Biologics for Asthma

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Key Objectives

• Identify and discuss biologic therapies available for use in the management of asthma
• Assess how to choose a therapy for a patient
The Big 5 Introduction

- Omalizumab (2003)
- Mepolizumab (2015)
- Reslizumab (2016)
- Benralizumab (2017)
- Dupilumab (2018)

Information obtained from prescribing information of the individual biologics:

The Big 5 Outcomes

- All reduce asthma exacerbations
- Dupilumab, Benralizumab, and Mepolizumab all reduced oral corticosteroid use
- There is no good biomarker indicator to show if the biologic is working
Pharmacology

- Omalizumab
  - Inhibits binding of IgE to the FceRI receptor on the surface of mast cells and basophils

- Dupilumab
  - Blocks intercellular signaling of IL-4 and IL-13

- Mepolizumab and Reslizumab
  - Binds to IL-5 which blocks the binding of the IL-5 receptor complex on eosinophils

- Benralizumab
  - Binds to the IL-5 receptor on eosinophils, induces apoptosis of eosinophils through NK cells

Where each of the biologics work on the type 2 inflammation pathway

Severity of Asthma

• Omalizumab
  • Moderate to Severe Persistent Allergic Asthma

• Dupilumab
  • Moderate to Severe Persistent Eosinophilic Asthma
  • Oral Corticosteroid Dependent Asthma

• Mepolizumab/ Reslizumab/ Benralizumab
  • Severe Eosinophilic Asthma

Age

• Omalizumab and Mepolizumab
  • 6yo and older

• Dupilumab and Benralizumab
  • 12yo and older

• Reslizumab
  • 18yo and older
Pregnancy & Breastfeeding

- **Omalizumab**
  - Pregnancy: Higher risk of low birth weight, no increase in major birth defects or miscarriage
  - Breastfeeding: no increase in infections or infestations

- **Dupixent**
  - Pregnancy: not known; no evidence of fetal harm in animal studies
  - Breastfeeding: not known if passes into breast milk
    - It is likely that very little would pass into breast milk since it is a large protein and not well absorbed by the gut but has not been well studied
    - 1 case report with no complications during the first 4 months of breastfeeding
  - Pregnancy exposure registry: www.mothertobaby.org/ongoing-study/dupixent/

- **Benralizumab**
  - Pregnancy: not known, no evidence of fetal harm in animal studies
  - Crossed the placenta in animal studies; eosinophil counts were suppressed with gradual recovery by 6 month postpartum
  - Breastfeeding: not known if passes into breast milk
    - It is likely that very little would pass into breast milk since it is a large protein and not well absorbed by the gut but has not been well studied
  - Pregnancy exposure registry: www.mothertobaby.org/fasenra

- **Mepolizumab**
  - Pregnancy: not known; no evidence of fetal harm in animal studies
  - Breastfeeding: not known; in animal studies levels were less than 0.5% of maternal serum concentration
  - Pregnancy exposure registry: www.mothertobaby.org/asthma

- **Reslizumab**
  - Pregnancy: not known; no evidence of fetal harm in animal studies
  - Breastfeeding: not known; in animal studies levels were 5-7% of maternal serum concentration

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*The Xolair Pregnancy Registry (EXPECT): Perinatal outcomes among pregnant women with asthma treated with omalizumab compared against those of a cohort of pregnant women with moderate-to-severe asthma. Namazy J, et al. Poster presented at The American Academy of Allergy, Asthma & Immunology Annual Meeting. February 22–25, 2019, San Francisco, Poster#907*
Other Indications

- **Omalizumab**
  - Nasal polyps
  - Chronic Idiopathic Urticaria

- **Dupilumab**
  - Moderate to Severe Atopic Dermatitis
  - Chronic Rhinosinusitis with nasal polyps

- **Mepolizumab**
  - Eosinophilic Granulomatosis with Polyangiitis (EGPA)
  - Hyper eosinophilic syndrome (HES) for >6 months without an identifiable non-hematologic secondary cause
  - Chronic Rhinosinusitis with nasal polyps

How it is administered

- **Omalizumab**
  - 75-375mg SC every 2 or 4 weeks, dose is based on weight and total IgE
  - Powder to reconstitute, prefilled syringe

- **Dupilumab**
  - 400mg SC loading dose followed by 200mg SC every 2 weeks OR
  - 600mg SC loading dose followed by 300mg SC every 2 weeks
  - Prefilled pen or syringe

- **Mepolizumab**
  - 40mg (6-11 yo) or 100mg SC every 4 weeks
  - Powder to reconstitute, prefilled syringe or pen

- **Reslizumab**
  - 3mg/kg IV every 4 weeks infused over 20-50 minutes, dose is weight based

- **Benralizumab**
  - 30mg every 4 weeks x 3 doses then every 8 weeks
  - Prefilled pen for home use and prefilled syringe for health care settings
Where it is administered

- **Omalizumab**
  - At home or in a health care setting
  - 6-11yo recommended to have a caregiver administer
  - 12-18yo ok to self inject with adult supervision

- **Dupilumab/Benralizumab**
  - At home or in a health care setting

- **Mepolizumab**
  - 6-11yo in a health care setting due to reconstituting a powder
  - 12yo at home

- **Reslizumab**
  - At home with the supervision of a healthcare professional or in a healthcare setting

How to store

- **All of the biologics**
  - Store in refrigerator between 36-46 degrees Fahrenheit
  - For injectables, allow around 30 minutes after removing from refrigerator to warm up on its own to room temperature
    - Not doing so causes it to be uncomfortable and harder to push through

- **How long can it be outside the refrigerator in an unopened box?**
  - **Omalizumab**
    - Room temperature x 4 hours
  - **Reslizumab**
    - 77 degrees F x 16 hours
  - **Dupilumab and Benralizumab**
    - 68-77 degrees F x 14 days
  - **Mepolizumab**
    - Up to 86 degrees F x 7 days
Safety

- Anaphylaxis black box warning
  - Omalizumab and Reslizumab
- Worsen hypereosinophilic conditions
  - Omalizumab and Dupilumab
- Herpes Zoster
  - Mepolizumab
- Conjunctivitis and Keratitis
  - Dupilumab (more so in atopic dermatitis)
- Malignancy
  - Omalizumab and Reslizumab
- Helminth infections
  - All; treat prior to starting any of the biologics
- Avoid abruptly stopping or reducing steroid use
  - All

Test to Run

- Omalizumab
  - IgE 30 or higher
  - Positive bloodwork or skin test to perennial allergen
- Dupilumab
  - CBC, works best with eosinophils >150
  - No live vaccines while being treated
- Mepolizumab
  - Eosinophils > 150 within last 6 weeks or 300 within the last 12 months
  - Herpes zoster vaccination
- Reslizumab
  - Eosinophils >400
- Benralizumab
  - CBC, works best with eosinophils >150
How to Pick a Biologic

• Triple pillar decision
  • Phenotype traits: Co-morbidities, exacerbations, lung function
  • Biomarkers: eosinophils, total IgE, FeNO
  • Outcome: safety, reduction in OCS/exacerbations

• Use shared decision making with patient

  • Agache, I., Aakdis C, Akdis M, et al. EAACI Biologicals Guidelines- Recommendations for severe asthma. Allergy 2021; 76; 14-44. https://doi.org/10.1111/all.14425

Rechecking

• Recheck after 4-6 months
  • There are no good definitions for defining efficacy
  • Patient specific

• If they are responding ➔ Continue biologic, recheck every 4-6 months
Rechecking

• If they are not responding
  • Make sure you have the right diagnosis with airway hyperresponsiveness or induced sputum
    • If neutrophilic inflammation or no inflammation: stop biologic and consider other treatment options for non-T2 asthmatics (macrolides, dual bronchodilators, bronchial thermoplasty)

Rechecking

• If they are not responding and you rechecked airway hyperresponsiveness or induced sputum with the correct diagnosis:
  • Check compliance with asthma management plan
    • Revisit patient goals and how to achieve them
  • Is it inadequate dosing (recall that Omalizumab and Reslizumab are weight based)
    • Readjust dosing, change to a different mechanism or route
  • Eosinophilia not driven by the used biologic pathway
    • Change to a biologic targeting a different pathway
  • Did they develop anti-drug antibodies?
    • Change to a different biologic

• Reassess in another 4-6 months
Practice

• Remember that for a lot of these there can be more than 1 right answer. It is a decision that you and the patient make together on what is best for them. These are just examples of where your mind may go first.

Practice 1

• A 8yo with severe persistent asthma who lives in a rural community 2 hours from clinic and is allergic to dogs and tree pollen.
  
  • A. Omalizumab
  • B. Mepolizumab
  • C. Reslizumab
  • D. Benralizumab
  • E. Dupilumab
Answer 1

• A 8yo with severe persistent asthma who lives in a rural community 2 hours from clinic. They are allergic to dog and tree pollen.

  • A. Omalizumab
  • B. Mepolizumab – 6yo and up however from 6-11 has to be administered in clinic due to powder form
  • C. Reslizumab – 18yo and up
  • D. Benralizumab – 12yo and up
  • E. Dupilumab – 12yo and up

Practice 2

• A 32yo with severe persistent asthma who travels overseas for work and is gone for a few weeks at a time. Eosinophils are 203.

  • A. Omalizumab
  • B. Mepolizumab
  • C. Reslizumab
  • D. Benralizumab
  • E. Dupilumab
Answer 2

- A 32yo with severe persistent asthma who travels overseas for work and is gone for a few weeks at a time. Eosinophils are 203.

  - A. Omalizumab – this requires an elevated IgE level
  - B. Mepolizumab
  - C. Reslizumab
  - D. Benralizumab – while the rest of them are options, since this patient is out of the country for weeks at a time, they may appreciate that Benralizumab is dose every 8 weeks at home
  - E. Dupilumab

Practice 3

- A 25yo with severe asthma who was not compliant with administering at home biologics or coming to appointments.

  - A. Omalizumab
  - B. Mepolizumab
  - C. Reslizumab
  - D. Benralizumab
  - E. Dupilumab
Answer 3

• A 25yo with severe asthma who was not compliant with administering at home biologics or coming to appointments.

  • A. Omalizumab
  • B. Mepolizumab
  • C. Reslizumab – Cinqair is administered at home with a HCP present since it is through IV
  • D. Benralizumab
  • E. Dupilumab

Practice 4

• A 16yo with moderate asthma and chronic rhinosinusitis with nasal polyps.

  • A. Omalizumab
  • B. Mepolizumab
  • C. Reslizumab
  • D. Benralizumab
  • E. Dupilumab
Answer 4

• A 16yo with moderate asthma and chronic rhinosinusitis with nasal polyps.
  
  • A. Omalizumab – indicated for moderate asthma but not for chronic rhinosinusitis with nasal polyps
  • B. Mepolizumab – Indicated for chronic rhinosinusitis with nasal polyps but not for moderate asthma- only severe asthma
  • C. Reslizumab – 18yo and up
  • D. Benralizumab – not indicated for moderate asthma or chronic rhinosinusitis with nasal polyps
  • E. Dupilumab – not indicated for chronic rhinosinusitis with nasal polyps until age 18 but would still get benefit for both conditions

Practice 5

• A 50yo with severe asthma on daily prednisone who doesn’t have time to come into the office on a regular basis. No history of allergies. Eosinophils 341.
  
  • A. Omalizumab
  • B. Mepolizumab
  • C. Reslizumab
  • D. Benralizumab
  • E. Dupilumab
Answer 5

• A 50yo with severe asthma on daily prednisone who doesn’t have time to come into the office on a regular basis. No history of allergies. Eosinophils 341.

  • A. Omalizumab — Requires elevated IgE and positive to perennial aeroallergen
  • B. Mepolizumab
  • C. Reslizumab – Has not been shown to reduce oral corticosteroid use
  • D. Benralizumab
  • E. Dupilumab
BIOLOGICS
WHEN, WHERE & WHY

Biologic Therapeutic Options in the Management of Atopic Dermatitis and Chronic Spontaneous Urticaria

Abby Allen RN, MSN CRNP

Atopic Dermatitis

› Define Atopic dermatitis
› Review current Biologic treatment options
› Discuss therapies currently being studied in the management of Atopic Dermatitis
What is Atopic Dermatitis

AD is a complex chronic inflammatory condition involving skin barrier dysfunction & immune dysregulation. Atopic Dermatitis commonly presents during early infancy and childhood but can persist or present in adulthood.

Atopic dermatitis (AD) is the most common form of eczema, affecting more than 9.6 million children and about 16.5 million adults in the United States.

Pruritus, scratching, and chronic, relapsing, or both eczematous lesions are major hallmarks of the disease. In infants and young children, there is a characteristic pattern of involvement of the face, neck, and extensor skin surfaces. In older children and adults, the skin lesions often involve lichenification and are usually localized to the flexural folds of the extremities.

Diagnosis

› The diagnosis of AD is based on its clinical presentation, rather than the results of diagnostic testing.


› A recent study of adults with moderate to severe AD found that 70.5% reported severe, unbearable itch in the past two weeks, 85.8% reported daily itch, and 62.8% reported itching at least 12 hours per day.

› Sleep disturbance occurs in approximately 60% of children with AD, and parents of children with AD are four to eight times more likely to average less than six hours of sleep per night compared with caregivers of healthy children.


### Statistics

- An estimated 16.5 million U.S. adults (7.3%) have AD that initially began at >2 years of age, with nearly 40% affected by moderate or severe disease.

- Children born outside the U.S. have a 50% lower risk of developing AD that increases after living in the U.S. for 10 years.

- The prevalence of childhood AD has steadily increased from 8% to ~12% since 1997. 4

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### Co-Morbidities

- Children with AD often develop other atopic conditions in a typical sequence of food allergy, allergic rhinitis and asthma – known as the atopic march.

- One in three children with AD will additionally develop asthma or allergic rhinitis. The risk of developing asthma increases with AD severity as more than 50% of children with severe AD will develop asthma.

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Co-Morbidities

Adults with AD have an increased risk of eye-related conditions including conjunctivitis, keratitis, and keratoconus; this risk increases with AD disease severity.

AD in adults is associated with other serious chronic conditions that contribute to poor health including diabetes, obesity, autoimmune disease, high blood pressure and heart disease. Risk for these conditions increases with AD severity.

Recent studies have suggested people with AD are up to 44% more likely to exhibit suicidal ideation, and 36% are more likely to attempt suicide.


The Cost of Atopic Dermatitis

- In 2013, the cost to the health system to treat atopic dermatitis patients was $314 million. 85

- The annual economic burden of eczema, including direct medical costs, indirect costs from lost productivity, and quality of life impacts, is conservatively estimated at $5.3 billion.


Management

PATIENT PROFILE: Stepping up from MILD to MODERATE AD:
Symptomatic despite appropriate use of low to medium potency TCS and following basic management recommendations for skin care, antimicrobial treatment and avoidance of allergens and irritants.***

Increase TCS dose or potency
→ Add TCI
→ Add crisaborole 2% ointment

3-month therapeutic trial with reassessment at 4-8 weeks

PATIENT PROFILE: Stepping up from MODERATE to SEVERE AD:
Symptomatic despite an aggressive course of topical prescription therapy (TCS, TCI, crisaborole) for ≥ 3 wks and following basic management recommendations for skin care, antimicrobial treatment and avoidance of allergens and irritants, and particularly when there is a severe and negative impact on daily activities, psychosocial health, and quality of life.**

Refer to specialist
Consider for some patients acute Tx to help gain control:
• Wet wrap therapy
• Hospitalization

3-month therapeutic trial with reassessment at 4-8 weeks

Non-Ietional

Non-Ietional

BASIC MANAGEMENT

1. Skin Care
   • Moisturizer, liberal and frequent (choice per patient preference)
   • Warm baths or showers using non-soap cleaners, usually once daily and followed by moisturizer (even on clear areas)

2. Trigger Avoidance
   • Proven allergens and common irritants (e.g., soaps, wool, temperature extremes)
   • Consider comorbidities

Maintenance Treatment

Apply TCS to Inflamed Skin
Low to medium potency TCS 2x daily for 3-7 days beyond clearance
[Consider TCI, crisaborole]

Mild

BASIC MANAGEMENT

1. Skin Care
   • Moisturizer, liberal and frequent (choice per patient preference)
   • Warm baths or showers using non-soap cleaners, usually once daily and followed by moisturizer (even on clear areas)

2. Antiseptic Measures
   • Dilute bleach bath (or equivalent) 1x/week according to severity (especially with recurrent infections)
   • Antibiotics, if needed

3. Trigger Avoidance
   • Proven allergens and common irritants (e.g., soaps, wool, temperature extremes)
   • Consider comorbidities

Severe

BASIC MANAGEMENT + REFERRAL to AD Specialist

Phototherapy
Dupilumab
Systemic Immunosuppressants
• Cyclosporine A²
• Methotrexate¹
• Mycophenolate mofetil³
• Azathioprine²
• Corticosteroids

Consider acute tx for some patients to help gain control:
• Wet wrap therapy
• Short-term hospitalization

Moderate

BASIC MANAGEMENT + TOPICAL ANTI-INFLAMMATORY MEDICATION

Apply on areas of previous or potential symptoms (aka flare)

Maintenance TCS
• Low potency 1x-2x daily (including face)
• Medium potency 1x-2x weekly (except face)

OR Maintenance TCI (pimecrolimus, tacrolimus)
• 1x daily
• 2x-3x weekly (not an indicated dosage)

OR Crisaborole 2%³
• 2x daily

Apply TCS to Inflamed Skin
Medium to high potency TCS 2x daily for 3-7 days beyond clearance
[Consider TCI, crisaborole]

If not Resolved in 7 Days, Consider (+)
Dupixent (Dupilimab)

According to the guidelines on treatment of atopic dermatitis, the only systemic medical therapies available for moderate to severe forms of the disease are cyclosporin and, since 2017, dupilumab, an antibody against the IL-4/IL-13 receptor [6, 7].
**Patient Selection**

- Have tried a variety of topical prescription therapies for moderate-to-severe atopic dermatitis and remain uncontrolled
- Suffer from inadequate control of pruritus
- Have ≥10% of their body covered with lesions and/or may involve problem areas, such as the face, hands, and feet
- Have moderate-to-severe erythema and moderate-to-severe papulation/infiltration (IGA 3 or 4)
Most common (> 5%) adverse reactions associated with dupilumab treatment in clinical trials were:

- Injection site reactions
- Conjunctivitis in up to 30%
- Dry eyes
- Allergic conjunctivitis
- Herpes infections
- Atopic dermatitis exacerbation
- Nasopharyngitis
- Headache
- Upper respiratory tract infection
Mild conjunctivitis is managed with lubricating eye drops. Patients on dupilumab should be advised to use these from the onset of treatment to prevent ocular symptoms. Some patients may require other treatment.

- Topical corticosteroid drops
- Topical tacrolimus eyelid ointment
- Referral to an ophthalmologist

**Dupixent Dosing (>= 18 years of age)**

18+ years

**LOADING DOSE**

600 mg

2 x 300 mg pre-filled pens or syringes

**EVERY 2 WEEKS**

300 mg

1 pre-filled pen or syringe

**DUPIXENT DOSING FOR PATIENTS 6-17 YRS OF AGE (ATOPIC DERMATITIS)**

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Dear Medical Director,

I am contacting you as an allergist caring for Abby Allen with regard to the patient's diagnosis of Atopic Dermatitis (L20.9). I recently prescribed this patient Dupixent (dupilumab), which required a prior authorization that was filed on 09/09/2021. The prior authorization was denied and the patient was unable to fill her prescription. I have reviewed the patient’s diagnosis, care plan and clinical guidelines for treatment and request a formal appeal of your denial for Dupixent.

When treating a patient with atopic dermatitis (L20.9), and depending on the severity of atopic dermatitis, it is necessary to have access to the full spectrum of approved treatments as patients may not be able to use one particular treatment due to suboptimal response, the potential for side effects or even an allergic reaction. Abby Allen has moderate-to-severe atopic dermatitis which has a significant impact on her quality of life. The patient has had to miss work or school 15 times during the past six months due to flares of her atopic dermatitis. During the past six months, itching has interfered with sleeping an average of 3 nights per week.

Dupixent (dupilumab) is indicated for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies.

The patient has failed the following therapies:

- The patient has adhered to an aggressive skin care regimen including frequent use of emollients and skin barrier care with ceramide containing products.
- The patient has properly used the following topical corticosteroids without sufficient relief:
  - Triamcinolone 0.5%
  - Triamcinolone 0.05%
  - Triamcinolone 0.1%
  - Triamcinolone 0.01%
- The patient has properly used tacrolimus and/or pimecrolimus, topical calcineurin inhibitors, without sufficient relief.
- The patient has not achieved sufficient relief with crisaborole after 4 weeks of treatment.
- Immunotherapy has not provided relief. Immunotherapy trialed:
  - Dust mite, Dog, Tree Pollens
- The patient did not tolerate the following topical treatments:
  - Nanest Levorphanol

I strongly believe Abby Allen needs access to Dupixent, which has an excellent safety profile. Other systemic anti-inflammatory treatments are not acceptable due to adverse effects.

My patient is not a good candidate for your suggested alternatives for the following reasons:

1. Systemic corticosteroids: The long-term use of systemic corticosteroids for treatment of patients with AD should be minimized or avoided. Side effects of corticosteroids can be significant and may pose a risk for serious adverse effects. Systemic corticosteroids can be associated with transient adverse effects, including weight gain, fluid retention, mood swings, hyperglycemia, and osteoporosis.

On behalf of Abby Allen, I would appreciate your prompt reconsideration of this denial. Please feel free to contact me at (302) 302-0000 for any additional information you may require. I look forward to receiving your response and approval of coverage for this medication.

Sincerely,

Abby Allen CRNP

References

Over 25 new biologics are in development for treatment of atopic dermatitis.

Tralokinumab, Lebrikizumab and Nemolizumab are the furthest along in clinical trials.
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Small – Molecule Drugs for the Treatment of Atopic Dermatitis


Small-Molecule

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<td>II</td>
<td>In recruitment</td>
</tr>
<tr>
<td>Topical Tofacitinib</td>
<td>JAK1/JAK2</td>
<td>II</td>
<td>Completed</td>
</tr>
<tr>
<td>Delgocitinib</td>
<td>JAK1/JAK2/JAK3</td>
<td>II</td>
<td>In recruitment</td>
</tr>
<tr>
<td>Ruxolitinib</td>
<td>JAK1/JAK2</td>
<td>III</td>
<td>In recruitment</td>
</tr>
</tbody>
</table>

The prospects of a patient severely affected with atopic dermatitis for example would be treatment with a biologic and a topical JAK inhibitor in the future.

Future studies are required to characterize in detail the selection of specific substances for individual patients and the optimal duration of therapy.

In addition to phenotypic features, a patient-oriented therapy also takes genetic and biological markers into account. This may then help to identify different endotypes that are optimally suited for defined therapeutic regimens.

Long-term data from registries such as TREAT [28], allow for extended monitoring of safety and disease modification in patients treated with biologics or small-molecule drugs. Beyond that, there is a lack of data on how the treatment of patients achieving clinical remission should be adjusted in the long term.

JAK enzymes can play a role in driving abnormal immune responses and have been found to be key components of several complex immune-mediated diseases including rheumatoid arthritis, psoriatic arthritis, ulcerative colitis and now, AD.

New medications called "JAK inhibitors" are used to close off overactive JAK pathways and to limit the cytokines associated with turning on eczema symptoms.

The JAK family has four members and JAK inhibitors can target one or more of these family members to hinder their effects, leading to improvement in signs and symptoms of AD.

JAK inhibitors are believed to block nerve itch signals, are anti-inflammatory, and work quickly.

For AD, JAK inhibitors are being investigated in both oral and topical dosage forms.

FDA has already approved oral JAK inhibitors to treat rheumatoid arthritis, psoriatic arthritis and ulcerative colitis.

Four JAK inhibitors are currently in the end stages of clinical trial investigation (i.e. Phase III) for AD:

- Abrocitinib (Pfizer)
- Baricitinib (Incyte and Lilly)
- Ruxolitinib (Incyte)
- Upadacitinib (Abbvie)

Abrocitinib (Pfizer) is an oral small molecule that selectively inhibits Janus kinase (JAK) 1. Inhibition of JAK1 is thought to modulate multiple cytokines involved in pathophysiology of atopic dermatitis, including interleukin IL-4, IL-13, IL-31, IL-22, and thymic stromal lymphopoietin (TSLP).

Abrocitinib

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Baricitinib

- Baricitinib (Lilly & Incyte) is an oral JAK inhibitor approved for the treatment of adults with moderately to severely active rheumatoid arthritis (RA) in more than 75 countries. It is also approved in over 40 countries for the treatment of adults with moderate to severe AD who are candidates for systemic therapy.
- Baricitinib is being studied in alopecia areata (AA), systemic lupus erythematosus (SLE) and juvenile idiopathic arthritis (JIA).

Lebrikizumab

- Lebrikizumab (Eli Lilly) also targets IL-13, preventing formation of the IL-13R alpha 1/IL-4R alpha receptor signaling complex.
- A Phase IIb study of safety and efficacy of lebrikizumab was published in 2020 with 280 adult AD patients split between the group who received the lebrikizumab and those who received the placebo.
- Phase III trials, long-term safety and efficacy studies and trials in adolescents (12 and older) are currently being recruited.
- In this published study, patients were injected subcutaneously with lebrikizumab at doses of 125 mg every four weeks, 250 mg every four weeks or 250 mg every two weeks. Improvement in the EASI score from the beginning of the study and 16 weeks was observed, as was lessening of itch as early as day two after the start of treatment.
- Side effects were injection site reactions, herpes virus infections and eye infections, but did not cause patients to leave the study.
Nemolizumab

- Nemolizumab (Galderma) targets the IL-31 receptor, which is a receptor on nerve cells and on immune cells called eosinophils that are activated by signals from T cells. Both eosinophils and nerve cells drive itch responses, and eosinophils also interfere with the ability of keratinocytes to maintain a good skin barrier.
- A Phase IIb study (24 weeks) of safety and efficacy of nemolizumab was published in 2020 with 226 patients split between those receiving placebo and those receiving 10 mg, 30 mg or 90 mg of the drug by subcutaneous injection every four weeks.
- All patients remained on their current topical steroid treatments during this study. Phase III trials and long-term trials are currently being recruited for nemolizumab.
- Researchers observed an improvement in the EASI score by week four of treatment, with the 30 mg dose being most effective. A decrease in itch was also observed during the study. The most common side effects were upper respiratory tract infection and infections/inflammation in the nose.

(Johnson, J. “Biologics are Changing the landscape of eczema treatment” NEA, Spring 2021, 8-11)

Upadacitinib (Rinvoq)

- RINVOQ (Abbvie) is a selective and reversible JAK inhibitor that is being studied in several immune-mediated inflammatory diseases
- August 2019, RINVOQ received U.S. FDA approval for adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate.
- Phase 3 trials of RINVOQ in rheumatoid arthritis, atopic dermatitis, psoriatic arthritis, axial spondyloarthritis, Crohn’s disease, ulcerative colitis, giant cell arteritis and Takayasu arteritis are ongoing.

(National Eczema Association. (July 22, 2021)”AbbVie Provides Update Regarding RINVOQ® (upadacitinib) for the Treatment of Moderate to Severe Atopic Dermatitis in the U.S.” [Press Release] https://nationaleczema.org/abbvie-71621/)
Ruxolitinib

- Ruxolitinib cream is a proprietary formulation of Incyte’s selective JAK1/JAK2 inhibitor
- **UPDATE** This was approved by the FDA (Opzelura) on September 21, 2021
- This is the 1st (and only) Janus Kinase (JAK) inhibitor approved in the US.
- It is approved for short term and non-continuous treatment of mild-moderate atopic dermatitis (AD) in non-immunocompromised patients 12 yrs up and older.


Tralokinumab

- Tralokinumab is the first fully human, monoclonal antibody developed to specifically neutralize the IL-13 cytokine, which plays a key role in driving the underlying atopic dermatitis signs and symptoms. Tralokinumab specifically binds to the IL-13 cytokine with high affinity, thereby inhibiting interaction with the IL-13 receptor α1-subunit of the type 2 receptor.
- Two long-term Phase III studies (52 weeks) of safety and efficacy of tralokinumab for treating moderate-severe AD were published in 2020 with hundreds of adults (18 and older) in each study.
- Trials for treatment of adolescents and more long-term trials are currently being recruited.
- In the published studies, patients were treated with 300 mg of tralokinumab injected subcutaneously every two weeks.
- Researchers noted improvement in Investigator's Global Assessment (IGA) and in the Eczema Area and Severity Index (EASI) by week 16 of treatment with tralokinumab compared to placebo, and these improvements continued for most patients through week 52.
- Improved sleep, itch and overall quality of life were noted for AD patients participating in the studies.
- Reported side effects included upper respiratory tract infections (common cold) and eye and skin infections, but for the most part these did not cause the patients to leave the study or quit taking tralokinumab.
- The majority of side effects happened during the first 16 weeks of treatment and did not continue as patients were on the drug for longer.
- FDA review of tralokinumab for moderate-severe AD is anticipated in the second quarter of 2021.
- (Johnson, J. “Biologics are Changing the landscape of eczema treatment” NEA, Spring 2021, 8-11)
Chronic Spontaneous Urticaria (CSU)

- Define Chronic Spontaneous Urticaria
- Review current Biologic treatment options
- Discuss therapies currently being studied in the management of CSU

Chronic Spontaneous Urticaria - No Specific Elicit ing Factor

Chronic Inducable Urticaria: Specific Elicit ing Factor- such as: Cold, heat, vibratory, cholinergic, aquagenic, solar, delayed pressure urticaria, etc.

These often co-exist in patients

Typical CU lesions are edematous pink or red wheals of variable size and shape with surrounding erythema and are generally pruritic.

(Painful or burning complaints raise the suspicion for cutaneous vasculitis).

Individual urticarial lesions fade within 24-48 hrs (although new lesions may simultaneously develop).

In contrast, vasculitis lesions are often palpable, non-blanching, lasting days or more and often leave residual areas of hyperpigmentation.

CU Characteristics

› Often Angioedema is present in patients with CU- this is often non-pruritic, brawny, non-pitting edema. These areas typically have well defined margins.

The most common cause is **Idiopathic/Undetermined**

- Chronic Infectious processes: Hepatitis B & C, EBV, HSV, H. Pylori, Helminthic parasitic infections
- Systemic Conditions: Cryoglobulinemia (Hep C and Chronic Lymphocytic Leukemia), Serum Sickness, Connective Tissue Disease (SLE, Juvenile Rheumatoid Arthritis), Thyroid disease, Neoplasms (lymphoreticular malignancy and lymphoproliferative disorders) and other endocrine disorders or hormonal therapies (ovarian tumors, oral contraceptives)

Auto-antibody-associated urticaria: Presence of autoantibodies (i.e., thyroid autoantibodies) in conjunction with urticaria

Numerous autoimmune disorders (SLE, dermatomyositis and polymyositis, Sjogren Syndrome, Still Disease) are associated with CU.

NO therapeutic or prognostic value has been identified with the identification of this sub-type of CU

Evaluation

Extensive lab evaluation with a unremarkable history and physical exam is not recommended.

Limited lab evaluation: CBCD, ESR and/or CRP, liver enzymes, and TSH.

In 2014, XOLAIR became the only FDA-approved CU treatment other than H1 antihistamines.

XOLAIR is a biologic used to treat CU in patients aged 12 and older who remain symptomatic despite antihistamine treatment.

Not indicated for inducible urticarias; however, there are some reports of effectiveness.

**Xolair**

Number of vials/injections and total injection volumes.

<table>
<thead>
<tr>
<th>XOLAIR dose, mg</th>
<th>Number of 150 mg syringes</th>
<th>Total volume injected, mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>2</td>
<td>2.4</td>
</tr>
<tr>
<td>150</td>
<td>1</td>
<td>1.2</td>
</tr>
</tbody>
</table>

**BY SUBCUTANEOUS INJECTION EVERY 4 WEEKS**

*Doses of more than 150 mg are divided among more than one injection site to limit injections to not more than 150 mg per site.*

*1.2 mL, maximum delivered volume per vial after reconstitution.


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**Xolair**

Number of prefilled syringes and total injection volumes.

<table>
<thead>
<tr>
<th>XOLAIR dose, mg</th>
<th>Number of 150 mg prefilled syringes</th>
<th>Total volume injected, mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>2</td>
<td>2.0</td>
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<tr>
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**BY SUBCUTANEOUS INJECTION EVERY 4 WEEKS**

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Clinical Communications

High-dose omalizumab use in patients with chronic spontaneous urticaria

Mehran Alizadeh-Aghdam, MD, Ronne Henriette Pedersen, BSC, Petra Adriana Kersten, MAPP, Feiko Rijsen, MD, PhD, Andre Cornelis Knuti, MD, PhD, and Henke Rickmann, MD, PhD

- 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


Clinical Communications

Effective omalizumab interval prolongation in the treatment of chronic urticaria

Mehran Alizadeh-Aghdam, MD,
Ronne Henriette Pedersen, BSC,
Petra Adriana Kersten, MAPP, Feiko Rijsen, MD, PhD,
Andre Cornelis Knuti, MD, PhD, and
Henke Rickmann, MD, PhD

- All patients treated with omalizumab 300 mg every 4 weeks x 6
- If urticaria controlled, interval increased by 1 week
- Treatment stopped at 8 weeks if well controlled
- Shared decision making allowed some to extend beyond 8 weeks
- Early clinical response more likely to extend treatment interval

Cyclosporine and omalizumab together: A new option for chronic refractory urticaria


Combination of OMA + CSA

Response in 2-4 months

Symptomatic Dermographism: A Systematic Review of Treatment Options

- 23 studies (15 RCTs)
- 1st gen AH most frequently studied
  - Variable efficacy and significant side effects
- 2nd gen AH
  - Effective and well tolerated
- H2 antagonists
  - No value by itself, may have added value with H1
- Omalizumab
  - 1 RCT with benefit

"Available studies are heterogeneous, mostly monocentric, old, small, and unreported, pointing to a high need for more and better studies"


Delayed Pressure Urticaria: A Systematic Review of Treatment Options

- 21 studies (8 RCTs)
- 2nd gen AH
  - Effective in 3 RCT
    - Updosing not studied
  - Other RCT showed benefit with 2nd gen AH + montelukast or theophylline
- Non RCT with effectiveness
  - Omalizumab (4 studies)
  - Dapsone (3 studies)

"Overall, the quality of studies on DPU is low"

**Biologic Treatments Under Evaluation for CU**

- Dupixent - IL-4 and IL-13
- Benralizumab, Mepolizumab, Reslizumab - IL-5
- Secukinumab - IL-17
- Ligelizumab - IgE
- Tezepelumab – anti-TSLP
- Avdoralimab - C5aR1

All in studies for various conditions including CU


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Future drugs and targets for the treatment of Chronic Spontaneous Urticaria (CSU)

Additional Sources

› Khan, D. JACI in Practice Year in Review: Drug Allergy and Urticaria/Angioedema

Updates on Biologics for Chronic Rhinosinusitis with Nasal polyps

Katie Kennedy MD
Attending Physician
Division of Allergy and Immunology
Children’s Hospital of Philadelphia

DISCLOSURES

I have no relevant financial disclosures or conflicts of interest pertaining to this talk
Objectives

- Discuss physiology and pathogenesis of CRSwNP
- Review role for biologic therapy
- Discuss FDA approved uses of biologics for treatment of nasal polyps
- How to choose?
- Discuss future research

Background

- Nasal polyps: inflammatory outgrowths of sinonasal tissue assoc with CRS
- Estimated to occur in 4% of US population
- Sx: persistent or chronic nasal congestion, anterior/posterior rhinorrhea, hyposmia, facial pressure
- Demographics:
  - Typical age at dx mid 40s-50s
  - Males more commonly affected
  - Females have more severe disease
- ***Impaired QoL

Burden of CRSwNP

- INS/OCS +/- surgery has high relapse rate, greater side effect profile
- Assoc with other Th2 mediated atopic conditions:
  - Asthma
  - ASA sensitivity
  - Atopic dermatitis
- In the US, pts with CRSwNP have higher medication use and more extensive surgery than CRS w/o NP
- Impaired: mental health, sleep quality

Pathophysiology

- **Th2 inflammatory milieu is predominant**
  - → chronic inflammatory state → chronic tissue remodeling → polyp growth
  - Significant elevations of:
    - IL-4, IL-5, IL-13
    - Eosinophils- eotaxins, eosinophilic cationic protein
    - Innate lymphoid cells, mast cells, macrophages from biopsied NP tissue
- **Mucosal defects**
  - Reduction in cell adhesion/tight junction proteins
- Damaged epithelium responds to irritants, allergens, pathogens by producing Th2 promoting cytokines

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FDA approved biologic therapy

- Dupilumab: June 2019
- Omalizumab: Dec 2020
- Mepolizumab: July 2021

Dupilumab

- **IL4Ra antagonist** --> inhibiting IL-4, IL-13
  - Blocks goblet cell metaplasia and mucus production, endothelial cell activation/recruitment and monocyte differentiation into M2 macrophages
- Approved for CRSwNP for +18 years
- Phase 2/Phase 3 clinical trials- most AEs occurring in placebo groups: worsening polyps, nasopharyngitis, HA, worsening of asthma, epistaxis, injection site erythema
- Dosing
  - 300mg SC every 2 weeks
  - No loading dose
  - Prefilled syringe vs pen

Dupilumab: Safety/Efficacy

- 2 multi-national/multi-center randomized, DBPC parallel group studies: Nov/Dec 2016- Aug 2017
  - N=710 at 24 weeks
  - Dupilumab added to standard of care for adults with severe CRSwNPs: adults, on INS, with b/l disease, hx of prior nasal surgery
  - LIBERTY NP SINUS-24
    - 1:1 randomized- 300mg q2 weeks for 24 weeks (placebo vs dupilumab)
  - LIBERTY NP SINUS-52
    - 1:1:1 dupilumab 300mg q2 weeks for 52 weeks OR dupilumab q2 weeks for 24 weeks then q4 weeks for remaining or placebo


Dupilumab: Safety/Efficacy

- Significant improvement of NPS at 24 weeks:
  - $-2.06$ (95% CI $-2.43$ to $-1.69$; $p<0.0001$) in SINUS-24 and $-1.80$ ($-2.10$ to $-1.51$; $p<0.0001$) in SINUS-52
  - Significant improvement in nasal congestion/obstruction
    - $-0.89$ ($-1.07$ to $-0.71$; $p<0.0001$) in SINUS-24 and $-0.87$ ($-1.03$ to $-0.71$; $p<0.0001$) in SINUS-52
- Most common AEs were more frequent in placebo
  - Nasopharyngitis, worsening of polyps/asthma, HA, epistaxis, injection site erythema
- Conclusion: Adults with CRSwNP- dupilumab reduced polyp size, sinus opacification, sx severity and is well tolerated

Omalizumab

- Approved in Dec 2020 for >18yo with CRSwNP
- Anti IgE
- Role of IgE:
  - Activates Type 2 inflammatory cells: mast cells, basophils, eos
  - Locally produced IgE via B cell class switching is involved in regulating inflammation and serving a function in that inflammation
- Dosing: Based on total IgE: 75-600mg SC every 2-4 weeks via pre-filled syringe


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Omalizumab: Safety/efficacy

- 2 multi-national/multi-center Phase 3 randomized, DBPC studies: Nov 2017-March 2019
  - N=265
  - POLYP1 and POLYP2- 1:1 omalizumab for 24 weeks or placebo
  - 75-600 mg q2 or q4 weeks depending on sIgE and TBW
- Significant improvement in NPS: -1.08 vs 0.06 (p<.0001) and -0.90 vs -0.31 (p=.0140)
- Significant improvement in nasal congestion score: -0.89 vs -0.35 (p=.0004) and -0.70 vs -0.20 (p=.0017)
- Significant improvement in SNOT-22 score: -24.7 vs -8.6 (p<.0001) and -21.6 vs -6.6 (p<.0001)

Mepolizumab

- FDA approved July 2021
- Anti IL-5
- 100mg SC q4 weeks
  - Prefilled syringe vs autoinjector
- Mepolizumab vs placebo for recurrent, severe b/l polyposis
  - Primary endpoint: surgery requirement at week 25
  - Pts receiving mepolizumab significant less surgery


Mepolizumab

- SYNAPSE: multi-national, multi-center randomized, DBPC, parallel group phase 3 trial
  - May 2017-DEC 2018
  - N=414 assigned patients
  - Placebo vs mepolizumab 100mg q4 weeks
- NPS significantly improved at week 52 (-0.73; 95% CI -1.11 to -0.34; p<0.0001)
- Nasal obstruction significantly improved (-3.14, -4.09 to -2.18; p<0.0001)
- AEs similar between two groups, not related to treatment

Comparing all 3 agents: 2021 Cochrane Review

- 10 studies; 1262 adult patients (1260 CRSwNP)
- Most subjects had severe disease and were on INS therapy
- Clinical response rate varies 50-70%
- Higher cost burden as compared to conventional tx

Dupilumab
- After 24 weeks of tx: better QoL, better sx, not more severe side effects

Mepolizumab
- Much smaller sample size, results less certain: effects may be similar to dupilumab

Omalizumab
- After 24 weeks of tx: better QoL, no inc side effects
Future of biologics and CRSwNP

- **Benralizumab**: monoclonal anti-IL5Ra
  - Currently in 2 Phase 3 clinical trials: OSTRO (NCT03401229) and ORCHID (NCT04157335)

- **Reslizumab**
  - *Asthma related outcomes* in pts w/ self reported CRSwNP
  - Post hoc analyses of pool data from 2 BREATH phase 3 clinical trials
  - Ages 12-75 yrs
  - Add on tx reduced asthma exac by 83% vs placebo in pts with CRSwNP


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**EUFORERA Consensus on biologics for CRSwNP**

<table>
<thead>
<tr>
<th>Indications for biological treatment in CRSwNP patients</th>
<th>Defining response to biological treatment in CRSwNP patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.</strong> Presence of bilateral nasal polyps</td>
<td>Evaluation of 5 criteria</td>
</tr>
<tr>
<td><strong>2.</strong> History of surgery</td>
<td>- Reduced nasal polyp size</td>
</tr>
<tr>
<td><strong>3.</strong> No history of surgery</td>
<td>- Reduced need for systemic corticosteroids</td>
</tr>
<tr>
<td>THREE of the below criteria are required</td>
<td>- Improved quality of life</td>
</tr>
<tr>
<td>FOUR of the below criteria are required</td>
<td>- Improved sense of smell</td>
</tr>
<tr>
<td></td>
<td>- Reduced impact of comorbidities</td>
</tr>
<tr>
<td>- Evidence of type 2 inflammation</td>
<td>Discontinue treatment if no response in any of the criteria</td>
</tr>
<tr>
<td>- Need for systemic corticosteroids</td>
<td>Evaluate treatment response after 16 wks</td>
</tr>
<tr>
<td>(2 or more courses in the past y)</td>
<td>Evaluate treatment response after 1 y</td>
</tr>
<tr>
<td>- Significantly impaired quality of life</td>
<td>No response 0 criteria</td>
</tr>
<tr>
<td>- Significant loss of smell</td>
<td>Poor response 1-2 criteria</td>
</tr>
<tr>
<td>- Diagnosis of comorbid asthma</td>
<td>Moderate response 3-4 criteria</td>
</tr>
</tbody>
</table>

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Fokkens WJ et al. EUFORERA consensus on biologics for CRSwNP with or without asthma. Allergy. 2019 Dec;74(12):2302-2310.
Morbidity and Cost

- Conventional therapy: Intranasal steroids +/- surgery
- Pre-biologics: Surgery- ESS w/ polyp removal
  - Perhaps more cost-effective than biologics\(^1\)
    - Upfront ESS vs dupilumab 300mg SC q2 weeks
    - ESS cost $50k, dupilumab cost $500k with less QALYs

- Polyp recurrence following surgery is common\(^2\)
  - Found in 30-40% 18mo post-op from ESS w/ polypectomy
  - RFs: Prior ESS ([OR]: 2.6, 95% [CI]: 1.5-4.6; p=.001), and worse pre-op polyposis severity (OR: 1.4, 95% CI: 1.1-1.8; p=.016)

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Our patients now

In summary:
- With the advent of biologics we can provide tailored care for individuals
- QoL is an important consideration
- More data is needed on biologic use and cost effectiveness
Thank you!