Update Hair Loss Disorders
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Disclosure; J&J, Samumed, Incyte, Kythera, Allergan, Concert, Lilly, Pfizer, Bayer, Aclaris, Pfizer, Lilly, Cassiopea, Eclipse, Bristol Myers, P&G
Outline

• Over view
• Case scenarios
  • Telogen Effluvium
  • Androgen Excess
  • Alopecia areata
• Evaluation
• Recommended treatments

Pilo-sebaceous unit and its environment
Permanent loss of follicles
Telogen Effluvium
Hair Loss Evaluation

- **History**
  - Medical/Surgical
  - Metabolic
  - Endocrine
  - Stress scale 1-10
  - Drugs

- **Gynecological**
  - Pregnancy

- **Diet**

- **Weight loss/gain**

- **Degree of exercise**

- **Family history**
  - Shedding, Alopecia, hormonal, endocrine, metabolic diseases & malignancy
Laborator Evaluation

• CBC
• CMP
• TSH
• Microsomal AB
• DHEAS
• Testosterone Free & Total

• Ferritin
• Zinc
• Vitamin D
• Vitamin A
• ANA
32 yo female G2P2

6 mo history of TE
Increase daily shedding
Most loss on Shampoo day

Trigger ?

Diet vegetarian
Exercise daily 1 hour
Wt stable

Exam

Diffuse thinning
Hair pull 20 Telogen
Wood’s light negative
Dermatoscopy negative

PMH
Irregular MP

FH
Diabetes II
Hypothyroidism
Colon cancer

Past treatment
MVI
Hair cosmetics
Evaluation
Low ferritin
Vitamin D
Low zinc
High DHEAS

Minoxidil 5% liquid or foam
Biotin forte 3-5mg with zinc
B-vitamins, vitamin C, zinc
Spironolactone 150 mg/day
24 year old
TE 4 months
Scalp pruritic and painful
Healthy
Low body weight
Normal menses
FMH
Hypothyroidism
MPHL
Diet: eats red meat
Exercise jogs 3 x wk

Exam
Diffuse thinning
Hair pull positive 10 hair telogen
Wood’s light positive
Malazia/seborrheic dermatitis
Findings

Low Vitamin D
High DHEAS
Seborrheic dermatitis

Treatment

Ketoconazole shampoo
Bioton forte 3 with Zinc
Vitamin D 50,000 IU BIW
Spironolactone 150 mg/d
SHEDDING

TELOGEN SHED -
> 35 % Loss
COMMON

ANAGEN SHED - RARE
> 80% Loss

Most Common Hair Loss Complaint

Acute: 6-12 weeks
Chronic: > 4 months
DHT - Hair Follicles
Anagen follicle

Local Production in Follicle
Circulating DHT Near Follicle

Androgen metabolism
Anagen DP, IRS, ORS, Sebaceous gland, Fibroblasts

Influenced
Gonadotrophins
Insulin growth factors
Cytokines-Wnt
Insulin
Glucocorticoids
Estrogens
Progesterone
Androgens
Antiandrogens
Prostaglandins
Thyroid-parathyroid
Nutrients

Blood Vessels
Nerves
Dermal papillae

**Target**

“Shed”

Effluvium

*Premature Shunt*

Anagen   Telogen

**Shunt 7-35%**

---

**The hair growth cycle and shedding**

- **Anagen (growing) phase**: Up to 85% of hair is in this phase at one time, which can last 2 to 5 years.
- **Catagen (involuting) phase**: Last 3 to 6 weeks.
- **Telogen (resting) phase**: Up to 15% of hair is in this phase at one time, which can last 3 to 5 months.
• Excessive shedding of Telogen hair
• Altered follicular growth cycle
• Each follicle has three growth phases + 1
  • Anagen + 5 years > 90% of hair follicles
  • Catagen + 6 weeks < 1% of follicles
  • Telogen + 3 months (10% of scalp hair follicles) - Shed shorten anagen
  • Exogen - Exiting hair

• Asynchronous cycling - each follicle independent
• Research suggests predetermined life cycle #70 (senescent alopecia)
Follicular cycling
Shed

• **Immediate release**
  • Most common mechanism for TE
  • **Significant number of** anagen follicles shift to telogen follicles prematurely
  • Seen with fever, drugs, stress etc

• **Delayed release**
  • **Prolongation** of anagen which delays telogen, and then a sudden release
  • Seen in post partum female
Micro Environment / Anagen Dermal Papillae

Stress hormone
Corticotropin releasing hormone (CRH)

Vascular/Nerves

Keratinocyte cytokines
Vit D & A
Iron & zinc

Hypo thalamic-pituitary-adrenal (HPA axis)

Micro Inflammation
Androgen inducing cytokines

Fibroblasts
Sebaceous glands
Pil Arrector muscle

Insulin Thyroid

Circulating DHT Near Follicle

Vascular/Nerves
Shedding Pattern - Triggers

Shed premature anagen shunt to telogen

7 - 35%

- Acute shedding
- Chronic shedding

20% to 30% increase in diffuse hair loss by 2 to 3 weeks after trigger

Increase in normal hair loss

Normal hair loss ≈ 100 hairs per day

Initial trigger

New trigger

New trigger

New trigger

Time course

Acute

Chronic

Chronic repetitive
Daily Hairs Shed

- Acute Shedding
- Chronic Shedding

120-150 plus

~100 (Normal)

Time Course

- Initial Trigger
- New Trigger
- New Trigger...

Graph showing the time course of daily hairs shed with acute and chronic shedding.
Telogen Hair Shedding

Acute Telogen Effluvium
<6 months

Chronic TE
>6 months

If sequential or ongoing triggers involved & hair thinning develops >6 months

Diffuse hair shedding - ongoing or - repetitive or sequential

Identify triggers

Female Pattern Hair Loss

Nutritional deficiencies
Iron Deficiency
Endocrine changes/disorders
Medications DRUGs
Autoimmune disease
Infection
Chronic renal failure
Hepatic failure
Scalp inflammatory disorder
Rarely advanced malignancy
Idiopathic
Inciting factors TE

• Acute & chronic diseases
• Febrile illness
• Major surgery
• Childbirth
• Rapid weight loss
• Nutritional deficiency
  • Protein, caloric
  • Vitamins, minerals
  • Iron deficiency
• Endocrine disorders
• Drugs
• Toxins
• Acquired zinc deficiency
• Significant emotional stress
• Inflammatory scalp conditions
Hair loss
Collagen Vascular Disease

**Telogen Effluvium**
- Most common hair loss
  - Dermatomyositis
  - Lupus
  - Scleroderma
  - Sjogren’s Syndrome
  - Mixed undifferentiated CTD

**Cicatrical alopecia**
- Discoid lupus
- Scleroderma
- Scleroderma coup de sabre
- Morphea localized

• Majority of drugs implicated
• *Important history*
  • Drug
  • Dose
  • *Change* in Dose
  • Duration
  • *History* of adverse drug reactions
## Drug induced TE

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Allopurinol</td>
<td>Androgens</td>
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<td>Androgens</td>
<td>Anti cholesterol-statins</td>
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<td>Psychotropics</td>
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<td>NASIDS</td>
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<tr>
<td>NASIDS</td>
<td>Heavy Metals</td>
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<tr>
<td>Heavy Metals</td>
<td>Serms &amp; Phytoestrogens</td>
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<tr>
<td>Serms &amp; Phytoestrogens</td>
<td>Vaccinations</td>
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Telogen Effluvium

Common findings

(Healthy skin, Healthy hair (reduced oxidative stress))

- Seborrheic dermatitis
  - Iron storage anemia
  - Low ferritin
  - Low zinc
  - Low Vitamin D, A
  - Diet
  - Stress
  - Endocrine disorders

- Hormonal changes
- Metabolic & Autoimmune Diseases
- Inflammatory diseases
- Poor health
- Drugs
- Surgery
- Unmasked Familial AGA
Physical Exam

- Scalp hair, eyebrows, eyelashes, body hair
- Erythema, scale, pustules
- Alopecic patches vs breakage
- Localized vs Diffuse
- Hair pull test
  Pull 40-60 hairs at 3 separate areas
  <6-10 is positive for telogen effluvium

Gorden & Tost, 2011
**TE Diagnostic Tools**

- **Clinical inspection**
  - Visual
  - Wood’s light (Blue light)
  - Dermatoscopy
  - Trichogram/Tricoscan
  - Standardized Photography
    - Global
    - Dermoscopy-Ipad
    - Videoscopy

- **Techniques**
  - Hair Pull
  - Hair Collection
  - Hair Pluck
  - Hair Clipping
  - Hair mounts
  - Scalp Biopsy

- **Skin - hair cultures**
19 year old female
Chronic shed

Telogen Effluvium >7-35%

Normal # anagen

Hair Pull
6-10 telogen hair

Increase Telogen >7%
1 T/ 8 A
Chronic TE
Follicular growth cycle shortening
Immediate telogen release

- Study 17 n FPHL vs 3 n Chronic TE
- Biopsy and IHC
  - FPHL - Significant miniaturization
  - FPHL - Increased density of non anagen follicles
  - FPHL - Increased Ki-67 follicular sheath
  - FPHL - Highest VEGF
  - CD31 equal in both

Patterned alopecia: Reduced PiloSebaceous Units & terminal follicles.

Increased vellus follicles.

NORMAL

Horizontal section (lower) of androgenetic alopecia, unmarked.
Trichoscan technique
Trichoscan TE

Study 100 female patients

• Mild, Moderate, Severe FPHL
  • 5mm area temporoparietal region
  • Shaved and stained
  • Trichoscan soft ware

Results

• Ferritin low in all groups
• Highest anagen mild
• Lowest anagen severe <p0.05 significant

• Trichoscan consistent with clinical dx

Ozkol H eta al. Turkish J Med Science 44(3):432-8, 2014
Laborator Evaluation

- CBC
- CMP
- TSH
- Microsomal AB
- DHEAS
- Testosterone Free & Total
- Ferritin
- Zinc
- Vitamin D
- Vitamin A
- ANA
Ferritin & Vitamin D

Study

- 80 females with TE, FPHL/ 40 female controls
  - 18-45 y
  - Dx based on clinical, trichogram, dermaRashscopy

Results

- Serum Ferritin
  - TE (14+/−22 mug/l)
  - FPHL (24+/−39 mug/l)
  - Control (44+/−20 mug/l)

- Vitamin D2
  - TE (29+/−11nmol/l)
  - FPHL (29+/−9 nmol/l)
  - Control (118+/− nmol/l)

Ferritin and Vitamin D

Study

- 80 females with TE, FPHL/ 40 female controls
  - 18-45 y
  - Dx based on clinical, trichogram, dermaRashscopy

Results

- Serum Ferritin
  - TE (14+/-22 mug/l)
  - FPHL (24+/-39 mug/l)
  - Control (44 +/-20 mug/l)

- Vitamin D2
  - TE (29+/-11nmol/l)
  - FPHL (29 +/-9 nmol/l)
  - Control (118 +/- nmol/l)

Zinc and Copper

• Study 312n with alopecia areata, MPHL, FPHL and TE vs controls

• Results;
  • In all groups-Zinc lower than control, copper wnl
  • Lowest zinc seen AA

Telogen Shed

Treatment

Find/ Remove/Rx Triggers

Many times multiple

Follow up important
Androgen Excess
Androgen Clinical Scenarios

- Hair Follicle
- Sebaceous gland
- Fibroblast
- Pili arrector muscle
19 year old female with ATE

ATE > 50% loss
Acne
Hirsutism- Obesity
Seborrheic dermatitis
• FHx: AGA, Diabetes
  Thyroid disorder
DHEAS elevated

Rx: OCP/Yasmin &
  Spironolactone 150mg/d
Androgenetic Alopecia (Patterned Hair Loss)

- Autosomal dominant
- Prevalence 23-28%
- Common Males & Females
- Central Scalp Alopecia
- Onset at puberty
- DHEAS
- Common signs of Androgen Excess
- Heralded TE

Savin scale
Female Pattern Hair Loss

Retention of hair line

Shorten anagen cycle

Widen part

Young

Older
Pattern Hair Loss

Men aged 18-29 years: 16%
Men aged 30-39 years: 49%
Men aged 40-49 years: 53%

Puberty
Menopausal

>50 years  Senescence

Similar mechanisms:
- Genes
- Androgens
- Nutrients
- Hormonal deficiency
- "Poop out"
Androgenetic Alopecia

Miniaturization
Drop out

Hirsutism

Enlargement

Androgenic Influence
Androgen Influence - Hair Follicle - Sebaceous Gland

- Prepubital vellus follicle
- Terminal hair follicle
- Androgen
- Sebaceous hair follicle

Influence site specific

- Sexual hair
- Balding scalp
- Acne-prone skin
Levels of Androgens
Unrelated to Severity of SAHA signs

• Non linear association
  • Plasma androgens
    • Hirsutism
    • Acne
    • Oligo/amenorrhea
    • PCOS morphology
  • Insulin levels

• Linear association with severity of Hirsutism
  • Sex Binding Hormone Globulin
    (suggest OCP helpful)
  • Free testosterone

PCOS and SAHA

- PCOS patient’s more likely to have SAHA
  - 56/254 patients PCOS (22%) AGA
  - PCOS + AGA more likely to have acne and hirsutism with and without AGA (96% vs 71%)
  - AGA patients more likely to be concerned about hair loss 70% vs 38%
Metabolic Syndrome

• Common metabolic syndrome
  • Diabetes II

• Pro-inflammatory state
  • *High risk of cardiovascular disease*

• Therapy:
  • Weight loss
  • Increased physical activity
Risks

**Androgen Excess**

- SAHA
- PCOS
- **Metabolic syndrome**
- Obesity
- Menstrual abnormalities
- **Infertility**
  - Vitamin D deficiency
- **Hyperlipidemia**
- Hypertension
- Insulin resistance
- Diabetes II
- Acanthosis nigricans
- **Endometrial carcinoma**
- ?Breast cancer
- Early cardiac disease & death
- Osteoporosis
- Prostate cancer men
PCOS Overlap

- Polycystic Ovaries
- Ovarian Androgen Excess
- Adrenal Androgen Excess
- LH Excess
- Insulin Excess
HYPERINSULINISM

Insulin Resistance

- PCOS  3- 11.2% female
  - 4% Males carrier
- High insulin levels
- Induces OVARIAN Testosterone
- UP-Regulates Testosterone Receptors +5AR
- Apple Obesity

- Androgen Excess Signs
  SAHA
  Acanthosis nigricans
PCOS 3.5-11.2% Reproductive Females

**Free testosterone** - Most sensitive marker

*Other markers*
- Total testosterone, DHEAS, Androstenedione,
- Free Androgen index

- >75% anovulatory infertility

- Risk PCOS First degree relatives- M & F
  - Metabolic syndrome
  - Early Diabetes 30-40%
  - Early Cardiovascular disease
  - Males Prostate cancer

Sharquie KE. Saudi Medical J. 2007;28(7):1039-43
Gorry A. Endocrine 2006;30(1):27-33
Insulin Resistance - PCOS

- High insulin levels - insulin resistance
  - Ovarian androgens/testosterone*

- Insulin Resistance
  - *Independent* of obesity
    - But obesity increases insulin resistance

- Thin women higher rate of insulin resistance
  - *Reduced SAHA signs > obese*

Atherogenic index-AGA females

- n40 F-AGA non obese women with early onset AGA vs 40 Healthy matched controls
  - Labs: total cholesterol, low density lipoprotein cholesterol and triglycerides
- Results F-AGA
  - Elevated Total Cholesterol (p<0.001)
  - LD Lipoprotein Cholesterol (p<0.03)
  - Triglycerides (p<0.008)

Conclusion

**Atherogenic index of plasma**
**Significantly higher in F-AGA > controls**

**Early onset F-AGA - unfavorable lipid profiles have increased risk of CVD**

Bakry GA et al. Atherogenic index of plasma in non-obese women with AGA. Int J Dermatology 2015;54(():e339-44
Inflammatory Markers
MPHL (AGA) increased LP(a) levels

- Case controlled study
  - MPHL and associated lipid panels, inflammatory markers, hormonal abnormalities and insulin resistance
    - 50 AGA and 50 Matched Controls

- Results
  - No significant differences (<0.05)
  - No differences for metabolic syndrome
  - AGA patients showed higher levels of fibrinogen (<p.016), CRP (P,0.019), Lipoprotein(a), (p<0.032)
    - Logistic analysis revealed only PCR >4mg/L, fibrinogen >395 mg/dl, Lp(a)>59; increased risk of CVD

- MPHL (AGA)
  - No differences in insulin resistance or Metabolic syndrome
  - **Higher incidence Cardiovascular disease characterized by increase in inflammatory markers and LP(a) levels**

Vaya A et al. Inflammatory markers and Llp(a) levels as Cardiovascular risk factors in AGA. Clin Hemorheology & Microcirculation. 2016; 61(3):471-7
PCOS
Post menopausal Women

• Hyperandrogenism - SAHA - Risk CVD
  • Common testosterone free/total
    Rarer DHEAS
    Late onset

• Hirsutism

• Insulin resistance

• Hair Loss
  • Female Pattern Hair Loss
  • Shedding

### Androgen Excess

#### Common Circulating Androgens

<table>
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<tr>
<th>DHEAS</th>
<th>Testosterone, total &amp; free</th>
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<tr>
<td></td>
<td>Androstenedione</td>
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<tr>
<td>DHT</td>
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<td>FAI</td>
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- DHEAS elevation < 50%
- Testosterone (free/total) < 20%
- Androstenedione < 5%
- Prolactin 2%
- Other androgens < 2%

<table>
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<tr>
<th>SHBG</th>
<th>FAI</th>
<th>3 a diol</th>
<th>Estradiol</th>
<th>Prolactin</th>
<th>FSH</th>
<th>LH</th>
<th>17-OH</th>
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<tr>
<td></td>
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<td>Progesterone</td>
<td>Cortisol</td>
<td>ACTH</td>
<td>Insulin</td>
<td>2 hr G TT</td>
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**Stimulation tests**
- Cortisol & Gonadotrophin
  - (increase detection by 30%)

**Combined best diagnosis**
- Androgen Excess
Anti-androgen Therapies

**Cytosol receptor Inhibition**
- Estrogen
- Progestins
- Spironolactone
- Finasteride
- Flutamide
- Corticosteroids
- Ketoconazole
- Cimitidine H2 antihistamines

**5 alpha R Inhibitor**
- Finasteride
- Dutasteride
- Estrogenic hormones
- Antiandrogens
- Anti diabetic drugs

- Nutrients
- Botanicals
- **SHBG**
  - Estrogen
- Weight loss
- Gonadotrophin antagonist
Spironolactone
Anti-Androgen - Most Common USA

- Competitive Antagonist-Mineral Corticoids Diuretic
- Nonsteroidal-Antiandrogen
  - Competitive Inhibition of 450 c receptor
  - Minor 5 ARI - inhibits conversion T to DHT
  - Progesterone activity decreases LH
- Dose 50-300 mg/d

- Pregnancy Category D
  - Fetal Teratogen

- Potassium saved
- Sodium lost
- Menstrual abnormalities
  - 75 MG
  - Oligomenorrhea
  - Amenorrhea
- Breast enlargement
  - Mastodynia
- Depressed libido
- Post menopausal bleeding
- Hirsutism

* No breast cancer BUT PDR black box
Oral Contraceptives

- **Suppress** Pituitary
  - * Gonadotrophins
- **Reduces** Ovarian androgens
  - * Testosterone
- **Increases** circulating SHBG
- **Reduces** Free Testosterone
- **Elevates** triglycerides
- **Persistent OCP greatest effect on reduction of androgens**

- **Anti - androgen**
- **Competitive p 450 cytochrome receptors**
- **Weak 5AR Inhibitor**
  
  *Avoid Androgenic progesterone*

CYPROTERONE ACETATE

• Progestin
• High anti-androgen activity

• WORLD WIDE USE
• Clinical activity = Spironolactone
• Usually combined with estrogen OC

• Teratogen-Fetal - Pregnancy Category D

• Europe: males and females treated
• Increased risk of venous thromboembolism
Hormone Replacement Therapy

**Supportive hormonal Rx**

**Enhances** Estrogen / Testosterone ratio

**Competitive** ~ androgen receptors

Dilemma: Breast Cancer Risk

Androgen excess

Estrogen / Testosterone Support Rx

- Risk = Increase - 2002 NEMJ
  - Breast cancer
  - Cardiac disease*
  - Thromboembolism
  - Hyperlipidemia*

? Should Post Menopausal women take HRT

Increased use of low dose HRT

Skin and vaginal topical estrogen use
Glucocorticoids
Rx- Androgen Excess - **Adrenal**

- Low dose HS dosing - Safe
  - Dexamethasone 0.25 mg/hs
  - Prednisone 1mg/hs
- Initially daily > pulse

  Competitive antagonist/inhibitor p 450 cytochrome receptor & steroid receptors

- Combined with antiandrogens

  *Enhanced - Longer Remissions*
Finasteride 1 mg for MPHL
FDA approved 1997

- 5 alpha reductase inhibitor type II
- Potential Fetal Teratogen- Females
- Class D

Finasteride 5 years Males

Results in decrease in serum DHT levels by about 65–70% and in prostate DHT levels by up to 85–90% - dominate isoenzyme.
Post Finasteride Syndrome

• n131 generally healthy males
• Mean age 24
• Possible post Finasteride Syndrome exists
• Reported physical symptoms/mail survey
  • Sexual libido
  • Ejaculatory disorders
  • Disorders of penis and testes
  • Cognitive symptoms
  • Psychological symptoms

Ganzer CA. Persistent sexual, emotional and cognitive impairment post-finasteride: a survey of men reporting symptoms. AM J of Men’s Health 2015; 9(3):222-8; Also FDA site
Topical Finasteride

• #2 randomized studies
  • (1) 18 M-AGA received 1 ml(2.75mg) once a day or twice a day or 1 mg po (3 arms)
  • (2) 32 M-AGA applied topical 100(0.2275 mg), 200(0.455 mg), 300 (0.6285mg) or 4k00 (0.91 mg) or vehicle x one week
  • Each study examined scalp and serum DHT and Testosterone

• Results
  • Inhibition of scalp DHT and T was seen in all active; 47-70% (70% 2.2275 mg) and in 5.6% in placebo
  • Serum DHT & T reduced 24-48%, lower-higher dose respectively

Finasteride lotion 0.25% applied daily once doses of 100-200 mul results in appropriate inhibition of scalp DHT which potentially reduces sexual adverse events linked to lower DHT

Elevated insulin levels
Increase fasting glucose
• Other
  • Hypertension
  • Low levels HDL Cholesterol
  • Hypertriglyceridemia
  • Visceral obesity-apple
  • Higher levels of CRP & Fibrinogen
    (predictive atherosclerosis)

• Study n30
  • n15 PCOS
  • n15 Controls

• Pioglitazone 5 mg/d vs Placebo
  • Improved irregular menses
  • Improved Hirsutism
  • Increased aponecint
  • Reduced insulin level
  • Reduced CRP & Fibrinogen

(randomized control study)
Finasteride 1 mg - Females

- FDA Pregnancy category D Fetal Teratogen
- Study AGA- post menopausal women #200
  - Results equal or worse then placebo

**New use in young women with SAHA**

Androgen Excess female patients - successful use in:
  - Hirsutism**
  - Alopecia
  - Acne

(Birth control is needed in the reproductive female)
Finasteride in Females

- Pregnancy Category X
- Half life 6-8 hrs  
  Wash out 6 mo
- 0.5mg/d

- More effective then lower doses
- Important to protect from pregnancy
Finasteride + OCP Rx
Patterned Hair loss Females

- #37 pre menopausal females FPHL
- Rx finasteride 2.5 mg + OCP / diospirenone + ethinyl estradiol
- Results 12 mo FU 23/37
  - 3 greatly improved
  - 8 moderately
  - 12 slightly
  - 1 worse

11/23 improved

Lorizzo, M. Arch Derm 2006;142:298-302

- #5 post menopausal females WithOUT hyperandrogenism, with AGA(FPHL)
- Rx 2.5mg & 5 mg of finasteride
- Clinical efficacy:
  Photographs+physician + patient assessments
- Results: 2.5 mg finasteride effective FPHL

Treub RM. Dermatology 2004;209(3):202-7
Dutasteride
“Avodart”

- Antiandrogen
  - Inhibitor of Type I,II - 5 alpha reductase
  - Interferes with cytochrome receptors
  - Class D-Fetal Teratogen
  - Males 1% - 2.5% sexual dysfunction
  - Dutasteride 0.5mg > Finasteride 5 mg *inhibitor of DHT*
- Primary use Prostate hypertrophy
- **Long half life 6 mo**
- Increased use in females alopecia
Dutasteride Rx MPHL

• 917n MPHL randomized: dutasteride 0.02, 0.1 or 0.5 mg /d, finasteride 1mg and Placebo
  • Measurements: Hair count, photographic assessments (investigator, panel, patient)
  • 24 week

• Results: Dutasteride 0.5mg/d significantly increased hair counts and within a 2.5 cm diameter > finasteride > placebo

Gubeline Harcha W et al. JAAD.70(3):489-498, 2014
Metformin (Glucophage)

• Treatment:
  • Insulin resistance
  • Diabetes II – Late onset

• Action
  Lower Insulin > Testosterone (ovarian)

• Dose: 500 – 1000 mg/d

• Adverse events - Lactic acidosis - gas

• Less side effects in young vs older

Mazza A et a.; In PCOS patients the addition of low dose spironolactone induces a more marked reduction of clinical and biochemical hyperandrogenism than metformin alone. Nutritional Metabolism & Cardiovascular Diseases 2014, 24(2):132-9
Statins / PCOS

Myo-inositol
• Insulin sensitizing properties
• Natural Statin (monacolin K)
• Reduced androgens
• Reduced Lipids

• Study 97n Simvastatin Metformin
• Results 6 mo
  • All groups reduced Testosterone 20-25%
  • Reduced SAHA/PCOS
  • DHEAs minor reduction

Simvastatin superior to Metformin

Comparison of spironolactone and spironolactone plus metformin in treatment PCOS

• Study 37 PCOS patients
  • Two arms 1) Spironolactone 100 mg, 2) Spironolactone 100 mg plus metformin 2000mg

• Results
  • **25.2% reduction of hirsutism, while combination 28.3% reduction  p>0.05**
  • No changes in BMI, FGS,Homa-Insulin resistance
  • In both groups hirsutism equally reduced
    • Spironolactone = Spironolacrtone + Metformin

PCOS Pioglitazone

- Elevated insulin levels
- Increase fasting glucose
- Indirect dx
  - Hypertension
  - Low levels HDL Cholesterol
  - Hypertriglyceridemia
  - Visceral obesity
  - Higher levels of CRP and Fibrinogen (predictive atherosclerosis)

- Study
  - 15 n PCOS
  - 15 n Controls
  - Pioglitazone 5 mg/d vs Placebo

- Results:
  - Improved irregular menses
  - Improved Hirsutism
  - Increased aponectin
  - Reduced insulin level
  - Reduced CRP and Fibrinogen

(randomized control study)
Androgen Excess – Obese

- Associated with PCOS
  - Elevated insulin
  - Insulin resistance
  - Increased 5RA
  - Elevated Testosterone
  - Elevated lipids
  - Increase peripheral Cortisol

• **Weight Loss**

  Insulin > Testosterone

*Weight Loss is a Treatment
Reduced calories–CHO diets or Bariatric surgery*
Weight loss
Bariatric Surgery <p.001

• Marked reduction of metabolic syndrome
• Reduced androgens
• Reduced glucose
• Reduced insulin levels (correlated with reduced androgens except DHEAS
• Reduced lipids, cholesterol and triglycerides
• Reduced inflammatory markers

Ernst B et al. Obesity Surgery. 23(5):602-7, 2013
5% minoxidil foam study

Females

Males

FDA approved 2014

Once a day application

Results With Rogaine® Foam (5% Minoxidil)

Baseline  Week 16

Baseline  Week 16

Baseline  Week 16
Novel Predictive Assay
Minoxidil response

- Topical minoxidil exhibits an excellent safety profile, but efficacy remains 30-40% in men and women with AGA - 4 months
- Minoxidil is converted by sulfotransferase enzyme SULT1A1 to its active form, minoxidil sulfate
- SULT1A1 enzyme follicle activity relates to response; increase activity increase growth
- Preliminary studies of SULT1A1 activity assay demonstrates 95% sensitivity, 73% specificity in predicting growth response

Comparison of Finasteride & Topical Minoxidil RX AGA

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Improved / regrowth</th>
<th>Regrowth lost with discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>450 M-AGA x 12 months– matched (p&gt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finasteride 1 mg n154/160</td>
<td>80.5%</td>
<td></td>
</tr>
<tr>
<td>Minoxidil 5% n122/130</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td>Combined n152/160</td>
<td>94.1%</td>
<td></td>
</tr>
</tbody>
</table>

Han Y et al. Combined treatment with oral finasteride and topical minoxidil in M-AGA; a randomized and comparative study in Chinese patients. Dermatologic Therapy 2105; 28(5):303-8
Combined therapies common
  Anti inflammatory
  Anti oxidants
  Antimicrobial
  Hair promoters
  Antiandrogens
  Hormonal
  Lipid lowering drugs
  Nutrients

Healthy skin leads to Healthy hair
Scalp and Hair Care
SAHA
*Treatment – Response expectations*

<table>
<thead>
<tr>
<th>2 months</th>
<th>3-7 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>TE ACNE HIRSUTISM</td>
<td>Alopecia regrowth</td>
<td>Alopecia regrowth Hirsutism reduced Acne stable STABLE</td>
</tr>
<tr>
<td></td>
<td>Hirsutism reduced</td>
<td></td>
</tr>
</tbody>
</table>

Improvement of laboratory parameters (androgens) if abnormal- 4-6 mo
Topical Rx
Increase and prolong anagen cycle

Growth Promotion
Anti-inflammatory
Antiandrogens
Hormones
Nutrients
Healthy scalp skin, Healthy Hair
Reduction of oxidative stress

• Antimicrobial and anti-inflammatory
  • Ketoconazole, Zinc pyrithione - <50% hair growth compared to minoxidil

• Anti-inflammatory and antiandrogen
  • Zinc, green tea

• Antiandrogen
  • Botanicals, ie. Saw Palmetto

Berger RS et al, Therapeutics, Brit J Dermatol
2003;149:354-364
Adjuvant Treatments

- Anti-inflammatory
  - Anti oxidants
- Immune modulators
- Anti-microbial
- Hormonal
  - Estrogen/Progest
  - Antiandrogen
- Hair Growth Promoters – Minoxidil
- New Prostaglandin I
- Nutrient support

- Nutrients
  - Antioxidants
  - Vitamins
  - Minerals
  - Protein

- Weight Control
- Camouflage
- Low light laser
- PRP
- Stem cells
- Surgery
Laser low light

Initiation or prolongation of anagen of Hair Growth

Reverse on set of catagen
Alopecia areata
Alopecia Areata with Tofacitinib citrate: Cleveland Clinic Experience
Alopecia Areata (AA)

- Autoimmune condition
- T-cell mediated
- Cytotoxic T-cells attack hair follicle
- IL-15 upregulated and propagates expansion of cytotoxic T cells

Tofacitinib citrate

- Janus kinase (JAK 1/3) inhibitor
- Blocks downstream signaling of IL-15
Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition

Luzhou Xing¹,⁷, Zhenpeng Dai²,⁷, Ali Jabbari²,⁷, Jane E Cerise²,³, Claire A Higgins², Weijuan Gong², Annemieke de Jong², Sivan Harel², Gina M DeStefano²,⁴, Lisa Rothman², Pallavi Singh², Lynn Petukhova², Julian Mackay-Wiggan², Angela M Christiano²,⁵,⁹, and Raphael Clynes¹,²,⁶,⁸

Killing Two Birds with One Stone: Oral Tofacitinib Reverses Alopecia Universalis in a Patient with Plaque Psoriasis

Journal of Investigative Dermatology (2014) 138, 2988–2990; doi:10.1038/jid.2014.260; published online 17 July 2014
CCF Tofa Jak 1/3 Protocol

Efficacy & Safety Tofacitinib Treatment Moderate to Severe AA

• Disease duration

• Treatment history

• Comorbidities:
  • Thyroid
  • Diabetes
  • Rheumatoid arthritis,
  • Other autoimmune disease

• Record: % hair loss of all sides of scalp (top, posterior, bilateral sides)
  • Eyelashes, eyebrows, body hair
  • Nails
  • Baseline photos
Laboratory Monitoring

Baseline
- CBC
- CMP
- Lipid panel
- Hepatitis panel
- HIV
- TB test
- Physical exam
- Photographs

Follow up
- Monthly visits x 2-3 mo
  > every 3-4 mo
- Repeat labs
  - CBC, CMP, Lipid panel
- Physical exam
- Photographs
- Titrate medication as needed
Treatment:

- Tofacitinib citrate 5 mg orally, twice daily (10 mg)

- Titrate dose monthly depending on patient’s response, tolerance, side effects
CCF Results Initial 13 patients

Moderate to Severe Alopecia areata treated with Jak 1/3 (Tofacinamib)

Experience now 2 years and 27 patients
Patients treated > 3 mos
(now 2 years follow up)
Photos
<table>
<thead>
<tr>
<th>Patient #</th>
<th>Sex</th>
<th>Age</th>
<th>Prior failed therapies</th>
<th>Disease duration (years since first diagnosis of AA)</th>
<th>Months until first signs of hair growth</th>
<th>Duration of therapy (months)</th>
<th>Holding dose (mg/day, split twice daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>20s</td>
<td>TC, ILC, MTX, DPCP</td>
<td>16</td>
<td>5</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>20s</td>
<td>TC, ILC</td>
<td>5</td>
<td>-</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>30s</td>
<td>MTX, Infx, TC, DPCP</td>
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<td>4</td>
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<td>15</td>
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<tr>
<td>4</td>
<td>F</td>
<td>30s</td>
<td>ILC, TC, DPCP, minoxidil</td>
<td>13</td>
<td>-</td>
<td>0.5</td>
<td>-</td>
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<tr>
<td>5</td>
<td>F</td>
<td>40s</td>
<td>ILC, TC, minoxidil, DPCP, anthralin</td>
<td>35</td>
<td>1</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>50s</td>
<td>ILC, TC, minoxidil, DPCP, anthralin</td>
<td>18</td>
<td>3</td>
<td>6</td>
<td>10</td>
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<tr>
<td>7</td>
<td>F</td>
<td>50s</td>
<td>ILC, TC, minoxidil, DPCP, excimer</td>
<td>30</td>
<td>3</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>50s</td>
<td>ILC, TC, minoxidil, DPCP</td>
<td>54</td>
<td>9</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>50s</td>
<td>ILC, TC, minoxidil, DPCP</td>
<td>11</td>
<td>2</td>
<td>4</td>
<td>25#</td>
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<tr>
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<td>50s</td>
<td>ILC, TC, minoxidil, DPCP</td>
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<td>4</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>50s</td>
<td>ILC, TC, minoxidil, DPCP, MTX</td>
<td>15</td>
<td>3</td>
<td>9</td>
<td>20</td>
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<tr>
<td>12</td>
<td>F</td>
<td>50s</td>
<td>SC, TC, Cys, Infx, squaric acid</td>
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<td>9</td>
<td>13</td>
<td>20</td>
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<tr>
<td>13</td>
<td>F</td>
<td>60s</td>
<td>ILC, TC, minoxidil, DPCP, anthralin</td>
<td>6</td>
<td>3</td>
<td>7</td>
<td>20</td>
</tr>
</tbody>
</table>

   Mean   18   4.2   6.4   15.8
Table 1: The treatment of alopecia areata with oral tofacitinib, cont.

<table>
<thead>
<tr>
<th>Patient #</th>
<th>Scalp₀ (SALT)</th>
<th>Percent regrowth</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100% (AU)</td>
<td>4 90%</td>
<td>10%</td>
</tr>
<tr>
<td>2</td>
<td>100% (AU)</td>
<td>1.5 100%</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>100% (AU)</td>
<td>3 98%</td>
<td>2% Liver enzyme abnormalities*</td>
</tr>
<tr>
<td>4</td>
<td>100% (AT)</td>
<td>1 -</td>
<td>- Rash, peripheral edema**</td>
</tr>
<tr>
<td>5</td>
<td>79.30%</td>
<td>- 40.00%</td>
<td>50%</td>
</tr>
<tr>
<td>6</td>
<td>78.30%</td>
<td>- 39.60%</td>
<td>49%</td>
</tr>
<tr>
<td>7</td>
<td>100% (AU)</td>
<td>1 10%</td>
<td>90%</td>
</tr>
<tr>
<td>8</td>
<td>100% (AU)</td>
<td>7 40.10%</td>
<td>60% Lipid abnormalities***</td>
</tr>
<tr>
<td>9</td>
<td>71.60%</td>
<td>- 35%</td>
<td>51%</td>
</tr>
<tr>
<td>10</td>
<td>100% (AT)</td>
<td>2 30.80%</td>
<td>69%</td>
</tr>
<tr>
<td>11</td>
<td>76%</td>
<td>- 15.00%</td>
<td>80%</td>
</tr>
<tr>
<td>12</td>
<td>100% (AU)</td>
<td>7 35.40%</td>
<td>65%</td>
</tr>
<tr>
<td>13</td>
<td>100% (AU)</td>
<td>3 95%</td>
<td>5%</td>
</tr>
<tr>
<td></td>
<td>92.70%</td>
<td>3.3 52.40%</td>
<td>44.30%</td>
</tr>
</tbody>
</table>
Patient 1

Pre

Current dose: 10 mg BID (20 mg), **Duration of therapy:** 10 mo
Age: 53, **Duration of disease:** 7 yrs

Post

Mild Response
Patient 3

Current dose: 10 mg BID (20 mg), *Duration of therapy: 7 mo*

Age: 61, *Duration of disease: 5 yrs*

Mild Response
White hair
Patient 3

Pre                   Post

Current dose: 10 mg BID (20 mg), **Duration of therapy: 7 mo**
Age: 61, **Duration of disease: 5 yrs**

Mild Response
Regrowth
Eyebrows
Lashes
Patient 4

Pre                   Post

Current dose: 5 mg BID (10 mg), **Duration of therapy: 3.5 mos**  
Age: 44, **Duration of disease: 34 yrs**

Moderate Response
Patient 4

Current dose: 5 mg BID (10 mg), Duration of therapy: 3.5 mos
Age: 44, Duration of disease: 34 yrs

Moderate Response
Patient 4

Pre                  Post

Current dose: 5 mg BID (10 mg), Duration of therapy: 3.5 mos
Age: 44, Duration of disease: 34 yrs

Moderate response
Patient 5

Pre                   Post

Current dose: 15 mg AM and 10 mg PM (25 mg), **Duration of therapy:** 7 mos, Age: 36, **Duration of disease:** 7 yrs

Mild Response
Patient 5

<table>
<thead>
<tr>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
</table>

Mild response- regrowth of eyebrows/lashes

Current dose: 15 mg AM and 10 mg PM (25 mg), Duration of therapy: 7 mos, Age: 36, Duration of disease: 7 yrs
Patient 6

Current dose: 10 mg BID (20 mg), **Duration of therapy:** 7 mos,
Age: 55, **Duration of disease:** 7 yrs

Mild Response*

*nails
Patient 6

Pre                   Post

Mild response*

Current dose: 10 mg BID (20 mg), Duration of therapy: 7 mos, Age: 55, Duration of disease: 7 yrs
Patient 7

Pre  Month 5  Month 6

Current dose: 5 mg BID (10 mg), Duration of therapy: 5 mos discontinued
Age: 53, Duration of disease: 30 yrs

Excellent response  No response 2mo off therapy
Patient 7
Pre    Month 5    Month 6

Excellent response    No response

Current dose: 5 mg BID (10 mg), **Duration of therapy: 5 mos**
Age: 53, Duration of disease: 30 yrs
Patient 8

Pre  Post

Current dose: 10 mg AM and 15 mg PM (25 mg), **Duration of therapy: 7 mos**
Age 54, **Duration of disease: 15 yrs**

Moderate Response
Patient 8

Pre                   Post

Current dose: 10 mg AM and 15 mg PM (25 mg), Duration of therapy: 7 mos
Age 54, Duration of disease: 15 yrs

Moderate response
Adverse Events:

• Two patients: URIs - mild

• One patient: rash, severe lower extremity edema

• One patient: mild elevation in creatinine and lipids (hyperlipidemia)

• New one patient with Herpes Zoster 2017
Summary

• 10/13 patients
• 7 treated > 3 mos
• 6/7 experienced regrowth
• Ranged ~ mild to excellent
• Response time: 1 – 9 months
• 1 serious AE- discontinued
• Hair growth 2-90%, mean 29%  (p<0.006, CL: 10.4-47.76)
• 4 patients (33.3%) regrowth 29% - excellent response
• 6 patients (50 %) regrowth >50%  Salt 50
• 3 patients (16.7%) no growth
Summary of follow up

• 10/13 patients remained on therapy with 54% regrowth in 44% of patients treated.

• Minimal side effects:
  • Rash, leg edema (1) discontinued
  • Lipid abnormalities managed - (2) patients
  • Two Patients lost insurance and lost all hair - 2 months
  • 36% patients noted increased body hair
  • One patient had reversal of onychodynia & nail dystrophy
Summary

• 13 patients with severe recalcitrant (10/13) AA/AT/AU treated Tofa
• Mean duration of AA – 18 years
• Dose: oral Tofacitinib 10- 25 mg/day
  • 10 mg dose had 54% regrowth in 44%
    • 7 patients - average time for regrowth 4.2 months
    • Range 1-9 mo for regrowth
Additional #14 patients since initial report 13 patients

5/14 no growth > 6mo
4/14 Mild – Moderate
5/14 Excellent regrowth
Total: 9/14 responded

Similar Adverse events- hyperlipidemia, minor infections

Currently all 27 patients under review outcomes 2016-2017
Regrowth eyebrows and lashes and some body hair
AD: Hyperlipidemia
Excellent Response

2/25/2015
Current dose: 20 mg/D
Age 55/PCOS

10/24/2016
Duration of therapy 10 mo
Duration of disease 25 years
11/23/2015
Current dose: 30 mg/D
Age: 22 /Psoriasis/PCOS

10/17/2016
Duration of therapy: 11 mo
Duration of disease: 7 years

Moderate response
AD: Hyperlipidemia
Excellent Response- flare RA- AU

1/4/2016
Current dose: 30 mg/D
Age: 56, RA

8/17/2016
Duration of therapy: 9 mo
Duration of disease: 9 years
Current dose: 10 mg/D
Age: 49/ PCOS

Duration of therapy: 12 mo
Duration of disease: 2 years

Excellence Response
12/9/2015
Current Dose: 20 mg/D
Age: 38

10/31/2016
Duration of therapy: 12 mo
Duration of disease: 2 yrs

Excellent Response
• Alopecia areata as a multi organ disease
  • High association with Atopy, Diabetes I, RA, Celiac disease- Inflammatory T cell diseases
  • Autoaggressive inflammatory disease
    • Loss of immune privilege
      • Role of down regulation MHC class I molecules, IP guardians (a- mSSH, TGFB2, IGF1) and NKG2D with up regulation CD8 suppressor cells

• Up reguation of immunosurvellance gamma/delta T cells-recognize distressed HF- induction catagen HF
AA & oral ruxolitinib (Jak I ½)
Columbia study 2016

- AA mod- severe #12n
  - Ruxolitinib 20 mg BID (40 mg)- 3-6 mo and 3 mo follow up
  - Endpoint Salt50 (50% response)
- 9/12 (75%) marked response 92%
- Biomarkers – revealed improvement
  - Gene expression profile- Treated-response group
    - Down regulation of inflammatory markers, CTLs and IFN response genes
    - Up-regulation of hair specific markers

JCI 2016
### Adults #90
- 65/90 responders AT/AU- +/- 10 y
- 77% clinical response
- 58% greater 50% response
  - Change Salt score
- 4-18 mo

### Adolescents (12-17) #13
- 9/13 responders
  - Change Salt score
    - Median 93%
      - (1-100%, mean 61%)
- Average 6.5 mo

Well tolerated with no significant Adverse Events
Results: AA/Tofa 10mg/day x 3 mo – open label

#66 AA, AT, AU, AO (mod-severe)

- 32% with 50% regrowth
- AA & AO (ophiasis) best responders

- Bx: peribulbar inflammation better responders

- Adverse events limited to grade I/II infections

- Drug discontinuation- loss of hair 2.5 mo
• #12, mean age 48. males>females
  • Topical Jak1/3 phosphate cream BID
  • Mean base line Salt score 56.2 (greater 50% loss)
  • 6mo results: Reduction of Salt score 26.7 (improvement 72%)
  • 9/12 had at least one AD
    • Grade 1- #3 - folliculitis, vulvar yeast, pruritus, dry skin, scaling
    • Grade 2- #2- non cardiac chest pain, sepsis
    • Grade 3 #! Pulmonary mass
    • Worsening of anxiety #1
  • Phase 3 studies underway
  • (CCF study completed)
New targets

- Mast cells & eosinophils (when present worse prognosis)
- PD-1 receptors – blockade enhances hair growth
- Identification of new signaling pathways- heterogeneous disease and associated with other Th1, Th2 diseases
- TCRReceptor sequences - targets
  - Vbeta12 (most widely expressed –CD8 cella
- Identification of commensal microbes / HF morphogenesis that drive Treg migration in neonatal skin
- Nutritional influence - low zinc associated - resistant AA
Future studies will define Jak I therapies and cytokine pathways

• Improvement independent of age, disease severity, and disease duration ???

• Why are results variable?
  - AA is multifactorial? Multiple inflammatory pathways, Th1, Th2
  - Under-dosing? Variable response
  - Severity/type of disease?
  - Co-morbidities? Co-existing inflammatory disease(s)

• Genetic- positive family history
  - Treatment duration- ? Intermittent , continuous

• Durability of treatment response /on & off tofa ?
Future Directions

• Action for Alopecia areata- at least 5 companies developing Biologics
  • Topical JAK-inhibitors
  • New JAK-inhibitors (Jak I1/2, Jak I 1/3)

• Variable response ? Other pathways important

• Future applications of JAK inhibitors:
  • Atopic dermatitis, vitiligo, psoriasis
Thank You