Alopecia areata: Workup and treatment

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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
Overview

• Epidemiology
  • Burden of disease
  • Health-related quality of life
  • Comorbidities

• Treatment
  • JAK inhibitors – oral/topical
  • Other new 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 considered less common under age 3 and mean age of onset is in 30s for men and women

Burden of disease is similar to psoriasis

• Disability-adjusted life year (DALY)
  • Combines yrs lost to disability (morbidity) and death (mortality)
  • One DALY = one year of healthy life lost

• WHO measured global DALYs lost in 2010
  • AA = 1,332,800
  • Psoriasis = 1,050,660
  • Diabetes mellitus = 46,857,100

• May underestimate true disease burden
  • Some patients with AA may not present for care
  • Disability imposed by emotional distress, interpersonal relationships, and financial impact were not considered
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 is in AA is comparable to psoriasis and atopic dermatitis.

Comorbidities

- Atopy (especially atopic dermatitis and allergic rhinitis)
- Thyroid disease – *particularly in adults*
- Autoimmune disorders
  - Systemic lupus – *particularly in younger patients*, vitiligo, psoriasis
- Psychiatric disorders
  - Depression, anxiety

Stroke risk and AA

- Case control study from Taiwan from 2004-2011
  - 3231 patients with AA compared to 16,155 matched controls
  - Risk of stroke within three years of AA diagnosis was increased independent of hyperlipidemia, hypertension, and heart disease (hazard ratio 1.61, 95% CI = 1.13-2.30)
  - Inflammation/oxidative stress associated with AA vs. treatment effects vs. other

Cardiovascular risk and AA

- Retrospective study from Boston, MA (2000-2010)
  - Decreased odds for developing ischemic stroke (odds ratio 0.39, 95% CI 0.18-0.87) and a trend toward decreased risk of acute myocardial infarction (odds ratio 0.91, 95% CI 0.59-1.39)
  - 1377 patients with AA compared to 4131 matched controls

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.

• Evaluation of 133 patients with AA out of 55,929 over 12 years in the Nurses’ Health Study showed no significant association with predicted vitamin D status.

Skin cancer risk reduced in AA

- Negative association with squamous cell carcinoma and basal cell carcinoma
- Trend for melanoma, but not significant
- Possibly related to genetics that may confer immunologic advantage
- Of note, the costimulatory pathway which has been identified in GWAS studies for AA has been targeted to treat melanoma

Summary of epidemiology studies

• Consider screening for lupus in younger patients, thyroid disease in older patients, and psychiatric comorbidities (referral to psychologist or psychiatrist)

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

• There may be surprising associations – clinical observation and continued epidemiological studies are important
Treatment and management

- JAK inhibitors
- Other biologics (ustekinumab, apremilast, abatacept)
- Simvastatin/ezetimibe – mixed results
- Hydroxychloroquine – not effective
- Platelet rich plasma
- Contact immunotherapy and anthralin
Janus kinase inhibitors

- **Ruxolitinib = Jakafi (~$11,000 for 30-day supply) = JAK1/JAK2 inhibitor**
  - Approved for use in myelofibrosis in 2011
  - 20 mg twice daily

- **Tofacitinib = Xeljanz (~$4,000 for 30-day supply) = pan-JAK inhibitor**
  - Approved for use in rheumatoid arthritis in 2012
  - 5 mg twice daily, increase to 10 mg qAM, 5 mg qPM
  - Extended release now available – 11 mg daily

- At least 7 others in clinical trials, and 1 approved for use in dogs for eczema
Janus kinase inhibitors

- Topical ruxolitinib in trials for alopecia areata
- Topical tofacitinib s/p trials for psoriasis
  - Both available through compounding pharmacies as cream or solution; some anecdotal improvement.
- Oral: open-label clinical trials done, but no randomized controlled trials
- Case report of baricitinib
- Adverse effects: diarrhea, headaches, other GI side effects. Liver function abnormalities, infection, possible malignancy, bowel perforation. Long term risk largely unknown.
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.

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
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.
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

• **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)

- Few studies, but many patients inquire about it
  - 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%

Hydroxychloroquine

- Case reports and anecdotally associated with regrowth
  - 200 mg twice daily
- Nissen et al (2016)
  - Series of 8 patients, 1 with extensive regrowth, but relapsed while on medication.
- Only use if possible connective tissue disease

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
  • 4/6 patients who either were not sensitized or failed to develop a reaction eventually had regrowth

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 this disease.
- Patient-centered outcomes will be a focus.
**Patient centered outcomes/research**

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

<table>
<thead>
<tr>
<th>Rank</th>
<th>Uncertainty</th>
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<tbody>
<tr>
<td>1</td>
<td>What are the causes of alopecia areata? For example- medications, medical problems, lifestyle, vaccinations.</td>
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<tr>
<td>2</td>
<td>Are immunosuppressant therapies (for example- methotrexate, mycophenolate mofetil) better than placebo in the treatment of alopecia areata?</td>
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<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>
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<td>4</td>
<td>Are psychological interventions helpful in alopecia areata?</td>
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<td>5</td>
<td>Can progression of alopecia areata be prevented by early diagnosis and treatment?</td>
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<tr>
<td>6</td>
<td>Do certain foods, vitamins or nutritional supplements improve hair re-growth in alopecia areata?</td>
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<tr>
<td>7</td>
<td>What can be learnt about alopecia areata from other autoimmune conditions?</td>
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<tr>
<td>8</td>
<td>In whom does alopecia areata hair loss progress and why?</td>
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<tr>
<td>9</td>
<td>Do any treatments have a long-term therapeutic benefit in alopecia areata?</td>
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<tr>
<td>10</td>
<td>How effective are alternative therapies in alopecia areata?</td>
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