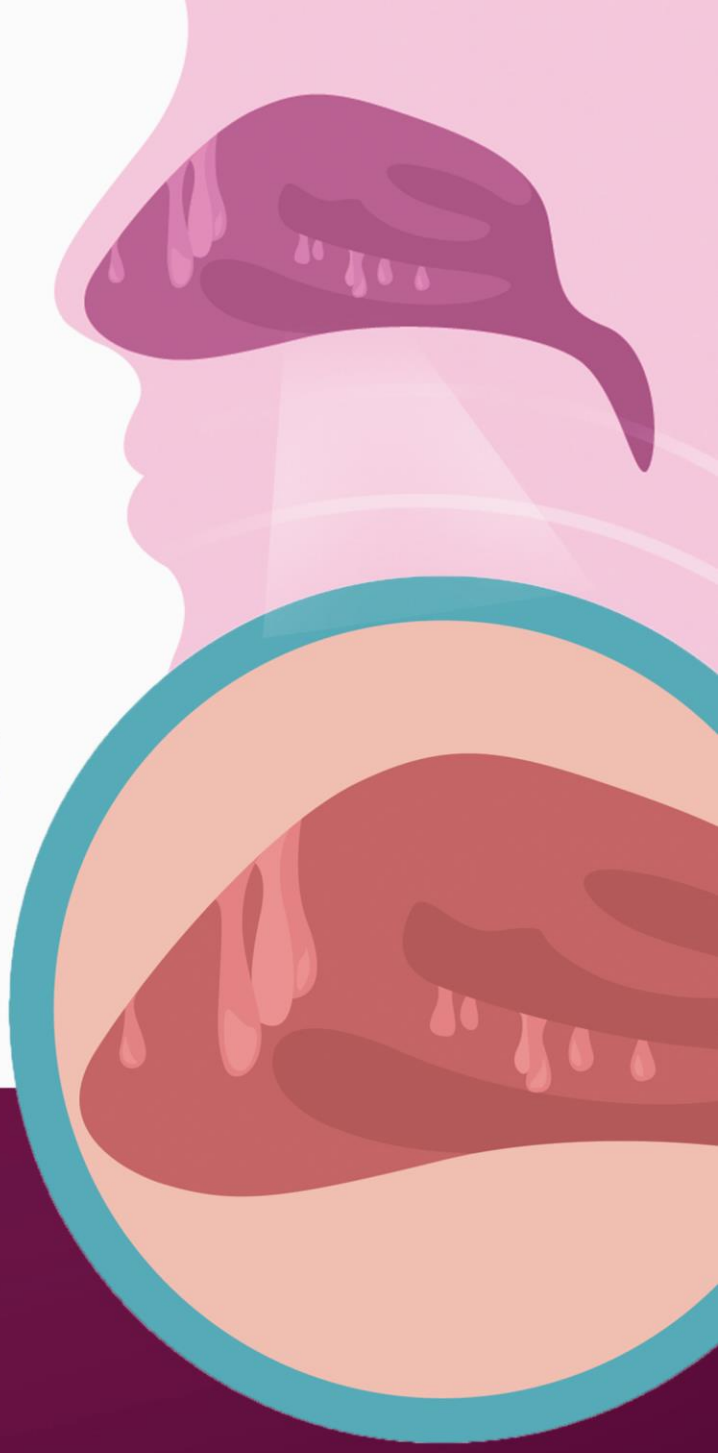
Addressing the Type 2 Inflammation *Signature Through The Management of* CHRONIC RHINOSINUSITIS with NASAL POLYPS



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Addressing the Type 2 Inflammation Signature Through the Management of CRSwNP

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PROGRAM OVERVIEW

This live virtual activity will cover the diagnosis, treatment, and management of chronic rhinosinusitis with nasal polyps.

TARGET AUDIENCE

This CME initiative is designed to meet the educational needs of the otolaryngologist involved in the health care of patients with chronic rhinosinusitis with nasal polyps.

LEARNING OBJECTIVES

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

- Review the disease mediators involved in the inflammatory pathology of moderate to severe CRSwNP
- Evaluate the clinical trial data of currently approved antibody therapy for patients with moderate to severe CRSwNP
- Discuss the personalization of treatment for patients with moderate to severe CRSwNP through interpretation and application of biomarkers

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Credit: 1.0 ANCC Contact Hour

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2. Participate in the live virtual activity
3. Submit the pre- and post-test and evaluation form to Med Learning Group

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Agenda

I. **Chronic Rhinosinusitis with Nasal Polyps (CRSwNP): An Overview**
   a. Epidemiology and burden
   b. Health-related quality of life issues with CRSwNP
   c. Classification
      i. Phenotypes and endotypes of CRS
      ii. Comparing CRSwNP and CRSsNP
   d. Pathophysiology
      i. Chronic type 2 inflammation
         1. Immunologic dysfunction and relevant molecules
         2. Inflammatory dysfunction and relevant molecules
         3. Whiteboard animation: Pathophysiology of CRSwNP
      ii. Role of biomarkers in managing CRSwNP
      iii. Disease course
   e. Comorbid conditions
      i. Asthma in patients with CRSwNP
      ii. Emphasis on other T_H2 diseases
   f. The importance of early diagnosis and intervention

II. **Treatment for Moderate to Severe CRSwNP**
   a. Diagnostic criteria
   b. Current standard of care for CRSwNP
   c. Assessing disease control
   d. Rationale for targeted biologic immunotherapies in T_H2 diseases
   e. Pharmacotherapeutic agents
      i. Mechanisms of action of approved and emerging biologics
      ii. Whiteboard animation: Targeting type 2 inflammation in managing CRSwNP
      iii. Efficacy and safety data

III. **Personalisation of Treatment for Moderate to Severe CRSwNP**
   a. Selecting the right treatment for each patient
   b. Identifying candidates for biologic therapy
   c. Assessing response to biologics
   d. Additional factors relevant to treatment decision-making

IV. **Case Studies**

V. **Conclusions**

VI. **Questions and Answers**

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Disclosures

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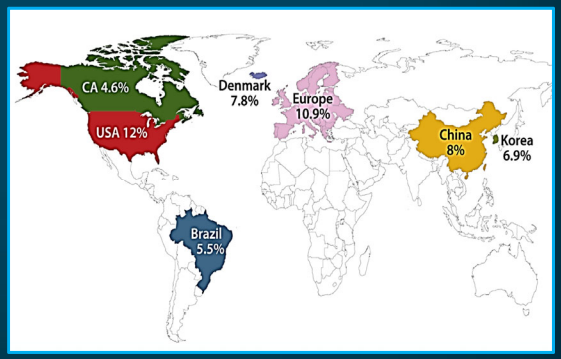
Learning Objectives

- Review the disease mediators involved in the inflammatory pathology of moderate-to-severe chronic rhinosinusitis with nasal polyps (CRSwNP)
- Evaluate the clinical trial data of currently approved antibody therapy for patients with moderate-to-severe CRSwNP
- Discuss the personalization of treatment for patients with moderate-to-severe CRSwNP through interpretation and application of biomarkers

Burden of Chronic Rhinosinusitis (CRS)

- In 2014, the annual economic burden of CRS in the US was ~$22 billion
- Nasal polyps are estimated to occur in 1–4% of the US population
- Among patients with CRS, 25–30% are estimated to have nasal polyps
- Nasal polyps are associated with reduced QoL, impaired sense of smell, and sleep disturbances
- Typical age of diagnosis ranges from 40–60 years



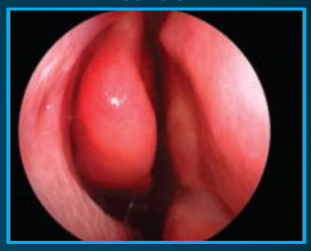
QoL = quality of life.

Stevens WW, et al. *J Allergy Clin Immunol Pract*. 2016;4:565-572. Smith KA, et al. *Laryngoscope*. 2015;125:1547-1556. Avdeeva K, Fokkens W. *Curr Allergy Asthma Rep*. 2018;18:25. Bachert C, et al. *J Allergy Clin Immunol*. 2015;136:1431-1440.

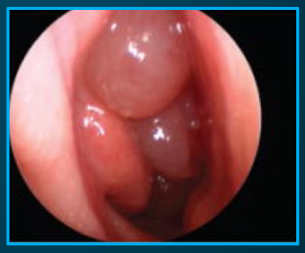
Burden of CRSwNP

- Polyps most commonly present as bilateral inflammatory outgrowths originating in the paranasal sinuses and projecting into nasal airway medial or lateral to middle turbinate
  - Concern of neoplasm or alternate diagnosis if new-onset polyps at advanced age, unilateral disease, bone erosion, or in atypical locations
- Females are more likely to:
  - Have significantly enhanced radiographic evidence of sinus disease
  - Take systemic corticosteroids at time of sinus surgery
  - Require revision sinus surgeries

Control



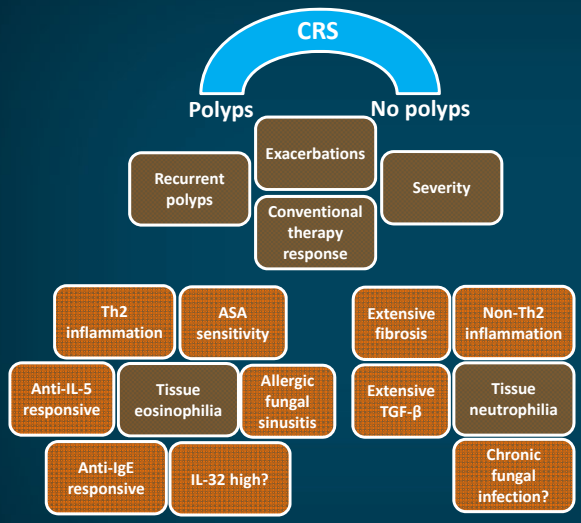
Severe CRSwNP



CRSwNP = CRS with nasal polyps.

Stevens WW, et al. *J Allergy Clin Immunol Pract*. 2016;4:565-572. Sedaghat AR. *Am Fam Physician*. 2017;96:500-506. Schleimer RP. *Annu Rev Pathol*. 2017;12:331-357.

Phenotypes and Endotypes in CRS



Phenotypes

Phenotypes are defined by an observable characteristic or trait

Endotypes

Endotypes define the underlying cellular and molecular pathophysiologic mechanisms of disease

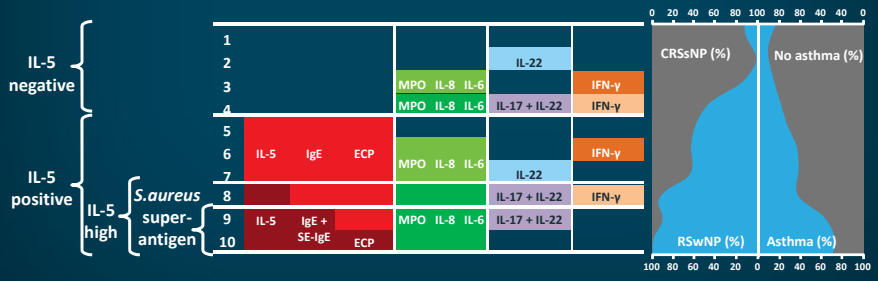
Th2 = type 2 helper T cell; IL = interleukin; IgE = immunoglobulin E; ASA = acetylsalicylic acid; TGF-β = transforming growth factor beta.

Akdis CA, et al. *J Allergy Clin Immunol*. 2013;131:1479-1490.

Endotype Clusters in CRS

Classification of 173 patients based on immune markers identified 10 endotype clusters

- IL-5 negative clusters were predominantly CRSsNP without concomitant asthma
- Moderate IL-5 clusters had mixed CRSsNP/CRSwNP and increased asthma phenotype
- High IL-5 clusters were predominantly CRSwNP with strongly increased asthma prevalence



CRSsNP = CRS without nasal polyps; ECP = eosinophilic cationic protein; SE-IgE = Staphylococcus aureus enterotoxin-specific IgE; MPO = myeloperoxidase; IFN-γ = interferon gamma.

Tomassen P, et al. *J Allergy Clin Immunol.* 2016;137:1449-1456.e4.

Pathophysiology of CRS Animation

https://youtu.be/pD75zkGpvfU

Common Comorbidities

- How many CRSwNP patients are sensitized to at least 1 aeroallergen? → 51–86%
- How many patients with CRSwNP have asthma? → 26–48%
- What percentage of patients with asthma have at least some radiographic evidence of sinonasal inflammation? → ~88%

Stevens WW, et al. *J Allergy Clin Immunol Pract*. 2016;4:565-572.

CRSwNP and Asthma

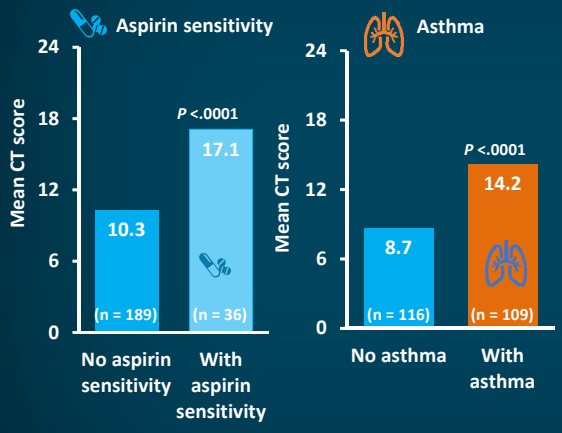
- CRSwNP and asthma share similar features of inflammation and remodeling, including high eosinophil counts, type 2 inflammation, and similar inflammatory mediators
- Patients with CRSwNP and comorbid asthma (with or without NSAID-exacerbated respiratory disease) have more severe disease, which is characterized by:
  - High NP scores
  - Recurrence of NPs after surgery
  - Frequent systemic corticosteroid dependence
  - Poor asthma control
  - High costs and use of health-care resources
- Treatment of CRS has been shown to decreases asthma severity

NSAID = nonsteroidal anti-inflammatory drug; NP = nasal polyp.

Bachert C, et al. *Lancet*. 2019;394:1638-1650. Orlandi RR, et al. *Int Forum Allergy Rhinol*. 2016;6(suppl 1):S22-S209.

Patients With CRS and Comorbidities May Have Greater Disease Severity and Greater Reductions in QoL

Disease severity measured by LMK-CT[1]*



Comorbidities may impact QoL[2]

SF-36 score			
Mean change†	CRSwNP	CRSwNP + Asthma	AERD
Physical (PCS)	–5.1 *P* <.0001	–6.9 *P* <.001	–7.5 *P* <.001

*LMK-CT scores (range 0–24), higher scores = greater severity. †N = 445 CRS patients compared to UK PN.

LMK-CT = Lund Mackay computed tomography; PCS = physical component summary; SF-36 = Short-Form Health Survey; AERD = aspirin-exacerbated respiratory disease; UK PN = United Kingdom population norm.

1. Batra PS, et al. *Laryngoscope*. 2013;123(suppl 7):S1-S11. 2. Khan A. *Allergy*. 2015;70(suppl 101):282-283 (abstract 1536).

Assessing for Comorbidities

- Recommended that patients with CRS be evaluated for asthma and allergy by history and physical exam
  - Validated questionnaires such as the ACT and AQLQ can be helpful
- If at risk of asthma, pulmonary evaluation may be warranted to assess lung function and multidisciplinary management of complex patients with both upper and lower airway inflammation
- Correspondingly, patients with asthma should be assessed for CRS and allergic rhinitis
  - Validated questionnaires
  - Nasal endoscopy
  - Skin-prick testing, measurement of specific blood IgE, and measurement of blood eosinophil counts

ACT = Asthma Control Test; AQLQ = Asthma Quality of Life Questionnaire;.

Fokkens WJ, et al. *Allergy*. 2019;74:2312-2319.

CRSwNP Biomarkers

- No accurate biomarkers for CRSwNP currently available
- Type 2 inflammation often predominates in CRSwNP
  - Associated with elevated levels of eosinophils and type 2 cytokines, including IL-4, IL-5, and IL-13
- Modalities utilized to obtain potential biomarkers:
  - Sinus-tissue biopsy or mucous—may be most accurate at assessing local processes underlying inflammation
  - Peripheral blood—does not always reflect local nasal inflammatory processes
  - With nasal lavage, inconsistent correlation between cytokines in nasal secretions compared to tissue

Biomarker	Source Medium	Targeted Therapy
Eosinophilia	Tissue, PB	
IgE	Tissue	Omalizumab
Cytokines: IL-4	Tissue	Dupilumab
IL-5	Tissue	Mepolizumab, reslizumab
IL-13	Tissue	Dupilumab
IL-25	Tissue	
IL-33	Tissue	
TSLP	Tissue	
Periostin	Tissue, NS	
P-glycoprotein	Tissue, NS	Verapamil
CXCL-12/CXCL-13	Tissue	
ILC2 cells	Tissue	
IgG/IgA autoantibodies	Tissue	
Nitric oxide	Exhaled breath	
Bitter and sweet taste receptors	Tissue, genotype, taste test	
Microbiome	NS	
IgE antibody to *S. aureus* enterotoxin	Tissue	
Matrix metalloproteinases	Tissue, NS	Doxycycline
Oncostatin M	Tissue	

PB = peripheral blood; NS = nasal secretions; TSLP = thymic stromal lymphoprotein.

Workman AD, et al. *Immunol Allergy Clin North* Am. 2018;38:679-692.

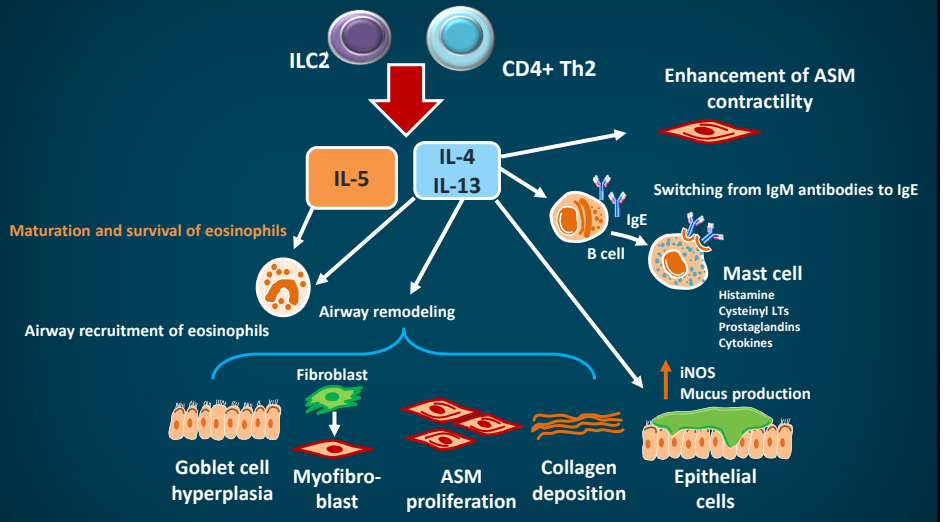
CRSwNP Biomarkers: Eosinophilia

- Eosinophilic nasal polyps are associated with increased objective and subjective disease severity and increased risk of disease recurrence following sinus surgery
- Eosinophilic polyps are generally more corticosteroid responsive than non-eosinophilic polyps
- Eosinophilia is often classified by tissue evaluation
  - No established cutoff point to date
  - Degree of eosinophilia cannot be predicted by clinical symptoms, SNOT-22 score, or concomitant presence of asthma or AERD

SNOT-22 = Sino-nasal Outcome Test 22.

Workman AD, et al. *Immunol Allergy Clin North Am*. 2018;38:679-692.

Pathways Involved in Type 2 Inflammation



iNOS = inducible nitric oxide synthase; LTs = leukotrienes; ASM = airway smooth muscle cell; ILC2 = type 2 innate lymphoid cells.

Modified from Vatrella A, et al. *J Asthma Allergy*. 2014;7:123-130.

CRSwNP Biomarkers: IgE and Cytokines

- Patients with CRS frequently demonstrate:
  - High serum and local IgE levels
  - Allergic sensitization to bacterial antigens (staph enterotoxin)
- High local IgE in tissue is predictive of recurrence, requiring repeat surgical intervention
- Increased expression of Th2 inflammatory cytokines are noted in patients with CRSwNP
  - IL-5 induces eosinophilia through recruitment, activation, and survival of eosinophils
  - IL-4 and IL-13 induce local IgE production and stimulate mucus secretion
  - IL-13 affects epithelial differentiation, resulting in decreased ciliation and goblet cell metaplasia, further contributing to leaky sinonasal epithelial barrier
  - IL-13 increases hyperactivity of airway and causes subepithelial fibrosis

Workman AD, et al. *Immunol Allergy Clin North Am*. 2018;38:679-692. Milonski J, et al. *DNA Cell Biol*. 2015;34:342-349.

Management of CRSwNP

Diagnosis of CRS in Adults

Inflammation of nose and paranasal sinuses is characterized by two or more symptoms:

- 1 symptom should be either nasal blockage/obstruction/ congestion or nasal discharge (anterior/posterior nasal drip)
- ± Facial pain/pressure
- ± Reduction or loss of smell

AND EITHER

Endoscopic signs of:
- Nasal polyps, **and/or**
- Mucopurulent discharge, primarily from middle meatus, **and/or**
- Edema/mucosal obstruction primarily in middle meatus

CT changes
- Mucosal changes within the ostiomeatal complex and/or sinuses

Fokkens WJ, et al. *Rhinology.* 2020;58(suppl S29):1-464.

Initial Management of CRSwNP

- **Topical corticosteroids and saline irrigation are recommended per ICAR**
- Nasal steroids improve symptoms and endoscopic appearance, reduce polyp size, and improve QoL
  - Well tolerated; most common AEs are epistaxis and nasal irritation
- Saline irrigations as adjunct to nasal steroids
  - Mechanical cleaning of sinonasal cavity to remove mucus, debris, and allergens
  - High-volume isotonic or hypertonic saline irrigation recommended as adjunct to other therapies

Nasal steroids (4–6 weeks)

Consider nasal irrigation

Consider course of oral steroids in case of severe disease

Consider oral antibiotics for acute exacerbation

Avoid smoking and other irritant exposures

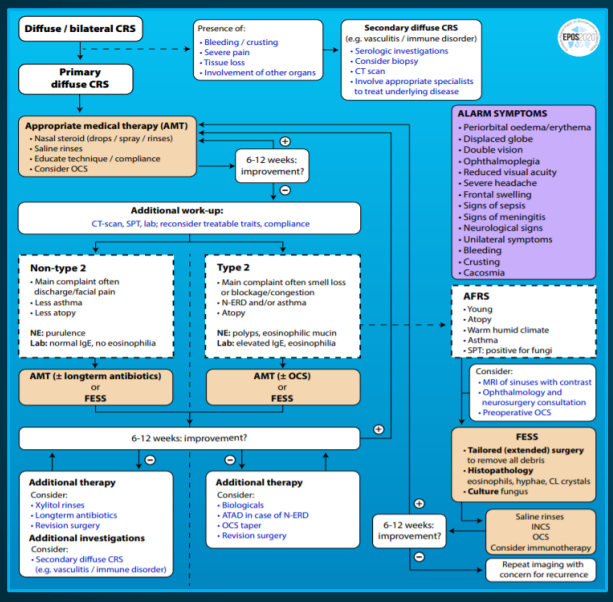
Treat comorbid allergy

Continue nasal steroids and treatment for as long as is needed

ICAR = International Consensus Statement on Allergy and Rhinology; AE = adverse event.

Orlandi RR, et al. *Int Forum Allergy Rhinol*. 2016;6(suppl 1):S3-S21. Akdis CA, et al. *J Allergy Clin Immunol*. 2013;131:1479-1490. Rosenfeld RM, et al. *Otolaryngol Head Neck Surg*. 2015;152(2 suppl):S1-S39.

Management of CRS



Fokkens WJ, et al. *Rhinology.* 2020;58(suppl S29):1-464.

AMT = appropriate medical therapy; ATAD = aspirin treatment after desensitization; FESS = functional endoscopic sinus surgery; INCS = intranasal corticosteroid spray; MRI = magnetic resonance imaging; NE = nasal endoscopy; N-ERD = NSAID-exacerbated respiratory disease; OCS = oral corticosteroids; SPT = skin-prick test.

How Would You Manage This Patient?

- Laura was initiated on topical corticosteroids and saline irrigation 6 weeks ago to control her CRSwNP.
- She has seen improvement in her symptoms and has regained her sense of smell.
- She reports that she no longer experiences facial pain or pressure, but she does have mucopurulent postnasal drip 4 or 5 days per week.

Is Laura's CRSwNP adequately controlled on her current treatment regimen?

Is Your Patient's CRS Under Control?

Assessment of current clinical control of CRS (in the last month)

	Controlled (all of the following)	**Partly controlled** (**at least 1** present)	**Uncontrolled** (**3 or more** present)
Nasal blockage*	Not present or not bothersome†	Present on most days of week‡	Present on most days of week‡
Rhinorrhea/postnasal drip*	Little and mucous†	Mucopurulent on most days of week‡	Mucopurulent on most days of week‡
Facial pain/pressure*	Not present or not bothersome†	Present on most days of week‡	Present on most days of week‡
Sense of smell*	Normal or only slightly impaired†	Impaired‡	Impaired[3]
Sleep disturbance or fatigue*	Not present	Present‡	Present‡
Nasal endoscopy (if available)	Healthy or almost healthy mucosa	Diseased mucosa§	Diseased mucosa§
Rescue treatment (in last 6 months)	Not needed	Need of 1 course of rescue treatment	Symptoms (above) persist despite rescue treatment(s)

***Symptoms of CRS; †For research VAS ≤5; ‡For research VAS >5; §Showing nasal polyps, mucopurulent secretions, or inflamed mucosa.**

VAS = visual analogue scale.

Fokkens WJ, et al. *Rhinolology*. 2020;58(suppl S29):1-464.

Antibiotics for CRSwNP

- Between 2006 and 2010, rhinosinusitis accounted for 11% of all primary care antibiotic-related visits—more than any other diagnosis
- Recommendation against IV or topical antibiotics and topical antifungals per ICAR
- Oral macrolides may reduce endoscopy scores and improve symptoms; limited evidence for use and concerns of resistance with long-term use
- Evidence for the use of antibiotics for CRS is sparse
  - Antibiotic selection should be guided by culture results when possible
  - Doxycycline plus methylprednisolone for 20 days decreased polyp size in one clinical trial
  - Options for CRS exacerbations may best be driven by endoscopically guided cultures

IV = intravenous.

Orlandi RR, et al. *Int Forum Allergy Rhinol*. 2016;6(suppl 1):S3-S21. Rosenfeld RM, et al. *Otolaryngol Head Neck Surg*. 2015;152(2 suppl):S1-S39. Cain RB, Lal D. *Infect Drug Resist*. 2013;6:1-14.

Short-Course Oral Steroids

- **Oral corticosteroids may be used for short-term management per ICAR**
  - **Long-term or frequent use is not supported by literature and carries increased risk of harm**
- In a review of 8 RCTs comparing oral corticosteroids to placebo or no intervention:
  - 1 study reported an improvement in QoL after 2–3 weeks of treatment with steroids
  - 2 studies showed an improvement in patient-reported symptoms following 2–3 weeks of oral steroids
  - Increased risk of GI disturbances and insomnia with steroids
  - Little to no improvement in QoL or symptoms 3–6 months after discontinuing oral steroids
- Unclear if there are benefits with oral corticosteroids as adjunct therapy

RCT = randomized controlled trial; GI = gastrointestinal.

Orlandi RR, et al. *Int Forum Allergy Rhinol*. 2016;6(suppl 1):S3-S21. Head K, et al. *Cochrane Database Syst Rev*. 2016;4:CD011991. Head K, et al. *Cochrane Database Syst Rev.* 2016;4:CD011992.

Endoscopic Sinus Surgery (ESS)

- ESS should be considered for the management of patients with:
  - Large symptom burden coupled with failure to respond to therapy
    and
  - Significant sinus disease on post-treatment CT scan
- Goals include:
  - Reducing burden of inflammatory tissue and osteitis
  - Improving ventilation of sinus outflow tracts
  - Restoring mucociliary function
  - Creating access for topical medications
  - Reducing acute exacerbations and systemic medication use
  - Improving QoL

Cain RB, Lal D. *Infect Drug Resist*. 2013;6:1-14.

Recurrence of Polyps Following ESS

- In a cohort study comparing continued medical management vs ESS, subjects undergoing ESS were significantly more likely to experience:
  - Improvement in thick nasal discharge (OR = 4.36)
  - Decreased facial pain/pressure (OR = 3.56)
  - Reduced blockage/congestion (OR = 2.76)
  - Return of smell and taste
- However, in a study of 560 patients 3–5 years post-ESS, 36.8% had partly controlled symptoms and 43.7% were uncontrolled

OR = odds ratio.

DeConde AS, et al. *Int Forum Allergy Rhinol*. 2015;5:36-45. van der Veen, J, et al. *Allergy*. 2017;72:282-290.

Revision Rates with ESS

- Small study of 47 patients found 78.9% of patients had disease recurrence and 36.8% required revision surgery over 12-year period
- Large study of Utah Population Database identified 29,934 subjects who underwent ESS between 1996 and 2016
  - Long-term revision rate was 15.9%
  - Mean time between surgeries decreased with higher number of revision surgeries
    - 4.39 years between 1st and 2nd surgery
    - 2.18 years between 4th and 5th surgery
  - Increased risk of requiring revision surgery with female gender, older age at first surgery, nasal polyps, comorbid asthma, allergy, and family history of CRS

Calus L, et al. *Clin Transl Allergy*. 2019;9:30. Smith KA, et al. *Int Forum Allergy Rhinol*. 2019;9:402-408.

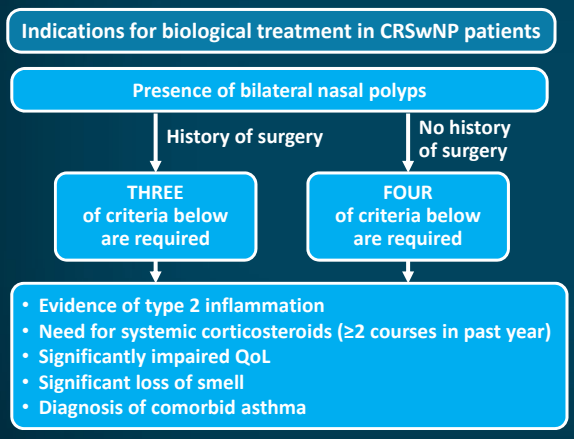
How Would You Manage This Patient?

- Paul is a 55-year old man with a history of CRSwNP.
- He underwent ESS 2 years ago but complains of worsening symptoms, including loss of smell, facial pressure, and significant nasal congestion and discharge.
- He received 2 short courses of oral corticosteroids in the last year to control his symptoms.
- His past medical history is significant for hypertension and asthma.

How would you manage Paul?

Proposed Indications for Biologics in CRSwNP

Indications for biological treatment in patients with CRSwNP as proposed by multidisciplinary EUFOREA Expert Board Meeting



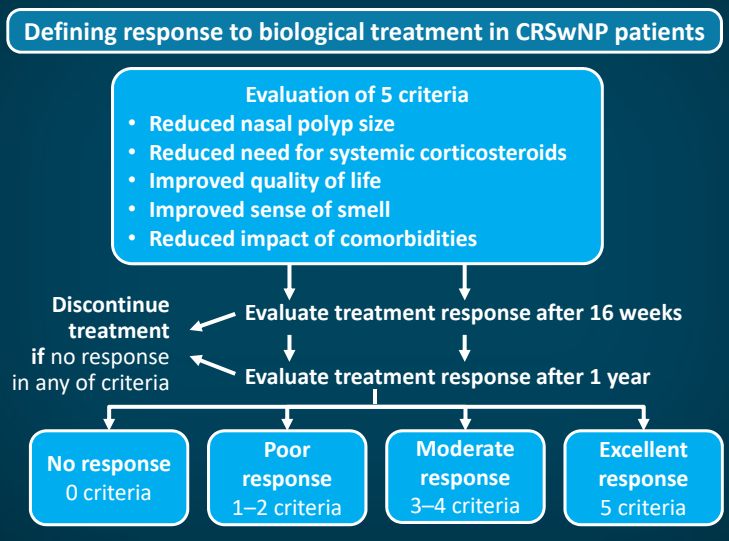
Do NOT initiate type 2 biological treatments in patients with:

- CRSsNP and lacking signs of type 2 inflammation
- Cystic fibrosis
- Unilateral nasal polyps
- Mucoceles
- General contraindications for biological treatments, such as immunodeficiencies
- Patient-related factors such as noncompliance to therapy

EUFOREA = European Forum for Research and Education in Allergy and Airway Diseases.

Fokkens WJ, et al. *Allergy*. 2019;74:2312-2319.

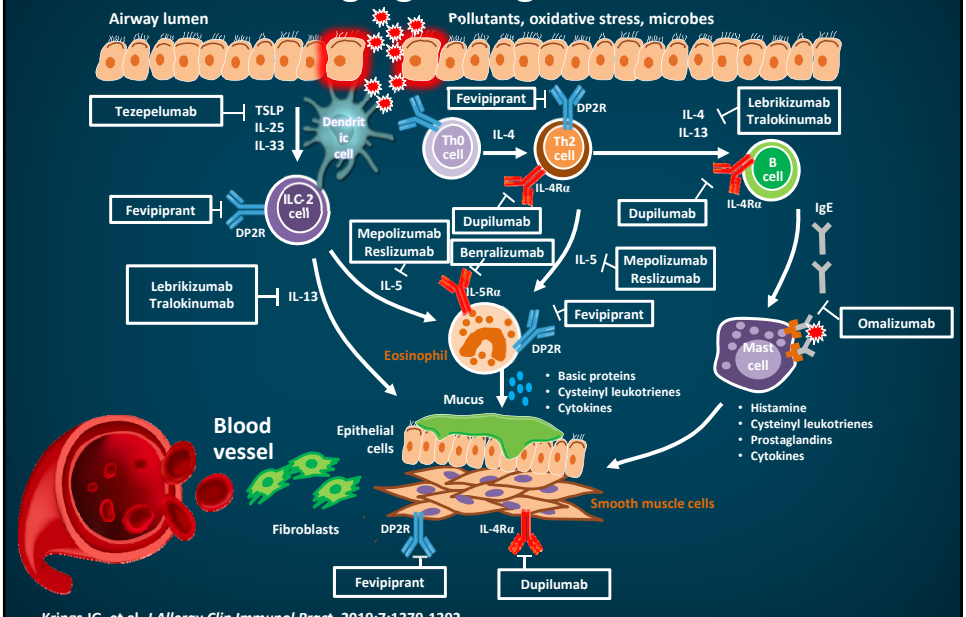
Proposed Response Criteria for Biologics in CRSwNP



Fokkens WJ, et al. *Allergy*. 2019;74:2312-2319.

Biologics in the Management of CRSwNP

Emerging Biologics for CRS



Krings JG, et al. *J Allergy Clin Immunol Pract*. 2019;7:1379-1392.

Omalizumab

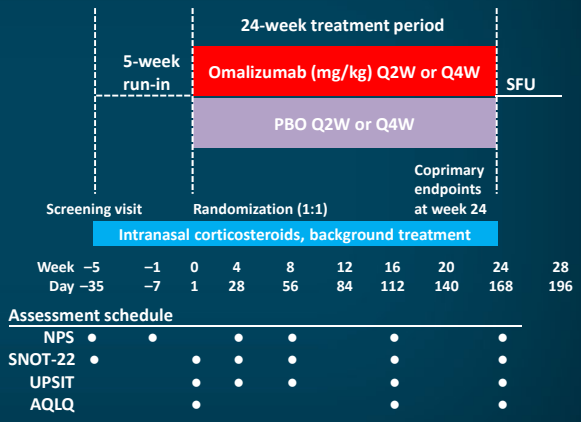
Anti-IgE Monoclonal Antibody

Omalizumab: Phase 3 POLYP 1 and POLYP 2 Trials

2 identical phase 3 trials investigating omalizumab in patients with inadequately controlled CRSwNP despite daily INCS therapy

Inclusion criteria:

- 18–75 years of age
- Persistent bilateral NPs
- Nasal congestion
- Impaired HRQoL
- Weight and serum IgE levels permitting omalizumab dosing
- ≤4 weeks of INCS therapy before screening
- Total NPS of ≥5 (≥2 for each nostril)
- NCS of ≥2 at day –35
- SNOT-22 score of ≥20 at day –35 and randomization

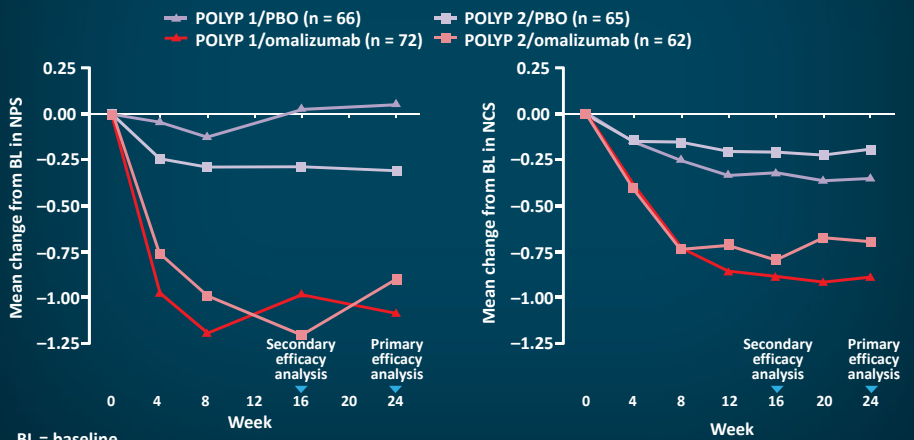


HRQoL = health-related QoL; NPS = Nasal Polyp Score; NCS = Nasal Congestion Score; SFU = safety follow-up; UPSIT = University of Pennsylvania Smell Identification Test; PBO = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks.

Gevaert P, et al. *J Allergy Clin Immunol.* 2020;146:595-605.

POLYP 1 and POLYP 2 Results

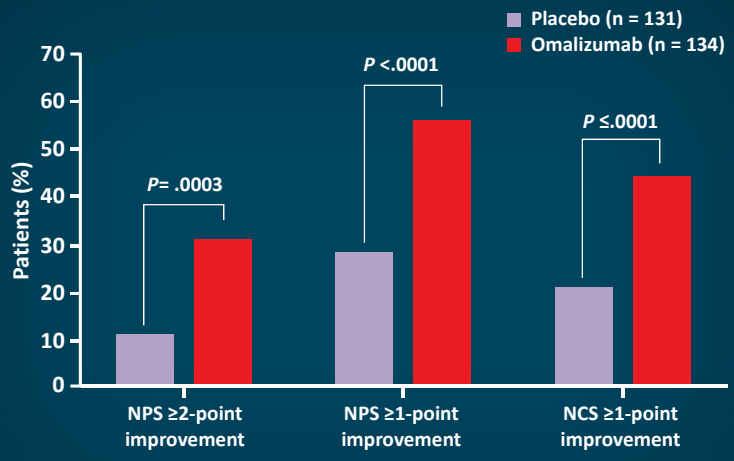
	POLYP 1			POLYP 2		
	Omalizumab	PBO	Treatment Difference (*P*-value)	Omalizumab	PBO	Treatment Difference (*P*-value)
NPS	**–1.08**	**0.06**	**–1.14 (*P* <.001)**	**–0.90**	**–0.31**	**–0.59 (*P*= .140)**
NCS	–0.89	–0.35	–0.55 (*P*= .0004)	–0.70	–0.20	–0.50 (*P*= .0017)



BL = baseline.

Gevaert P, et al. *J Allergy Clin Immunol.* 2020;146:595-605.

POLYP 1 and POLYP 2: More Results

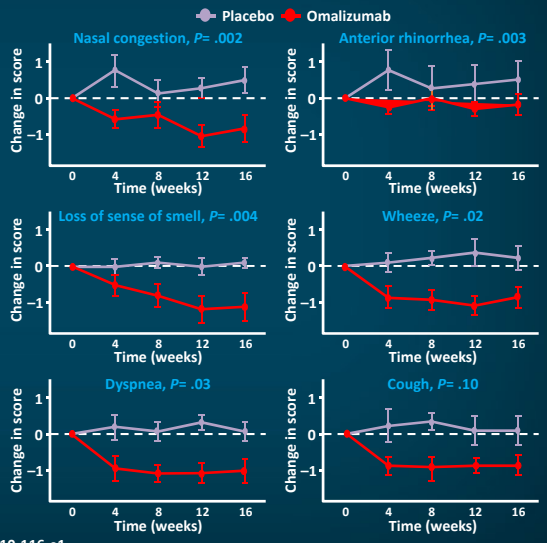


50.4% of omalizumab-treated patients and 58.5% of placebo-treated patients experienced at least 1 treatment-emergent AE

Gevaert P, et al. *J Allergy Clin Immunol.* 2020;146:595-605.

Omalizumab in Allergic and Nonallergic Patients with Nasal Polyps and Asthma

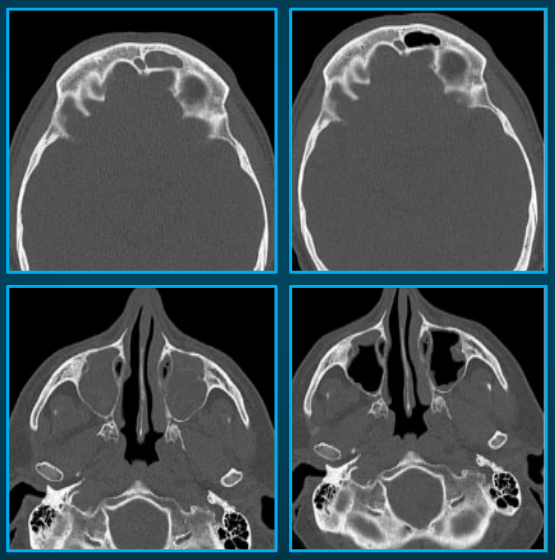
- RDBPC study of 24 patients with NPs and comorbid asthma
- Dosing based on IgE levels and body weight (max dose of 375 mg)
- Decrease in NPS after 16-week treatment (–2.67, *P*= .001)
- Improvement in nasal and asthma symptom scores



RDBPC = randomized, double-blind, placebo-controlled.

Gevaert P, et al. *J Allergy Clin Immunol.* 2013;131:110-116.e1.

CT Scans of Sinuses Before and 3 Months After Omalizumab



Bachert C, et al. *J Allergy Clin Immunol.* 2015;136:1431-1440.

Conflicting Data

- RDBPC trial of CRS patients was conducted by Pinto et al
- Study results
  - No significant difference between treatments in radiographic scores on imaging, NPIF rates, or UPSIT
  - SNOT-20 scores improved at 3, 5, and 6 months in the omalizumab group compared with placebo group
- Investigators concluded that IgE plays a small role in mucosal inflammation in CRS

NPIF = nasal peak inspiratory flow (rates).

Pinto JM, et al. *Rhinology*. 2010;48:318-324.

Malignancy with Omalizumab

- Neoplasia reported more frequently in omalizumab-treated patients vs controls (0.5% vs 0.2%)
- Evaluating Clinical Effectiveness and Long-Term Safety in Patients with Moderate-to-Severe Asthma (EXCELS)
  - Prospective observational cohort study
  - Median follow-up of 5 years
  - Malignancy rates similar in omalizumab and non-omalizumab cohorts
    - HR (omalizumab vs non-omalizumab) of 1.09 (95% CI, 0.87–1.38) for all malignancies
    - HR of 1.15 (95% CI, 0.83–1.59) for all malignancies, excluding NMSC

HR = hazard ratio; CI = confidence interval; NMSC = non-melanoma skin cancer

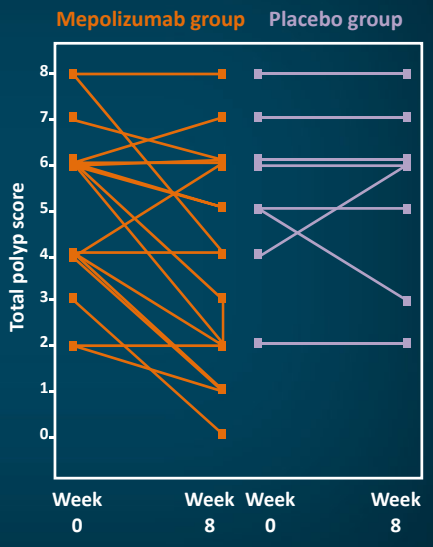
Long A, et al. *J Allergy Clin Immunol*. 2014;134:560-567.e4.

Mepolizumab

Anti-IL-5 Monoclonal Antibody

Mepolizumab for CRSwNP

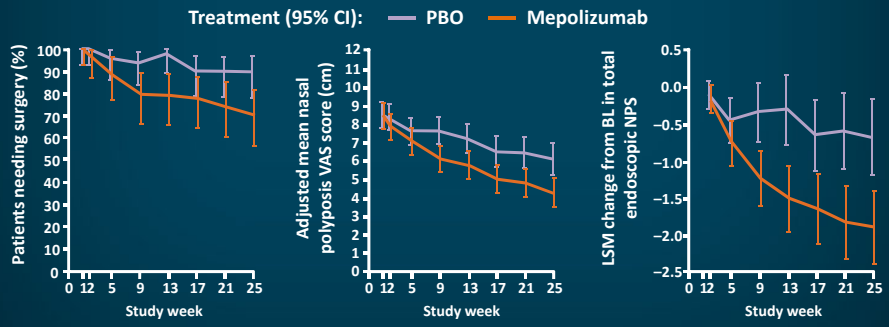
- RDBPC study of patients with NPs refractory to corticosteroid therapy
- 12/20 receiving mepolizumab had decreased NPS compared with 1/10 in PBO group (–1.30, *P*= .028)
- No significant difference in symptom scores
- Most common AEs were headache (19%), injection-site reaction (8%), back pain (5%), and fatigue (5%)
- Herpes zoster occurred in 2 patients who received mepolizumab vs placebo



Gevaert P, et al. *J Allergy Clin Immunol*. 2011;128:989-995.e1-8.

Reduced Need for Surgery with Mepolizumab

- RDBPC of 105 patients receiving 750 mg IV mepolizumab or PBO Q4W x 6 doses
- Greater number of patients in mepolizumab group no longer needed surgery at week 25 (n = 5, 10%) compared with placebo group (n = 26, 30%) (*P*= .006)
- Improved VAS score, endoscopic NPS, and SNOT-22 in treatment group



LSM = least squares mean.

Bachert C, et al. *J Allergy Clin Immunol.* 2017;140:1024-1031.e14.

Emerging Data: SYNAPSE Study

- Randomized, double-blind, parallel group, phase 3 study of subcutaneous (SC) mepolizumab 100 mg versus placebo every 4 weeks for 52 weeks in >400 adults
- Inclusion criteria
  - Severe bilateral nasal polyps defined as those with an average nasal obstruction VAS symptom score >5 and an endoscopic score of ≥5 (≥2 in each nostril)
  - History of ≥1 prior surgery for nasal polyps in the last 10 years
  - Recurrent nasal polyps despite treatment with standard of care
- Results
  - Difference in median change from baseline for total endoscopic NPS: –0.73 (95% CI, –1.11 to –0.34; *P* <.001)
  - Difference in median change from baseline for nasal obstruction VAS score: –3.14 (95% CI, –4.09 to –2.18; *P* <.001)
  - 57% reduction in time to first nasal surgery (up to 52 weeks) with mepolizumab

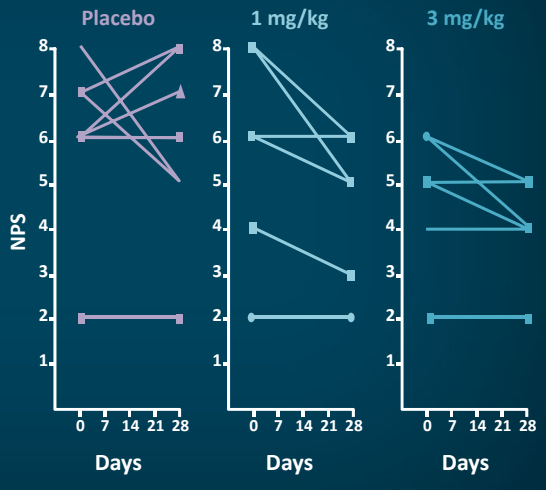
GlaxoSmithKline press release, 4/3/2020 (www.gsk.com/en-gb/media/press-releases/nucala-mepolizumab-is-the-first-anti-il5-biologic-to-report-positive-phase-3-results-in-patients-with-nasal-polyps/). Accessed 10/12/2020.

Reslizumab

Anti-IL-5 Monoclonal Antibody

Nasal IL-5 Levels Determine Response to Anti-IL-5 Treatment in Patients with Nasal Polyps

- RDBPC of 24 patients receiving a single infusion of reslizumab at 3 mg/kg, 1 mg/kg, or placebo
- Nasal polyp scores decreased in half of treated patients for up to 4 weeks
- Increased IL-5 in nasal secretions before treatment-predicted response
- Nasal IL-5 levels decreased only in responders



Gevaert P, et al. *J Allergy Clin Immunol.* 2006;118:1133-1141.

Dupilumab

Anti-IL-4R Monoclonal Antibody

Type 2 Inflammation and Dupilumab Animation

https://youtu.be/y3WIirr7ncQ

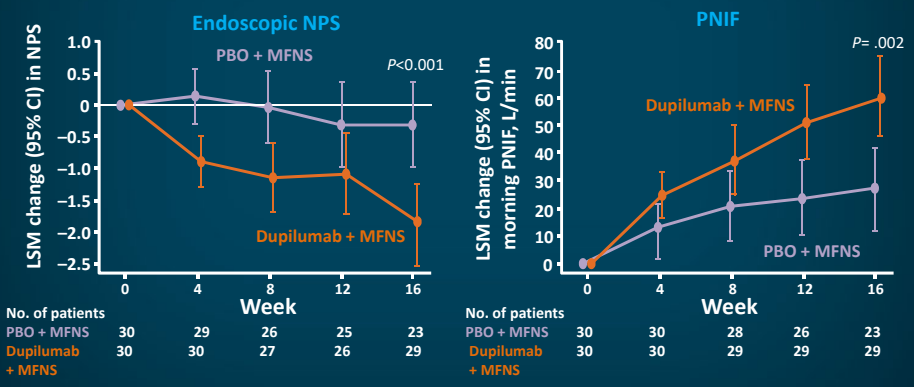
Phase 2 Trial of Dupilumab in CRSwNP

- 60 adults with moderate-to-severe CRSwNP with (n = 35) and without (n = 25) asthma
- SC dupilumab 600 mg loading dose followed by 300 mg weekly (n = 30, placebo n = 30) + mometasone furoate spray for 16 weeks
- Eligible patients
  - Failed ≥8 weeks of intranasal corticosteroids
  - Had ≥2 symptoms of CRSwNP
  - Bilateral endoscopic NPS of ≥5 with a score of ≥2 for each nostril
- Primary endpoint was change in endoscopic NPS range 0–8 after 16 weeks
  - Secondary endpoints included sinus CT scores, olfaction, validated symptom scores, biomarkers, and safety assessments

Bachert C, et al. *JAMA*. 2016;315:469-479.

Decreased Polyp Size and Improved Nasal Airflow

- LSM change in NPS was –1.9 with dupilumab and –0.3 with placebo (*P* <.001)
- LSM change from BL to week 16 for morning PNIF was 60.2 L/min with dupilumab and 27.1 L/min with placebo (*P*= .002)



PNIF = peak nasal inspiratory flow; MFNS = mometasone furoate nasal steroids.

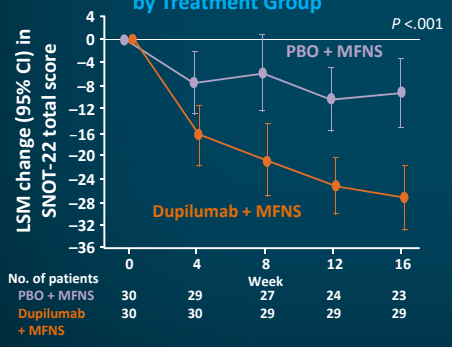
Bachert C, et al. *JAMA*. 2016;315:469-479.

Improved QoL and Olfaction with Dupilumab

Significant improvements in SNOT-22 and UPSIT scores observed with dupilumab

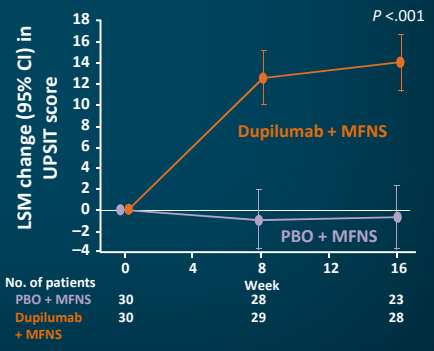
- SNOT-22: LSM difference between groups of –18.1 (*P* <.001)
- UPSIT: LSM difference of 14.8 (*P* <.001)

22-Item SNOT-22 Total Score by Treatment Group



No. of patients					
PBO + MFNS	30	29	27	24	23
Dupilumab + MFNS	30	30	29	29	29

UPSIT Score by Treatment Group



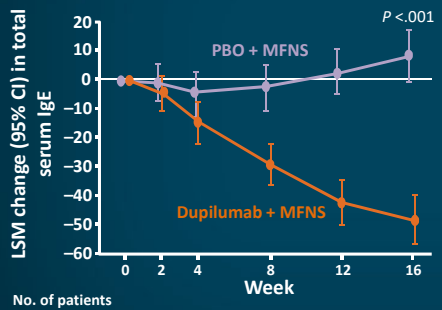
No. of patients					
PBO + MFNS	30		28		23
Dupilumab + MFNS	30		29		28

Bachert C, et al. *JAMA*. 2016;315:469-479.

Decreased IgE and Eotaxin-3 with Dupilumab

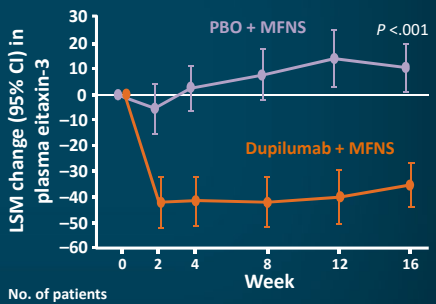
Significant reductions in IgE (*P* <.001) and eotaxin-3 (*P* <.001) with dupilumab compared to placebo

Total IgE



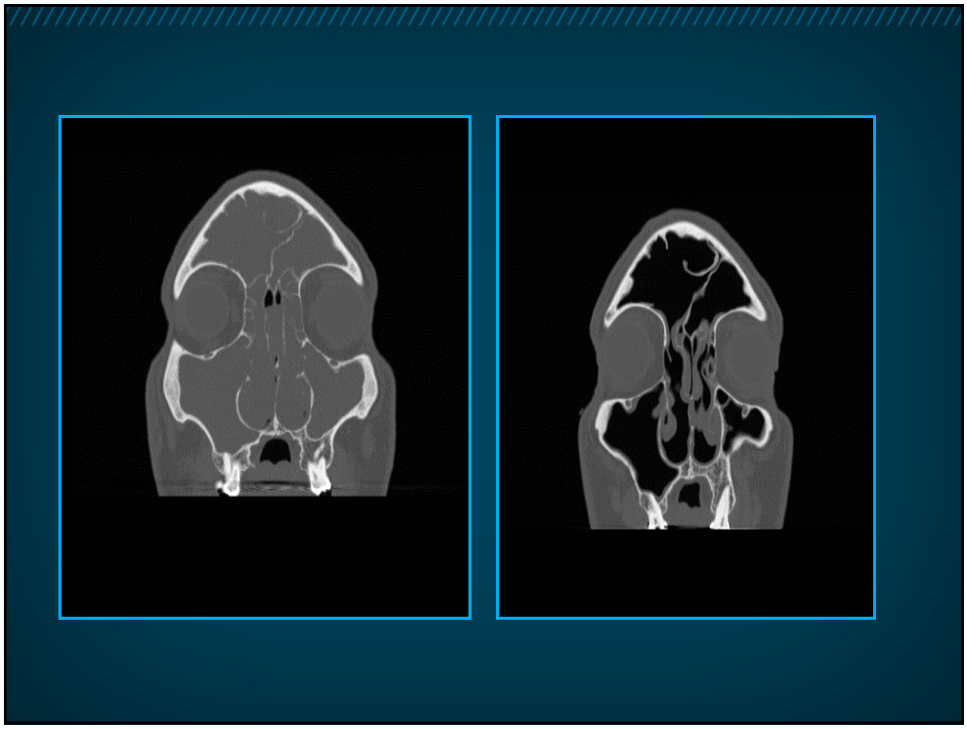
No. of patients						
PBO + MFNS	26	23	26	23	21	20
Dupilumab + MFNS	26	26	26	25	25	25

Plasma Eotaxin-3

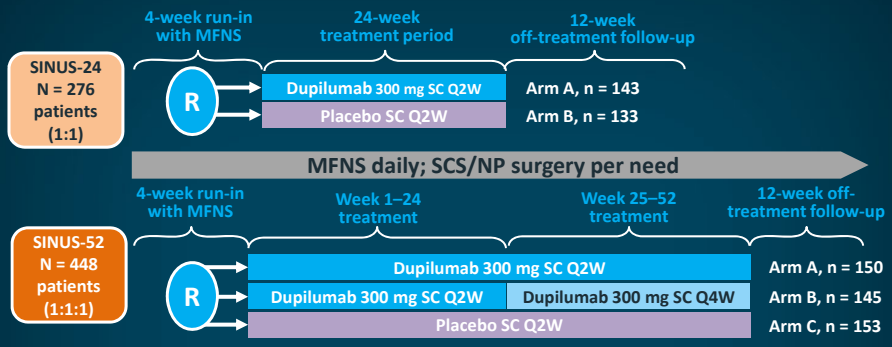


No. of patients						
PBO + MFNS	26	24	26	22	20	20
Dupilumab + MFNS	26	23	25	24	24	25

Bachert C, et al. *JAMA*. 2016;315:469-479.



Dupilumab: LIBERTY NP SINUS-24 and SINUS-52



- **Main inclusion criteria:** Adults aged ≥18 years who have undergone prior treatment with, or have contraindication/intolerance to, SCS in the past 2 years, or have had prior surgery for NP, with a bilateral endoscopic NPS ≥5 (out of 8), and ≥2 for each nostril
- 2 or more of the following symptoms:
  - Nasal congestion/blockage/obstruction (symptom severity score ≥2 out of 3) **AND**
  - Rhinorrhea (anterior/posterior) **OR**
  - Reduction or loss of sense of smell

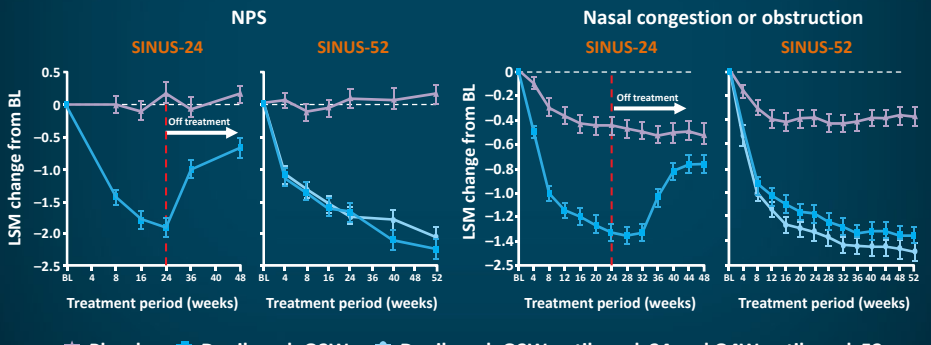
SCS = systemic corticosteroid(s).

Bachert C, et al. *Lancet*. 2019;394:1638-1650.

SINUS-24 and SINUS-52 Results
NPS and Nasal Congestion or Obstruction

Dupilumab reduced polyp size, sinus opacification, and severity of symptoms in all patients with severe CRPwNP

Change from baseline in NPS and NCO



Placebo · Dupilumab Q2W · Dupilumab Q2W until week 24 and Q4W until week 52

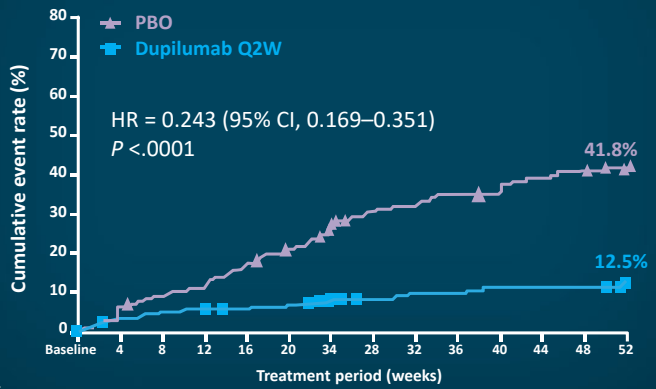
··· Treatment ended at week 24

NCO = nasal congestion or obstruction.

Bachert C, et al. *Lancet*. 2019;394:1638-1650.

SINUS-24 and SINUS-52 Results
Systemic Corticosteroids or Nasal Polyp Surgery

Time to first SCS use or nasal polyp surgery during treatment period



No. at risk

PBO	286	276	260	253	238	224	187	99	97	93	91	86	83	61
Dupilumab Q2W	438	423	416	411	407	404	376	131	129	129	127	127	127	100

Bachert C, et al. *Lancet*. 2019;394:1638-50.

SINUS-24 and SINUS-52 Results

	LIBERTY SINUS-24			LIBERTY SINUS-52		
	Placebo (n = 133)	Dupilumab Q2W (n = 143)	LSM difference vs PBO (95% CI; *P* value)	Placebo (n = 153)	Dupilumab Q2W (n = 295)	LSM difference vs PBO (95% CI; *P* value)
1° and 2° endpoints at week 24						
Bilateral NPS (scale 0–8)	0.17 (0.15)	–1.89 (0.14)	–2.06 (–2.43 to –1.69; *P*<0.0001)	0.10 (0.14)	–171 (0.11)	–1.80 (–2.10 to –1.51; *P* <.0001)
NCO score (scale 0–3)	–0.45 (0.07)	–1.34 (0.07)	-0.89 (–1.07 to –0.71; *P* <.0001)	–0.38 (0.07)	–1.25 (0.06)	–0.87 (–1.03 to –0.71; *P* <.0001)
Lund-Mackay CT score (scale 0–24)	–0.74 (0.37)	–8.18 (0.34)	**–7.44 (–8.35 to –6.53; *P* <.0001)**	–0.09 (0.31)	–5.21 (0.24)	–5.13 (–5.80 to –4.46; *P* <.0001)
Total symptom score (scale 0–9)	–1.17 (0.17)	–3.77 (0.16)	–2.61 (–3.04 to –2.17; *P* <.0001)	–1.00 (0.20)	–3.45 (0.15)	–2.44 (–2.87 to –2.02; *P* <.0001)
Smell test score (UPSIT; scale 0–40)	0.70 (0.71)	11.26 (0.67)	10.56 (8.79 to 12.34; *P* <.0001)	–0.81 (0.71)	9.71 (0.56)	10.52 (8.98 to 12.07; *P* <.0001)
Loss-of-smell score (scale 0–3)	–0.29 (0.07)	–1.41 (0.07)	–1.12 (–1.31 to –0.93; *P* <.0001)	–0.23 (0.08)	–1.21 (0.06)	–0.98 (–1.15 to –0.81; *P* <.0001)
SNOT-22 score (scale 0–110)	–9.31 (1.62)	–30.43 (1.54)	–21.12 (–25.17 to –17.06; *P* <.0001)	–10.40 (1.61)	–27.77 (1.26)	–17.36 (–20.87 to –13.85; *P* <.0001)
Secondary endpoints (week 52)				**150 in each group**		
Bilateral NPS (scale 0–8)				0.15 (0.15)	**–2.24** (0.15)	**–2.40** (–2.77 to –2.02; *P* <.0001)
NCO score (scale 0–3)				–0.37 (0.08)	**–1.35** (0.07)	**–0.98** (–1.17 to –0.79; *P* <.0001)
SNOT-22 score (scale 0–110)				-8.88 (1.61)	**–29.84** (1.63)	**–20.96** (–25.03 to –16.89; *P* <.0001)

Bachert C, et al. *Lancet*. 2019;394:1638-50.

SINUS-24 and SINUS-52
Pooled Safety Population at Week 24

- Dupilumab was well tolerated
- Incidence of AEs during 24-week period was lower with dupilumab than placebo
- During 52-week period of SINUS-52, cough, bronchitis, arthralgia, accidental overdose, and injection-site reactions were slightly more common with dupilumab than placebo

Treatment-Emergent Adverse Events (TEAEs)			
	PBO (n = 282)	Dupilumab Q2W (n = 440)	Risk Difference (%[95% CI]) Dupilumab Q2W vs PBO
	n (%)		
Any TEAE	208 (74%)	305 (69%)	–6.48 (–13.04 to 0.08)
Any serious TEAE	16 (6%)	15 (3%)	–2.80 (–6.30 to 0.70)
Leading to death	0	0	0
Leading to permanent treatment discontinuation	15 (5%)	11 (3%)	–2.66 (–6.01 to 0.69)
Occurring in ≥5% of patients			
Asthma	20 (7%)	7 (2%)	—
Epistaxis	20 (7%)	25 (6%)	—
Headache	24 (9%)	32 (7%)	—
Injection-site erythema	22 (8%)	28 (6%)	—
Nasal polyps	33 (12%)	12 (3%)	—
Nasopharyngitis	41 (15%)	55 (13%)	—

Bachert C, et al. *Lancet*. 2019;394:1638-1650.

SINUS-24 and SINUS-52 Conclusions

- In patients with severe uncontrolled CRSwNP, dupilumab as add-on to MFNS:
  - Significantly improved NP size, sinus opacification, and CRS symptoms
  - Reduced anosmia and improved HRQoL
  - Improvements in all outcome measures were noted at first assessment time point and continued to improve across 52-week treatment period
- Dupilumab reduced SCS use and need for NP surgery
- Dupilumab improved lung function and asthma control in CRSwNP patients with comorbid asthma, a difficult-to-treat patient population
- Compared with 300 mg Q2W-Q4W, the 300 mg Q2W regimen had:
  - Better sustained improvements in objective measures of NPS and LMK-CT scan score
  - Fewer breakthrough TEAEs of worsening of nasal polyps, asthma, and sinusitis

Bachert C, et al. *Lancet*. 2019;394:1638-1650.

Summary

- CRS is defined as symptomatic inflammation of paranasal sinuses for >3 months
  - CRSwNP is found in up to 4% of Americans and is associated with reduced QoL, sleep quality, and productivity
- CRS is classified into 2 phenotypes based on presence or absence of nasal polyps
  - Each phenotype is associated with several endotypes, or underlying pathologies
  - CRSwNP is commonly associated with high tissue eosinophil counts and Th2 inflammation
- Initial treatment of CRSwNP includes intranasal steroids and saline irrigation
- Endoscopic surgery may be considered in patients with significant disease burden or who do not respond to other therapies
- Dupilumab is an anti-IL-4R monoclonal antibody FDA approved as an add-on maintenance treatment for adults with inadequately controlled CRSwNP
  - Dupilumab use is associated with reduced polyp size and symptoms in patients with CRSwNP

Addressing the Type 2 Inflammation Signature Through the Management of CRSwNP

Resource	Address
Fokkens WJ, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinol*. 2020;58(Suppl S29):1-464.	https://pubmed.ncbi.nlm.nih.gov/32077450/
Orlandi RR, et al. International consensus statement on allergy and rhinology: rhinosinusitis. *Int Forum Allergy Rhinol.* 2016;6(suppl 1):S22-S209.	https://onlinelibrary.wiley.com/doi/full/10.1002/alr.21695
Rosenfeld RM, et al. Clinical practice guideline (update): adult sinusitis. *Otolaryngol Head Neck Surg.* 2015;152(2 suppl):S1-S39.	https://www.ncbi.nlm.nih.gov/pubmed/25832968
Fokkens WJ, et al. EUFOREA consensus on biologics for CRSwNP with or without asthma. *Allergy*. 2019;00:1-8.	https://onlinelibrary.wiley.com/doi/full/10.1111/all.13875
Akdis CA, et al. Endotypes and phenotypes of chronic rhinosinusitis: a PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol*. 2013;131(6):1479-1490.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4161279/
Tomassen P, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. *J Allergy Clin Immunol* 2016;137(5):1449-1456.e4.	https://www.jacionline.org/article/S0091-6749(16)00184-6/pdf
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