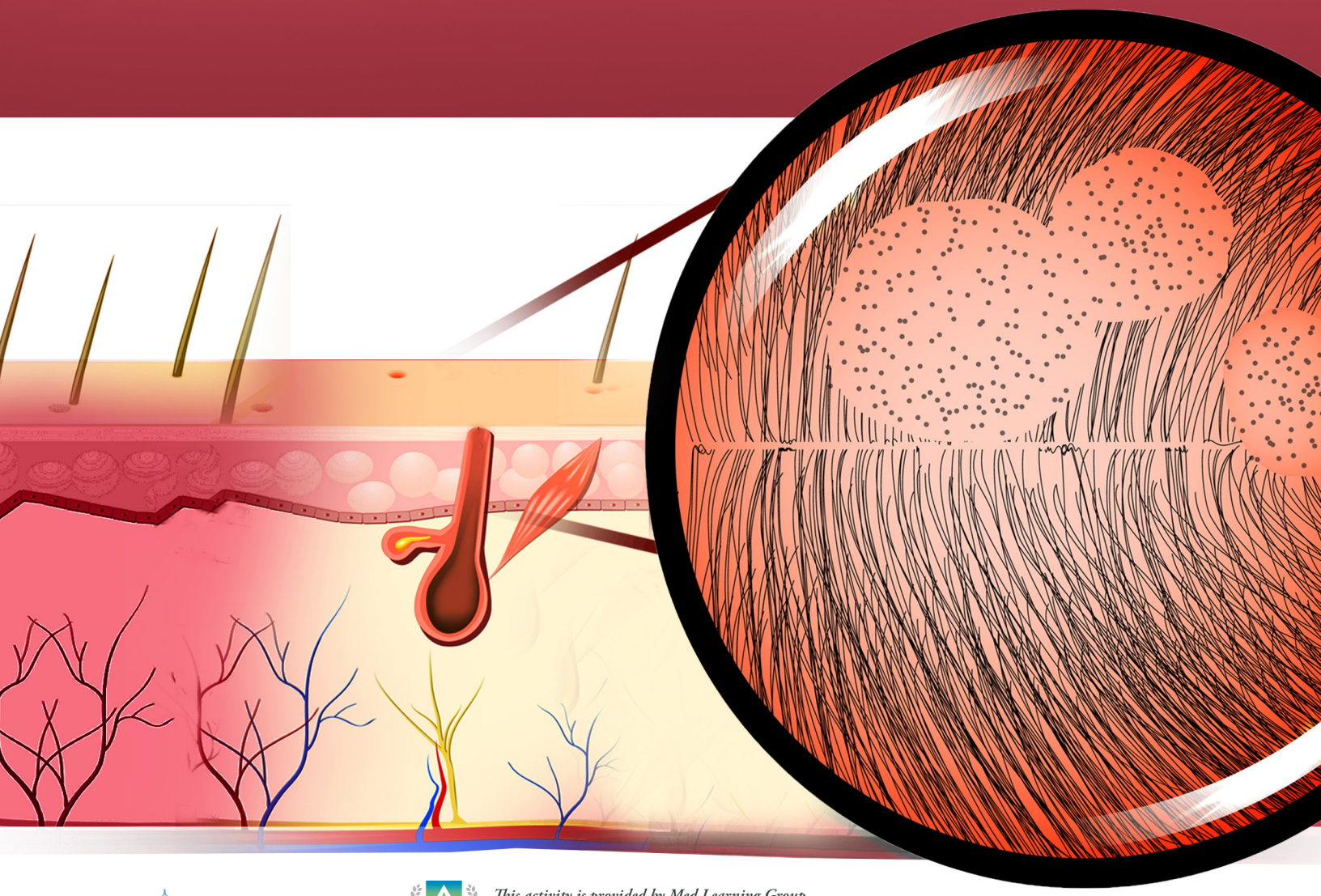
A Whiteboard View of the New Era in **Alopecia Areata:**
THE ROLE OF JAK INHIBITORS

MEETING INFORMATION



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This activity is supported by an educational grant from Lilly.

A Whiteboard View of the New Era in Alopecia Areata: The Role of JAK Inhibitors

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Program content was co-created by Dr. Brett King and Dr. Rodney Sinclair

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PROGRAM OVERVIEW

This live, case-based activity targets health care gaps related to the underlying autoimmune causes of alopecia areata (AA) and targeted treatment approaches, which can have a profound impact on health-related quality of life through burden of disease and associated comorbidities.

- By addressing these gaps, you can assess whether your approach to AA management using immune-related targeted treatment approaches and comorbidity assessment could be modified to help close these gaps.
- Expert discussion will guide you in analyzing and identifying appropriate candidates for immune-targeted treatment of alopecia with JAK inhibitors, as well as assessment and management strategies for associated comorbidities.
- You will also be immersed in dynamic animations using a whiteboard platform to memorably highlight key points related to immune pathways in the development of alopecia areata and patient counseling techniques for tailored disease and comorbidity management.

TARGET AUDIENCE

This educational activity is intended for dermatology professionals who care for patients with AA.

LEARNING OBJECTIVES

After completing the CME activity, learners should be better able to:

- Elucidate the immune pathways involved in the pathogenesis of AA and their implications for targeted treatment
- Identify patients in practice who may potentially benefit from JAK inhibitors for treating AA based on clinical trial data on their safety and efficacy
- Select optimal approaches for identifying and addressing the physical and psychological comorbidities of AA

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NURSING CREDIT INFORMATION

Purpose: This program would be beneficial for nurses involved in caring for patients with AA.

Credit: 1.0 ANCC Contact Hour

CNE Accreditation Statement: Ultimate Medical Academy/CCM is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Awarded 1.0 contact hour of continuing nursing education of RNs and APNs.

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	Consultant	Aclaris Therapeutics, Almirall, Arena Pharmaceuticals, Bristol-Meyers Squibb Company, Concert Pharmaceuticals, Dermavant Sciences, Eli Lilly, Pfizer, and Viela Bio
	Clinical trial investigator	Arena Pharmaceuticals, Concert Pharmaceuticals, Eli Lilly, NIH, and Pfizer
Rodney Sinclair MD, MBBS, FACD	Speakers bureau	Pfizer and Eli Lilly
	Consultant/Advisory Board	Pfizer, Eli Lilly
	Clinical Investigator	Pfizer, Eli Lilly, LEO Pharma, Gaderma, Reistone
Sergio Vañó Galván, PhD	Nothing to disclose	
Bianca Maria Piraccini, MD	Nothing to disclose	
Elise A. Olsen, MD	Nothing to disclose	
Amy McMichael, MD	Consultant	Allergan, Almirall, Bioniz, Cassiopea, Covance, eResearch Technology, Inc, Galderma, Incyte, Johnson & Johnson, Keranetics, Lilly, Merck & Co, Inc, Pfizer, Procter & Gamble, Revian, Samumed
	Research and Grant Funding	Allergan, Cassiopea, Concert Pharmaceuticals, Incyte, Procter & Gamble, and Samumed
	Royalties	Informa Healthcare and UpToDate
Antonella Tosti, MD	Consultant	DS Laboratories, Monat Global, Almirall, Tirthy Madison, Lilly, Leo Pharmaceuticals, Bristol-Myers Squibb, and P&G

CME Content Review

The content of this activity was independently peer reviewed.

The reviewer of this activity has nothing to disclose.

CNE Content Review

The content of this activity was peer reviewed by a nurse reviewer.

The reviewer of this activity has nothing to disclose.

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1. Read the CME/CNE information and faculty disclosures
2. Participate in the live virtual activity
3. Submit the pre- and post-test and evaluation form to Med Learning Group

You will receive your certificate as a downloadable file.

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Agenda

1. Alopecia areata (AA) overview
    a. Incidence/prevalence
    b. Spectrum of disease and presentation
    c. Risk factors
    d. Disease pathophysiology **(Animation: immune pathways implicated in AA development)**
2. Patient impact
    a. Comorbid conditions
    b. Psychosocial burden
3. Therapeutic strategies
    a. Conventional medications
    b. Targeted therapies
        i. JAK inhibitors
            1. Clinical trial data
            2. Potential role in treatment strategies
    c. Psychosocial considerations and approaches **(Animation: techniques for counseling patient distressed by AA, identifying and addressing disease burden and comorbidities)**
        i. Health-related Quality of Life (HRQoL) in AA
4. Case studies
    a. 38-year-old male patient; eight-year history of severe AA in the context of 30-year history of AA
    b. 29-year-old female patient; 40% scalp hair loss beginning eight months ago after steroid injection for eczema
5. Q&A

A Whiteboard View of the New Era in Alopecia Areata: The Role of JAK Inhibitors

Disclosures

- This content was co-created by Dr. Brett King (New Haven, CT) and Dr. Rodney Sinclair (Melbourne, Australia)

Disclosures

- Dr. Brett King discloses the following:
  - Receiving fees from Aclaris Therapeutics, Almirall, Arena Pharmaceuticals, Bristol-Meyers Squibb Company, Concert Pharmaceuticals, Dermavant Sciences, Eli Lilly, Pfizer, and Viela Bio
  - Being a clinical trial investigator for Arena Pharmaceuticals, Concert Pharmaceuticals, Eli Lilly, NIH, and Pfizer
  - Being on a speaker's bureau for Regeneron and Sanofi Genzyme

Disclosures

- Professor Rodney Sinclair discloses the following:
  - Consultant—honoraria from CSL Limited and Ascend Therapeutics
  - Advisory board—compensation received from Leo Pharma, Samson, Pfizer, and Eli Lilly
  - Speaker—honoraria from Bayer and Novartis
  - Investigator—grants from Novartis, GSK, Medimmune, Pfizer, Janssen Cilag, Regeneron, Principia, Merck, Medpace, Johnson and Johnson, InVentiv Health Pharmaceuticals, Coherus BioSciences, Celgene, Amgen, Boehringer Ingelheim, Eli Lily, Reistone Biopharma, Galderma, AbbVie, Sun Pharma, Dermira, Astra Zeneca, and Ascend Therapeutics
- During the course of this lecture, the faculty may mention the use of medications for both US Food and Drug Administration (FDA)-approved and non-FDA-approved indications

This activity is supported by an educational grant from Lilly.

Educational Objectives

- Elucidate the immune pathways involved in the pathogenesis of alopecia areata (AA) and their implications for targeted treatment
- Identify patients who may benefit from Janus kinase (JAK) inhibitors for the treatment of AA based on clinical trial data on their efficacy and safety
- Select optimal approaches for identifying and addressing the physical and psychological comorbidities of AA

Alopecia Areata Incidence/Prevalence (US and Worldwide)

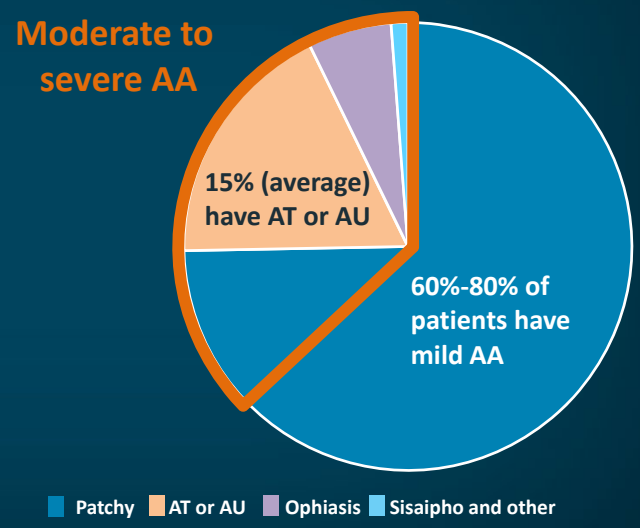
Alopecia areata affects:

- ☑ Males and females are similarly affected
- ☑ Onset typically in the first 4 decades of life
- ☑ No known racial preference

Mirzoyev SA, et al. *J Invest Dermatol*. 2014;134:1141-1142. Safavi KH, et al. *Mayo Clin Proc*. 1995;70:628-633. Muller SA, Winkelmann RK. *Arch Dermatol*. 1963;88:290-297. Liu LY, et al. *J Am Acad Dermatol*. 2017;76:22-28. Fricke ACV, Miteva M. *Clin Cosmet Investig Dermatol*. 2015;8:397-403. Strazzulla LC, et al. *J Am Acad Dermatol*. 2018;78:15-24.

Natural History of Alopecia Areata

- **Most** cases are ***mild* at onset,** and many patients will recover within 6 months to 1 year, although most will experience another episode
  - *AA is a chronic **relapsing and remitting** disease*
- **Progression to *more severe disease* *can* occur *over weeks to years***
- Scalp is involved in the ***vast majority*** of cases, but all hair-bearing sites may be affected



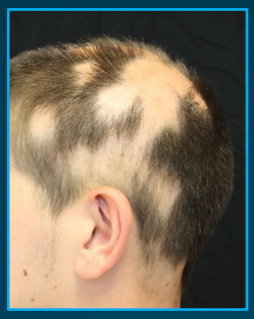
AT = alopecia totalis; AU = alopecia universalis.

Muller SA, Winkelmann RK. *Arch Dermatol*. 1963;88:290-297. Fricke ACV, Miteva M. *Clin Cosmet Investig Dermatol*. 2015;8:397-403. Safavi KH, et al. *Mayo Clin Proc*. 1995;70:628-633. Lepe K. *Stat Pearls*. Updated 2020 (https://www.statpearls.com/articlelibrary/viewarticle/17385). Accessed December 11, 2020. Cranwell WC, et al. *Austral J Dermatol*. 2019:60:163-170.

Spectrum of Disease

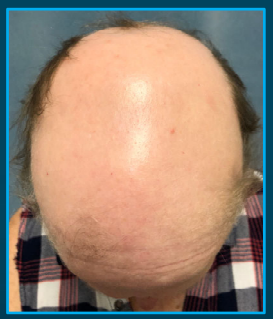
Patchy AA

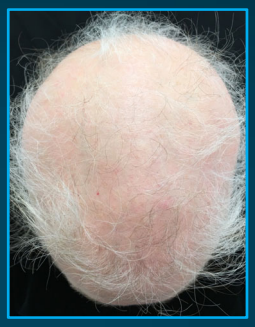
Circular areas of hair loss



Sisaipho AA

Involvement of top of scalp, sparing lateral scalp and occiput



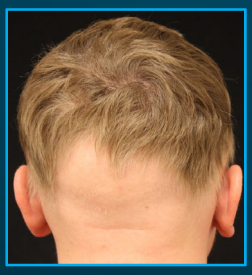


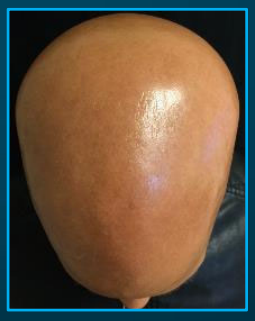
Diffuse AA

Diffuse thinning of scalp hair

Ophiasis AA

Band-like area extending from right to left ear





AT/AU

Total loss of hair over scalp (totalis) or entire body (universalis)

Images courtesy of Dr. Brett King.

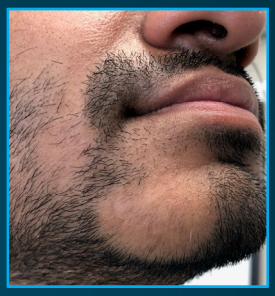
Messenger AG. *UpToDate*. 2019 (https://www.uptodate.com/contents/alopecia-areata-clinical-manifestations-and-diagnosis?topicRef=7631&source=see_link). Accessed December 11, 2020.

Spectrum of Disease (continued)

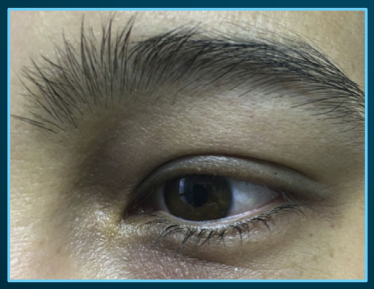
Eyebrow Involvement

Eyebrow and Eyelash Involvement

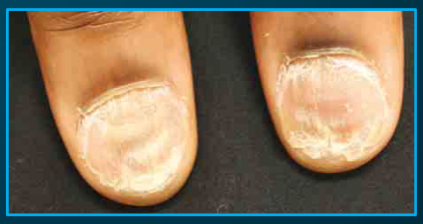
Beard Involvement



Eyelash Involvement



Nail Involvement

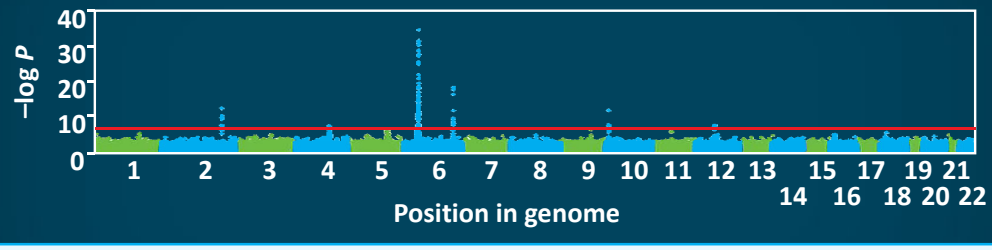


Dhayalan A, King BA. *JAMA Dermatol.* 2016;152:492-493. Craiglow BG, King BA. *J Invest Dermatol.* 2014;134:2988-2990. Craiglow BG. *JAAD Case Rep.* 2018;4:988-989. *Additional images courtesy of Dr. Brett King.*

Risk Factors for Alopecia Areata

- **Up to ≈20%** of patients with AA ***can identify a family member who also has AA***
- Concordance among monozygotic twins is 55%

Manhattan plot of joint analysis of the discovery GWAS and the replication GWAS



Genetics are ***IMPORTANT*** **AND** There are *other factors in addition to genetic susceptibility* that cause AA to manifest

We don't yet know what the other factors are—that is, what "triggers" AA to happen—or what makes AA remit at any moment in time

GWAS = genome-wide association study.

Jackow C, et al. *J Am Acad Dermatol.* 1998;38:418-425. Petukhova L, et al. *Nature.* 2010;466:113-117. Whiting D. *JAMA Dermatol.* 2003;139:1555-1559.

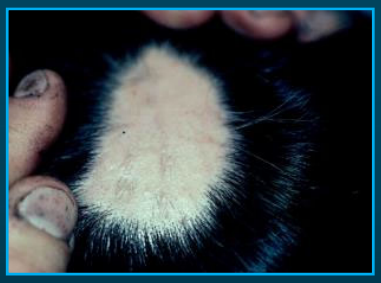
Presentation of Alopecia Areata

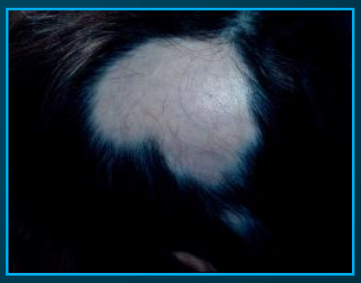
General features

- Altered sensation
- Patches appear overnight due to breakage
- Circular bald patches that enlarge circumferentially
- Colliding patches produce polycyclic shapes
  - Associated ↑ hair shedding that can be localized or generalized
  - Exclamation mark hairs
- Sparing of grey hairs
- Grey regrowth
- Nail pits and trachyonychia

Histology

- Peribulbar lymphocytic inflammatory infiltrate
- Multiple catagen hairs
- Multiple vellus-like hairs
- Non-scarring





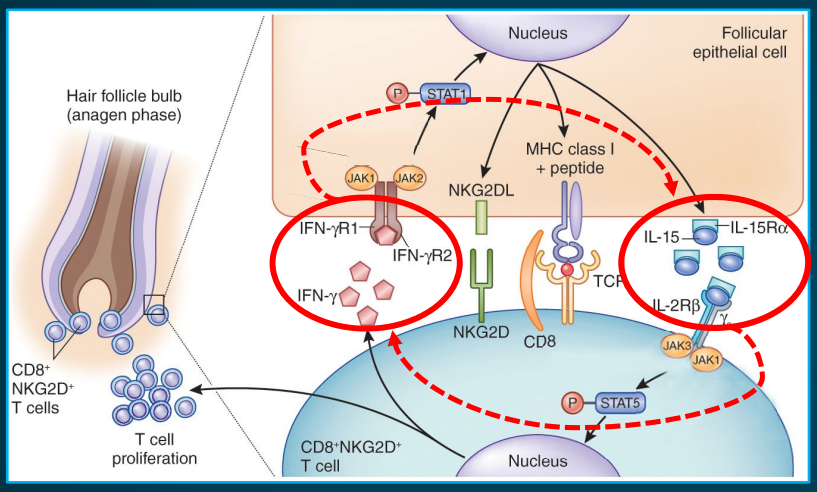
Gilmore S, Sinclair RD. *Exp Dermatol.* 2010;19:575. Baldari M, et al. *J Eur Acad Dermatol Venereol.* 2009;23:733-734. University of Michigan. Alopecia Areata. 2019 (https://www.uofmhealth.org/health-library/ug2838spec). Accessed December 14, 2020. Whiting D. *JAMA Dermatol.* 2003;139:1555-1559. Majid I, Keen A. *BJMP.* 2012;5:a530.

Whiteboard Presentation

We will now watch a brief animation investigating the immune pathways implicated in the development of AA

[Insert Whiteboard—immune pathways animation here]

Alopecia Areata Pathogenesis



AA involves cytotoxic T lymphocytes

- **Secretion of IL-15** in follicular epithelial cells recruits and activates cytotoxic T cells
- Cytotoxic T cells **secrete IFN-γ**, which binds its receptor on the follicular epithelial cell, ***leading to further secretion of IL-15***
- This **cyclical action** leads to inflammation and subsequent hair loss

CD = cluster of differentiation; IFN = interferon; IL = interleukin; MHC = major histocompatibility complex; NKG2DL = NKG2D ligand; R = receptor; STAT = signal transducer and activator of transcription; TCR = T-cell receptor; P = phosphorylate.

Gilhar A, et al. *J Clin Invest.* 2007;117:2019-2027. Xing L, et al. *Nat Med.* 2014;20:1043-1049. Divito SJ, Kupper TS. *Nat Med.* 2014:20:989-990.

The Impact of Alopecia Areata

The Impact of Alopecia Areata

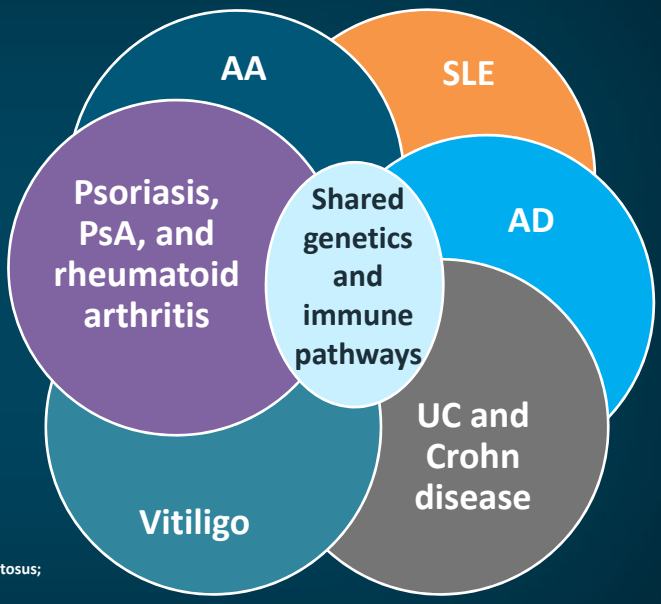
HAIR IS A BIG DEAL!

- Comorbid autoimmune and inflammatory diseases are common in patients with AA
- AA can have a significant negative impact on patients *and* their families

Lee S, et al. *J Am Acad Dermatol*. 2019;80:466-477.e16. Liu L et al. *J Am Acad Dermatol*. 2018;79:556-558

Alopecia Areata: Comorbidities

- Comorbid **autoimmune disease**
  - Thyroid disorders: Hashimoto's thyroiditis (OR = 2.15) and Graves' disease (OR = 2.07)
- Comorbid **atopic disease**
  - AD (OR = 2.36), asthma (OR = 1.24), and allergic rhinitis (OR = 1.33)
- Comorbid **psychiatric disease**
  - Lifetime prevalence of depression and anxiety of up to 39%

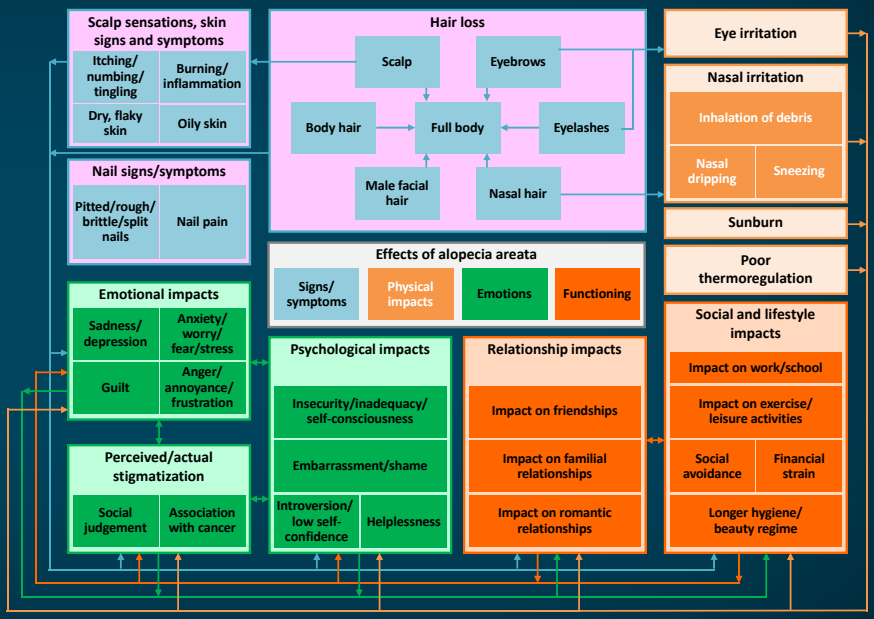


AD = atopic dermatitis; OR = odds ratio; PsA = psoriatic arthritis; SLE = systemic lupus erythematosus; UC = ulcerative colitis.

Lee S, et al. *J Am Acad Dermatol*. 2019;80:466-477.e16. Colón EA et al. *Compr Psychiatry*. 1991;32:245-251. Petukhova L, et al. *Nature*. 2010;466:113-117. Gilhar A, et al. *J Allergy Clin Immunol*. 2019;144:1478-1489. Damsky W, King BA. *J Am Acad Dermatol*. 2017;76:736-744.

Qualitative Model of Psychosocial Burden of Alopecia Areata

From interviews with 45 patients with AA, concepts were elicited and grouped into either physical or psychosocial domains and further separated into subdomains



Adapted from Aldhouse NVJ, et al. *J Patient Rep Outcomes*. 2020;4:76.

Therapeutic Strategies

Intralesional and Topical Treatments*

Agent	Cellular Effect	Adverse Events
Intralesional triamcinolone	Inhibits T cells	Skin atrophy at injection site; small risk for ↑ IOP, glaucoma, cataracts with injections near eyes
Topical corticosteroids	Inhibits T cells	Mild itching, burning, acneiform eruption, striae, telangiectasia, skin atrophy
Topical immunotherapy (eg, diphenylcyclopropenone, squaric acid)	Alters immune milieu via allergic contact dermatitis	Teratogenic effects, severe eczema, cervical/occipital lymphadenopathy
Topical minoxidil	Mechanism of action unknown	Scalp itching, dermatitis, vellus hairs on other body parts, tachycardia

IOP = intraocular pressure.

See PI for individual agents. PDR. Strazzulla LC, et al. *J Am Acad Dermatol*. 2018;78:15-24. Minoxidil. 2020 (https://www.pdr.net/drug-summary/Minoxidil-minoxidil-774). Accessed December 11, 2020.

**None of the treatments above are FDA-approved for the treatment of AA.*

Systemic Treatments*

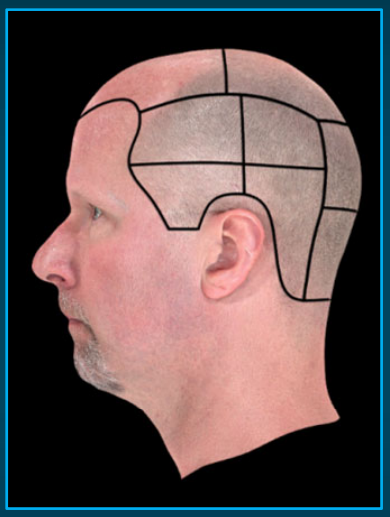
Agent	Description	Cellular Effect	Adverse Events
Azathioprine	Antimetabolite	Inhibits T cells	Serious infection, nausea, vomiting, diarrhea, hepatotoxicity ■
Cyclosporine	Calcineurin inhibitor	Down-regulation of NFAT transcription factor, preventing transcription of T-cell effector cytokines	Serious infection, nephrotoxicity, hepatotoxicity, neurotoxicity ■
Methotrexate	Antimetabolite	Interferes with DNA synthesis, repair and cellular replication	Serious infection; renal, GI, hepatic, pulmonary toxicity; hypersensitivity and dermatologic reactions ■
Prednisone/ prednisolone	Corticosteroid	Inhibits T- and B-lymphocyte proliferative responses	Osteopenia/porosis, osteonecrosis, glaucoma, cataracts, steroid myopathy, weight gain, mood change, HTN, DM, pituitary-adrenal axis suppression
Minoxidil	Non-specific hair growth stimulator	Mechanism of action in hair cycle unknown	Hypertrichosis, pruritis, xerosis, nausea, vomiting, edema, CV events ■

CV = cardiovascular; DM = diabetes mellitus; GI = gastrointestinal; HTN = hypertension; NFAT = nuclear factor of activated T cells; black box symbol = black box warning.

See PI for individual agents. Cyclosporine A (www.invivogen.com/cyclosporin-a). Accessed December 7, 2020. Chow CW, et al. *Mol Cell Biol.* 1999;19:2300-2307. Lai VWY, Sinclair R. *J Eur Acad Dermatol Venereol.* 2020;34:2606-2612. Minoxidil. 2020 (https://www.pdr.net/drug-summary/Minoxidil-minoxidil-774.98). Accessed December 11, 2020. Strazzulla LC, et al. *J Am Acad Dermatol.* 2018;78:15-24.

**None of the treatments above are FDA-approved for the treatment of AA.*

Hair-Bearing Surface Area



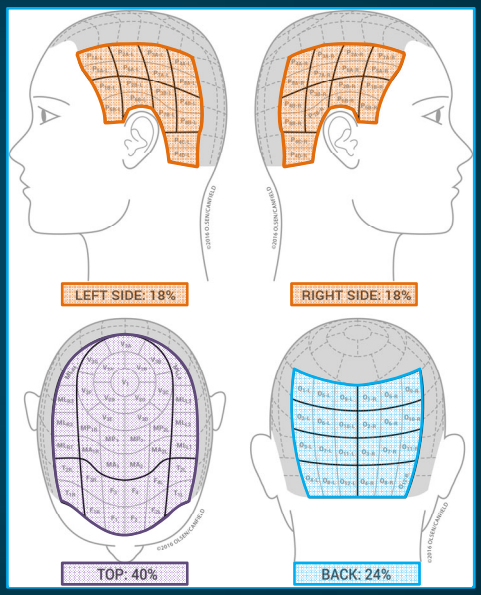
The average hair-bearing surface area of the scalp is 705 cm^2*

*Olsen EA, Canfield D. *J Am Acad Dermatol.* 2016;75:1268-1270. *Images courtesy of Mr. Doug Canfield.*

Intralesional Treatment Considerations

- 1% of the SSA is ≈7 cm^2
- Intralesional triamcinolone 0.1 mL every 1-2 cm^2
- 10% loss = ≈70 cm^2 = average ≈35 injections
- 20% loss = ≈140 cm^2 = average ≈70 injections

AA involving >20% of the SSA may be an indication for systemic therapy



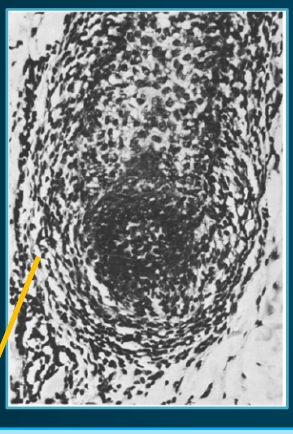
SSA = scalp surface area.

Cranwell WC, et al. *Australas J Dermatol*. 2019:60:163-170. Olsen EA, Canfield D. *J Am Acad Dermatol*. 2016;75:1268-1270. Messenger AG. *UpToDate*. 2019 (https://www.uptodate.com/contents/alopecia-areata-management?topicRef=3320&source=related_link#H2659264073). Accessed December 11, 2020.

Targeted Treatment Approaches

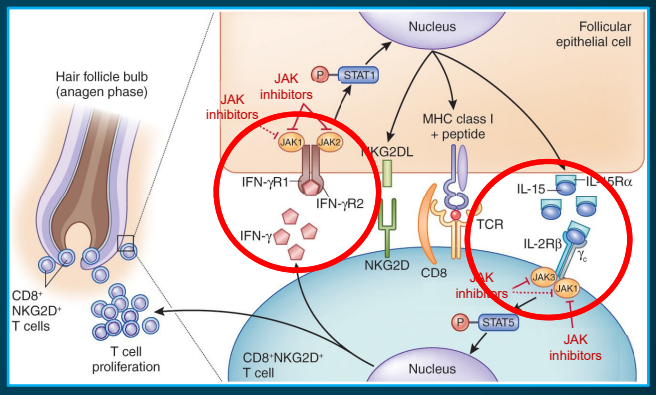
Evolving Understanding of Disease Pathogenesis

1982



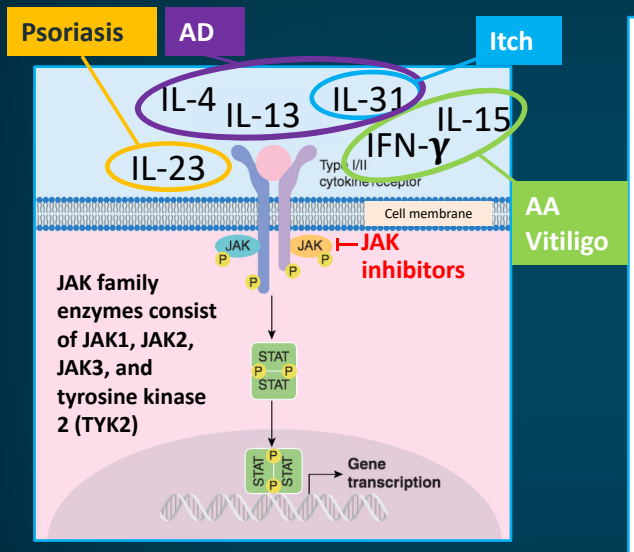
Hair bulb surrounded by lymphocytic infiltrate

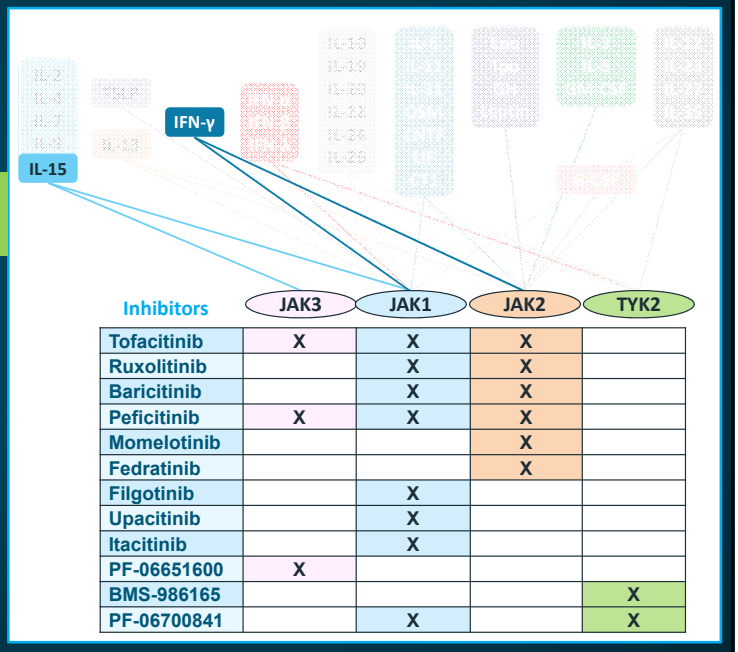
2014



Perrett C, et al. *Arch Dermatol Res.* 1982;273:155-158. Petukhova L, et al. *Nature.* 2010;466:113-117. Divito SJ, Kupper TS. *Nat Med.* 2014:20:989-990. Xing L, et al. *Nat Med.* 2014;20:1043-1049.

JAK Inhibitors Modulate Skin Disease and Cytokine Signaling



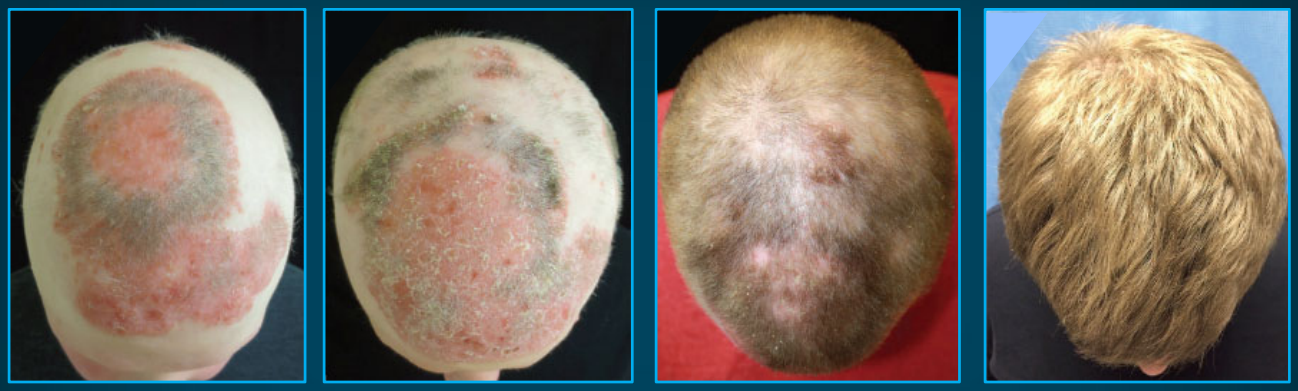


Inhibitors	JAK3	JAK1	JAK2	TYK2
Tofacitinib	X	X	X	
Ruxolitinib		X	X	
Baricitinib		X	X	
Peficitinib	X	X	X	
Momelotinib			X	
Fedratinib			X	
Filgotinib		X		
Upacitinib		X		
Itacitinib		X		
PF-06651600	X			
BMS-986165				X
PF-06700841		X		X

CNTF = ciliary neurotrophic factor; CT1 = cardiotropin-1; Epo = erythropoietin; G-CSF = granulocyte colony stimulating hormone; GH = growth hormone; GM-CSF = G-macrophage-CSF; LIF = leukemia inhibitor factor; OSM = oncostatin M; Tpo = thrombopoietin; TSLP = thymic stromal lymphopoietin.

Adapted from Gadina M et al. *J Leukoc Biol.* 2018:104:499-514. Torti DC, Feldman SR. *J Am Acad Dermatol.* 2007;57:1059-1068.

Effect of Oral Tofacitinib on AU in Patient With Plaque Psoriasis



Baseline	2 months Tofacitinib 5 mg BID	5 months Tofacitinib 10 + 5 mg daily	8 months Tofacitinib 10 + 5 mg daily

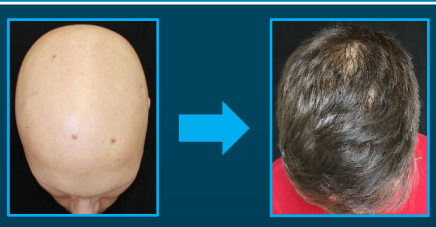
BID = twice daily.

Craiglow BG, King BA. *J Invest Dermatol.* 2014;134:2988-2990.

Randomized Controlled Trials of JAK Inhibitors* in AA

- Topical ruxolitinib 1.5% cream
- Ritlecitinib (PF-06651600) and brepocitinib (PF-06700841)
- CTP-543
- Baricitinib

The primary outcome measure in AA clinical trials is scalp hair regrowth over the period of the trial. The Severity of Alopecia Tool (SALT) score is an assessment of the amount of scalp hair loss in a patient.



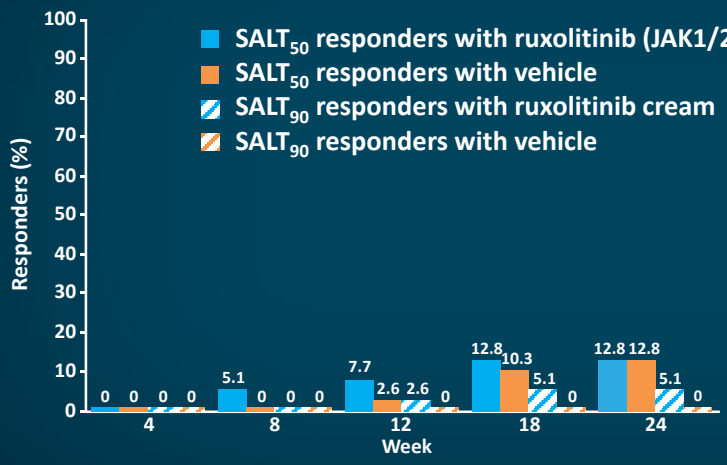
SALT score = 100 SALT score = 0

Olsen EA, et al. *J Am Acad Dermatol.* 2020;82:412-419. Gilhar A, et al. *Lancet.* 2019;393:318-319. NCT04517864 (https://clinicaltrials.gov/ct2/show/NCT04517864). NCT02974868 (https://clinicaltrials.gov/ct2/show/NCT02974868). Sinclair R. 27th EADV Congress. Presentation. NCT03137381 (https://clinicaltrials.gov/ct2/show/NCT03137381). NCT03570749 (https://clinicaltrials.gov/ct2/show/NCT03570749). NCT03899259 (https://clinicaltrials.gov/ct2/show/NCT03899259). Olsen EA, et al. *J Am Acad Dermatol.* 2004;51:440-447. All accessed February 8, 2021. *Images courtesy of Dr. Brett King.*

**JAK inhibitors are not FDA approved for treatment of AA.*

Ruxolitinib* Cream for the Treatment of Patients With AA

A 2-part, double-blind, randomized, vehicle-controlled phase 2 study



Ruxolitinib 1.5% cream was ***ineffective*** in the treatment of AA

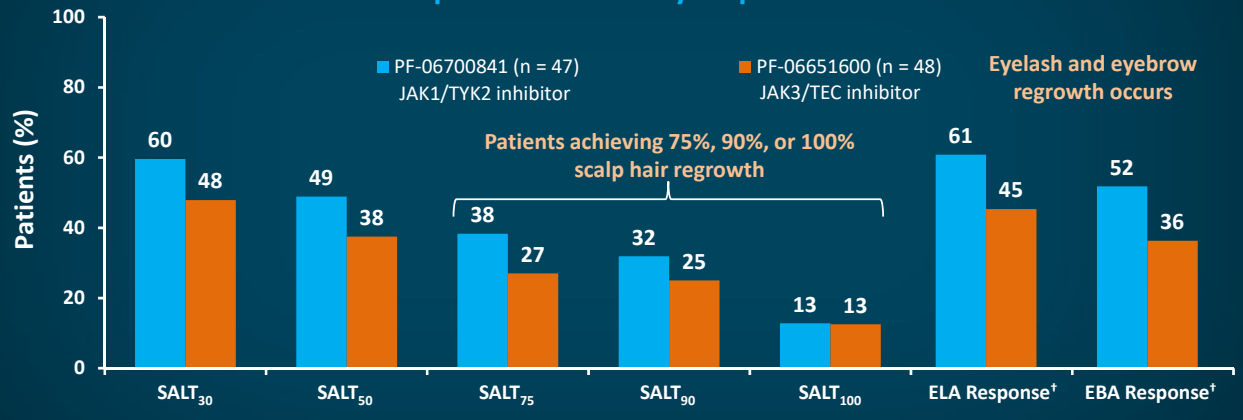
$SALT_{50}$ = 50% improvement in SALT score; $SALT_{90}$ = 90% improvement in SALT score.

Olsen EA, et al. *J Am Acad Dermatol.* 2020;82:412-419.

**JAK inhibitors are not FDA approved for treatment of AA.*

Phase 2a Randomized, Placebo-Controlled Study to Evaluate Efficacy and Safety of JAK Inhibitors Ritlecitinib and Brepocitinib in AA*

Difference from placebo in efficacy responses at Week 24

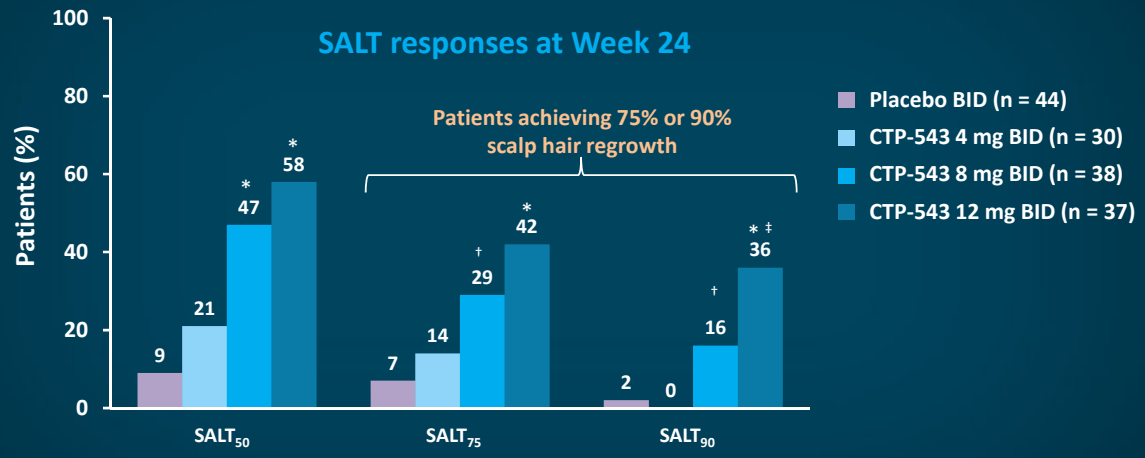


†ELA and EBA responses defined as 1-point improvement from baseline.
EBA = eyebrow assessment scale; ELA = eyelash assessment scale; $SALT_{30}$ = 30% improvement in SALT score; $SALT_{75}$ = 75% improvement in SALT score; $SALT_{100}$ = 100% improvement in SALT score; TEC = tyrosine kinase expressed in hepatocellular carcinoma.

Peeva E, et al. 2019 AAD Annual Meeting. Presentation.

**JAK inhibitors are not FDA approved for treatment of AA.*

Safety and Efficacy of CTP-543 (JAK1/2 Inhibitor*) in Adult Patients With Moderate-to-Severe AA



*P< .001 vs PBO; †P< .05 vs PBO; ‡P< .05 vs CTP-543 8 mg BID.
PBO = placebo.

Casella J, et al. 28th EADV Congress. Presentation.

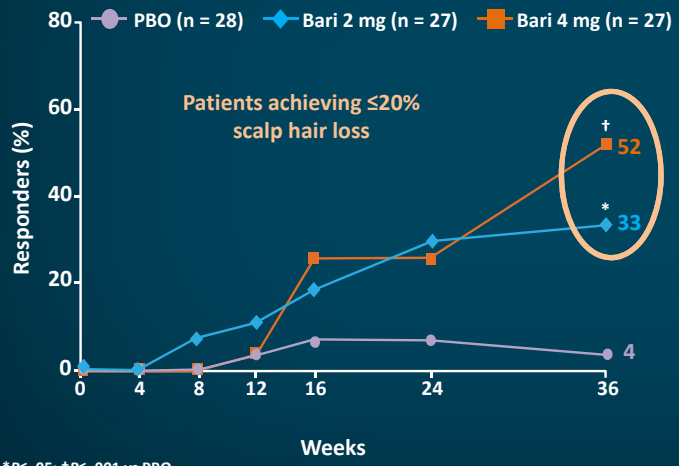
JAK inhibitors are not FDA approved for treatment of AA.

Efficacy and Safety of Baricitinib* in Severe or Very Severe AA

Phase 2 Portion of BRAVE-AA1 Randomized Controlled Trial

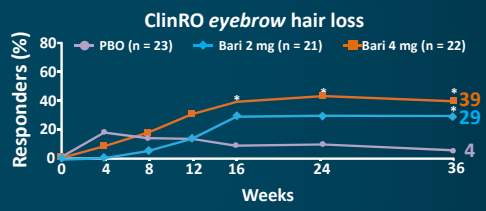
SALT ≥ 50% at baseline, current AA episode > 6 months to < 8 years

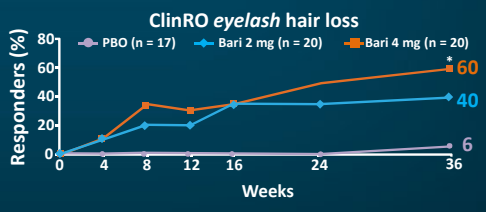
Proportion of patients achieving SALT score ≤20 through week 36



Patients achieving ClinRO measure for eyebrow and eyelash hair loss (0, 1) through week 36

(0 = full coverage on both eyes, 1 = minimal gaps and even distribution)





*P≤ .05; †P≤ .001 vs PBO.
Bari = baricitinib; ClinRO = clinician-reported outcome. *Baricitinib is not FDA approved for treatment of AA.*

King B, et al. FALLCDC 2020. Presentation. Baricitinib (Olumiant) PI 2018 (https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/207924s000lbl.pdf). Accessed February 9, 2021.

JAK Inhibitors* for Which There Are Reports of Efficacy or Clinical Trials Showing Efficacy in AA

The mechanism of action of JAK inhibitors includes blocking signaling of JAK-STAT–dependent cytokines, including IL-15 and IFN-γ

JAK Inhibitors Showing Efficacy in AA		
Agent	**JAK Specificity**	**Adverse Events**
Baricitinib	JAK1/2 inhibitor	Infection, URI, nausea, herpes simplex, herpes zoster
Tofacitinib	JAK1/3 inhibitor	Infection, thrombosis, URI, nasopharyngitis, diarrhea, headache, ↑ serum CPK, rash, herpes zoster
Ruxolitinib	JAK1/2 inhibitor	Infection, thrombocytopenia, anemia, neutropenia
Ritlecitinib (investigational)	JAK3/TEC inhibitor	Infection, arthralgia, pruritis, hepatoxicity *(phase 2 findings)*
CTP-543 (investigational) *Deuterium-modified ruxolitinib*	JAK1/2 inhibitor	Nasopharyngitis, acne, headache, ↑ serum CPK, URI, ↑ weight, ↑ lipase *(phase 2 findings)*

CPK = creatinine phosphokinase; URI = upper respiratory infection.

See individual PIs for information on agents with an indication. Robinson MF, et al. *Arthritis Rheumatol.* 2020;72:1621-1631. Concert Pharmaceuticals press release 2020 (https://ir.concertpharma.com/node/11551/pdf). Accessed December 7, 2020. Bechman K, et al. *Pharmacol Res.* 2019;147:104392. Cassella J, et al. 28th EADV Congress. Presentation. Gadina M et al. *J Leukoc Biol.* 2018:104:499-514.

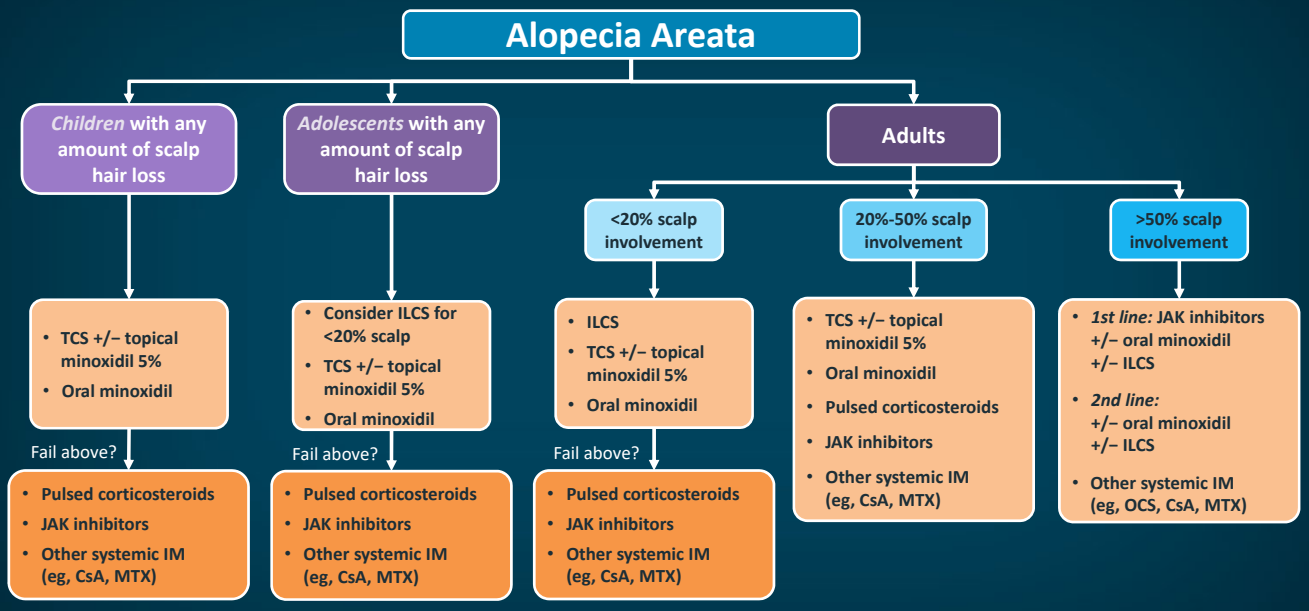
**JAK inhibitors are not FDA approved for treatment of AA.*

Developing a Treatment Algorithm

Important considerations **are:**

1. **Age of the patient**
2. **Severity or amount of hair loss**
3. **Impact of AA on the patient**

Proposed AA Treatment Algorithm



CsA = cyclosporin; ILCS = intralesional corticosteroid; IM = immunomodulator; MTX = methotrexate; OCS = oral corticosteroid; TCS = topical corticosteroid.

Algorithm courtesy of Dr. Brett King with adaptation from Strazzulla LC, et al. *J Am Acad Dermatol.* 2018;78:15-24.

**None of the therapies listed above are FDA approved for treatment of AA.*

Psychosocial Considerations and Approaches

Whiteboard Presentation

We will now watch a brief animation exploring the psychosocial implications and approaches to counseling in AA

[Insert Whiteboard—patient counseling animation here]

Patients With AA Often Feel HCPs Are Dismissive of Them and Their Disease

- There is history of AA being said to be caused by patients' stress/depression/anxiety

AA is an autoimmune disease with genetic predisposition that has a profound negative impact on HRQoL

- Support groups may provide some benefit from patients knowing they are not alone
- As with ANY disease or event that causes distress, therapy/counseling may provide some benefit to those suffering distress from AA

Counseling and/or medical management of patients' stress/depression/anxiety *must never be confused with treatment of their AA*

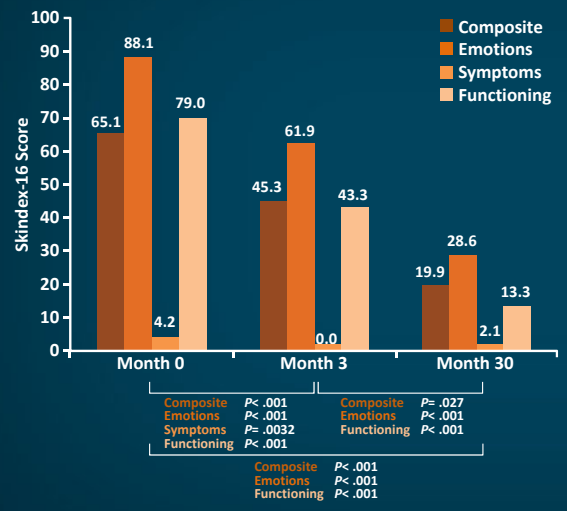
What we want for patients with AA is what patients with AA want and that is *effective treatment of their AA…*

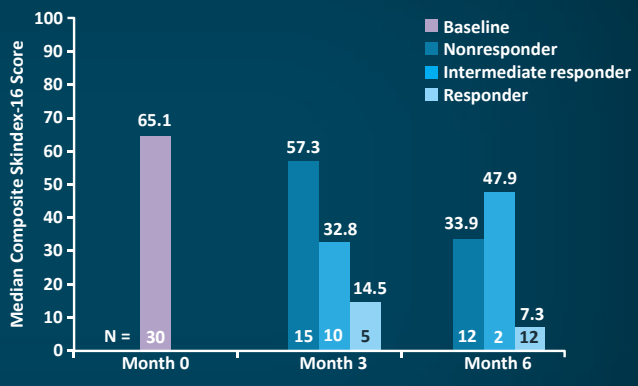
HCP = healthcare provider; HRQoL = health-related quality of life.

Liu L et al. *J Am Acad Dermatol.* 2018;79:556-558. Shapiro J. *J Investig Dermatol Symp Proc.* 2013;16:S42-S44. Cipriani R, et al. *Int J Dermatol.* 2001;40:600-601. Liu LY, et al. *J Am Acad Dermatol.* 2018;78:597-599.e2.

Treatment Success and HRQoL in Moderate-to-Severe AA

Skindex-16* scores improve with hair growth





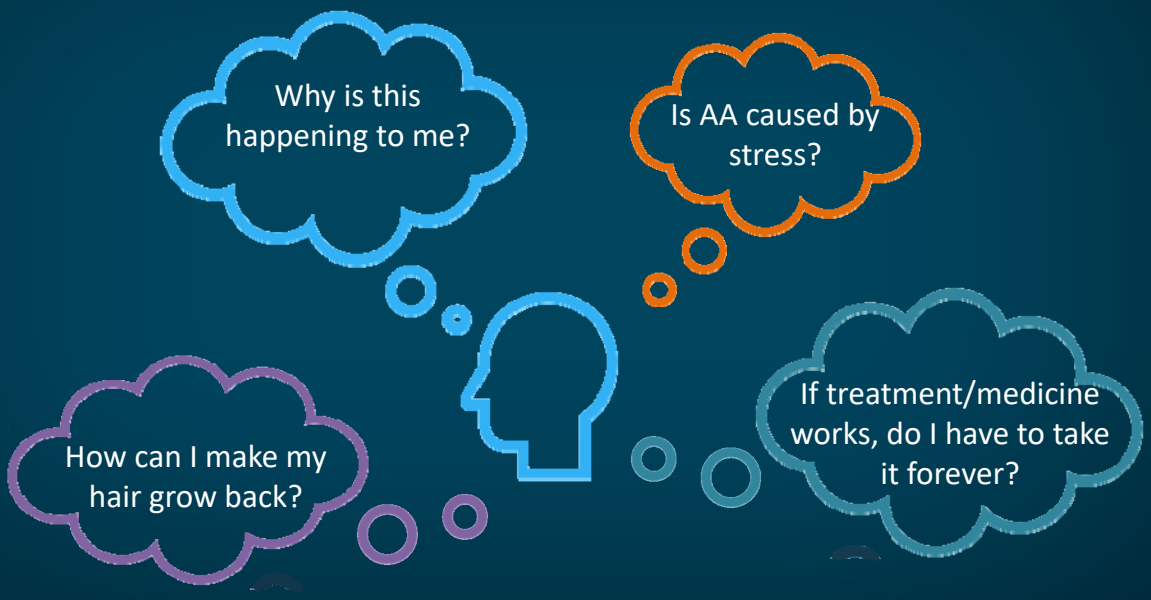
Patients with AA who are **successfully treated** experience ***improved HRQoL***

*Skindex-16 is a survey assessing how skin disease affects emotions, symptoms, and functioning.

Liu LY, et al. *J Am Acad Dermatol.* 2018;78:597-599.e2.

Patient Concerns

Every patient with AA wants to know…



The Importance of Communication

Ask Patients About…

- **Psychosocial impact of AA**
  - On a scale of 0 to 10, how bothered are you by your hair loss?
  - Does your hair loss keep you from participating in activities? If so, what activities? Why?
  - **How many times each day do you think about your hair?**
- **Their understanding of AA**
  - What do you know about AA?
  - Do you have ideas about what caused it?
  - Do you have ideas about ways to make it better?

Ask kids specifically about:

- Days missed at school
- Participation in extracurricular and social activities

The Importance of Communication

Acknowledge the patient…

"You are not alone. Many people with AA experience severe distress. It's a really natural response."

"We know a lot about what causes AA, and it's not because of anything you did or didn't do or ate or didn't eat…AA is an autoimmune disease."

"There are promising treatments for AA that are being developed."

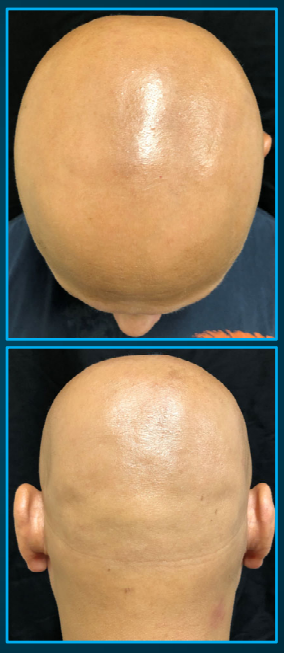
Case Studies

Case Study 1: Severe AA in Setting of Long-Standing AA

- 38-year-old man presents with 8-year history of severe AA in context of a 30-year history of AA

History of Present Illness:

- At age 8 years, he developed a quarter-sized round spot of alopecia that was attributed to a "bad haircut." The spot spontaneously resolved over several months
- At age 13 years, he developed 2 quarter-sized spots of alopecia for which he saw a dermatologist. He was treated with combination clobetasol solution and topical minoxidil 5% liquid BID for 6 months with hair regrowth
- At age 30 years, he developed a quarter-sized spot of alopecia that progressed over 8 months to complete scalp hair loss as well as involvement of the eyebrows, eyelashes, and facial and body hair



Case Study 1: Severe AA in Long-Standing AA—Interval History

- He has seen 4 dermatologists in the past 8 years for AA
- Treatment in the past 8 years includes:
  - Clobetasol solution and cream BID for months
  - Topical minoxidil 5% solution BID for months
  - Pimecrolimus cream BID for 3 months
  - ILK every 4-8 weeks for 1 year
  - Prednisone taper (3 different times)
  - Methotrexate for months
  - Excimer laser for few months
  - PRP (3 times)

PRP = platelet-rich plasma.

Case Study 1: Severe AA in Long-Standing AA—Interval History (continued)

Past Medical History

- AD
- Hashimoto thyroiditis (taking levothyroxine)

Family History

- Father with androgenetic alopecia
- Mother with thyroid disease (also takes levothyroxine)

Case Study 1: Severe AA in Long-Standing AA—Patient Concerns

What questions does the patient have?

"Why does this keep happening?"

"It's an autoimmune disease. We know a lot about the genetics, and we know a lot about the immune reaction happening around the hair follicles."

**"I have been under a lot of stress in the past 8 years because…
Is this problem caused by stress?"**

"Remember, this is an autoimmune disease, and we know a lot about the genetics underlying the disease. You did NOT cause your genetics. You did NOT make AA happen."

Case Study 1: Severe AA in Long-Standing AA—Patient Concerns (continued)

"How can I make my hair grow back?"

"There is a very good chance we can make your hair grow back. Indeed, there are several promising treatments in development."

"If treatment/medicine works, do I have to take it forever?"

"I don't know. It is likely that you will need treatment for a long time, and maybe forever. But, just as your disease once remitted for a very long time, it may be that after we treat you successfully for a while you will be able to stop treatment."

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Case Study 1: Severe AA in Long-Standing AA—Question 1

What would you want to ask the patient to ascertain the individual impact of AA?

a) How bothered are you by your hair loss?
b) Does your hair loss keep you from participating in activities?
c) Has your hair loss affected your personal or professional relationships?
d) How many times a day do you think about your hair?
e) At least you don't have cancer. It's just hair, right?
f) B + C
g) A + D
h) A, B, C, + D
i) All of the above

Slide 50

NL488 Answers to case questions in speakers notes

Nicole Longo, 2/11/2021

Case Study 1: Severe AA in Long-Standing AA—Communication Approaches

Ask patients about:

- Psychosocial impact of AA
  - How bothered are you by your hair loss?
  - Does your hair loss keep you from participating in activities? If so, what activities? Why?
  - Has your hair loss affected your personal or professional relationships? How so?
  - **How many times each day do you think about your hair?**
- Their understanding of AA
  - What do you know about AA? What have you read about it?

Case Study 1: Severe AA in Long-Standing AA—Communication Approaches (continued)

Explain their disease to them

- You *did not* give yourself AA – you *did not* make this happen
- AA is an autoimmune disease
- People with AA have a genetic predisposition
- There are emerging therapies for the treatment of AA that are *often* (but not always) effective

Case Study 1: Severe AA in Long-Standing AA—Question 2 Management Approach?

What would you consider for the next step in management?

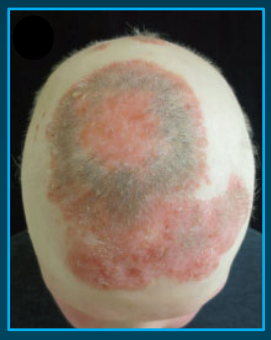
a) Diphenylcyclopropenone
b) Methotrexate + prednisone
c) Baricitinib
d) Cyclosporine
e) Gluten-free diet

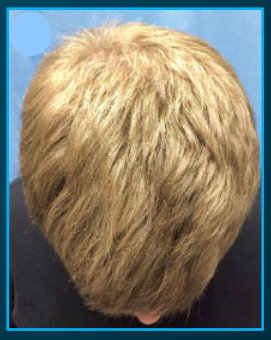
** None of the above listed pharmaceutical treatments are FDA-approved for treatment of AA.*

Case Study 1: Severe AA in an Adolescent—Why a JAK Inhibitor?

Why JAK inhibitor treatment?

- AA mechanism of disease involves IL-15 and IFN-γ
- Both IL-15 and IFN-γ signal via the JAK-STAT pathway
- Case reports and case series support JAK inhibitor treatment of AA, including in adolescents and preadolescents
- Randomized placebo-controlled trials of investigational JAK inhibitors seem to show efficacy for the treatment of AA





Craiglow BG, King BA. *J Invest Dermatol.* 2014;134:2988-2990. Ismail FF, Sinclair R. *Exp Rev Clin Pharmacol.* 2020;13:43-51.

Case Study 2: Hair Loss After Steroids

- 29-year-old woman presents with 40% scalp hair loss

History of Present Illness

- She states that the hair loss started 8 months ago after she got an IM steroid shot for treatment of her eczema. At first, there were 3 coin-sized spots, and she was told it would not get worse
- 1 month later she was treated with ILK and started minoxidil 5% solution. When all 3 spots remained 1 month later, in addition to developing 2 more spots, she was given IMK
- Hair loss has continued to progress; she believes that IMK initially caused her hair loss and that additional IMK and ILK only made it worse. At first, she could cover up spots of hair loss by carefully styling her hair, but she started wearing a wig 2 months ago
- She reports being depressed about her hair loss and is "terrified" she is going to go "bald"

IMK = intramuscular triamcinolone acetonide.

Case Study 3: Hair Loss After Steroids—Question 1

Why did this patient develop AA?

a) IM steroids
b) ILCS
c) Stress about the hair loss
d) Genetic predisposition
e) Eczema
f) A + C

Case Study 2: Hair Loss After Steroids—HPI Highlights

- Everybody looks for a reason to explain their hair loss or a cause for their AA. For this person, it was IMK. **Her "proof" is that her hair loss worsened with additional IMK and ILK**
- Predicting disease course is impossible, so it is inadvisable to do it
- Instead, say what we know
  - In this case, when the patient first presented with 3 spots, the HCP might have said: "I can't know what will happen to you, BUT we know that the majority of people with AA have relatively mild disease. Although you are unlikely to progress to significant scalp-hair loss, there is a chance you will. What is reassuring, though, is that if you do progress, there are emerging treatments that are effective for AA."
- **Patients want to know that their hair loss can be effectively treated**

Case Study 2: Hair Loss After Steroids—HPI Highlights (continued)

Questions to ask the patient…

(we already know from the history of present illness that AA is affecting her significantly)

"Tell me more about your eczema? How long have you had it? How is your eczema being treated? Is it well controlled?"

AD since childhood treated with TCS (always) and IMK 1-3 times every year

Skin sometimes gets better, but is always itchy

Sometimes she has trouble going to sleep and/or wakes from sleep scratching

"What other health conditions do you have?"

Seasonal allergies (takes antihistamines as needed)

Case Study 2: Hair Loss After Steroids—Question 2

Does this additional past medical history influence the way we think of this patient and her AA?

a) Yes

b) No

- **JAK inhibitors are also showing efficacy for the treatment of moderate-to-severe AD**, and so we have an opportunity with a JAK inhibitor to treat both her AD (which is uncontrolled) and her AA
- AD and AA often co-occur

He H, Guttman-Yassky E. *Am J Clin Dermatol.* 2019;20:181-192. Smogorzewski J, et al. *JAAD Case Rep.* 2019;5:116-117.

Case Study 2: Hair Loss After Steroids—Points to Address With the Patient

- "Your history of AD and allergies and now AA is really revealing, because we know that these conditions often occur together, which is **likely related to the genetics underlying each condition**."
- "The IMK did not cause your AA. Again, we know a lot about what causes AA and it seems that people with this condition **are genetically predisposed to develop it**."
  - "This doesn't mean that somebody else in your family needs to have it…it's more complicated than that."
- "I want to also talk about your eczema and its treatment. I know you are here for help to make your AA better but *what if we could make both your eczema and AA better*?"

Siedlikowski S, et al. *EMJ Dermatol*. 2019;7:89-100. He H, Guttman-Yassky E. *Am J Clin Dermatol.* 2019;20:181-192. Ismail FF, Sinclair R. *Exp Rev Clin Pharmacol.* 2020;13:43-51.

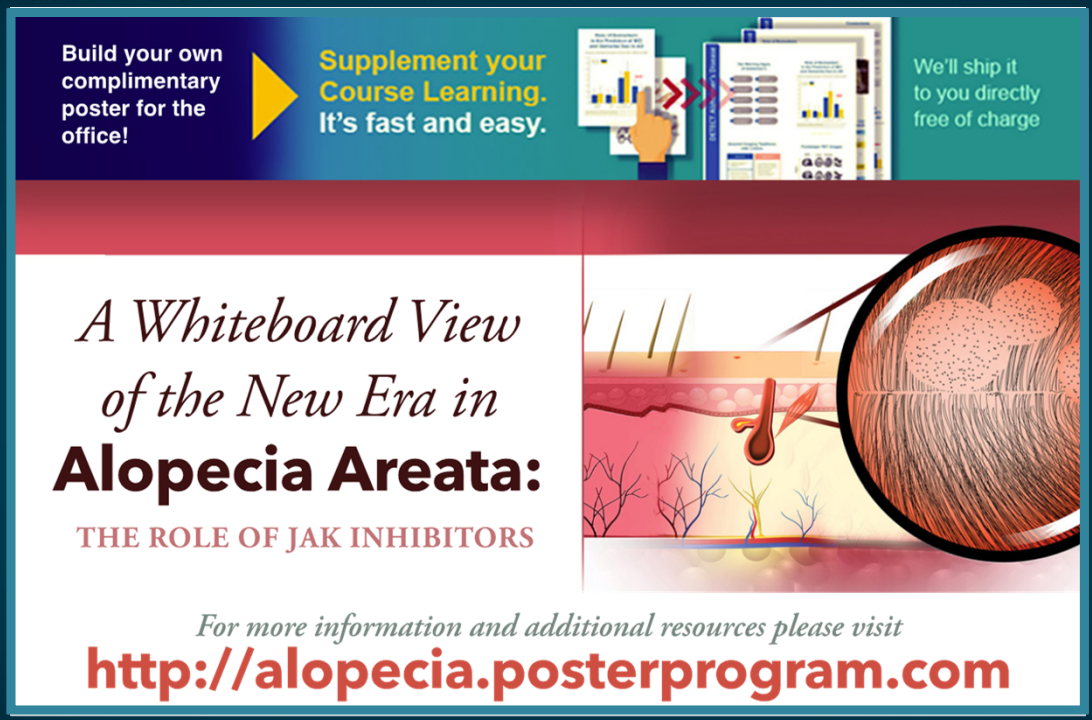
Conclusions

- AA is a complex polygenic disease with an unknown environmental trigger
- There is a long history of attributing AA to stress. But, with recent advancements in our understanding of AA, **we can move beyond stress and instead describe the genetics and autoimmune pathogenesis, including IL-15 and IFN-γ**, as important mediators of AA; this has led to therapeutic advances
- Moderate-to-severe AA may be *defined as* ***≥20% scalp hair loss***
- Intralesional therapy is the ***mainstay of therapy*** for adults with <20% scalp hair loss

Conclusions (continued)

- Patients with extensive disease (eg, *≥20% scalp hair loss*), chronic AA, or severe emotional distress may be candidates for systemic therapy
- In the absence of evidence-based guidelines, use **expert consensus opinion to guide therapy in AA**
- **JAK inhibitors are an emerging therapy for AA**
- Promising results have been presented for phase 2 clinical trials of JAK inhibitors, and phase 3 clinical trials are underway

Thank You!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Overview of Alopecia Areata

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