Emerging Therapies in Atopic Dermatitis

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ATOPIC DERMATITIS

Common, yet complex inflammatory skin condition with many factors contributing to its pathogenesis.

Clinical features include onset during infancy or early childhood, intense pruritus, and a chronically relapsing course:

- acute inflammation and predilection for cheeks, scalp, and extensor sites (infants)
- chronic inflammation with lichenification and a predilection for flexural sites (children/adults)

Often associated with asthma, allergic rhinoconjunctivitis, and food allergies (Atopic March).
Pathogenesis

Divided into three major categories

- epidermal barrier dysfunction
- immune dysregulation
- alteration of the microbiome

Each of these can be modulated by genetic and environmental factors

Treatment: General Approach

- A “proactive approach” may modify the overall disease course and prevent atopic comorbidities
- Management includes
  - education
  - gentle skin care
  - moisturizer use
  - topical agents
- Severe Disease
  - phototherapy
  - systemic medications

Tool Box

- Topical Steroids
- Topical Calcineurin Inhibitors
- Systemic Steroids
- Cyclosporine
- Methotrexate
- Azathioprine
- Mycophenolate mofetil (MMF)
IS ATOPIC DERMATITIS THE NEW PSORIASIS?
NEW TARGETS

- PDE4 inhibition
- IL-4 antagonism
- IL-13 antagonism
- IL-31 antagonism
- IL-22 antagonism
- Janus Kinase inhibition
- Neurokinin-1 Receptor inhibition
- IL-12/23 antagonism
- IL-17 antagonism
- TSLP inhibition

**TABLE I. New or in the pipeline: Topicals**

<table>
<thead>
<tr>
<th>Target</th>
<th>Compound</th>
<th>Indication</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>AhR</td>
<td>Tapinarol/henavitomod</td>
<td>Moderate-severe</td>
<td>2a →</td>
</tr>
<tr>
<td>PDE4</td>
<td>Criasorol (Eucrisa)</td>
<td>Mild-moderate</td>
<td>3 in EU (FDA 2016)</td>
</tr>
<tr>
<td>PDE4</td>
<td>Rolflumilast</td>
<td>Moderate</td>
<td>2a →</td>
</tr>
<tr>
<td>PDE4</td>
<td>RVT-501</td>
<td>Mild-moderate</td>
<td>2a →</td>
</tr>
<tr>
<td>JAK1, JAK3</td>
<td>Tofacitinib</td>
<td>Moderate-severe</td>
<td>2a → STOP</td>
</tr>
<tr>
<td>JAK1, JAK2</td>
<td>INCB18424</td>
<td>Moderate</td>
<td>2a →</td>
</tr>
<tr>
<td>JAK1, JAK3</td>
<td>LEO 124249/JTE-052</td>
<td>Mild-moderate</td>
<td>2a →</td>
</tr>
<tr>
<td>S aureus</td>
<td>R mucosa bacteria</td>
<td>Antecubital AD</td>
<td>1/2</td>
</tr>
<tr>
<td>S aureus</td>
<td>Coagulase-negative Staphylococcus</td>
<td>Moderate-severe on ventral arms</td>
<td>1/2</td>
</tr>
</tbody>
</table>

→, Drug development program is ongoing, phase 3 is planned but not yet running; → ?, unknown future of drug development program; → STOP, drug development program has been stopped; EU, European Union; FDA, US Food and Drug Administration.

**TABLE II. New or in the pipeline: Biologics**

<table>
<thead>
<tr>
<th>Target</th>
<th>Compound</th>
<th>Indication</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSLP</td>
<td>Teczepclumab</td>
<td>Moderate-severe</td>
<td>2a →</td>
</tr>
<tr>
<td>Oral</td>
<td>Anti-Oral</td>
<td>Moderate-severe</td>
<td>2a →</td>
</tr>
<tr>
<td>IL-4/IL-13R</td>
<td>Dupilumab (Dupixent)</td>
<td>Moderate-severe</td>
<td>Approved by FDA, 2017; approval pending in EU</td>
</tr>
<tr>
<td>IL-4</td>
<td>Pirakinan</td>
<td>Moderate-severe</td>
<td>2a →</td>
</tr>
<tr>
<td>IL-13</td>
<td>Tralokinumab</td>
<td>Moderate-severe</td>
<td>3</td>
</tr>
<tr>
<td>IL-13</td>
<td>Lebrizumab</td>
<td>Moderate-severe</td>
<td>3</td>
</tr>
<tr>
<td>IL-5</td>
<td>Mepolizumab</td>
<td>Moderate-severe</td>
<td>2a</td>
</tr>
<tr>
<td>IgE</td>
<td>QGE031/ligelizumab</td>
<td>Moderate-severe</td>
<td>2a →</td>
</tr>
<tr>
<td>IL-12/IL-23</td>
<td>Ustekinumab (Stelara)</td>
<td>Moderate-severe</td>
<td>2a →</td>
</tr>
<tr>
<td>IL-22</td>
<td>Fexakinumab (intravenous)</td>
<td>Moderate-severe</td>
<td>2a →</td>
</tr>
<tr>
<td>IL-17A</td>
<td>Secukinumab (Cosentyx)</td>
<td>Moderate-severe</td>
<td>2a →</td>
</tr>
<tr>
<td>IL-31 receptor A</td>
<td>CIM331/nemolizumab</td>
<td>Moderate-severe</td>
<td>2b →</td>
</tr>
<tr>
<td>IL-31</td>
<td>BMS-981164</td>
<td>Moderate-severe</td>
<td>1b →</td>
</tr>
</tbody>
</table>

→, Drug development program is ongoing, phase 3 is planned but not yet running; → ?, unknown future of drug development program; EU, European Union; FDA, US Food and Drug Administration.
THE NEW KIDS ON THE BLOCK?
Phosphodiesterase 4 inhibitors

Rema Zebda, DO, and Amy S. Paller, MD
Chicago, Illinois
<table>
<thead>
<tr>
<th>Study no.</th>
<th>Site</th>
<th>Stage</th>
<th>Disease</th>
<th>Randomization type</th>
<th>Randomization method</th>
<th>Participant details</th>
<th>Primary end point</th>
<th>Primary efficacy endpoint</th>
<th>Other details</th>
<th>References</th>
<th>Notes</th>
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<td>NCT01728230</td>
<td>United States</td>
<td>Phase II, randomized, double-blind, placebo-controlled</td>
<td>RA</td>
<td>2:1 (treatment:placebo)</td>
<td>stratified randomization</td>
<td>in center</td>
<td>no SJC, DAS28 EC, DAS44</td>
<td>European RA in remission</td>
<td>ESR/CRP</td>
<td>None</td>
<td>In or out of remission and HS</td>
</tr>
<tr>
<td>NCT02189371</td>
<td>United States</td>
<td>Phase II, randomized, double-blind, placebo-controlled</td>
<td>RA</td>
<td>1:1 (treatment:placebo)</td>
<td>stratified randomization</td>
<td>in center</td>
<td>no SJC, DAS28 EC, DAS44</td>
<td>European RA in remission</td>
<td>ESR/CRP</td>
<td>None</td>
<td>In or out of remission and HS</td>
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<tr>
<td>NCT02290635</td>
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<td>Phase II, randomized, double-blind, placebo-controlled</td>
<td>RA</td>
<td>1:1 (treatment:placebo)</td>
<td>stratified randomization</td>
<td>in center</td>
<td>no SJC, DAS28 EC, DAS44</td>
<td>European RA in remission</td>
<td>ESR/CRP</td>
<td>None</td>
<td>In or out of remission and HS</td>
</tr>
</tbody>
</table>
Topical Anti-Inflammatory Therapy: Crisaborole 2%

- Crisaborole 2% ointment is a phosphodiesterase-4 (PDE-4) inhibitor FDA-approved for the treatment of mild-moderate AD in patients ≥ 2yrs
- PDE-4 inhibitor ↑ intercellular cAMP → ↓ production of proinflammatory cytokines
- Common side effect
  - stinging or burning (4.4%)
<table>
<thead>
<tr>
<th>SCORE</th>
<th>CATEGORY</th>
<th>DEFINITION</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>Clear</td>
<td>No signs of inflammatory AD</td>
</tr>
<tr>
<td>1</td>
<td>Almost Clear</td>
<td>Faint, barely detectable erythema and/or trace residual elevation in limited areas; neither excoriation nor oozing/crusting are present</td>
</tr>
<tr>
<td>2</td>
<td>Mild</td>
<td>Light pink erythema and slightly perceptible elevation; excoriation, if present, is mild</td>
</tr>
<tr>
<td>3</td>
<td>Moderate</td>
<td>Dull red, clearly distinguishable erythema and clearly perceptible elevation but not extensive; excoriation or oozing/crusting, if present, are mild to moderate.</td>
</tr>
<tr>
<td>4</td>
<td>Severe</td>
<td>Deep/dark red erythema, and marked and extensive elevation; excoriation and oozing/crusting are present.</td>
</tr>
</tbody>
</table>
OPA-15406, a novel, topical, nonsteroidal, selective phosphodiesterase-4 (PDE4) inhibitor, in the treatment of adult and adolescent patients with mild to moderate atopic dermatitis (AD): A phase-II randomized, double-blind, placebo-controlled study

Jon M. Hanifin, MD, a Charles N. Ellis, MD, b Ilona J. Frieden, MD, c Regina Fölster-Holst, MD, d
Linda F. Stein Gold, MD, e Angelo Secci, MD, f Angela J. Smith, PA, f Cathy Zhao, PhD, g
Elena Komereyeva, MD, PhD, h and Lawrence E. Eichenfield, MD i

Portland, Oregon; Ann Arbor and Detroit, Michigan; San Francisco and San Diego, California; Kiel, Germany; and Princeton, New Jersey

---

**B**

<table>
<thead>
<tr>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
<th>Week 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>39.0%</td>
<td>39.0%</td>
<td>39.0%</td>
<td>39.0%</td>
<td>39.0%</td>
</tr>
</tbody>
</table>

p = 0.0005  p = 0.0056  p = 0.0594  p = 0.0485

---

**A**

IGA score of 0 or 1 with ≥2-grade change

20.9%

p = 0.0165  p = 0.0650  p = 0.3022

---

**B**

![Graph showing success rate over weeks]
IL-4 and IL-13

Transgenic mice with ↑IL-4 in epidermis have↓
- Atopic dermatitis-like lesions
- Pruritus
- Altered microbiome
- ↑ IgE levels

Key roles
- IgE production
- Eosinophil recruitment
- Th2 differentiation (activation of IL-4Ra → STAT6)
- Dupilumab (a monoclonal antibody that targets the IL-4Ra, is FDA-approved in adults for the treatment of AD)

3. GR Lee, RA Flavell: Transgenic mice which overproduce Th2 cytokines develop spontaneous atopic dermatitis and asthma. Int Immunol. 16:1155-1160 2004 [15226271]
Dupilumab Treatment in Adults with Moderate-to-Severe Atopic Dermatitis

Lisa A. Beck, M.D., Diament Thaçi, M.D., Jennifer D. Hamilton, Ph.D., Neil M. Graham, M.D., Thomas Bieber, M.D., Ph.D., M.D.R.A., Ross Rocklin, M.D., Jeffrey E. Ming, M.D., Ph.D., Haobo Ren, Ph.D., Richard Kao, Dr. P.H., Eric Simpson, M.D., Marius Ardeleanu, M.D., Steven P. Weinstein, M.D., Ph.D., Gianluca Pirozzi, M.D., Ph.D., Emma Guttman-Yassky, M.D., Ph.D., Mayte Suárez-Fariñas, Ph.D., Melissa D. Hager, M.A., Neil Stahl, Ph.D., George D. Yancopoulos, M.D., Ph.D., and Allen R. Radin, M.D.
## WHAT IS THE EASI?

### Recording the EASI score

<table>
<thead>
<tr>
<th>Body region</th>
<th>Redness</th>
<th>Thickness</th>
<th>Scratching</th>
<th>Lichenification</th>
<th>Severity score</th>
<th>Area score</th>
<th>Multiplier</th>
<th>Region score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head/neck</td>
<td>______</td>
<td>+________</td>
<td>+________</td>
<td>+________</td>
<td>=____</td>
<td>X____</td>
<td>X 0.1 (if ≤7 yrs, X 0.2)</td>
<td>=_____</td>
</tr>
<tr>
<td>Trunk</td>
<td>______</td>
<td>+________</td>
<td>+________</td>
<td>+________</td>
<td>=____</td>
<td>X____</td>
<td>X 0.3</td>
<td>=_____</td>
</tr>
<tr>
<td>Upper limbs</td>
<td>______</td>
<td>+________</td>
<td>+________</td>
<td>+________</td>
<td>=____</td>
<td>X____</td>
<td>X 0.2</td>
<td>=_____</td>
</tr>
<tr>
<td>Lower limbs</td>
<td>______</td>
<td>+________</td>
<td>+________</td>
<td>+________</td>
<td>=____</td>
<td>X____</td>
<td>X 0.4 (if ≤7 yrs, X 0.3)</td>
<td>=_____</td>
</tr>
</tbody>
</table>

The final EASI score: add up the 4 region scores

https://www.dermnetnz.org/topics/easi-score/
Two Phase 3 Trials of Dupilumab versus Placebo in Atopic Dermatitis


A IGA

Patients with Qualifying IGA Score (%)

- Placebo
- Dupilumab every other wk
- Dupilumab every wk

\[ \cong 40\% \]

SOLO 1

SOLO 2

B EASI-75

Patients with EASI75 (%)

- Placebo
- Dupilumab every other wk
- Dupilumab every wk

\[ \cong 50\% \]

SOLO 1

SOLO 2

QOW = QW
Dosing: 600 mg (SubQ) initially; then 300 mg QOW

Main Side Effects:
- **Injection site reactions** 10-20% vs Placebo 7-8%
- **Conjunctivitis** 7-12% vs Placebo 2%
Gene expression profiles of inflammatory genes at baseline vs. after dupilumab therapy

- Inflammatory genes strongly downregulated after dupilumab therapy
Dupilumab Trials for Children

- Efficacy and Safety of Dupilumab in Patients ≥12 to <18 Years of Age, With Moderate-to-Severe Atopic Dermatitis
- Safety, Pharmacokinetics and Efficacy of Dupilumab in Patients ≥6 Months to <6 Years With Severe Atopic Dermatitis (Liberty AD PRESCHOOL)
- Study to Investigate the Efficacy and Safety of Dupilumab Administered With Topical Corticosteroids (TCS) in Participants ≥6 to <12 Years With Severe Atopic Dermatitis (AD)
OTHER TARGETS IN THE PIPELINE?
Monoclonal antibodies against interleukin 13 and interleukin 31RA in development for atopic dermatitis

Carsten R. Hamann, MD, and Jacob P. Thyssen, MD, PhD, DMSc
Hellerup, Denmark

<table>
<thead>
<tr>
<th>Monoclonal antibodies against IL-13 and IL-31RA in development</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Table I.</strong></td>
</tr>
<tr>
<td><strong>Trade name</strong></td>
</tr>
<tr>
<td>Tralokinumab</td>
</tr>
<tr>
<td>Lebrikizumab</td>
</tr>
<tr>
<td>Nemilizumab</td>
</tr>
<tr>
<td>BMS-981164</td>
</tr>
</tbody>
</table>
TRALOKINUMAB: IL-13 Ab

NCT02347176, NCT03131648, NCT03160885, NCT03363854

<table>
<thead>
<tr>
<th>Participants Analyzed</th>
<th>Placebo</th>
<th>Tralokinumab Dose 1</th>
<th>Tralokinumab Dose 2</th>
<th>Tralokinumab Dose 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Units: Participants)</td>
<td>41</td>
<td>45</td>
<td>47</td>
<td>48</td>
</tr>
<tr>
<td>Percentage of Participants Achieving 50 Percent (%) Reduction From Baseline in Eczema Area and Severity Index (EASI) at Week 12</td>
<td>61.0</td>
<td>64.4</td>
<td>72.3</td>
<td>75.0</td>
</tr>
<tr>
<td>(Units: Percentage of participant)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Monoclonal antibodies against interleukin 13 and interleukin 31RA in development for atopic dermatitis

Carsten R. Hamann, MD, and Jacob P. Thyssen, MD, PhD, DMSc
Hellerup, Denmark

- **EASI scores** at baseline (24.8 to 27.3)
- After 2 week period TCS, 300 mg of tralokinumab vs. placebo given QOW
- The aEASI scores from baseline
  - -15.7 (tralokinumab)
  - -10.8 (placebo) ($P = .011$)
Efficacy and safety of lebrikizumab (an anti-IL-13 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical corticosteroids: A randomized, placebo-controlled phase II trial (TREBLE)

Results

- 209 patients received study drug
- At Week 12, significantly more patients achieved EASI-50 with lebrikizumab 125 mg Q4W \((82.4\%; p=0.026)\) versus placebo (62.3%)

Conclusion

Lebrikizumab 125 mg Q4W led to significant improvement in patients with moderate-to-severe AD, when added to TCS, and was well tolerated.
What we know about IL-31

- Th2 cytokine highly expressed in lesions of AD
- Staphylococcal superantigen rapidly induces IL-31 expression in AD pts
- IL-31R is expressed by keratinocytes, eosinophils, activated macrophages, cutaneous C nerve fibers, and dorsal root ganglia
- Establishing a link between S. Aureus and pruritus

Nemolizumab (Phase 2, RCT)

- A humanized monoclonal antibody against the IL-31RA which significantly reduces pruritus in pts with moderate to severe AD
- EASI score reduction from baseline was
  - $-23.0 \pm 7.5\%$ with 0.1 mg per kilogram
  - $-42.3 \pm 7.3\%$ with 0.5 mg per kilogram
  - $-40.9 \pm 7.5\%$ with 2.0 mg per kilogram
  - $-26.6 \pm 8.1\%$ with placebo

References:
Janus Kinase–Signal Transducer and Activator of Transcription (JAK-STAT) pathway is an intracellular signaling pathway in which many different proinflammatory cytokines (eg, IL-4, IL-5, IL-13, and IL-31) elicit their pathophysiologic functions. 

Baricitinib: Percentage of patients achieving EASI-50 (A) and percentage change from baseline in EASI score (B)

Efficacy and safety of topical JTE-052, a Janus kinase inhibitor, in Japanese adult patients with moderate-to-severe atopic dermatitis: a phase II, multicentre, randomized, vehicle-controlled clinical study*

H. Nakagawa, O. Nemoto, A. Igarashi and T. Nagata*

Department of Dermatology, The Jikei University School of Medicine, Tokyo, Japan
Kojimakai Seipou Skin Clinic, Hokkaido, Japan
Division of Dermatology, NTT Medical Center Tokyo, Tokyo, Japan
Pharmaceutical Division, Japan Tobacco Inc., 4-1, Nihombashi-Honcho 3-chome, Chuo-ku, Tokyo, Japan


Summary
Background JTE-052 is a novel Janus kinase inhibitor presently under clinical development for the topical treatment of atopic dermatitis (AD).

Objectives To evaluate the efficacy and safety of JTE-052 ointment in Japanese adult patients with AD.

Methods Patients with moderate-to-severe AD were randomized (2: 2: 2: 1: 1) to receive JTE-052 ointment at 0.25%, 0.5%, 1%, or 3%, the vehicle ointment or tacrolimus 0.1% ointment (reference) twice daily for 4 weeks. The primary efficacy endpoint was the percentage change in modified Investigator Area Severity Index (mIASI) score from baseline at the end of treatment (EOT). Secondary efficacy end points included change from baseline in the pruritus numerical rating scale (NRS) score.

Results In total, 327 patients were enrolled. At EOT, the least-squares mean percentage changes from baseline in mIASI score for JTE-052 at 0.25%, 0.5%, 1% and 3% and the vehicle ointment were −41.7%, −57.1%, −54.9%, −73.9% and −12.1%, respectively. All JTE-052 groups showed significant reductions of mIASI score vs. the vehicle group (P < 0.001 for all). In the tacrolimus group, the mean percentage change in mIASI score was −62.0%. The JTE-052 groups also showed significant improvement in other parameters; notably, the pruritus NRS score was reduced as early as day 1 night-time. JTE-052 ointment at doses up to 3% was safe and well tolerated.

Conclusions Topical JTE-052 markedly and rapidly improved clinical signs and symptoms in Japanese adult patients with moderate-to-severe AD, with a favourable safety profile. The study results indicate that topical JTE-052 is a promising therapeutic option for AD. The trial registration number is JapicCTI-152887.
TSLP is highly expressed in acute and chronic lesions of AD, but not in the nonlesional skin of patients with AD or in unaffected individuals.

OX40 is a member of the TNF receptor superfamily. TSLP-activated dendritic cells express OX40L and are activated in the lymph nodes by OX40 → Th2 inflammatory cytokine production.
THE FUTURE IS BRIGHT

Menu AD

PDE4 inhibition
IL-4 antagonism
IL-13 antagonism
IL-31 antagonism
IL-22 antagonism
Janus Kinase inhibition

Menu AD

Neurokinin-1 Receptor inhibition
IL-12/23 antagonism
IL-17 antagonism
TSLP inhibition
THANK YOU!
Alopecia Areata
A brief review and up-to-date information on treatment

NADY HIN, DO, PGY-3
DR. BRAD GLICK, DO, MPH, FAOCD, FAAD
LARKIN COMMUNITY HOSPITAL PALM SPRINGS CAMPUS – LECOMT/OPTI
Introduction – Alopecia Areata

- **Non-scarring** hair loss
- **Third** most common form of hair loss
  - 0.1-0.2% of US
  - Average lifetime risk of 1.7-2.1%
- **Males = Females**
- **Onset: Mean Age 30**
  - 60% present by age 20
- **Spontaneous resolution rates : 8-68%**
  - Tosti et Al(2006)
    - 2/3 with <25% scalp involvement had complete resolution for mean of 17 yrs w/o tx
    - 34.6% of 51-75% hair loss recovered or developed milder disease w/o tx
Likely Autoimmune, due to T-lymphocyte interaction with follicular antigens

Current thought:
- Loss of immune privilege by Anagen bulb

Evidence for such:
- Oligoclonal and autoreactive T-lymphocytes are present in peribulbar inflammatory infiltrate
Clinical presentations include:
- Alopecia Areata - Patch
- Alopecia Totalis
- Alopecia Universalis
- Ophiasis Pattern
- Sisaipho Pattern
- Acute Diffuse and Total Alopecia (ADTA)
Alopecia Areata - Patch

- Clinically, sudden onset of well-demarcated round or oval patches of non-scarring hair loss
- Location: **Scalp is MC**
  - **In Men: Beard**
- Pull Test (+)
- Worst prognostic factors:
  - Younger age at initial presentation
  - Severity at Onset
  - Family history
  - Ophiasis Subtype
Alopecia Totalis / Universalis

- Advanced forms of Alopecia Areata
  - 5% progression rate from Patch AA
  - Alopecia Totalis
    - Loss of all scalp hair
  - Alopecia Universalis
    - Loss of all scalp and body hair
Alopecia Areata - Ophiasis

- Band-like alopecia
  - Occipital hairline extending towards temples
- Rarely can present at frontal hairline
  - Can be confused with Frontal Fibrosing Alopecia
- Worst Prognosis of all clinical subtypes
AlopeciaAreata - Sisaipho

- Opposition configuration of Ophiasis subtype
- Hair loss centrally but sparing hairs at margin of scalp
  - Can be confused with androgenetic alopecia
Acute Diffuse and Total Alopecia (ADTA)

- More common in women
- Sudden and diffuse hair loss that lasts around 3 months followed by rapid regrowth over 4-9 months
- Favorable Prognosis but it may recur in future
Nail Changes

- Nail Pitting (MC)
- Trachyonychia
- Longitudinal Ridging
- Red Lunulae
Comorbidities

- Higher incidence noted in patients with:
  - Atopic Dermatitis (MC)
    - **Higher risk of severe AA phenotype**
  - Autoimmune Diseases (SLE, Thyroiditis, DM, Myasthenia Gravis, Vitiligo)
    - Patel et al (2017) conducted a retrospective analysis of 298 patients with AA
      - **Thyroid abnormalities discovered in 20% of the pediatric patients**
      - Screening should be done in those with thyroid symptomology
  - Vitamin D Levels
    - Tsai et al (2018)
    - Retrospective analysis showed **association with severity**
    - Meta-analysis of studies show **association between Vit D deficiency and AA**
Diagnosis

- Pull Test
  - Sign of active disease
- Trichoscopy
  - See Next Slide
- Biopsy
  - Peribulbar lymphocytic infiltrate
Trichoscopy

Yellow Dots
Infundibula with Sebum and Keratin

Exclamation Mark Hairs
Broken hair with a thick pigmented tip

Black Dots
Destroyed hairs in hair follicle opening
Treatment

- AA is often **self limiting**
- Current first line treatments
  - Corticosteroids (Topical and Intralesional)
  - Minoxidil (5%)
  - Topical Immunotherapy
- Newer Treatments
  - JAK Inhibitors
  - PRP
- Others
  - Immunomodulators
  - Anti Inflammatories
  - Targeted Therapies
  - Devices (Lasers, Cryotherapy)
But Where Do I Start?

Alopecia Areata

Topical Corticosteroids (mometasone) +/- Topical 5% minoxidil

Age

< 10yr

Less than 50% scalp involvement

Topical Corticosteroids +/- Intralesional corticosteroids +/- Topical 5% minoxidil

Successful response

YES

Topical immunotherapy

NO

Continue as needed

> 10yr

Greater than 50% scalp involvement

Topical immunotherapy (DPCP)

Successful response

YES

Continue JAK inhibitor therapy +/- Intralesional corticosteroids

NO

SADBE

Scalp prosthesis

Extended Disease

JAK Inhibitors +/- Intralesional corticosteroids

Successful response

YES

Topical immunotherapy

NO
Current Treatments
Generally considered first-line

- **Corticosteroids**
  - Topical and Intrallesional
- **Minoxidil 5%**
- **Contact Immunotherapy**
  - With Anthralin
Treatment – First Line

- **Corticosteroids**
  - **Intralesional** - First line for limited disease
      - Recommend: *low concentration, higher volume*
      - 2.5mg/CC was as effective as 5-10mg/cc
  - **Topical**
    - Clobetasol vs Mometasone (for pediatric patients)
      - **Clobetasol foam** in Double Blind RCT, greater regrowth in 89% vs 11%
  - Monitor for side effects such as skin atrophy
- **Minoxidil 5%**
  - Insufficient as monotherapy
    - In long term studies, mild hair growth without statistical significant
  - Use for maintenance with other treatments
Treatment – First Line

- **Contact Immunotherapy**
  - Anthralin Cream, DPCP Solution, Squaric Acid, topical anthralin
  - Usually at alopecia treatment centers

  **Overall:**
  - ~50-70% rate response rate with some responses occurring after 1-2 years
  - Remission for >1 year
  - DPCP with Anthralin 0.5% ointment
  - Reserved for AU, AT
  - Issues: High dropout rates, level of evidence poor

- Chiang et al (2014) - 50 case review using DPCP
  - 71% of AT, 56% of AU had >50% regrowth
  - 15% of responders did not respond until 1-2 years

  - DPCP + Anthralin 0.5% ointment
  - 88% vs 54.5% had >50% terminal hair regrowth after 30 weeks

  - 11 Studies with 500 patients, no RCTs, 10 ½-head studies with no tx, variety of AA severity
  - ~50% response rate overall, remission >1 year
  - High dropout rates, level of evidence poor

12 year old female AA patient noted on initial exam to have sparse hairs only on the top of the scalp, treated with 1.5% DPCP.
High Dropout Rates
- Often due to expected SE
- Patient compliance is a strong factor in decreased relapse rates (Duh)

Choe et al (2018)
- Retrospective analysis, 159 pts
- Modified DPCP treatment protocol with subclinical sensitization
  - Sensitized with 0.1% and tx with 0.01% QWeekly
- Sensitization with an eczematous reaction may not be required for successful contact immunotherapy
- 46 (28.9%) complete response, 59 (37.1%) partial response
New and More Recent Treatments

- JAK Inhibitors
- Platelet Rich Plasma (PRP)
Treatment – What’s New-Ish?
JAK Inhibitors

- **JAK – STAT Pathway**
  - Cytokine binding
  - JAK receptors dimerize, phosphorylated, recruit STAT molecules to activate target gene transcription
  - Mediates downstream IL-15 signaling of T-cells

- **Baseline lab monitoring**: CBC, CMP, Lipids, HIV, Quant-Gold, CXR

- Avoid in: Hx of Malignancy, Tb, Hepatitis

- Cost: $2000-$5000 per month

---

![Diagram](image.png)

**Fig 1.** Janus kinase—signal transducer and activator of transcription (JAK-STAT) signaling pathway. JAK inhibitors antagonize JAK protein function and prevent activation of the pathway.
- Tofacitinib (JAK1/3)
  - Dose: 5-10mg BID, or 11mg ER QD
    - Shapiro: Recommends 15mg QD + Intralesional Corticosteroids
- Ruxolitinib (JAK1/2)
  - 20mg BID
- Oclacitinib (JAK 1)
- Issues:
  - Relapse once taken off medication
  - Adverse Effects
  - Higher doses have unknown safety profile
  - Topical route safer but unknown benefit
  - Long term likely necessary
  - Longer duration and extent often has poorer response

Table II. Correlation between characteristics of alopecia areata patients (n = 32) treated with tofacitinib and percentage of hair regrowth at last visit

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hair regrowth, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of current episode</td>
<td>-0.434</td>
</tr>
<tr>
<td>Age at onset of first episode</td>
<td>0.370</td>
</tr>
<tr>
<td>Duration of disease since first onset</td>
<td>-0.436</td>
</tr>
<tr>
<td>Age</td>
<td>0.003</td>
</tr>
<tr>
<td>Body mass index (n = 29)</td>
<td>-0.248</td>
</tr>
<tr>
<td>Initial Severity of Alopecia Tool score</td>
<td>0.170</td>
</tr>
<tr>
<td>Tofacitinib duration</td>
<td>0.487</td>
</tr>
<tr>
<td>Total tofacitinib dose</td>
<td>0.098</td>
</tr>
</tbody>
</table>

*P value <.05.
<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 adol, 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>
Treatment – JAK Inhibitors

- Kennedy Crispin et al (2016) – Tofacitinib (5mg BID)
  - 66 pts with AA, AT, AU
  - >66% showed regrowth by 3 months (32% had >50% SALT)
  - Relapse by 8.5 weeks
  - AE: 25% with Infxn (UTI/URI)

  - 90 pts with AA, AT, AU
  - Pulsed oral CST 300 mg monthly x 3 months
  - 77% achieved clinical response (55% had >50% regrowth)

  - 10 patients, 24 weeks
  - 3/10 experienced hair regrowth with Salt improvement of 34.6%
Treatment – JAK Inhibitors (adolescents)

- Craiglow et al (2017) – Tofacitinib 5mg BID
  - 10/14 pts with Salt 20-100%
    - Mean SALT improvement over 2-16 months of 88%
    - Mild AE, no treatment interruptions
- Castelo-Soccio (2017) – Tofacitinib 5-10mg BID
  - 8 patients age 12-19 with AU
    - All pts had >50% hair regrowth
    - 1st 3 months – slow growth, rapid thereafter
    - No AE or infections noted
- Bayart et al (2017) – Tofacitinib and Ruxolitinib 1% and 2% topical
  - 6 patients, 3AU, 2AT, 1AA
  - Ruxolitinib (1 success, 1 fail)
    - 75% eyelash regrowth
  - Tofacitinib (3 success, 1 fail)
    - 20% medial eyebrow regrowth
    - 20% 1 month, 80% 1 year
    - Fail with verabase cream, 95% regrowth with liposomal base of scalp
- 12 pts
- 20mg BID for 3-6 mos
  - 9/12 pts with marked response
  - Average of 92% hair regrowth
- Issue: Relapse over 3-6 months
Treatment - PRP

Advantages:
- Ability to induce longer disease remission
- Regrow pigmented hairs from beginning of hair regrowth
- Safe – autologous material
- No lab monitoring, drug interactions, side effects

Issue: non standardized protocol

Trink et al (2013) - Double blind placebo, half head x 3 months
- Significant improvement monthly PRP(60%) vs ILK(27%) vs placebo

Singh (2015) – Monthly x 6 months
- 19/20 with regrowth

- RCT, 90 patients with no treatment for 3 months before therapy.
- 3 groups:
  - Minoxidil 5% BID vs PRP injections Q4 weeks vs Topical Panthenol BID (placebo)
  - PRP more effective than minoxidil in same treatment period
  - Showed reduction in short vellus hairs
Existing treatments with possible utility

- **Immunomodulators**
  - Systemic Corticosteroids
  - Mycophenolate Mofetil
  - Methotrexate
  - Cyclosporine
  - Sulfasalazine
  - Azathioprine
  - Prostaglandin Analogs

- **Anti-Inflammatories**
  - Simvastatin/Ezetimibe
  - Anti-histamines (Fexofenadine)
  - Low Dose Naltrexone
Treatment – Immunomodulators

- Systemic Corticosteroids
  - Shreberk-Hassidim et al (2016)
  - Pulsed recommended if deciding on this route
  - 41 Studies, various protocols with IV/IM/PO q-monthly
    - Route was not statistically significant
  - RCT Study
  - Complete response in 40% on CST, 0% in placebo

<table>
<thead>
<tr>
<th>Table II. Summary of the response, relapse, and side effects, divided by different routes of treatment and pediatric-only studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate</td>
</tr>
<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td>All studies</td>
</tr>
<tr>
<td>Complete response</td>
</tr>
<tr>
<td>Partial response</td>
</tr>
<tr>
<td>No response</td>
</tr>
<tr>
<td>Relapse (% of responders)</td>
</tr>
<tr>
<td>Side effects</td>
</tr>
<tr>
<td>Pediatric-only studies</td>
</tr>
<tr>
<td>Complete response</td>
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<tr>
<td>Partial response</td>
</tr>
<tr>
<td>No response</td>
</tr>
<tr>
<td>Relapse (% of responders)</td>
</tr>
<tr>
<td>Side effects</td>
</tr>
</tbody>
</table>

Data are presented as total No. of patients and percentage. IM, Intramuscular; IV, intravenous; mini-PO, pulse corticosteroids given once weekly; PO, oral.
*Complete response is defined as >75% of hair regrowth.
†Partial response is defined as 25%-75% of hair regrowth.
‡Relapse is defined as recurrence in responders to therapy.
Treatment – Immunomodulators

- **Mycophenolate Mofetil**
  - Systemic: 500mg BID – 1500mg BID
  - Topical: 2% Cream

- **Methotrexate**
  - Comparative Study, MTX + Prednisone vs Prednisone alone
  - 5/14 pts had >50% hair growth with combo MTX + Prednisone

- **Cyclosporine**
  - Ranges from 25-76.7% success rate >50% regrowth
  - One uncontrolled study – 45.4% of 25 pts showed sig. regrowth

- **Sulfasalazine**
  - Pilot study
  - 43% of 14 pts showed complete regrowth
    - 66% showed no signs of relapse after treatment discontinuation
    - 33% relapsed after 2.5 months
**Treatment – Immunomodulators**

- **Azathioprine**
  - Prospective Study (Vano-Galvan et al 2015)
  - **Azathioprine dosage 2.5 mg/kg/day**
  - 14 patients with AU, recalcitrant to oral CST and DPCP
  - **Response in 6/14 patients**
    - Response in 4.7 months response
    - Relapse: 2 patients after 2.5 months, remaining 4 persistent

- **Prostaglandin Analogs (Lee et al, 2015)**
  - Studies have wide range of variable therapeutic effect
  - Consider for eyebrows
  - Lee et al (2015)
    - Tac + Latanoprost > Tac alone
    - 45% vs 0% improvement
Treatment – Anti-Inflammatories

- Simvastatin/Ezetimibe – 40/10mg QD
    - 29 patients, 40-70% SALT
    - 73% responded after 16-24 weeks (>24% regrowth)
  - Other study, 82.4% showed no improvement
  - Choi et al (2017)
    - Non responders, 14 patient open prospective study
    - 4 responded with 30-80% after 3 months

- Antihistamines (Lee et al, 2017)
  - Cohort Study
    - DPCP + Fexofenadine > DPCP monotherapy

- Low-dose Naltrexone
  - 1-4.5mg QD
  - Possible use for anti-inflammatory
Targeted Therapies

- Ustekinumab
- Apremilast
- Secukinumab
- Abatacept
Treatment - Targeted Therapy

- **Ustekinumab** – 90mg Q12 weeks
  - Guttmann-Yassky E Et Al (2016)
  - **3/9 pts with complete response** after 12 months, 1 had AU

- **Apremilast** – 30mg BID x 3-6 months (mean 4.2mos)
  - Liu et Al (2017)
  - 9 patients (1 AA, 8AU)
    - Duration of disease 23.3 years
  - **None showed improvement over 3-6 months**

- **Secukinumab**
  - RCT was **terminated in 2017** due to low enrollment
Abatacept (CTLA4 Agonist) – 125mg SC weekly


SALT 30-100% (3/15 improved)

1/15 pts with 98% regrowth after 6 months
2/15 with 23% regrowth
Devices

- Superficial Cryotherapy
- Carboxytherapy
- Excimer Laser
- Fractional Photolasers
- Fecal Transplant.. Device?
Treatment - Devices

- **Superficial Cryotherapy**
  - Comparative Study (Faghihi and Radan 2014)
    - 80% vs 91.5% (clobetasol)
  - Jet cryotherapy
    - 11 recalcitrant AA patients
    - 5 excellent response, 3 satisfactory response
    - Most effective at 2 weeks or less
  - **Half head study** (Jun et al, 2017)
    - Superficial cryotherapy showed increased hair thickness and eyebrow density
    - Tx: Each patch 3-4 times for 2-3 sec q 2 weeks
    - 11 of 15 responded, with maintenance 1 month.
    - Improvement by 1.6 x of terminal hair on treated side
    - SALT score of 40% improvement vs 9.6%
  - Rationale: Readily available at most offices, inexpensive, no systemic side effects
Carboxytherapy

- Doghaim et al (2018)
- **80 pts (40 AA, 40 AGA)**, 4 groups (1a, 1b, 2a, 2b)
- Placebo was intradermal distilled water
- Injection: 30g Needle, 2mL CO2 per injection site
- **Significant improvement**
  - 3 months after last session
  - SALT from 9 -> 5.7
  - Control group: 12.5 -> 16.0
- Before, after 6 sessions, then 3 months after last session
- Rationale: Inexpensive
Excimer Laser

- **308nm Excimer**
- Pilot study
  - 42 recalcitrant patches in 18 patients
  - Twice per week for max of 24 sessions
  - 50mJ/cm² less than MED
  - **Complete regrowth in 13/42 lesions, excellent in 5/42**
  - Presence of Atopic Diathesis had an unfavorable prognosis

**Rationale**
- Minimal side effects, ideal for pediatric patients
Treatment - Devices

- Fractional Photothermolysis
  - Controlled clinical trial
  - 32 subjects, 21pAA, 2AT, 1AU, 8 ophiasis
  - 3 patches on each subject
    - Control patch, Nd:YAG patch (2-3 sessions with 2-8 week intervals), fractional CO2 patch (3-6 sessions with 2-4 week intervals)
  - No significant difference between baseline and final hair counts between treated patches and the control patch

- But other studies have reported some improvement
  - Cho et al (2013)
  - 17 patients with 10,600 nm Co2
    - 30-50mJ, spot 150 spots/cm2, 8-22 sessions
    - 12/17 reported clinical response
Fecal Microbiota Transplant

Rebello et al (2017)

Pt A
- 38yoM with recalcitrant AU (Dx at 28yo), p/w C. Diff and tx with FMT. 8 weeks later, patchy hair growth on beard, arms, scalp, face.

Pt B
- 20yoM with Pmhx of Crohn’s and recalcitrant AU (Dx at 18yo)
- Pt previously tx with ILK, Topical CST, Laser, Squaric Acid with no improvement
- C. Diff tx with FMT at 20yo
  - Improved from AU to 25-49% Hair loss with body hair regrowth as well

But what does this mean?
- Microbiota and the immune system
Conclusion

- Alopecia Areata can and almost always will self resolve... eventually
- Initial treatment should follow an algorithmic approach with corticosteroids, minoxidil, immunotherapy
- Widespread and recalcitrant cases
  - JAK inhibitors, PRP, immunomodulators, and various devices
- Be aware of the comorbidities of AA
  - Thyroid Disorders
  - Vitamin D deficiency
  - Atopic Diathesis
  - Anemia
References

References

- Trink, A., Sorbellini, E., Bezzola, P., Rodella, L., Rezani, R., Ramot, Y., &
Thank you!
Granuloma Annulare: A Brief Review and Up-to-date Information on Treatment

RACHEL WHITE, DO, PGY-3
DR. BRAD GLICK, DO, MPH, FAOCD, FAAD
LARKIN COMMUNITY HOSPITAL PALM SPRINGS CAMPUS – LECOMT/OPTI
Background

- Benign, often self-limited granulomatous skin disease
- Clinically – pink annular plaques with raised border and central clearing
- Histologically – interstitial or palisading granulomas, degenerated collagen and mucin
- Most common in children and young adults
- More common in females
Pathogenesis – Mechanisms

- Unknown mechanism; theories originate from histologic findings
- Original theory – immune-mediated type III hypersensitivity reaction ➔ vasculitis
  - Sensitized Th1 lymphocytes ➔ macrophages ➔ proinflammatory cytokines & collagen-degrading enzymes ➔ tissue injury
- Recent theory – cell-mediated delayed-type IV hypersensitivity reaction to unknown antigen
- Other theories – injury to dermal elastic fibers
Pathogenesis – Inciting Factors

- **Trauma/foreign body** – insect bite, tuberculin skin testing, vaccinations, subcutaneous immunotherapy for allergies, tattoo, isomorphic response
- **Infectious** – viruses (Hep B, Hep C, EBV, HIV); *Borrelia* species
- **Drugs** – TNF-α inhibitors, allopurinol, topiramate, gold therapy
- **Genetic** – familial cases including identical twins, HLA-Bw35 (generalized GA)
Associated Disorders

- Diabetes
  - Definitive evidence lacking and conflicting data
- Dyslipidemia
  - Evidence shows link with adult GA
- Malignancy
  - No causative relationship
  - Seen in atypical GA variants
  - Most common malignancy is lymphoma
- Thyroid disease – autoimmune
- HIV – atypical variants
Clinical – Localized GA

- Most common form
- Skin-colored to pink erythematous annular or arcuate plaques with raised border and central clearing
- Discrete papules at periphery
- Location – wrists, ankles, dorsal hands and feet
- Asymptomatic
- Onset – children, young adults
- ~50% patients have >1 lesion
Clinical – Disseminated/Generalized GA

- Widespread skin-colored to pink erythematous papules and plaques of varying sizes
- Location – trunk and extremities
- Asymptomatic or pruritic
- Onset – adulthood
- Associated with HLA-B35
Clinical – Deep/Subcutaneous GA

- Large skin-colored nodules, overlying skin uninvolved
- Location – scalp, buttocks, extremities
- Painless
- Onset – children <6 yo
Clinical – Perforating GA

- Yellow umbilicated papules with scale crust and focal ulceration
- Location – localized on extremity or widespread
- Asymptomatic, pruritic, or painful
- Onset – children, young adults
Clinical – Patch GA

- Symmetric annular patches
- Location – proximal extremities, dorsal feet
- Onset – adults
Pathology

- Lymphohistiocytic infiltrate forming interstitial or palisading granulomas, degenerated collagen, and mucin
- Both patterns in localized and generalized GA
- Patch GA – interstitial
- Subcutaneous GA – palisading
- Perforating GA – transepidermal elimination of mucin and degenerated collagen fibers
Differential Diagnoses – Annular Lesions

- Annular elastolytic giant cell granuloma (actinic granuloma)
- Interstitial granulomatous dermatitis
- Tinea corporis
- Annular lichen planus
- Erythema annulare centrifugum
- Sarcoidosis
- Nodular tertiary syphilis
- Mycosis fungoides
- Borderline leprosy
Differential Diagnoses

- Generalized GA
  - Arthropod assault
  - ID reaction
  - Interstitial granulomatous dermatitis
  - Secondary syphilis
  - Eruptive xanthomas
  - Eruptive syringomas
  - Histiocytomas

- Subcutaneous GA
  - Rheumatoid nodules
  - Epithelioid sarcoma
  - Sarcoidosis
  - Deep fungal infection
  - Tendinous xanthomas

- Perforating GA
  - Reactive perforating collagenosis
  - Perforating folliculitis
  - Elastosis perforans serpiginosa
  - Calcinosis cutis
  - Perforating gout
  - Sarcoidosis
  - Molluscum contagiosum
Diagnosis and Work Up

- Clinical diagnosis
- Punch biopsy with H&E for atypical presentations
- Lipid panel in adults
- Review signs/symptoms/risk factors for diabetes, HIV
- Age-appropriate cancer screening in elderly patients with atypical presentations
Treatments – Overview

- No treatment necessary – often self-limited
- 50% localized GA resolve within 2 years
- Generalized GA more persistent – 25% courses >5 years
- Resolves without scar
- Treatment dependent on type, symptoms, cosmesis
Treatment – Localized GA

- First-line
  - High-potency corticosteroids topical +/- intralesional
    - Clobetasol 0.05% cream BID x 2-4 w
    - Triamcinolone acetonide 2.5-10 mg/cc q 6-8 w
- Others (limited evidence)
  - Cryotherapy
  - Topical calcineurin inhibitors – tacrolimus, pimecrolimus
  - Phototherapy – PUVA, UVA1, NB-UVB, PDT
  - Topical dapsone
  - Intralesional IFN-γ
  - Imiquimod
Treatments – Generalized GA

- **First-line**
  - High potency topical/intralesional corticosteroids
  - Topical calcineurin inhibitors
    - Tacrolimus 0.1% ointment BID x 6 w
    - Pimecrolimus 1% cream
  - Phototherapy
    - UVA1 – high cumulative doses most effective = 1770 – 1840 J/cm²
    - PUVA – oral or bath PUVA with cumulative dose 60.4 J/cm²
    - Narrow-band UVB – cumulative dose 47.7 J/cm² → 54% complete/partial response
    - Photodynamic therapy
Treatments – Generalized GA

- **Systemic treatment**
  - **Antimalarials – first line**
    - Hydroxychloroquine – 3 – 6 mg/kg/d
    - Chloroquine – 3 mg/kg/d
  - **TNF-α inhibitors**
    - Adalimumab – 80 mg at week 0 → 40 mg every other week SQ
    - Infliximab – 5 mg/kg at weeks 0, 2, 6 → every month IV
  - Isotretinoin – 0.5-1 mg/kg/d
  - Dapsone – 100 mg/d
  - **Pentoxifylline – 400 mg TID**
  - **Nicotinamide – 500 mg TID**
  - **Cyclosporine – 3-4 mg/kg/d**
  - **ROM (rifampin, ofloxacin, minocycline)**
  - **Vitamin E oral – 400-600 IU daily**
  - **Fumaric acid esters – used in Europe**
  - **Other case reports: doxycycline, clofazimine, allopurinol, methotrexate, hydroxyurea, alkylating agents (chlorambucil), oral calcitriol, defibrotide, etretinate**
Treatments – Lasers

- Pulsed dye laser
  - Localized or generalized GA
  - ~1/3 no improvement; ~1/3 some improvement; ~1/3 >50% improvement
- Fractional photothermolysis
  - Case reports – significant improvement in height and diameter
- Excimer laser – complete remission ¾ patients
Treatments - Upcoming

- Radial pulse therapy – indirect mechanotherapy
  - 500 shots, pressure 2.5 bars, frequency 4 pulses/sec
  - Positive effects in all treated GA plaques

| TABLE 1. Plaque characteristics and response to treatment |
|---------------------------------|----------------------|------------------|-----------------|-----------------|------------------------|-----------------------------|
| PLAQUE | LOCATION         | DIAMETER | SHAPE                                      | NUMBER OF RPT SESSIONS | DURATION OF TREATMENT | RESULTS                        |
| A      | Left dorsal forearm | 35mm     | Approximately square; has raised and indurated annulare ridge | 34     | 26 weeks | Smooth; no ridges, less erythema |
| B      | Left dorsal forearm | 5mm      | Round; smooth                                | 5      | 2 weeks   | Extinct                      |
| C      | Right dorsal forearm | 44mm     | L-shaped; raised and indurated open ridge     | 25     | 23 weeks | Partial smoothed ridge, less erythema |
| D      | Right dorsal forearm | 8mm      | Oval; smooth                                  | 25     | 23 weeks | Split; demonstrated two smaller point-shaped plaques |

RPT: radial pulse therapy
Treatments – Subcutaneous GA

- Treatment not indicated
- Surgical excision – recurrence common
- Local hyperthermia – case report
  - 44°C for 30 min, improvement after 10 treatments
Conclusion

- Benign, often self-limited disease
- Work up may include history/labs for diabetes, dyslipidemia, malignancy, and HIV
- Pathogenesis involves possible cell-mediated delayed type IV hypersensitivity reaction to unknown antigen
- Many treatments available from topical and light-based therapy to systemic and biologic medications
- Prospective double blind randomized control trials need to be performed for improved evidence-based treatment
References


Thank you!

- Contact information:
- rwhite@larkinhospital.com