Emerging Technology in the Treatment of Androgenetic Alopecia

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Disclosure

- Allergan – Advisor
- Cassiopea - Advisor
- Follica – Advisor, Stock Options
- Kerastem – Advisor, Clinical Investigator

- Board Member of non-profit organizations that have received contributions from industry
  - North American Hair Research Society
  - International Society of Hair Restoration Surgery
  - Cicatricial Alopecia Research Foundation
  - Hair Foundation
Emerging Therapies

- Prostaglandins
- JAK Inhibition
- Adipocytes
- Quorum Sensing
- Post-Finasteride Update
Prostaglandin Related Regulation of Hair Growth

- Prostaglandin F$_2$$\alpha$ analogs / prostandimes
- Prostaglandin D$_2$
Prostaglandins and Hair Growth

**Bimatoprost in the treatment of eyelash hypotrichosis**

Approved as a stimulator of eyelash growth in 2008

- 0.3 % bimatoprost
- qD x 16 wks

Prostaglandins and Hair Growth

• Phase I and 2 trials of topical bimatoprost in MPHL and FPHL completed
• Initial phase II trial did not yield suitable efficacy
• No data yet available from second phase 2 trial with higher concentration
Prostaglandins and Hair Growth

• Latanoprost Solution
  – Eye drops for glaucoma
  – Prostaglandin F$_2$\(\alpha\) analog
  – 77% developed increased eyelash growth (317 patients)*

Prostaglandins and Hair Growth

• Latanoprost solution in the balding stump-tailed macaque
  – Small study of 8 macaques
  – Minimal growth with 50 ug/ml daily for 5 months
  – Moderate to marked regrowth with 500 ug/ml daily for 3 months (similar to results in previous 5% minoxidil studies)
Prostaglandin Related Regulation of Hair Growth

- Prostaglandin $F_{2\alpha}$ analogs / prostandamides
- Prostaglandin $D_2$
Prostaglandins and Hair Growth Inhibition

• Prostaglandin D$_2$ associated with hair loss in balding men
  – Significantly higher levels in balding skin

Prostaglandins and Hair Growth Inhibition

- Prostaglandin D$_2$ inhibited hair growth in mice (topically and in transgenic model) and in \textit{in vitro} human hair follicles
- A number of receptor, DP-2, antagonists are already in clinical development for asthma and allergic rhinitis

• Setipiprant, a potent oral PGD$_2$ receptor antagonist
• Safety established in multiple clinical trials for asthma and allergic rhinitis
• No previous work done on potential effect on hair
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JAK Inhibitors (Jakinibs) for Alopecia Areata

• Angela Christiano, PhD found clues from genome wide association studies (GWAS) utilizing the NAAF gene registry

• Janus Associated Kinases 1,2,3

*Peter Znamenkiy, www.wikipedia.org
JAK Inhibitors (Jakinibs) for Androgenetic Alopecia?

Pharmacologic inhibition of JAK-STAT signaling promotes hair growth


Harel et al. Sci Adv. 2015; Oct:1-12
JAK Inhibitors Promote Hair Growth

- Topical treatment of mice induces anagen, likely through the Wnt, Shh pathways
- Induces hair growth in human skin grafts and in human follicles in culture
- Regulates activation through hair follicle stem cells
- Promotes (tofacitinib) hair follicle inductivity of human dermal papillae
- Direct hair follicle effect, lymphocyte independent
JAK Inhibitors Promote Hair Growth

Anagen Induction

Harel et al. Sci Adv. 2015; Oct:1-12
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The Role of Adipose Tissue in Hair Cycling

- Fat in the scalp may play a role in hair loss and hair growth.
- Festa et al. reported that adipocyte lineage cells support the follicular stem cell niche and the hair growth cycle.
European Proof of Concept Study: Fat in the Treatment of Pattern Hair Loss

• Evaluate the role of purified lipoaspirate plus the stromal vascular fraction (SVF) in treating hair loss patients with male and female pattern hair loss.

• SVF is a heterogenous population of adipose derived regenerative cells (ADRCs), preadipocytes, endothelial progenitor cells, mast cells, adipose tissue macrophages.

  – SVF has been shown to improve the viability\(^1\) of grafted adipocytes.

European Proof of Concept Study: Fat in the Treatment of Pattern Hair Loss

Injection into dermis and subcutaneous adipose layer

Perez-Mesa, ISHRS Meeting, Chicago 2015
Results

• A total of 6 patients were analyzed at 6-month, 3 patients were lost to follow-up.
• Average of 14% increase (95% CL = 10.2-46.5; p = 0.01) in hair count (mean difference of 28 hairs per square centimeter).
• All patients at 6-months demonstrated some degree of response.
Global Photographic Assessment

Baseline

5/6 months
Global Photographic Assessment

Baseline

5-months
The Role of Adipose Tissue in Treating Pattern Hair Loss

- Phase 2 multicenter, randomized, blinded trial using enzymatically prepared stromal vascular fraction (SVF) enriched adipose cells in the men and women with androgenetic alopecia
- 12 month trial comparing a single treatment of SVF enriched adipose tissue versus adipose tissue alone versus saline

http://www.clinicaltrials.gov
• In mice, neogenic follicles induce myofibroblasts to differentiate into adipocytes in scars.

• Adipocytes formed from human keloid fibroblasts when placed with human hair follicles in vitro.

This is a comparison of wounds healing with and without hair follicles.

Credit: Penn Medicine

Emerging Therapies

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• JAK Inhibition
• Adipocytes
• Quorum Sensing
• Post-Finasteride Update
Plucking hair at different densities leads to a regeneration of up to five times more neighboring, unplucked resting hairs.

Indicating activation of a collective decision-making process.
Update on the Post Finasteride Syndrome Controversy
Disclosure - Merck

- No equity interest or stock ownership
- Previous Speakers Bureau member
- Clinical investigator on previous clinical trials
- My practice has realized revenue from finasteride sales
- My practice has been named in finasteride lawsuits
- Finasteride user and prescriber
Finasteride Mechanism of Action

Testosterone $\xrightarrow{\text{NADPH}}$ 5α-Reductase Type II $\xrightarrow{}$ DHT

Decreased 60 – 70%

Finasteride
Finasteride Efficacy

Fig 5. Global photographic assessment mean rating score (± 1 SE) from the combined US and international studies for men who entered the extension studies.

Fig 6. Patient 1. A, Baseline. B, Month 12: Slightly increased hair growth. C, Month 24: Moderately increased hair growth.

Finasteride Safety

Table IV. Adverse events occurring in 1% of patients or more

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<th>Table IV. Adverse events occurring in 1% of patients or more*</th>
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<td><strong>Original studies (first year)</strong></td>
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| Finasteride
| Placebo           | Fin→Fin (n=547) | Pbo→Fin (n=543) | Fin→Pbo (n=65) | Pbo→Pbo (n=60) |
| (n=779)           | (n=774)         |                 |                |                |
| Genitourinary system                                      |                                                             |
| Urinary frequency                                         | 0               | 0               | 0              | 0              | 1 (1.7)       |
| Sexual function                                            |                                                             |
| Libido decreased                                           | 15 (1.9)        | 10 (1.3)        | 6 (1.1)        | 7 (1.3)        | 0              | 1 (1.7)       |
| Erectile dysfunction                                       | 11 (1.4)        | 7 (0.9)         | 4 (0.7)        | 6 (1.1)        | 0              | 0              |
| Decreased ejaculate volume                                 | 8 (1.0)         | 3 (0.4)         | 1 (0.2)        | 0              | 0              | 0              |
| Skin and skin appendages                                   |                                                             |
| Body hair growth increased                                 | 7 (0.9)         | 7 (0.9)         | 1 (0.2)        | 4 (0.7)        | 0              | 3 (5.0)       |

Resolved with continued use or discontinuation of drug

Finasteride Persistent Side Effects Controversy

• Post-marketing reports of side effects persisting after the discontinuation of finasteride have appeared over the years.

• The UK and Swedish regulatory agencies added notice of these reports to the package inserts for finasteride.

• Two Journal of Sexual Medicine articles on the subject were published in 2011.
Adverse Side Effects of 5α-Reductase Inhibitors Therapy: Persistent Diminished Libido and Erectile Dysfunction and Depression in a Subset of Patients
Abdulmaged M. Traish, PhD,* John Hassani, MA,* Andre T. Guay, MD,† Michael Zitzmann, MD, PhD,‡ and Michael L. Hansen, MD§

Persistent Sexual Side Effects of Finasteride for Male Pattern Hair Loss
Michael S. Irwig, MD* and Swapna Kolukula, MB BS†
*Center for Andrology and Division of Endocrinology, The George Washington University, Washington, DC, USA
†Department of Medicine, Greater Baltimore Medical Center, Baltimore, MD, USA

J Sex Med. 2011 Mar;8(3):872-84

FDA Adds Sexual Side Effects to Propecia and Proscar Labels

The FDA maintains that finasteride is safe and effective, but notified health care professionals who commonly prescribe finasteride — dermatologists, family practice professionals, internists and urologists — about the data review and warning changes.

“It’s important to note that these labeling changes are not new warnings, as characterized by other news reports. Sexual adverse events were reported in clinical trials, and this information was included in the finasteride drug labels at the time of approval,” says Stephanie Yao of the FDA Office of Public Affairs. In those clinical trials, the side effects resolved in patients who stopped using finasteride, as well as in most patients who continued therapy.

dysfunction from users. The FDA reviewed 421 post-marketing reports of sexual side effects related to Propecia from 1998 to 2011. Of these, 59 cases reported adverse sexual effects that lasted longer than three months after drug discontinuation. The agency also reviewed 251 cases associated with semen quality; 13 had enough information for evaluation. For Proscar,
Post-Finasteride Syndrome

- Persistent sexual, neurological, and physical adverse reactions that patients claim originated after starting or stopping finasteride but do not resolve off the drug.

  - **Sexual**
    - Libido, erection, orgasm, ejaculatory, penile shrinkage, Peyronie’s Disease, testicular shrinkage

  - **Neurological**
    - Memory, cognition, depression, anxiety, insomnia, tinnitus, suicidal ideation

  - **Physical**
    - Gynecomastia, fatigue, muscle weakness and atrophy
Post-Finasteride Syndrome Controversy

• The statements below are based on a meeting convened in November 2011 by the Sexual Medicine Society of North America.

• “However, at this time, human scientific evidence does not allow us to define the prevalence or the cause of these symptoms.”

• “…it is currently impossible to definitively link, as cause and effect, these medications to the long-lasting symptoms these men experience.”

http://www.smsna.org/about/position.asp
Sexual Dysfunction

• Survey of patients in a Canadian primary care setting
  – 49.4% prevalence of erectile dysfunction in 3921 men aged 40-88 years of age (avg = 56.7)
  – 30% prevalence in men in their 40’s

  *Arch Intern Med. 2006;166:213-219*

• 30 million men estimated to suffer from ED in the US
  – 617,000 new cases expected per year in men 40 – 69 years of age

  *Boston University School of Medicine Center for Sexual Medicine.*
  http://www.bumc.bu.edu/sexualmedicine/informationsessions
Impact of Nocebo Effect


Finasteride 5 mg and sexual side effects: how many of these are related to a nocebo phenomenon?

- Without Counseling  With Counseling
- Any           15.3%  43.6%
- ED            9.6%  30.9%
- EjD           5.7%  16.3%
- Libido        7.7%  23.6%

RESULTS: One hundred seven patients completed the study. Group 2 patients (N = 55) reported a significant higher proportion of one or more sexual side effects as compared to group 1 (N = 52) (43.6% vs. 15.3%) (P = 0.03). The incidence of ED, decreased libido, and ejaculation disorders were 9.6, 7.7, and 5.7% for group 1, and 30.9, 23.6, and 16.3% for group 2, respectively (P = 0.02, P = 0.04, and P = 0.06).
SOMERSET, N.J., March 18, 2013 -- The Post-Finasteride Syndrome Foundation today announced that it has been granted 501(c)(3) status by the Internal Revenue Service. According to IRS regulations, the nonprofit status is retroactive to July 15, 2012, meaning all donations made to the PFS Foundation on or after July 14, 2012 are tax deductible in the United States. Donations made from outside the U.S. may also be tax-deductible, depending on local tax codes.

“We thank the IRS for classifying us as a public charity,” said PFS Foundation CEO Dr. John Santmann. “Through thousands of men worldwide are likely suffering from post-finasteride syndrome—with potentially millions more at risk of developing the condition in the coming years—only a handful of medical professionals recognize the symptoms. And even when they do, there are no effective treatments. Those will only come through research at the molecular level.

“Nonprofit status will allow us to put more dollars to work pursuing our core goal, which is funding research on the characterization, underlying biologic mechanisms and treatments of PFS,” added Dr. Santmann.
Participants: (1) finasteride users who reported persistent sexual symptoms after discontinuing finasteride; (2) finasteride-users who did not report sexual symptoms; (3) healthy men who never used finasteride

Conclusions: We found no evidence of androgen deficiency, decreased peripheral androgen action, or persistent peripheral inhibition of SRD5A in men with persistent sexual symptoms after finasteride use. Symptomatic finasteride-users revealed depressed mood and fMRI findings consistent with those observed in depression.

“Men seeking treatment for alopecia have higher prevalence of depression and sexual dysfunction than the general population”
• Self reported
  – “PFS patients were recruited through the Italian network finasteride side effects.”
  – No diagnostic criteria for post-finasteride syndrome
• Improper control group – healthy orthopedic patients
• “Although not validated,…”
• “…neuroactive steroid changes in PFS patients remain heterogeneous.”
• “…the pathogenic mechanism underlying the PFS is not yet understood.”
• Funded by the PFS Foundation
The only high-quality study documenting persistent sexual side effects showed that these were more frequent in the placebo than in the treatment group.

Persistent sexual and psychiatric side effects after 5αRIs are not documented by high-quality studies, and prospective studies to establish true incidence and frequency of the problem are really needed.
Finasteride Persistent Sexual Dysfunction Controversy

Summary

• There are patients suffering from persistent sexual dysfunction (as well as other complaints).
• They have taken finasteride.
• No causal relationship between the two has been established.
• They deserve a thorough evaluation and treatment.
• Persistent side effects to finasteride after discontinuing the drug are not consistent with my clinical experience.
• I strongly agree that patients should be informed of this issue when they are considering finasteride therapy.
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