione zinc shampoo, the total hair visible hair counts tended to peak at 9 weeks and then decline over the remainder of the treatment period.

Table 2. Increased hair density (hair counts cm^{-2}) relative to baseline for each treatment group ($n = 50$) after 9, 17 and 26 weeks

Treatment	9 weeks (SEM = 1·98)	17 weeks (SEM = 2·03)	26 weeks (SEM = 2·05)
5% minoxidil + 1% pyrithione shampoo	12·46**	9·47	6·23*
5% minoxidil + placebo shampoo	14·17**	11·36	12·32**
1% pyrithione zinc shampoo	5·20*	4·04	5·69*
Placebo shampoo	−1·29	0·62	−0·58

*$P < 0·05$, **$P < 0·01$ relative to the placebo treatment.

The group using the 1% pyrithione zinc shampoo also showed a significant ($P < 0·05$) net increase in total hair counts, relative to the placebo group, after 9 weeks of treatment. The relative increase in hair count for this group was slightly less than half that for the minoxidil-treated groups. The increase in total hair count for the 1% pyrithione zinc shampoo group was essentially maintained throughout the treatment period. Statistical analyses showed these increases, relative to the placebo treatment, to be significant ($P < 0·05$) except at the 17-week assessment, which was due to a significant treatment-by–clinical site interaction at this visit.

There was a small increase in hair diameter in the minoxidil treatment groups at week 17, which was not seen at the end of the study (week 26) (Table 3). The improvements with minoxidil were consistently ($P < 0·05$) observed by the investigator and patients throughout the study, while the shampoo containing 1% pyrithione zinc only tended to be better than the placebo shampoo and then only sporadically. The perception results at the end of the 26-week treatment

Table 3. Change in mean hair width (mm) relative to baseline for each treatment group after 9, 17 and 26 weeks

Treatment	9 weeks (SEM = 0·01)	17 weeks (SEM = 0·01)	26 weeks (SEM = 0·01)
5% minoxidil + 1% pyrithione shampoo	0·01[a]	0·02**	−0·01
5% minoxidil + placebo shampoo	0·00	0·03**	−0·01
1% pyrithione zinc shampoo	−0·02	−0·02	−0·04
Placebo shampoo	−0·02	−0·03	−0·04

**$P < 0·01$; [a]$P < 0·10$ relative to the placebo treatment ($n = 50$ for 1% pyrithione zinc shampoo with and without 5% minoxidil, $n = 49$ for placebo shampoo with and without 5% minoxidil).

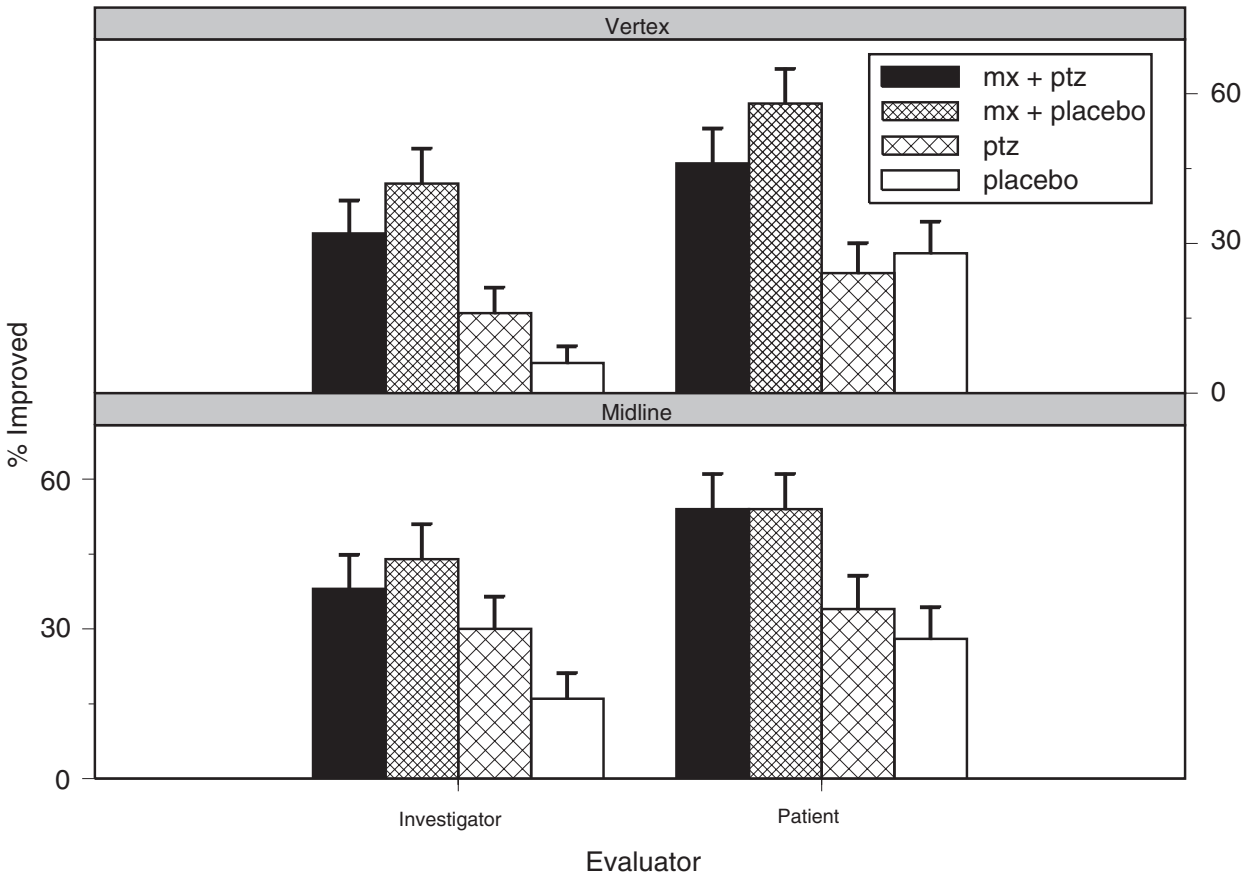

Figure 1. Perception of improvement results obtained from investigator and patient assessments of global photographs at the end of the 26-week treatment period. Percentage of patients improved relative to baseline as perceived by the investigator and patients viewing the midline and posterior vertex global views of the scalp. mx, minoxidil; ptz, pyrithione zinc. Error bars indicate SEM.

period are shown in Figure 1. For both the midline and vertex views the effect of minoxidil on the proportion of patients improved was apparent ($P < 0{\cdot}008$) to both the patients and investigator, whereas the effect of the 1% pyrithione shampoo alone tended to be apparent only to the investigator ($P < 0{\cdot}10$).

Discussion

Of the results shown in Table 2, those for the 1% pyrithione zinc shampoo are of particular interest. The activity of the 1% pyrithione zinc shampoo was maintained throughout the 26-week treatment period at a level slightly less than half that of the 5% minoxidil topical solution. The significance of the hair growth activity of the 1% pyrithione zinc shampoo was reinforced by an examination of the distribution of hair growth responses across the treatment groups at the 26-week evaluation. Figure 2 shows the proportion of patients with each percentage change in total visible hair counts from baseline for each treatment group. Comparison of the 1% pyrithione zinc shampoo group with the 5% minoxidil topical solution groups shows a similar apparent rightward shift in the distribution of patients experiencing a positive increase in total visible hairs. The key difference between these two treatment groups was the relatively small number of patients who experienced very positive results with the 5% minoxidil topical solution.

The present study found a trend towards a small increase in hair diameter over the 6-month treatment period for the minoxidil treatment groups. No change in hair diameter was evident for the 1% pyrithione zinc shampoo.

The results of the global evaluations are interesting in terms of showing that a readily apparent improvement can be seen when hair counts are increased by about 12 cm^{-2}, but are substantially more difficult to discern at the 5–6 cm^{-2} level. Because there were trends in the investigator's evaluations in discerning a

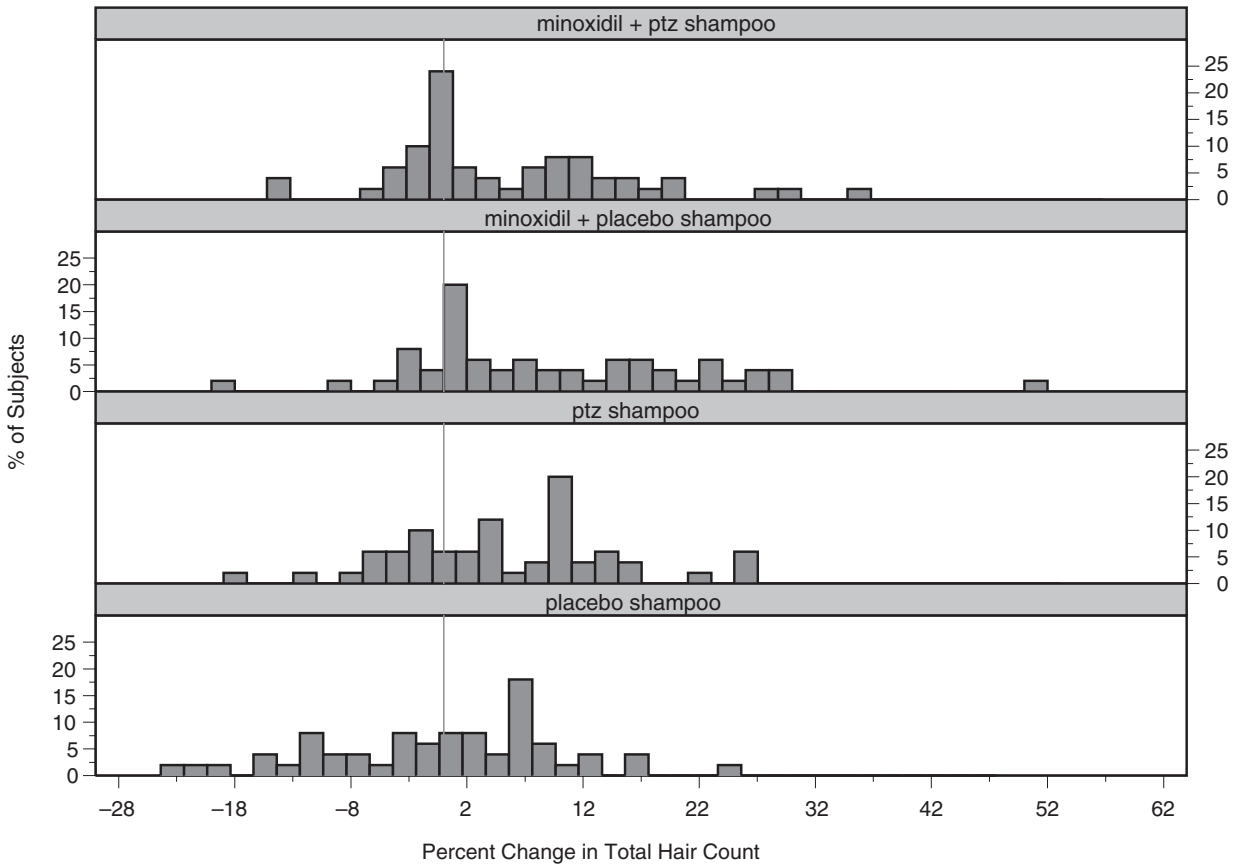

Figure 2. Distribution of percentage increase in hair counts for the treatment groups in the study. Rightward shift from zero in the distribution indicates patients who had increases in hair growth after 26 weeks of treatment. $n = 50$. ptz, pyrithione zinc.

global benefit for the 1% pyrithione zinc shampoo, one would expect a larger or longer study to be necessary to demonstrate the cosmetic effectiveness of the 1% pyrithione zinc shampoo alone.

The use of a flexible head microscope, digital imaging system and a permanent tattoo allowed for near perfect registration of the treatment-phase images with the baseline image, as shown in Figure 3. This contributed to the sensitivity of the method in finding significant treatment effects down to an approximately 4% change in hair density.

Several studies have found a microscopic cellular inflammation around the hair follicles in the transitional zone of the balding scalp.[3,12–14] The impact of this inflammation on the balding process has not been fully elucidated; however, it is known that proinflammatory cytokines inhibit hair growth in *in vitro* studies.[13] It has been hypothesized[13] that the inflammation and associated cytokine milieu may play a role in the process of hair follicle miniaturization characteristic of androgenetic alopecia. It has also been suggested[14] that the scalp microflora may induce this inflammation either through some secreted products or metabolites, or by acting as antigens. Several studies[3,4] have found changes in hair diameter and/or the anagen/telogen ratio suggestive of a hair growth benefit from antimicrobial products. The current study confirms and extends the observations of Pierard-Franchimont *et al.*[4] who studied another topical antifungal, ketoconazole, in androgenetic alopecia. They found changes in both the anagen/telogen ratio and hair diameter consistent with a hair growth benefit. The present study of pyrithione zinc shampoo showed a direct benefit in improving hair density.

Thus, one potential mechanism of action for pyrithione zinc in androgenetic alopecia would be its potent antimicrobial properties.[5] Pyrithione zinc would also be expected to release zinc ion, which has specific activities resulting in anti-inflammatory effects,[15] is an important skin antioxidant[16] and inhibits 5α-reductase *in vitro*;[17] all of these could

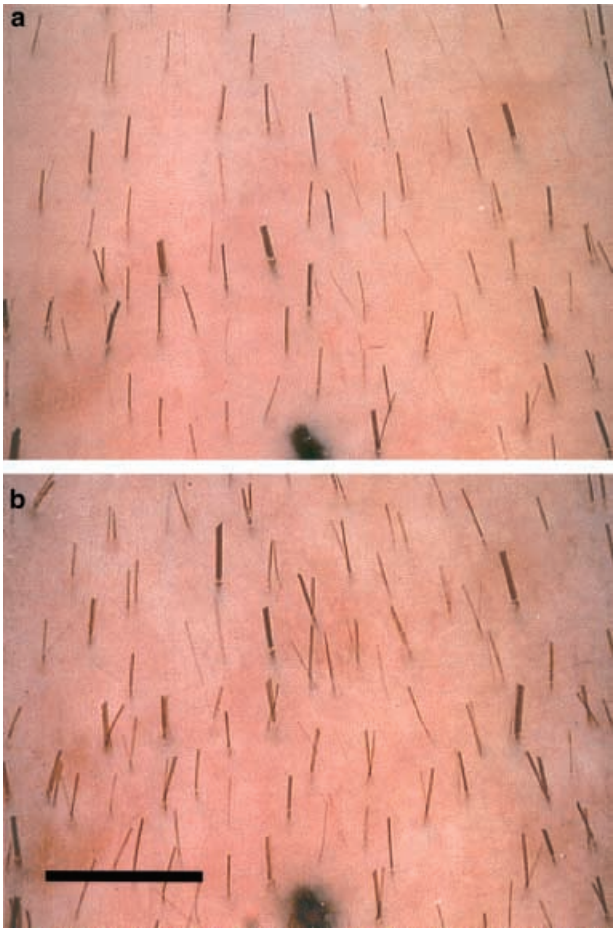

Figure 3. Precise realignment of fibre-optic probe with the tattooed scalp site. Micrographs at ×25 magnification taken from a patient (a) at baseline and (b) after 17 weeks of treatment.

potentially be involved in the therapeutic benefit for androgenetic alopecia.

Antidandruff efficacy studies of pyrithione zinc[6] indicate that less frequent usage (twice weekly) may be sufficient to maintain dandruff control. Although the dosing requirements for antidandruff efficacy may be different than those for hair growth, the known persistence of pyrithione zinc on the scalp suggests that such dosing may also be sufficient for a hair growth benefit in androgenetic alopecia if both rely on an antimicrobial mechanism of action.

The lack of an additive benefit from the combined use of minoxidil and pyrithione zinc was surprising, as the mechanisms of action would appear independent. We can only speculate that there might be some chemical incompatibility *in situ* or some shared benefit pathway that prevented a combined benefit.

In summary, the results of the present study show a modest and sustained improvement in hair growth with daily use of a 1% pyrithione zinc shampoo over a 26-week treatment period. Follow-up longer term and larger clinical studies are indicated to study the persistence of this therapeutic benefit, and to determine whether one can achieve a hair growth benefit that can be easily appreciated by the patient.

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