Skin Therapy Letter ©

Volume 3 • Number 4 • 1998

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New Drug Spotlight

Finasteride for Male Pattern Hair Loss

Finasteride 1 mg (Propecia®, Merck) was approved by the US FDA December, 1997 for the treatment of male pattern hair loss (androgenetic alopecia, AGA) in men only. Safety and efficacy were demonstrated in men between 18 and 41 years of age with mild to moderate hair loss of the vertex and anterior mid-scalp area. Efficacy in bi-temporal recession has not been established.[1] Propecia® is not approved for use in women or children. *Finasteride has been approved for this same indication in Australia, Argentina, Mexico and New Zealand and approval is being sought in more than 20 other countries.*

Hair loss has a significant psychosocial effect on some men. In these men, safe and effective treatment of hair loss is important to quality of life.[2]

Efficacy of finasteride[1]

Efficacy has been demonstrated in three double-blind, randomized, placebo-controlled studies in 1,879 men between 18–41 years of age with mild to moderate androgenetic alopecia. Two of the studies enrolled men with mild to moderate vertex loss, the third investigated mild to moderate loss in the anterior mid-scalp area with or without vertex balding. Primary end-points were hair count (assessed by photographic enlargements of a representative area of active hair loss) and patient self-assessment; secondary end-points were investigator assessment and ratings of global photography.

Clinical improvement was seen as early as three months in the patients treated with finasteride and led to a net increase in scalp hair count and hair regrowth. These effects have been maintained through two years in these studies and for up to three years in open-extension studies. Improvements have been seen across all racial groups.

Side effects

Adverse effects are minimal. Results in men treated with finasteride for benign prostatic hyperplasia, where five times the dose has been studied in men for up to 6 years, have revealed no long-term problems or new effects over the longer period. In patients with AGA treated with 1 mg of finasteride daily for 12 months in controlled studies, 1.4% of finasteride treated patients versus 1.6% of placebo treated patients discontinued therapy because of adverse drug experiences, and 1.2% of finasteride treated patients versus 0.9% of placebo treated patients discontinued because of drug-related sexual experiences. Sexually related adverse effects reported as possibly, probably or definitely drug or placebo related were decreased libido, erectile dysfunction and ejaculation disorder. Analysis showed that 4% of 945 men treated with finasteride and 2% of 934 men treated with placebo reported one or more of these adverse effects ($p=0.04$). These problems resolved in all men who stopped therapy with finasteride because of these effects, and in 58% of those who continued therapy.[1]

In older men with benign prostatic hyperplasia, PSA levels are decreased by 50% with finasteride therapy and consideration should be given to doubling the test level returned by men undergoing this test while taking finasteride.[1]

Contraindications

Finasteride is not indicated for use in women.[1]

Pregnancy Use of finasteride is contraindicated in women when they are pregnant or potentially may be pregnant, because of the risk to a male fetus.[1]

Precautions[1]

Liver function abnormalities Finasteride is metabolized extensively in the liver and caution should be used when treating patients with liver function abnormalities.

Handling Pregnant or potentially pregnant women should not handle *crushed or broken* Propecia® tablets because of the possibility of absorption of drug and subsequent potential risk to a male fetus.[1]

Pharmacokinetics

The bioavailability of finasteride is not affected by food. Following oral dosage of finasteride, a mean of 39% (almost entirely as metabolites) is excreted in the urine and 57% in the feces. The metabolites in the urine possess no more than 20% of the 5α-reductase inhibitory activity of finasteride.[3] At steady state, the mean terminal half-life of elimination is approximately 5–6 hours in men 18–60 years of age, increasing to 8 hours in men more than 70 years of age. No dosage adjustment is necessary in the elderly or in patients with renal insufficiency.[1]

Drug interactions

No drug interactions of clinical importance have been identified. Finasteride does not appear to affect the cytochrome P450-linked drug metabolizing system.[1]

Mechanism of action

It is thought that finasteride interrupts a key step in the pathogenesis of AGA, in those patients who are genetically predisposed. Finasteride is a preferential, competitive inhibitor of the intracellular, Type II, 5α-reductase isoenzyme which converts testosterone into dihydrotestosterone (DHT), a more potent androgen. *In humans, the Type II 5α-reductase isoenzyme is primarily found in the root sheath of the hair follicle,* prostate, seminal vesicles, epididymis, fetal genital skin and in fibroblasts from normal adult genital skin[1,3], as well as liver, and is responsible for two-thirds of circulating DHT. *In target organs, finasteride treatment is thought to result in selective androgen deprivation affecting DHT without lowering circulating levels of testosterone, thus preserving the desired androgen mediated effects on muscle strength, bone density and sexual function.*[4] In AGA, the balding scalp contains miniaturized hair follicles and increased amounts of DHT compared with non balding scalp, and finasteride treatment produces inhibition of the isoenzyme, resulting in a rapid reduction in scalp and serum DHT concentrations.[1]

Finasteride has no affinity for the androgen receptor, no androgenic, anti-androgenic, estrogenic, anti-estrogen or progestational effects, no effect on cortisol, thyroid-stimulating or thyroxine levels, and no effect on plasma lipid profile or bone mineral density. Circulating levels of testosterone and estradiol are increased by 15% but remain within the physiologic range.[1]

Dosage and administration

The recommended dosage is one mg once a day. *Because of the psychosocial impact of hair loss, it is important to explain what the patient may expect in terms of continuing hair loss. The response to any therapy may be slow and may include hair regrowth and/or retardation of further thinning.*[5,6] In general, daily use for at least three months or more is necessary before benefit is observed. Continued use is recommended to sustain benefit as withdrawal of treatment leads to reversal of effect within 12 months.[1]

Treatment of male pattern hair loss		**Cost to the Pharmacist**
Finasteride, *Propecia*®	1 mg tablet / day	US$47 / month[7,8]
Minoxidil 2%, *Rogaine*®, & others	apply lotion twice daily	US$11-23 / month[7,8]
5%, *Rogaine Extra Strength for Men*®		US$28 per month
Hair transplants	multiple sessions are usual	US$3500-10,000 / session[6]

There has been some controversy in newspapers and on the Internet about the cost of 1 mg tablets of Propecia® compared to the cost of 5 mg tablets of Proscar.® The New York Times on January 20th, 1998 used the heading, "New Baldness Drug Is Older Product at a Premium Price" and highlighted the statement that "A prostate treatment grows in value when it grows hair." Some price difference is reasonable, as Merck has had to finance development and clinical trials for this new indication and their costs must amount to at least tens of millions of dollars. While some user groups have been advocating splitting the 5 mg tablets, there is no data on the stability of tablet fragments, or the efficacy of this approach as Proscar® tablets have only been approved for the treatment of benign prostatic hyperplasia.

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Tinea capitis

Tinea capitis, the most contagious of all the tineas caused by dermatophytes, has been described as a scourge of young children.[1] *Children are most susceptible before puberty, and the infection develops less commonly in older age groups. Tinea capitis is caused by a variety of dermatophytes in the genera* Trichophyton *and* Microsporum. *The common etiologic agents vary from country to country and continent to continent. At present, the organisms responsible for most infections are* Trichophyton tonsurans *in North America;* Microsporum canis *in Europe, South America, Australia, Asia, North Africa and the Middle East;* Trichophyton violaceum *in the Indian subcontinent and parts of Europe and Africa.*[2]

Treatment with griseofulvin

Griseofulvin is still considered to be the treatment of choice for tinea capitis.[3,4] The absence of pivotal clinical trials comparing griseofulvin with newer antifungals such as fluconazole, itraconazole or terbinafine, may explain why regulatory authorities in North America have not approved any one of the three newer drugs for this indication. Griseofulvin is administered orally generally for a treatment period of four to six weeks. The dosage depends in part on whether microsized or ultramicrosized griseofulvin is used.[5] Griseofulvin has shortcomings in treating some infections due to *T. violaceum* or *T. tonsurans*.[6] Also, infections due to *M. canis* may respond poorly to griseofulvin. Another drawback in using griseofulvin to treat children may be its taste.[3]

Clinical experience with newer antifungal agents

The advantage that terbinafine, itraconazole and fluconazole have over griseofulvin is a shorter course of treatment.[6] All three drugs are also generally safe,[6] and are replacing griseofulvin in the treatment of other fungal skin infections. The big question with all of these newer antifungals is what is their role in infection due to the *Microsporum* species?[4] There is a suspicion from early data that they are not quite as good, but this may be simply that they are much better in *Trichophyton* infections.[4]

Fluconazole is available in a liquid form[3], but there is little data available on its efficacy in children.[2] One open-label, pilot study treated *T. tonsurans* infections in 41 children aged between two and 15 years, with 1.5, 3 or 6 mg/kg for 20 days. Twenty seven patients completed the study and, four months after discontinuation of therapy, the clinical and mycological cure rates in each group were 25%, 60% and 89% respectively.[8]

Itraconazole seems a logical agent for children that are unable to tolerate or are non-responsive to griseofulvin.[2] In one study which compared itraconazole to griseofulvin (for *M. canis* and *T. violaceum,* not *T. tonsurans*), they were roughly equivalent.[3] Anecdotally, some patients do better on one and some on the other, but itraconazole may be better than griseofulvin, especially for *M. canis*.[3] In a multicenter study in 50 patients (48≤18 years) with tinea capitis, pulse therapy with itraconazole seemed effective and safe and was associated with a high degree of compliance.[9] As with other antifungal drugs, the results in a clinical setting may not be as good as those obtained in well monitored and controlled clinical trials. In a very recent study, 25 children with proven *T. tonsurans* infections were treated with itraconazole 100 mg/day and a selenium sulfide containing shampoo for four weeks. In this open-label study in a clinical setting, only 40% of children responded to therapy.[10] With the oral solution being available now, a dose of 5 mg/kg/ day or pulse therapy is preferable to the fixed

Treatment of tinea capitis with griseofulvin

Treatment duration		generally four to six weeks[5]		
Dose in children	> 2 years	Ultramicrosize	5-10 mg/kg/day as a single daily dose*	
		Microsize	20 mg/kg/day in up to two divided doses*	
	when response is poor	Ultramicrosize	15-25 mg/kg/day	
Dose in adults		Ultramicrosize	330-375 mg daily	
Average cost in children		Suspension	Canada	formulation not available
			UK	£3-5
	15 kg child	20 mg/kg/day	US	$130
		tablets	US	$39#

Note * Recommended by the American Academy of Pediatrics.[7]
Some parents have trouble getting their children to take this form of griseofulvin – even when the tablets are crushed and added to pudding or jam.[3]

Treatment of tinea capitis with the newer antifungal agents

(alternatives to griseofulvin in the case of treatment failure or adverse side effects)

Antifungal	Dosage		Duration
Fluconazole Diflucan® *Pfizer* 200mg	6 mg/kg/day		3 weeks
Itraconazole Sporanox® *Janssen-Ortho* 100mg	5 mg/kg/day	*Daily therapy*	4 weeks
	5 mg/kg/day *Off therapy* 5 mg/kg/day *Off therapy* 5 mg/kg/day Generally 2−3 pulses, depending on the severity of the tinea capitis.	***Pulse therapy***[8]	1 week *2 weeks* 1 week *3 weeks* 1 week
Terbinafine Lamisil® *Novartis* 250mg	1/4 tablet /day 1/2 tablet /day 1 tablet /day	> 20 kg 20−40 kg > 40 kg	4 weeks is recommended[11] (1 or 2 weeks might be equally effective.[12])

dose used in this study. Studies are underway investigating the efficacy of different dosage regimens of itraconazole.[13]

Terbinafine This is an allylamine that is fungicidal *in vitro*. It is effective in tinea capitis due to endothrix species but less effective in *M. canis* infections. As with the triazoles, fluconazole and itraconazole, short-term therapy lasting four weeks may be effective in endothrix infections (e.g. due to *T. tonsurans*)[12] and recent studies suggest that even two weeks[13] of treatment, instead of the usual four weeks, might be all that is required.[13] With *M. canis* infections, it has been suggested that longer than six weeks of treatment may be required.[14]

Does shampoo treatment or prophylactic use provide any benefit?

Ketoconazole shampoo, once daily for the first week and then twice daily for the next three to four weeks, is being considered by some as an adjunct to oral treatment.[6] All siblings and other family members may also benefit from the use of ketoconazole shampoo.[13] Use of *selenium* sulfide, 1-2.5%, to decrease spore shedding may be another alternative.[3]

Practical therapeutic summary

- *Griseofulvin is still the treatment of choice.*[3,4,13] Although response rates in controlled trials are as high as 80-90%, in the clinical setting response rates may be significantly lower because of non-compliance, inadequate drug absorption, re-exposure or resistance.[15]
- *At this time, none of the newer drugs have regulatory approval for tinea capitis but they are alternatives to griseofulvin in the case of treatment failure or adverse side effects.*
- Use a shampoo such as ketoconazole or equivalent as an adjunct to oral therapy.[13]
- Discourage sharing of hats, combs etc.[13]
- All family members should be examined and should consider using ketoconazole shampoo for their scalp.[13]
- With *M. canis* or a zoophilic fungus, look for an animal source of infection.[13]

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Future developments

Finasteride may hold promise for other DHT-mediated disorders such as facial hirsutism and frontal alopecia.[9] Several companies are developing combination Type I and Type II 5α-reductase inhibitors which may be regarded as candidates for treatment of androgen-dependent skin disorders such as seborrhea, acne, hirsutism and/or androgenetic alopecia.[9]

The place of finasteride in therapy

A recent review in the Medical Letter™ concluded that finasteride can produce a modest increase in hair on the scalps of young men with mild-to-moderate hair loss.[7] They also note that treatment must be continued indefinitely to maintain the effect.[7]

There is no question that oral finasteride (Propecia®) is effective in the oral treatment of AGA. Oral finasteride has now become the standard against which all future therapies for male AGA should be compared.

Dr. Jerry Shapiro, Vancouver

This is the first time that a systemic agent has been approved for use to treat male pattern hair loss. On the basis of our experience with minoxidil, if patients get sufficient hair growth for a cosmetic improvement, they will use finasteride on a continuing basis. In this respect, treating male pattern hair loss is little different to treating many other chronic diseases!

Dr. Stuart Maddin, Editor

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Drug Treatments Introduced in 1997

Indication	Generic / Trade Name		Company	Country
Actinic Keratosis	Hyal-CT-1101	*Solarase*	Hyal Pharmaceuticals	UK
Anti-acne	Tazarotene	*Tazorac*	Allergan	USA
	Tretinoin	*Retin-A-micro*	Advanced Polymer System & Ortho-McNeil	USA
	Tretinoin	*Avita*	Penederm	USA
Anti-eczema	Fluticasone	*Fluticasone*	Glaxo Wellcome	USA
Antifungal	Amphotericin B	*Abelcet*	The Liposome Co.	Austria, France
Antiherpetic	Penciclovir	*Vectavir*	SmithKline Beecham	Germany
Antipsoriatic	Acitretin	*Soriatane*	Roche	USA
	Tazarotene	*Tazorac*	Allergan	Canada, Germany, Italy, UK, USA
(severe recalcitrant)	Cyclosporine	*Neoral*	Novartis	USA
Antiviral	Imiquimod	*Aldara*	3M Pharmaceuticals	USA
	Penciclovir	*Denavir*	SmithKline Beecham	USA
	Valaciclovir	*Valtrex*	Glaxo Wellcome	Australia, Spain
Aphthous ulcer	Amlexanox	*Apthasol*	Block Drugs	USA
Kaposi's Sarcoma	Daunorubicin	*DaunoXome*	Nexstar	Russia
Male pattern baldness	Finasteride	*Propecia*	Merck & Co.	USA
	Minoxidil 5%	*Rogaine*	Pharmacia Upjohn	USA
Malignant melanoma	Virulizin	*Virulizin*	Imutec Pharma	Mexico
Wound healing	Human Skin Equivalent	*Apligraf*	Novartis	Canada
	Skin substitute	*Dermagraft-TC*	Advanced Tissue Sciences	USA
(diabetic foot ulcer)	Becaplermin	*Regranex*	Rhone-Poulenc Rorer / J&J / Chiron	USA
(diabetic foot ulcers)	Artificial skin	*Dermagraft*	Smith & Nephew	Canada

Of the more than 40 new molecular entities approved in the US in 1997, only two had dermatologic usage – imiquimod (Aldara®, *3M*) and tazarotene (Tazorac®, *Allergan*). Becaplermin (Regranex®, *Ortho-McNeil*), for diabetic and foot ulcers, was the only significant new biologic introduced for dermatologic use.

Stuart Maddin, Editor

Update on Drugs

Class	Name/Company	Approval Dates and Comments
Acne vulgaris	**Norgestimate / Ethinyl estradiol** Tri-Cyclen® *Janssen-Ortho*	Approved by the Canadian HPB March, 1998 for the new indication of treatment of moderate acne vulgaris in females who have no known contraindications to oral contraceptive therapy. Previously approved in the US in 1997.
Topical anesthetic	**Lidocaine / Prilocaine Cream** Emla® *Astra*	Approved by the FDA February, 1998 as a pre-procedural application to adult male genital skin prior to site-specific subcutaneous infiltration with lidocaine for the removal of genital warts.
New Formulations		
Acne vulgaris	**Tretinoin gel 0.025%** Avita® *Penederm*	This new gel formulation was approved by the FDA February, 1998 for the treatment of acne vulgaris.
Acne vulgaris & oily skin	**Adapalene solution 0.1%** Differin® *Galderma*	Applied once a day in the evening for the treatment of acne. The solution also provides a drying effect for patients with oily skin.
US FDA – Recommendations		
Wound closure	**Topical tissue adhesive** Dermabond® *Closure Medical*	An FDA advisory panel recommended approval of this sterile, liquid, topical tissue adhesive to hold closed trauma-induced lacerations or surgical incisions (including punctures from minimally invasive surgery) which otherwise would be closed with sutures of USP size 5-0 or smaller in diameter, staples or adhesive strips.
Labelling Changes		
Atorvastin calcium Lipitor® *Parke-Davis*	This lipid reducing agent has been reported to cause angioneurotic edema in some patients and labelling has been changed accordingly.	
Isotretinoin Accutane® *Hoffman La Roche*	*Upon advice from the FDA in early March, Roche sent out* ***Dear Doctor*** *letters to US physicians advising them of labelling changes.* The Warnings section will now begin with the following paragraph in bold type: **Psychiatric disorders: Accutane may cause depression, psychosis and, rarely, suicidal ideation, suicide attempts and suicide. Discontinuation of Accutane therapy may be necessary. No mechanism of action has been established for these events.** The adverse events section is also revised.	

Published six times yearly by International Skin Therapy Newsletter Inc., 835 West Tenth Avenue, Vancouver, British Columbia, Canada V5Z 4E8. Tel: (604) 874-6112. Fax: (604) 873-9919. Annual subscription: Canadian $85 individual; $155 institutional (GST included). US $60 individual; $110 institutional. Outside North America: US$80 individual; $130 institutional. Quotes on multiple subscriptions and student rates supplied upon request.

Printed in Canada