Systemic and Novel Management of Alopecia Areata in Children

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S006 - Treating Severe Skin Disease in Children
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Alopecia Areata

Autoimmune non-scarring alopecia
US Lifetime risk: 2%
- Prevalence 0.1-0.2% of general population
- No gender predilection
- Pediatric prevalence higher than adults vs. peak in 2nd to 3rd decade
Most Alopecia Areata (AA) presents as localized patches of non-scarring alopecia

Alopecia Areata: Prognosis

Course unpredictable:
- Up to 50% improve spontaneously within 1 year
- 8% for extensive disease (>50% scalp involvement)
- 68% for limited disease (<25% scalp involvement)
- 5% develop Alopecia Totalis (AT) or Alopecia Universalis (AU) or overlap

Alopecia Areata: Pathogenesis

Exact trigger not known:
- Genetic and environmental factors play a role
Collapse of immune privilege in hair follicle
Cytotoxic NK T-cell infiltration
- Histologic “Swarm of Bees”
Inflammatory attack on the hair bulb forces hair follicle out of anagen into catagen

Alopecia Areata: Treatment Algorithm

Consider age, extent of involvement, years since onset, effect on child and family,
response to initial therapies
Address quality of life
Address no treatment, support groups/counseling, hair prosthesis


DISCLOSURES
I do not have any relevant relationships with industry.
*Off-label use of medications will be discussed.
Alopecia Areata: Treatment
- Topical steroids +/- minoxidil
- IL TAC
  - 2.5 mg/ml TAC same benefit as 5 or 10 mg/ml
  - 2.5mg/ml, adult max 8 ml, eyebrows <0.5ml each eyebrow
- Side effects: atrophy, HPA axis suppression. Caution eyebrows: small risk increased intraocular pressure, glaucoma, cataracts.
- Topical immunotherapy


Alopecia Areata: Methylprednisolone Pulse Therapy
- Retrospective review
  - 19 children with severe AA < 17 years (range 2.1-16.5 years)
  - 2-3 cycles of IV methylprednisolone pulse therapy (IV-MPPT) monthly intervals (maximum 500 mg/day on 3 consecutive days)
- Results:
  - 10/18 good response (>75% regrowth)
  - 1 moderate response (50-74% regrowth), 3 poor response (<49% regrowth), 4 (with AT or AU) had no response.
  - 7 of 10 good responders relapsed with marked hair loss after last IV-MPPT session. Median time to relapse was 8 months.
- Conclusion: “IV-MPPT, even early in the course of disease, did not affect long-term outcome of alopecia areata in our group of severely affected patients.”


Efficacy and Tolerability of Methotrexate in Severe Childhood Alopecia Areata
- Retrospective review
  - >50% hair regrowth in 5 out of 14 children (age 8-18 yrs) with severe AA who were treated with MTX 15-25 mg/week.
  - No serious side effects were reported.


Methotrexate for the Treatment of Pediatric Alopecia Areata
- Retrospective review of 14 children
  - 8/14 (57%) good regrowth
  - 3/14 could not be assessed
- Conclusion: “This review suggests that methotrexate is a generally safe and often effective medication in pediatric alopecia areata.”


Alopecia Areata: Genetic Basis
- 2010 Genome-Wide Association Study (GWAS)
  - 1,054 patients from National Alopecia Areata Registry
  - 8 regions of the genome identified as significantly associated with AA


GWAS in Alopecia Areata: Manhattan Plot
- Highest peak: HLA
- Second highest peak: ULBP3/ULBP6
  - ULBP gene function: NKG2D-activating Ligand
  - Stress-induced “danger signals”
  - Attract NK, NKT, CD8+ T cells

Swarm of Bees:
NKG2DL “Danger signal”
Killer CD8+ T cells attracted
2010 “Swarm of Bees” identified

GWAS:
Genes with Significant Associations to AA
- Shared mechanism: NK Ligand in the end organ:
  - Type 1 Diabetes
  - Rheumatoid Arthritis
  - Celiac Disease


Genetic studies led to translational research and new clinical approaches to treatment

Alopecia Areata Reversed by JAK Inhibition
- Preclinical studies:
  - Cytotoxic CD8+NKG2D+ T cells are both necessary and sufficient for the induction of AA
  - JAK inhibition reverses AA, prevents AA
- Clinical study: 3 patients
  - Oral ruxolitinib, JAK1/JAK2 inhibitor
  - Near-complete hair regrowth within 5 months of treatment.


Breaking News:
“RA Drug Treats AA”
- 25 year old with Psoriasis and Alopecia Universalis
- Tofacitinib 5 mg po BID x 2 months, then increased to 10 mg, 15 mg x 3 months
- Complete hair regrowth


What are JAKs?
- Janus kinase (JAK) family of proteins:
  - JAK1, JAK2, JAK3, JAK4, Tyk2
- Involved in transcription of cytokine signaling inside the cell
  - Alopecia Areata: IL-15 and IFN-γ

O’Shea, Immunity 2012.
**Tofacitinib**

- JAK1/3 inhibitor (pan JAK)
- FDA approved in 2012 for Rheumatoid Arthritis treatment in adults
  - 5 mg po BID, or 11 mg XR
- Clinical trial open for Pediatric JIA age 2-17 yrs
- Black box warning:
  - Lymphoma
  - Immunosuppression: r/o TB, hepatitis prior to treatment

**JAK Inhibitor Tofacitinib for AA**

- 66 adults, AA >50%, AT, AU
- Tofacitinib 5 mg po BID x 3 months
  - 32 experienced >50% improved SALT score
  - AA and ophiasis subtypes responded better than AT/AU


**JAK Inhibitor Tofacitinib for AA**

- 90 adult patients, retrospective review
  - Tofacitinib 5 mg BID x 2-3 months
  - Then 57% went on to 5 mg BID
  - +/- pulsed prednisone (300 mg monthly x 3 months)
- Observations:
  - 50% >50% SALT score improvement over 4-18 mos
  - Duration of AT/AU > 10 years less likely to respond


**Ruxolitinib**

- JAK1/JAK2 inhibitor
- FDA Approved Indications:
  - Myelofibrosis (approved in 2011)
  - Polycythemia Vera (approved in 2014)
- Warnings include:
  - Infections
  - Progressive Multifocal Leukoencephalopathy (PML)

**JAK Inhibitor Ruxolitinib for AA**

- 9/12 patients experienced significant regrowth
- Post-treatment follow up: hairloss recurred in the months following therapy

Mackay-Wiggan J et al, JCI Insight 2016;1(15):e89790

**Alopecia Areata Disease Activity Index: ALADIN**

- Biomarker tool for tracking disease severity and response to treatment
- 3 dimensional quantitative composite gene expression score
- Can you predict non-responders prior to therapy?
  - Non-responders marked similar to control patients without AA

Pediatric Alopecia Areata: Off-label Use of Jak Inhibitors

Tofacitinib for Severe Alopecia Areata in Adolescents
- 13 adolescent patients with AA, AT, AU
- Age 12-17 years
- Retrospective review
- Tofacitinib 5 mg po BID
  - one increased to 10mg/5 mg
- 9 experienced significant hair regrowth
- Adverse events were mild

Tofacitinib for Alopecia Universalis in Adolescents
- 8 adolescent patients with AU
- Age 12-19 yrs
- Tofacitinib 5 mg po BID x 5-18 months
- All had slow but significant regrowth first 3 months, followed by more rapid regrowth
  - Mean 58% improvement in SALT score at 6 mos
  - 52-78% percent improvement in SALT score at 12 mos

Topical JAK Inhibitors
- Clinical trials in adults
  - Psoriasis: topical tofacitinib 1%
  - Atopic Dermatitis: topical tofacitinib 2%
    - Bissonette et al. Br J Dermatol 2016;175, 902-911
  - Vitiligo: INCB018424 cream
  - Alopecia Areata: topical tofacitinib, topical ruxolitinib

Topical JAK Inhibitors
- 6 pediatric AA, AU, AT patients
- Age 3-17 years
- Topical Tofacitinib 2% liposomal base
  - One pt no response Versabase, responded to liposomal base
- Topical Ruxolitinib 1-2% liposomal base
  - 4/6 experienced some hair regrowth
  - 2 pts had 80-95% regrowth

Topical JAK Inhibitor: Alopecia Areata
- Case report
  - Teenage girl with AU
  - Ruxolitinib 0.6% cream
    - Compounded
  - Significant hair regrowth of eyebrows
  - Regrowth 10% of scalp hairs
  - Small decrease in WBC count 3,800/μL over 12 weeks of treatment

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JAK Inhibitor Cost?
- Tofacitinib $3,800/month
- Ruxolitinib $10,000/month

Take Home Points:
- Knowledge regarding the genetic basis of alopecia areata is increasing and leading to translation clinical research.
- Jak inhibitors show promise in the treatment of off-label treatment of alopecia areata.
- We need more clinical trials for safe and effective treatments for our pediatric patients with AA!