Alopecia areata: Workup and treatment

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DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

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Symposium S042: Alopecia: Work-up and Treatment

02/18/2018, 1:00-4:00 pm

DISCLOSURES

I do not have any relevant relationships with industry.

I will be discussing off-label uses of medications.
Introduction

- Common non-scarring patchy alopecia
- Lifetime risk estimated at 2.1%
- Estimated to comprise 0.7-4% of all patients seen by dermatologists
- Autoimmune cell-mediated process thought to be due to loss of immune privilege of the anagen hair follicle
- Genetic polymorphisms have been identified in some populations
Background

• Worse prognosis: extent of hair loss, age at onset (younger), family history, ophiasis subtype

• Approximately 5% of cases of patchy AA progress to AT/AU (Safavi et al, 1995)

• Spontaneous resolution is common, but so is relapse.

• However, one series showed that about 2/3 (67%) with <25% scalp involvement at presentation had complete resolution at a mean of 17 years. (with or without treatment) (Tosti et al, 2006)
Background (cont)

- Incidence may be increasing like other autoimmune diseases
- Appears to be equal across races and ethnicities
- Mean age of onset in the 30s, but can occur at any age

Overview

• Epidemiology
  • Health-related quality of life
  • Comorbidities

• Treatment
  • JAK inhibitors – oral/topical
  • Other immunomodulators
  • Updated information on traditional treatments
New pediatric data

- Two studies showed female predominance of AA in children
  - One was practice based – 1.25:1, f:m (p=0.004)
  - The other based on the national registry -1.5:1, f:m (p<0.001)
    - Boys had higher likelihood of severe disease (p=0.009)
    - Congenital AA in 0.04% of patients
  - Possible selection bias.
- 25% of children had positive family history, 8% with at least three affected first degree relatives

Alopecia Areata Registry, Biobank & Clinical Trials Network
Health-related quality of life (HRQOL)

• Measure of physical, mental, emotional, and social functioning

• Rencz et al (2016) and Liu et al (2016) reviewed HRQOL studies in AA

• Overall, there is significantly reduced HRQOL in emotional, mental health, and vitality domains.

• Wearing a wig has a positive impact on HRQOL and scalp involvement, anxiety and depression have a negative impact.

• HRQOL in AA is comparable to psoriasis and atopic derm


HRQoL in families

- Impairment of QoL in children and adults with AA
  - 91 children with AA, 292 adults with AA, 229 family members
  - About 50% with small to no effect on QoL
- Family members also with impaired QoL
  - Not as severe as atopic derm, but comparable to psoriasis
  - Families of children more impacted than those of adults
  - Parents more impairment of QoL than their affected children
- Adults tried 2.9 +/- 1.4 medical therapies, children 2.1 +/- 1.4 (including medications and procedures)
  - 37.9% tried alternative therapies

Comorbidities

• Atopy (especially atopic dermatitis and allergic rhinitis)
  • But asthma similarly associated in children with AA
• Thyroid disease – *particularly in adults*
• Autoimmune disorders
  • Systemic lupus – *particularly in younger patients*, vitiligo, psoriasis
• Psychiatric disorders
  • Depression, anxiety

Thyroid screening in children

• Patel et al (2017) performed a retrospective analysis of 298 patients (ages 0-21) who had AA and thyroid function testing

• 59 (20%) had abnormalities on thyroid tests

• Significant associations with Down syndrome, atopy, family history of thyroid disease.

• No association with age, duration of disease, pattern of alopecia, and diagnosis of other autoimmune disease
New data regarding co-morbidities

• Big data/precision medicine to find co-morbid conditions may be helpful in elucidating mechanism of disease and finding unexpected treatments.

• Lim et al (2018) looked at three different large databases, an EHR, a phenome-wide analysis (using genomic data) in both humans and mice (C3H/HeJ mouse model)

  • Immune-related, neuropsychiatric, and metabolic conditions found to be associated, including known and new associations

### Table 1. Alopecia areata comorbidities suggested by big data

<table>
<thead>
<tr>
<th>Disease/Trait Category</th>
<th>ICD Co-occurrence (Rzhetsky et al. 2007)</th>
<th>PheWAS (phewascatalog.org)</th>
<th>C3H/HeJ (phenome.jax.org)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune</td>
<td>Rheumatoid arthritis</td>
<td>Rheumatoid arthritis</td>
<td>Prone to colitis</td>
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<tr>
<td></td>
<td>Multiple sclerosis</td>
<td>Multiple sclerosis</td>
<td>Thyroid hormone abnormalities</td>
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<td></td>
<td>Systemic lupus Erythematosus</td>
<td>Systemic lupus Erythematosus</td>
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<td></td>
<td>Type 1 diabetes mellitus</td>
<td>Type 1 diabetes mellitus</td>
<td></td>
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<tr>
<td></td>
<td>Psoriasis</td>
<td>Psoriasis</td>
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<td></td>
<td></td>
<td>Ulcerative colitis</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Grave’s disease, Thyroiditis</td>
<td></td>
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<tr>
<td>Inflammatory Metabolic</td>
<td>Allergic rhinitis</td>
<td>Allergic rhinitis</td>
<td>Elevated total cholesterol</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity angiitis</td>
<td>Asthma</td>
<td>Elevated phospholipids</td>
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<tr>
<td></td>
<td>Disorders of lipid metabolism</td>
<td>Disorders of lipid metabolism</td>
<td>Decreased circulating alanine transaminase</td>
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<tr>
<td></td>
<td>Type 2 diabetes mellitus</td>
<td>Type 2 diabetes mellitus</td>
<td>Elevated heme oxygenase</td>
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<tr>
<td></td>
<td>Cholelithiasis</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>AA metabolism (aromatic)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Acanthosis nigricans</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>Attention deficit disorder</td>
<td>Attention deficit disorder</td>
<td>Prone to impulsivity, anxiety</td>
</tr>
<tr>
<td></td>
<td>Epilepsy</td>
<td>Epilepsy</td>
<td>Absence seizures (Gria&lt;sup&gt;qbeta&lt;/sup&gt;)</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td></td>
<td>Attenuated response to tactile and thermal stimulation</td>
</tr>
<tr>
<td></td>
<td>Bipolar disorder</td>
<td></td>
<td>Disruptions in social behavior</td>
</tr>
<tr>
<td></td>
<td>Migraine</td>
<td></td>
<td></td>
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<tr>
<td>Cardiovascular</td>
<td>Atherosclerosis</td>
<td></td>
<td>Abnormal ECG findings</td>
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<tr>
<td></td>
<td>Myocardial infarction</td>
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<td></td>
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<tr>
<td></td>
<td>Blood pressure</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Heart failure</td>
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</tr>
</tbody>
</table>

Three datasets were queried to identify conditions and traits that could be associated with AA. The table reports only conditions related to the four categories of focus in our commentary. Additional traits may be found in each source. ICD co-occurrences were identified in an analysis of 161 ICD codes in 1.5 million patient records (Rzhetsky et al, 2007). We identified 28 SNPs associated with AA in our recent meta-analysis in the PheWAS catalogue and extracted all reported ICD code associations. For the C3H/HeJ, we manually curated a list of all traits for which this strain was reported to be an outlier.
Lipid metabolism and cardiovascular risk

• Lim et al (2018) found that women with AA had an elevated LDL level compared to controls, but not men.
• Kang et al (2015) found risk of stroke within 3 years of AA diagnosis was increased independent of hyperlipidemia, hypertension, and heart disease.
• However, Huang et al (2016) found decreased odds of ischemic stroke and a trend toward decreased risk of acute myocardial infarction.

Vitamin D in AA

• Some retrospective analyses have shown an association between low vitamin D (25OH) levels and alopecia areata, some showing an association with severity.

• Meta-analysis of these studies does also support an association between vitamin D deficiency and alopecia areata

  • 1, 25 dihydroxyvitamin D inhibits Th1 cytokine secretion

  Thompson et al, Arch Dermatol Res 2016;308: 671-676
Cancer risk in AA

- Negative association with squamous cell carcinoma and basal cell carcinoma with trend for melanoma
- Possibly related to genetics that confer immunologic advantage
- The costimulatory pathway which has been identified in GWAS studies for AA has been targeted to treat melanoma.
- Thyroid cancer appears to be increased in AA, but decreased risk was found in a Korean population for breast, colorectal, stomach, liver, and lung cancer
  - A smaller study in the US did not find an association between AA and systemic malignancy

Summary of epidemiology studies

- For pediatric patients, focus screening for thyroid disease on those with Down syndrome, atopy, family history of thyroid disease, or signs or symptoms of thyroid disease.

- Consider screening for vitamin D deficiency
  - new definitions for vitamin D deficiency (<20 ng/ml considered inadequate and 20-50 ng/ml considered adequate)

- Big data may be helpful in AA

- Associations with malignancy or lipids may be present
Treatment and management

• JAK inhibitors are promising
• Other biologics (ustekinumab, apremilast, abatacept) less promising
• Simvastatin/ezetimibe – mixed results
• Platelet rich plasma therapy and microneedling
• Contact immunotherapy
• Support and counseling
Janus kinase inhibitors

• Ruxolitinib = Jakafi (~$12,000 for 30-day supply) = JAK1/JAK2 inhibitor
  - Approved for use in myelofibrosis in 2011, polycythemia vera in 2014
  - 20 mg twice daily

• Tofacitinib = Xeljanz (~$4,000 for 30-day supply) = pan-JAK inhibitor
  - Approved for use in rheumatoid arthritis in 2012, psoriatic arthritis in 2017
  - 5 mg twice daily, in AA, may require 10 mg twice daily
  - Extended release now available – 11 mg daily

• At least 10 others in clinical trials, plus deuterated compounds, and 1 approved for use in dogs for eczema
JAK inhibitors in AA

• Most data on tofacitinib, ranging from 5-10 mg twice daily
  • Small study on ruxolitinib 20 mg twice daily
  • Initial response often seen within 3 months
  • Combination with pulsed corticosteroids may be helpful
  • Relapse within 2-6 months, with mild relapse when dose is reduced
  • Few adverse effects reported, including in adolescents.

# Summary of JAK inhibitor data

<table>
<thead>
<tr>
<th>Authors</th>
<th>Drug</th>
<th>Dose</th>
<th>%pts with SALT 50</th>
<th>timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mackay-Wiggan, J., et al. (2016)</td>
<td>Ruxolitinib</td>
<td>20 mg BID</td>
<td>75% (n=9/12)</td>
<td>4-6 mos</td>
</tr>
<tr>
<td>Kennedy Crispin, M., et al. (2016)</td>
<td>Tofacitinib</td>
<td>5 mg BID</td>
<td>32% (n=21/66)</td>
<td>3 mos</td>
</tr>
<tr>
<td>Liu, L. Y., et al. (2017)</td>
<td>Tofacitinib</td>
<td>5-10 mg BID +/- pulsed pred</td>
<td>58% (n=37/65)</td>
<td>4-18 mos</td>
</tr>
<tr>
<td>Craiglow BG, et al (2017)</td>
<td>Tofacitinib (in adul, n=14)</td>
<td>5 mg BID</td>
<td>n/a (71% pts mean SALT88)</td>
<td>2-16 mos</td>
</tr>
<tr>
<td>Park H-S, et al (2017)</td>
<td>Tofacitinib</td>
<td>5 mg BID</td>
<td>56.3% (n=18/32)</td>
<td>3 mos</td>
</tr>
</tbody>
</table>
Topical JAK inhibitors

• **Tofacitinib 2% ointment:**
  - 3/10 adult patients over 6 months with regrowth with mean 34.6% SALT score improvement.

• **Tofacitinib 2% or ruxolitinib 1-2% cream**
  - 4/6 pediatric patients had some growth, some with eyebrow, lash growth and scalp 85-90% improvement (3 months to 18 months of treatment); lipodermal base seems best.


Off-label use

- CBC, CMP, Hep B, Hep C, HIV, Quantiferon gold (or PPD), lipids, CXR possibly
  - CBC, CMP, lipids 4-6 weeks after first dose, then q3 months
- 5-10 mg twice daily, or extended release 11 mg 1-2 times daily
- Photos at baseline and each follow up; SALT score
- Consider intralesional, intramuscular, or oral corticosteroids
- Adverse effects: diarrhea, headaches, other GI side effects. Liver function abnormalities, infection, possible malignancy, bowel perforation. Long term risk largely unknown.
Considerations

• Very difficult to obtain coverage from insurance, though new data may be helpful

• May require longer term treatment. Combination treatment seems helpful, even just with intralesional triamcinolone injections.

• Rheumatology referral may be helpful
  • Familiarity with drug, adverse effects, and alternatives
  • More time for appointments to discuss risks
  • Samples – but may not be reliable source.
• Although the actual rate of response in the trials is comparable to data available for traditional therapies, there are a few points to ponder

  • Dose – higher dose necessary? Is it safe?
  • Is this safe for long-term use? RA use would be long-term.
  • Does this work better for more severe AA than other treatments?
Other targeted therapies

• **Ustekinumab (IL12-23/p40 inhibitor)**
  
  • 90 mg q12 wks; 1/3 with complete response after 12 months, others with moderate response, but AA has developed in pts on ustekinumab

• **Apremilast (PDE4 inhibitor)**
  
  • prevents AA in human skin grafts on mouse model
  
  • Recent study showed no benefit in 9 patients; trial in progress.

• **Abatacept (CTLA4 agonist) - 125 mg SC weekly**
  
  • SALT 30-100% 1/15 patients with 98% regrowth after 6 months, 2/15 with 23% regrowth

Simvastatin/ezetimibe – 40/10 mg daily

- **Lattouf et al (2015) - Pilot study of 29 patients**
  - 40-70% SALT score, 73% responded after 16-24 wks (>20% regrowth), +relapse, No adverse effects

- **Loi et al (2016) – 20 patients**
  - >70% SALT, no patients with >20% regrowth.
  - Simvastatin with JAK inhibition, modulates lymphocyte activity, ezetimibe antioxidant effects and possible role in autophagy

Platelet rich plasma (PRP) and microneedling

• A few studies for PRP
• Monthly for 3-6 months, half head and placebo controlled studies
• Regrowth seen with greater remission rates and lower relapse rates.
• Better results in those with limited disease.
• Minimal information for microneedling

El Taieb et al, Platelets rich plasma versus minoxidil 5% in treatment of alopecia areata: A trichoscopic evaluation. Dermatol Ther. 2017 Jan;30(1)
Contact immunotherapy

• Overall, meta-analysis shows ~50% response rate with DPCP contact immunotherapy (Kuin et al, 2015)
• Prior sensitization may not be necessary
• Patch testing after sensitization reduces time to regrowth, but does result in increased adverse effects
• Maintenance may prevent relapse
• Adding anthralin topical can improve efficacy

## Estimated rates of efficacy

<table>
<thead>
<tr>
<th>Authors</th>
<th>Drug</th>
<th>% response</th>
<th>Number of studies or patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shreberk-Hassidim et al, 2016</td>
<td>Pulsed corticosteroid</td>
<td>40% in RCT, 43% overall</td>
<td>41 studies</td>
</tr>
<tr>
<td>Kuin et al, 2015</td>
<td>DPCP</td>
<td>~50%</td>
<td>11 studies</td>
</tr>
<tr>
<td>Tan et al, 2002</td>
<td>Intralesional corticosteroid</td>
<td>82.1%</td>
<td>127 pts (&lt;25% SALT)</td>
</tr>
<tr>
<td></td>
<td>JAK inhibitors</td>
<td>31-58%</td>
<td>4 studies</td>
</tr>
</tbody>
</table>
Unconventional therapies

• Antihistamines – particularly fexofenadine
• Cryotherapy
• Low dose naltrexone
Support and counseling
Treatment summary

- JAK inhibitors seem to be most promising
  - Higher doses – unknown safety
  - Combination therapy may be necessary
  - Topical route likely better safety profile, but so far it doesn’t appear to be as effective, but would be nice for localized disease
  - Long term use likely necessary
  - Patients with longer duration of disease and more extensive disease still have poorer response
Treatment summary

• Other biologics may be helpful, but minimal data
• Traditional therapies still reliable
  • May take longer than many studies (>3 months; maybe 1-2 years)
• Camouflage options and support helpful either when treatments fail or while undergoing treatment
Updated therapeutic ladder

• <25% hair loss
  • intralesional triamcinolone injections or topical steroid if patient prefers
  • If fails, then consider adding simvastatin/ezetimibe or start contact immunotherapy or other
  • Topical JAK inhibitors could play a role here
Updated therapeutic ladder

• 50% hair loss or more
  - Contact immunotherapy or oral JAK inhibitor
  - If fails, consider cyclosporine, systemic corticosteroids, methotrexate; Intralesional triamcinolone still can be done if patient prefers
  - Combination therapy
Future

• Randomized controlled trials are needed
• Continue to improve studies on “old” treatments
• More targeted therapies on the horizon
• Clinical observation in conjunction with translational research can continue to help us better understand and treat this disease
• Patient-centered outcomes will be a focus
<table>
<thead>
<tr>
<th>Rank</th>
<th>Uncertainty</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>What are the causes of alopecia areata? For example- medications, medical problems, lifestyle, vaccinations.</td>
</tr>
<tr>
<td>2</td>
<td>Are immunosuppressant therapies (for example- methotrexate, mycophenolate mofetil) better than placebo in the treatment of alopecia areata?</td>
</tr>
<tr>
<td>3</td>
<td>In alopecia areata, are biological therapies (including janus kinase (JAK) inhibitors and anti-cytokine therapies) more effective than placebo in causing hair regrowth?</td>
</tr>
<tr>
<td>4</td>
<td>Are psychological interventions helpful in alopecia areata?</td>
</tr>
<tr>
<td>5</td>
<td>Can progression of alopecia areata be prevented by early diagnosis and treatment?</td>
</tr>
<tr>
<td>6</td>
<td>Do certain foods, vitamins or nutritional supplements improve hair re-growth in alopecia areata?</td>
</tr>
<tr>
<td>7</td>
<td>What can be learnt about alopecia areata from other autoimmune conditions?</td>
</tr>
<tr>
<td>8</td>
<td>In whom does alopecia areata hair loss progress and why?</td>
</tr>
<tr>
<td>9</td>
<td>Do any treatments have a long-term therapeutic benefit in alopecia areata?</td>
</tr>
<tr>
<td>10</td>
<td>How effective are alternative therapies in alopecia areata?</td>
</tr>
</tbody>
</table>
