



Hautklinik

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Local Therapy of Androgenetic Alopecia with a New Synthetic Peptide Library - A Pilot Trial with Thymuskin GKL 02

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Introduction

The cosmetic product Thymuskin has been used successfully in the treatment of alopecia since two decades in many countries. Several publications report about the efficacy of the product in alopecia androgenetica, areata and in the reduction of hair loss secondary to cytostatic chemotherapy. Thymuskin contains the partially hydrolyzed extract from calf thymus. The mode of action is unknown.

The trial substance GKL 02 contains a synthetic thymus peptide combinatorial library, which is close to identical with the natural bovine thymus extract in Thymuskin. Both, the biological extract as well as the synthetic product show biological activity in the mitogenic co-stimulation test. In order to obtain some evidence for the clinical efficacy of the synthetic GKL 02 with regard to hair growth in the indication of androgenetic alopecia (male pattern hair loss) a clinical pilot dose-finding study was performed.

Methods

The study was conducted at the Clinic of Dermatology in Darmstadt, Germany, between July 1998 and August 2000 in 21 patients with a mean age of 35 years (14 males and 7 females with a mean age of 31 and 43 years respectively) and alopecia stage 2 (hardly visible) in 14 and of stage 3 (visible) in 7 cases. The patients applied a topical ointment of GKL 02 two times daily to their scalp for 6 to 9 months and used a hair shampoo, containing also the trial substance, as needed. The GKL 02 ointment was used in a concentration of 5‰ in 8 and in a concentration of 2.5‰ in 14 patients.

Written informed consent was obtained from all patients. Before enrolment a medical check-up and the usual standard laboratory investigations for alopecia were performed. Special investigations comprised the count of lost hairs in 24 hours (effluvium), and the microscopic determination of anagen and telogen type hairs from a frontal and occipital region. These objective investigations were performed at baseline, after 3 and 6 months in all 21 patients and after 9 months in only those 18 patients who showed up. In addition on visits at 3, 6 and 9 months the physician and the patient rated the therapeutic success. Scores on patients' satisfaction were recorded at the last visit and are available for 21 patients.

Analysis and Results

Daily loss of hairs (effluvium)

Complete data for the last visit at 9 months are only available from 18 patients. Up to the visit at 6 months the data set is complete. Therefore two evaluations were performed, namely over 6 month of treatment with GKL in all 21 patients and over the whole study period of 9 months in those 18 patients with complete data. According to the aim of the study, to compare the efficacy of the two concentrations of the ointment, two respective subgroups were formed and compared. In addition, two further subgroups were analysed with regard to gender, in order to determine potential differences, because of the unknown mode of action. A two-sided T-test was applied to determine the p-value of the data versus the respective baseline.

The reduction in daily hair shedding is progressing from visit to visit, as shown in figure 1, in the two total cohorts as in all subgroups. For the cohort of 21 patients the result is statistically significant at 6 months and for the cohort of 18 patients as well at 6 as at 9 months. Concerning the subgroups, the result becomes statistically significant for the 2.5‰ ointment at 6 and 9 months. The better performance versus the 5‰ concentration might be due to the higher baseline value and the larger sample size. The reduction in hair shedding in female patients, though, is greater than in male patients and reaches statistical significance at 9 months in spite of the small sample size of 5 patients. The conclusion, that GKL 02 is more effective in women with androgenetic alopecia than in men might be premature, but the probability is high that GKL 02 might be very efficacious in women. The magnitude in the reduction of daily hair loss ranges in the various groups between 31% and 65%.

Determination of anagen and telogen hairs (trichogram)

At each visit hair was to be removed under standardized conditions from a predetermined frontal and an occipital region for microscopic determination of percentage of anagen and telogen growth stages. Complete trichogram data for the 6 months visit are available for 19 patients. In the comparison with baseline there is in both scalp regions a non-significant increase in the percentage of anagen hairs, while the telogen hairs decrease, as shown in figure 2. The reduction in the portion of telogen hair amounts in the mean to 15% in the frontal and to 10% in the occipital region respectively. Though these changes are very small, they point into the right direction.

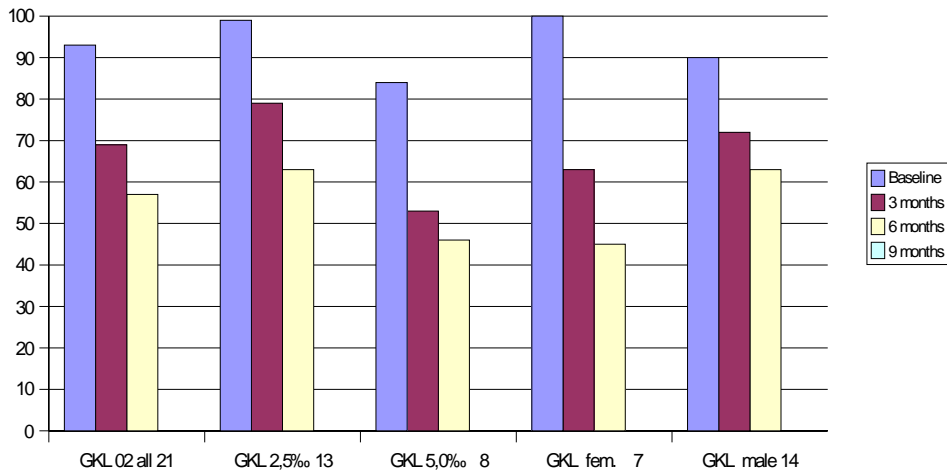
Figure 1

ANALYSIS OF HAIR LOSS

21 patients for 6 months

Subgroups n	Baseline	3 months	6 months	9 months	T-test,2-sided	Reduction
GKL 02 all 21	93	69	57		P = 0,02	39,27%
GKL 2,5‰ 13	99	79	63		P = 0,02	45,35%
GKL 5,0‰ 8	84	53	46		P = 0,38	44,78%
GKL fem. 7	100	63	45		P = 0,07	55,00%
GKL male 14	90	72	63		P = 0,15	30,56%

Hairloss/day (n=21), subgroups



18 patients for 9 months

Subgroups n	Baseline	3 months	6 months	9 months	T-test,2-sided	Reduction
GKL 02 all 18	91	69	55	50	P=0,01	45,05%
GKL 2,5‰ 13	105	85	68	59	P=0,02	43,81%
GKL 5,0‰ 5	63	38	31	30	P=0,21	52,38%
GKL fem. 5	96	68	40	34	P=0,03	64,58%
GKL male 13	89	70	61	57	P=0,10	35,96%

Hairloss/day (n=18), subgroups

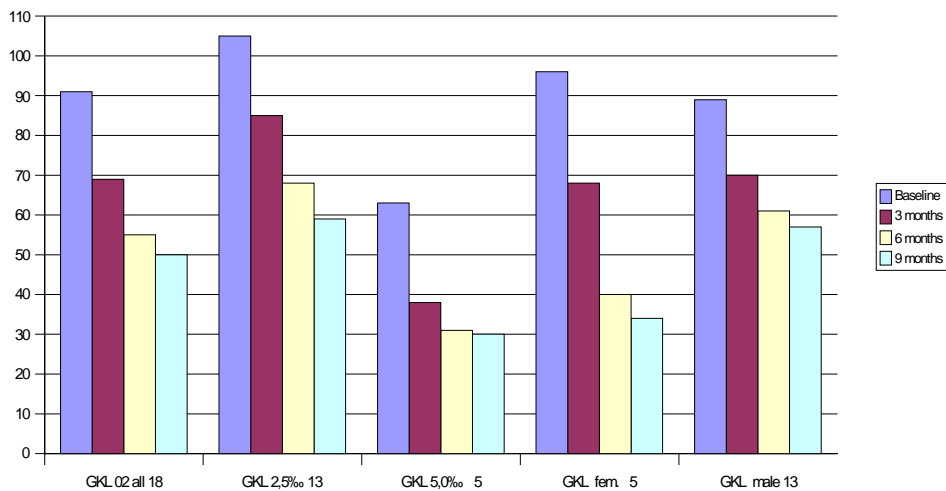


Figure 2
DISTRIBUTION OF TYPES OF HAIR BEFORE AND AFTER THYMUSKIN GKL 02

Location	Baseline			6 months		
	% anagen B	% katagen C	% telogen D	% anagen E	% katagen F	% telogen G
Frontal	73	6	21	74	8	18
Occipital	68	10	12	73	16	11

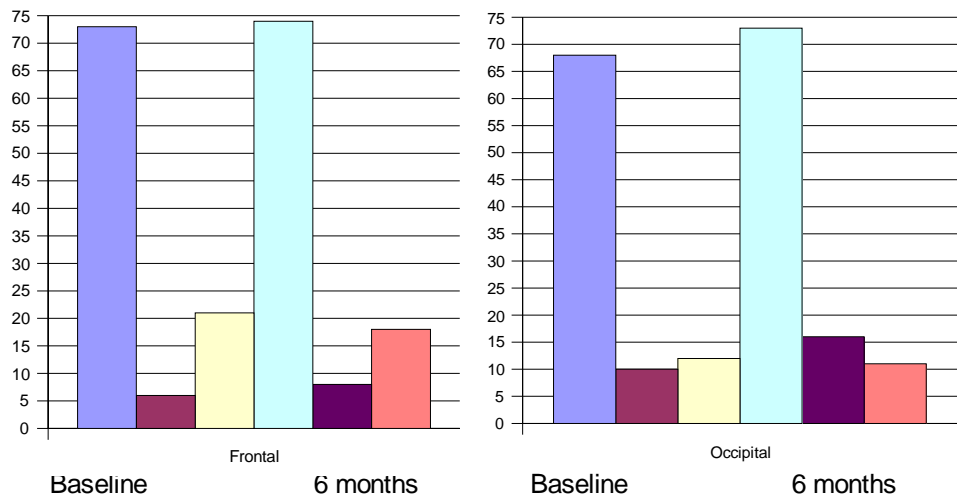
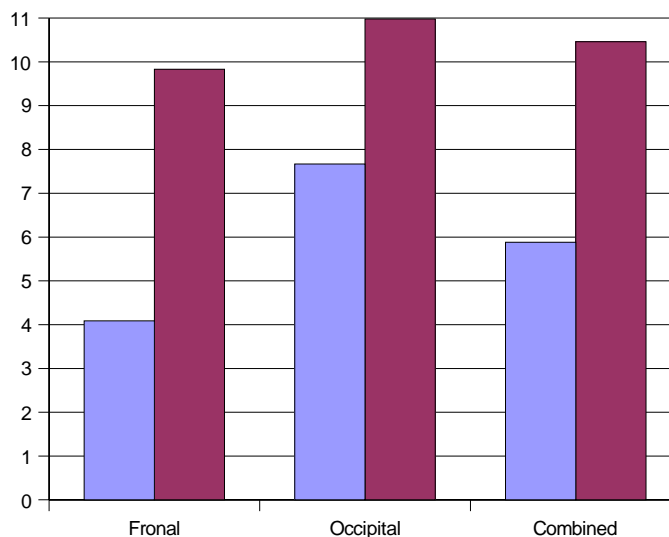


Figure 3
Increase in anagen/telogen ratio in 19 patients with Complete data at 6 months in the trichograms

Scalp	Baseline	6 months	T-test 2sided
Fronal	4,09	9,83	0.22
Occipital	7,67	10,98	0.26
Combined	5,88	10,46	0.10

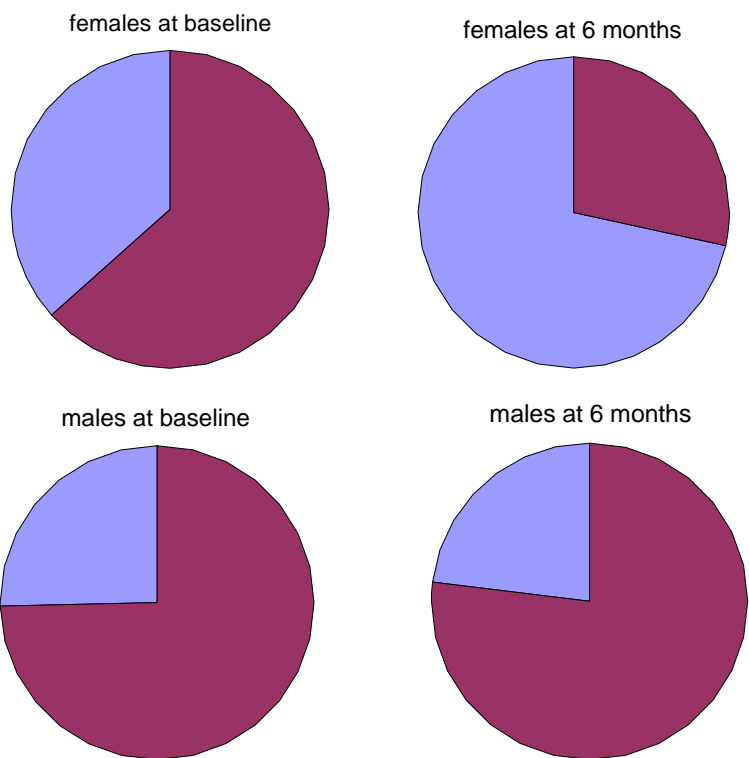


From this set of data also the anagen/telogen ratio was calculated. This ratio increases greatly in the frontal (140%) and in the occipital (43%) region (figure 3), indicating a shift to growth of more healthy anagen hair. In spite of its magnitude this increase does not reach statistical significance, probably because of the large variance of the data. By combining both locations total increase amounts to 83% and by the increase in sample size $P=0.1$ comes close to significance (figure 3).

Figure 4

GKL 02
 RATIO OF ANAGEN/TELOGEN HAIR IN FRONTAL AND OCCIPITAL REGION
 Comparison women versus men

Patient Number	Patient Gender	Baseline		6 month	
		ana/telo front	ana/telo occ.	ana/telo front	ana/telo occ.
8	F	1,86	1,67	2,4	1,41
5	F	6,48	20,5	13,37	10,6
4	F	2,24	6,37	3,44	8
21	F	1,84	3,73	5,2	6,64
15	F	3,45	8,62	89,91	8,73
3	F	7,69	6,89	22,95	12,5
13	F	6,91	5,03	3,67	7,76
Mean		4,35	7,54	20,13	7,95
T-test,2-sided				0,21	0,88
16	M	2,07	10,36	2,07	10,43
14	M	7,04	6,82	5,67	2,17
1	M	2,91	1,72	5,13	8,13
20	M	3,88	7	3,57	55,09
19	M	4,12	2,51	2,61	2,57
18	M	9,19	51,69	7,63	5,94
9	M	2,57	9,57	4,37	12,88
2	M	2,57	8,9	6,11	13,02
7	M	4,1	18,66	2	4,37
6	M	3,04	3,17	3,81	16,6
17	M	4,27	5,91	1,78	5,24
10	M	1,52	13	1,46	17
Mean		3,94	11,61	3,85	12,79
T-test,2-sided				0,3	0,84



A further non-significant finding is that the gain in anagen hairs appears to be confined in women to the frontal region in contrast to men (figure 4). But this might merely reflect the difference in the appearance of baldness between the two genders.

Table 1:

GKL 02: Subjective evaluation at last visit (6 or 9 months)					
Patient Characteristics			Doctors evaluation	Patients evaluation	Patients satisfaction*
1	m	5.0‰	good	better	9
2	m	5.0‰	good	better	8
3	f	2.5‰	very good	better	9
4	f	2.5‰	good	better	8
5	f	2.5‰	very good	better	8
6	m	2.5‰	good	better	7
7	m	5.0‰	good	better	7
8	f	5.0‰	moderate	unchanged	3
9	m	2.5‰	good	unchanged	6
10	m	5.0‰	good	better	9
11	m	5.0‰	good	better	8
12	m	2.5‰	moderate	unchanged	2
13	f	2.5‰	moderate	better	6
14	m	2.5‰	good	better	8
15	f	5.0‰	moderate	unchanged	5
16	m	2.5‰	moderate	unchanged	5
17	m	5.0‰	moderate	unchanged	5
18	m	2.5‰	good	unchanged	5
19	m	5.0‰	good	unchanged	7
20	m	2.5‰	good	unchanged	7
21	f	2.5‰	good	better	8
RESULTS					
All 21			15/21 ≥ good = 71%	12/21 better = 57%	15/21 ≥ 6 = 71%
12		2.5‰	9/12 ≥ good = 75%	7/12 better = 58%	9/12 ≥ 6 = 75%
9		5.0‰	6/9 ≥ good = 67%	5/9 better = 56%	6/9 ≥ 6 = 67%
7	fem.		4/7 ≥ good = 57%	5/7 better = 71%	5/7 ≥ 6 = 71%
14	male		11/14 ≥ good = 78%	7/14 better = 50%	10/14 ≥ 6 = 71%

* Score from 1 to 10 (1 = not satisfied, 10 = very satisfied)

Subjective Evaluation

A subjective evaluation by the physician and two by the patient was given at each visit. The physicians rating ranged in four steps between “very good“ and “bad“. The patient judged the change relative to the previous visit as “better“, “unchanged“ or „worse“ and in addition expressed his/her satisfaction on a 10

scored rating scale, where 1 means „not satisfied“ an 10 „very satisfied“. All judgements at the last visit, be it at 6 or at 9 months, are broken down into subgroups and presented in table 1.

There is no incidence of deterioration. The physician rated the result as good or better in 71% of cases. The patients judged the result as better in 57%. It is noteworthy that the highest rating of 71% improvement occurred in the subgroup of female patients. The satisfaction score ranged between 2 and 9. A satisfaction ranking of 6 and higher was expressed by 71% of the patients.

Conclusion

So far only two medical products, namely topical minoxidil and systemic finasteride, have been approved for the treatment of male pattern hair loss in restricted groups of patients. In the pivotal studies efficacy was evaluated by photographic scalp hair counts, patients and investigators assessment, and a global evaluation of standardized photographs by an expert panel. Since then these parameters are considered by the regulatory authorities as the accepted and validated endpoints of efficacy.

Actually in this study, documentation by photography was intended, but had to be omitted due to emerging technical reasons. But besides the patients and investigators assessment two other relatively objective parameters were measured. The reduction of hair loss (effluvium) becomes statistically significant for the total cohort as well as for several of the subgroups. A non-significant increase in number of anagen hair and a corresponding reduction of telogen hair is seen in the trichogram. The reduction in the proportion of telogen hair by more than 10% is to be considered as improvement, according to Wüstner and Orfanos. The increase in the anagen/telogen ratio is impressive and marginally fails with a p-value of 0.1 to reach statistical significance. The positive assessments by investigators and patients range between 57 and 71%.

In the studies of the competitors their efficacy is compared versus the respective placebo groups. Since this study on GKL 02 did not involve a placebo control a comparison with the competitors is not possible. Nevertheless there is a high probability of efficacy of GKL 02. Especially the excellent results in females are promising.

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