Choosing Among the Biologics for Severe Asthma

Can Biomarkers Help Us in Our Choices

Elliot Israel, M.D.

Gloria and Anthony Simboli Professor of Medicine

Harvard Medical School

Pulmonary & Critical Care Medicine

Allergy & Immunology

Partners' Asthma Center

I disclose the following relationships in the past year:

- Asthma Education Prevention Program (NAEPP) Coordinating Committee 2017- 2021
- AB Science — Consultant
- Amgen — Consultant
- AstraZeneca — Consultant & Clinical Research Support
- Avillion — Consultant & Clinical Research Support
- Circassia Pharmaceuticals — Clinical Research Support
- Cowen — Consultant
- GlaxoSmithKline — Consultant
- Novartis — Consultant, DSMB
- Regeneron Pharmaceuticals — Consultant
- Sanofi — Consultant
- TEVA — Consultant & Clinical Research Support

SEVERE ASTHMA PROGRAM

PARTNERS ASTHMA CENTER

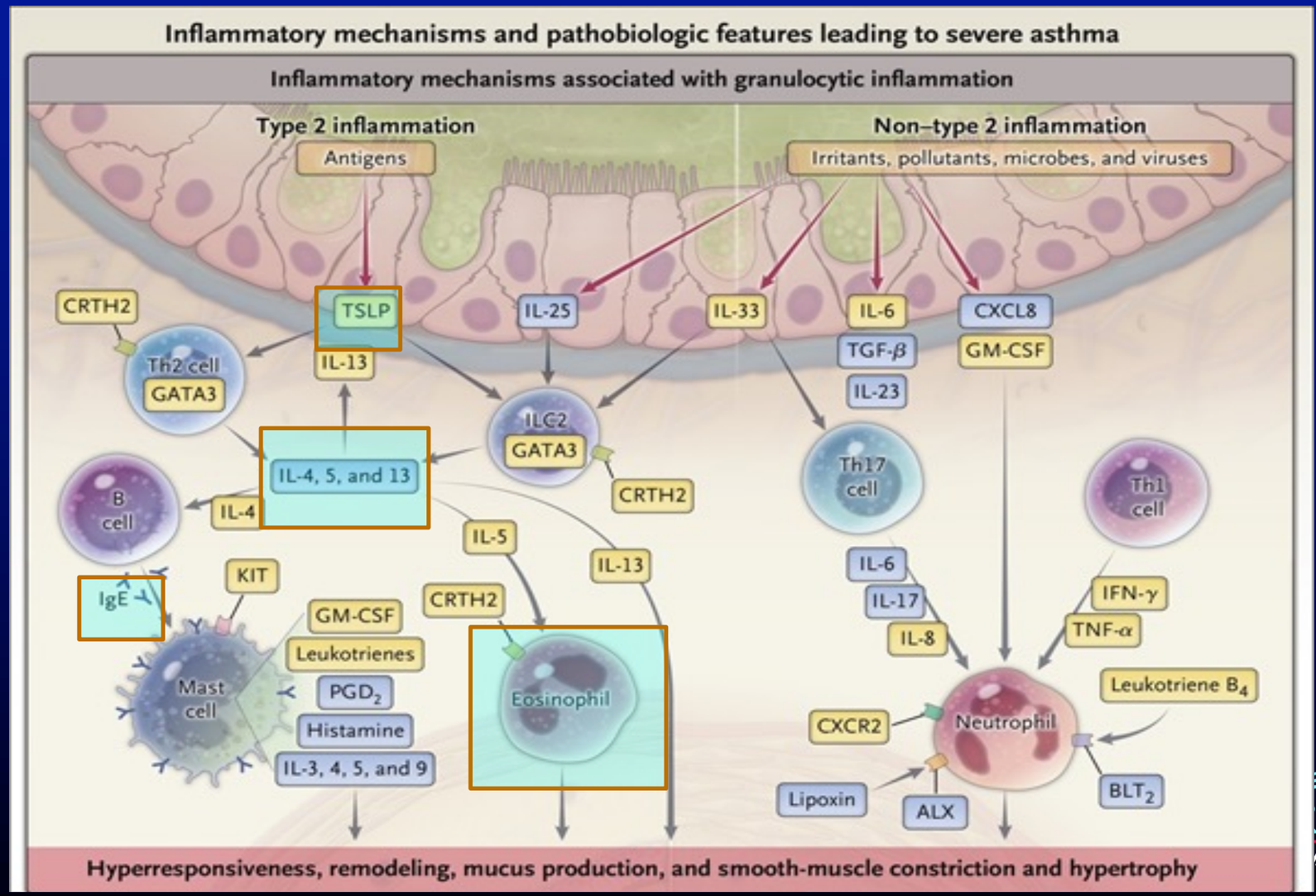
Outline

- 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

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.

Type 2 Inflammatory Targets



• Israel & Reddel, NEJM, 2017

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

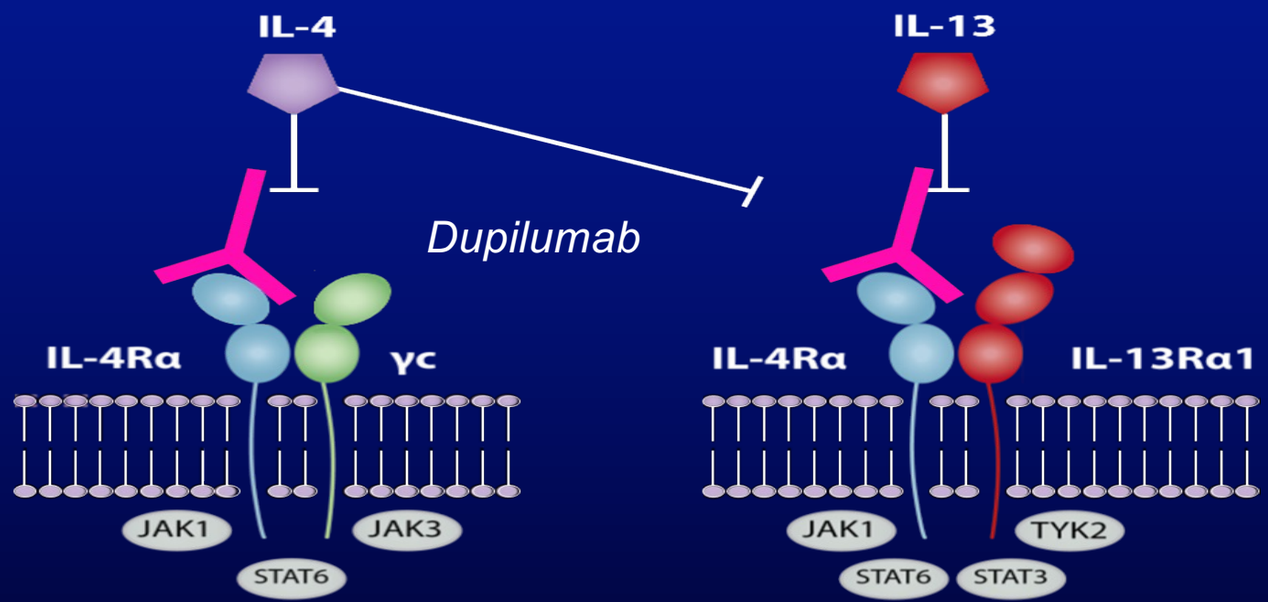
- Qualifications – IgE 30 to 700 and a positive skin test or RAST to a perennial inhalant allergen
- Toxicity – rare anaphylaxis
  - Had been question about increased rate of cancer
  - Large observational study has not confirmed

Anti-IL5 Drugs

- Mepolizumab and Reslizumab bind to IL5 itself and reduce eosinophils by blocking IL5
- Benralizumab binds to the IL5 receptor and also activates NK cells
  - Blocks IL5 signaling
  - Directly toxic to eosinophils
- All indicated for eosinophilic moderate-severe asthma

Blockade of IL-4R alpha

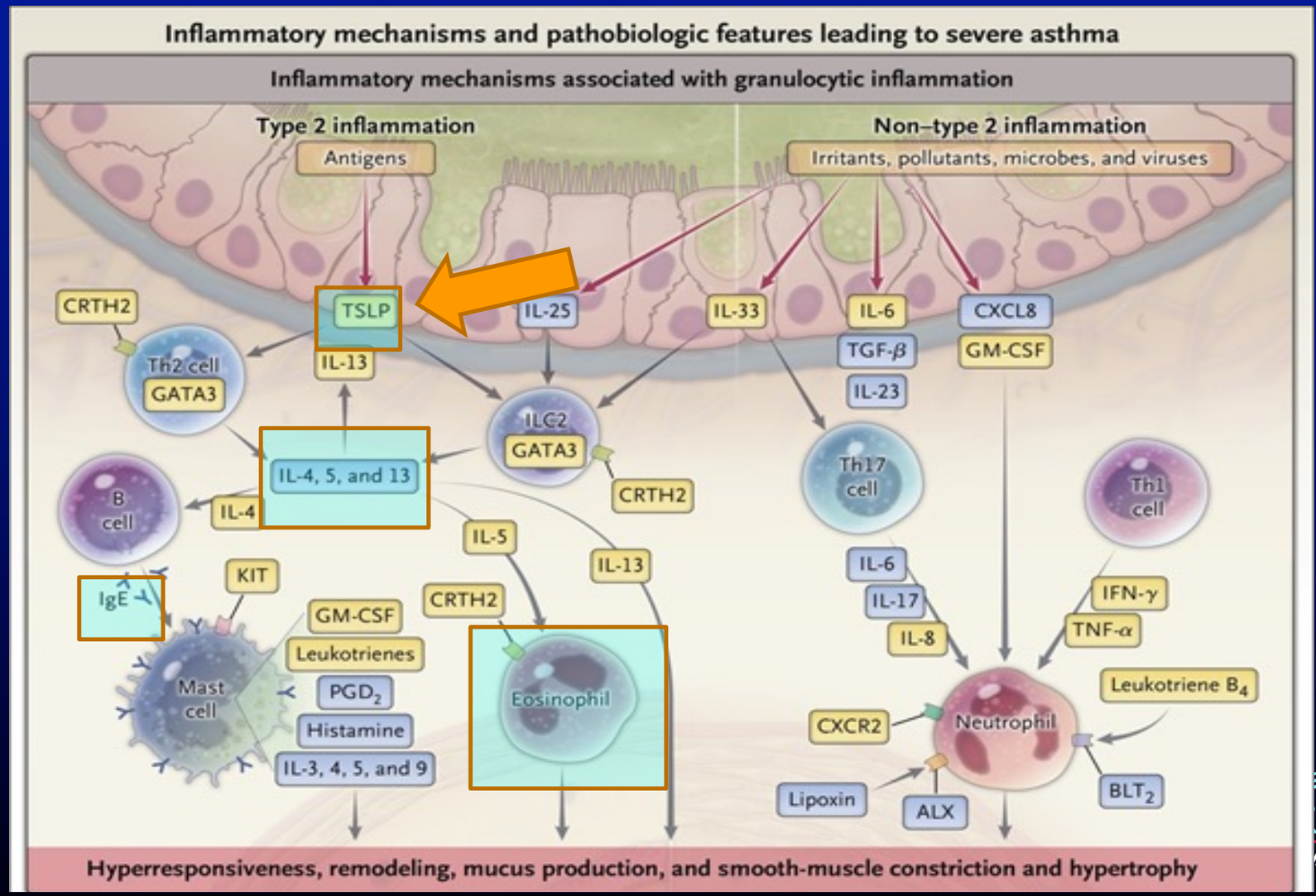
Blocking IL-4R alpha (Dupilumab) Blocks both IL4 and IL13



SEVERE ASTHMA PROGRAM

PARTNERS ASTHMA CENTER

Type 2 Inflammatory Targets



• Israel & Reddel, NEJM, 2017

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

Reduction in Exacerbations in Patients with Eosinophils ≥300/ul (Studies Required ≥12% Bronchodilator Response and ACQ ≥0.5 on Study Entry)

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab	Tezepelumab
% Reduction in Exacerabation	32	61	In >400/ul ~55	~35	66	70

SEVERE ASTHMA PROGRAM

PARTNERS ASTHMA CENTER

Improvement in FEV_1 (cc) in Patients with Eosinophils ≥300/ul and ≥12% Bronchodilator Response on Study Entry

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab	Tezepelumab
FEV1	40	202	126	~138	~225	230

SEVERE ASTHMA PROGRAM

PARTNERS ASTHMA CENTER

Improvement in ACQ (Studies Required ACQ ≥1.5 at entry in addition to exacerbations and BD response)

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab	Tezepelumab
ACQ	0.36	~0.48	~0.24	~0.2	~0.4	0.33

OCS-Sparing Effects

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

Effects on Biomarkers

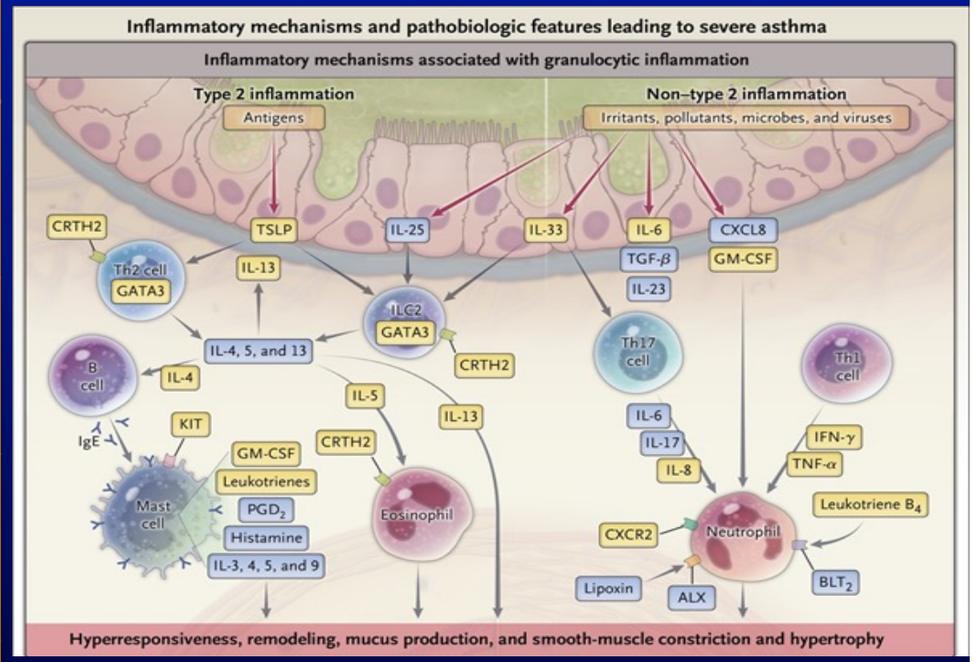
Effect of the Biologics on Outcomes in Severe Asthma

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab	Tezepelumab
IgE	+++[x]	=	=	=	+[#]	+[#]
FeNO	+[#]	=	=	=	+	++
Eosinophils	+[#]	+++	+++	+++/++++	-/+*	++

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

[#]Gradually reduced

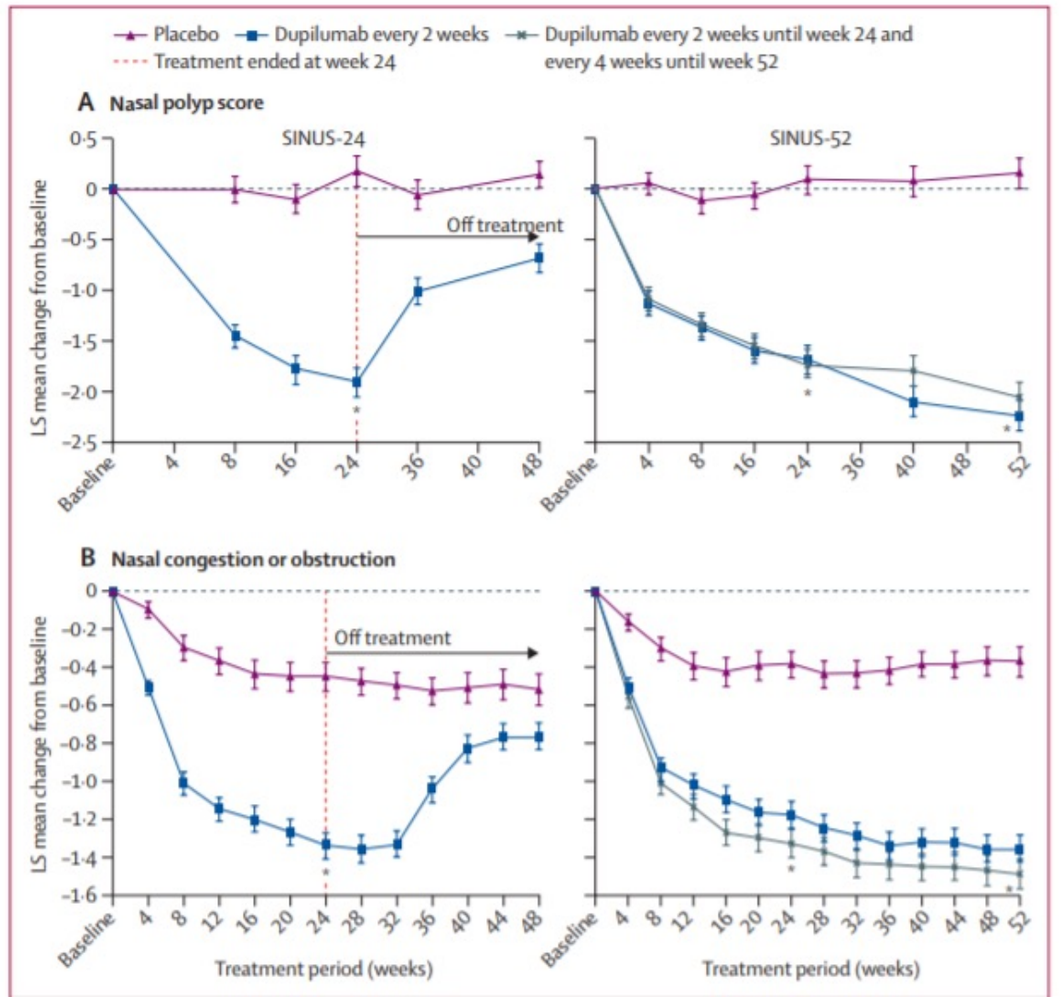
*Eosinophils may rise especially in those with high baseline eosinophils



PARTNERS ASTHMA CENTER

Effects on Co-Morbidities

Dupilumab First Shown Effective in Nasal Polyposis

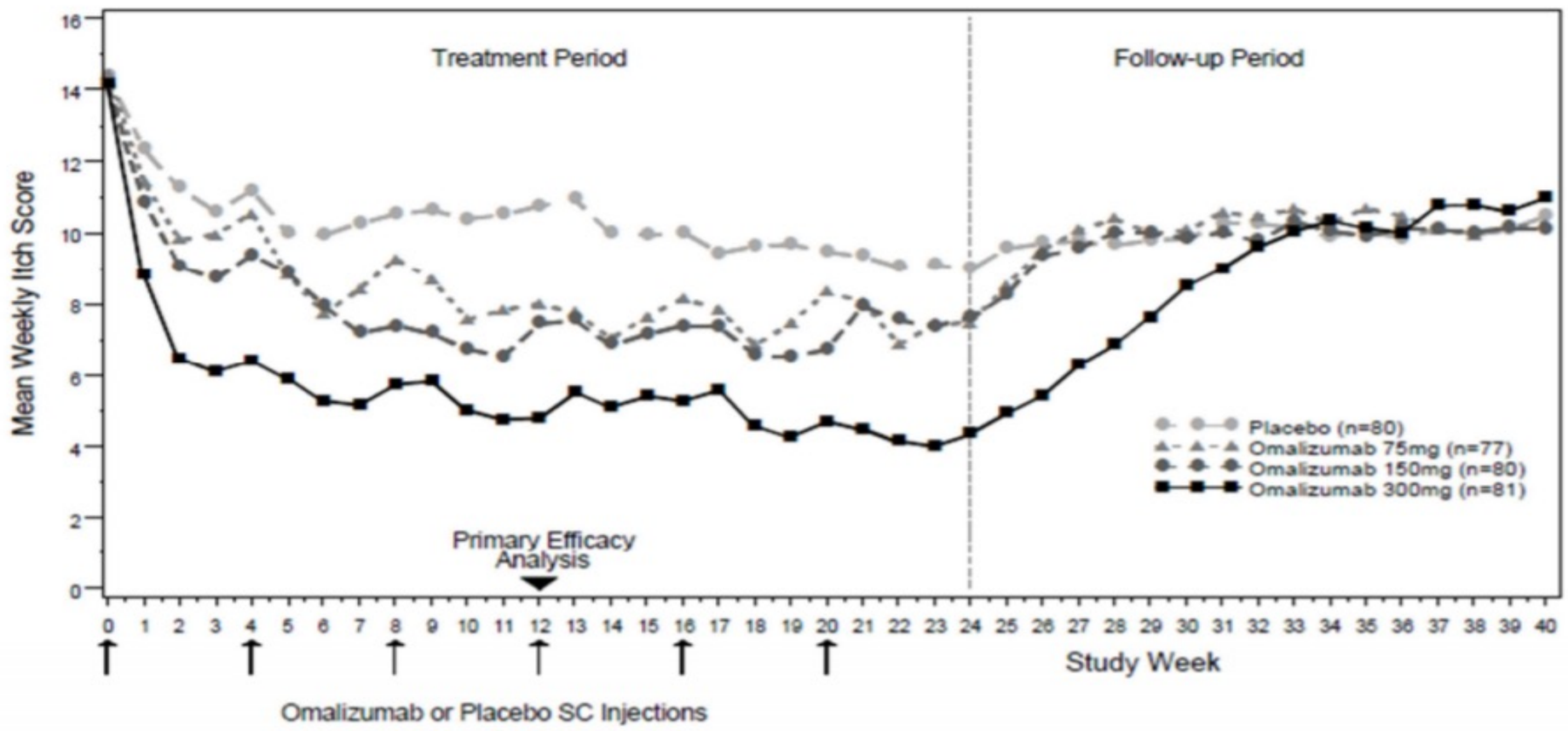


Now shown for:
-Mepolizumab
-Omalizumab

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+

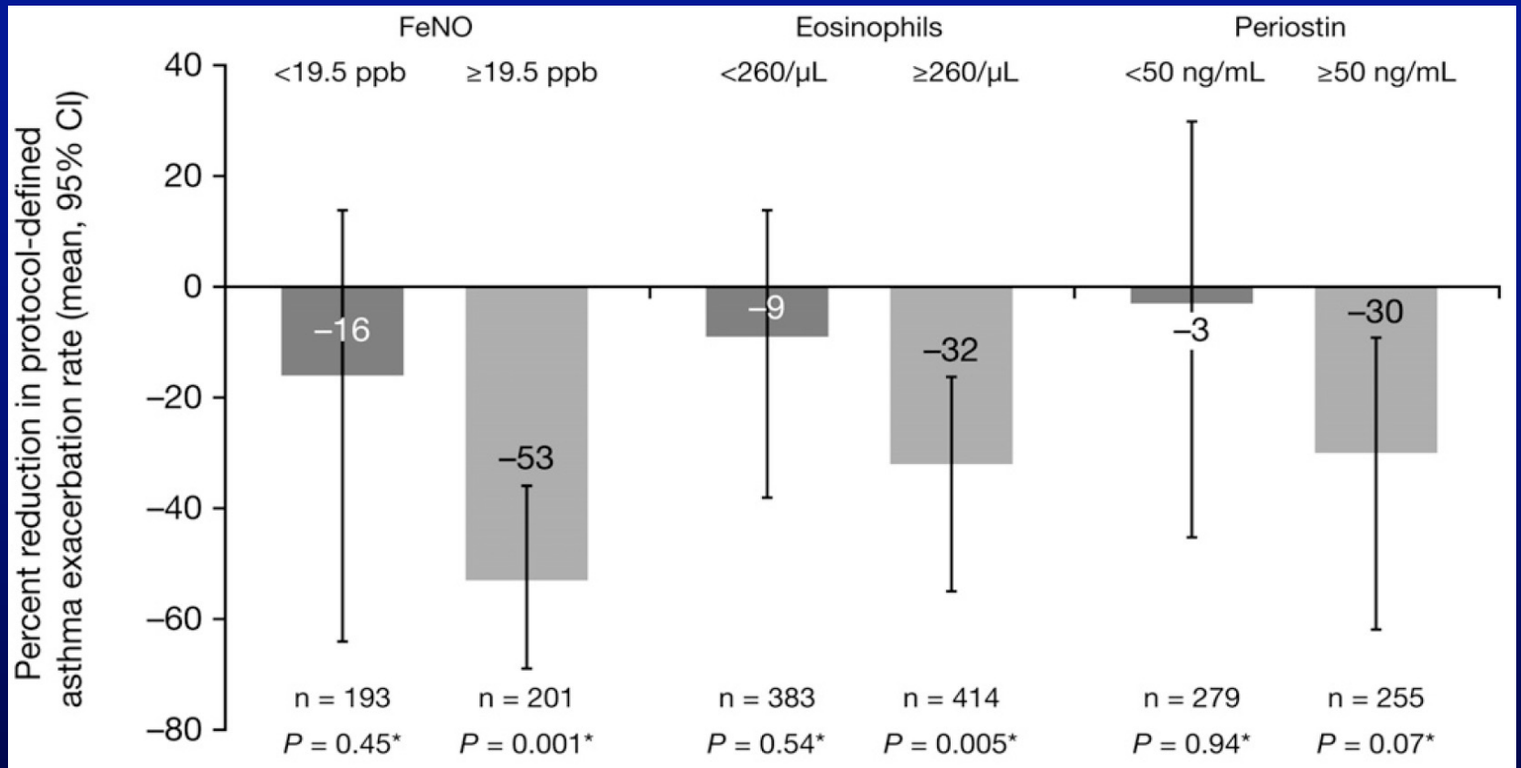
-Approved for prurigo nodularis

SEVERE ASTHMA PROGRAM

PARTNERS ASTHMA CENTER

WHO RESPONDS?

FeNO Best Predictor of Response to Omalizumab



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

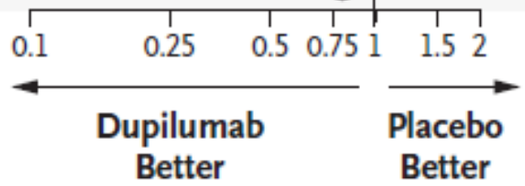
Hanania , Am J Respir Crit Care Med , 2013

Isloated FeNO elevation 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

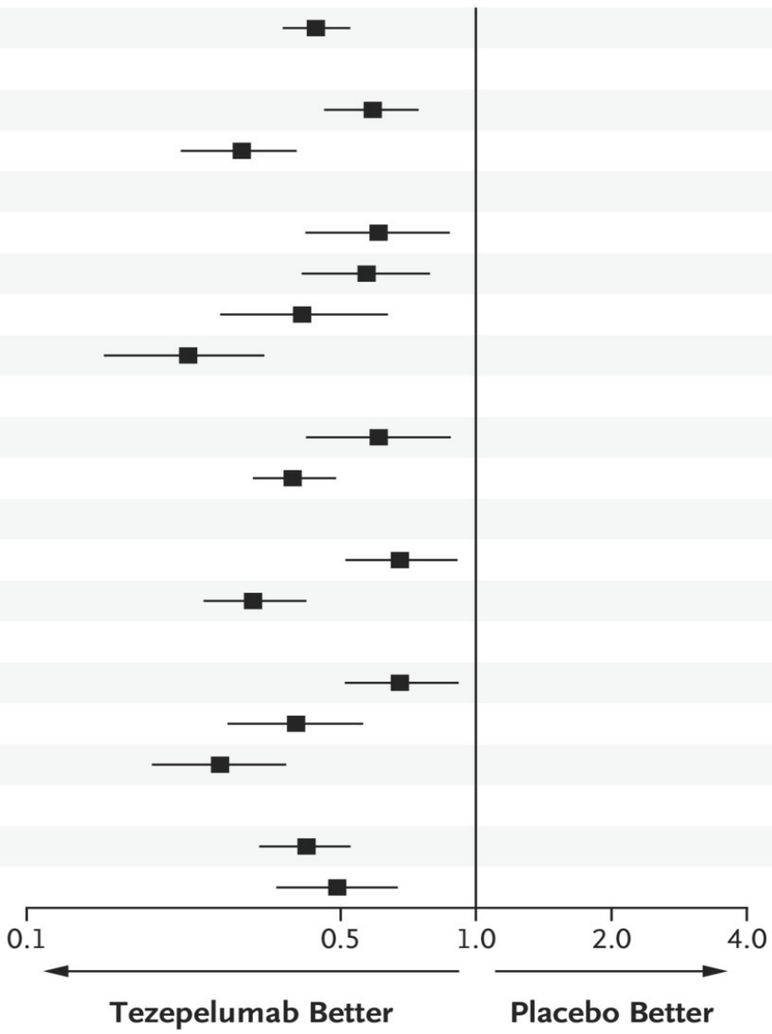
Subgroup	No. of Patients		Relative Risk vs. Placebo (95% CI)
	Placebo	Dupilumab	
Overall	321	633	0.54 (0.43–0.68)
Eosinophil count			
≥300 cells/mm^3	142	277	0.33 (0.23–0.45)
≥150 to <300 cells/mm^3	95	175	0.56 (0.35–0.89)
<150 cells/mm^3	83	181	1.15 (0.75–1.77)
FE_{NO}			
≥50 ppb	75	124	0.31 (0.19–0.49)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



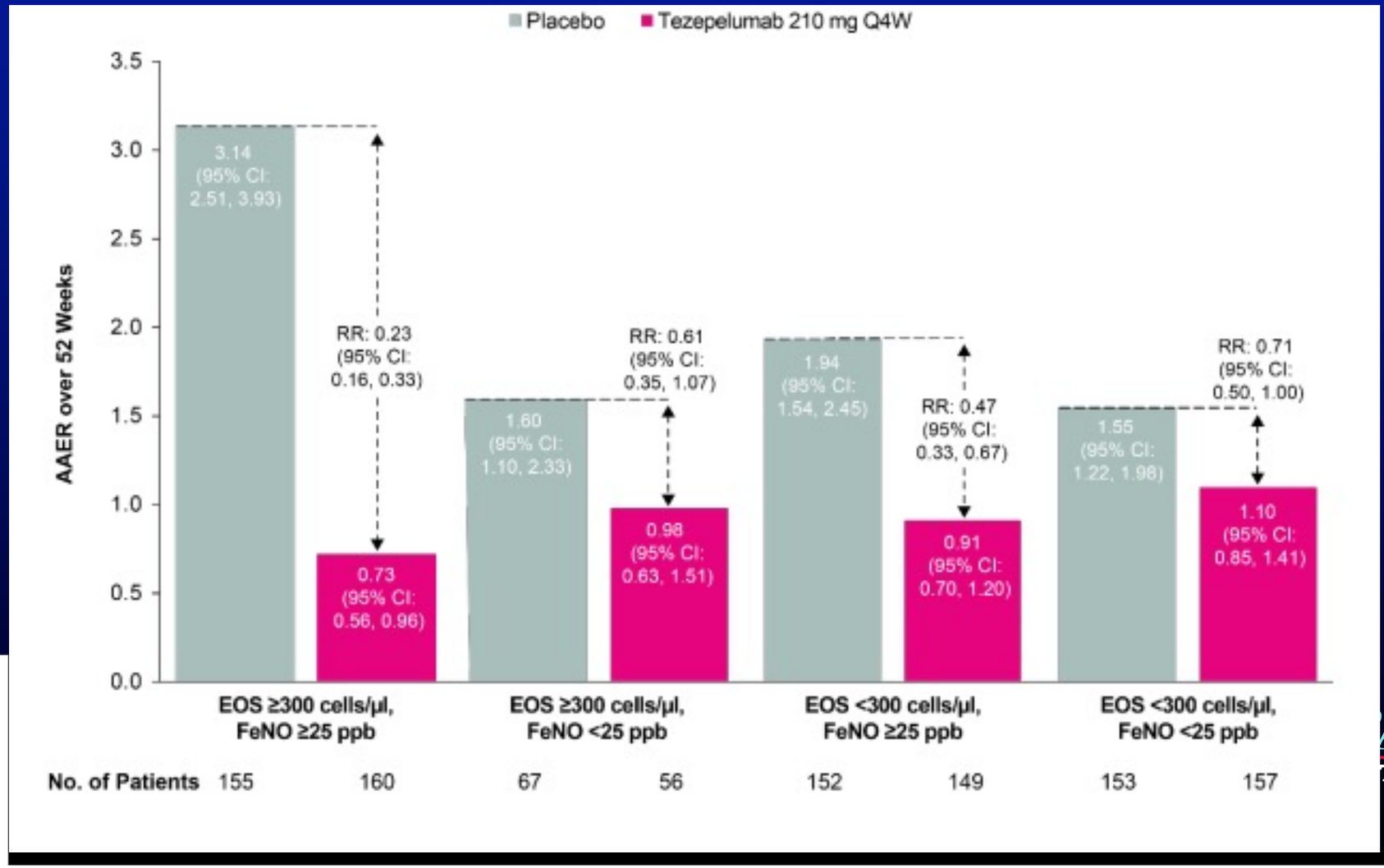
Castro et al , NEJM, 2018

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 in Combined Low Eos/Low FeNO



Menzies-Gow, NEJM, 2021

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.

Administration of the Biologics in Severe Asthma in USA

	Omalizumab	Mepolizumab	Reslizumab	Benralizumab	Dupilumab	Tezepelumab
Lowest age for asthma	6	6	18	12	12	12
Frequency	2-4 wks	4 wks	IV 4 weeks	8 wks after first 3 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 - Conjunctivitis	

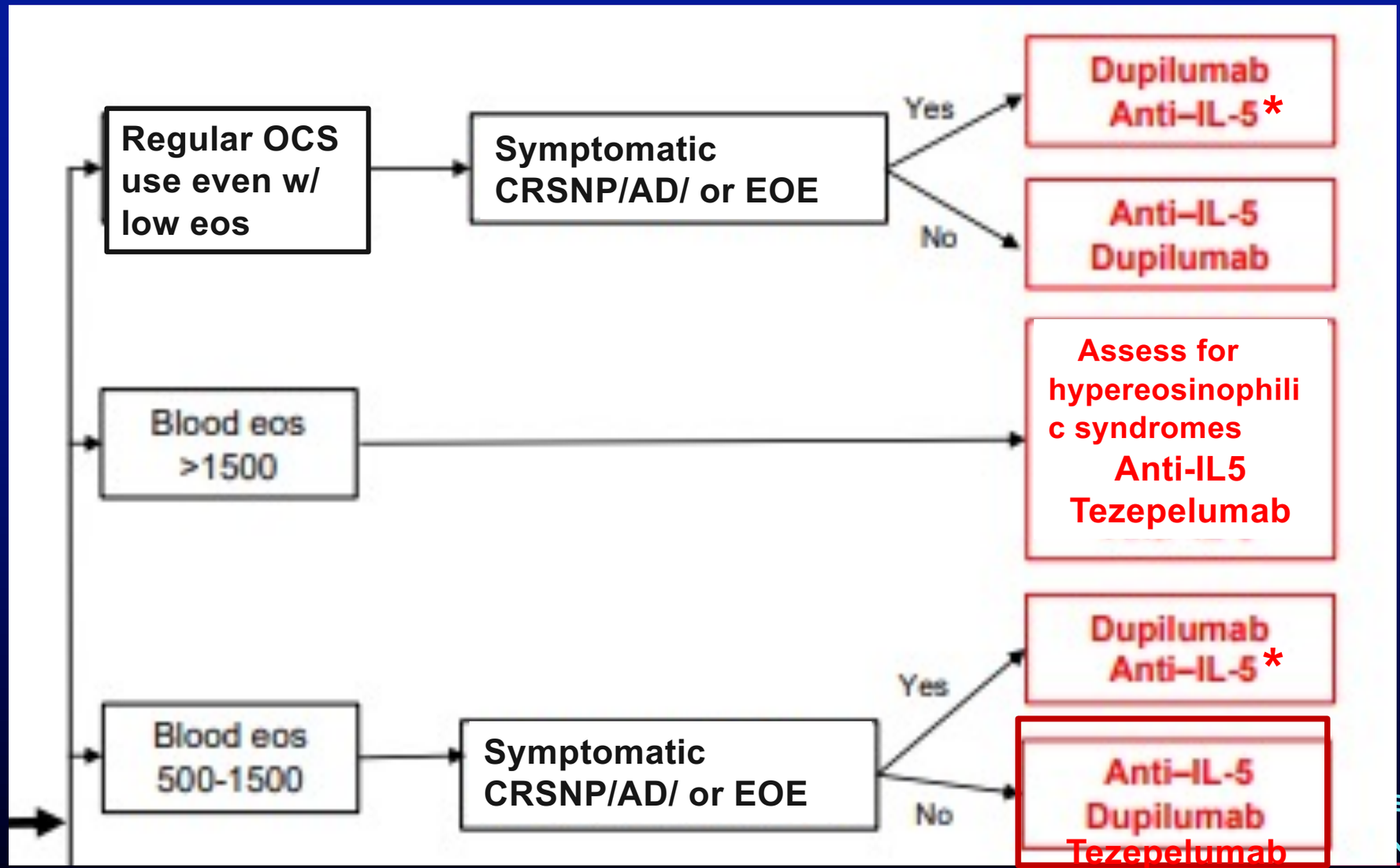
Biomarkers of Patients Likely To Respond

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 (<150-300/ul)	0	0	0	0	0	++
Low Eos/Hi FeNO	0	0	0	0	++	++
Low Eos/Lo FeNO	0	0	0	0	0	+/-
OCS Dependent	N.D.	+	N.D.	+	+	-

Co-Morbidities or Phenotypes	Suggested Greater Effectiveness
Seasonal Sx and Exacerbations +/- Allergic Rhinitis	Omalizumab > ? Dupilumab
OCS Dependent	Mepolizumab, Benralizumab, Dupilumab (not shown for Tezepelumab)
Nasal Polyposis	Dupilumab, Omalizumab, Mepolizumab
Atopic Dermatitis or Eosinophilic Esophagitis	Dupilumab
Lower Lung Fx	? Dupilumab, ? Tezepelumab
High FeNO but low eosinophils	Dupilumab, Tezepelumab
Idiopathic Urticaria	Omalizumab
Frequency of Administration	
Low FeNO and Low eosinophils	Tezepelumab

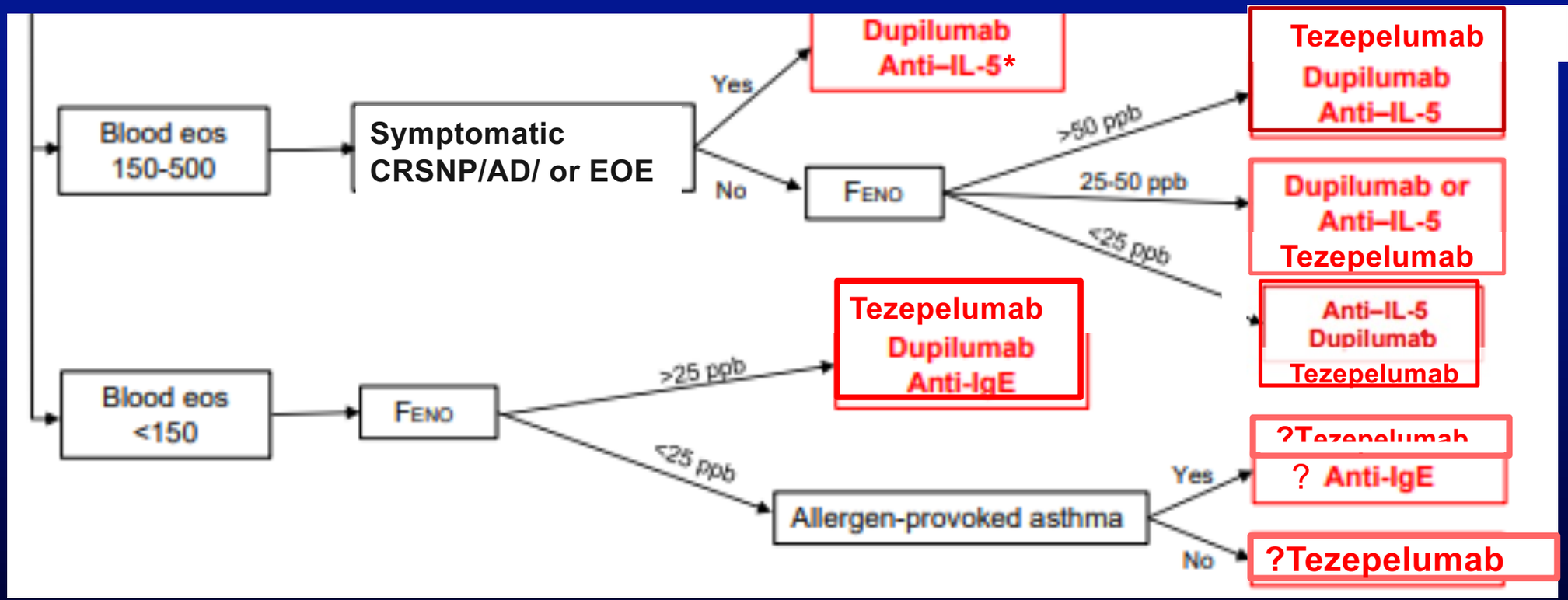
Adherent to Max Tolerated ICS/LABA w/≥2 exacs/yr



*Only applicable w/ CRSNP

Modified from Pavord, JACI In Practice, 2022

Adherent to Max Tolerated ICS/LABA w/≥2 exacerbations/yr or regular OCS



*Only applicable w/ CRSNP

Modified from Pavord, JACI In Practice, 2022

Tezepelumab

Thank You