Fluridil, a Rationally Designed Topical Agent for Androgenetic Alopecia: First Clinical Experience

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BACKGROUND. **Fluridil, a novel topical antiandrogen, suppresses the human androgen receptor. While highly hydrophobic and hydrolytically degradable, it is systemically nonresorbable. In animals, fluridil demonstrated high local and general tolerance.**

OBJECTIVE. **To evaluate the safety and efficacy of a topical antiandrogen, fluridil, in male androgenetic alopecia.**

METHODS. **In 20 men, for 21 days, occlusive forearm patches with 2, 4, and 6% fluridil, isopropanol, and/or vaseline were applied. In 43 men with androgenetic alopecia (AGA), Norwood grade II–Va, 2% fluridil was evaluated in a double-blind, placebo-controlled study after 3 months clinically by phototrichograms, hematology, and blood chemistry including analysis for fluridil, and at 9 months by phototrichograms.**

RESULTS. **Neither fluridil nor isopropanol showed sensitization/irritation potential, unlike vaseline. In all AGA subjects, baseline anagen/telogen counts were equal. After 3 months, the average anagen percentage did not change in placebo subjects, but increased in fluridil subjects from 76% to 85%, and at 9 months to 87%. In former placebo subjects, fluridil increased the anagen percentage after 6 months from 76% to 85%. Sexual functions, libido, hematology, and blood chemistry values were normal throughout, except that at 3 months, in the spring, serum testosterone increased within the normal range equally in placebo and fluridil groups. No fluridil or its decomposition product, BP-34, was detectable in the serum at 0, 3, or 90 days.**

CONCLUSION. **Topical fluridil is nonirritating, nonsensitizing, nonresorbable, devoid of systemic activity, and anagen promoting after daily use in most AGA males.**

M. SOVAK, MD, A. L. SELIGSON, PHD, R. KUCEROVA, MD, M. BIENOVA, MD, M. HAJDUCH, MD, AND M. BUCEK, MD HAVE INDICATED NO SIGNIFICANT INTEREST WITH COMMERCIAL SUPPORTERS.

THE PATHOPHYSIOLOGY of androgenetic alopecia (AGA) is not yet fully understood and there is no optimal therapy.[1] AGA is androgenetic because it can be either an autosomal or polygenic trait,[2] and because whatever the underlying mechanism, androgens play a pivotal role in first promoting and later suppressing hair growth. Androgens act in numerous ways, but the common denominator is binding to a protein transcription factor, the androgen receptor (AR). The resulting complex, after entering the cell nucleus, binds to DNA to initialize the pathway via RNA polymerase II.[3] A specific and limited interference with androgens thus should be useful in AGA treatment.

To this end, inhibitors of type II 5α-reductase, an enzyme that converts testosterone into much more potent dihydrotestosterone (DHT), were explored. Finasteride at 1 mg/day in men was shown to increase the growth rate and thickness of hair.[4] Side effects such as decreased libido and erectile function are reportedly minimal and reversible.[1] Limited to blocking DHT formation, finasteride does not affect other androgens and has to be taken daily. Although subjects with a congenital 5α-reductase deficiency do not manifest any side effects,[5] there is no proof yet that systemic manipulation of hormone balance in normal subjects would be innocuous.

Developed originally for the treatment of prostate cancer, the nonsteroidal oral antiandrogens were considered for topical use in AGA. Antiandrogens contain a phenyl moiety substituted with a nitro or cyano adjacent to a trifluoromethyl group, which closely mimics the steroidal androgen's binding region to ARs (Figure 1).[6] Systemic antiandrogens block all AR indiscriminately and they adversely affect libido and male sexual functions.

Flutamide applied topically to bald human scalp grafted into nude mice was shown to induce hair growth and longer hair shafts.[7] It is, nevertheless, probable that in humans, topical flutamide induces

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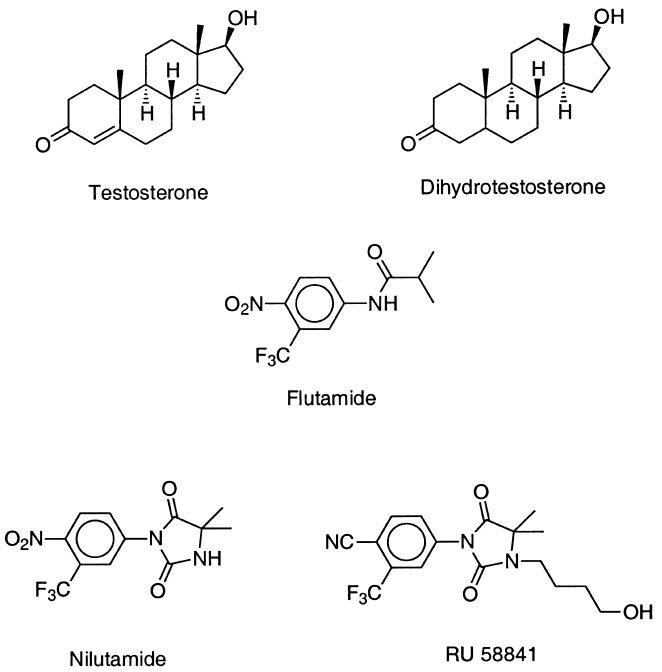

Figure 1. Testosterone, dihydrotestosterone, flutamide, nilutamide, and RU-58841.

systemic antiandrogenic effects since at least 16% is transcutaneously resorbed.[8] Preclinical data of another oral antiandrogen, an N-substituted aryl hydantoin, RU-58841 (Figure l), suggested topical safety since the cutaneous resorption was low,[9,10] however, one of the metabolites proved stable and strongly antiandrogenic,[11] and further development was abandoned. Another agent used in AGA is minoxidil, an antihypertensive drug which, by a mechanism yet to be clarified, increases hair thickness and anagen count. Some minoxidil is resorbed systemically, but the effect on hemodynamics, if any, is very low.[12]

Design and Primary Evaluation of Fluridil

Androgens are continuously synthesized from the circulating pool of dehydroepiandrosterone in a balanced way. 5α-reductase converts testosterone into DHT, while aromatases convert testosterone into estradiol. An approach to AGA treatment should neutralize the effects of all androgens, not only DHT, on the hair and its appendages, while maintaining an unperturbed androgen physiologic balance. As an alternative, selectively inhibiting AR binding in the scalp thus appears preferable. In reviewing the subject, Sawaya and Hordinsky[13] noted that "the antiandrogen will also have to be safe, have minimal systemic absorption, be locally metabolized, and have minimal or no effects on other target tissues, sex organs, and gonadotropin levels. Such an antiandrogen or compound may still be thought of as a 'fantasy'drug."

It occurred to us that a compound would meet these criteria if it, upon encountering the aqueous milieu of the microcirculation, would degrade into nontoxic, excretable fragments devoid of antiandrogenic activity. Incorporation of a hydrolyzable bond seemed a plausible solution, and we noted that the electron-withdrawing nature of perfluoroalkyl moieties destabilize the otherwise stable carboxamide bond. We also surmised that a highly hydrophobic moiety at the terminal region of the molecule would provide for strong binding. Applying this design, we synthesized a series of analogues of which 2-hydroxy-2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]-3-(2,2,2-trifluoroacetylamino) propanamide—fluridil (Figure 2)—was selected for further development.[14,15]

Synthesis, analysis, and preclinical evaluation of fluridil is described in detail elsewhere[14] (Seligson AL and Sovak M, manuscript submitted). Briefly, to simulate the shelf life of 2% fluridil in anhydrous isopropanol, an accelerated stability study was conducted at 50°C for 8 weeks, equivalent to 5 years at 20°C.[16] Only traces of decomposition were observed. After 8 months at ambient temperature, no decomposition could be identified by high-performance liquid chromatography (HPLC).

Fluridil's in vitro biodegradability in human serum (0.5 mg/ml) was assessed after incubation at 38°C; its half life was found to be about 6 hours and only traces were seen after 48 hours. In vivo, the decomposition must be much faster, as no fluridil or its decomposition products could be found in the serum. The oral toxicity of fluridil was determined by median lethal dose (LD_{50}) using doses of 1500, 2000, and 2500 mg/kg. In NMRI mice, LD_{50} was 2871.7 mg/kg (males) and 2232.0 mg/kg (females). In Wistar rats, the LD_{50} could not be calculated since only one male rat died (at the 1500 mg/kg dose) and none of the female rats died, suggesting an LD_{50} greater than 2500 mg/kg.

The systemic toxicity of fluridil was orientationally evaluated in mice by seven daily intraperitoneal injections of doses increased from 300 to 500 mg/kg. The LD_{50} was estimated as 450 mg/kg and the maximum tolerated dose (MTD) as 300 mg/kg. Fluridil therefore does not fall into the category of a harmful or toxic substance as defined by the National Institute of Environmental Research.[17]

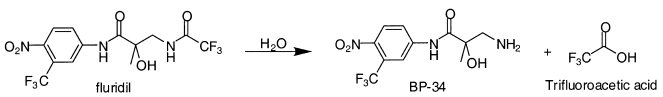

Figure 2. Fluridil and its hydrolytic decomposition.

The degradation products of fluridil are BP-34 and trifluoroacetic acid (Figure 2). In mice, intraperitoneal 100–300 mg/kg BP-34 produced no mortality. Morbidity was observed at 300 mg/kg, suggesting a murine MTD of about 250 mg/kg, corresponding to about 25 mg/kg or 1730 mg in an average human. Tolerance of trifluoroacetic acid is reportedly high.[18]

The interaction of fluridil and/or BP-34 with human AR was studied using immortalized human LNCaP cells and a standard Western blot. At 10 μm, AR suppression by the antiandrogens bicalutamide and hydroxyflutamide was only 2–3% compared to 97% for fluridil. The degradation product BP-34 was inactive, and the results were validated in a transfected cell line which expresses stable levels of human ARs and MMTV-CAT sequences, as described by Fuhrmann et al.[19] Since BP-34 from 0.3 nM/L to 1 μM/L in the assay, using 2 nm of tritium-labeled R-1881, demonstrated no measurable affinity (Thierauch KH, Schering AG, Berlin, personal communication; we thank Dr. Thierauch for kindly providing the data to us), it is not expected to be an antiandrogen.

A standard contact sensitization test was conducted on 20 guinea pigs exposed once a week to the test material soaked into filter paper and applied for 6 hours. After 2 weeks, fluridil or its vehicle (anhydrous isopropanol) applied with an occlusive patch elicited no allergic skin or adverse systemic responses. A patch test on covered and noncovered sites in 10 rabbits found fluridil to be equal to its vehicle according to the irritation index (with nonirritability defined as less than 0.4), which was 0.14 for the noncovered and 0.11 for the covered group, indicating a negligible potential to irritate rabbit skin.

To simulate the intended human cosmetic use (0.6 mg/kg/day), fluridil was applied topically twice a day for 10 days on two separate 10 cm^2 areas of closely shaved skin in four rabbits. Serum was obtained at 2, 5, and 21 hours after the first application, and then once every other day. Using spiked and blank serum to ascertain linearity, the limits of reliable quantification by HPLC of fluridil and BP-34 were approximately 20 ng/ml, about three times the detectability level. Peaks representing either compound could not be discerned in the chromatograms, although the cutaneous absorption in rabbits is known to be about five to six times greater than in humans.[20] The quantity of fluridil, if resorbed systemically and remaining intact, thus would have to be less than its detectability limit of 5 ng fluridil/ml serum, and therefore, at most, its total amount in the circulation could not exceed 0.25 μg/kg, that is, 17.5 μg in a 70 kg human. Ames reversion assay determined that fluridil and its metabolites have no mutagenic potential.[21]

Based on experimental efficacy proof, acceptable topical and systemic tolerance, and extremely low—if any—systemic resorption from the skin, we concluded that fluridil as a cosmetic topical hair growth agent qualified for clinical safety and efficacy evaluation.

Materials and Methods

Cumulative Irritancy Assay in Human Subjects

(This study was conducted by the laboratories of Professor H. Maibach, MD, San Francisco, CA.) A group of 20 men, 18–60 years of age, were recruited, examined, and found free of active skin pathology. Medical histories and informed consents were obtained from all subjects. The study protocol of Phillips et al.[22] was used. Briefly, 2, 4, and 6% fluridil in anhydrous isopropanol was applied 5 days a week (excluding weekends) for 21 days to the same site using occlusive patches. The patch was an occlusive plastic chamber held in place by paper tape. As controls, isopropanol and Vaseline Intensive Care Lotion (Chesebrough-Ponds) were used. There were 15 days of readings that were made at each removal of the patch using an erythema score scale of 0–4.

Efficacy and Safety of Fluridil in Male AGA

Two percent fluridil was formulated in anhydrous isopropanol under Good Manufacturing Practice (GMP) and filled into 50 ml class I glass penicillin vials capped with a polypropylene/Teflon-coated, inert stopper. Identical vials contained neat anhydrous isopropanol as placebo. A 2 ml syringe was provided with each coded vial. Forty-three male subjects of phototype II–IV and AGA of degree II–Va (II and IIa [2 patients], III [10 patients], IIIa [1 patient], IV [9 patients], IVa [6 patients], V [5 patients], and Va [8 patients]) according to the Hamilton–Norwood classification were recruited from the Department of Dermatology, Ambulatory Services (20–56 years of age, average 33.6 years) for this double-blind study. The institutional review board approved the study and all subjects signed an informed consent. None of the subjects received systemic or local alopecia therapy for at least 1 month prior to the recruitment.

The subjects were randomized: 23 received fluridil and 20 placebo. On day 0, a baseline phototrichogram was obtained by closely shaving a permanently tattooed round area 1.2 cm in diameter, corresponding to about 1.1 cm^2.[23] The area was photographed with a close-up lens using a digital camera, a global view of the scalp was also recorded, and the data stored. On day 3, the area was again imaged. The follicles/hairs were counted manually using a televised display; anagens and/or telogens were calculated as a percentage of the total. On day 3, 10 ml of venous blood was taken for hematology and blood chemistry (Table 1).

Subjects were instructed to keep the fluridil vials in a cool, dry place and open them only to draw 2 ml to be applied to the skin by circular movement of a blunt syringe over the scalp before bed. The subjects were also instructed to complete a clinical questionnaire, to avoid direct sun exposure, and to reduce the use of liquid shampoos. They were advised to limit hair washes to twice a week using only

Table 1. Hematologic and Blood Chemistry Parameters

Hematology	*Blood chemistry*
Leukocytes	Urea
Erythrocytes	Creatinine
Hemoglobin	ALT
Thrombocytes	AST
Lymphocytes	ALP
Monocytes	Ca^{2+}
Granulocytes	Mg^{2+}
Eosinophils	Na^{+}
Basophils	K^{+}
Total Protein	Cl^{-}

warm water and were provided with dry shampoo to use ad libitum.

On day 90, the tattooed scalp area was again closely shaved and imaged, and hematology and blood chemistry reevaluated. The subjects were queried specifically about any changes in sexual function and libido. The study protocol envisioned follow-up at 6, 9, and 12 months for clinical assessment, at 9 and 12 months for phototrichograms, and at 12 months for final blood chemistry and hematology. Further, a provision was made for breaking the code at 90 days should AGA manifestly improve in at least 40% of all subjects, to offer the fluridil treatment to all placebo subjects, and to continue the study as an open label.

Blood collected from subjects on day 0, 3, and 90 was analyzed for fluridil and its hydrolysis product, BP-34, in the following fashion: For fluridil, 1.0 ml samples were treated with 1.0 ml 0.05 M NaH_2PO_4 (pH 3.5), 1.0 μg/ml flutamide (internal standard) and loaded on a 200 mg phenyl extract clean column pretreated with acetonitrile (2 × 1 ml), methanol (2 × 1 ml), and 1% methanol in water (2 × 1 ml). After elution of the serum sample, the cartridge was washed with 1% methanol in water (2 × 1 ml) and the analyte and internal standard eluted with methanol (2 × 1 ml). The eluent was filtered through a 0.45 μm polytetrafluoroethylene (PTFE) filter. The samples were evaporated under N_2 flow and reconstituted in acetonitrile for HPLC analysis on a Waters Symmetry C-18 column at a flow rate of 1.0 ml/min using a 0.005 M KH_2PO_4 buffer (pH 3.5)/acetonitrile gradient at 290 nm. Using spiked and blank serum samples, a linear concentration relationship was observed for fluridil with a quantification limit of 20 ng/ml and a detection limit of about 5–7 ng/ml.

For BP-34, 1.0 ml samples were treated with 600 ng/ml flutamide (internal standard) and loaded on a 200 mg extraction column pretreated with 1 ml acetonitrile, 1 ml methanol, water (2 × 1 ml), 1 ml 1.0 N NaOH, and 0.05 m NaH_2PO_4 (pH 3.0) buffer (4 × 1.0 ml or until eluent from the cartridge is acidic). After elution of the serum sample, the cartridge was washed with 1 ml 95% 1.0 mm HCl/5% methanol, 1 ml 95% 0.1 m HCl/5% methanol and the analyte and internal standard eluted with 1 ml 90% methanol/10% 1.0 m HCl. The samples were evaporated under N_2 flow and reconstituted in mobile phase for HPLC analysis on a Waters Symmetry C-18 column at a flow rate of 1.0 ml/min using a 0.005 m KH_2PO_4 buffer (pH 4.0)/acetonitrile gradient at 290 nm. Using spiked and blank serum samples, a linear concentration relationship was observed for fluridil with a quantification limit of 20 ng/ml and a detection limit of about 5 ng/ml.

Results

Cumulative Irritancy Assay in Human Subjects

Fluridil, in all three concentrations in its vehicle, isopropanol, as well as neat isopropanol, proved nonirritating to human forearm skin. Response to the induction was minimal, with a score of 0.5 for isopropanol and the three fluridil concentrations, and up to 4 for the vaseline control. On the delayed challenge, only 6% fluridil induced macular erythema, and then only to a slight degree (1.4 of the attainable score). Two percent and 4% fluridil and/or isopropanol proved nonirritating and devoid of sensitization potential.

Efficacy and Safety of Fluridil in Male AGA

Blood Chemistry, Hematology, and General Observation. At 90 days, substantial individual variation and an increase in average serum testosterone, statistically equal in both groups, and within normal range, was seen (3.8 nM/L in the fluridil group and 3.2 nM/L in the placebo group) (Table 2). Upon direct questioning and using a questionnaire, neither placebo nor fluridil subjects indicated any change in their health, libido, or sexual perfor-

Table 2. Serum Testosterone Levels After Topical Application of Fluridil and/or Placebo[a]

	Testosterone levels (nM/L)							
	Fluridil (day 0)	*Fluridil (day 90)*	*Placebo (day 0)*	*Placebo (day 90)*	*Fluridil (day 0)*	*Placebo (day 0)*	*Fluridil (day 90)*	*Placebo (day 90)*
n	23	23	20	20	23	20	23	20
Mean	15.53	19.34	13.75	16.91	15.53	13.75	19.34	16.91
SD	9.5	8.29	7.24	7.27	9.5	7.24	8.29	7.27
t test paired		0.0046		0.0150		0.2463		0.1555

n = number of subjects.
$P < 0.05$ signifies statistically significant difference between two groups.
[a]Note: 12-month testosterone data recently obtained were 15.15 ± 5.64 nM/L for the placebo and 17.88 ± 7.85 nM/L for the fluridil group.

Table 3. Initial Trichologic Assessment of AGA in Male Subjects Randomized into Fluridil and Placebo Groups

	Anagens		*Telogens*	
	Placebo (0 months)	*Fluridil (0 months)*	*Placebo (0 months)*	*Fluridil (0 months)*
n	20	23	20	23
Mean	70.13	75.68	29.51	25.41
Median	71.45	78.1	30.6	19.8
SD	13.26	14.27	11.42	12.95
t test paired	0.2189		0.3301	

n = number of subjects.
$P < 0.05$ signifies statistically significant difference between the groups.
Anagens as a percentage of total hairs/follicles counted.

mance, nor were there any statistically significant differences in their hematology or blood chemistry parameters.

Hair Growth. The phototrichogram data show no statistical difference in the average percentage of anagens/telogens in the fluridil and placebo groups at the study's outset, indicating the clinical material's homogeneity (Table 3).

Since practically all participants in the study followed the fashion of shorn hair, it was not possible to evaluate effluvium clinically, but in the fluridil group three subjects observed a substantial decrease. The effects of fluridil and/or placebo at 3 months, derived from phototrichograms, and comparison of the two groups is shown in Table 4. It can be seen that, after 3 months, there was no significant difference in the anagen count/telogen count in the placebo group, but an increase in anagen count and a decrease in telogen count in the fluridil group was significant, and so was the difference between fluridil and placebo.

In accordance with the study protocol, the obvious improvement seen clinically and gleaned from the phototrichograms in the majority of the participants justified discontinuation of placebo and administration of fluridil to all participants for another 6 months. Table 5 shows the results in the fluridil group after 9 months and in the former placebo group after 6 months. It can be seen that in both these groups, the differences in anagen count/telogen count after 6 or 9 months were highly significant, but it also appears, as shown by the data in Table 6, that there was no significant change whether fluridil was used for 3, 6, or 9 months. There were no discernible correlations among the follicle or anagen count levels, AGA duration, or the grade of AGA

Table 4. Effect of Fluridil and Placebo on the Average Anagen/Telogen Counts as a Percentage of the Total Hair Count

	Anagens				*Telogens*			
Panel A	*Placebo (0 months)*	*Placebo (3 months)*	*Fluridil (0 months)*	*Fluridil (3 months)*	*Placebo (0 months)*	*Placebo (3 months)*	*Fluridil (0 months)*	*Fluridil (3 months)*
n	20	20	23	23	20	20	23	23
Mean	70.13	77.25	75.68	85.09	29.51	21.87	25.41	14.61
Median	71.45	79.8	78.1	87.5	30.6	21.65	19.8	12.3
SD	13.26	11.17	14.27	8.73	11.42	11.46	12.95	9.189
t test paired	0.0738		0.0099		0.0413		0.0021	

	Anagens		*Telogens*	
Panel B	*Placebo (3 months)*	*Fluridil (3 months)*	*Placebo (3 months)*	*Fluridil (3 months)*
n	20	23	20	23
Mean	77.25	85.09	21.87	14.61
Median	79.8	87.5	21.65	12.3
SD	11.17	8.73	11.46	9.189
t test unpaired	0.0136		0.0264	

A double-blind study of male subjects with AGA, randomized into two groups, evaluated by phototrichograms before and after 3 months (panel A) and compared to each other at 3 months (panel B).
n = number of subjects.
$P < 0.05$ signifies statistically significant difference between the groups.
Anagen/telogen averages as a percentage of total hairs/follicles counted.

Table 5. Effects of Fluridil After 6 or 9 Months on the Average Anagen/Telogen Counts as a Percentage of the Total Hair Count

	Anagens				*Telogens*			
	Placebo (3 months)	*Placebo (9 months)*	*Fluridil (0 months)*	*Fluridil (9 months)*	*Placebo (3 months)*	*Placebo (9 months)*	*Fluridil (0 months)*	*Fluridil (9 months)*
n	20	16	23	20	20	16	23	20
Mean	77.25	84.54	75.68	87.38	21.87	14.71	25.41	13.12
Median	79.8	87.2	78.1	88.75	21.65	12.05	19.8	11.2
SD	11.17	2.68	14.27	7.73	11.46	10.72	12.95	8.089
t test	0.0314		0.007		0.0139		0.0153	

An open-label study including, for 6 months, the former placebo group.

(according to Norwood). Rather it appears that the degree of response to fluridil is individual. Neither the trichographic nor clinical observation has demonstrated a correlation between the grade of androgenic alopecia classified according to Norwood and the outcome of the trial. Figure 3 shows a global scalp view of one subject typically representing those who responded well to fluridil. Phototrichogram data were obtained only from the subject's frontal scalp area by clinical observation; no difference in response was observed between the frontal and vertex regions.

There were no local side effects after 3 months of use, except for the following: one subject, after exposure to the sun, reported yellowing of the scalp; the tinge was washed away by water. One subject interrupted application upon reactivation of seborrheic dermatitis by sun exposure. Another, upon application of a deodorant, developed an allergic reaction in the nuchal region; after 4 weeks he continued applying fluridil with no side effects. There were no further side effects reported in either of the groups for the additional 6 months of the study.

Serum Content of Fluridil and BP-34

The serum from 43 patients (23 from the fluridil group and 20 from the placebo group) was evaluated on days 0, 3, and 90 for fluridil and its hydrolysis product BP-34. In 40 patients, no detectable quantities of either substance were found beyond the limit of quantification of 20 ng/ml and the limit of visual detection of 5 ng/ml. Three patients could not be evaluated for fluridil content because of a coeluting interference in the baseline which was present prior to fluridil administration as well as during follow-ups.

Discussion

After 3 months of daily topical use, there was no significant change in the placebo group, but a significant increase in anagen count and a concomitant decrease in telogen count in the fluridil group was seen, similar to 6 months of use by the former placebo group, or to 9 months use in the fluridil group. Since there was no statistically significant difference in the above parameters between 3 and 9 months in the subjects using fluridil, and since there was no significant difference between 6 and 9 months, it is apparent that the maximum attainable effect of fluridil is achieved within the first 90 days of use. The group was reasonably homogeneous as to the diagnosis and degree of AGA, age, sex, hair care, and time of the year, but the data statistics indicate a relatively large degree of variation and thus an individual response to topical fluridil.

The antiandrogenic properties of fluridil, previously ascertained by its effect on human ARs, should ac-

Table 6. Comparison of Fluridil Effects After 6 Months With 9 Months' Use Within the Same Group ("Fluridil") and the Former Placebo Group ("Placebo")

	Anagens		*Telogens*		*Anagens*		*Telogens*	
	Fluridil (3 months)	*Fluridil (9 months)*	*Fluridil (3 months)*	*Fluridil (9 months)*	*Placebo (9 months)*	*Fluridil (9 months)*	*Placebo (9 months)*	*Fluridil (9 months)*
n	23	20	23	20	16	20	16	20
Mean	85.09	87.38	14.610	13.12	84.54	87.38	14.71	13.12
Median	87.5	88.75	12.3	11.2	87.2	88.75	12.05	11.2
SD	8.73	7.73	9.189	8.089	12.68	7.73	10.72	8.089
t test unpaired					0.4117		0.6146	
t-test paired	0.1056		0.2558					

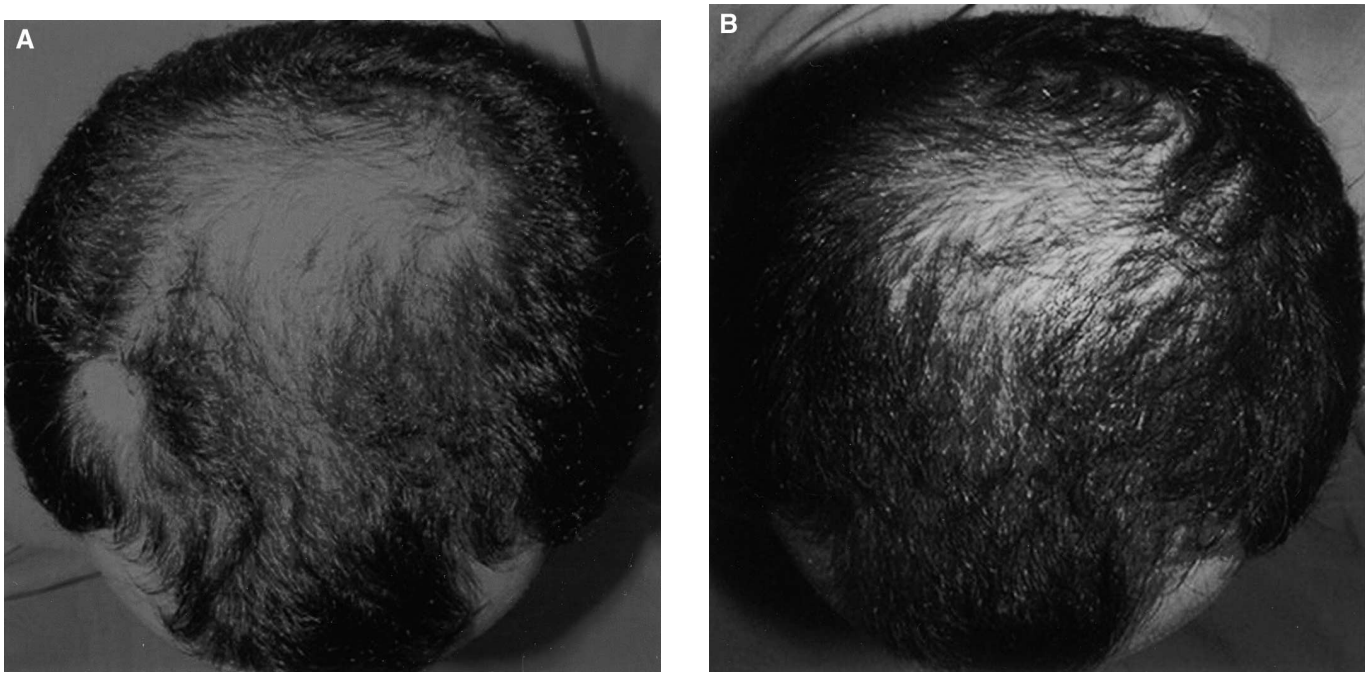

Figure 3. A global scalp view of one subject A) before and B) 6 months after daily topical fluridil showing a positive response.

count for the positive results in male AGA. A small statistically insignificant anagen count increase in the placebo group indicates that a subtle trend toward alopecia improvement may be attributable to the vasodilation induced by isopropanol and by abstention from shampoos containing surface tension reducers, known to effectively remove fat not only from the hair, but also from the scalp skin.

Anhydrous isopropyl alcohol ("rubbing alcohol") is recognized as innocuous by most pharmacopoeias. Its use in the formulation is dictated by the molecular design of fluridil, to decompose rapidly in the aqueous milieu. The formulation is topically well tolerated and, further, isopropanol integrates fluridil into the skin fat, thus facilitating its delivery to the follicles. We did not detect either fluridil or BP-34 in the serum of rabbits or of the subjects enrolled in this study. Our analytical armamentarium limits the visual detectability to about 5 ng/ml and the quantifiability to about 20 ng/ml. Even if transcutaneously resorbed, fluridil would hydrolytically decompose into the androgenically inactive BP-34 and trifluoroacetic acid. On the other hand, it can be seen that, at the detectability limit of 5 ng/ml, the total serum content of fluridil in a 70 kg person would not exceed 15 μg. At that level, an effect would not seem plausible. Had a pharmacologically active dose of fluridil been absorbed, the serum total testosterone would have initially reactively increased, and clinical effects ensued, but such was not the case. None of the subjects reported any change, although the questionnaire specifically and extensively addressed the issue of libido and sexual performance. There was, as expected, considerable individual variability in serum testosterone values, but they were all within the physiologic range (8–35 nm/L). The average increase in testosterone we saw was not statistically significantly different between the two groups, neither initially nor after 3 months, and as this study coincided with the spring season, the increase appears to be attributable to a seasonal variation.[24] Neither fluridil nor placebo affected the other blood chemistry or hematologic parameters.

It remains to be seen, in a longer study, how fluridil influences the hair substance, the anagen/telogen cycle, the growth of vellus-like (miniaturized) hair, and its conversion into terminal hair forms. This 9-month experience indicates that topical fluridil is safe and effective in improving AGA by increasing the anagen:telogen ratio. Since the increased ratio was attained within the first 3 months and remained for 9 months, fluridil appears to be a promising agent in the management of incipient or recent male AGA. Studies are currently under way to assess fluridil's safety and effectiveness in female AGA and hirsutism.

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