Biologics for Severe Asthma: What, Who and When

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I disclose the following relationships in the past year:

- Asthma Education Prevention Program (NAEPP) Coordinating Committee 2017-

• AB Science	Consultant
• Amgen	Consultant
• AstraZeneca	Consultant & Clinical Research Support
• Avillion	Consultant & Clinical Research Support
• Circassia Pharmaceuticals	Clinical Research Support
• Cowen	Consultant
• GlaxoSmithKline	Consultant
• Gossamer Bio	Clinical Research Support
• Merck	Consultant
• Novartis	Consultant
• Pneuma Respiratory	Consultant
• PPS Health	Consultant
• Regeneron Pharmaceuticals	Consultant
• Sanofi	Consultant
• TEVA	Consultant & Clinical Research Support

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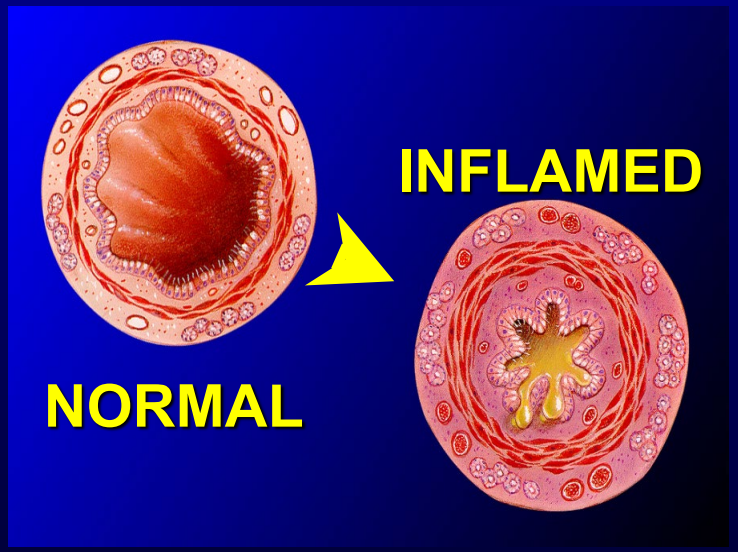
Outline

- Review the mechanism of action of the biologics
- Compare and contrast the biologics
  - Administration and indications
  - Effects on outcomes
  - Effects on biomarkers
  - Effects on co-morbidities
  - Phenotypic characteristics of patients most likely to respond
- Considerations in making choices

Inflammatory Changes in Chronic Asthma

- Mucus secretion
- Inflammatory cell infiltration
- Edema
- Smooth muscle constriction & hypertrophy
- BM thickening and subepithelial collagen

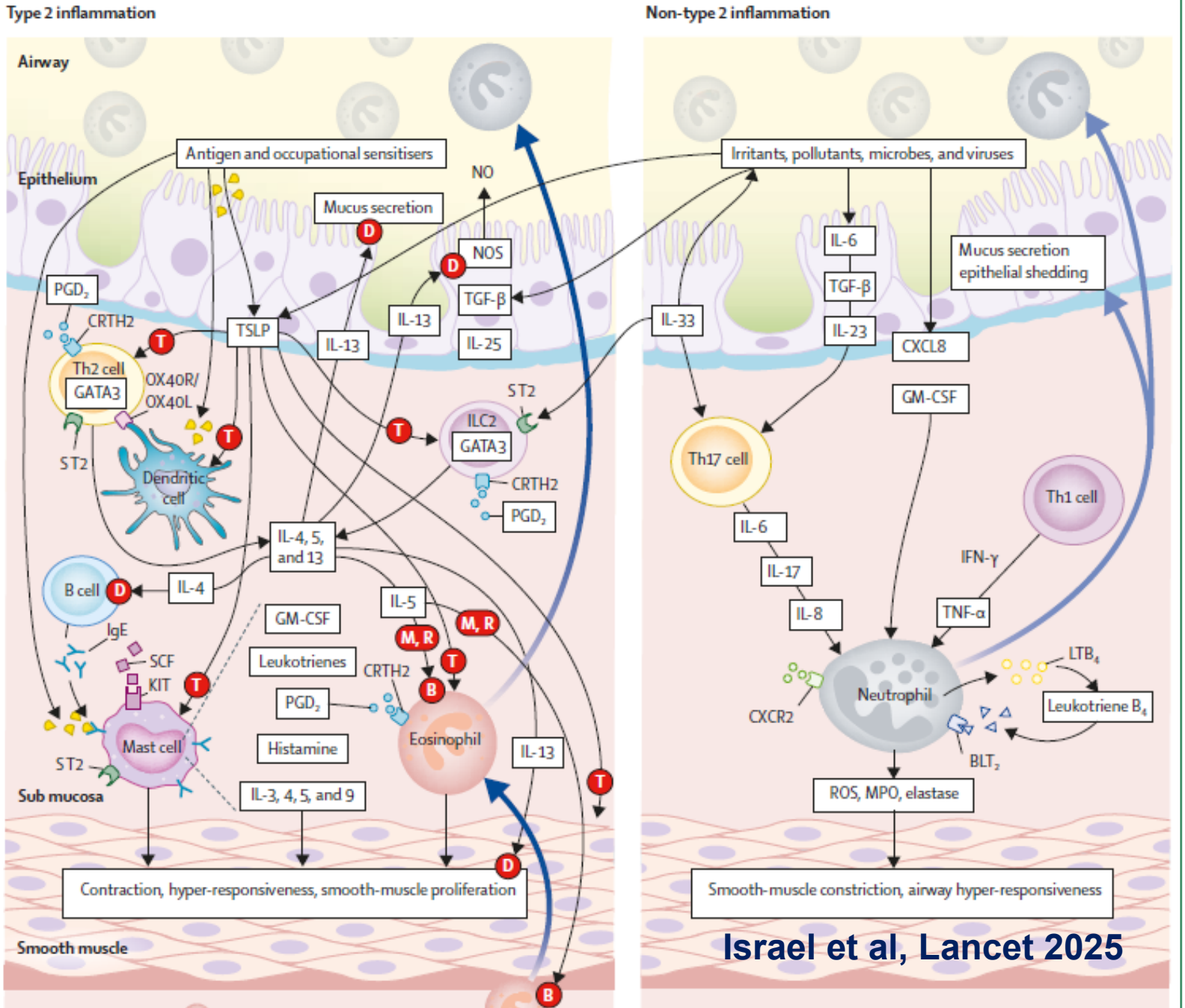


Definition of Type 2 Immunity

- Immune response involving the innate and the adaptive arms of the immune system to promote barrier immunity on mucosal surfaces
- Cells
  - T helper 2 (T^H2) CD4+ T cells and B cell production of the immunoglobulin E (IgE) antibody subclass.
  - Innate response includes ILC 2 innate lymphoid cells, eosinophils, basophils, mast cells and interleukin-4 (IL-4)-and/or IL-13-activated macrophages.
- Associated with IL-4, IL-5, and IL-13.

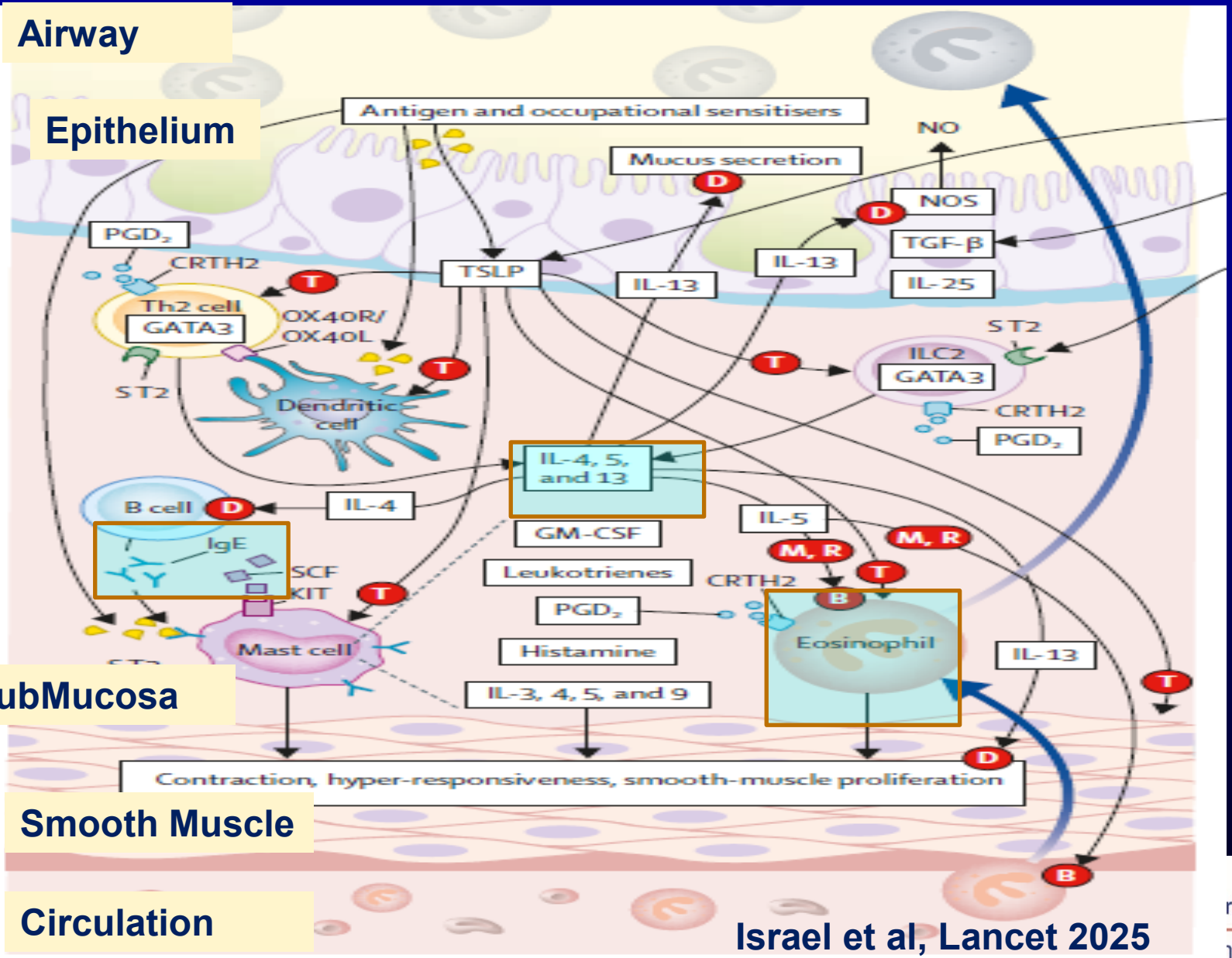
Gandhi

Inflammatory Pathways in Asthma



Israel et al, Lancet 2025

Inflammatory Targets



Biologics

- Anti-IgE
  - Omalizumab
- Anti-Eosinophilic
  - Anti-IL5
    - Mepolizumab
    - Reslizumab
  - Anti-IL5 receptor
    - Benralizumab
- Anti-IL4/IL13
  - IL4R-alpha antagonist – Dupilumab
- Anti-TSLP
  - Tezepelumab

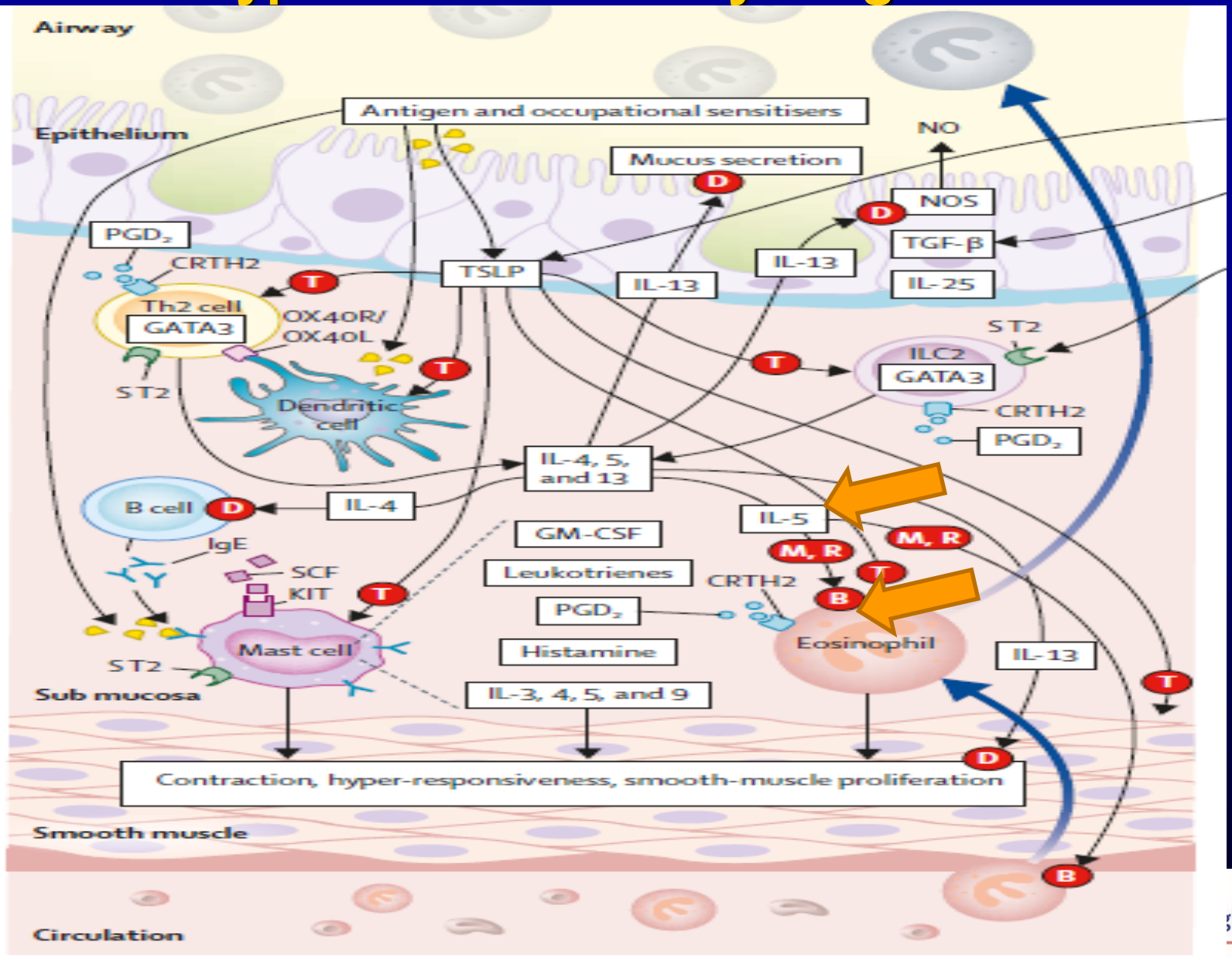
Anti-IgE

- Binds to the Fc portion of IgE
- Does not directly reduce IgE levels but prevents IgE from binding to its receptor on effector cells
  - Primarily mast cells and basophils
- Circulating total IgE levels are not initially reduced but free IgE is reduced dramatically
  - No clinical test for free IgE
- Administered on a weight and IgE level basis to stoichiometrically bind to most circulating IgE

Anti-IgE

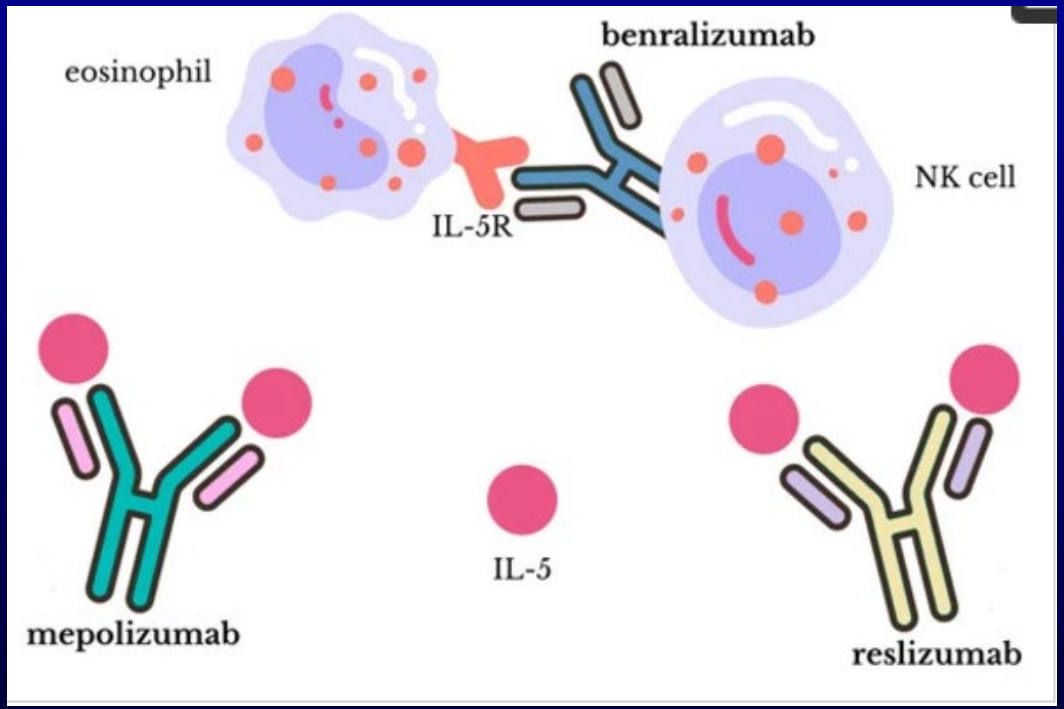
- Qualifications – IgE 30 to 700 and a positive skin test or RAST to a perennial inhalant allergen
- Toxicity – rare anaphylaxis
  - Had been question about increased rate of cancer
  - Large observational study has not confirmed

Type 2 Inflammatory Targets – IL5



•Israel & Reddel, NEJ

Mechanism of Action of the Different Anti-IL5's



Antosz K, *Biomedicines* **2024**

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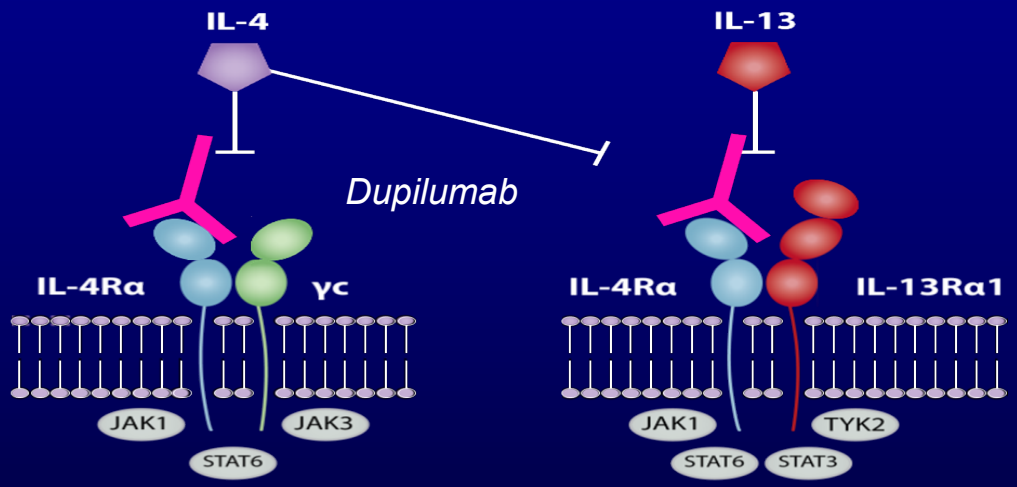
Anti-IL5 Drugs

- All indicated for eosinophilic moderate-severe asthma
  - Mepolizumab SC q month
  - Reslizumab IV q month
  - Benralizumab SC q month x3 then q 2 months

Blocking IL-4Ralpha (Dupilumab) Blocks both IL4 and IL13



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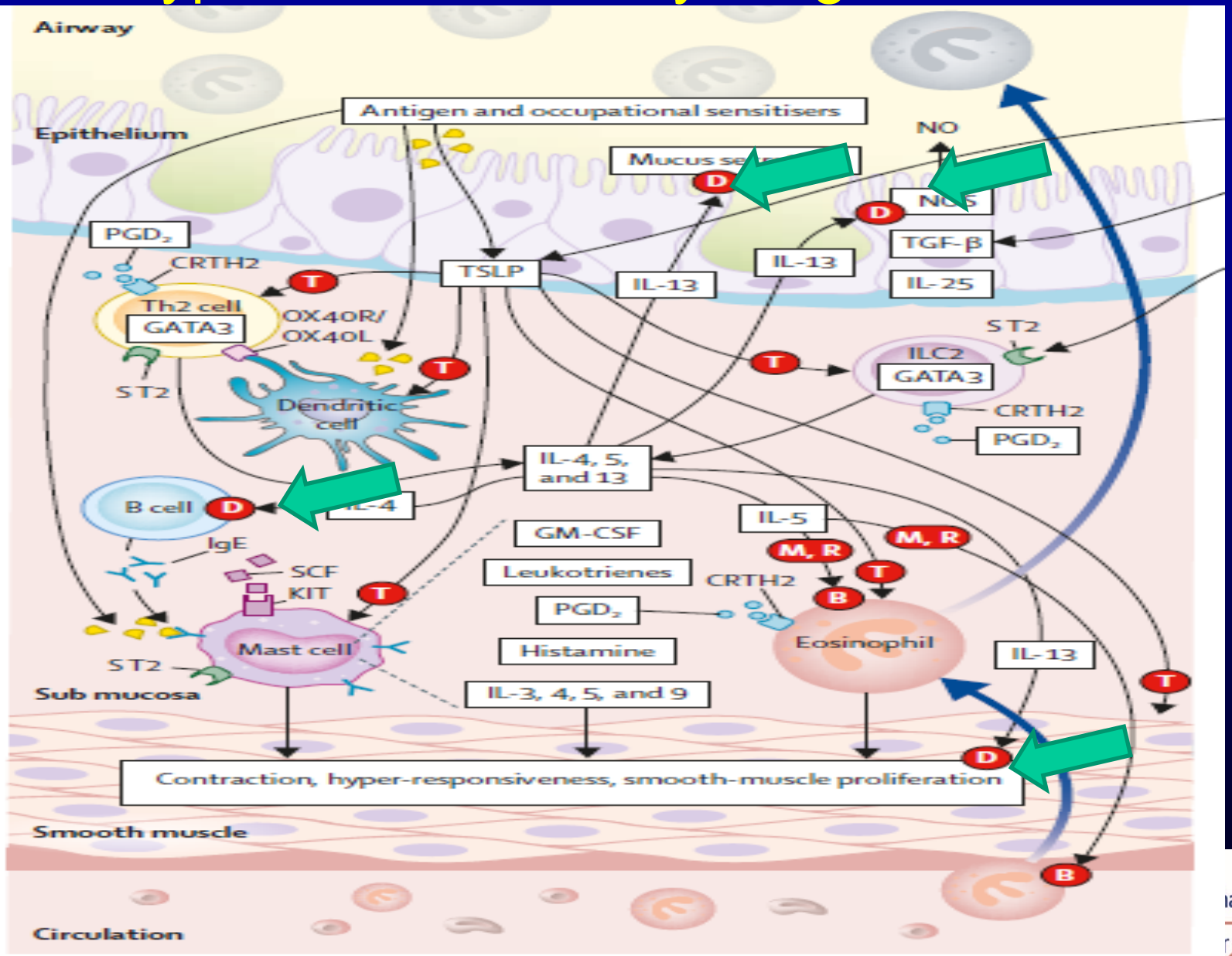
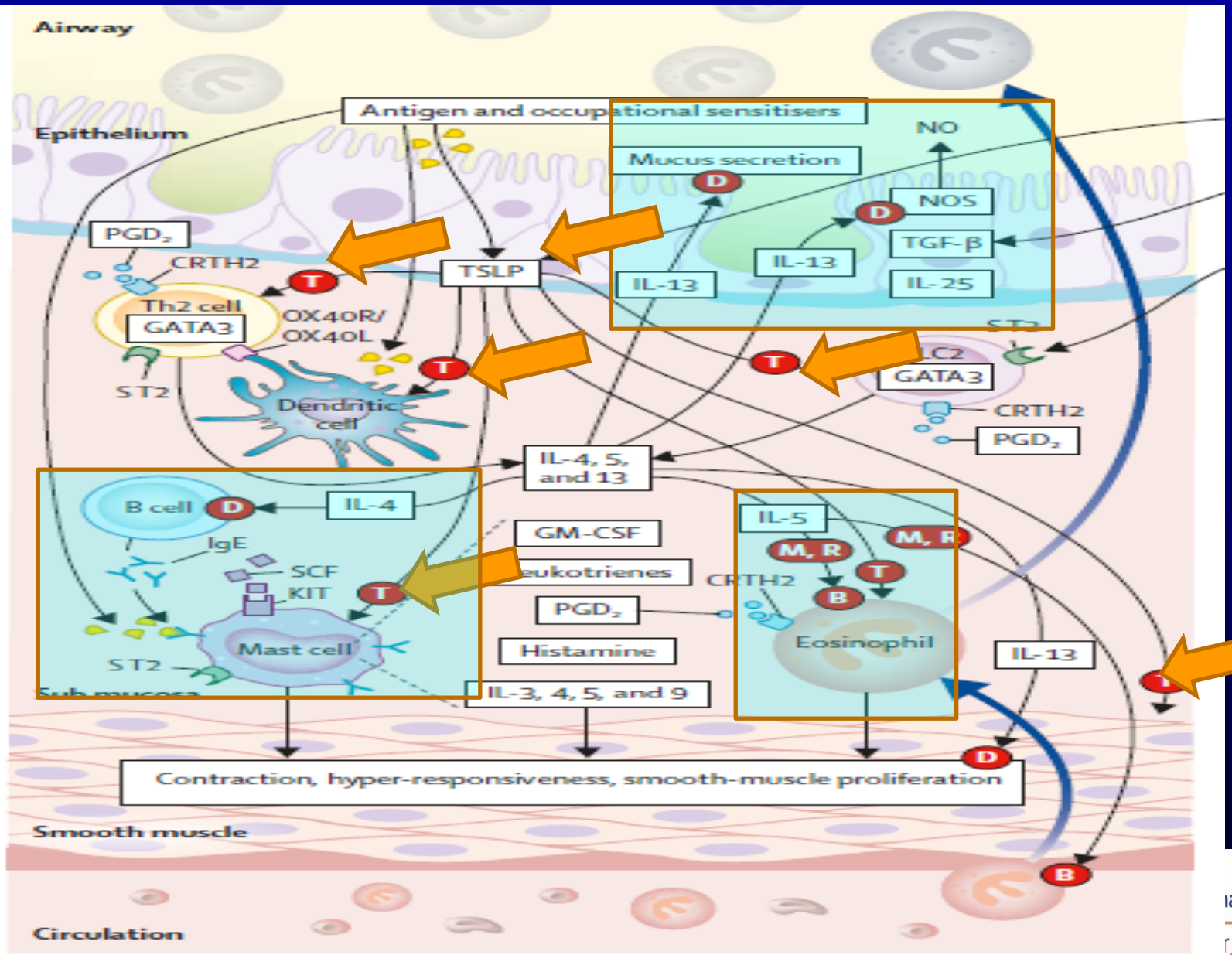
Type 2 Inflammatory Targets – IL4RA



ADMINISTRATION

- Dupilumab
  - —Age 6 or older
  - —400 mg followed by 200 mg home injected every 2 weeks
  - —In those on OCS start with 600 mg followed by 300 mg every 2 weeks
  - —Eosinophils frequently rise and then come down

Type 2 Inflammatory Targets – TSLP



Tezepelumab

- Age 12 and above
- 210 mg SC q4 weeks

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What are the effects of these drugs on the different asthma domains in their indicated patient populations?

Comparison of the Effect of ACBs on Asthma Domains

(Pivotal trials in the subset of patients with ≥2 AEX and BEC of ≥300 cells per µL)

	Mean reduction in AEX* vs placebo (95% CI)	Mean change in FEV_1 vs placebo (95% CI)	Mean improvement in ACQ score (95% CI)	Absolute difference in percentage of patients achieving remission with drug vs placebo†
Mepolizumab[23]	61% (45–72)	128 mL (25–232)	−0·73 (−0·95 to −0·50) ACQ-5	NA
Reslizumab‡[24]	65% (51–74)	223 mL (117–329)	−0·53 (−0·77 to −0·28) ACQ-6	NA
Benralizumab[25,26]	43% (31–53)	146 mL (82–206)	−0·29 (−0·43 to −0·16) ACQ-6	11–12%[46]
Dupilumab[45]	67% (55–77)	230 mL (150–310)	−0·44 (−0·24 to −0·64)† ACQ-5	15%[46]
Tezepelumab[28]	70% (60–78)	230 mL (150–310)	−0·50 (−0·69 to −0·31) ACQ-6	7%[47]

ACQ=Asthma Control Questionnaire. AEX=asthma exacerbation. BEC=blood eosinophil count. FEV_1=forced expiratory volume in 1 s. NA=not applicable. *Defined as requiring at least 3 days of oral or parenteral corticosteroids. †Remission defined as no AEXs over 1 year, ACQ <1·5, and FEV_1 decline no greater than 5%. ‡Reslizumab data available solely in patients with BEC ≥400 cells per µL.

Table 3: Clinical outcomes of pivotal trials in the subset of patients with ≥2 AEX and BEC of ≥300 cells per µL*

Israel et al. Lancet 2025

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OCS-Sparing Effects

- Effective
  - Mepolizumab
  - Benralizumab
  - Dupilumab
- Did not Show Effectiveness in Pivotal Trial
  - Tezepelumab
- Not tested
  - Reslizumab

Effects on Biomarkers

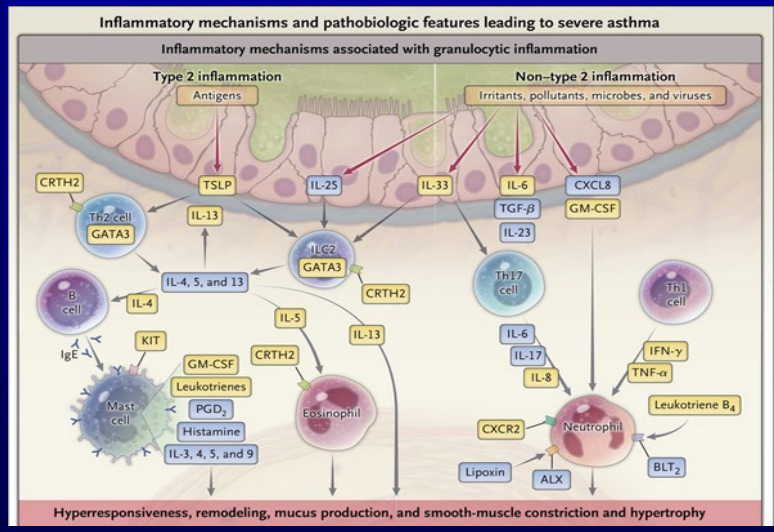
Effect of the Biologics on Biomarkers in Severe Asthma

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab	Tezepelumab
IgE						
FeNO						
Eosinophils						

[x]Reduction in free IgE (commercial assays detect TOTAL igE)

[#]Gradually reduced

*Eosinophils may rise especially in those with high baseline eosinophils



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Effect of the ACBs on Biomarkers

	Mepolizumab	Reslizumab	Benralizumab	Dupilumab	Tezepelumab
IgE	<10% reduction	<10% reduction	<10% reduction	10–25% reduction; months	26–50% reduction; months
Blood eosinophil count	51–75% reduction; days	51–75% reduction; weeks	76–100% reduction; days	Variable increase of up to 100% or more, with eventual return to near baseline	51–75% reduction; weeks
FeNO	<10% reduction	<10% reduction	<10% reduction	26–50% reduction; weeks	26–50% reduction; weeks

FeNO=fractional exhaled nitric oxide.

Table 2: Effect of anticytokine biologics on clinically available biomarkers

Israel et al, Lancet 2025

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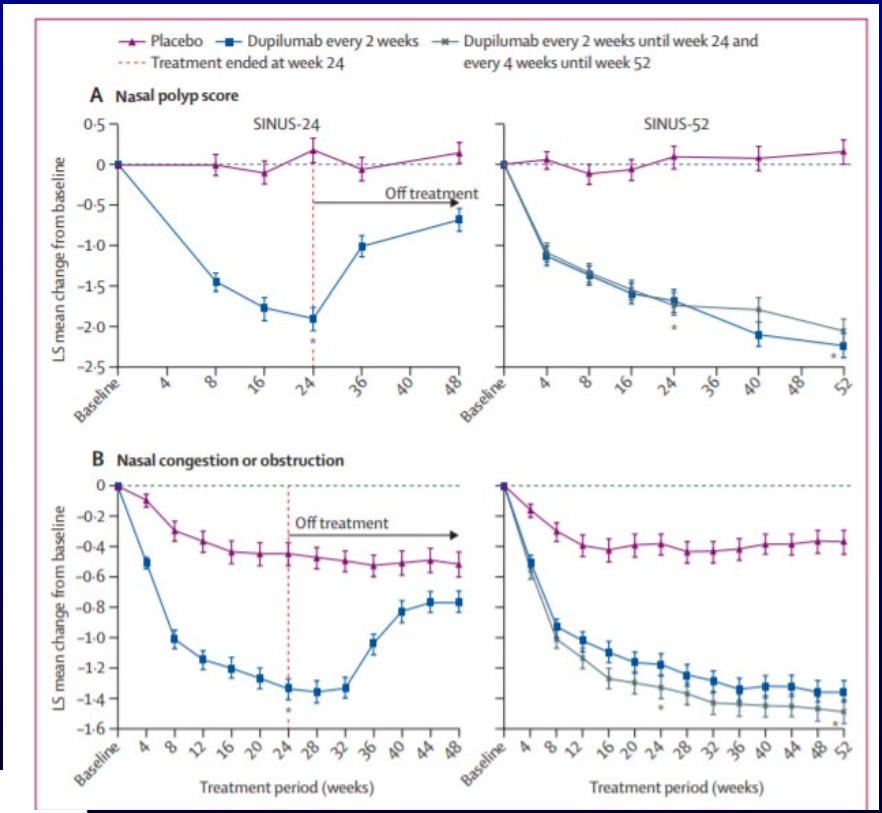
Effects on Co-Morbidities

Dupilumab First Shown Effective in Nasal Polyposis

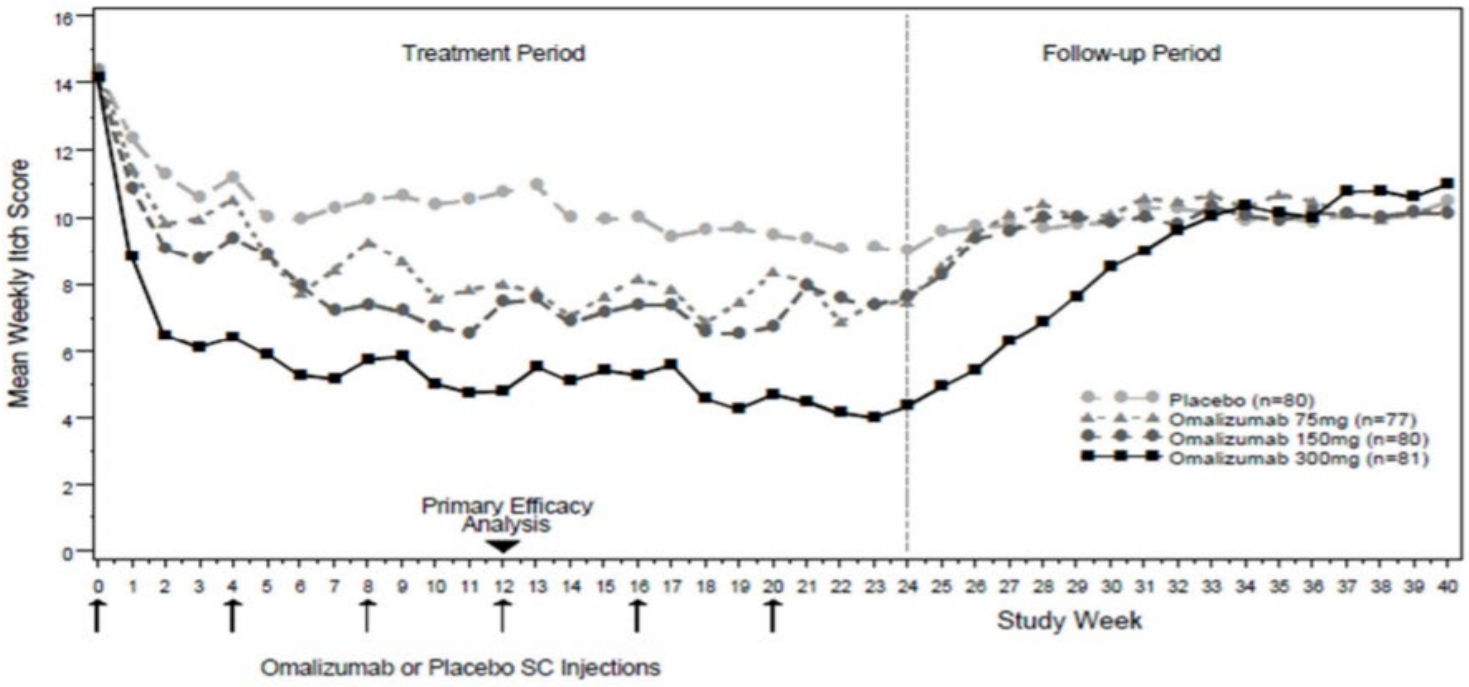


Now shown for:
-Mepolizumab
-Omalizumab
-Tezepelumab

Bachert, Lancet, 2019

Omalizumab is Effective in Chronic Idiopathic Urticaria

Figure 2. Mean Weekly Itch Severity Score by Treatment Group
Modified Intent to Treat Patients in CIU Trial 1



Dupilumab is Very Effective in Atopic Dermatitis and Is Approved for that Indication in Age 6 months and above

-Also approved for eosinophilic esophagitis age 12+

-Approved for prurigo nodularis

-Approved for eosinophilic COPD

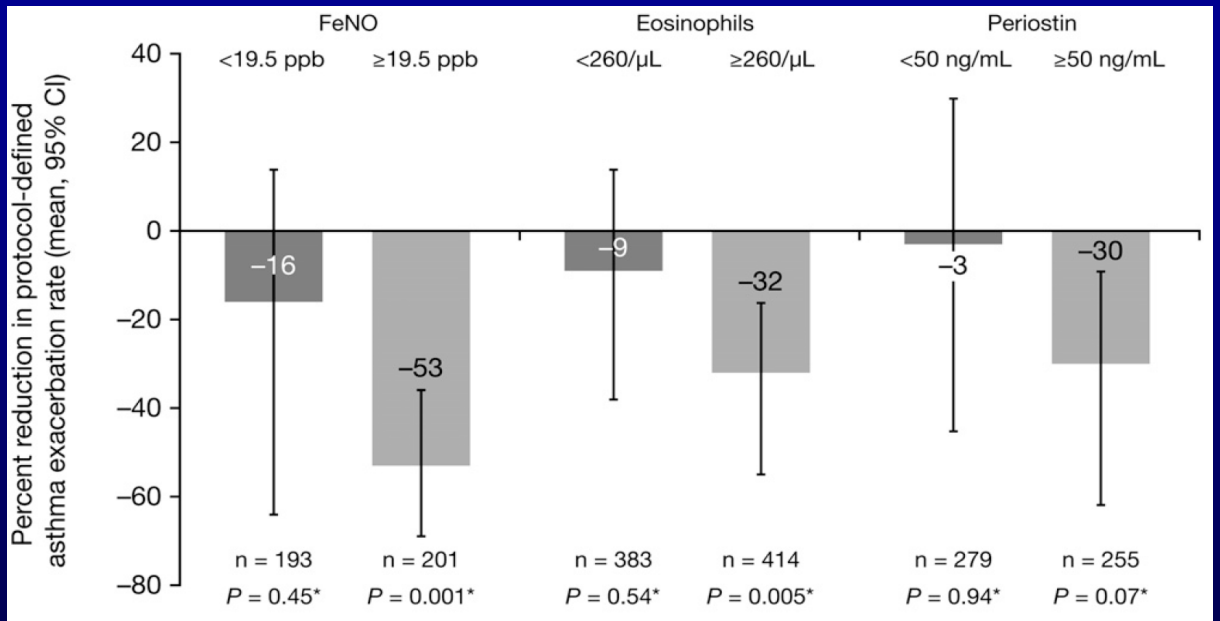
-Approved for idiopathic urticaria

-Bullous Pemphigoid

-Chronic spontaneous urticaria

WHO RESPONDS?

FeNO Best Predictor of Response to Omalizumab in Pre-selected Pts



Exacerbation rates						
	Low FeNO at baseline	High FeNO at baseline	Low eosinophils at baseline	High eosinophils at baseline	Low periostin at baseline	High periostin at baseline
Omalizumab	0.60	0.50	0.65	0.70	0.73	0.66
Placebo	0.71	1.07	0.72	1.03	0.72	0.93

Hanania , Am J Respir Crit Care Med , 2013

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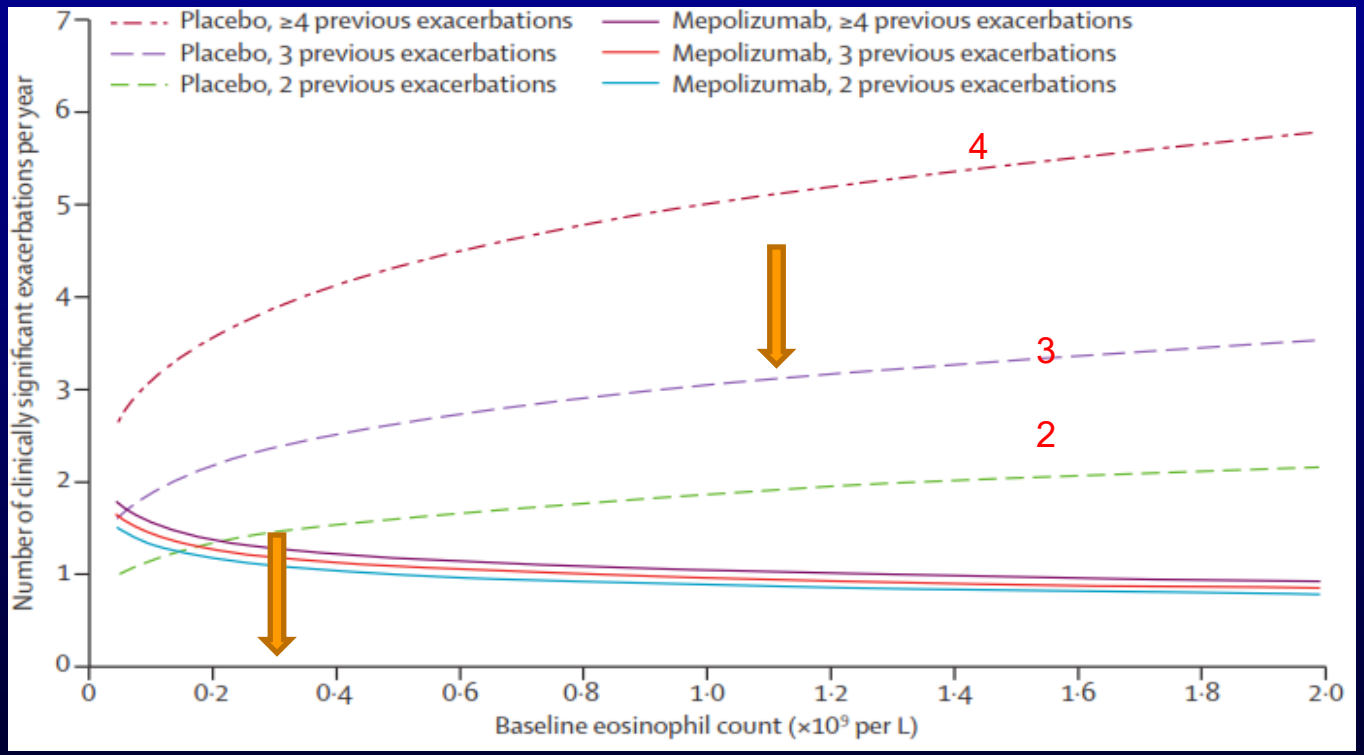
Modeling Suggests that Mepo's Greatest Effect is on Patients with 3 or more Exacerbations or Very High Eosinophils



Pavord, Lancet, 2012

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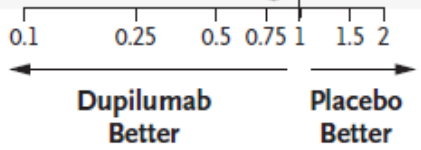
FeNO is not a predictor of response to anti-IL5 drugs

FeNO or Eosinophils Predict Reduced Exacerbations w/ Dupilumab

B Dupilumab, 300 mg Every 2 Wk, vs. Matched Placebo

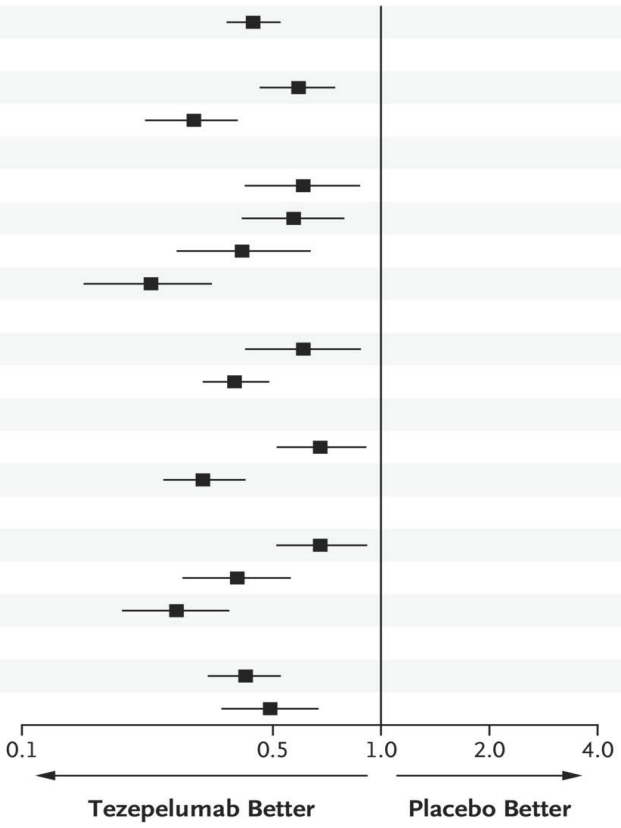
Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	321	633	0.54 (0.43–0.68)
Eosinophil count			
≥300 cells/mm^3	142	277	0.33 (0.23–0.45)
≥150 to <300 cells/mm^3	95	175	0.56 (0.35–0.89)
<150 cells/mm^3	83	181	1.15 (0.75–1.77)
FE_{NO}			
≥50 ppb	75	124	0.31 (0.19–0.49)
≥25 to <50 ppb	97	186	0.44 (0.28–0.69)
<25 ppb	144	317	0.79 (0.57–1.10)



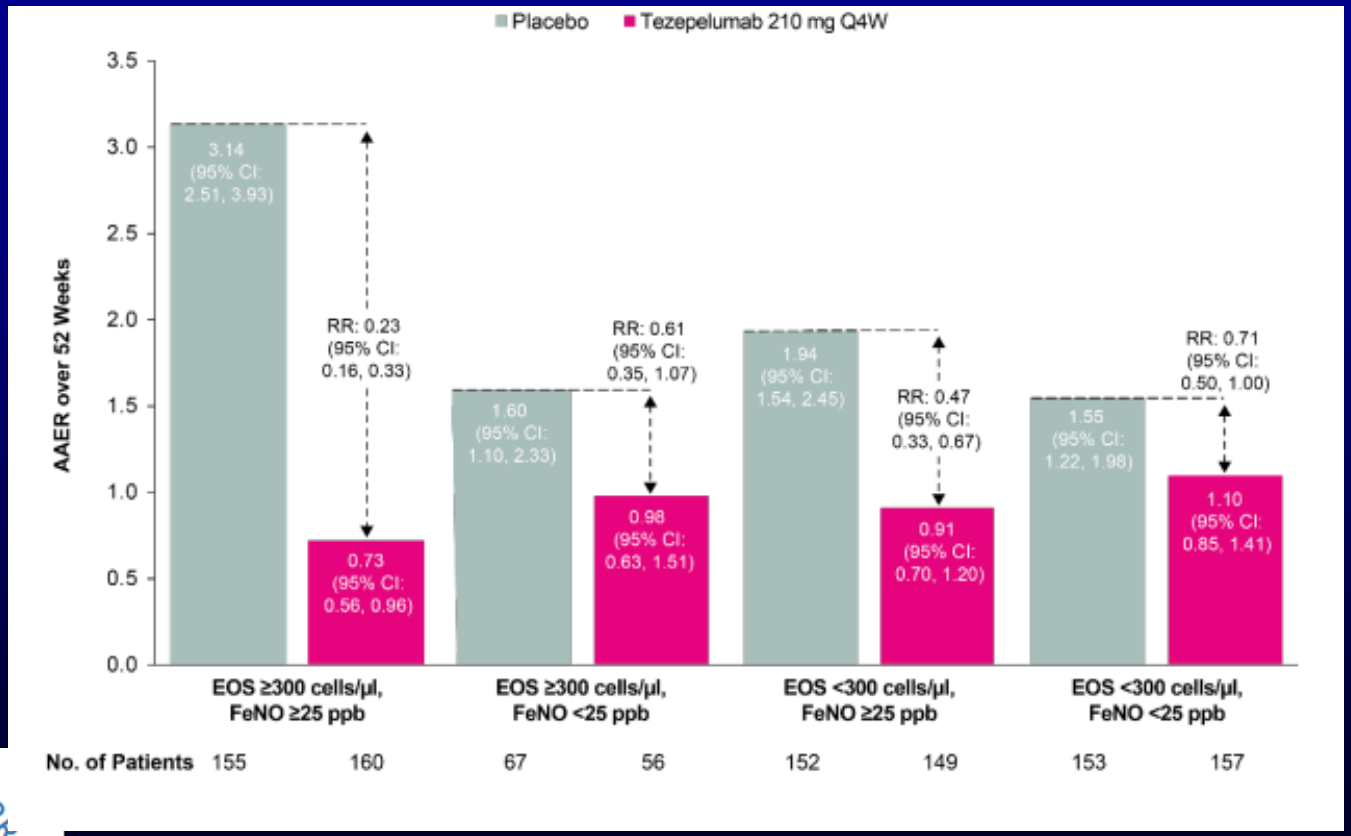
Castro et al , NEJM, 2018

Tezepelumab Reduces Exacerbations Even in Those with Low T2 Markers but is even more effective in high T2

Subgroup	Tezepelumab	Placebo	Rate Ratio (95% CI)
	no. of patients/annualized rate of asthma exacerbations		
Overall	528/0.93	531/2.10	0.44 (0.37–0.53)
Eosinophil count at baseline (cells/μl)			
<300	309/1.02	309/1.73	0.59 (0.46–0.75)
≥300	219/0.79	222/2.66	0.30 (0.22–0.40)
Eosinophil count at baseline (cells/μl)			
<150	138/1.04	138/1.70	0.61 (0.42–0.88)
150 to <300	171/1.00	171/1.75	0.57 (0.41–0.79)
300 to <450	99/0.92	95/2.22	0.41 (0.27–0.64)
≥450	120/0.68	127/3.00	0.23 (0.15–0.34)
Eosinophil count at baseline (cells/μl)			
<150	138/1.04	138/1.70	0.61 (0.42–0.88)
≥150	390/0.89	393/2.24	0.39 (0.32–0.49)
FENO at baseline (ppb)			
<25	213/1.07	220/1.57	0.68 (0.51–0.92)
≥25	309/0.82	307/2.52	0.32 (0.25–0.42)
FENO at baseline (ppb)			
<25	213/1.07	220/1.56	0.68 (0.51–0.92)
25 to <50	158/0.87	151/2.20	0.40 (0.28–0.56)
≥50	151/0.75	156/2.83	0.27 (0.19–0.38)
Allergic status at baseline			
Positive for any perennial allergens	339/0.85	341/2.03	0.42 (0.33–0.53)
Negative for all perennial allergens	184/1.09	177/2.21	0.49 (0.36–0.67)

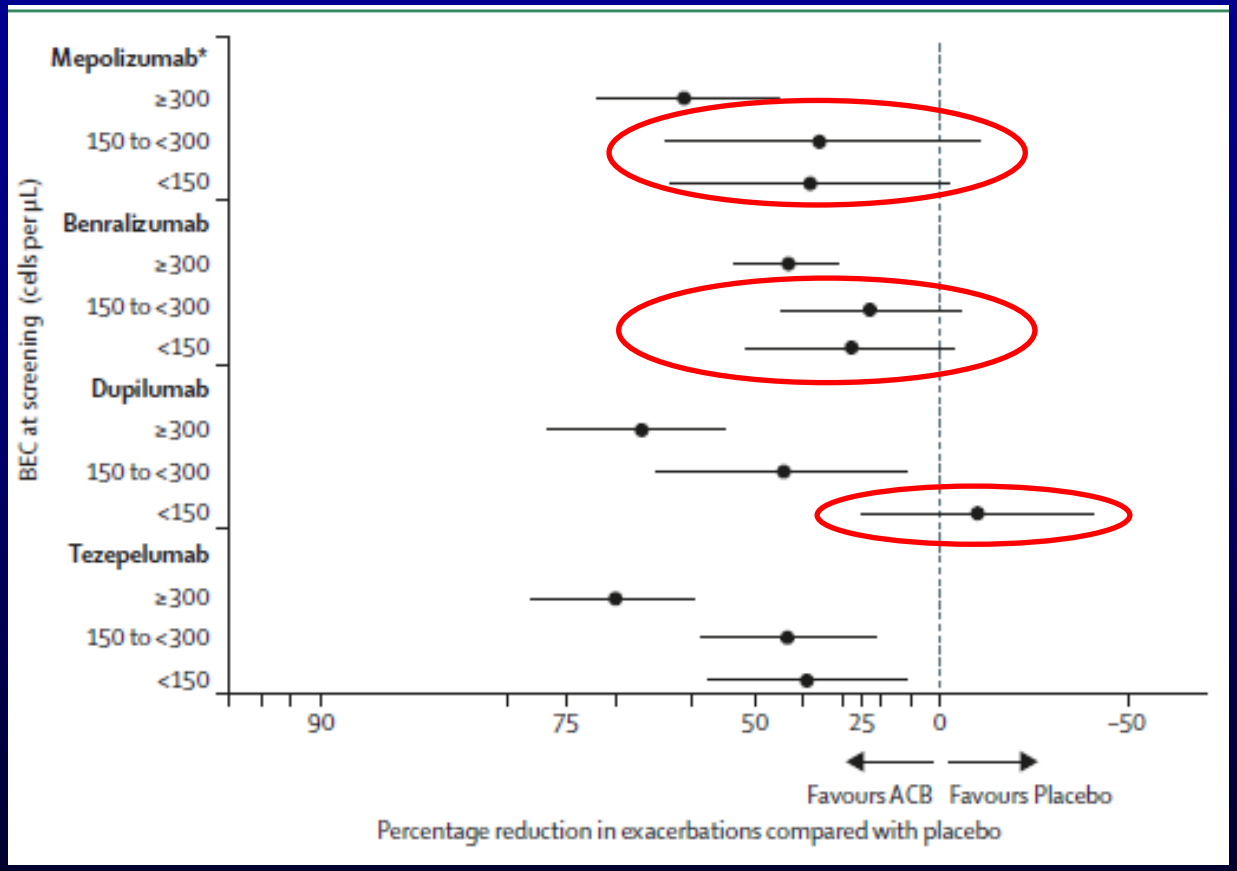


Tezepelumab Effect Based on BEC and FeNO Combinations



Menzies-Gow, NEJM, 2021

Effect of baseline BEC on the percentage reduction in exacerbations produced by the ACBs



Israel et al, Lancet 2025

How do we choose?

- Without head to head studies it is difficult to definitively ascertain superiority of one biologic over another
- However, we can use characteristics of these drugs in a shared decision making model to outline possible preferences.

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Administration of the Biologics in Severe Asthma

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab	Tezepelumab
Lowest age	6	6	18	12	6	12
Frequency	2-4 wks	4 wks	IV 4 weeks	8 wks after first months	2 wks	4 wks
Mode	SC	SC	IV	SC	SC	SC
Home Administration	Y	Y	N	Y	Y	Y
Anaphylaxis	0.1-0.3%	NR	0.3%	NR	NR	NR
Additional Notes	-	-	-	-	Temporary increase in eosinophils	

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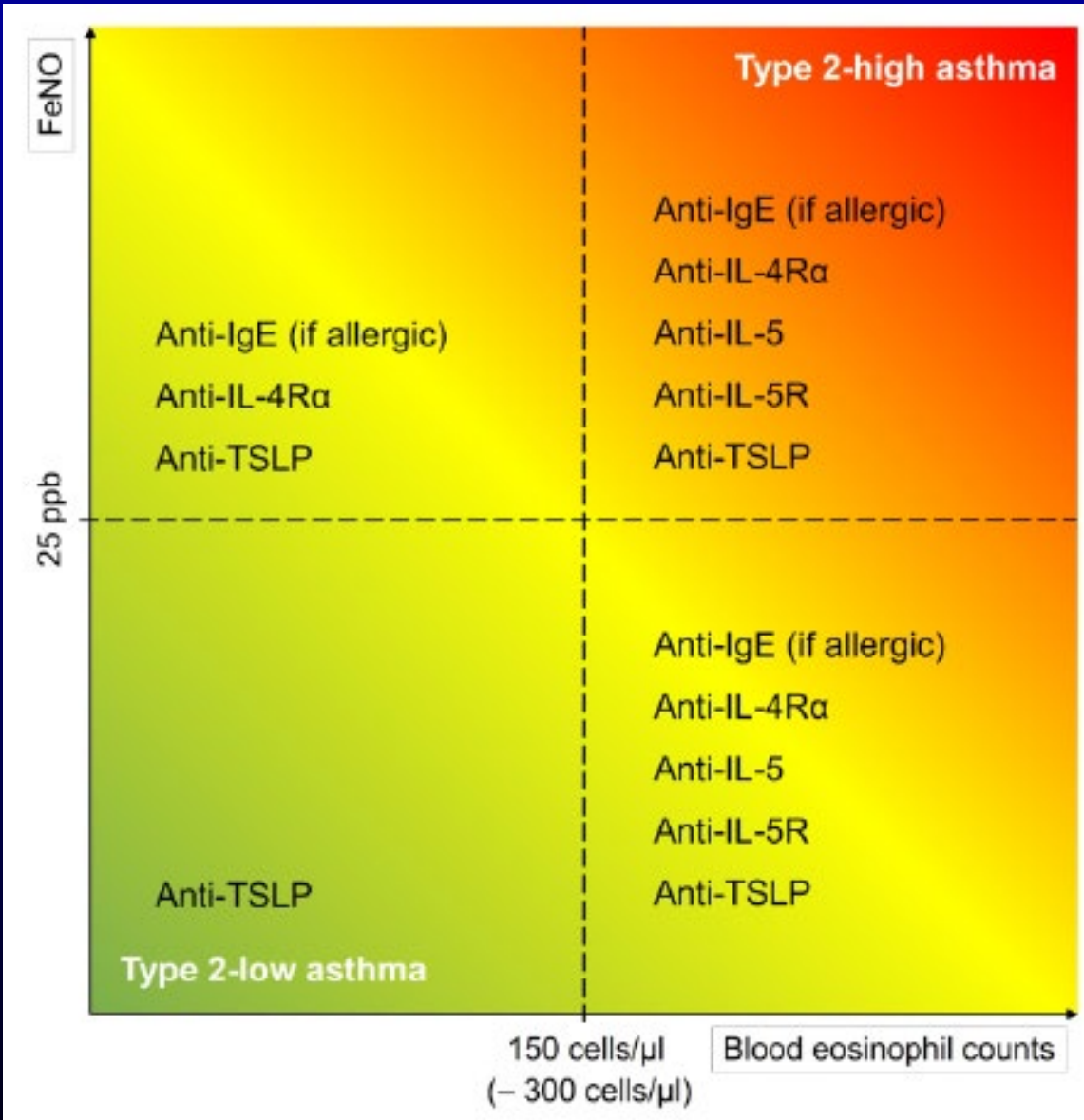
Biomarkers of Patients Likely To Respond

ALL PATIENTS STUDIES HAD TO HAVE ≥1-2 EXACERBATIONS AT BASELINE AND BD BY ≥12%

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab	Tezepelumab
Eosinophils	++	+++	+++	+++	+++	+++
FeNO	++	0	0	0	+++	+++
Low Eosinophils	0	0	0	0	0	++
Low Eos/Hi FeNO	0	0	0	0	++	++
Low Eos/Lo FeNO	0	0	0	0	0	+/-

Interaction of FeNO and BEC in Predicting Response to Biologics



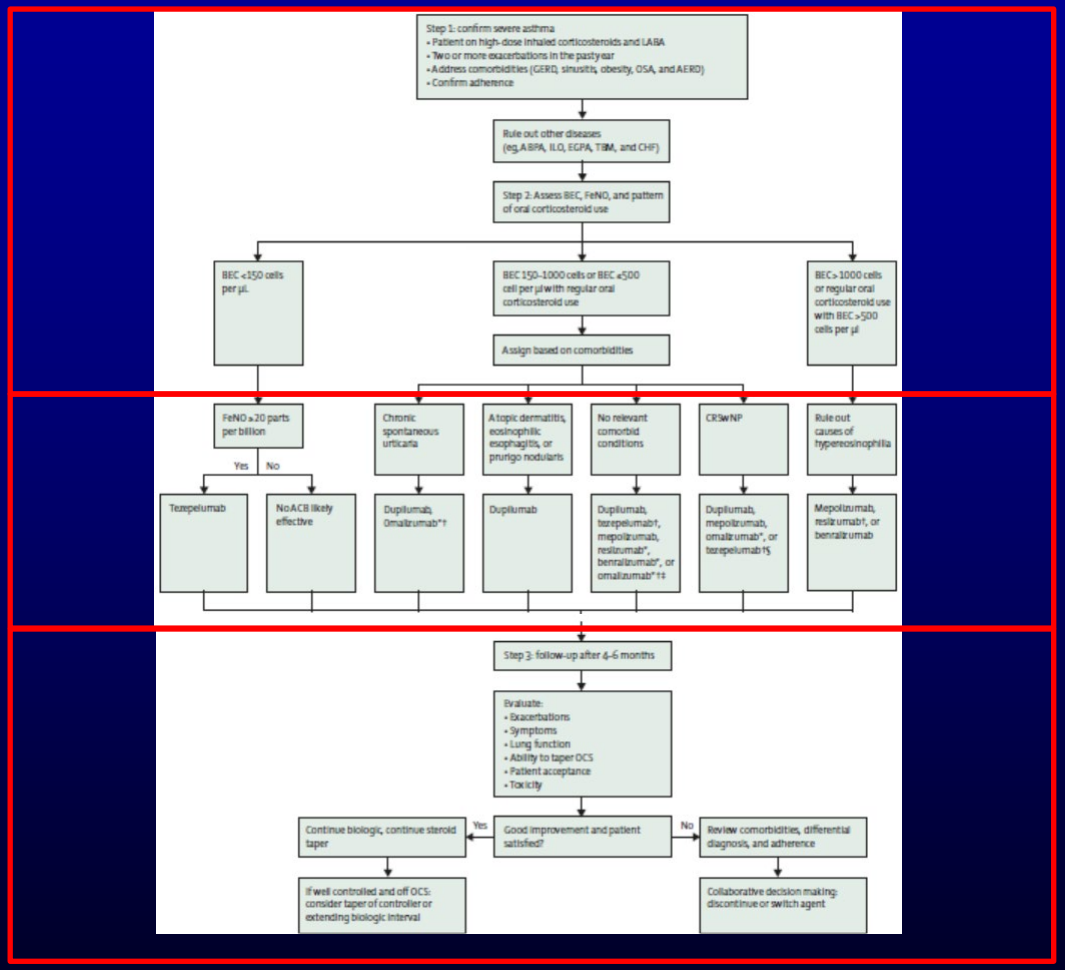
Brussel (supp), NEJM, 2023.

Flow Diagram for Decision Making

Confirm Severe Asthma and Basic Phenotyping and Biomarkers and Categorization

Assign Therapy Based on Co-Morbidities & Precision Associated Properties of ACBs

Follow Up



Israel et al, Lancet 2025

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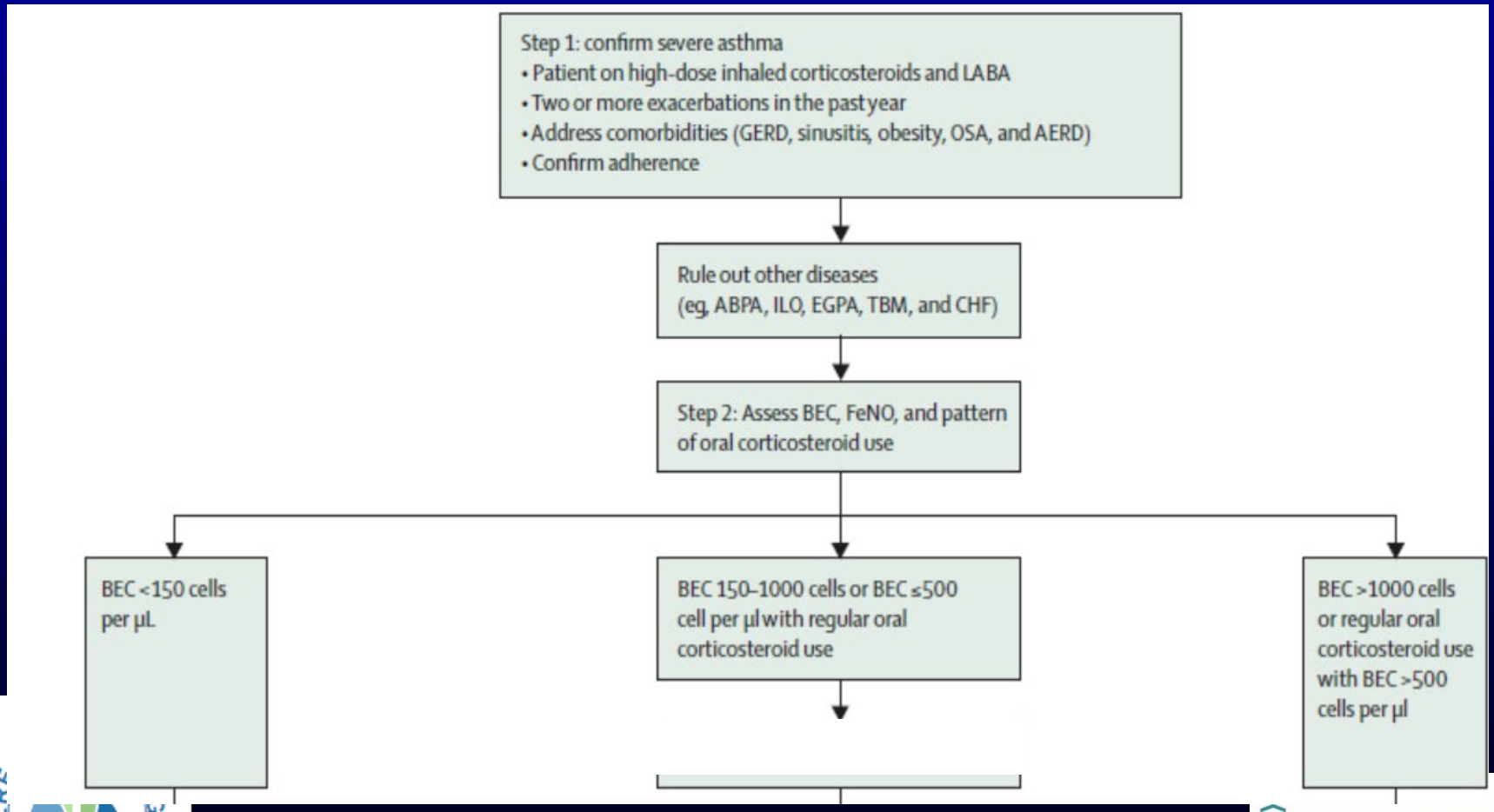
Confirm Severe Asthma and Basic Phenotyping and Biomarkers and Categorization



Israel et al, Lancet 2025

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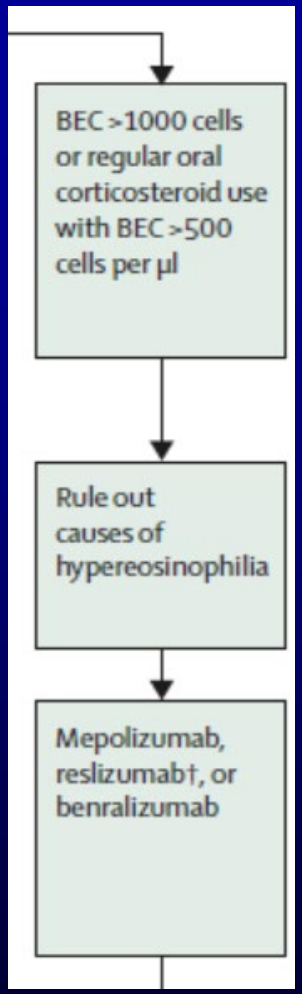
Patients with BEC ≥1000 ul or Regular OCS >500 ul

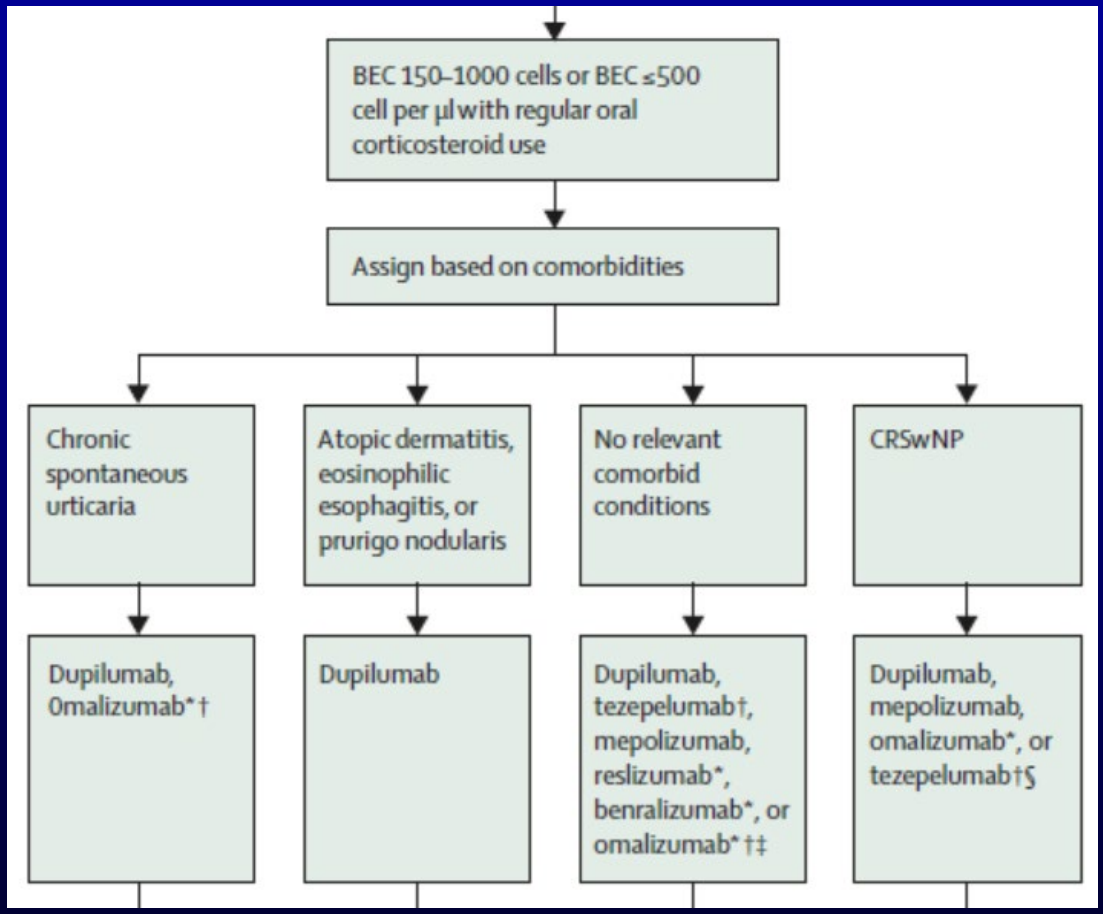


- **-Should Be Evaluated for other Causes of Eosinophilia**
  - **-Lower threshold for eosinophilia investigation in OCS users due to OCS suppressive effects on eosinophils**
- **-Preferentially be Treated with Anti-IL-5 Agents**
  - **-Due to potential eosinophilia with dupilumab**
  - **-Lack of robust data in OCS users or very high eosinophils population with tezepelumab**

Israel et al, Lancet 2025

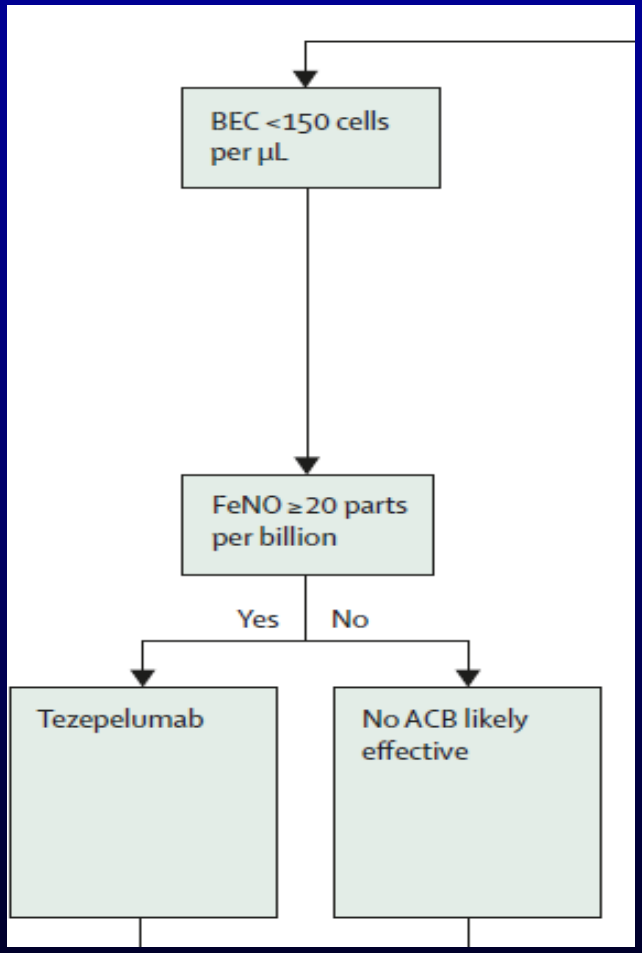
Patients with BEC 150-1000/ul or Regular OCS ≤500/ul

- ACBs should be chosen based on particular efficacy in co-morbidities, if present, and known efficacy
- Considerations
  - -Reduced efficacy of anti-IL-5s and omalizumab in BEC ≤300 ul
  - -Lack of trials for OCS withdrawal with tezepelumab and omalizumab,



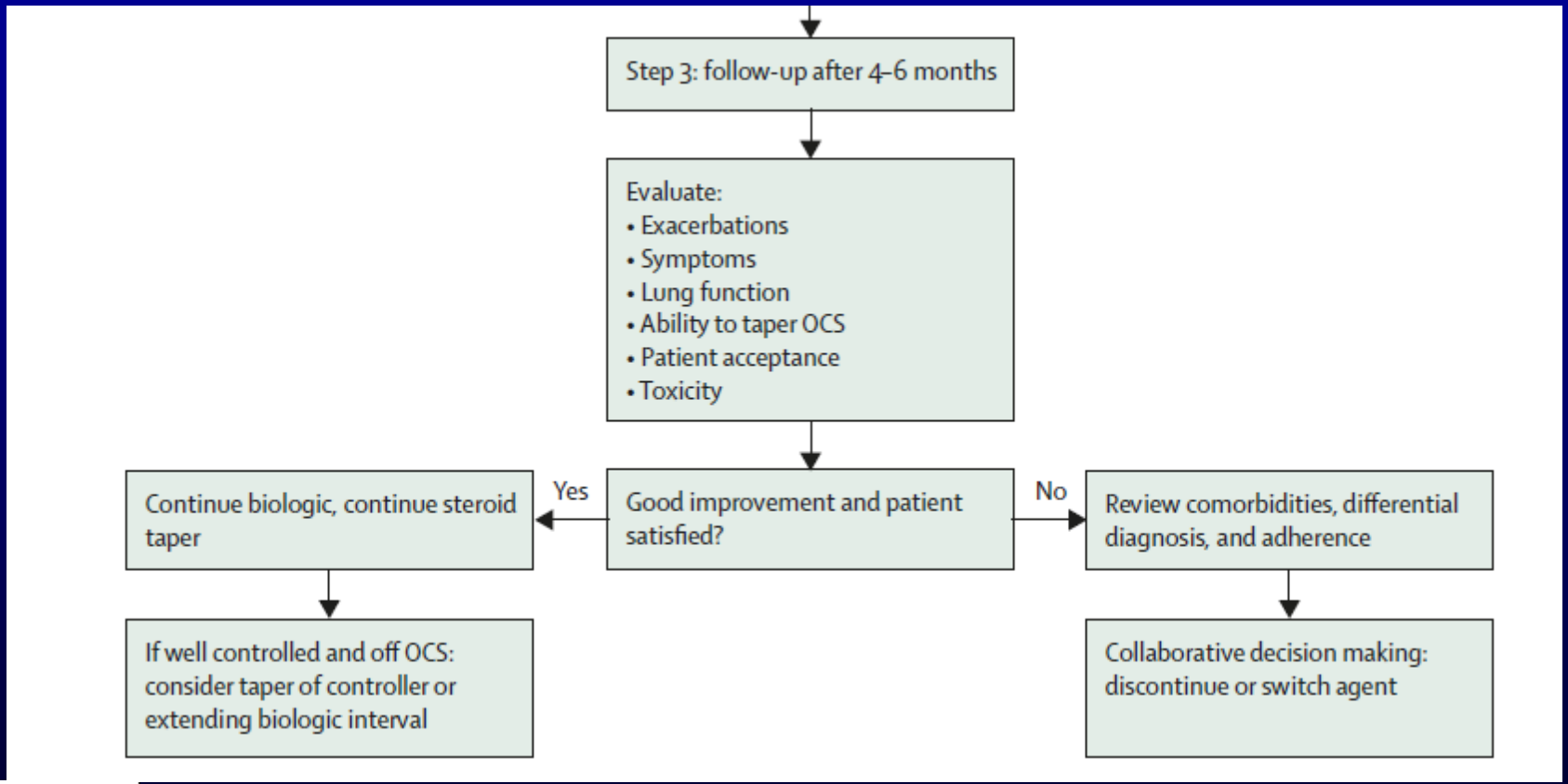
Israel et al, Lancet 2025

Patients with BEC <150 (not on OCS) FeNO Identifies Patients Still Responsive to Tezepelumab



Israel et al, Lancet 2025

Follow-Up



Israel et al, Lancet 2025

Ongoing Questions Related to the Use of Biologics

- **What can we do to increase the relatively low rates of remission compared to placebo?**
- **In whom can we reduce background anti-inflammatory therapy**
  - Studies with benralizumab suggested that even in patients who may achieve symptom control some will have reduced lung function with concomitant increase in FeNO
- **Combining ACBs**
  - Sometimes considered, especially if one was started for a different indication
  - No controlled studies currently available on combination therapy
- **Discontinuation of ACBs**
  - Stopping after 1–2 years often leads to symptom relapse and more exacerbations
  - Lowering the dose or increasing dosing interval may be an option, but not yet tested
- **When to Start ACBs**
  - Will earlier use lead to better responses (suggested by post-hoc/population data)
  - Will early initiation in patients with frequent exacerbations prevent lung function loss
  - Will patients with T2 inflammation but controlled symptoms benefit from ACBs
  - Can initiation in children prevent progression of asthma

Israel et al, Lancet 2025

Summary of Use of Drugs Active on Type 2 Pathway

- Effectiveness shown for patients with 2 or more exacerbations
  - Generally patients with >300 eosinophils or currently 150 with a h/o eosinophils >300
  - Most effective for exacerbations
  - Some effect on symptoms and FEV1
  - Except for tezepelumab most have been shown to allow taper of oral CS
- Dupilumab and Tezepelumab effective for those with high FeNO even if eosinophils not elevated
- Tezepelumab effective in effective in FeNO low/eos 150-300
  - Possible effectiveness even in double negative

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Summary

- ACBs targeting T2 inflammation have dramatically improved outcomes for some severe asthma patients
- Patients with higher levels of T2 biomarkers are most likely to respond
- Precision medicine using clinical traits and biomarker characterization can increase the likelihood of a response to therapy
- While many precision medicine selected patients benefit, a proportion do not
- While remission occurs in some patients, the rate is disappointing
- Better understanding of mechanisms behind partial and non-responders is needed

Israel et al, Lancet 2025

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