What To Do When Your Severe Asthma Patient Does Not Respond to Biologics

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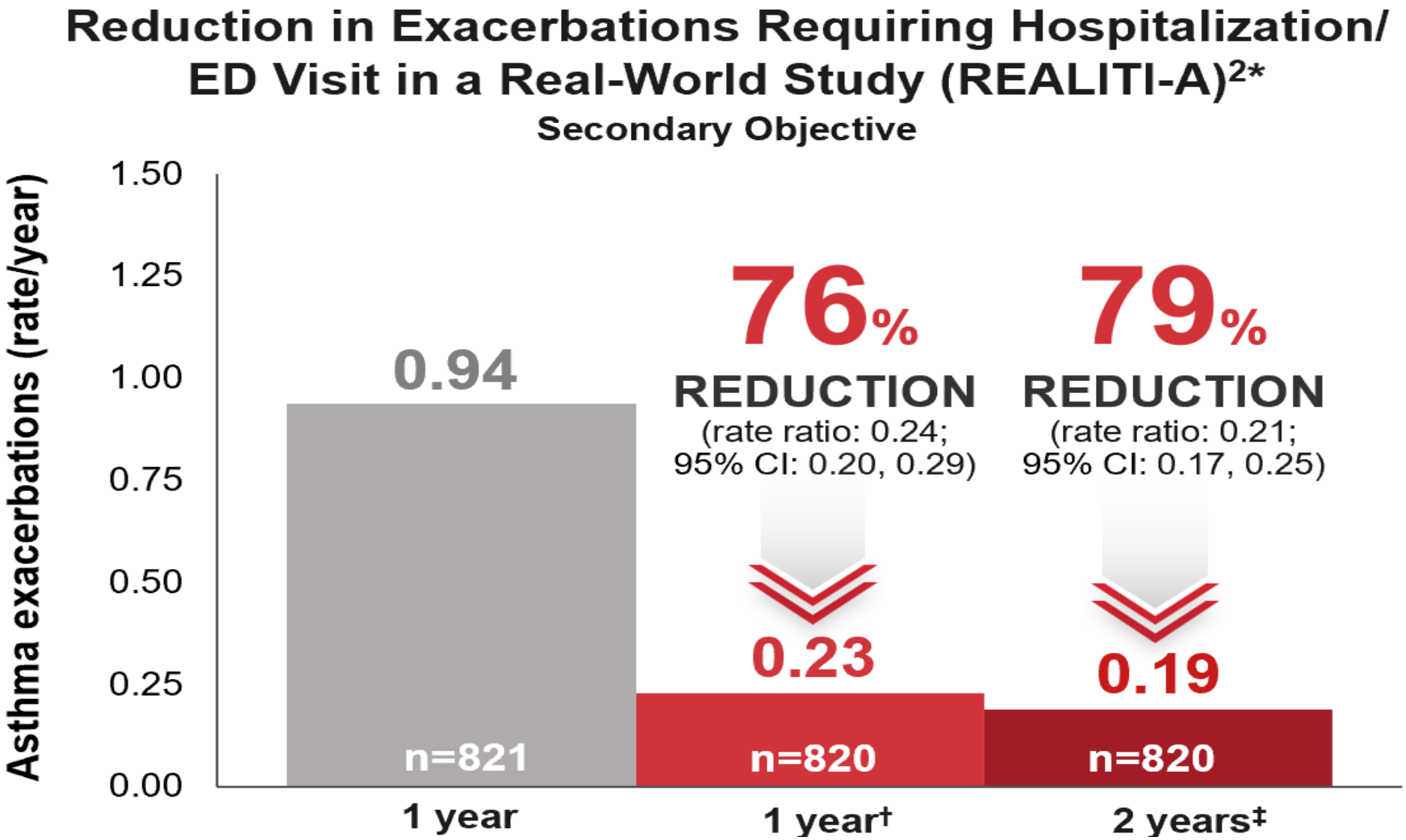
Learning Objectives

- Participants will recognize alternative diagnoses when severe asthma does not respond to biologic therapy
- Participants will identify other therapeutic options when severe asthma does not respond to biologic therapy

What is meant by ‘does not respond’?

- All biologic therapies improve asthma but do not cure disease
  - 50-80% reduction in exacerbations
  - Possible remission with therapy
- Exacerbations are variable in number and not easily predicted
  - Exacerbations more common in spring and fall and historically regress to the mean (frequent exacerbations in one year likely will regress to fewer the following)
  - Higher in spring and fall making start date of biologic important for early response
- Symptom response or PROM in biologic trials show improvement from baseline but little change from placebo
- Dissatisfaction or unmet expectations do not equal lack of response

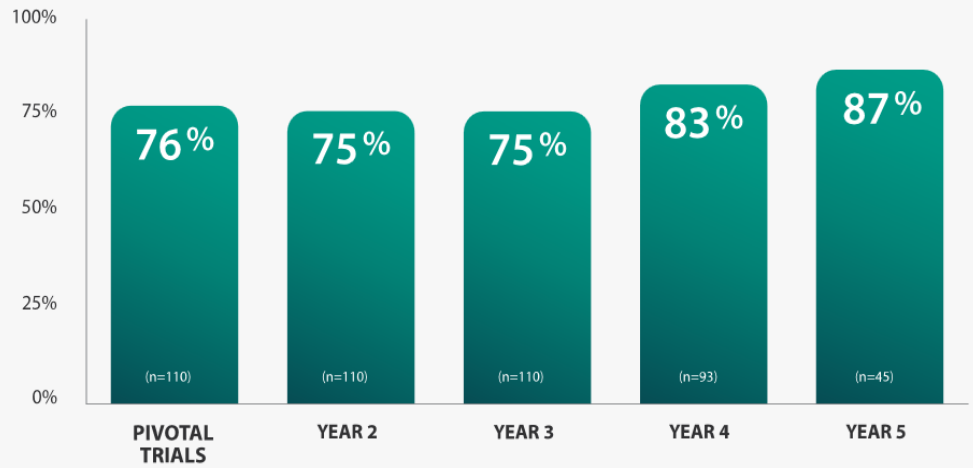
Mepolizumab real world data



Allergy Proceedings 2024;45:219-231/ Clin Exp Allergy 2022;52:616-627

Percentage of Patients With Zero Exacerbations Over 5 Years in MELTEMI

MELTEMI: 5-year Open-Label Extension Study[4]



Results are descriptive only.

In MELTEMI, patients could continue in the study until FASENRA was commercially available in their local market or for 130 weeks in countries in which a marketing application was not submitted.[4] As FASENRA became approved in various markets, patient numbers declined.

- **Over 5 years, at least 75% of patients had zero exacerbations each year[4]**
- **At Year 5, 87% of patients had zero exacerbations[4]**

MELTEMI (Phase 3 Open-Label Safety Extension Trial)
Study limitations: Patients who did not experience benefits with their asthma treatment may have been more likely to discontinue the study vs those who did experience benefits, and similarly, patients who experienced certain SAEs in predecessor studies were not eligible to enter MELTEMI, both of which could contribute to selection bias.[4]

JACI Practice 2021;12:4381-4392

Original Paper

Chronic Respiratory Disease

Comparison of the sensitivity of patient-reported outcomes for detecting the benefit of biologics in severe asthma

Chronic Respiratory Disease
Volume 18: 1–7

DOI: 10.1177/14799731211043530
journals.sagepub.com/home/crd
SAGE

Michael E Hyland[1,2], Joseph W Lanario[2], Andrew Menzies-Gow[3], Adel H Mansur[4], James W Dodd[5], Stephen J Fowler[6], Gemma Hayes[7], Rupert C Jones[1] and Matthew Masoli[8]

PROM in Severe Asthma

- Study limited by COVID epidemic
- Only included benralizumab, mepolizumab, omalizumab and resliziumab
- Improvement noted with PROM instruments specific for asthma

Table 5. Effect sizes (Cohen's D) for change in SAQ subscale scores at three follow-up time points.

	4 weeks		8 weeks		16 weeks	
	ITT	PP	ITT	PP	ITT	PP
SAQ-My Life	0.39	0.49	0.35	0.65	0.56	0.79
SAQ-My Mind	0.36	0.57	0.24	0.49	0.49	0.77
SAQ-My Body	0.42	0.69	0.41	0.84	0.58	0.97

SAQ: Severe Asthma Questionnaire; ITT: intention to treat; PP: per protocol.

› World Allergy Organ J. 2024 Aug 20;17(9):100957. doi: 10.1016/j.waojou.2024.100957. eCollection 2024 Sep.

Effect of biologic therapies on quality of life in severe asthma: Findings from the PRISM study

Hyo-In Rhyou [1], Hyun-Kyoung Kim [2], Woo-Jung Song [2], Sang Min Lee [3], Sang-Ha Kim [4], Jae-Woo Kwon [5], Han-Ki Park [6], Hye-Kyung Park [7], Sang Hoon Kim [8], Jeong-Hee Choi [9], Sujeong Kim [10], So-Young Park [11], Sae-Hoon Kim [12], Ji-Yong Moon [13], Jae-Woo Jung [14], Young-Joo Cho [15], Chan Sun Park [1], Byung Keun Kim [16], Joo-Hee Kim [17], Min-Suk Yang [18], Min-Hye Kim [19], Young-Hee Nam [20], Taehoon Lee [21], Byung-Jae Lee [22], Pankaj Bhavsar [23], Ian M Adcock [23], Kian Fan Chung [23], Tae-Bum Kim [2]

Affiliations + expand

PMID: 39252792 PMCID: PMC11382106 DOI: 10.1016/j.waojou.2024.100957

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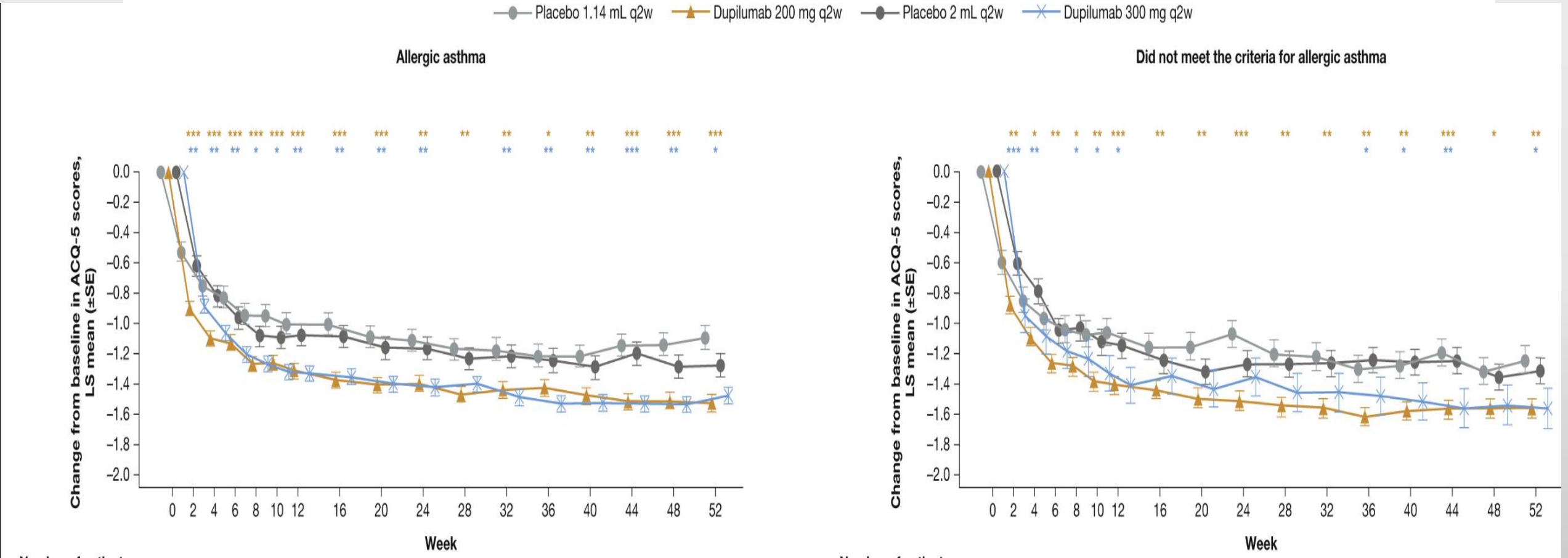
Affiliations + expand

Conclusion: QoL was worse in severe asthma than in mild-to-moderate asthma and other chronic diseases. T2 biologics equally improved QoL in patients with severe asthma.

Placebo Effect in PROM in Biologic Studies of Severe Asthma

JACI Practice 2020;8: 516-526



Number of patients

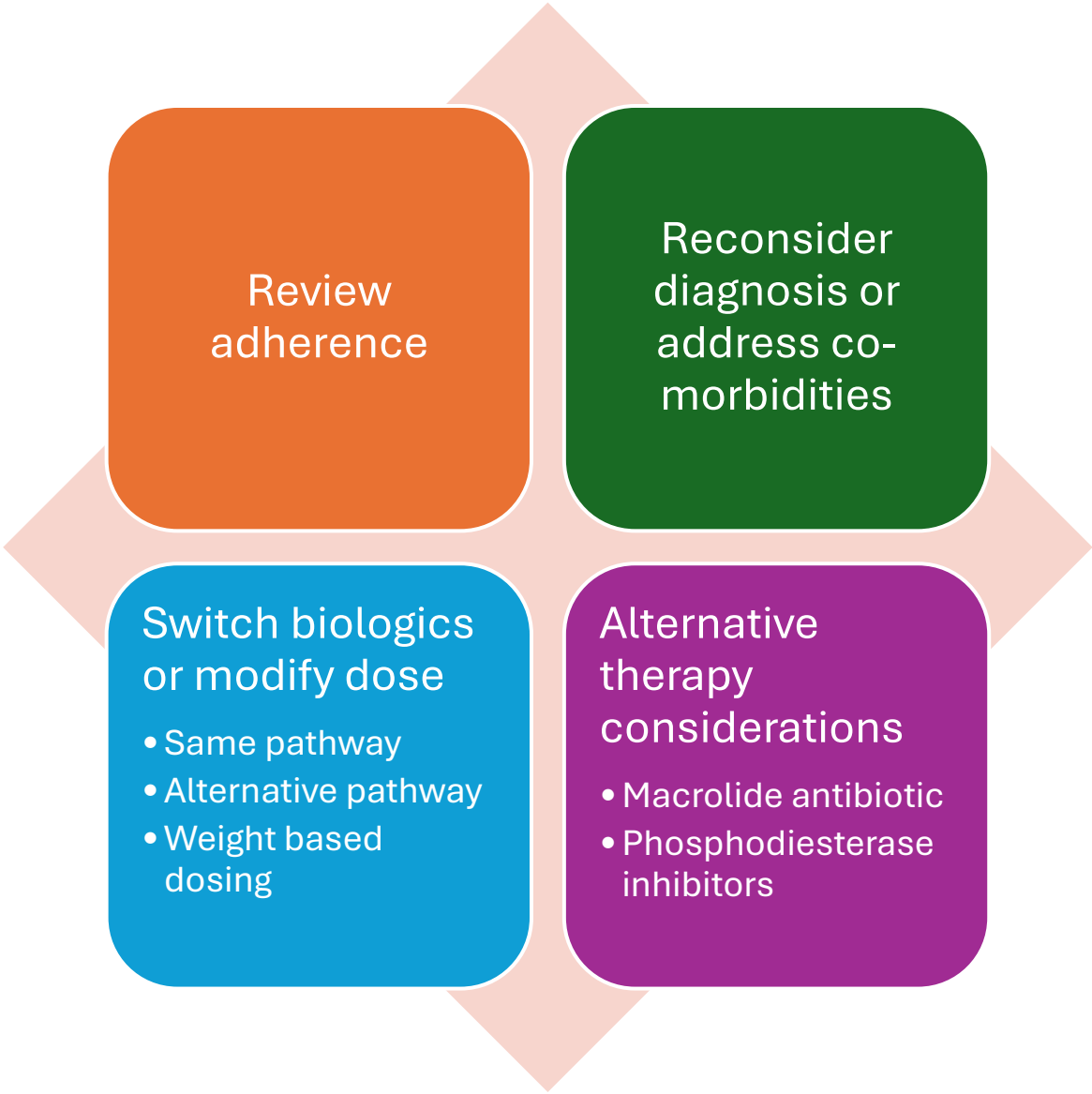
Placebo 1.14 mL q2w	183	176	174	175	177	175	178	174	174	171	166	167	170	167	166	164	145
Dupilumab 200 mg q2w	360	347	345	344	344	340	346	343	340	339	337	329	333	322	321	313	272
Placebo 2 mL q2w	179	169	171	170	173	170	175	171	164	164	170	167	165	165	160	158	137
Dupilumab 300 mg q2w	361	350	344	343	340	339	348	348	338	339	336	331	331	326	322	316	273

Number of patients

Placebo 1.14 mL q2w	134	128	123	121	124	123	125	120	122	125	120	113	115	114	116	109	91
Dupilumab 200 mg q2w	271	252	254	255	251	257	259	252	256	251	247	247	250	244	248	245	198
Placebo 2 mL q2w	142	136	134	140	137	135	137	137	137	133	135	131	134	129	130	125	108
Dupilumab 300 mg q2w	272	265	261	258	253	254	255	255	248	246	244	237	241	242	230	231	204

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ vs matched placebo.

Options When My Patient Does Not Respond



Adherence with Asthma Therapy

- Inhaler use is confusing with differing devices and techniques
- Intentional nonadherence
  - Asthma only exists when symptoms noted
  - Underperceivers and overperceivers
  - Cost of therapy
  - Concern about side-effects
    - “Doctor, I do not want to use too much medicine.”
    - “Won’t I become addicted to this?”
    - “Does this have any side effects?”
- Most studies show small molecule use is about 60%
- Conflicting evidence relating adherence and exacerbations

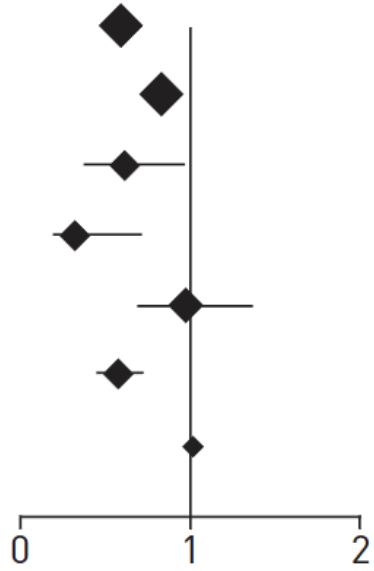
Medication adherence and the risk of severe asthma exacerbations: a systematic review

Marjolein Engelkes[1], Hettie M. Janssens[2], Johan C. de Jongste[2], Miriam C.J.M. Sturkenboom[1] and Katia M.C. Verhamme[1]

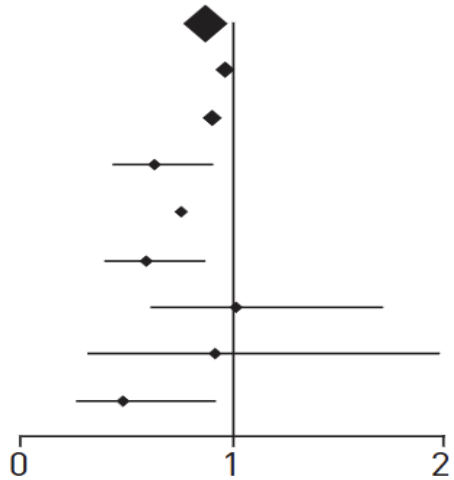
Eur Respiratory Journal 2015;45: 296-407

Good adherence tended to be associated with lower risk of severe asthma exacerbations. Future studies should use standardised methodology to assess adherence and exacerbations, and should consider inhaler competence.

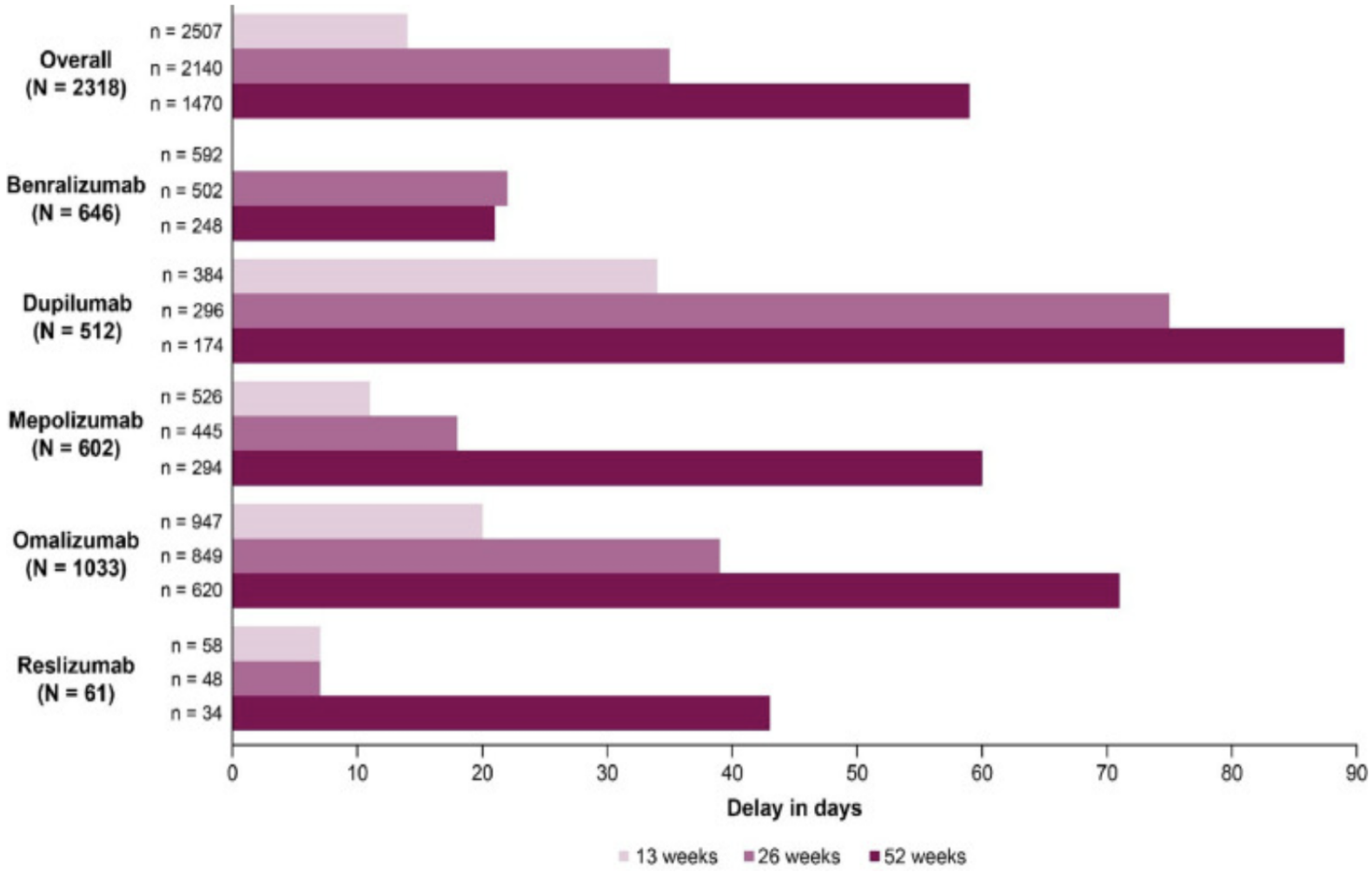
First author [ref.]	Quality score	Participants n	Design	Outcome	Adherence	OR
Rust [21]	8	43 166	Cohort	Hosp	CTR: <0.5 or >0.5	0.59
				ED	CTR: <0.5 or >0.5	0.83
Bukstein [23]	8	11 407	Cohort	Comb: ED/hosp	Prescriptions: ⩾2 *versus* 1	0.60
Camargo [22]	8	10 976	Cohort	Comb: ED/hosp	MPR: median (0.08) *versus* less	0.32
Herndon [26]	7	10 878	Cohort	Hosp	MPR: >50% *versus* <19%	0.96
				ED	MPR: >50% *versus* <19%	0.56
Elkout [25]	7	3 172	Cohort	OCS	MPR: 80–120% *versus* less	1.02



First author [ref.]	Quality score	Participants n	Design	Outcome	Adherence	OR
Stern [33]	8	97 743	Cohort	Comb: ED/hosp	MPR: 75th perc *versus* less	0.86
Delea [32]	8	12 907	Cohort	OCS	Mean MPR: +25%	0.97
				Comb: ED/hosp	Mean MPR: +25%	0.90
Balkrishnan [30]	8	751	Case–control	Comb: ED/hosp	Refills: 2 *versus* 0	0.62
Williams [29]	8	405	Cohort	OCS	Median CMA: +25%	RR 0.75
Williams [28]	8	298	Cohort	Comb: ED/hosp/OCS	MPR: >75% *versus* <25%	0.58
McMahon [34]	7	4535	Cohort	Hosp+OCS	Adh: 90 *versus* 1–89 days	1.02
				Hosp	Adh: 90 *versus* 1–89 days	0.91
Smith [35]	7	3013	Cohort	Comb: ED/hosp	MPR: >80% *versus* <50%	0.47

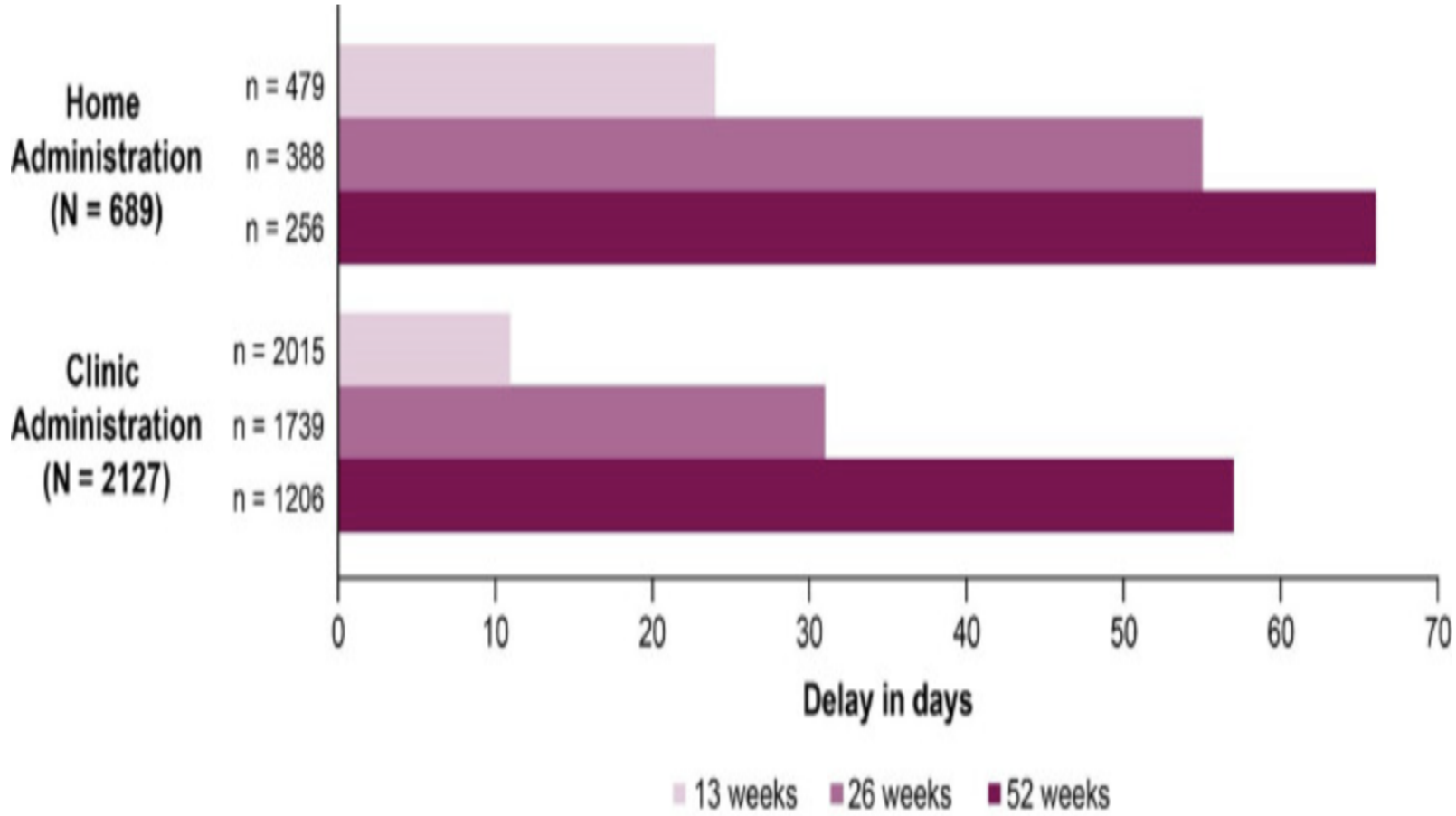


Adherence with Biologic Therapy



Annals Allergy Asthma Immunol 2023;131:598-605

Adherence with Biologic Therapy



Annals Allergy Asthma Immunol 2023;131:598-605

Reconsider Diagnosis and Address Co-Morbidities

- Asthma is a variable syndrome with symptoms and signs which overlap with many diseases or conditions
- Reversibility may be a treatable trait but may not be an accurate diagnostic test
- Therapeutic trials can be misleading
- Clinical trials typically exclude co-morbidities that contribute to symptom burden but patients with co-morbidities are the patients for whom we care

Common Asthma Mimickers/Comorbid Conditions

- Vocal cord dysfunction/Inducible laryngeal obstruction (VCD/ILO)
  - Laryngopharyngeal reflux (LPR)
- COPD
- Bronchiolitis
- Bronchiectasis
  - Cystic fibrosis
  - Allergic bronchopulmonary aspergillosis/fungosis
- Eosinophilic bronchitis

Reversibility

Prevalence, Diagnostic Utility and Associated Characteristics of Bronchodilator Responsiveness

Richard Beasley[1], Rod Hughes[2], Alvar Agusti[3], Peter Calverley[4], Bradley Chipps[5], Ricardo del Olmo[6], Alberto Papi[7], David Price[8,9], Helen Reddel[10,11], Hana Müllerová[12], and Eleni Rapsomaniki[12]

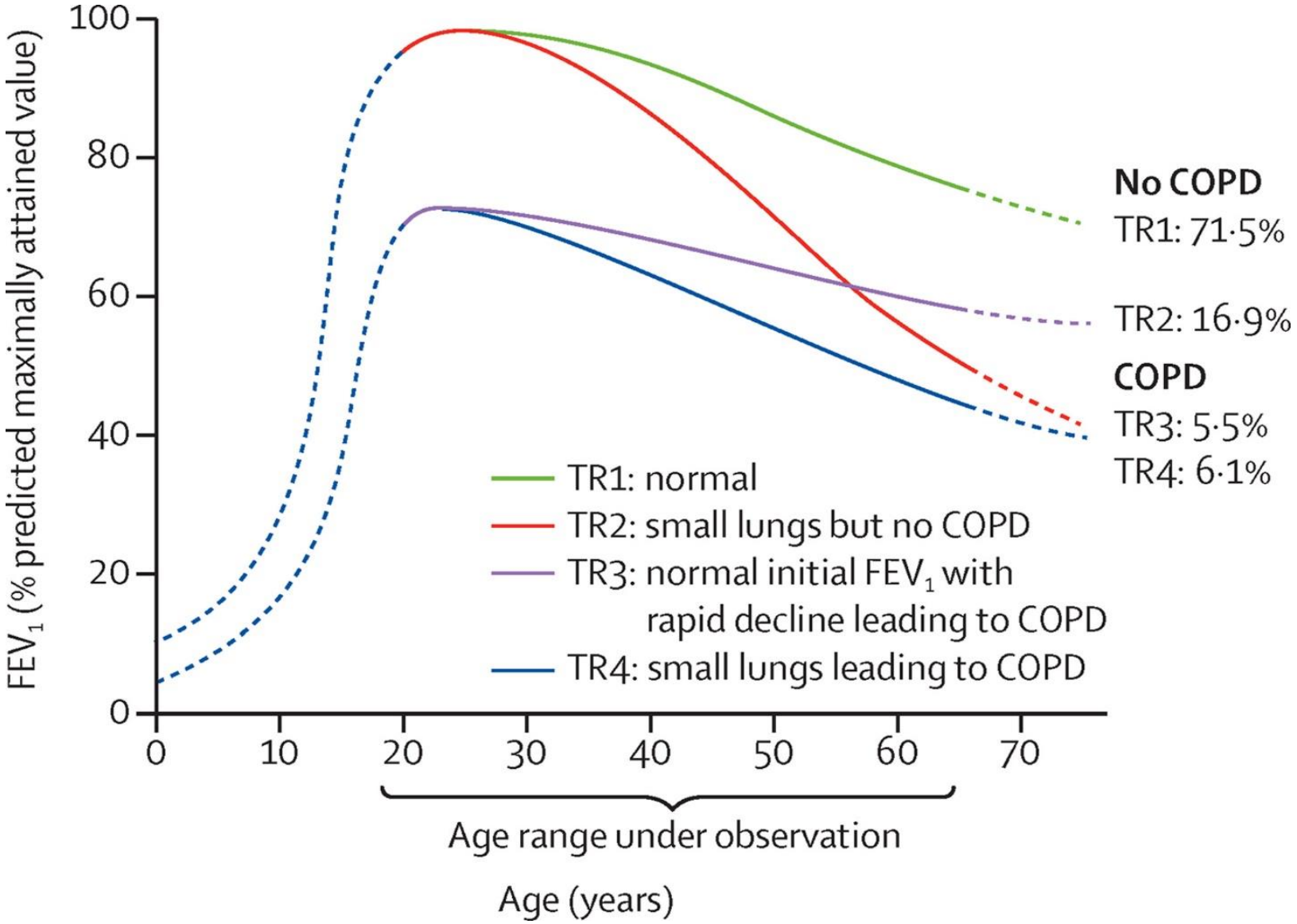
Am J Rev Resp Crit Care Med 2024

Novelty Study

2005 Criteria: **Increase FEV1 or FVC ≥12% and at least 200 ml**

2021 Criteria: **Increase FEV1 or FVC PREDICTED > 10%**

	2005	2021
Asthma (3519)	19.7%	18.1%
COPD (2436)	24.7%	18.0%
Asthma + COPD(833)	29.6%	23.3%


100
80
60
40
20
0
FEV1 (% predicted maximally attained value)
0
10
20
30
40
50
60
70
Age range under observation
Age (years)
TR1: normal
TR2: small lungs but no COPD
TR3: normal initial FEV1 with rapid decline leading to COPD
TR4: small lungs leading to COPD
No COPD
TR1: 71·5%
TR2: 16·9%
COPD
TR3: 5·5%
TR4: 6·1%

JACI The Journal of Allergy and Clinical Immunology

REVIEW ARTICLE · Articles in Press, November 12, 2024

Asthma and Respiratory Co-Morbidities

Dennis K. Ledford, MD [1] · Tae-Bum Kim, MD, PhD [2] · Victor E. Ortega, MD, PhD, ATSF [3] · Juan Carlos Cardet, MD, MPH [1]

What are the challenges in clinic?

- Asthma is common so it is likely other conditions will co-exist depending on age and circumstance
- Asthma is a clinical diagnosis without a test to prove (multiple phenotypes)
  - Airflow limitation shared with multiple conditions
  - Reversibility may not be a diagnostic test but a ‘treatable trait’ (Beasley Am J Resp Crit Care Med 2024)
  - Airway inflammation is not usually measured and is heterogeneous (Type 2, Type 1, Type 17, Paucigranular..)

What are the challenges in clinic?

- Asthma symptoms (cough, chest tightness, wheeze, mucous production) are shared by many conditions
- Asthma is variable making interpretation of spirometry difficult and therapeutic trials may be misleading as spontaneous improvement is misattributed to Rx
- Therapeutic trials ‘exclude’ patients with co-morbidities but it seems *every* patient in clinic has a co-morbidity
- Corticosteroids are effective for asthma but improve multiple conditions

Asthma Exacerbations

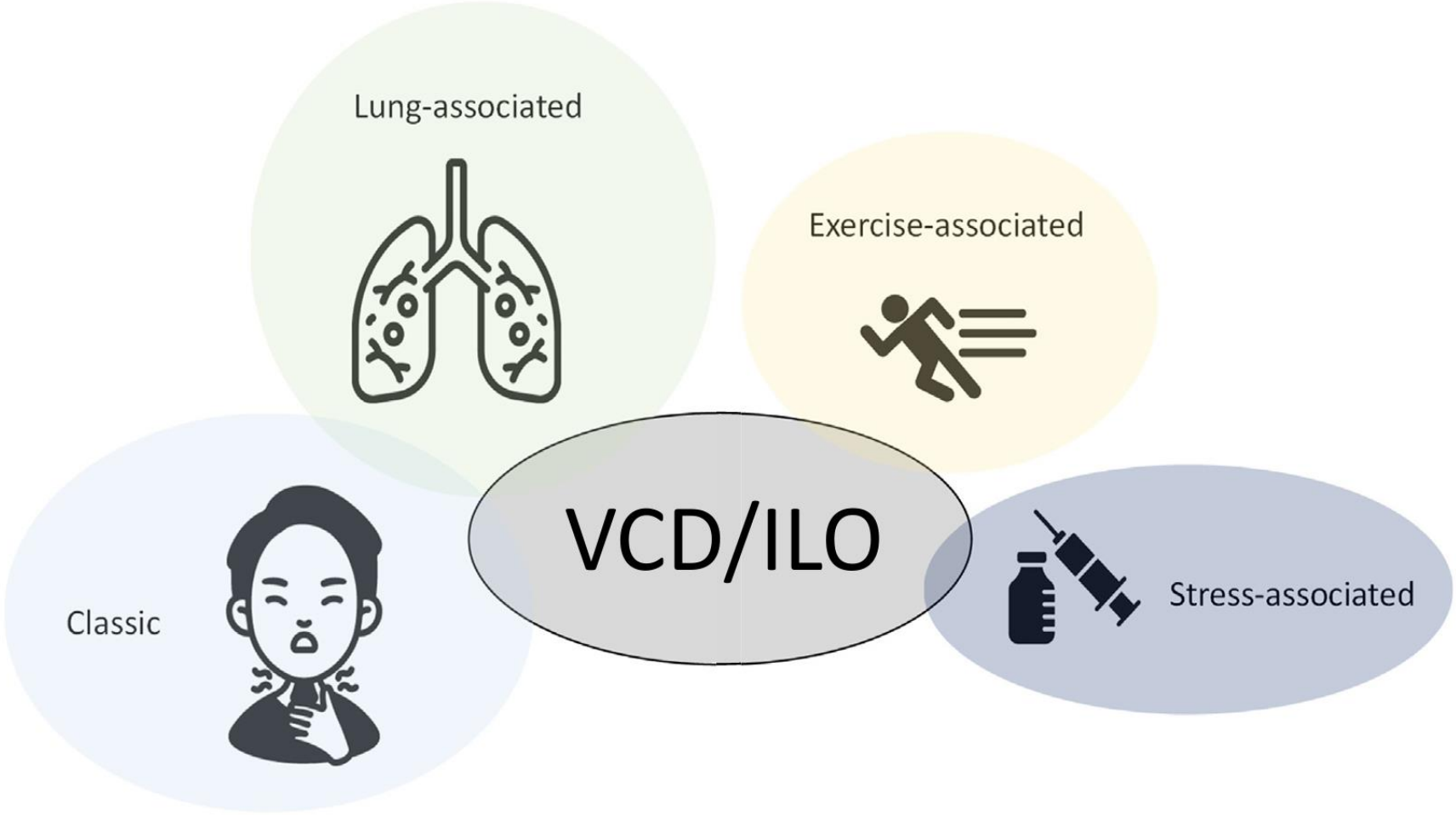
- Odds ratio (OR) associated with 3 exacerbations
  - a) Severe sinus disease, OR 3.7
  - b) GERD, OR 4.9
  - c) URIs, OR 6.9
  - d) Psychological dysfunction, OR 10.8
  - e) Obstructive sleep apnea, OR 3.4

- All patients with frequent exacerbations had 1/5 while 52% had 3/5

Brinke , et al. *Eur Respir J 2005; 26: 812.*

VCD/ILO

JACI 2024;154:1370



Vocal Cord Dysfunction Associations

- Irritation of larynx/hypopharynx (LPR)
- Dysfunctional breathing
- Psychological trauma (PTSD)
- Physical trauma/sexual abuse
- Throat or laryngeal injury
- Health care professional or family

Diagnosis of LPR/VCD

- No consensus
- Suspect in persistent complaints particularly with laryngeal wheeze, paroxysmal wheeze, SOB not consistent with spirometry
- Spirometry with inspiratory flattening
- Visualization of larynx essential with fiberoptic rhinolaryngoscopy, do not treat hoarseness without visualization (findings are variable with time/scoring systems of ?value)
- GERD evaluation a consideration (pH probe, impedance, barium swallow, esophageal endoscopy) but likely therapeutic trial first

Bronchiectasis

- May be restrictive, obstructive or mixed
- Reversibility variable
- CT imaging with **1-1.5 mm** reconstruction (high resolution) necessary to confirm
- Mucous production typical, usually discolored
- Up to 50% of severe, eosinophilic asthma have bronchiectasis (JACI Global 2023;2:36-42, JACI Practice 2021;9:3188-3195)
- Consider humoral immunodeficiency

Bronchiectasis

- Antibiotic therapy likely helpful, oral & nebulized
- Physical measures to help with mucous clearance
- Consider ciliary evaluation (low FeNO)
- ABPA and CF in differential
- Neutrophil peptidase inhibitors may be useful in future (dipeptidyl peptidase 1) [ERJ Open Res 2024, Eur Resp J 2024]
- Sputum culture + for *P. aeruginosa, Stenotrophomonas maltophilia, H. influenza, A. fumigatus*

ABPA

- Typical more central bronchiectasis rather than lower lobe (not always)
- IgE > 500 kU/L
- Variable, fleeting infiltrates, mucous plugging, specific IgG and IgE for fungal organisms (which ones?)
- Corticosteroid therapy, antifungal therapy for 3 months, ?type 2 biologic Rx (not approved)

ABPA

- Monitor IgE, should decrease by at least 33% with systemic CS and an increase of 50% suggests exacerbation
- Always consider CF

Cystic Fibrosis

- Highly variable presentation and may not have GI features
- CF and asthma may co-exist (CFAOS)
- Asthma in CF registry is over 30%, possibly due to selection bias
- ICS responsiveness suggests CFAOS
- ABPA and bronchiectasis suggests CF
- Genetic testing may be less reliable in people of color

Bronchiolits With or Without Pneumonia

- Smoking related v Collagen vascular disease v Post infectious
  - 90% of biopsied lungs from cigarette smokers
  - *Mycoplasma pneumonia*
  - Drug induced (sulfasalazine, oncologic therpies)
  - Eosinophilic bronchitis and asthma
- Usually results in restrictive pattern but there are obstructive presentations
- Associated with RA and other connective tissue/autoimmune disease, usually obliterative bronchioloitis
- High resolution CT of chest (<1 mm cuts) important
  - May have ground glass changes
- Diffusion capacity usually reduced

Eosinophilic Bronchitis

- No other atopic features
- No airway hyperreactivity
- May have increased FeNO
- Respond to CS but somewhat less than asthma
- Increase in connective tissue disease
- Consider ANCA, HES, parasitic disease, drug causation (NSAID, minocycline, macrodantin, anticonvulsants)

Hypersensitivity pneumonitis

- Chronic disease almost always provides restrictive and not obstructive features
- Chronic disease may occur with low level exposure without acute exacerbations
  - Parakeets or other birds
  - Buckwheat pillows
  - Hot tubes
  - Humidifiers or dehumidifiers
  - Life guards

Switch Biologics or Modify Dose

- Options are limited due to overlap in pathways treated
- Generally switch from one class of inhibitor to another
  - IgE: omalizumab
  - IL-5: benralizumab, mepolizumab, reslizumab
  - IL-4/IL-13: dupilumab
  - TSLP/Alarmin: Tezepelumab
- Weight based dosing
- Limited options with dosing due to package label, cost and lack of data

Switch from Resilzumab to Mepolizumab

Frontiers Allergy 2023

TABLE 3 Comparing the mean values of the five clinical parameters measured in this study 1 year before switching from reslizumab to mepolizumab to the mean values of the same parameters 6 months after switching.

Clinical Parameter Mepolizumab $n = 8$	1-year pre switch, Mean (SD)	6 months post switch, Mean (SD)	*p*-value
Hospital admissions (adjusted)	0.06 (0.18)	0	0.33
Exacerbations	0.44 (0.62)	0.13 (0.36)	0.24
Maintenance OCS dose (mg)	2.5 (5.18)	2.5 (5.18)	–
FEV_1 (%), $n = 7$	78.8 (26.4)	67.6 (28.8)	*0.02*
ACQ score	1.6 (1.6)	1.5 (1.4)	0.43

J Asthma Allergy. 2020 Nov 11:13:605-614. doi: 10.2147/JAA.S270298. eCollection 2020.

Switch from IL-5 to IL-5-Receptor α Antibody Treatment in Severe Eosinophilic Asthma

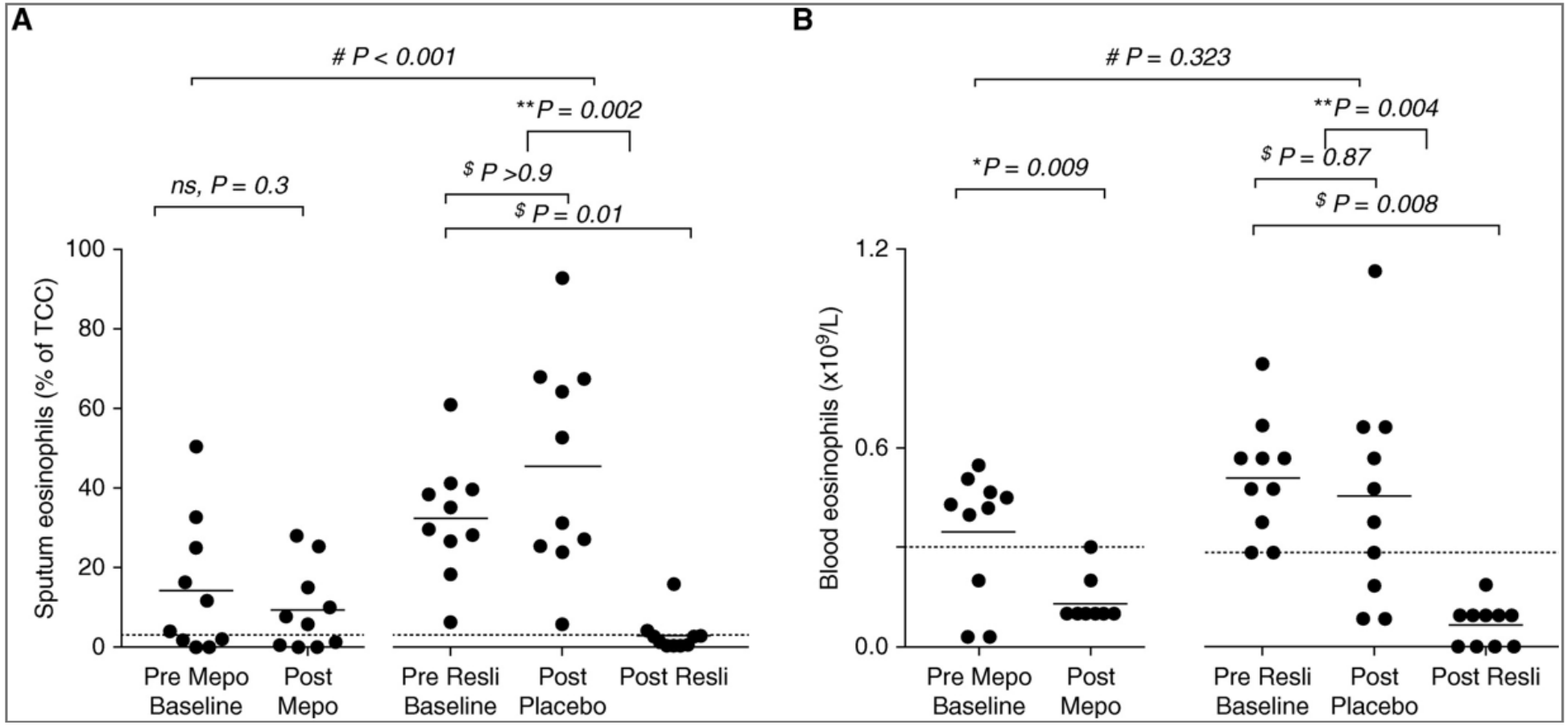
Conclusion: Switching from anti-IL-5 to anti-IL-5Rα therapy in patients with inadequate response was associated with significantly improved FEV_1, asthma control and OCS reduction.

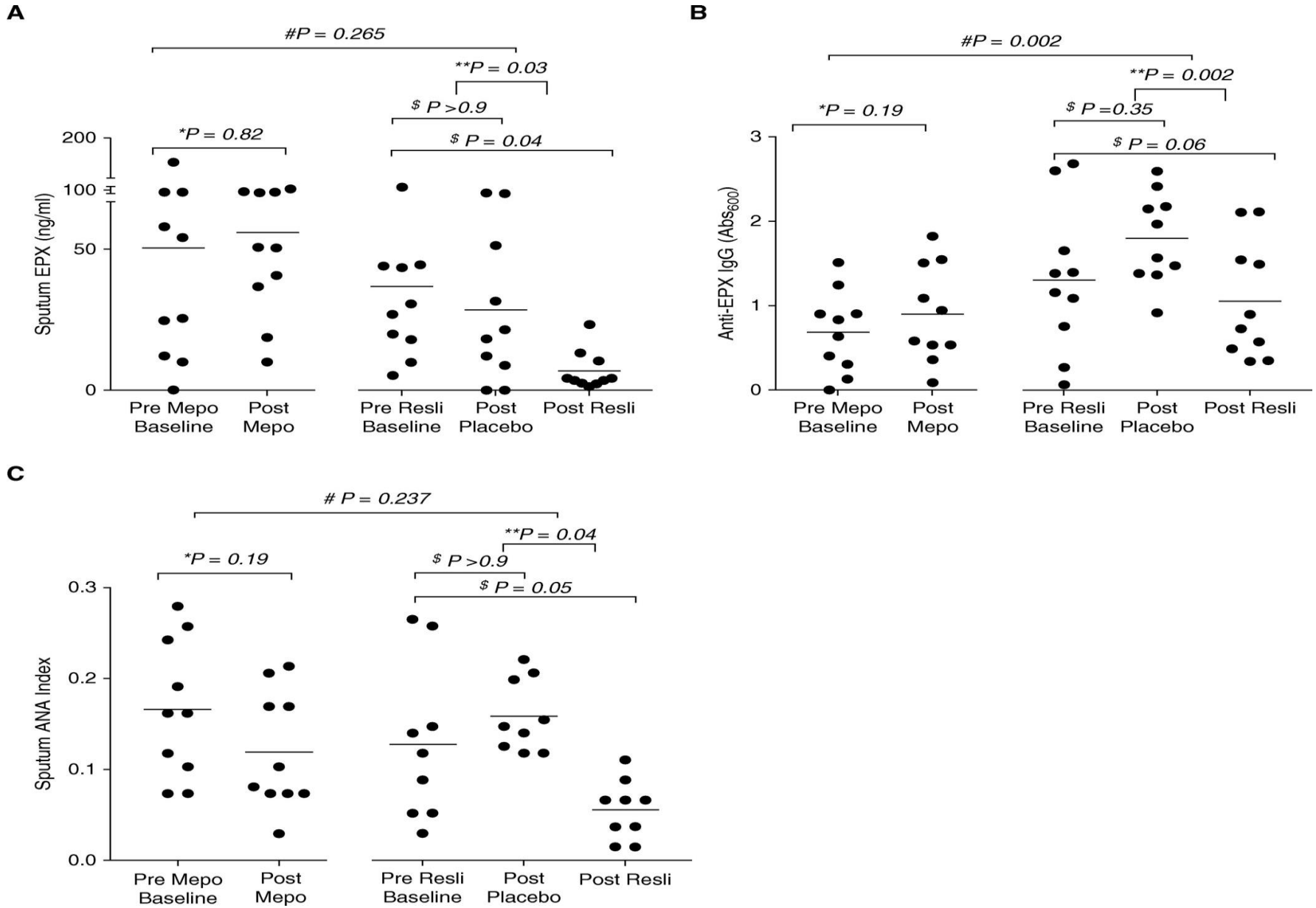
J Allergy Clin Immunol Pract. 2021 Mar;9(3):1194-1200. doi: 10.1016/j.jaip.2020.10.010. Epub 2020 Oct 15.

Long-Term Therapy Response to Anti-IL-5 Biologics in Severe Asthma-A Real-Life Evaluation

Results: After 2-year anti-IL-5 treatment, 14% of patients were super responders, 69% partial responders, and 11% nonresponders. Super response was predicted by shorter asthma duration and higher FEV_1, and tended to be associated with adult-onset asthma, absence of nasal polyps, and lower body mass index. Switches between anti-IL-5 biologics occurred frequently (41%). After 2-year treatment, most common residual disease manifestations included impaired lung function (59%), uncontrolled sinonasal disease (58%), and uncontrolled asthma symptoms (48%).

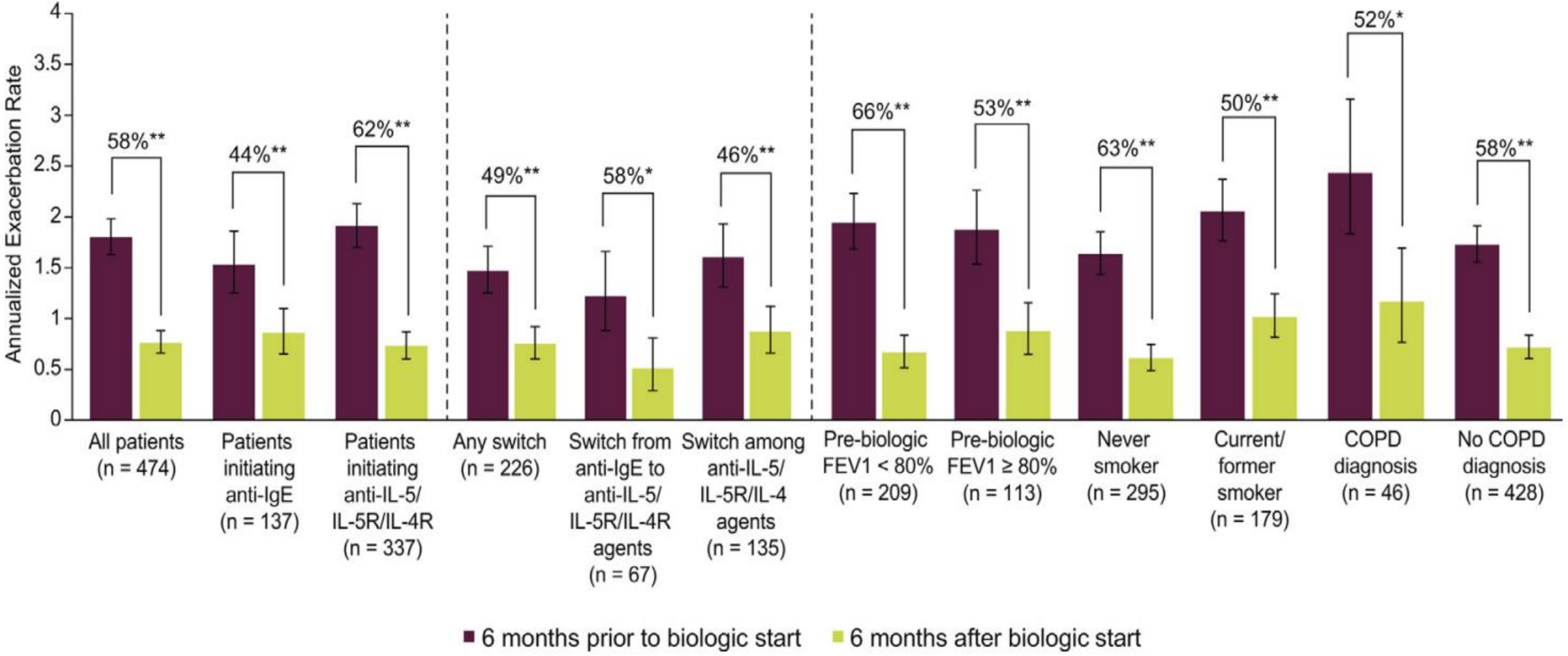
Weight-adjusted IV reslizumab in severe asthma with inadequate response to fixed-dose SQ mepolizumab. AJRCCM 2017 doi: 28915080




A
#P = 0.265
**P = 0.03
$ P >0.9
*P = 0.82
$ P = 0.04
200
100
50
0
Sputum EPX (ng/ml)
Pre Mepo Baseline
Post Mepo
Pre Resli Baseline
Post Placebo
Post Resli
B
#P = 0.002
**P = 0.002
*P = 0.19
$ P =0.35
$ P = 0.06
3
2
1
0
Anti-EPX IgG (Abs600)
Pre Mepo Baseline
Post Mepo
Pre Resli Baseline
Post Placebo
Post Resli
C
P = 0.237
**P = 0.04
*P = 0.19
$ P >0.9
$ P = 0.05
0.3
0.2
0.1
0.0
Sputum ANA Index
Pre Mepo Baseline
Post Mepo
Pre Resli Baseline
Post Placebo
Post Resli

AJRCCM 2017

Asthma Biologic Switch



Ann Allergy Asthma Immunol 2022:467-474

Alternative Therapies for Asthma

- Current Considerations
  - Macrolide antibiotics
  - Alternative bronchodilators/anti-inflammatory therapy
    - PDE4 inhibitors (Roflumilast)
    - Theophylline (‘low dose’)
- Future Considerations
  - Mast cell signaling inhibitors
  - Mast cell depleting strategies
  - Alternative anti-inflammatories (Cathepsin G Inhibitors, anti-IL6)
  - Mucous suppression
  - Smooth muscle regulators

Test Considerations in Difficult to Treat Asthma

- Asthma biomarkers (Blood eosinophils, specific and total IgE, FeNO)
- Quantitative immunoglobulins
- Review history (age of onset, atopic features)
- Alpha-1-antitrypsin
- Consider CF evaluation (genetic testing less reliable in people of color)
- High resolution CT of chest
- Sleep study and evaluation for pulmonary HBP

Options When My Patient Does Not Respond