New and Emerging Therapies for Atopic Dermatitis (AD)

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Inside-out vs outside-in hypothesis

Allergens
S. aureus

Outside-in

Immune response

IL-4
IL-13
IL-31
IL-22

Inside-out

FLG
LOR
Lipids

Skin barrier

Brough et al. Allergy 2021
**Dupilumab (Dupixent®): Anti-IL-4Rα**

- Initially approved for moderate-severe AD in **March 2017** for ages ≥18 yrs
- Label expanded to ≥12 yrs in **2019**.
- Approved for ≥6 yrs for AD in late **May 2020**
- Ongoing studies down to 6 months of age
- 75% of the kids achieved EASI 75.

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**Immune Pathways in Atopic Dermatitis**

Type 2 cytokines including IL-33
Emerging Treatments in AD

- **Topical JAK Inhibitors**
  - Ruxolitinib
  - Delgocitinib
- **Oral JAK Inhibitors**
  - Baricitinib
  - Upadacitinib
  - Abrocitinib
- **IL-13 Inhibitors**
  - Tralokinumab
  - Lebrikizumab
- **Other topicals**
  - Roflumilast- topical PDE4 inhibitor
  - Tapinarof- aryl hydrocarbon receptor modulator

LEBRIKIZUMAB AND TRALOKINUMAB TARGET IL-13

Is IL-13 inhibition enough to control AD, or do we need to inhibit both IL-4 and IL-13?

ECZTRA 1–3: Primary endpoints among adults with AD treated with tralokinumab for 16 weeks (with or without concomitant TCS)

- ECZTRA 1: 35.8% in TLO group and 46.2% in placebo group; ECZTRA 2: 22.8% in TLO group and 44.3% in placebo group; ECZTRA 3: 2.8% in TLO + TCS group and 10.2% in placebo + TCS

*P<0.05, †P<0.01, ‡P<0.001 vs placebo (±TCS);


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ECZTRA 1–3: Safety through Week 16

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=196)</th>
<th>TLO 300 mg q2w (n=602)</th>
<th>Placebo (n=200)</th>
<th>TLO 300 mg q2w (n=592)</th>
<th>Placebo + TCS (n=126)</th>
<th>TLO 300 mg q2w + TCS (n=252)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 AE</td>
<td>131 (77)</td>
<td>460 (76)</td>
<td>132 (66)</td>
<td>364 (61)</td>
<td>84 (67)</td>
<td>180 (71)</td>
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<tr>
<td>≥1 serious AE</td>
<td>8 (4)</td>
<td>23 (4)</td>
<td>5 (3)</td>
<td>10 (2)</td>
<td>4 (3)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>AE leading to trial withdrawal</td>
<td>8 (4)</td>
<td>19 (3)</td>
<td>2 (1)</td>
<td>9 (2)</td>
<td>1 (1)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>AEs reported by ≥5% patients in any treatment group*</td>
<td>75 (38)</td>
<td>206 (44)</td>
<td>67 (34)</td>
<td>17 (9)</td>
<td>98 (17)</td>
<td>49 (8)</td>
</tr>
<tr>
<td>Atopic dermatitis</td>
<td>3 (2)</td>
<td>156 (26)</td>
<td>19 (10)</td>
<td>33 (6)</td>
<td>22 (12)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Viral URTI</td>
<td>4 (2)</td>
<td>156 (26)</td>
<td>67 (34)</td>
<td>98 (17)</td>
<td>10 (8)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>UTI</td>
<td>5 (3)</td>
<td>156 (26)</td>
<td>67 (34)</td>
<td>98 (17)</td>
<td>10 (8)</td>
<td>6 (2)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>4 (2)</td>
<td>43 (7)</td>
<td>3 (2)</td>
<td>18 (3)</td>
<td>4 (3)</td>
<td>28 (11)</td>
</tr>
<tr>
<td>URTI</td>
<td>15 (8)</td>
<td>156 (26)</td>
<td>19 (10)</td>
<td>33 (6)</td>
<td>22 (12)</td>
<td>13 (7)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10 (5)</td>
<td>32 (5)</td>
<td>5 (3)</td>
<td>12 (2)</td>
<td>6 (3)</td>
<td>16 (3)</td>
</tr>
<tr>
<td>Headache</td>
<td>10 (5)</td>
<td>28 (5)</td>
<td>6 (3)</td>
<td>16 (3)</td>
<td>6 (3)</td>
<td>16 (3)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>5 (3)</td>
<td>156 (26)</td>
<td>19 (10)</td>
<td>33 (6)</td>
<td>22 (12)</td>
<td>13 (7)</td>
</tr>
</tbody>
</table>

Data are n (%); *Reported by system organ class and preferred term according to MedDRA 20.0

- Authors reported safety profiles at Week 52 (ECZTRA 1 and 2) and 32 (ECZTRA 3) were comparable with the initial treatment periods
- 97% of conjunctivitis cases in ECZTRA 1 and 2, and all cases in ECZTRA 3 were mild to moderate – across trials there were 2 treatment discontinuations because of conjunctivitis
- In ECZTRA 3 lower rates of severe and serious infections and eczema herpeticum were reported for tralokinumab and TCS versus placebo and TCS

JAK-Targeted Therapy for Atopic Dermatitis

- Atopic dermatitis (AD) is a chronic, intensely pruritic, inflammatory skin dermatosis.¹

- Janus kinases (JAKS) act downstream of proinflammatory cytokines and itch mediators involved in AD pathogenesis.¹,²

- Ruxolitinib (RUX) cream is a topical selective inhibitor of JAK1 and JAK2³

- In a phase 2 study (NCT03011892), RUX cream provided high rates of strength-dependent efficacy in patients with AD and a safety profile similar to vehicle⁴

- **Objective:** to evaluate the efficacy and safety of RUX cream using pooled data from two phase 3 AD studies of identical design (TRuE-AD1 [NCT03745638] and TRuE-AD2 [NCT03745651]) in adolescent and adult patients with AD

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**Ruxolitinib Cream vs Triamcinolone 0.1% Cream**

![Graph showing efficacy comparison between Ruxolitinib Cream and Triamcinolone 0.1% Cream](image-url)

JAK Inhibition Safety and Monitoring

- **Monitor for:**
  - Decreased hemoglobin, neutrophil, lymphocyte, and platelet levels
  - Elevated LFTs, creatinine (Cr), HDL, LDL, and creatine phosphokinase (CPK)

- **Mild infections, nasopharyngitis and URI, are the most common reported adverse events**

- **Increased risk:**
  - Herpes zoster (rate 3.8-5.2 per 100 patient years)
  - TB (rate 0.2 per 100 patient years)
  - Serious infections (rate 2.6-3.6 per 100 patient years)
Key Points Summary

- Emerging therapies are based on our current understanding of mechanisms underlying AD
- The pathophysiology of AD is based on a combination of skin barrier dysfunction and polarized immune responses
- Targeting key molecules in inflammatory cascade offers therapeutics that are precise and steroid-sparing
Treatment Approaches for Difficult to Control Urticaria:
(in 10 minutes)

David A. Khan, MD
Professor of Medicine and Pediatrics
Allergy & Immunology Program Director

Disclosures

- Author the UptoDate Chapters on Chronic Urticaria

All medications other than antihistamines and omalizumab are considered “off-label” for treatment of chronic urticaria
Objectives

- To be able to discuss management options for refractory chronic urticaria

Initial Approach to Refractory Urticaria

- Make sure its urticaria
- Antihistamine refractory?
  - Appropriate dose?
  - Appropriate duration?
  - 1st generation failure?

**1st Generation Antihistamines: Hydroxyzine and Doxepin**

- Not therapeutically equivalent
- Which agent to choose?
  - Usually based on which one they haven’t tried
  - Doxepin associated with weight gain and likely more sedating
- My dosing preferences
  - Usually 10-25 mg qhs as a single dose
  - Increase dose by 10-25 mg weekly as tolerated
  - Target of 50-150 mg qhs

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Antihistamine Refractory Urticaria

- Omalizumab usual choice (proven safety and efficacy)
- 300 mg every 4 weeks superior than 150 mg
- 6 month treatment considered adequate to see response


Failure of Omalizumab 300 mg q 4 weeks

- Reconsider diagnosis
- Change omalizumab dosing interval
- Change omalizumab dose
  - No controlled trials for either approach
Two-week intervals during omalizumab treatment may provide better symptom control in selected patients with chronic urticaria

Murat Türk, MD,1 Emek Kocatürk, MD,2 Kübra Cüre, MD,3 and Insu Yılmaz, MD4

TABLE I. Patient characteristics and treatment descriptions

<table>
<thead>
<tr>
<th>No.</th>
<th>Age/Gender</th>
<th>Diagnosisa</th>
<th>Total duration of omalizumab treatment (wk)</th>
<th>Treatment description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22/F</td>
<td>CSU</td>
<td>9</td>
<td>150 mg/4 wk; first 3 wk: AH once in the first half of the interval and 3 × 1 per day in the second half; 300 mg/4 wk: for complete response, took AH once in the first half of the interval and 3 × 1 per day in the second half; 150 mg/2 wk: had complete response (UAst ≥ 0) without any AH.</td>
</tr>
<tr>
<td>2</td>
<td>41/M</td>
<td>SD</td>
<td>30</td>
<td>Cannot tolerate less than 2 × 1 AH per day from the beginning of omalizumab treatment.</td>
</tr>
<tr>
<td>3</td>
<td>49/F</td>
<td>CSU</td>
<td>14</td>
<td>300 mg/4 wk: symptomatic (UAst &gt; 14) in the second half of the interval despite 4 × 1 AH per day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>150 mg/2 wk: complete response with 2 × 1 AH per day (UAst = 0).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Still symptomatic (UAst &gt; 14) in the last week despite 4 × 1 AH per day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>150 mg/2 wk: well controlled with 1 × 1 AH per day (UAst = 2).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>300 mg/4 wk: symptomatic in the last week of the interval (UCT &lt; 12) for 5 mo.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>150 mg/2 wk: well controlled at the end of the second half of the interval (UCT = 12).</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>300 mg/4 wk: symptomatic despite 2 × 1 AH per day (UCT = 8) for 2 mo.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Symptoms dramatically increase in the second half of the interval.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>150 mg/2 wk: well controlled with 2 × 1 AH per day at the end of the third month (UCT = 12).</td>
</tr>
</tbody>
</table>

Omalizumab for severe chronic spontaneous urticaria: Real-life experiences of 280 patients

Zahava Vadasz, MD, PhD, Yuval Tal, MD, Menachem Rotem, MD, Vered Schichter-Confino, MD, Keren Mahlab-Guri, MD, Yoel Graft, MD, Aharon Kessel, MD, Nancy Agron-Levin, MD, Ramit Mazet-Segal, MD, Shmuel Kivity, MD, Shira Benor, MD, Idit Lachover-Roth, MD, Yuri Zeldin, MD, Miguel Stein, MD, On Toker, MD, Gamal Hassoun, MD, Shira Bezalel-Rosenberg, MD, Elias Toumi, MD, Ilan Asher, MD, and Zev Stroinger, MD, for The Israeli Forum for investigating and treating Chronic Spontaneous Urticaria (CSU)

Clinical Communications

FIGURE 1. The percentage of well-controlled patients, fair-weak, and failure in all omalizumab-treated patients with CSU. pt., Patient.

Clinical Implications

- In severe chronic spontaneous urticaria, attempts at increasing omalizumab dosing intervals or stopping therapy typically failed, suggesting that continuous treatment is needed to maintain remission.


166 CSU patients treated with omalizumab
- 122 (300 mg q 4 weeks)
- 11 (450 mg every 4 weeks)
- 33 (600 mg every 4 weeks)
  - 9 received 600 mg every 2-3 weeks
  - None improved
- 61% improved with updosing
- Dosing > 600 mg every 4 weeks does not appear beneficial

Majority of CU patients used corticosteroids


Combination of OMA + CSA

Response in 2-4 months


Evidence for Alternative Therapies in CU

- Overall the evidence for most other alternative therapies is weak
- Few agents have well designed randomized placebo-controlled studies
- Most studies have small number of participants
TABLE II. Beyond guideline alternative agents for refractory CU

<table>
<thead>
<tr>
<th>Alternative agent</th>
<th>Typical dose</th>
<th>Onset of improvement</th>
<th>Evidence</th>
<th>Lab monitoring</th>
<th>Reports of benefit as add-on to standard of care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultraviolet light therapy</td>
<td>200-1000 ml/m² 3 times a week</td>
<td>2 wk</td>
<td>2 RCTs</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>100-250 mg/d with reduction of dose as tolerated</td>
<td>1-6 wk</td>
<td>1 RCT, case series</td>
<td>Baseline: GFR, CBC, LFT; Monthly: CBC, LFT; U&amp;L &gt;6 months then periodically</td>
<td>No</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>200 mg twice/d</td>
<td>Up to 12 wk</td>
<td>1 RCT</td>
<td>Baseline: GFR, LFT, BUN/C</td>
<td>No</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>1 mg/kg/d</td>
<td>2-6 wk</td>
<td>Noninferiority study to cyclosporine</td>
<td>Baseline: CBC, LFT; Every 2 wk CBC with dose escalation; Monthly: CBC, LFT</td>
<td>Yes</td>
</tr>
<tr>
<td>Montelukast</td>
<td>10 mg/d</td>
<td>2-4 wk</td>
<td>Multiple RCTs (mixed results)</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>500 mg twice/d, increasing to 1 g twice/d</td>
<td>&lt;4 wk</td>
<td>Case series</td>
<td>Baseline: CBC, LFT, BUN/C; Monthly: CBC, LFT; BUN/C x 3 mo then every 3 mo</td>
<td>No</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>1 mg twice/d, increasing to 2-3 mg twice/d if needed</td>
<td>1-2 wk</td>
<td>Case series</td>
<td>Baseline: CBC, LFT, BUN/C; LFT, BUN/C x 3 mo then every 3 mo</td>
<td>Yes</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>1000 mg twice/day, increasing to 4-6 g/d if needed</td>
<td>1-2 wk</td>
<td>Case series</td>
<td>Baseline: CBC, LFT, BUN/C; First month: weekly CBC then every 2 wk for 2-3 mo then monthly</td>
<td>No</td>
</tr>
<tr>
<td>Cilomilast</td>
<td>0.6 mg twice/d</td>
<td>Unclear</td>
<td>Case series</td>
<td>RCT in DPU was negative</td>
<td>No</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>10-15 mg weekly</td>
<td>1-6 mo</td>
<td>2 RCTs and meta-analysis were negative</td>
<td>Baseline: CBC, LFT, BUN/C, CXR; Every 2 wk CBC, LFT, BUN/C</td>
<td>Yes</td>
</tr>
</tbody>
</table>

No permanent complications observed

Original Article

The Comparative Safety of Multiple Alternative Agents in Refractory Chronic Urticaria Patients

Sharon Seth, MD, and David A Khan, MD Dallas, Texas

TABLE III. The most common AEs and reasons for discontinuation of the most commonly used agents

<table>
<thead>
<tr>
<th>Medication (no. of patients treated)</th>
<th>Most common AEs</th>
<th>Reason for discontinuation (no. of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapsone (73)</td>
<td>Asymptomatic drop in hemoglobin level</td>
<td>Symptomatic methemoglobinemia (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Racing heart (1)</td>
</tr>
<tr>
<td>Sulfasalazine (47)</td>
<td>GI symptoms and headaches</td>
<td>GI symptoms (6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flu-like symptoms (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drop in WBC count (1)</td>
</tr>
<tr>
<td>Hydroxychloroquine (45)</td>
<td>GI symptoms</td>
<td>GI symptoms (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paresthesia and rash (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Headaches (1)</td>
</tr>
<tr>
<td>Tacrolimus (36)</td>
<td>GI symptoms and headaches</td>
<td>GI symptoms (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Headaches (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rise in creatinine level (1)</td>
</tr>
<tr>
<td>Mycophenolate (27)</td>
<td>GI symptoms and headaches</td>
<td>Leukopenia (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Irritability (1)</td>
</tr>
<tr>
<td>Omalizumab (24)</td>
<td>Mild flushing (rare)</td>
<td></td>
</tr>
<tr>
<td>Cyclosporine (8)</td>
<td>GI symptoms</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions

- Antihistamines are effective in many patients and higher doses or multiple agents may be additive
- Omalizumab is effective in most patients with antihistamine refractory CSU
- In those who fail standard omalizumab dosing, adjustments to frequency and dose may be considered
- Evidence for alternative agents other than omalizumab is weak and limited but omalizumab refractory CSU patients may still have benefit without toxicity of systemic steroids
Long Term Prophylaxis for Hereditary Angioedema

Timothy Craig, FAACAI, FAAAAI, FACP, FACOI
Professor of Medicine and Pediatrics
Distinguished Educator
AAAAI Board of Directors
Section Chief
Director Alpha-1-Antitrypsin Deficiency Center
Director of International Angioedema Center (ACARE)
Vietnam Education Foundation Scholar
Honorary Board of Directors, Lam Dong Medical College

Conflicts of Interest:

<table>
<thead>
<tr>
<th>Company</th>
<th>Research</th>
<th>Consultant</th>
<th>Speaker</th>
<th>Travel</th>
<th>Grant</th>
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<tbody>
<tr>
<td>CSL Behring</td>
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<td>Grifols</td>
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<td>Taketa</td>
<td>x</td>
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<td>x</td>
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<td>Biocryst</td>
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<td>Pharming</td>
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<td>Spark</td>
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<td>x</td>
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<td>BioMarin</td>
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<td>x</td>
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<tr>
<td>KalVista</td>
<td>x</td>
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<tr>
<td>Pharvaris</td>
<td>x</td>
<td></td>
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</tr>
</tbody>
</table>
Objectives:

1. To understand the most recent HAE Guidelines for Long Term Prophylaxis.
2. To understand the efficacy of the medications for Chronic Prophylaxis.
3. To improve care and outcomes of patients with Hereditary Angioedema (HAE)

(Xu, Craig. Clin Exp Allergy 2013)
Effect of C1-inhibitor (C1 INH) on bradykinin and bradykinin effect on the B-2 Bradykinin receptor

Bradykinin

Non stimulated

Increased vascular permeability

VE-cadherin

Actin stress fibers

Stimulated


(Xu, Craig. Clin Exp Allergy 2013)
3C: Long term prophylaxis (LTP) in type 1 and 2

- Recommended: C1-inhibitor IV or SQ, and lanadelumab
- Berotralstat was not yet approved, but would be recommended
- Second line androgens, tranexamic acid
- C1-inhibitor intravenous dose can be increased to 2500 units, but avoid ports
- Lanadelumab: suggest reducing to once a month after 6 months of control
- Avoid androgens under the age of 16, pregnancy and lactating
- Antifibrinolytics secondary to lack of efficacy should seldomly be used
- Recombinant C1-INH may be considered for prophylaxis, but is not approved

Busse P et al. JACI-IP 2021
Recommendations 9, 10, 11, 12

• 9: We suggest that prophylaxis be discussed at every visit and disease burden and preference should be taken into account.
• 10: We recommend C1-inhibitor be first-line prophylaxis
• 11: We suggest to use androgens as second line therapy
• 12: We suggest alter prophylaxis dose and or interval to minimize disease burden

2022 WAO Guideline added lanadelumab and berotralstat as first line therapies for prophylaxis

WAO HAE Guidelines 2018. WAO Online Journal 2018

Recommendation 15:

• We recommend C1-inhibitor as the preferred therapy for HAE attacks during pregnancy and lactation.

WAO HAE Guidelines 2018. WAO Online Journal 2018
How do we determine who needs prophylaxis?

Factors to Consider in Treatment Decision

- Overall burden of disease
- Angioedema attack frequency
- History of severe debilitating or life-threatening attacks
- Access to urgent care
- Anxiety about future attacks
- Ability to attend work or school
- Ability to plan future life events
- Ability to conduct activities of daily living
- Benefit-risk profile and treatment burden of available acute and prophylaxis therapies

Annals of Allergy Asthma and ImmunologyCraig et al 2018

Reduction of attacks with IV C1-inhibitor at 1000 units twice a week

IV C1-INH Major Events During CHANGE Trial

50% reduction of attacks

Main adverse effects are local injection site reactions
Reduction of attacks with SQ C1-inhibitor at 40 and 60 units per kg twice a week

Median 95% reduction of attacks

Main adverse effects are local injection site reactions

Lanadelumab for prophylaxis?

Mean 87% reduction of attacks

Main adverse effects are local injection site reactions
Efficacy Results for berotralstat

Berotralstat Reduced Attack Rates, Attack Duration, and Use of On-Demand Medications in Subjects Assigned to Placebo in Part 1 and Re-Randomized to 150mg in Part 2

Mean reduction of attacks of 47%

Wedner H et al. Berotralstat poster. ACAAI Nov 2020

Safety Results (continued)

Most Common Treatment Emergent Adverse Events (TEAEs)*
Occurring ≥10% in all subjects and ≥5% more frequently with berotralstat than placebo

<table>
<thead>
<tr>
<th>TEAE, n (%)</th>
<th>110 mg (N=41) 48 weeks</th>
<th>150 mg (N=40) 48 weeks</th>
<th>110 mg after Placebo (N=17) 24 weeks</th>
<th>150 mg after Placebo (N=17) 24 weeks</th>
<th>Placebo (N=39)b 24 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper respiratory tract infection</td>
<td>15 (36.6%)</td>
<td>21 (52.5%)</td>
<td>4 (23.5%)</td>
<td>3 (17.6%)</td>
<td>11 (28.2%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4 (9.8%)</td>
<td>12 (30.0%)</td>
<td>2 (11.8%)</td>
<td>2 (11.8%)</td>
<td>4 (10.3%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (12.2%)</td>
<td>7 (17.5%)</td>
<td>0</td>
<td>1 (5.9%)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (9.8%)</td>
<td>6 (15.0%)</td>
<td>0</td>
<td>2 (11.8%)</td>
<td>1 (2.6%)</td>
</tr>
</tbody>
</table>

*The terms abdominal pain, diarrhea, and upper respiratory tract infection are medical concepts which contain multiple preferred terms.

aTime on study drug represents the maximum possible exposure. Some subjects discontinued prior to the Week 48 study visit.

bOne subject in the placebo group was randomized but not dosed. Five patients on the placebo in Part 1 did not transition to Part 2.

Wedner H et al. Berotralstat poster. ACAAI Nov 2020
During an attack

After successful treatment of an attack
Before control

After control
Summary

- In the past we focused on treating attacks.
- Now we focus on preventing attacks.
- My suspicion is that we are approaching a “relative cure” for HAE and we need up to date guidelines that focus on prophylaxis
- Thank you
- Please get vaccinated

Thank you from Penn State Allergy Have a great day. Questions?
OBJECTIVES:

• Upon completion of this learning activity, participants should be able to:
• Describe delayed cutaneous reactions to the various SARS Co-V2 vaccines
Delayed injection-site reactions (onset on or after day 8) to the mRNA COVID 19 Moderna vaccine occurred in 0.8% of participants (244 of the 30,420 participants) after the first dose and in 0.2% (68 participants) after the second dose.

Symptoms included erythema, induration and tenderness which typically resolved after 4-5 days.

Other skin reactions included vesicular, urticarial, exfoliative, macular, and papular rashes, as well as facial swelling after cosmetic filler injections.

Series of 12 patients who developed delayed large local reactions to the mRNA-1273 vaccine (Moderna vaccine).

Onset range of 4-11 days. Five were large with a diameter ≥ 10 cm.

Symptom resolution occurred between 2-11 days with median of 6 days.

Patients were treated with antihistamines, topical and systemic corticosteroids.

All patients received their 2nd dose of the vaccine.

½ did not have symptoms, ¼ had milder symptoms, and ¼ had similar symptoms.

Most patients had the vaccine on the opposite arm and were treated with short or long-acting antihistamines as premedication.

The onset of reactions after the 2nd dose, if they occurred, was sooner (median day 2).

Table 1: Incidence of localized cutaneous adverse reactions reported in Moderna phase 3 trial.

Fifteen patients developed erythematous painful local reactions near the injection site a median of 7 days (range 2-12) after injection.

Majority of patients were Caucasian females.

Symptoms lasted a median of 5 days (range 1-21 days).

Most were treated with either topical CS, oral antihistamines, cold compresses or a combination.

Eleven patients had a recurrence of similar symptoms with the second injection that occurred sooner, lasted a shorter period, and were treated similarly.

Skin biopsy report in one patient: consisted of a perivascular and interstitial inflammatory infiltrate with lymphocytes and eosinophils.

“COVID ARM”

A delayed hypersensitivity reaction occurring approximately 1 week after administration.

It appears as a red, warm, pruritic, indurated, or swollen area in the vicinity of the vaccine site.

Pruritus is a common finding, along with lack of progression of symptoms, response to topical steroids, and/or spontaneous resolution usually over 4 to 5 days.

A series of 3 patients reported local reactions after the mRNA 1273 (Moderna) vaccine-2 misdiagnosed as cellulitis.

The 2 patients were prescribed antibiotics but did not take after consultation with dermatology.

All 3 patients improved with use of topical CS.
A report of 55 events in Black, Indigenous Persons, and People of Color (BIPOC).

The reactions were reported in patients who were:
- Asian (n=27)
- Mixed race [American Indian–Alaska Native and Native Hawaiian–Pacific Islander] (n=22)
- Black (n=6)
- Six patients were of Hispanic ethnicity

The majority of the DLLRs occurred after the receipt of the 1st vaccine dose (in 53 patients [96%]) and after the receipt of the mRNA-1273 vaccine (in 47 [85%]).

The mean time from vaccination until symptoms onset was 8±2 days (range, 4-14 days).

Eleven patients (20%) had cutaneous reactions other than DLLR-diffuse itching, hives or other rash, or angioedema.

38-year-old woman who had received the first dose of the BNT162b2 vaccine. Six days after the injection, she developed erythema of the upper arm with associated numbness of the fingers.

The symptoms resolved within 5 days.

Skin-biopsy displayed a sparse, superficial, deep lymph-histiocytic infiltrates with CD3+ (including CD8+ and CD4+) T cells and some eosinophils.

An immediate reading (at 30 minutes) and late readings (on days 2, 4, and 7) of skin tests (patch, prick, and intradermal tests) with BNT162b2 vaccine were negative.

The patient did not have a recurrence of the delayed local reaction after she received the second dose of the BNT162b2 vaccine.
Data recorded from December 2020 to February 2021:

- 414 cutaneous reactions to mRNA COVID-19 vaccines from Moderna (83%) and Pfizer (17%).
- DLLRs were most common primarily after Moderna vaccination (94%) at a median of 7 days after the 1st vaccine and lasted a median of 4 days. The reaction occurred more quickly after the 2nd dose, at a median of 2 days and lasted a median of 3 days. Some occurred after the 2nd dose ONLY and lasted a median of 2 days.
- Other reactions included local injection site reactions, urticarial eruptions, and morbilliform eruptions.
- Less commonly seen: pernio/chilblains, cosmetic filler reactions (n=8 Moderna vaccine/n=1 Pfizer vaccine), zoster, herpes simplex flares, and pityriasis rosea-like reactions.
- 43% of patients with 1st-dose reactions experienced 2nd-dose recurrence.

COVID TOES:

- Case report: A 76-year-old man reported developed toe discoloration 1 week after receiving his second dose of the Moderna mRNA COVID-19 vaccine.
- Ultrasound studies did not reveal any evidence of venous or arterial thrombosis nor an embolic source.
- Immunoglobulin G antibody to SARS-CoV-2 nucleocapsid protein was negative.
- Immunoglobulin G antibody to SARS-CoV-2 spike protein was positive (consistent with an immune response to vaccination but no prior infection).
- Punch biopsy demonstrated a brisk perivascular and interstitial lymphocytic inflammatory infiltrate with associated interface dermatitis and necrotic keratinocytes.

- The lesions resolved over the course of 6 weeks.
- Additional two cases reported in the literature. 1-3

1. "COVID Toes" after mRNA COVID-19 Vaccines. John M. Kelso, MD, Alvin B. Coda, MD, Richard M. Kearing, MD, and Dana M. Vaccari, MD.
A series of 26 patients who developed delayed skin reactions after COVID-19 mRNA vaccines.

- 23 after 1st dose/3 after 2nd dose
- 14/23 had delayed large local reactions (DLLR) = erythematous and edematous plaques 10 cm in diameter accompanied by pain or pruritus
- 6 developed a generalized maculopapular exanthema
- 2 exfoliation on the palms
- 1 AGEP
- 1 generalized micro-papular exanthema accompanied by a 7-cm blister
- 1 fixed drug eruption
- 1 eyelid edema
- 11/26 patients were treated with topical corticosteroids & 4/26 with oral antihistamines.

- The mean duration was 5+/1.4 days when treated & 4.84+/0.60 days w/out treatment.
- Patch tests were negative in all (100%).
- With subsequent dosing, DLLR reoccurred in 62% (8/13) of a similar (38%) or smaller size (63%); resolved earlier (mean: 1.7 days) (P < .05). Five of 13 patients (38%) had no recurrence of DLLR.

**WHAT IS THE CAUSE?**

<table>
<thead>
<tr>
<th>Components of Moderna Co-V-2 mRNA vaccine</th>
<th>Delayed Cutaneous Reactions Reported in Literature (Yes/No)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SM-102 (1.93 mg)</td>
<td>No</td>
</tr>
<tr>
<td>Polyethylene glycol (PEG) 2000 dimyristsyl glycerol (OMG) (1.93 mg)</td>
<td>Yes</td>
</tr>
<tr>
<td>Cholesterol (1.93 mg)</td>
<td>No</td>
</tr>
<tr>
<td>1,2-distearyl-sn-glycero-3-phosphocholine (DSPC) (1.93 mg)</td>
<td>No</td>
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<tr>
<td>Ceramides (0.31 mg)</td>
<td>No</td>
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<tr>
<td>Tromethamine hydrochloride (1.18 mg)</td>
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</tr>
<tr>
<td>Acetic acid (0.043 mg)</td>
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</tr>
<tr>
<td>Sodium acetate (0.12 mg)</td>
<td>No</td>
</tr>
<tr>
<td>Sucrose (43.3 mg)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Components of Pfizer Co-V-2 mRNA vaccine</th>
<th>Delayed Cutaneous Reactions Reported in Literature (Yes/No)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-hydroxybutyl)tetrahydroxy(1-bis(hexa-6,1-diy(bis(3-hexyldecanato) (0.43 mg)</td>
<td>No</td>
</tr>
<tr>
<td>2[[polyethylene glycol]2000]-N,N-distearylesteamide (0.05 mg)</td>
<td>Yes</td>
</tr>
<tr>
<td>1,2-distearyl-sn-glycero-3-phosphocholine (0.09 mg)</td>
<td>No</td>
</tr>
<tr>
<td>Cholesterol (0.3 mg)</td>
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<tr>
<td>Potassium chloride (0.01 mg)</td>
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<tr>
<td>Monoethyl potassium phosphate (0.01 mg)</td>
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</tr>
<tr>
<td>Sodium chloride (2.16 mg)</td>
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</tr>
<tr>
<td>Dibasic sodium phosphate dihydrate (0.07 mg)</td>
<td>No</td>
</tr>
<tr>
<td>Sucrose (8 mg)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

- Polyethylene glycol (PEG) is suspected allergen.
- PEG is a component of medications, as well as consumer products.
- Molecular weight varies from 200 Da to 10,000 Da.
- High molecular weight PEG is included in bowel preparations and methylprednisolone injections.
- Lower molecular weight preparations include antimalarial medications.
- Higher molecular weight PEG products have been associated with anaphylaxis reactions.
- Lower molecular PEG associated with delayed, contact hypersensitivity reactions.
- Contact dermatitis with positive patch testing (PT) has been associated with PEG in topical nitrofurazone, minoxidil, and corticosteroids.
DERMAL FILLER REACTIONS:

Three patients in the experimental arm of the trial Moderna COVID 19 vaccine developed swelling associated with filler injections.\(^1\)\(^2\)

- One patient had facial swelling with report of filler injection 6 months prior to vaccination.
- One patient had facial swelling with report of filler injection 2 weeks prior to vaccination.
- The third patient had lip swelling only and the timing of the last filler injection was unknown (also had similar symptoms after an influenza vaccination in the past).
- All reactions resolved.

Immunogenic dermal filler reactions are rare, with both immediate & delayed type hypersensitivity reactions reported.

- Incidence of delayed reactions 0.42%.
- Mediated by macrophage and T-cell interactions.
- Typically develop 48 to 72 hours after injection but may occur weeks-months after.\(^3\)
- Symptoms include swelling and erythema at the filler site or granuloma formation at the site months or even years later.\(^4\)

The incidence of delayed inflammatory reactions to hyaluronic acid (HA) soft tissue fillers ranges between 0.3% and 4.25%. HA fillers last on average of 3-12 months.

These reactions are mediated by T-lymphocytes and can be triggered by flu-like illnesses, including SARS-CoV-2 infection. Presents as tender and erythematous swelling or nodules.

Vaccination may also induce hypersensitivity reactions.

Reactions tend to be transient. Nodules that are small and not painful do not need intervention.

If nodules are painful, tender or erythematous-treatment is recommended with hyaluronidase.

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