Biologics for Nasal Polyps: Silver Bullet or Important Adjunct?

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Disclosures

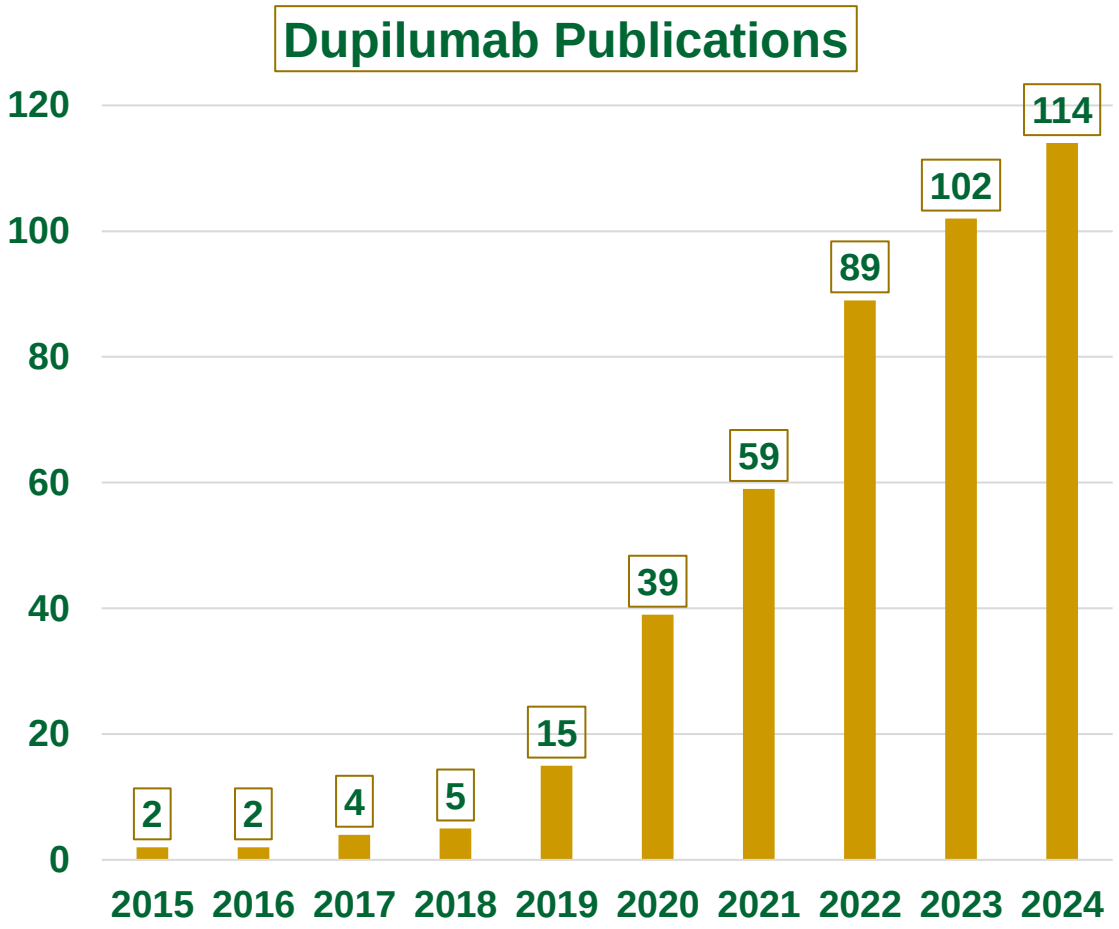
- Site PI: Cyrano Therapeutics FDA trial
- Advisory Board meeting: Neurent Medical

Objectives

- Comprehend the mechanism of action of key biologics
- Appreciate data for key pivotal phase III clinical trials
- Recognize indications, benefits, and risks of biologics
- Understand the economics of biologics

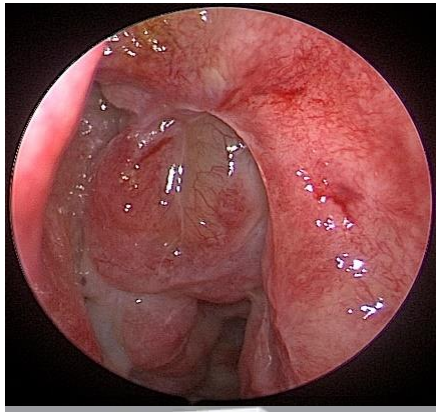
Biologics for Nasal Polyps

- Dupilumab and nasal polyps: 364
- Omalizumab and nasal polyps: 221
- Mepolizumab and nasal polyps: 219



https://pubmed.ncbi.nlm.nih.gov/ Accessed 10-19-24.

Biologics: Background



- Initial description of biologics for nasal polyps in 2006[1]
  - 24 subjects with bilateral nasal polyps
  - Single IV infusion reslizumab (anti-IL-5) or placebo
  - Individual polyp scores improved in 50% at 4 weeks
- Initial use of omalizumab for polyps in setting of asthma[2]
  - 24 allergic and non-allergic patients (anti-IgE vs placebo)
  - Significant decrease in polyp scores
  - Reduction in CT scores and symptoms
- **Prof. Heinz Stammberger** circa 2008 ARS meeting
  - Discussed biologics for polyps as paradigm shift

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[1]Gevaert P, et al. *J Allergy Clin Immunol* 2006;118:1133-41.
[2]Gevaert P, et al. *J Allergy Clin Immunol* 2013;131:110-6.

Biologics: Mechanism of Action

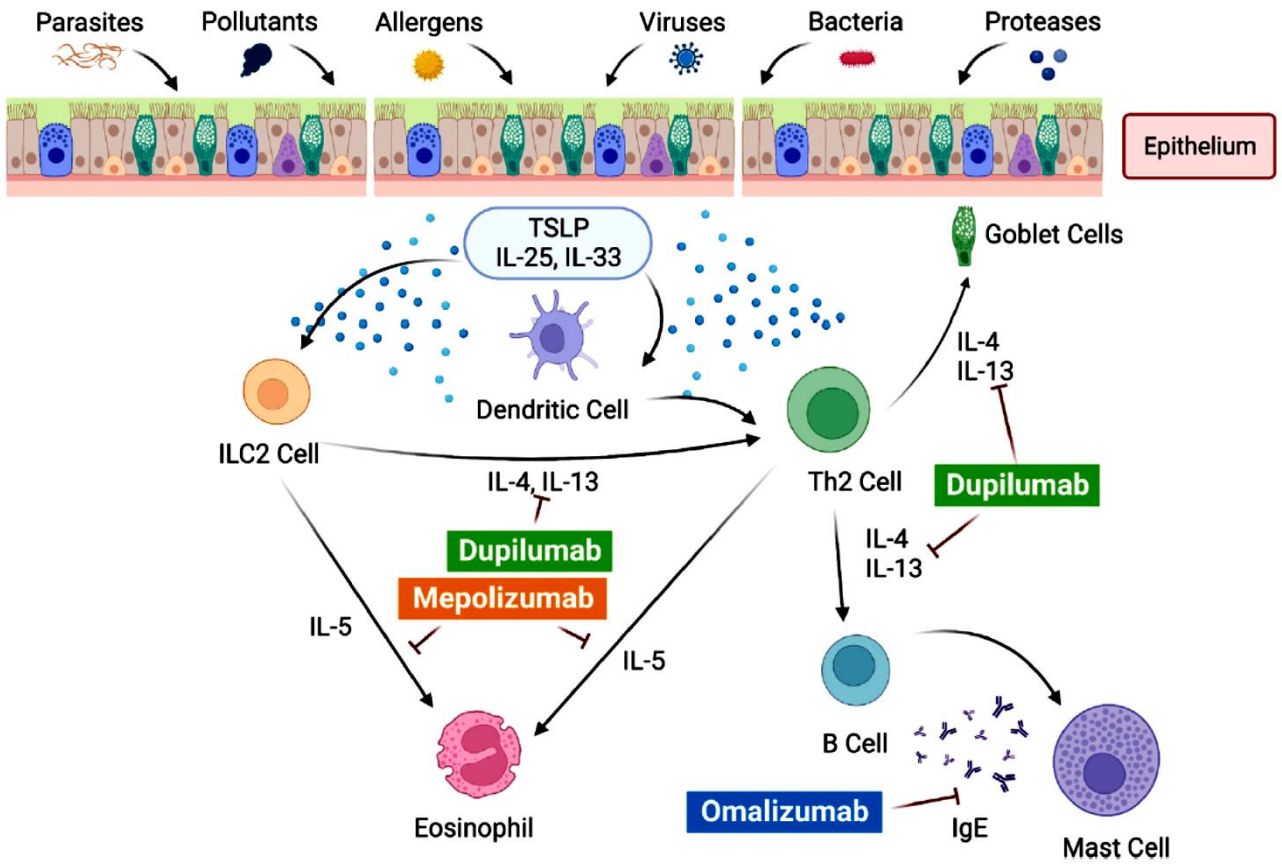
- 85% of CRSwNP reveal type 2 inflammatory signature with expression of IL-4, IL-5, and IL-13 and ↑IgE concentrations
- Biomarkers form targets for therapeutic approaches with monoclonal antibodies

Inflammatory mediator	Drug	Action
IgE: Activates allergic inflammatory cascade	Omalizumab	Anti-IgE MAb; binds to the Fc region of IgE, which reduces circulating IgE and produces extensive anti-inflammatory effects with eosinophilic apoptosis induction; FcεRI receptor, which binds specific IgE on basophils, mast cells, and dendritic cells, is downregulated with time, leading to a general step-down in overall allergic inflammation
IL-5: Key mediator in chemotaxis, differentiation, activation, and survival of eosinophils	Reslizumab, mepolizumab, bendralizumab	Anti–IL-5 MAb; binds and inhibits IL-5Ra subunit depleting eosinophils.
IL-4: Produced by Th2; class switching of B cells to plasma cells and IgE production; IL-13: Th2 inflammation initiation and amplification	Dupilumab	Anti–IL-4 MAb; targets the IL-4 receptor α subunit to inhibit IL-4 and IL-13 cytokines central to TH2 mediated inflammation.

Iqbal IZ, et al. *Int Forum Allergy Rhinol* 2020;10:165-74.

Biologics: Mechanism of Action

Biologic name	Pharmacology	FDA approval for treatment of CRSwNP (y)
Dupilumab	Anti−IL-4Rα	Yes (2019)
Omalizumab	Anti-IgE	Yes (2020)
Mepolizumab	Anti−IL-5	Yes (2021)

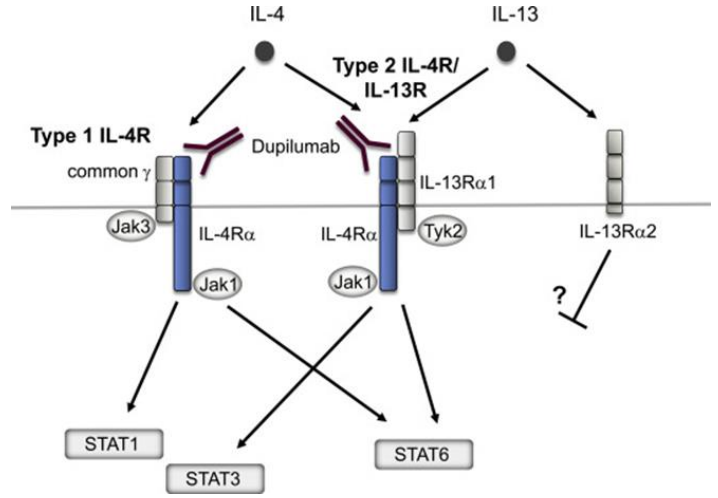


Wautlet A, et al. *J Allergy Clin Immunol Pract* 2023;11:2642-51.

Pivotal Phase 3 Trials

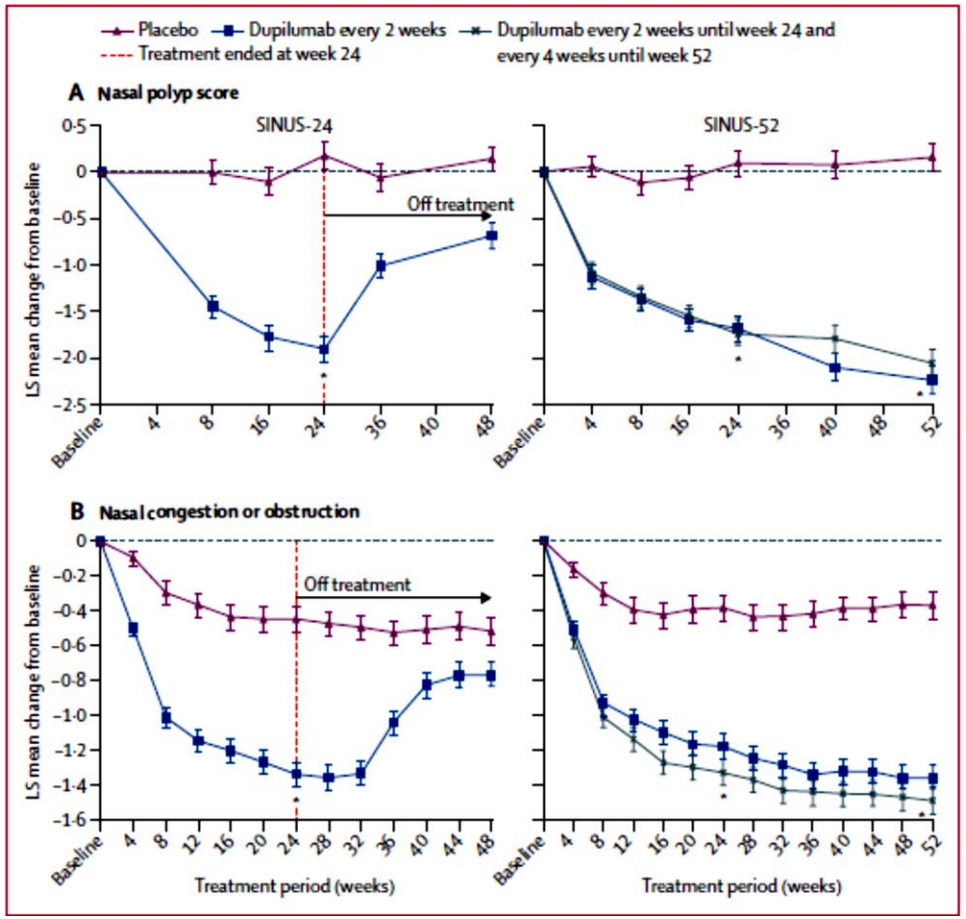
Dupilumab: LIBERTY SINUS-24 and SINUS-52 Trials

- 2 multinational, multicenter RDBPC parallel-group
- Adult patients with bilateral CRSwNP and symptoms despite intranasal corticosteroid use, systemic steroids in past 2 years, or previous sinus surgery
- **SINUS-24:** 67 centers in 13 countries
  - 143 in dupilumab, 133 in placebo over 24 weeks
- **SINUS-52:** 117 centers in 14 countries
  - 150 in dupilumab every 2 weeks, 145 in dupilumab every 2 weeks for 24 weeks, then every 4 weeks, 153 in placebo over 52 weeks



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

LIBERTY SINUS-24 and SINUS-52 Trials



At 24 weeks:

- Difference in NPS of dupilumab vs placebo was −2·06 (p<0·0001) in SINUS-24 and −1·80 (p<0·0001) in SINUS-52
- Difference in nasal congestion or obstruction score was −0.89 (p<0·0001) in SINUS-24 and −0.87 (p<0·0001) in SINUS-52
- Difference in Lund-Mackay CT scores was −7.44 (p<0·0001) in SINUS-24 and −5.13 (p<0·0001) in SINUS-52

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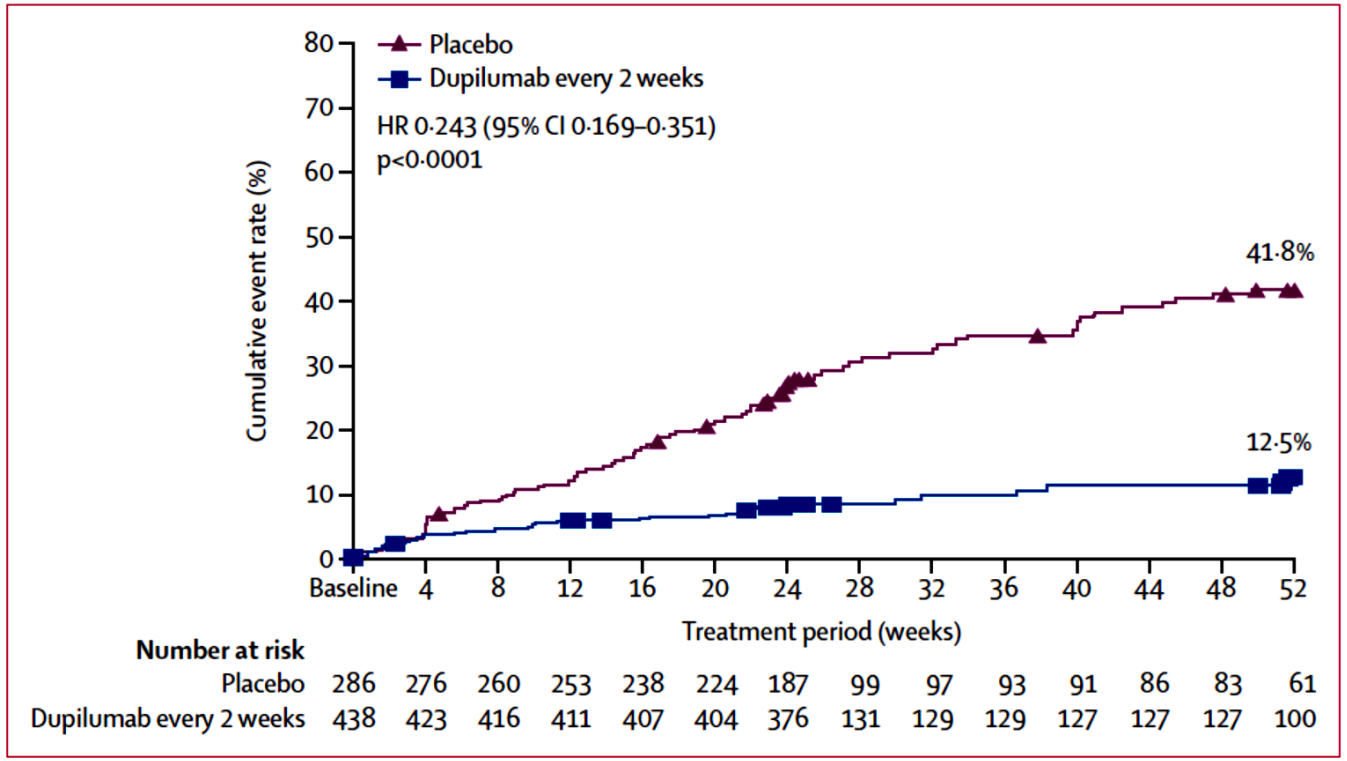
Bachert C, et al. *Lancet* 2019;394:1638–50.

LIBERTY SINUS-24 and SINUS-52 Trials



- Time to first systemic corticosteroid use or nasal polyp surgery during the treatment period in the pooled analysis of SINUS-24 and SINUS-52 studies

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

LIBERTY SINUS-24 and SINUS-52 Trials

	Placebo (n=282)	Dupilumab q2w (n=440)
Treatment-emergent adverse events		
Any	208 (74%)	305 (69%)
Any serious	16 (6%)	15 (3%)
Any leading to death	0	0
Any leading to permanent treatment discontinuation	15 (5%)	11 (3%)
Treatment-emergent adverse events 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%)

- 2 deaths (AMI, ICH, both unrelated)
- 7 with conjunctivitis (mild to moderate)
- 3 with clinically significant eosinophilia (2 EGPA)

Higher conjunctivitis incidence in atopic dermatitis (17.9% – 21.1%)
(Akinlade B, et al. *Br J Dermatol* 2019)

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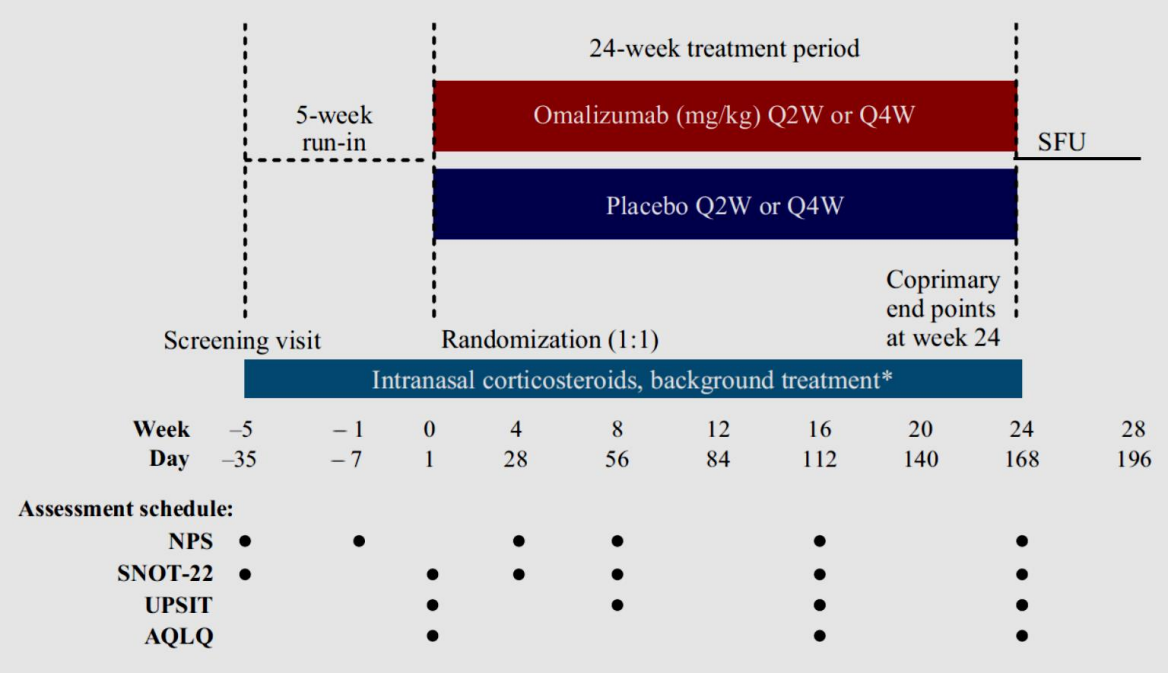
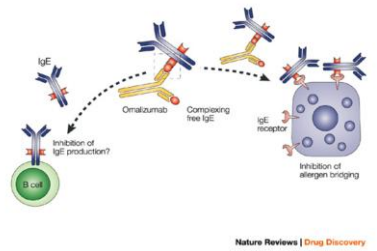
Bachert C, et al. *Lancet* 2019;394:1638–50.

Omalizumab: POLYP 1 and POLYP 2 Trials

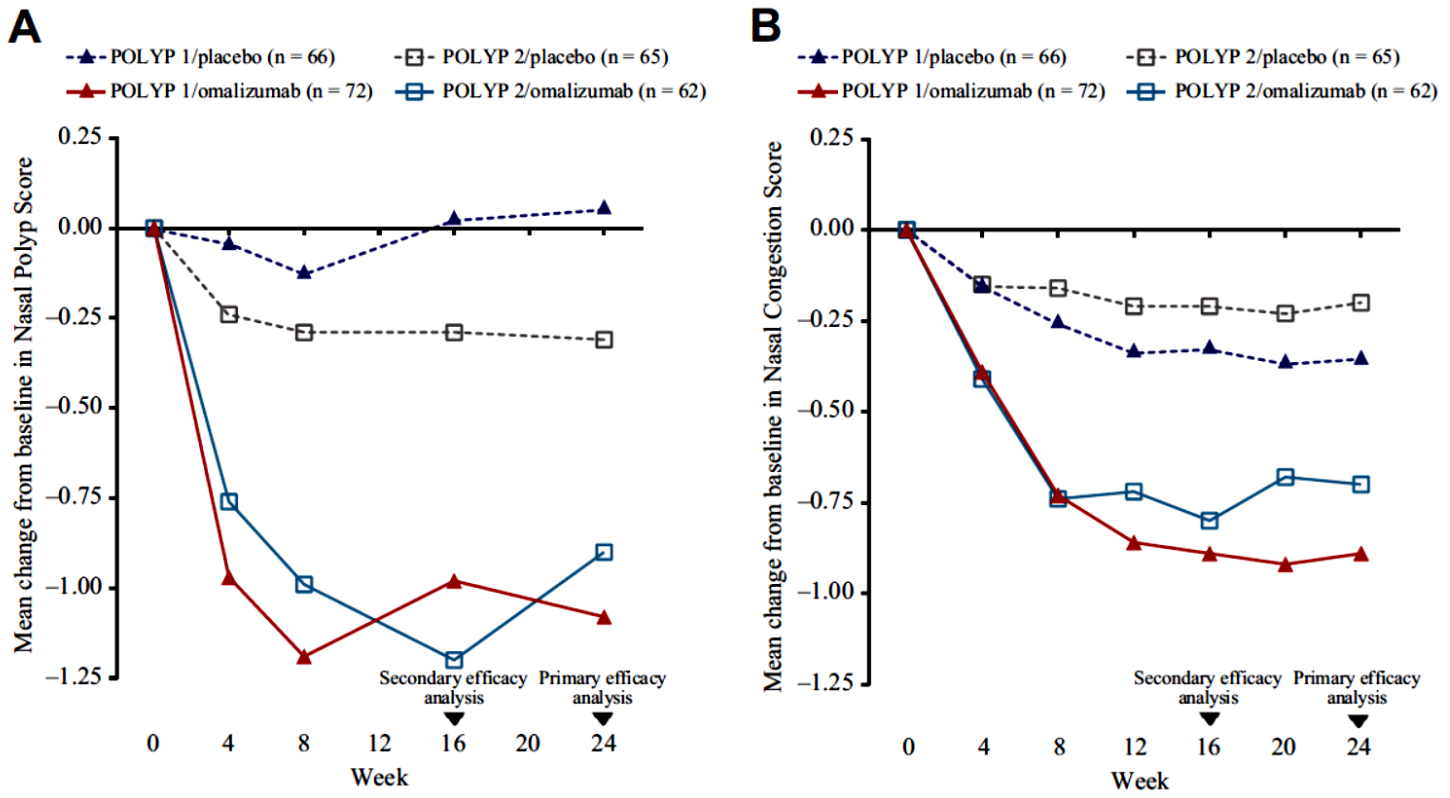
- Adults with refractory CRSwNP randomized (1:1) to omalizumab or placebo
- Intranasal mometasone for 24 weeks
- **Coprimary endpoints:** change from baseline in nasal polyp and nasal congestion scores
- **Secondary endpoints:** change from baseline SNOT-22 score, UPSIT, AEs





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

Omalizumab: POLYP 1 and POLYP 2 Trials

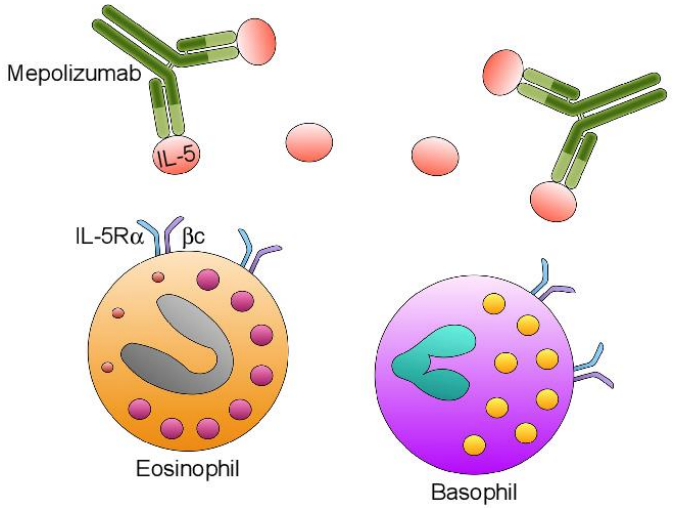


- Statistical reduction in SNOT-22 and TNSS
- Statistical improvement in UPSIT scores
- Adverse events included headaches (8.1%), nasopharyngitis (5.9%), injection site rxns (5.2%), asthma exacerbation (3.7%), arthralgias (3%)

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

Mepolizumab: SYNAPSE Trial

- Randomized, DBPC, parallel-group, phase 3 trial
- 93 centers across 11 countries
- Eligibility: >18+ years with recurrent bilateral nasal polyps despite standard of care treatment and at least 1 nasal surgery past 10 years
- Randomly assigned (1:1) either 100 mg mepolizumab subQ or placebo q4 weeks for 52 weeks
- Also receive standard of care (MF nasal spray, saline irrigations, systemic corticosteroids or antibiotics, or both)
- 206 received mepolizumab and 201 received placebo



www.semanticscholar.org

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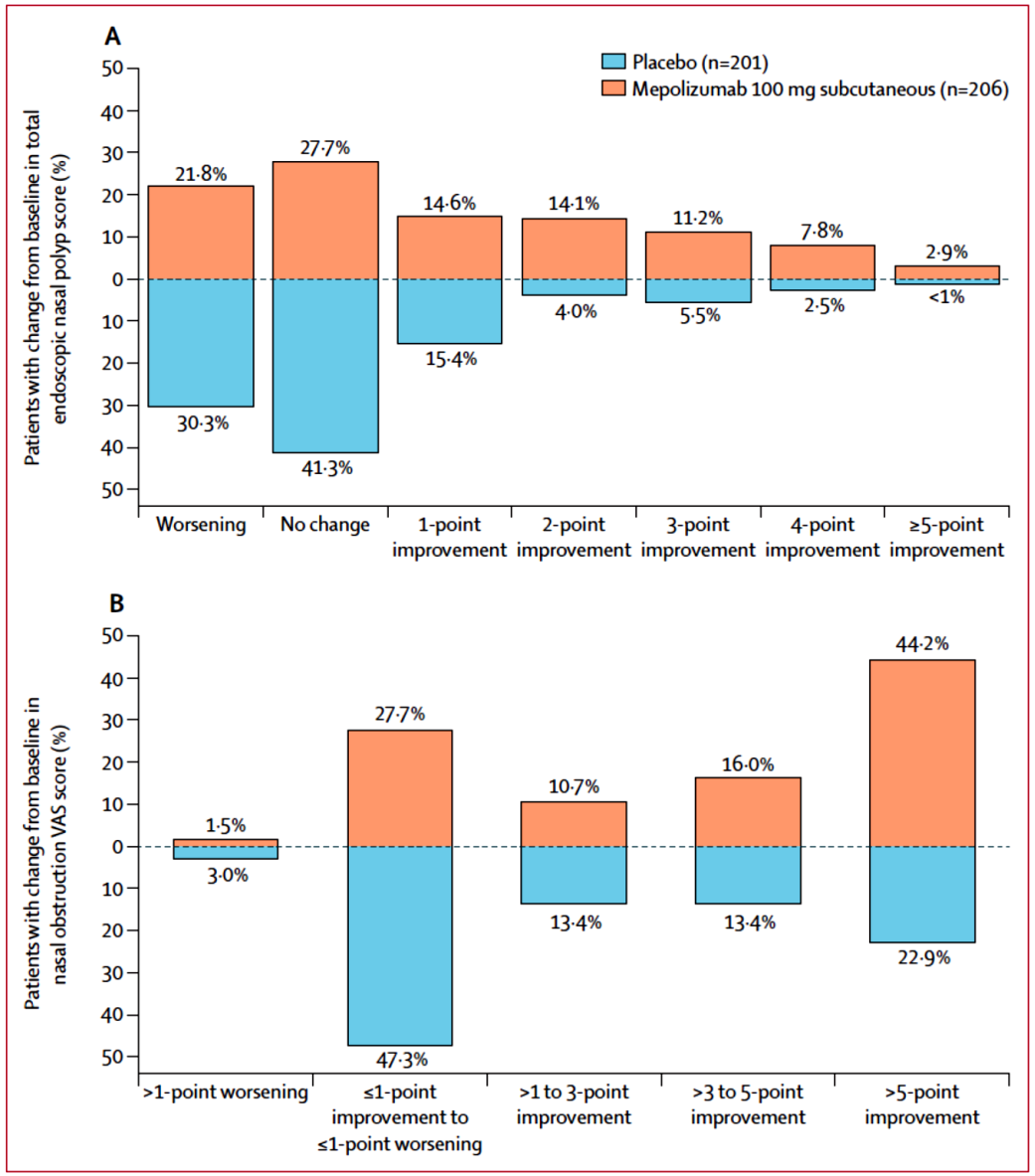
Han JK, et al. *Lancet Respir Med* 2021;9:1141–53.

Mepolizumab: SYNAPSE Trial

- **Adverse events:** 30 (15%) receiving mepolizumab and 19 (9%) receiving placebo
- **SAEs:** 12 (6%) patients receiving mepolizumab and 13 (6%) receiving placebo (none related to treatment in those receiving mepolizumab)
- **Most common:** headache, nasopharyngitis, epistaxis, sinusitis, oropharyngeal pain, arthralgias



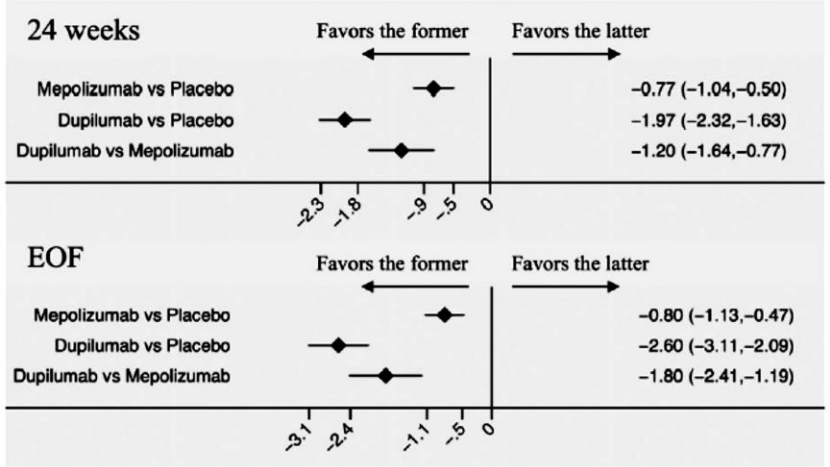
Han JK, et al. *Lancet Respir Med* 2021;9:1141–53.

Comparative Data

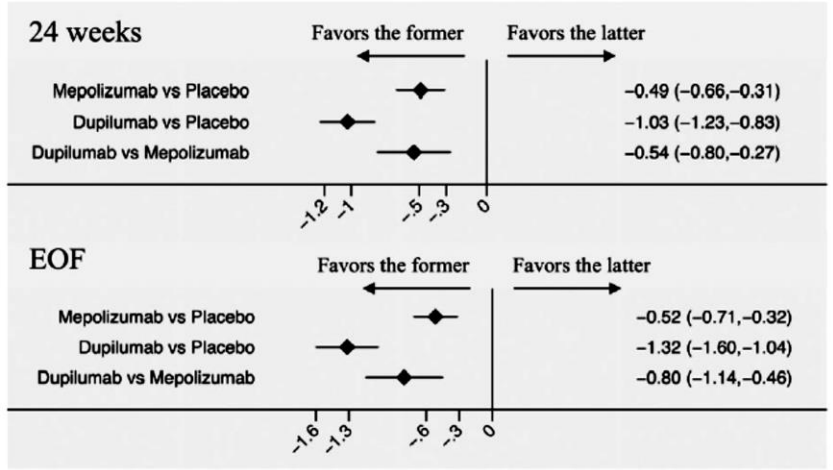
Which Biologic is Better???

- Seven RCTs involving 1913 patients[1]
  - 4 biologics (benralizumab, dupilumab, mepolizumab, and omalizumab)
  - Dupilumab better in decreasing NPS and nasal congestion severity compared to other biologics
  - Benralizumab least effective in reducing nasal congestion and SNOT-22 scores
- Network meta-analysis 9 RCTs with 1,190 pts[2]
  - Dupilumab best choice and omalizumab second best option for CRSwNP
  - Mepolizumab ranked second in efficacy but highest risk of AEs

MD in NPS (95% CI) -with prior surgery



SMD in nasal congestion severity (95% CI) -with prior surgery



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[1]Cai S, et al. J *Allergy Clin Immunol Pract* 2022;10:1876-86.
[2]Wu Q, et al. *Int Arch Allergy Immunol* 2022;183:279-88.

Comparison of Surgery Vs. Biologics

- Prospective, multicenter cohort of CRSwNP patients, undergoing ESS (2011-19) compared to phase-3 biologic trial data
- 111 CRSwNP patients met modified inclusion criteria
- No difference in baseline data, symptom, endoscopy, and CT scores
- At 24 weeks, ESS demonstrated significantly greater improvements in SNOT-22 compared to one dupilumab trials and both omalizumab trials
- ESS associated with significantly lower nasal polyp scores compared to dupilumab ($p < 0.001$) and omalizumab ($p < 0.001$)
- At 52 weeks, ESS resulted in statistically similar improvement in SNOT-22 scores compared to dupilumab, but NPS remained significantly lower in the ESS group compared to dupilumab and mepolizumab

Chen J, et al. *Clin Transl Allergy* 2023;13:e12269.

Comparison of Surgery Vs. Biologics

TABLE 6 Distribution of nasal polyp scores at 24 weeks

Variable	Patients with NPS = 0 *n* (%)	Patients with NPS = 1 *n* (%)	Patients with NPS = 2 *n* (%)	Patients with NPS = 3 *n* (%)	Patients with NPS = 4 *n* (%)	Patients with NPS ≥ 5 *n* (%)
ESS ($n = 79$)	48 (61)	7 (9)	14 (18)	10 (13)		
Dupi-24 ($n = 143$)	66 (46)				27 (19)	50 (35)
Oma-1&2 ($n = 128$)	42 (31)				30 (25)	56 (44)

TABLE 7 Distribution of nasal polyp scores at 52 weeks

Variable	Patients with NPS = 0 *n* (%)	Patients with NPS = 1 *n* (%)	Patients with NPS = 2 *n* (%)	Patients with NPS = 3 *n* (%)	Patients with NPS = 4 *n* (%)	Patients with NPS ≥ 5 *n* (%)
ESS ($n = 20$)	9 (45)	4 (20)	6 (30)	1 (5)		
Dupi-52 ($n = 295$)	136 (46)				47 (16)	112 (38)
Mepo ($n = 206$)	6 (2.9)	16 (7.8)	23 (11.2)	29 (14.1)	30 (14.6)	104 (50)

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Miglani A, et al. *Int Forum Allergy Rhinol* 2023;13:116-28.

Cost Utility Analysis: Dupilumab Vs. ESS

- Markov decision tree economic evaluation over 10-year time horizon
- Scangas et al.[1]
  - ESS cost total of $50,426.99 and produced 9.80 QALYs and dupilumab cost $536,420.22 and produced 8.95 QALYs
  - 10 times higher treatment cost for dupilumab over surgical intervention
- Parasher et al.[2]
  - Dupilumab costs $195,164 and produced 1.78 QALYs, versus ESS costing $20,549 and producing 1.53 QALYs
  - Implies incremental cost of $691,691 for dupilumab for every 1-unit increase in QALY compared with ESS

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[1]Scangas, GA, et al. *Laryngoscope* 2021;131:E26–E33.
[2]Prasher AK, et al. *Int Forum Allergy Rhinol* 2022;12:813–20.

Economics of Dupixent®

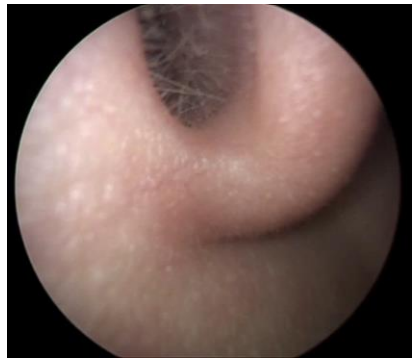
- Received regulatory approvals in more than 60 countries
- **Indications:** atopic dermatitis, asthma, CRSwNP, eosinophilic esophagitis, prurigo nodularis, chronic spontaneous urticaria, and COPD
- 1,000,000+ patients being treated with Dupixent globally (www.sanofi.com)
- Monthly retail list price of Dupixent®: $3,803.20 per carton with 300 mg/2 mL 2 prefilled syringes (www.dupixent.com)
  - "Uninsured" cost $49,441.60 (26 doses)

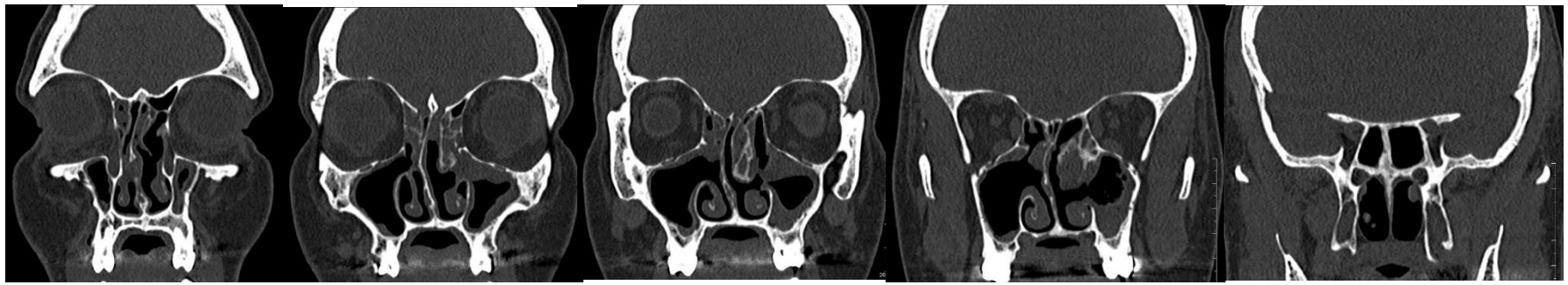
- Q2 2024 Dupixent sales: $3.6 billion
- Q2 2024 rise YOY in Dupixent sales: 29.2%
- Forecast for 2024 Dupixent sales: $14.1 billion (www.pharmavoice.com)

Patient Cases and Indications

Patient Case 1

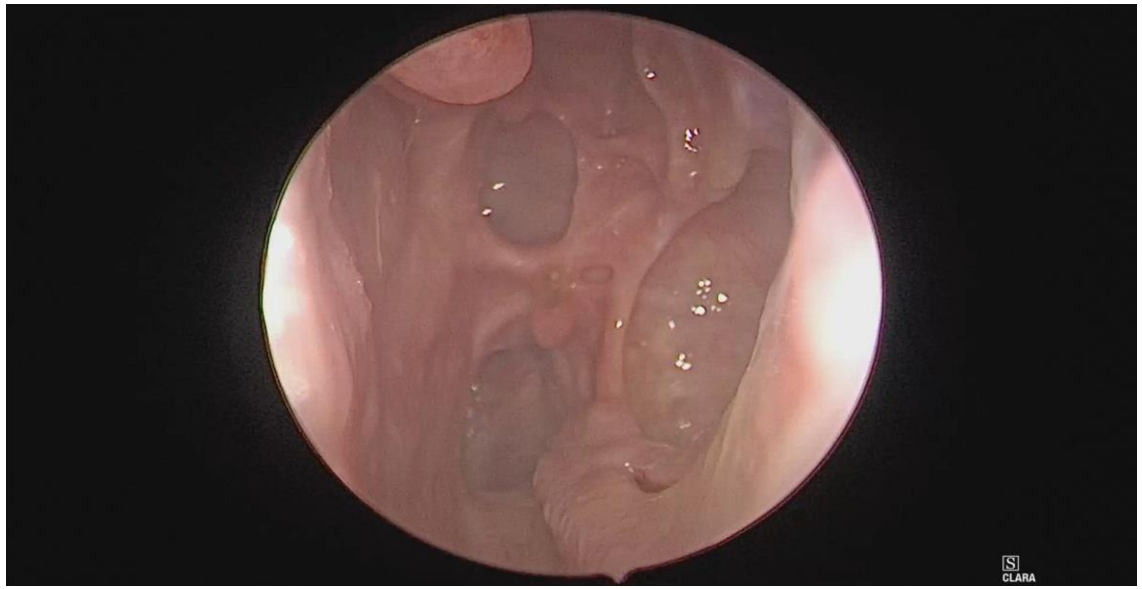
- 48 y/o female with refractory CRSwNP
- Inhalant allergies, asthma, and AERD
- Previous sinus surgery 20 years ago
- Dupilumab 300mg subQ q2 weeks
- Dexamethasone nasal drops, cetirizine, and fluticasone/salmeterol





Patient Case 1

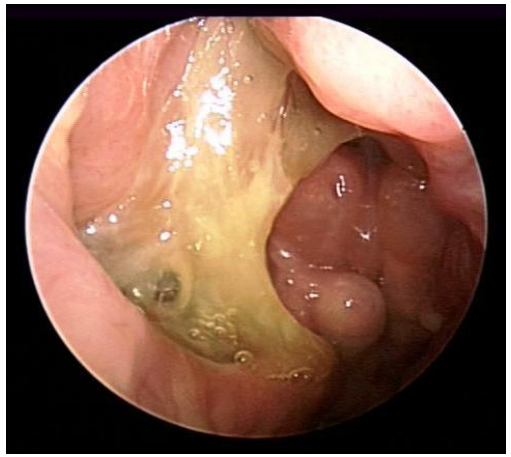
- Full-house FESS, left CB resection, and septoplasty
- Mometasone irrigations 2mg bid
- Cetirizine and fluticasone/salmeterol
- Dupilumab weaned off after 3 months

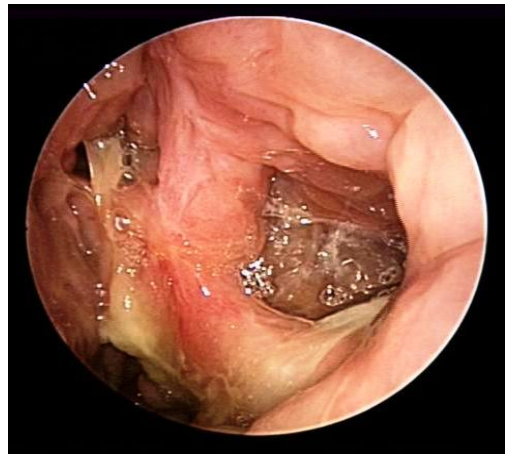


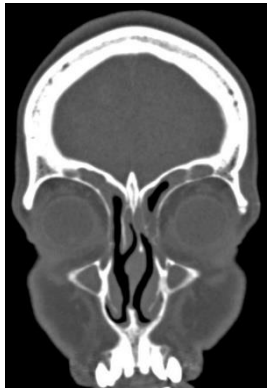
12 months

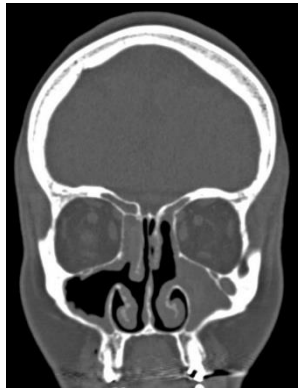
Patient Case 2

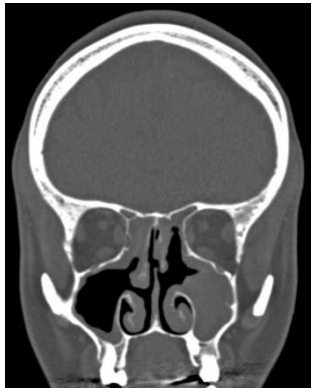
- 42 y/o female with 5-year h/o protracted sinus issues (2014)
- Negative allergy testing and immune w/u
- Asthma and AERD
- 3 previous sinus surgeries

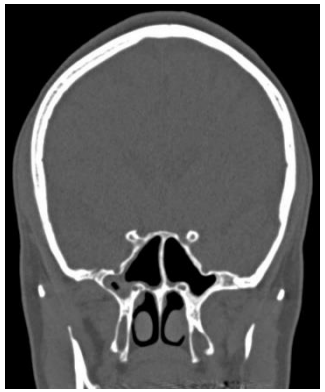












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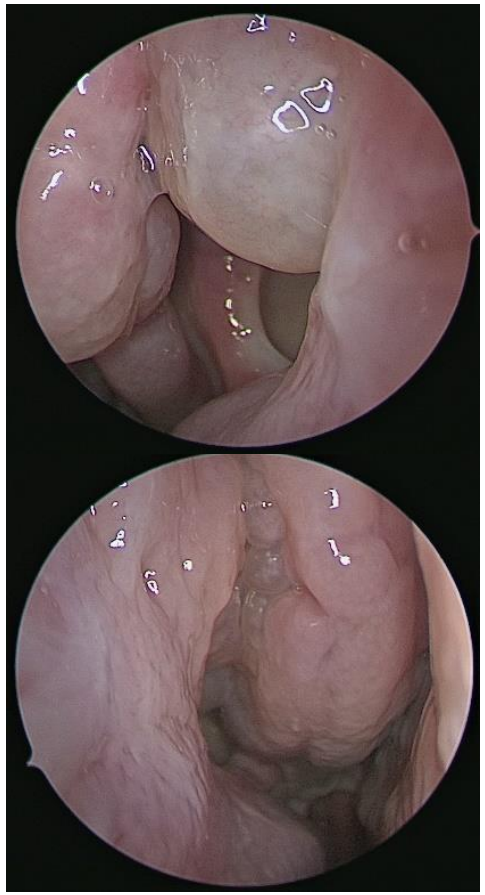
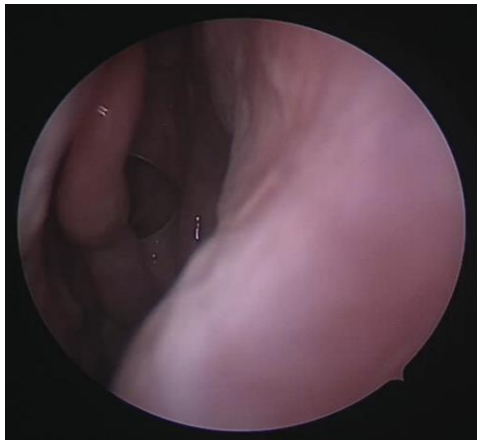
Patient Case 2

- Full-house FESS (2015)
- **Relapse at 1 year**
- 2016: omalizumab
- 2017: levofloxacin/mometasone rinses
- 2018: office polypectomy/steroid implants
- 2018: Nucala injections for asthma
- March 2019: transitioned to dupilumab
  - Improvement with 2 doses
- Maintained on dupilumab q2 weeks
- SNOT-22 score: 6/110 (July 2024)

2015





January 2023

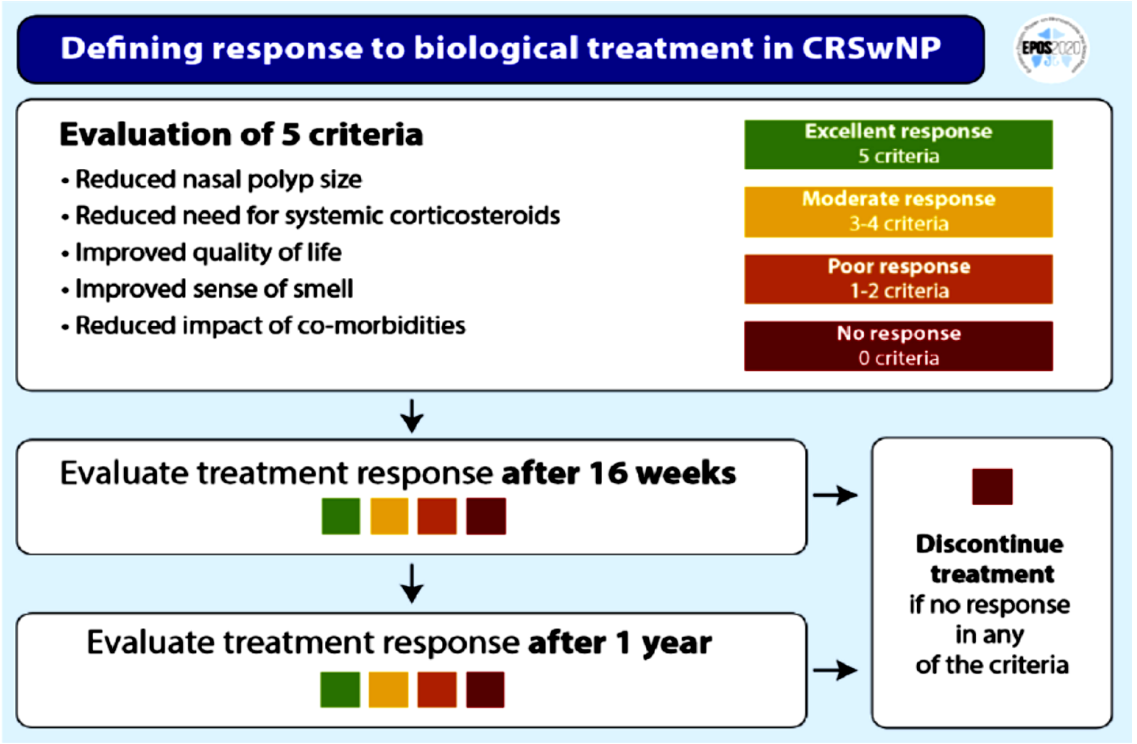
EPOS/EUFOREA 2023 Indications for Biologics

Indication for biological treatment in CRSwNP

Presence of bilateral polyps in patient who had ESS**

THREE criteria are required

Criteria	Cut-off points
Evidence of type 2 inflammation	Tissue eos ≥10/hpf, OR blood eos ≥ 150 OR total IgE ≥100
Need for systemic corticosteroids or contraindication to systemic steroids	≥2 courses per Yr OR long term (> 3 months) low dose steroids
Significantly impaired quality of life	SNOT-22 ≥40
Significant loss of smell	Anosmic on smell test (score depending on test)
Diagnosis of comorbid asthma	In case of asthma: regular need for inhaled corticosteroids



Fokkens WJ, et al. *Rhinology* 2023;61:194 - 202.

EUFOREA Consensus on Biologics for CRSwNP

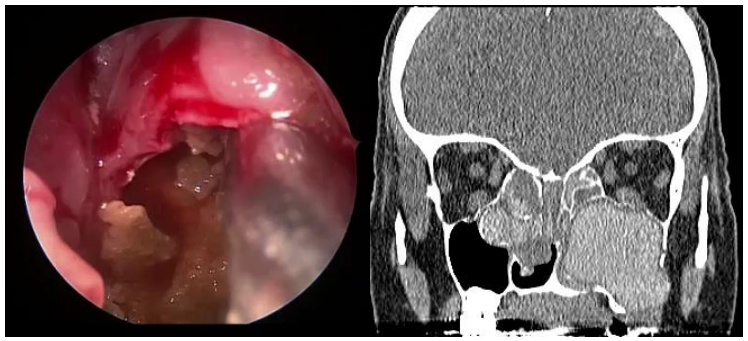
No Indication for biologics:

- CRSsNP and lack of 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

Fokkens WJ, et al. *Allergy* 2019;74:2312–9.

Limitations of Biologics

- CRSwNP is a heterogeneous disorder – does not account for variability in patient disease process
- Does not address sinus obstruction, mucous stasis, or infectious issues
- Avoid binary choice of biologic vs. surgery
- **Not a silver bullet but critical adjunct….**



Conclusions

- Rapid expansion on body of knowledge on CRS and biologics
- Comprehensive surgery coupled with medical therapy (steroid irrigations/exhaled delivery system) leads to symptom improvement and mucosal disease control
- Biologics represent an important advance in recurrent polyp disease management (paradigm shift)
- *Idea of repeated sinus surgery has become a thing of the past…*
- Need to thoughtfully integrate biologics into the treatment algorithm weighing benefits, side effects, and costs

Thanks!

Questions?

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