

# Comparison of the efficacy and safety of topical minoxidil and topical alfatradiol in the treatment of androgenetic alopecia in women

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## Keywords

- androgenetic alopecia in women
- minoxidil
- alfatradiol
- efficacy
- tolerance
- hair density
- cumulative hair thickness
- TrichoScan®

## Summary

**Background:** Two drugs which are approved for the treatment of androgenetic alopecia in women in Germany were compared with regard to their influence on hair growth.

**Patients and Methods:** Patients were randomized to group I (n = 52) who used 2% minoxidil solution twice daily for a period of 12 months or to group II (n = 51) who used 0.025% alfatradiol solution once daily for 6 months and were then switched to 2% minoxidil solution for months 7–12. Changes in hair growth parameters were determined using the TrichoScan®.

**Results:** Topical treatment with 2% minoxidil solution for 6 months resulted in a significant increase of cumulative hair thickness (p < 0.0001) and absolute hair density (p ≤ 0.0025), whereas these parameters of hair growth remained nearly unchanged after 6 months of treatment with alfatradiol solution.

Evaluation of the same parameters from month 7 to month 12 demonstrated that 12 months minoxidil treatment resulted in an increasing stabilization (group I). After the alfatradiol→minoxidil switch in group II a significant increase in cumulative hair thickness (p < 0.0001) and absolute hair density (p < 0.0001) was achieved. Both study medications were well tolerated.

**Conclusions:** Treatment with minoxidil can induce an increase in hair density and hair thickness, whereas treatment with alfatradiol results in deceleration or stabilization of hair loss.

## Introduction

Human scalp hair contributes to outward appearance and to socially active communication. Disturbances of hair growth with visibly manifest hair loss can be a burden on self-esteem and the quality of life of those affected [1, 2]. Androgenetic alopecia (AGA) is the most common form of hair loss, and 20–30 % of all women display a variable degree of AGA [3]. About 10 % of these women have such a great genetic predisposition that they already display central parietal loss of hair

density at an age of 20 to 30 years, whereas others start losing hair only around menopause [4]. Without treatment, AGA takes a chronic progressive course with an average hair loss of 5–6 % annually with great interindividual variability [5, 6].

The goal of treating AGA is to stop active hair loss, prevent further loss and retain existing hair. If possible, an attempt to reactivate the hair follicle and to stimulate new hair growth should be undertaken [7]. In Germany two medications are licensed for treating AGA in

women: a 2 % minoxidil solution (Regaine® Frauen) and a 0.025 % alfatradiol solution (Ell-Cranell® alpha and Pantostin® solution).

A direct comparative study of these two medications in treating AGA has been lacking. The presented randomized study on efficacy and tolerability of both medications on changes in cumulative hair thickness and absolute hair density in treated women was done using an objective measuring system, the TrichoScan® [8].

## Materials and methods

The protocol of this open, randomized, multicenter comparative phase IV study was approved by the responsible ethic commission and reported to the Federal Institute for Drugs and Medical Products (Bundesinstitut für Arzneimittel und Medizinprodukte BfArM). A total of 103 adult women with AGA grade I or II according to Ludwig [9] from four study centers in Germany (Freiburg, Munich, Wetter, Berlin) were recruited into the study after written consent. The 103 women were randomized online into two treatment groups: 52 patients into group I (50.7 years of age on average) and 51 into group II (45.6 years of age). Due to the available therapeutic options for AGA in women, we waived a placebo control on ethical grounds.

The effect of topical treatment with minoxidil or alfatradiol solution on hair growth was assessed in all patients with the help of TrichoScan<sup>®</sup>, epiluminescence microscopy with digital image analysis [8, 10]. For this purpose, a Nikon Coolpix<sup>®</sup> 4500 digital camera with maximum optical zoom was employed, allowing for analysis of an area of 0.56 cm<sup>2</sup>. The intra- and interclass reliability for TrichoScan<sup>®</sup> with this camera for hair thickness as well as hair density is over 90 % (www.trichoscan.de). An external validation study by the firm Bioskin (www.bioskin.de) showed very low variability of TrichoScan<sup>®</sup> analysis in comparison to manual counting and very high reproducibility.

In all patients before first treatment (visit 1) an area in the central parietal region of the scalp was defined and marked centrally with a semipermanent tattoo in order to insure exact location of the area for the entire duration of the study. At visit 1 (baseline), after 3 months (visit 2) after 6 months (visit 3) and after 12 months (visit 4) this area was shaved in a standardized fashion. As weakly pigmented hair is too poor in contrast for the analytic software, hair was dyed with eyebrow color for 10 minutes in the area. Quality control of the photo-documentation demanded visibility of the central tattoo, a high degree of sharpness and approval of the study center. Using the TrichoScan<sup>®</sup> software, all protocol-conform pictures after exclusion of non-compliant patients were analyzed to determine hair density [n/cm<sup>2</sup>], the thickness of all hairs and thus cumula-

tive hair thickness as well as the density of terminal (> 40 μm) and vellus hair (hairs with a diameter < 40 μm).

A total of 75 protocol-conform patients from both groups could be included in the statistical analysis after 6 months. These 75 patients regularly applied the test solutions as stated in the recommendations of the manufacturer and appeared at each control examination. In group I, 38 patients applied 1 ml of 2 % minoxidil solution (Regaine<sup>®</sup> Frauen) twice daily onto the central parietal scalp region. In group II, 37 patients applied 3 ml of 0.025 % alfatradiol solution (Ell-Cranell<sup>®</sup> alpha) once daily for 6 months. During months 7–12, 31 of 38 women using minoxidil (group I) continued treatment with minoxidil. Of 37 women using alfatradiol (group II), 29 applied minoxidil for months 7–12. Drug accountability demonstrated high compliance of the patients.

### Statistical analysis

Included in the statistical analysis were all patients who appeared at least at visit 1 (baseline) and visit 3 (6 months) before the examining physician and whose TrichoScan<sup>®</sup> photography was technically correct, according to protocol and was analyzable. Differences within the groups were analyzed using Wilcoxon signed rank test, differences between the groups with Wilcoxon rank sum test. In the last case, differences between the respective visits were analyzed.

## Results

### Efficacy

The various hair growth parameters measured after 3, 6 and 12 months of treatment were compared with baseline before treatment. Similarly, the measured parameters were compared between both treatment arms.

**Cumulative hair thickness (mm/cm<sup>2</sup>):** The primary criterion of this study was to examine the difference between minoxidil and alfatradiol with regards to changes in cumulative hair thickness after 6 months.

Before treatment, patients treated with minoxidil (group I) displayed on average a lower mean value (14.8 ± 4.8 mm/cm<sup>2</sup>) as did patients treated with alfatradiol (group II, (14.8 ± 4.8 mm/cm<sup>2</sup>). Therefore, for the graphic portrayal in Figure 1, both initial values were set at 0 and the difference of increase or decreases pictured. After 6

months of treatment, the minoxidil group showed a significant increase (p < 0.0001) of cumulative hair thickness of 1,8 ± 2.3 mm/cm<sup>2</sup> in comparison to baseline, while in the alfatradiol group cumulative hair thickness remained statistically unchanged compared to baseline (Figure 1, Table 1). Comparing this hair growth parameter between both study groups showed a significantly better (p > 0.0002) result for minoxidil (group I).

Evaluation after 12 months (visit 4) showed a further, even though lesser and not significant increase in group I over the first 6 months of 0.8 ± 2.6 mm/cm<sup>2</sup> (p = 0,055). After months 7–12, group II displayed a significant increase (p < 0.0001) of cumulative hair thickness by 1.9 ± 1.9 mm/cm<sup>2</sup> (Figure 1).

**Hair density (number of hairs/cm<sup>2</sup>):** The baseline value for hair density was almost equal in both groups with 175.1 ± 54.7/cm<sup>2</sup> in group I and 180.0 ± 50.7/cm<sup>2</sup> in group II (Table 2). In Figure 2, also, graphic portrayal was made as difference in comparison to baseline hair density for a better comparison of both groups. After 6 months, group I using minoxidil demonstrated a significant increase of 15.3 hairs/cm<sup>2</sup> (p = 0.0025), while in group II using alfatradiol hair density decreased in comparison to baseline by 7.8 hairs/cm<sup>2</sup> (statistically not significant). Treatment of AGA with minoxidil in the first 6 months showed significantly better results (p < 0.0005) in comparison to alfatradiol.

In months 7–12, both groups showed increase in hair density, well as after switching from alfatradiol to minoxidil (group II). Group II displayed a significant increase in hair density of 17.6 hairs/cm<sup>2</sup> (p < 0.0001) during months 7–12 during minoxidil therapy. In group I, hair density improved on average by about 1.9 hairs/cm<sup>2</sup> (Figure 2) and after 12 months reached a higher hair density than the alfatradiol/minoxidil group despite having a lower baseline value (Table 2).

**Terminal hair density:** In order to determine the quality of hair leading to an increased hair density, it is important to differentiate the number of terminal and vellus hair. In TrichoScan<sup>®</sup> all hair with a diameter ≥ 40 μm are categorized as terminal hair, all with lesser diameter as vellus hair. In group I after 6 months terminal hair density rose significantly by 14.0 ± 25.7 hairs/cm<sup>2</sup> (p = 0.003), while in group II using alfatradiol a slight, statis-

tically not significant, decline in terminal hair density of  $6.0 \pm 24.6$  hairs/cm<sup>2</sup> was observed (Figure 3). The increase of terminal hair density was significantly higher using minoxidil than using alfatradiol ( $p < 0.001$ ).

In group I, continuing minoxidil therapy for months 7–12 resulted in a further increase of  $0.9 \pm 24.6$  terminal hairs/cm<sup>2</sup>. In group II, after switching from alfatradiol to minoxidil, a significant increase in terminal hair density of  $11.9 \pm 20.4$  hairs/cm<sup>2</sup> was observed ( $p = 0.0002$ ).

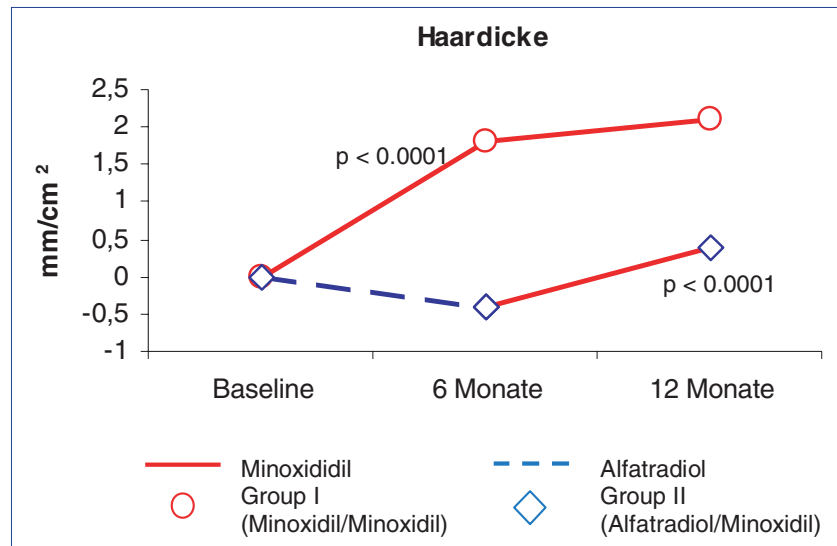
**Vellus hair density:** No significant difference with regard to vellus hair density could be found between the two treatment groups ( $p = 0.119$ ). The mean number of vellus hair after 6 months of treatment increased in the minoxidil group by  $1.2 \pm 9.7$  hairs/cm<sup>2</sup> and declined in the alfatradiol group by  $1.7 \pm 5.7$  hairs/cm<sup>2</sup> (Figure 4). Between the 7<sup>th</sup> and 12<sup>th</sup> treatment month the number of vellus hairs in group again increased slightly ( $+1.0 \pm 8.5$  hairs/cm<sup>2</sup>). In the alfatradiol/minoxidil group (group II) vellus hairs increased by  $5.6 \pm 7.8$  hairs/cm<sup>2</sup> in months 7–12 (Figure 4).

**Tolerability**

Patients and examining physicians were asked to rate tolerability of treatment after 12 months (on a scale form 1–5, i.e. from 1 = excellent to 5 = unsatisfactory). In groups I and II a mean value of 1.95 and 2.1, respectively, was accounted by the patients, among the examining physicians 1.87 and 2.06, respectively. No unwanted event or side effect was reported, not even by patients who prematurely dropped of the study for personal reasons. In two cases, treatment was suspended due to pregnancy.

**Discussion**

In the present randomized clinical study, women with androgenetic alopecia were followed with TrichoScan® to determine the effects of topical treatment with 2 % minoxidil solution in comparison to 0.025 % alfatradiol solution. Due to the differences in application (minoxidil 1 ml twice daily, alfatradiol 3 ml once daily) the study was not blinded. In 4 study centers in Germany 103 patients were randomized and assigned to the two treatment arms: group I received 2 % minoxidil solution for 12 months, group II 0.025 % alfatradiol solution for 6 months and then switched to 2 %



**Figure 1:** Change in cumulative hair thickness Significant increase in cumulative hair thickness from baseline to 6 months with minoxidil (group I). Months 7–12: after switch from alfatradiol to minoxidil (group II) significant increase in cumulative hair thickness.

**Table 1:** Change of cumulative hair thickness [mm/cm<sup>2</sup>] after 6 and 12 months of treatment with minoxidil or alfatradiol [mean (± standard deviation)].

	Minoxidil/Minoxidil		Alfatradiol/Minoxidil	
	Patients [n]	Cum. hair thickness (± SD)	Patients [n]	Cum. hair thickness (± SD)
Baseline	38	14.8 (4.8)	37	16.1 (5.4)
6 months	38	16.6 (4.7)	37	15.6 (4.9)
12 months	31	16.9 (5.0)	29	16.5 (5.0)
Change from baseline – 6 months		1.8 (2.3) $p < 0.0001$		-0.5 (2.5) ns
Change from 6–12 months		0.3 (2.6) ns		0.9 (1.9) $p < 0.0001$

minoxidil solution for the subsequent 6 months (A/M switch). Treatment results were assessed after 3, 6 and 12 months in comparison to baseline (day 0), using TrichoScan®, epiluminescence microscopy with digital image analysis [8, 10].

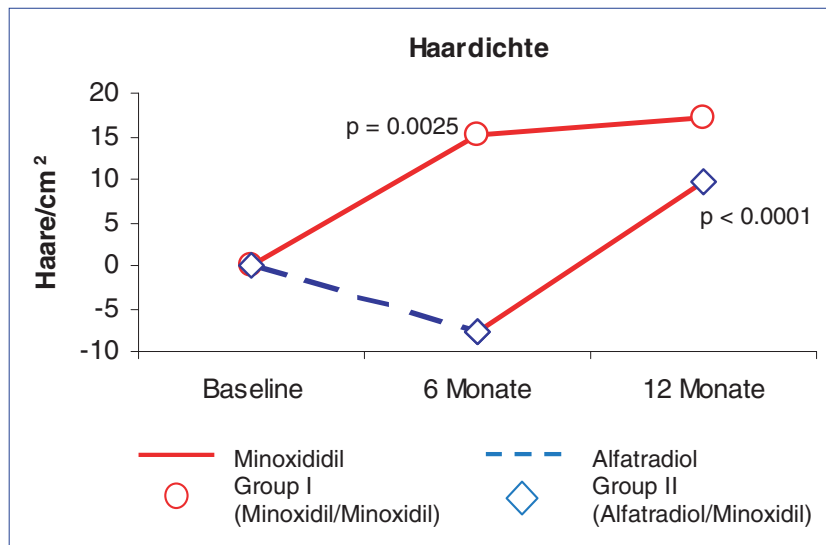
In the final analysis, 75 patients treated according to protocol, who had regularly applied one of the two topical preparations and appeared at all visits to measure objective parameters, could be evaluated.

During the first 6 month controlled treatment phase, a significant difference in relation to the main parameters of

hair growth could be found between the treatment groups. Both groups were of comparable size (group I: n = 38, group II: n = 37). Both in regards to cumulative hair thickness as well as to absolute hair density and terminal hair density, topical treatment with minoxidil in group I led to a significant increase in comparison to baseline, while treatment with alfatradiol solution resulted in stable or slightly decreased values for these parameters. Similar results were found in a post-marketing trial by Wozel et al. [11]. The latter study on women with androgenetic alopecia treated with alfatradiol showed an increase in the anagen

**Table 2:** Change of hair density [n/cm<sup>2</sup>] after 6 and 12 months of treatment with minoxidil/minoxidil or alfatradiol/minoxidil [mean (± standard deviation)]

	Minoxidil/Minoxidil		Alfatradiol/Minoxidil	
	Patients [n]	Hair density (± SD)	Patients [n]	Hair density (± SD)
Baseline	38	175.1 (54.7)	37	180.0 (50.7)
6 months	38	190.4 (50.8)	37	172.2 (44.6)
12 months	31	192.3 (46.7)	29	189.8 (49.8)
Change from baseline – 6 months		15.3 (29.0) p = 0.0025		-7.8 (24.6) ns
Change from 6–12 months		1.0 (22.6) ns		17.6 (22.9) p < 0.0001

**Figure 2:** Change in absolute hair density From baseline to 6 months of treatment with minoxidil significant increase in hair density (group I). Months 7–12: after switch from alfatradiol to minoxidil in group II also significant increase in hair density.

hair rate ( $\geq 10\%$ ) in 29% of the women, a slight increase (0 to  $\leq 10\%$ ) or unchanged rates in 59% and a decrease in the anagen hair rate in 12%. An older, placebo-controlled study on 51 patients (9 women [2]) over 6 months also demonstrated the stabilizing or delaying effect of alfatradiol on hair loss due to androgenetic alopecia in women with a reduction of hair loss but no regrowth of hair.

In the present randomized clinical trial treatment of androgenetic alopecia during months 7–12 was continued in both groups with 2% minoxidil solution. In both groups increased hair growth could thus be achieved, even in the group orig-

inally treated with alfatradiol who, in the first 6 months, showed delayed hair loss but no regrowth. Even in those women initially treated with alfatradiol, switching to minoxidil (A/M switch) led to a significant increase of both cumulative hair thickness as well as absolute hair density. Thus, minoxidil stimulated hair growth successfully in both groups, even though group II (initial alfatradiol) despite higher baseline values for hair density and cumulative hair thickness remained slightly lower than the group treated continually with minoxidil.

Our current understanding is that new growth of hair by means of topical treatment is only possible with minoxidil.

Various clinical studies have definitely shown that topical treatment with minoxidil can increase hair density significantly [13, 14]. The analysis of terminal and vellus hair densities in both treatment groups and of their contribution to absolute hair density further shows that the successful increase in absolute hair density during minoxidil therapy is primarily due to the increase in terminal hair. Therefore, the clinically observed increase in hair density is a product of qualitatively thick, volume-giving hair, which is important for the cosmetic result and the satisfaction of patients.

The increase in number of pigmented hair during minoxidil therapy and the resulting clinical improvement of hair fullness was already previously shown in a double-blind, placebo-controlled, randomized study on the efficacy of 2% minoxidil solution in the treatment of androgenetic alopecia in women [15].

Furthermore, a comparative study of minoxidil and other substances such as cyproterone acetate [16] showed that topical minoxidil solution was superior to systemic administration of cyproterone acetate for androgenetic alopecia in the absence of signs of hyperandrogenemia.

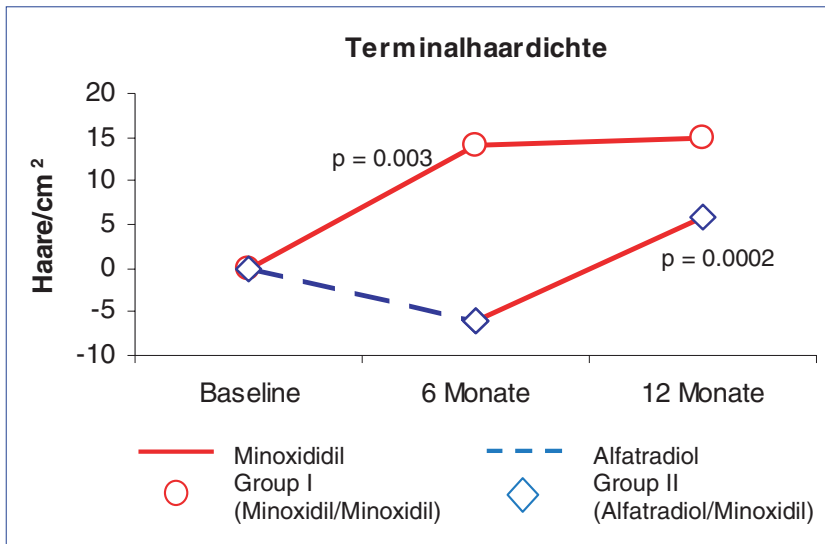
Both study preparations were, in the opinion of examining physicians and patients, equally tolerable and no side effects were observed during the entire treatment duration.

#### Conflicts of interest

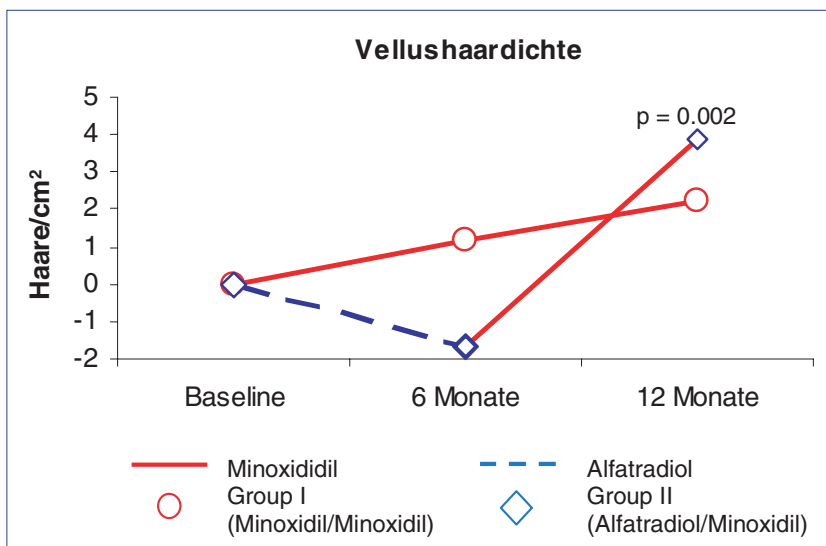
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**Figure 3:** Change in density of terminal hairs From baseline to 6 months: significant increase in the number of terminal hairs under minoxidil (group I). Months 7–12: after switch from alfatradiol to minoxidil significant increase in the number of terminal hairs (group II).



**Figure 4:** Change in density of vellus hairs From baseline to 6 months: continuous non-significant increase of vellus hairs under minoxidil. Month 7–12: after switch from alfatradiol to minoxidil significant increase of vellus hairs in group II.

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