Alopecia areata: Workup and treatment

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DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

Carolyn Goh
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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
Review

• 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 for a mean of 17 years. (with or without treatment) (Tosti et al, 2006)
Overview

• Epidemiology
  • Health-related quality of life
  • Comorbidities

• Treatment
  • JAK inhibitors – oral/topical
  • Other immunomodulators
  • Updated information on traditional treatments
Epidemiology

• 2.1% lifetime risk of developing alopecia areata – extrapolated from Mayo Clinic study in Olmstead County\(^1\)
  • Previous data 1975-1989 showed 1.7%
  • Other autoimmune diseases have shown increased incidence
• Appears to be equal across ethnicities and gender
• Can occur at any age, but less common under age 3 and mean age of onset is in 30s for men and women

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
- 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 dermatitis.


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

Patel et al, Screening guidelines for thyroid function in children with alopecia areata JAMA Dermatol 2017;153(12):1307-10
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 AA (C3H/HeJ mouse model)
  - Immune-related, neuropsychiatric, and metabolic conditions found to be associated, including known and new associations

<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.jac.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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<td></td>
<td>Multiple sclerosis</td>
<td>Multiple sclerosis</td>
<td>Thyroid hormone abnormalities</td>
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<td>Systemic lupus Erythematosus</td>
<td>Systemic lupus Erythematosus</td>
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<td>Type 1 diabetes mellitus</td>
<td>Type 1 diabetes mellitus</td>
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<td></td>
<td>Psoriasis</td>
<td>Psoriasis</td>
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<td></td>
<td></td>
<td>Ulcerative colitis</td>
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<td></td>
<td>Grave’s disease, Thyroiditis</td>
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<td>Inflammatory Metabolic</td>
<td>Allergic rhinitis</td>
<td>Allergic rhinitis</td>
<td>Elevated total cholesterol</td>
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<td></td>
<td>Hypersensitivity angiitis</td>
<td>Asthma</td>
<td>Elevated phospholipids</td>
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<td></td>
<td>Disorders of lipid metabolism</td>
<td>Disorders of lipid metabolism</td>
<td>Decreased circulating alanine transaminase</td>
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<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>Cholelithias</td>
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<td></td>
<td>AA metabolism (aromatic) canthosis nigricans</td>
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<tr>
<td>Neuropsychiatric</td>
<td>Attention deficit disorder</td>
<td>Attention deficit disorder</td>
<td>Prone to impulsivity, anxiety</td>
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<tr>
<td></td>
<td>Epilepsy</td>
<td>Epilepsy</td>
<td>Absence seizures (Grisk)</td>
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<tr>
<td></td>
<td>Depression</td>
<td></td>
<td>Attenuated response to tactile and thermal stimulation</td>
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<tr>
<td></td>
<td>Bipolar disorder</td>
<td></td>
<td>Disruptions in social behavior</td>
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<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>
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<td></td>
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<tr>
<td></td>
<td>Heart failure</td>
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</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
• Of note, 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
Treatment and management

- JAK inhibitors
- Other biologics (ustekinumab, apremilast, abatacept)
- Simvastatin/ezetimibe – mixed results
- Platelet rich plasma therapy and microneedling
- Contact immunotherapy
- Support
# Therapeutic Ladder for Alopecia Areata

<table>
<thead>
<tr>
<th>Step</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Topical and intralesional corticosteroids</td>
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<tr>
<td></td>
<td>Topical irritants (e.g. anthralin, tazarotene, azelaic acid)</td>
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<td></td>
<td>Topical minoxidil</td>
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<tr>
<td>2</td>
<td>Topical immunotherapy (e.g. squaric acid dibutyl ester, diphenylcyclopropenone)</td>
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<tr>
<td></td>
<td>Systemic corticosteroids, pulsed dosing* (especially if rapidly progressive)</td>
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<td></td>
<td>Topical or oral photochemotherapy (PUVA)</td>
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<td></td>
<td>Excimer laser</td>
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<td></td>
<td>Photodynamic therapy</td>
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<tr>
<td>3</td>
<td>Systemic corticosteroids, chronic</td>
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<tr>
<td></td>
<td>Systemic cyclosporine</td>
</tr>
</tbody>
</table>

*e.g. oral prednisolone 300 mg (5 mg/kg for children) monthly for a minimum of three doses.

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**Table 68.5 Treatment options for the management of alopecia areata.** Key to evidence-based support: (1) prospective controlled trial; (2) retrospective study or large case series; (3) small case series or individual case reports.

From Bolognia, Jorizzo & Rapini: Dermatology 2e. © 2008 Elsevier, Ltd.
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

• Ruxolitinib (20 mg twice daily) – 9/12 (75%) patients SALT 30-70% with >50% regrowth after 4-6 months. +relapse over 3-6 months.

• Low IFN and cytotoxic lymphocyte signatures on gene expression profiles associated with lack of response

Tofacitinib

• Tofacitinib (5 mg twice daily) 66 pts, SALT 50-100% – 32% with >50% regrowth within 3 months, 32% with 5-50% regrowth. + relapse ~8.5 weeks

• Tofacitinib (5-10 mg twice daily) +/- pulsed oral corticosteroid (300 mg monthly x 3 mos) – 65 pts, SALT >40%, 58% with >50% change in SALT score in 4-18 mos.


Tofacitinib (cont.)

• Tofacitinib in adolescents ages 12-17
  • 10/14 patients with SALT 20-100% with mean SALT improvement of 88% over 2-16 months
  • Dose 5 mg twice daily except one on 10 mg qam, 5 mg qpm
  • Mild adverse effects, no treatment interruptions

• Anecdotally – intralesional corticosteroid injections seem to help as well.

Topical tofacitinib
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

• 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

- **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

• El Taieb et al (2017)
  • Significant improvement monthly PRP vs. placebo and minoxidil 5%, patchy better than AT or AU. (x 3 months)

• Singh (2015) – 19/20 with regrowth, monthly x 6 months

• Trink et al (2013) – double blind, placebo, half head x 3 months
  • Significant improvement monthly PRP (60% complete) vs. ILK (27%) vs. placebo, even after 1 year; baseline SALT ~32-36%
Intralesional triamcinolone injections

- 4 patients
- Placebo-controlled and randomized within each patient
- Q6 weeks for 42 weeks
- No difference between 2.5 mg/ml, 5 mg/ml, and 10 mg/ml

Contact immunotherapy

• Chiang et al (2014) reviewed 50 cases using DPCP
  • 71% of AT and 56% of AU patients >50% regrowth
  • 15% of responders did not respond until 1-2 years
• DPCP + anthralin 0.5% ointment
  • 88% (n=22) vs. 54.5% (n=12) had 50% or greater terminal hair regrowth after 30 weeks
• Prior sensitization may not be necessary
Reviews

• **Pulsed corticosteroid therapy (Shreberk-Hassidim et al, 2016)**
  - 41 studies, various protocols (IV, IM, PO; once monthly or once weekly), only one randomized controlled trial
  - Complete response in 40% of patients in the RCT (0% in placebo group), 43% in the study population, 51% in pediatric-only studies.

• **DPCP (Kuin et al, 2015)**
  - 11 studies with 500 patients, no RCTs, 10 half head studies with no treatment, variety of AA severity.
  - ~50% response rate overall, remission tended to last > 1 year
  - High dropout rates, level of evidence poor.
Treatment summary

- JAK inhibitors seem to be most promising
  - Higher doses – unknown safety
  - Combination therapy may be necessary – is effectiveness as great, then?
  - Topical route likely better safety profile, but unknown benefit
  - 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)
- Camouflage options and support helpful either when treatments fail or while undergoing treatment
Future

• Randomized controlled trials are needed.

• Continue to improve studies on “old” treatments.

• 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 1- Top 10 research uncertainties for alopecia areata prioritized by consensus.

<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>
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</tbody>
</table>