WHAT’S NEW IN PEDIATRIC AD?

PETER LIO, MD, FAAD

DISCLOSURE

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Manufacturer</th>
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</thead>
<tbody>
<tr>
<td>Speaker</td>
<td>Regeneron/Sanofi Genzyme, Pfizer, Eli Lilly, LEO, Galderma, and L’Oreal</td>
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<tr>
<td>Advisory Board</td>
<td>Almirall, ASLAN Pharmaceuticals, Dermavant, Regeneron/Sanofi Genzyme, Pfizer, LEO Pharmaceuticals, AbbVie, Eli Lilly, Micreos, L’Oreal, Pierre-Fabre, Johnson &amp; Johnson, Level Ex, KPAway, Unilever, Menlo Therapeutics, Theraplex, Exeltis, AOBiome, Altus Labs, Galderma, Verrica, Arbonne, Amyris, Bodewell, YobeeCare, Burt’s Bees, My-Or Diagnostics, and Kimberly-Clark.</td>
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<tr>
<td>Stockholder</td>
<td>Micreos, YobeeCare, and Altus Labs, KPAway, LearnSkin</td>
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Akdis CA. Does the epithelial barrier hypothesis explain the increase in allergy, autoimmunity and other chronic conditions? *Nat Rev Immunol* (2021). https://doi.org/10.1038/s41577-021-00538-7


DEFINITIONS

- **PROBIOTICS**: SUPPLEMENTS OR FOODS THAT CONTAIN VIABLE MICROORGANISMS THAT ALTER THE MICROFLORA OF THE HOST.
- **PREBIOTICS**: SUPPLEMENTS/FOODS THAT CONTAIN A NONDIGESTIBLE INGREDIENT THAT SELECTIVELY STIMULATES THE GROWTH AND/OR ACTIVITY OF INDIGENOUS BACTERIA.
- **POSTBIOTICS** (AKA: "PARABIOTICS"): NON-VIABLE BACTERIAL PRODUCTS OR METABOLIC BYPRODUCTS THAT HAVE BIOLOGIC ACTIVITY IN THE HOST.
- **ANTIBIOTICS**: THE SUBGROUP OF ANTI-INFECTIVES THAT ARE DERIVED FROM BACTERIAL SOURCES AND ARE USED TO TREAT BACTERIAL INFECTIONS, CAN BE BROAD- OR NARROW-SPECTRUM.
- **ANTISEPTICS**: SUBSTANCE WHICH INHIBITS THE GROWTH AND DEVELOPMENT OF MICROORGANISMS, TYPICALLY VERY BROAD-SPECTRUM.

**DILUTE BLEACH BATHS?**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Chlorine (as Cl)</th>
<th>Water (as Cl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>5 (19.2)</td>
<td>10 (38.5)</td>
</tr>
<tr>
<td>Severe</td>
<td>13 (50.0)</td>
<td>10 (38.5)</td>
</tr>
<tr>
<td>Worst</td>
<td>8 (30.8)</td>
<td>6 (23.1)</td>
</tr>
</tbody>
</table>

**Conclusion**: "This study demonstrated that a four-week, twice-weekly regime of diluted bleach baths may not be useful in reducing S. aureus colonization/infection and improving AD. Instead, regular water baths would be a more efficacious alternative for AD."


BLEACH: NOT ANTIMICROBIAL

DILUTE BLEACH BATHS?

**A TANGLED WEB OF FOOD REACTIONS**

**DEFINITIONS**

- **Foods含有的微生物**:相爱微生物的种类、微生物的数量和优势菌的数量。
- **食物添加剂**:食物中添加的化学物质，包括食品添加剂、色素、香料等。
- **过敏反应**:因食物引起的免疫反应，包括速发型过敏反应和迟发型过敏反应。
- **食物不耐受**:因食物引起的非免疫反应，如肠道功能紊乱、代谢障碍等。
- **食物中毒**:因食物引起的急性中毒，包括食物中毒、食物过敏等。

**TIMING**

- **Immediate**: Immediate or delayed, minutes to days
- **Immediate or delayed, minutes to weeks
- **Immediate or delayed, minutes to days
- **Immediate or delayed, minutes to weeks
- **Delayed, days to weeks

**SEVERITY**

- **Often life-threatening, very serious
- **Not usually life-threatening, can be uncomfortable
- **Not usually life-threatening, can be uncomfortable
- **Serious, permanent condition that can be life-threatening
- **Serious, though not usually life-threatening

**EXAMPLES**

- Peanuts, shellfish
- Lactose intolerance, histamine reactions
- MSG, food additives, gluten outside of celiac
- Tomatoes, citrus
- Dairy, carbohydrates, refined sugars
- Milk (35%), egg (13%), others

**NB**: Not to be confused with "Sensitized" in the allergic context meaning a positive IgE blood test to an allergen.
2020: CRISABOROLE APPROVED DOWN TO 3 MONTHS

MITIGATING PAIN

1. USE A TCS FOR SEVERAL DAYS TO REDUCE INFLAMMATION BEFORE STARTING A STEROID SPARING AGENT (SSA)
2. USE SSAS STRATEGICALLY: MILD-MODERATE ONLY, AVOID BROKEN SKIN, EXTRA CAUTION ON FACE AND NECK (DELICATE AREAS)
3. APPLY MOISTURIZER BEFORE APPLYING THE SSA

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MITIGATING PAIN

4. STORE MOISTURIZER IN THE REFRIGERATOR TO COOL THE SKIN
5. TRY A SMALL TEST AREA BEFORE BROAD APPLICATION
6. APPLY SSAS ON DRY SKIN RATHER THAN DAMP SKIN (WATER IS AN AMAZING PENETRANT!)
7. CONSIDER USING ASPIRING FOR THE APPROPRIATE PATIENT (500 MG 1 HOUR PRIOR TO TACROLIMUS APPLICATION IN ADULTS HAS SHOWN PROMISE)

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DUPILUMAB IN CHILDREN AGED 6 TO 11 YEARS

• PHASE 3 RCT DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL IN 367 CHILDREN WITH SEVERE AD
• 90% RED >1 ATOPIC COMORBIDITY
• RESULTS AT 16 WEEKS.
• 33% OF PATIENTS WHO RECEIVED DUPILUMAB Q4W (300 MG REGARDLESS OF WEIGHT) AND 30% OF PATIENTS WHO RECEIVED DUPILUMAB Q2W (100 MG OR 200 MG BASED ON WEIGHT) ACHIEVED CLEAR OR ALMOST CLEAR SKIN (IGA 0 OR 1) COMPARED WITH 11% FOR TCSS ALONE (P ≤.0001 AND P ≤.001, RESPECTIVELY)

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DUPILUMAB

• IT APPEARS MUCH SAFER THAN CONVENTIONAL IMMUNOSUPPRESSANTS, BUT OTHER POTENTIAL CONSIDERATIONS INCLUDE:
  • CONJUNCTIVITIS IN UP TO 10% OF PATIENTS
  • INJECTION SITE REACTION/SYSTEMIC REACTIONS
  • COST MAY BE A FACTOR
  • INJECTION
  • CURRENTLY APPROVED FOR INDIVIDUALS AS YOUNG AS 6 YEARS OF AGE, BUT YOUNGER GROUPS ARE BEING STUDIED

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SAFETY IN 6-12 AGE GROUP

**Fig.**

**Table:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
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<tbody>
<tr>
<td><strong>TOPICAL</strong></td>
<td></td>
</tr>
<tr>
<td>Baricitinib</td>
<td>JAK1, JAK2, JAK3, TYK2</td>
</tr>
<tr>
<td>Abrocitinib</td>
<td>JAK1, JAK2</td>
</tr>
<tr>
<td>Ruxolitinib</td>
<td>JAK1 and JAK2</td>
</tr>
<tr>
<td><strong>ORAL</strong></td>
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</tr>
<tr>
<td>Abrocitinib</td>
<td>JAK1</td>
</tr>
<tr>
<td>Baricitinib</td>
<td>JAK1 and JAK2</td>
</tr>
<tr>
<td>Upadacitinib</td>
<td>JAK1</td>
</tr>
<tr>
<td><strong>SYSTEMIC INJECTION</strong></td>
<td></td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>IL-6</td>
</tr>
<tr>
<td>Neulasta™</td>
<td>IL-3</td>
</tr>
<tr>
<td>Palidasaro</td>
<td>IL-3</td>
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</table>

**JAK INHIBITORS: SYSTEMIC**

**Objective:**

- REQUIRED BREAKTHROUGH THERAPY DESIGNATION IN FEBRUARY 2018
- BASED ON TOPLINE RESULTS FROM PHASE 3 TRIAL IN PATIENTS AGED ≥12 YEARS WITH SEVERE DISEASE
- BY WEEK 12, PERCENTAGE OF PATIENTS WHO MET EACH CO-PRIMARY EFFICACY ENDPOINT AND EACH KEY SECONDARY ENDPOINT WITH EITHER 100 MG OR 200 MG WAS SIGNIFICANTLY HIGHER THAN PLACEBO

**Background:**

- BY A PHASE 2 TRAIL INVOLVED 386 PATIENTS ACHIEVED AN EASI 75 AND PLACEBO AT 16 WEEKS
- ALL PATIENTS WERE USING TCSS FOR 1 MONTH PRIOR TO INITIATION
- MULTIPLE PHASE 3 TRIALS FOR ADULTS ARE EVALUATING SAFETY AND EFFICACY AND USE AS MONOTHERAPY

**UPADACITINIB**

- REQUIRED BREAKTHROUGH THERAPY DESIGNATION IN JANUARY 2018
- PHASE 2 TRAIL REVEALED THAT 30 MG DOSE THAN PLACEBO AT 16 WEEKS
- PRIMARY ENDPOINT: PROPORTION OF PARTICIPANTS ACHIEVING A≥12 EASI SCORE IMPROVEMENT AND PRURITUS RESOLUTION

**Systemic JAK Inhibitors for AD**

- ALL WORK RAPIDLY WITHIN DAYS
- BIODISTRIBUTION AND SAFETY DEPEND ON MOLECULE AND DOSE
- JAK INHIBITORS MAY BE APPROPRIATE AS FIRST-LINE SYSTEMIC THERAPY WITH PROPER SHARED DECISION-MAKING PROCESS AND PATIENT INCLUSION
- JAK INHIBITORS DO NOT APPLY FOR THE TREATMENT OF AD

**Safety and Tolerability Outcomes to Pay Attention to:**

- HEADACHE AND AGGRAVATION
- ACNE
- HERPES SIMPLEX AND HERPES ZOSTER VIRUSES
- SEVERE INFECTION
- ADVANCED CARDIOVASCULAR EVENTS, STROKE, AND MI
- MAJOR ADVERSE CARDIOVASCULAR EVENTS, STROKE, AND MI

**Abrocitinib In Pediatric AD**

- INHIBITS JAK1, JAK2, JAK3, AND JAK12
- PHASE 3 JADE PROGRAM IN PATIENTS WITH MODERATE-TO-SEVERE AD
- THE 12-WEEK STUDY COMPARED ABROCITINIB (PF-06658142), 87451012) 200 MG AND 100 MG WITH PLACEBO IN 387 PATIENTS AGED ≥12 YEARS
- PRIMARY ENDPOINT: PROPORTION OF PATIENTS EXPERIENCING AN EASI SCORE OF CLEAR (0) OR ALMOST CLEAR (1) SKIN AND ≥20-POINT IMPROVEMENT RELATIVE TO BASELINE
- CO-PRIMARY ENDPOINT: PROPORTION OF PARTICIPANTS ACHIEVING ≥75% CHANGE IN EASI SCORE FROM BASELINE

**References:**

2. CLINICAL TRIALS ARENA. PRESS RELEASE. OCTOBER 29, 2019 (WWW.CLINICALTRIALSARENA.COM/NEWS/PFIZER-ABROCITINIB-BREAKTHROUGH-THERAPY-DESIGNATION-GRANTED-04965842; B7451012) 200 MG AND 100 MG DOSE THAN PLACEBO AT 16 WEEKS
3. SIMPSON EL, ET AL. RAD 2020. ABSTRACT 148
5. CLINICAL TRIALS ARENA. PRESS RELEASE. OCTOBER 29, 2019 (WWW.CLINICALTRIALSARENA.COM/NEWS/PFIZER-ABROCITINIB-BREAKTHROUGH-THERAPY-DESIGNATION-GRANTED-04965842; B7451012) 200 MG AND 100 MG DOSE THAN PLACEBO AT 16 WEEKS

**COMPARISON**

- **DELUOCTINIB**
  - Doses ranging (0.25%-3%) ointment vs vehicle vs tacrolimus 0.1% twice daily x 4 weeks
  - All doses > vehicle by EASI (75% vs 15% in 3% group)
  - Tacrolimus = 85% reduction
  - No serious AEs
- **RUXOLITINIB**
  - Phase 2 randomized, dose-ranging, vehicle- and active-controlled study to evaluate safety and efficacy in adult patients
  - 1.5% twice daily group > vehicle in EASI (71.6% improvement at 4 weeks) and noninferior to triamcinolone cream 0.1%
  - Phase 1 study in children aged 2-7 years and 2 phase 3 studies in patients aged ≥12 years (TRUE AD1 and TRUE AD2) are underway

**TOPICAL AHR RECEPTOR LIGAND**

- Activates epidermal AHR, hydrocarbon receptors
- Improves barrier function and ceramide production
- Coal tar may work through a similar mechanism
- Randomized, vehicle-controlled, double-blind phase 2B dose-finding adolescents and adults with moderate to severe AD
  - 1% bid vs. vehicle 53% vs. 24%
  - Itch reduction at 1 week
  - AE: stinginess/burning

**MECHANISM**


KEY TAKEAWAYS

• THE PAST 50 YEARS HAVE BEEN RELATIVELY QUIET FOR AD... BUT THAT’S NOT PREDICTIVE OF THE NEXT 5-10!
• WE ARE ON THE VERGE OF A GIANT LEAP IN BOTH UNDERSTANDING AND TREATING AD.
• WHILE AD IS MORE TERRIBLE THAN EVER, NEW MODALITIES HAVE THE POTENTIAL TO PUSH BACK WITH UNPRECEDENTED POWER.

THANK YOU!

peterlio@gmail.com