Biologics 처방해보기

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Lessons from patients with severe asthma

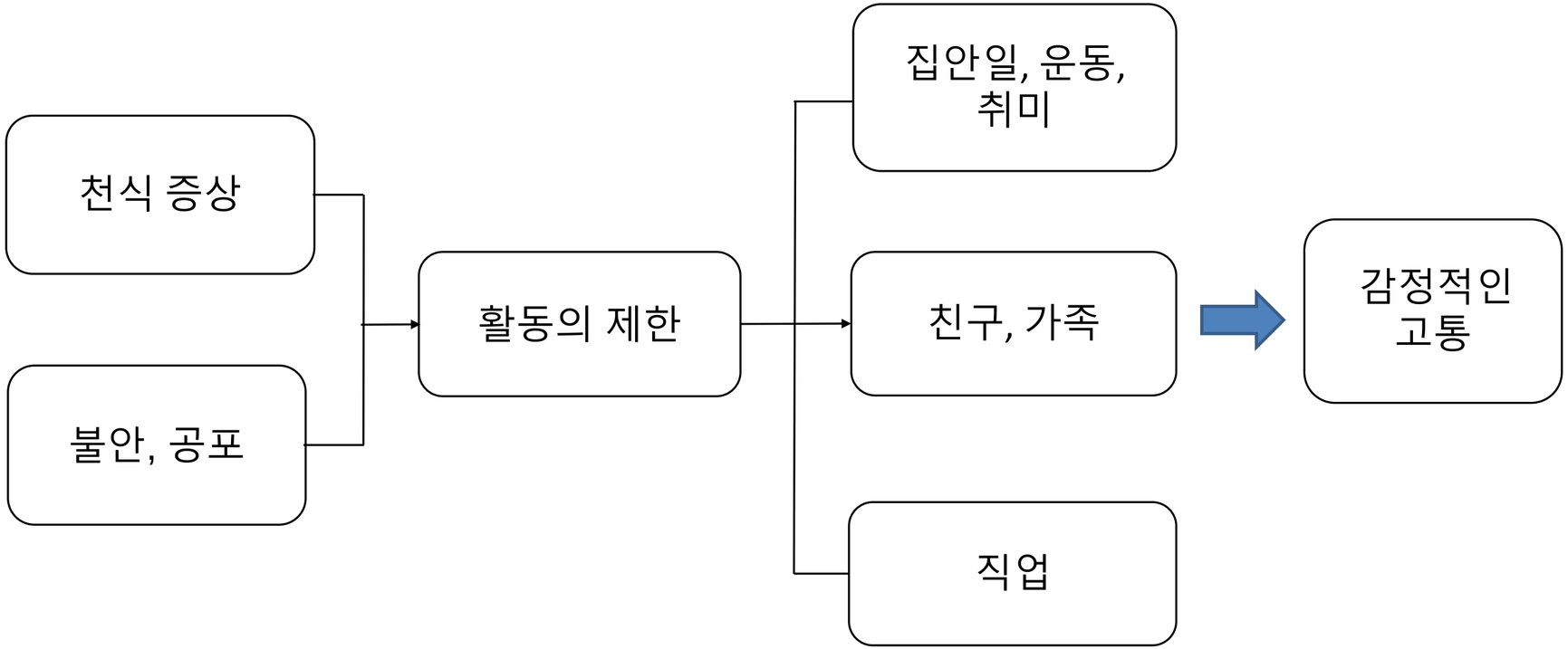
- 중증 천식 대상 환자 찾기
- 중증 천식: 기존의 천식과는 다른 질환으로 이해할 필요성 (의사, 환자, 사회)
- Biologics 사용의 필요성을 설명 (or 설득)
- 환자로부터의 긍정적인 피드백 (“처음으로 등산을 다녀왔어요”)
- 처방까지 많은 노력이 필요하지만, 일단 효과를 경험하면… (to be continued)

Contents

- Burden of severe asthma
- Assessment of severe asthma
- Treatment goals of biologics
- Cases
  - Biologic treatment eligibility
  - Selection of biologics
  - Switching biologics

Disease burden of severe asthma

- *Qualitative studies*

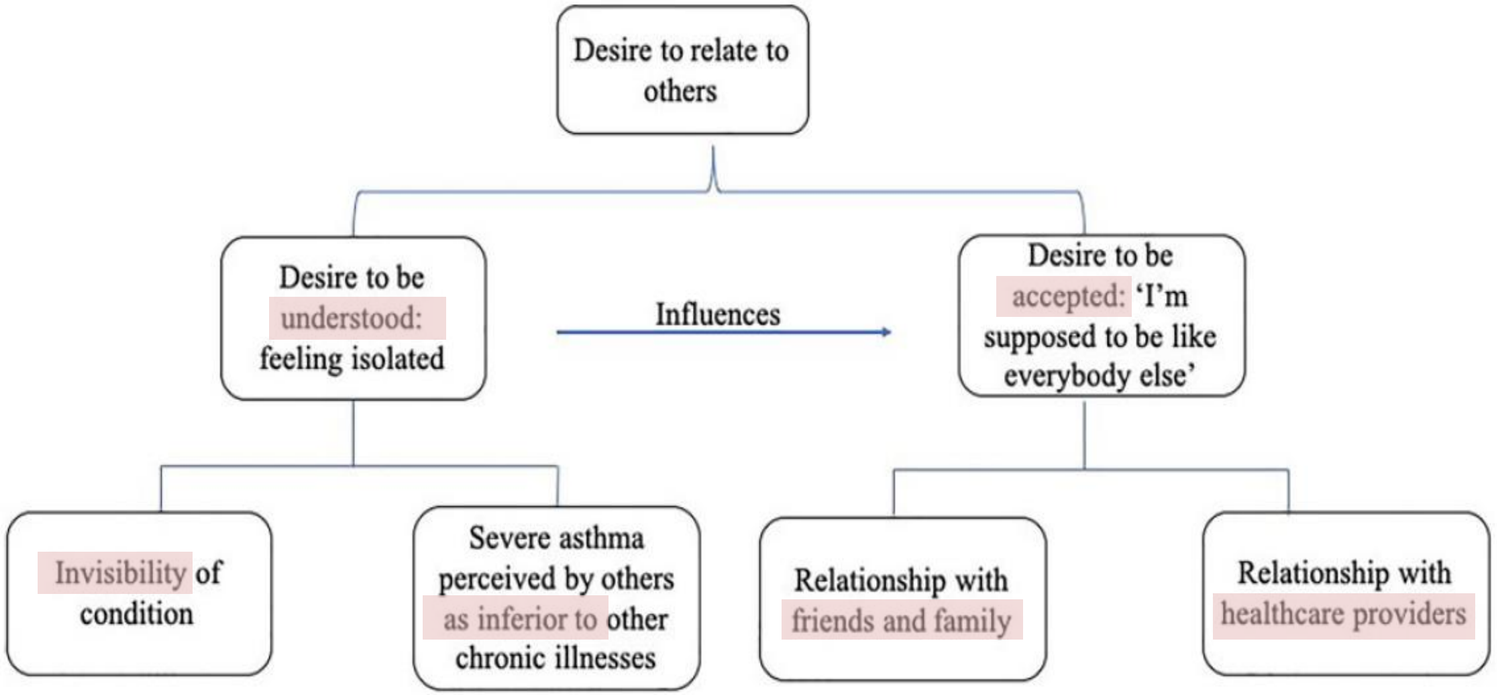


- 쓸모 없다는 느낌, 소외, 절망, 좌절, 죄책감, 분노

Apps LD et al. J Allergy Clin Immunol Pract 2019;7:2613-21.
Foster JM et al. Eur Respir J 2017;50:1700765.

Disease burden of severe asthma

- *Qualitative studies*



- 중증 천식에 대한 **이해**와 **공감** 부족 (환자, 의사, 가까운 인간관계, 사회)

Eassey D et al. J Asthma 2021;58:1-9.

Disease burden of severe asthma

- *Qualitative studies (Korea)*

TABLE 6 Theme cluster 4: perception of severe asthma

Theme 4.1: gaps in disease perception among patients

"I suffered from severe cold last month" (Patient 6)

"There is nothing more important than this (asthma). But I may look fine to them. Then, who will accept it as a disability?" (Patient 11)

Theme 4.2: gaps between patients and health professionals

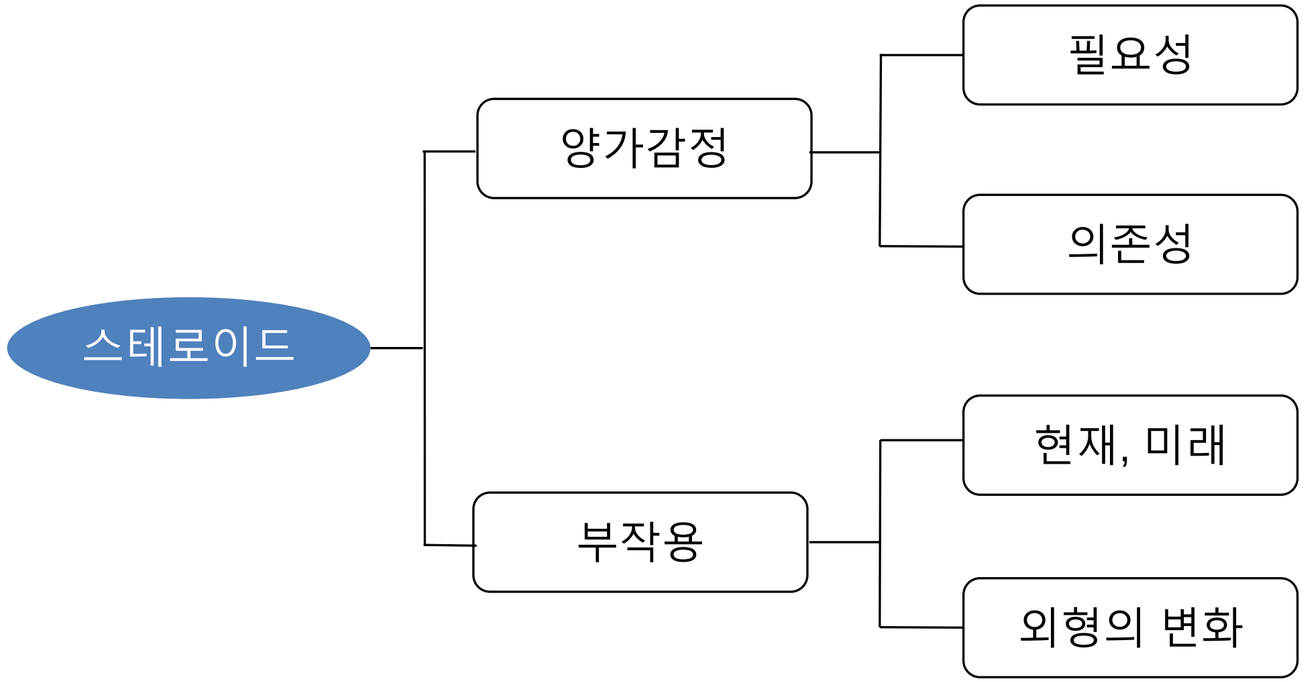
"I have not heard about severe asthma... I guess that my doctor made the diagnosis (of severe asthma) for my severe bronchitis" (Patient 5)

- Few of patients clearly recognized that they had severe asthma.
  - Most participants were unfamiliar with the term "severe asthma"
  - Little opportunity to get information about severe asthma.

Song WJ et al. ERJ Open Res 2021;7:00528.

Treatment burden of severe asthma

- *Qualitative studies*



- OCS의 효과, 필요성, 의존성, **부작용**에 대한 걱정

Foster JM et al. Eur Respir J 2017;50:1700765.

Treatment burden of severe asthma

Q. Ultimately, what led your decision not to take biologic therapies?

My **insurance company** wouldn't pay for it and I couldn't afford the out-of-pocket with the whole price.
Cost, how it would be, you know…
Cost I would say…

- Biologics를 사용하지 못하거나, 중단하는 이유 (**비용**)

Gelhorn HL et al. Patient Prefer Adherence 2019;13:1253-68.

Assessment of severe asthma

Questionnaire	Item	Symptom	Activity limitation	Emotional impact
ACQ	7	++	+	-
AQLQ	32	+++	+++	+
SGRQ	50	+++	+++	+
SAQ	16	+	+++	++

Asthma Control Questionnaire (ACQ),
Asthma Quality of Life Questionnaire (AQLQ)
St. George's Respiratory Questionnaire (SGRQ),
Severe Asthma Questionnaire (SAQ)

- Need for multidimensional assessment
- Patients’ satisfaction > modest improvement in quality of life questionnaire of RCT

Clark VL et al. J Asthma Allergy 2021;14:245-258.

Severe Asthma Questionnaire

1. My social life. For example, visiting friends, walking with friends, talking with friends, going to bars/restaurants, and parties.
2. My personal life. For example, washing, dressing, looking after myself, love life.
3. My leisure activities. For example, walking for pleasure, sports, exercise, travelling, taking vacations.
4. My jobs around the house. For example, housework, shopping, home maintenance, gardening.
5. My work or education. For example, missing days, can't do all I want to do.
6. My family life – how it affects me. For example, caring for children, family responsibilities.
7. My family life – how it affects others. For example, others taking time off work, problems with childcare, family members becoming upset.
8. Depression. For example, feeling sad, fed up, blue.
9. Irritable. For example, snap at people, get angrier than I should.
10. Anxiety in general. For example, worry about things, always on edge.
11. Worry that asthma may get worse. For example, medicines no longer help, more frequent attacks.
12. Worry about long-term side effects of medicines. For example, worry about cataracts, diabetes, bone fracture.
13. Getting tired. For example, feeling tired for no reason, waking in the morning feeling tired.
14. Problems at night. For example, difficulty going to sleep, being woken very easily, waking often at night.
15. The way I look. For example, my weight, my skin bruises easily, using medicines in public, other people judging me
16. Problems with food. For example, I find I get very hungry, I just can't stop eating, stomach problems (*e.g.* pain, bloating, etc.)

#: interpretation of mean in relation to quality of life, 1=very, very difficult (worst possible); 2=very difficult; 3=difficult; 4=moderately difficult; 5=slightly difficult; 6=very slightly difficult (just noticeable); 7=no problem.

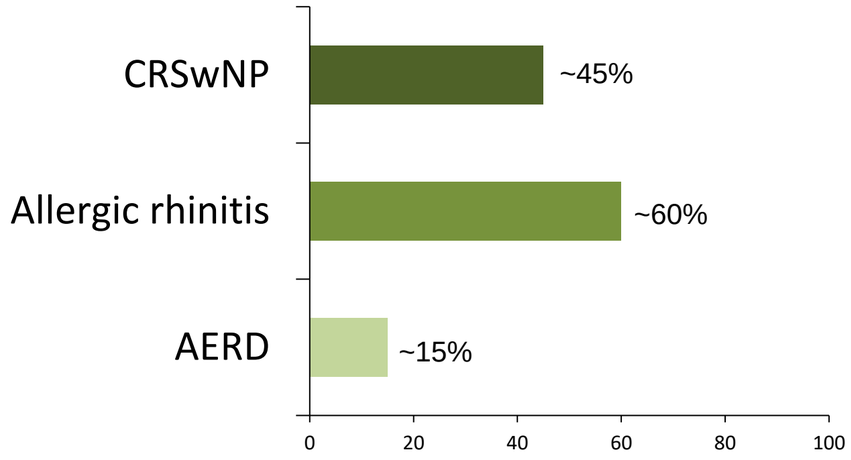
Hyland ME et al. Eur Respir J 2018;52:1800618.

Assessment of comorbidity

- *Chronic rhinosinusitis with nasal polyp (CRSwNP)*

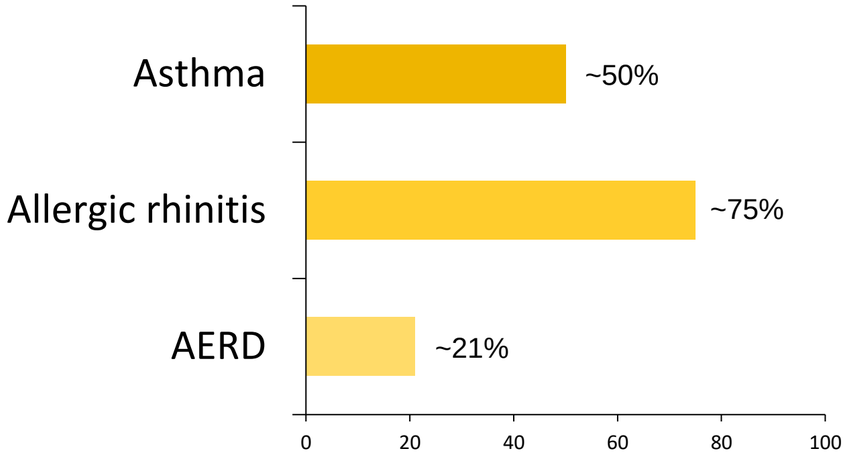
- **Asthma** often coexists with other type 2 inflammatory diseases

  Proportion of severe asthma patients with coexisting disease



- **CRSwNP** often coexists with other type 2 inflammatory diseases

  Proportion of CRSwNP patients with coexisting disease



Heffler E et al. J Allergy Clin Immunol Pract 2019;7:1462-1468.
Khan A et al. Rhinology 2019;57:32-42.

Assessment of comorbidity

- *Allergic bronchopulmonary aspergillosis (ABPA)*

  - GINA guideline for assessment of severe asthma
    - Consider **fungal precipitins and/or HRCT**
    - Consider AERD, **ABPA**, chronic rhinosinusitis, nasal polyposis, atopic dermatitis

- **Modified ISHAM criteria**

  Presence of all the following:

  1. Asthma.
  2. Aspergillus-specific IgE > 0.35 kUA/L
  3. **Serum total IgE > 500 IU/mL (← > 1000 IU/mL)**

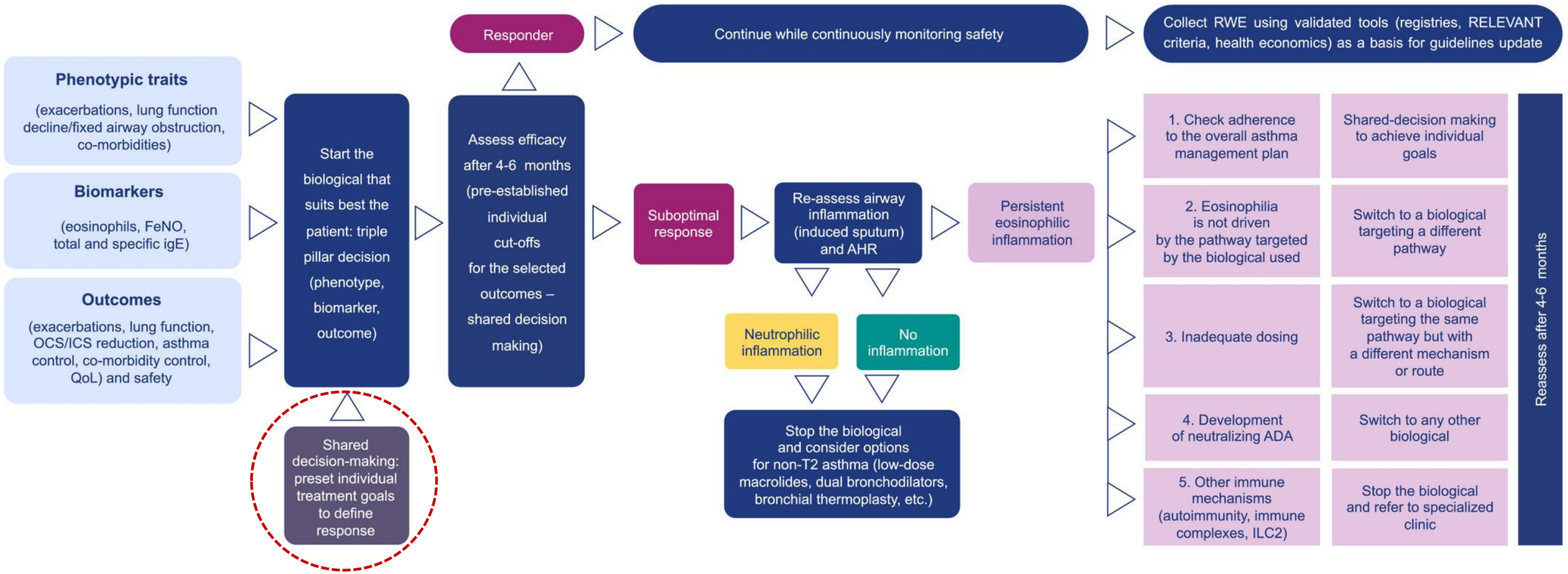
  And at least 2 of the following:

  1. A. fumigatus specific IgG > 27 mgA/L
  2. **Bronchiectasis on CT chest (← chest radiograph favoring ABPA)**
  3. Peripheral blood eosinophilia > 500 cells/µL.

Saxena P et al. J Allergy Clin Immunol Pract 2021;9:328-35.

Treatment goals

EAACI guideline



✓ Preset individual treatment goals to define treatment response

Agache I et al. Allergy 2021;76:14-44.

Treatment goals

- No defined criteria for a good response.

Outcome	Importance
Severe asthma exacerbations Asthma control Quality of life Safety (adverse events)	Critical
Lung function (FEV_1) Decrease in ICS dose and OCS dose Rescue medication use	Important
FeNO, sputum and blood eosinophils	Low importance

✓ Preset individual treatment goals to define treatment response

Agache I et al. Allergy 2021;76:14-44.

Case 1

- 34/F, C.C: dyspnea
- Allergic rhinitis (5 years)
- Total IgE: 245 IU/mL

  Specific IgE to Dp/Df: 18.8/25.0, Cat 9.7, Dog 6.3, Birch 1.9 IU/mL

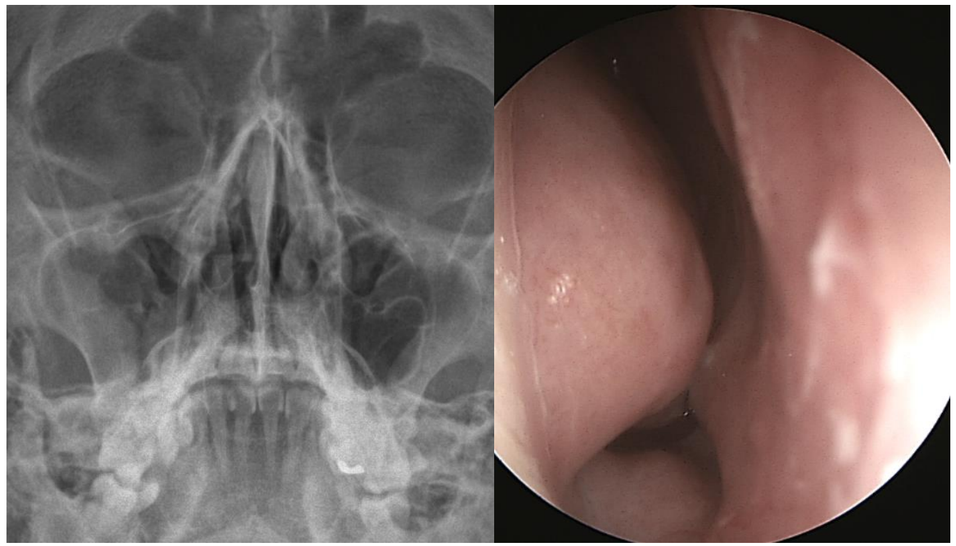
  Blood eosinophils: 980/μL

  FeNO: 99 ppb

  MPT: PC20=0.1 mg/mL
- Allergic asthma with CRScNP

  : Eosinophilic + atopic
- Uncontrolled asthma and allergic rhinitis

  : Consider add-on biologics



Case 1

- Omalizumab 300mg SQ start

4th 50% 정도의 증상 호전

5th **Spirometry**

		(BTPS) PRED	PRE-RX BEST	PRE-RX %PRED	POST-RX BEST	POST-RX %PRED
FVC	Liters	3.71	3.75	101	4.02	108
FEV1	Liters	2.92	2.69	92	3.08	105
FEV1/FVC	%	78	72		76	

FeNO: 153 ppb

6th **Spirometry**

		(BTPS) PRED	PRE-RX BEST	PRE-RX %PRED	POST-RX BEST	POST-RX %PRED
FVC	Liters	3.71	2.63	71	2.75	74
FEV1	Liters	2.92	1.48	51	1.56	54
FEV1/FVC	%	78	56		57	

→ 매일 야간 증상과 쌕쌕거림, 가래
OCS 효과 있으나, 중단 후 계속 증상 발생

Case 1

- Dupilumab 300mg SQ monthly start ↔ 초회 용량 600 mg투여 후 유지 용량으로 300 mg을 2주 간격

1st “많이 좋아졌어요” (ACT 5 → 22)

4th “완벽했어요” (OCS withdrawal, ACT 25)

6th Monthly injection

2개월 간격으로 연장

7th

Spirometry

	(BTPS)	PRED	PRE-RX BEST	PRE-RX %PRED	POST-RX BEST	POST-RX %PRED
FVC	Liters	3.71	4.19	113	4.07	110
FEV1	Liters	2.92	3.24	111	3.32	114
FEV1/FVC	%	78	77		82	

FeNO: 58 ppb

→ 비염 증상 있으나 천식 증상 조절되어 OCS 없이 유지

Biologic treatment eligibility

- *Eligibility criteria*

Anti-IgE

Is the patient eligible for anti-IgE for severe allergic asthma?
- **Sensitization** on skin prick testing or specific IgE
- Total serum IgE and weight within dosage range
- Exacerbations in last year

Anti-IL5/Anti-IL5R

Is the patient eligible for anti-IL5/anti-IL5R for severe eosinophilic asthma?
- Exacerbations in last year
- **Blood eosinophils**, e.g. ≥150/µL or ≥300/µL

Anti-IL4R

Is the patient eligible for anti-IL4R for severe eosinophilic/Type 2 asthma?
- Exacerbations in last year
- **Blood eosinophils:**150/µL − 1500/µL or **FeNO** ≥25 ppb or taking **maintenance OCS**

Predictor of good response to anti-IgE?
- Blood eosinophils ≥260/µL ++
- FeNO ≥20 ppb +
- Allergen-driven symptoms +
- Childhood-onset asthma +

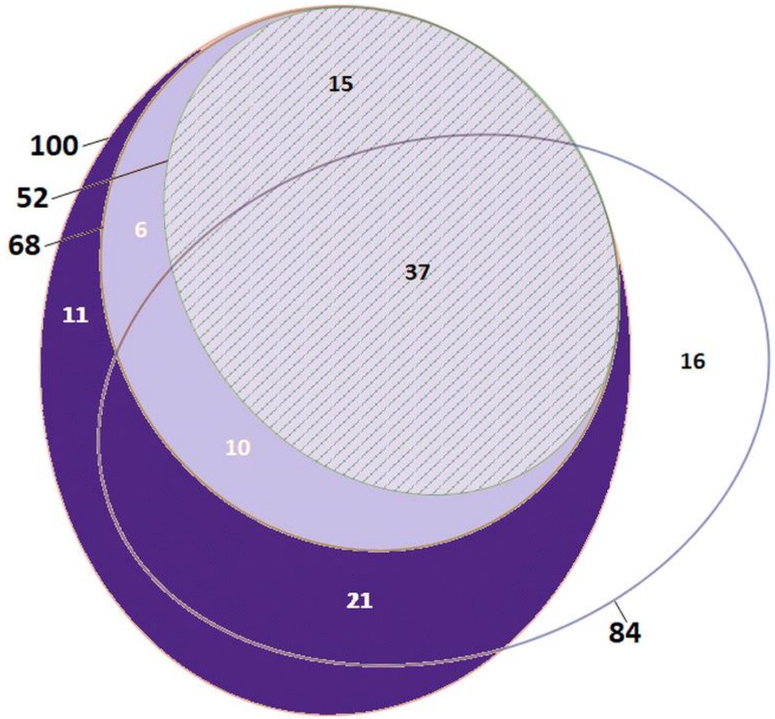
Predictor of good response to anti-IL5/5R?
- Higher blood eosinophils +++
- More exacerbations in previous year +++
- Adult-onset of asthma ++
- Nasal polyposis ++

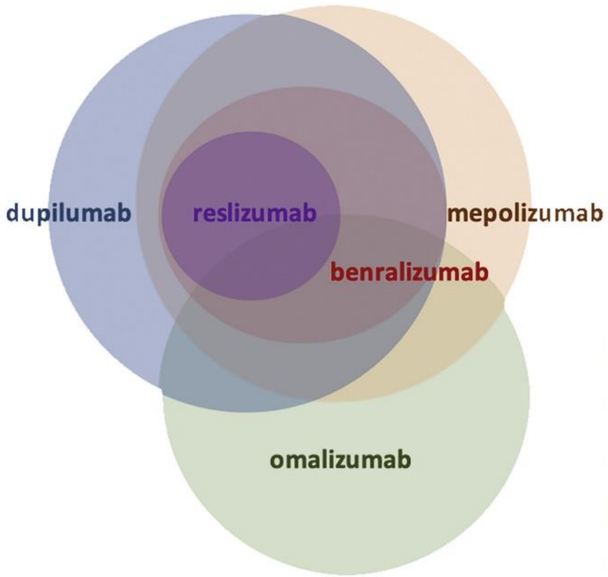
Predictor of good response to anti-IL4R?
- Higher blood eosinophils +++
- Higher FeNO+++

Choose one if eligible; trial for at least 4 months and assess response

Biologic treatment eligibility

- 68 (53%) patients were eligible for both omalizumab and mepolizumab.





	Omalizumab	Dupilumab	Mepolizumab	Benralizumab	Reslizumab
Omalizumab		79%	73%	44%	16%
Dupilumab	44%		91%	55%	22%
Mepolizumab	44%	93%		56%	21%
Benralizumab	39%	100%	100%		40%
Reslizumab	37%	100%	100%	100%	

Jeimy S et al. Allergy Asthma Clin Immunol 2018;14:68
Akenroye A et al. J Allergy Clin Immunol 2020;145:1295-1297.

Indication of biologics in Korea

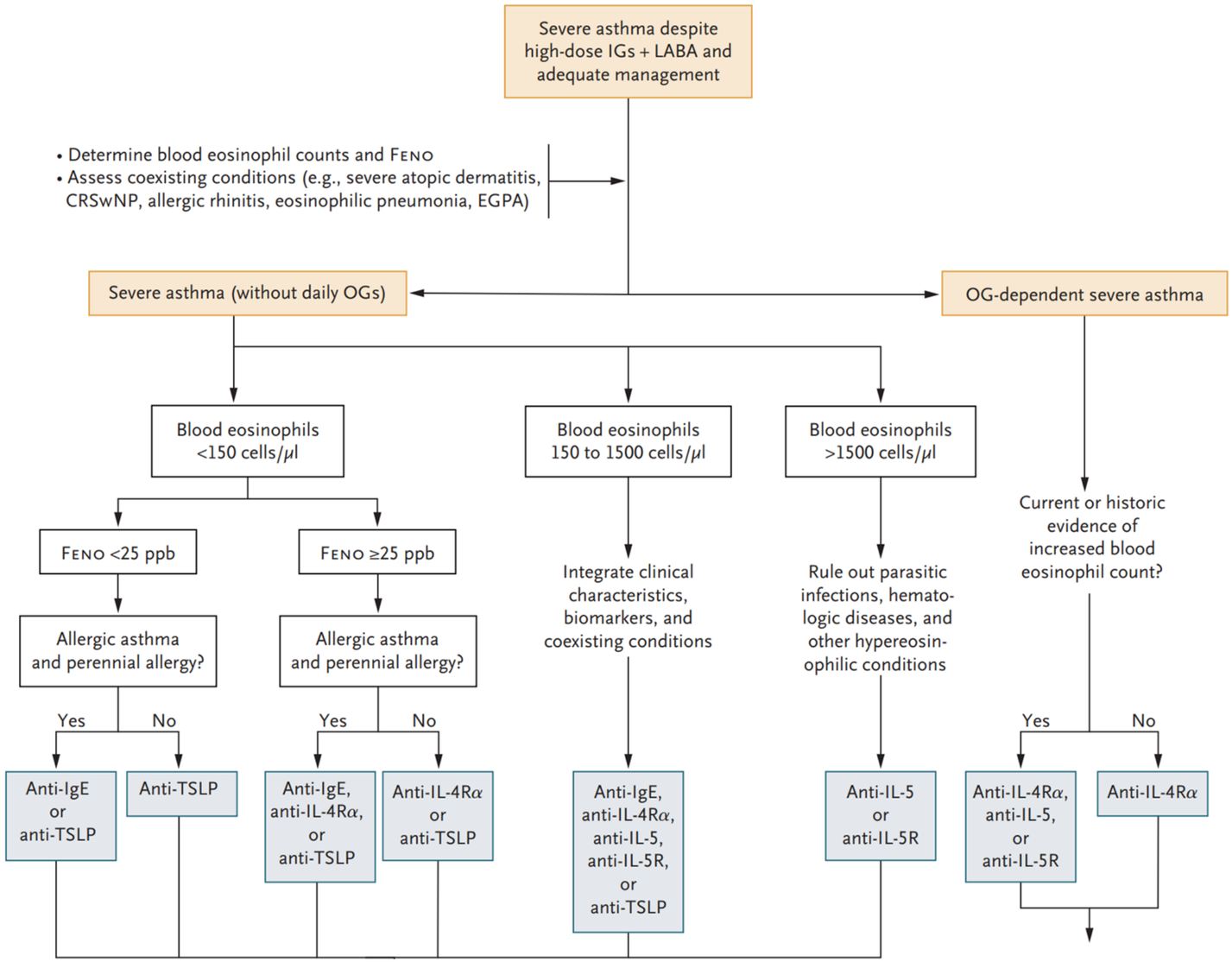
- Omalizumab is the only drug approved for insurance coverage of severe asthma.

보험급여기준

성인 및 청소년(만 12세 이상): 알레르기성 중증 지속성 천식 환자 중 **고용량의 흡입용 코르티코스테로이드-장기지속형 흡입용 베타2 작용제** (ICS-LABA)와 **장기지속형 무스카린 길항제**(LAMA-스피리바 레스피멧)의 투여에도 불구하고 적절하게 조절이 되지 않는 경우로서 다음의 조건을 **모두 만족**하는 경우

- 다음 -
(1) 치료 시작 전 면역글로불린 E의 수치가 76 IU/mL 이상
(2) 통년성 대기 알러젠에 대하여 시험관 내(in vitro) 반응 또는 피부반응 양성
(3) FEV_1 (1초 강제호기량) 값이 예상 정상치의 80% 미만
(4) 치료 시작 전 12개월 이내에 전신 코르티코스테로이드가 요구되는 천식 급성악화가 2회 이상 발생한 경우

Selection of biologics



Listed in alphabetical (and numerical) order

Brusselle GG et al. N Engl J Med 2022;386:157-171.

Indirect comparison of biologics

Study	Comparison	Population	Methodology	Findings: Exacerbations (rate ratio for first named)	Findings: FEV_1 (L)	Comments
Cockle et al[28]	Mepolizumab vs omalizumab	RCT in patients with severe asthma and an exacerbation history. Overlap (eligible for both) and trial population. No biomarker matching	Indirect treatment comparison (Bayesian framework)	Overlap: Rate ratio 0.66 (0.37, 1.19) Trial: Rate ratio 0.63 (0.45, 0.89)	Overlap: −0.1 L (−6.35, 4.36) Trial: 0.24 (−3.61, 4.1)	Only trials using standard dosing compared
Iftikhar et al[29]	Benralizumab vs dupilumab vs lebrikizumab vs mepolizumab vs reslizumab vs tralokinumab	Heterogeneous but inclusive, with all placebo- controlled RCTs with data on FEV_1, ACQ, and AQLQ included. No biomarker matching	Systematic review and network meta-analysis	Only reslizumab (0.64; 0.53, 0.78) and dupilumab (0.37; 0.17, 0.8) were significant vs placebo	Dupilumab (0.16) > reslizumab (0.14) > benralizumab (0.13) > mepolizumab (0.1) > lebrikizumab (0.1) > tralokinumab (0.07)	Included studies before and after importance of stratification by type-2 biomarkers was recognized
Bourdin et al[30]	Benralizumab vs other anti−IL-5	Severe asthma with an exacerbation history and selection (and matching) on basis of blood eosinophils (varying criteria)	Systematic review and matching-adjusted indirect comparison	0.94 (0.78, 1.13) vs mepolizumab No comparison possible with reslizumab because populations too different	0.03 (−0.06, 0.12) vs mepolizumab No comparison possible with reslizumab	Included phase 2b DREAM study for mepolizumab but only phase 3 studies for benralizumab
Busse et al[31]	Mepolizumab vs benralizumab and reslizumab	Severe eosinophilic asthma. Matching by baseline blood eosinophils and prior exacerbation history	Eligible studies selected from Cochrane review followed by indirect treatment comparison	Significant benefit vs benralizumab at all eosinophil thresholds (0.55-0.66) vs reslizumab 0.55 (0.36-0.85)	No significant differences vs benralizumab at all eosinophil thresholds. Benralizumab > reslizumab in those with eosinophils >400 (0.11; 0.01, 0.2)	Phase 2b DREAM study not included. Matches the 2 key predictive variables
Bateman et al[32]	Dupilumab vs all other available biologics	Patients with moderate to severe eosinophilic asthma and an exacerbation history selected from QUEST phase 3 study to match the populations in comparator trials	Systematic review followed by Bucher indirect treatment comparison	vs benralizumab 0.46 (0.32, 0.67) vs mepolizumab 0.72 (0.57, 0.92) vs reslizumab 0.62 (0.48, 0.79) vs omalizumab 0.73 (0.38, 1.42)	vs benralizumab 0.12 (0.02, 0.22) vs mepolizumab 0.08 (−0.08, 0.24) vs reslizumab 0.08 (−0.02, 0.18) vs omalizumab 0.06 (−0.04, 0.17)	Could not be fully matched with mepolizumab because of historical criteria for mepolizumab trials. Omalizumab comparison was the ITT population, with no type-2 biomarker stratification

✓ Not provide conclusive results with criticism to methodology

Pavord ID et al. J Allergy Clin Immunol Pract 2022;10:410-419.

Indirect comparison of biologics

	Mepolizumab		Benralizumab			Reslizumab	Dupilumab		Omalizumab
Variable	MENSA[5]	SIRIUS[8]	CALIMA[9]	SIROCCO[10]	ZONDA[11]	Castro et al[3]	QUEST[2]	VENTURE[12]	EXTRA[7]
Blood eosinophils (cells/mm^3)	>150 and/or >300 in last year	>150 and/or >300 in last year	>300	>300	>150	>400	Unselected	Unselected	Unselected
No. of patients	580	135	881	805	148	953	1902	210	850
Placebo exacerbation rate (/y)	1.75	2.12	0.93	1.33	1.83	1.8-2.1	0.87-0.97	1.60	0.88
% reduction in exacerbations with active treatment	53	38	28	51	55	50-59	46-47.7	59.3	25
% reduction in exacerbations resulting in hospitalization	61	0 vs 7 patients	−23	63	93	31-34	46.8	NA	NA
Improvement in pre-BD FEV_1 (mL)	98	114	116	159	112	90-126	130-140	220	NA
Improvement in post-BD FEV_1 (mL)	138	128	NA	NA	NA	NA	NA	NA	NA
Reduction in ACQ score	0.44	0.52	0.1	0.29	0.55	0.2-0.27	0.31-0.34	0.47	0.36
Reduction in SGRQ score	7	5.8	NA	NA	NA	NA	NA	NA	NA
Injection-site reactions (placebo vs active %)	3 vs 9	NA	2 vs 3	2 vs 3	2 vs 2	NA	7.9 vs 16.8	4 vs 9	3.1 vs 1.2
OCS-sparing effect (active vs placebo %)	NA	50 vs 0	NA	NA	75 vs 25	NA	NA	70.1 vs 41.9	NA
Exacerbation reduction (%) in patients with blood eosinophils >0.3 × 10^9/L	61	NA	28	51	NA	NA	66-67	NA	32§
Improvement in pre-BD FEV_1 (mL) in patients with blood eosinophils >0.3 × 10^9/L	202	NA	116	159	NA	NA	210-240	NA	40‖

✓ Dupilumab: greater improvement in exacerbations and FEV_1 (eosinophils > 300/µL)

Pavord ID et al. J Allergy Clin Immunol Pract 2022;10:410-419.

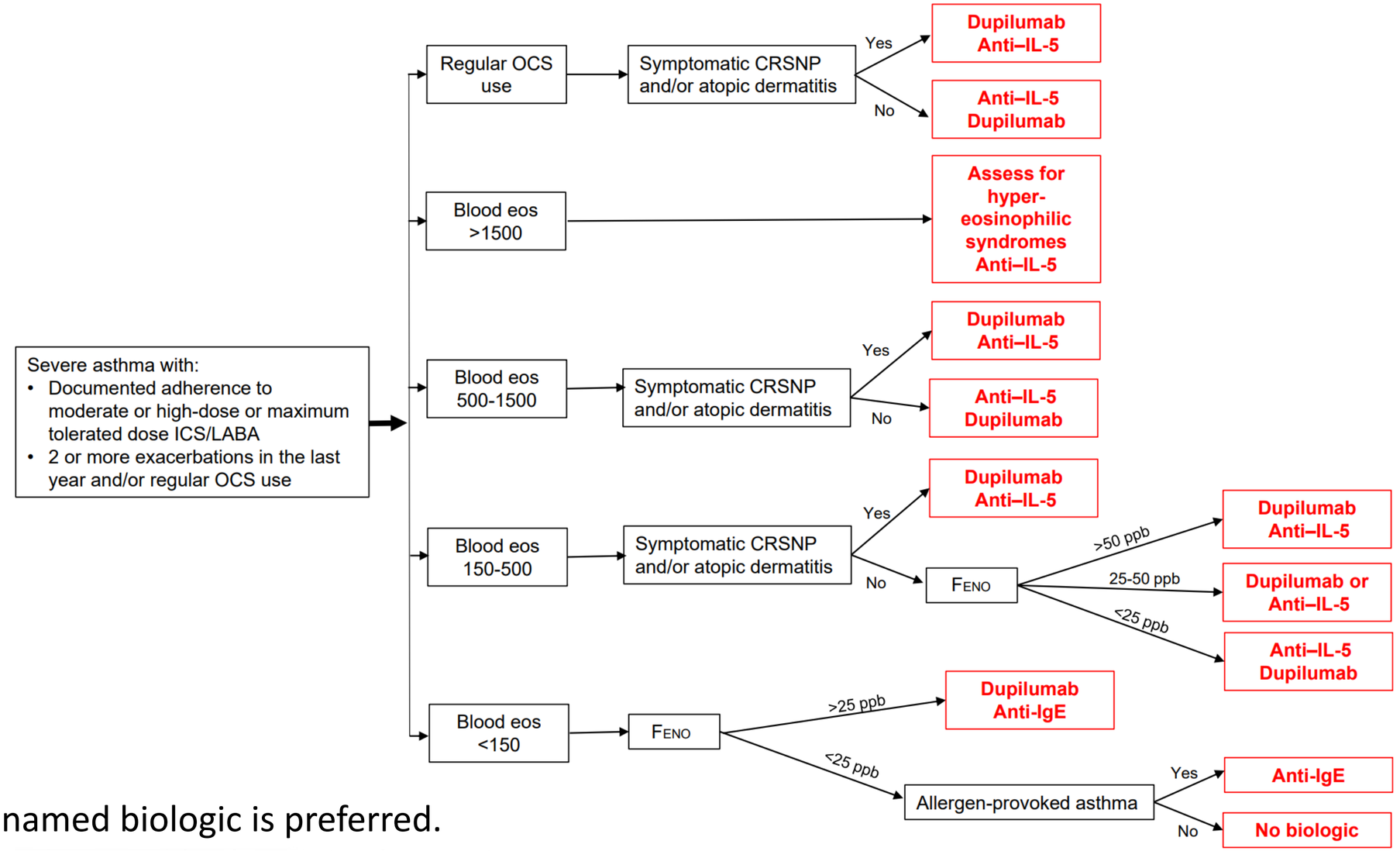
Indirect comparison of biologics

Clinical trial	Sinus 24[40]	Sinus 52[40]	Polyp1 and Polyp 2[17]	Synapse[20]
Population	Adults with bilateral CRSNP and symptoms despite topical CS. Surgery or systemic CS in last 2 y		Adults with corticosteroid- refractory CRSNP	Patients with CRSNP with previous surgery and in need of repeat
Intervention	Dupilumab 300 mg subcutaneously every 2 wk		Omalizumab by subcutaneous injection every 2-4 wk, dose based on weight and serum IgE	Mepolizumab 100 mg subcutaneously every 4 wk
Duration	24 wk	52 wk	24 wk	52 wk
Reduction in nasal polyp score (0-8)	2.06 (baseline 5.6)	1.8 (baseline 6.1)	0.59-1.14 (baseline 6.2 and 6.4)	0.73 (baseline 5.4)
Reduction in congestion score (0-3)	0.89 (baseline 2.3)	0.87 (baseline 2.5)	0.5-0.55 (baseline 2.4 and 2.3)	3.14* (baseline 8.9)
Recovery of sense of smell (USPIT 0-40)	10.6 (baseline 14.7)	10.5 (baseline 13.5)	3.8-3.9 (baseline 12.8 and 12.8)	−0.37† (baseline 9.6)
Improvement in SNOT-22 score (0-110)	21.1 (baseline 48)	17.4 (baseline 50.2)	15-16.1 (baseline 59.8 and 59.2)	16.5 (baseline 63.7)
Reduction in need for OCS	74%		62.5%	25% mepolizumab, 37% placebo

✓ Dupilumab: greatest positive impact across a range of outcome measures (CRSwNP)

Pavord ID et al. J Allergy Clin Immunol Pract 2022;10:410-419.

Selection of biologics

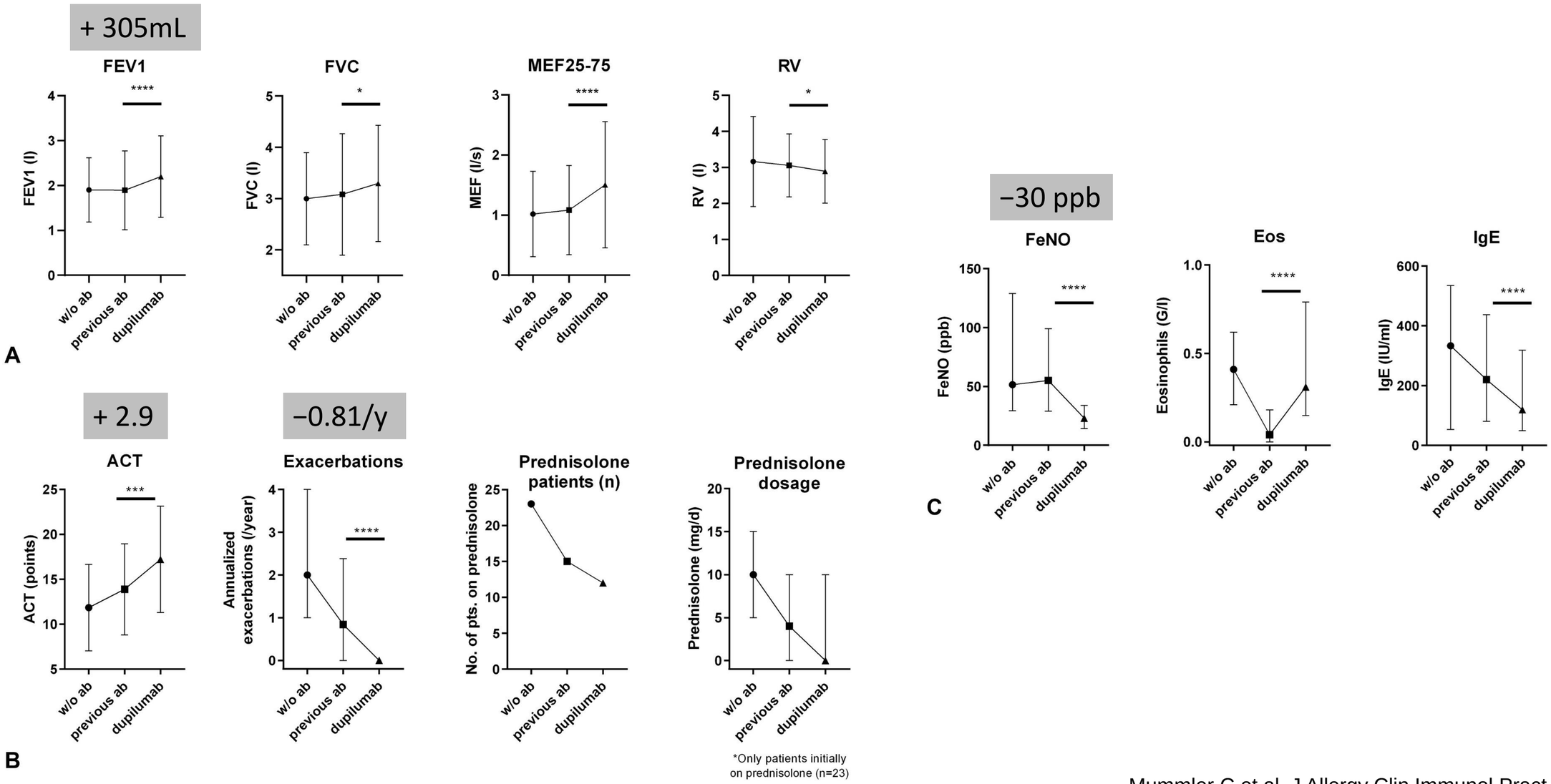


- First named biologic is preferred.
  ; Second named biologics is alternative.

Pavord ID et al. J Allergy Clin Immunol Pract 2022;10:410-419.

Switching biologics

- Switched to **dupilumab** from <u>anti-IgE or anti-IL-5/IL-5 receptor</u> because of insufficient outcome



Mummler C et al. J Allergy Clin Immunol Pract 2021;9:1177-85.

Switching biologics

- Switched to **dupilumab** from anti-IgE or anti-IL-5/IL-5 receptor because of insufficient outcome

Classification of response to dupilumab

Group	n = 38
Responder group, n (% of all patients)	n = 29 (76%)
ACT score increase (≥3 points),	12 (32)
FEV_1 increase (≥150 mL)	24 (63)
OCS reduction (≥50%)	7 (47)
Response of comorbidities	10 (26)
Nonresponder group	n = 9 (24%)
ACT score reduction (≥3 points)	2 (5)
FEV_1 reduction (≥150 mL)	3 (8)
OCS increase (>50%)	4 (27)
Increase in exacerbations	1 (3)

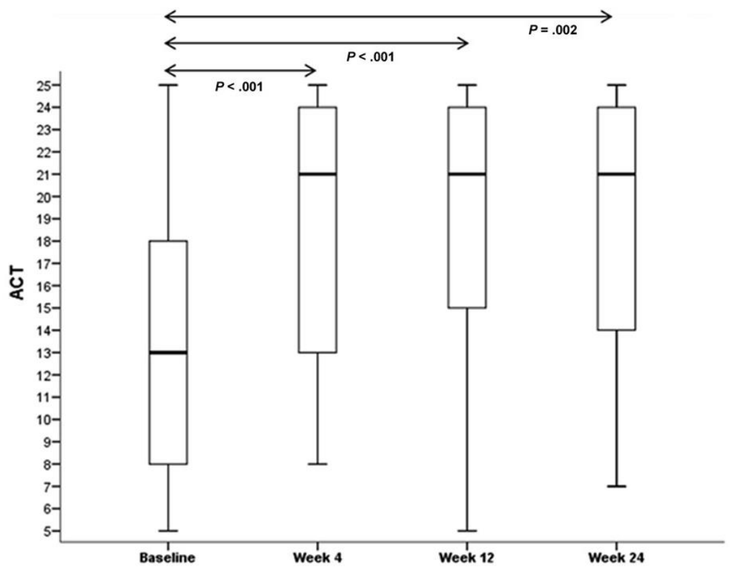
FENO category	Nonresponder	Responder	Total
FENO ≥ 25 ppb	4	23	27
FENO < 25 ppb	5	3	8
Total	9	26	35

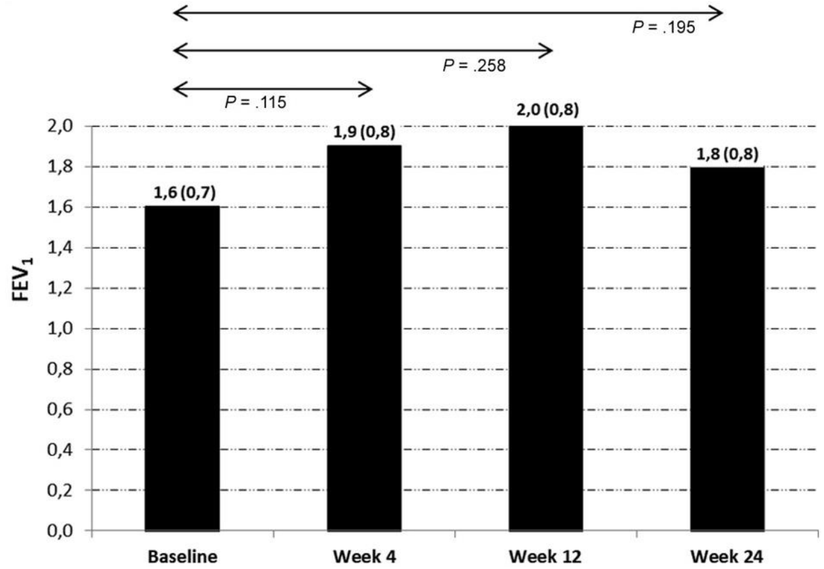
- ✓ No significant differences in clinical characteristics between responders and nonresponders.
- ✓ Patients with high FeNO (≥ 25) were more often responders than patients with low FeNO ($P < 0.05$).

Mummler C et al. J Allergy Clin Immunol Pract 2021;9:1177-85.

Switching biologics

- Efficacy of **reslizumab** in patients with inadequate response to <u>omalizumab (n = 25, 24 weeks)</u>



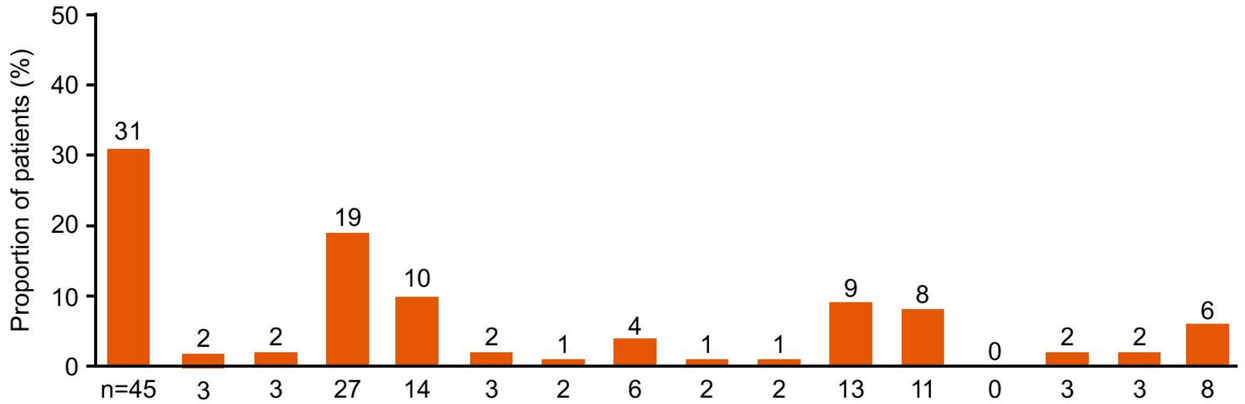


- ✓ Only 2 of 29 patients developed severe exacerbation (no hospitalization).
- ✓ 15/25 patients (60%) were at controlled (ACT ≥ 20 and no exacerbations).
- ✓ Patients receiving daily OCS significantly decreased from 72.4% to 52.0% (*P* = 0.019).

De Llano LAP et al. J Allergy Clin Immunol Pract 2019;7:2277-83.

Switching biologics

- Benefit of switching to **mepolizumab** from <u>omalizumab</u> in severe eosinophilic asthma



– 50%	Exacerbations	+	+	+	+	-	+	+	+	-	-	-	+	-	-	-	-
≥ 100mL	FEV_1	+	+	+	-	+	+	-	-	+	+	-	-	+	-	-	-
≥ 0.5	ACQ-5	+	+	-	+	+	-	+	-	+	-	+	-	-	+	-	-
≥ 4	SGRQ	+	-	+	+	+	-	-	+	-	+	+	-	-	-	+	-

✓ 137/145 (94%) were identified as responders (at least 1 outcomes)

: 120 (83%) for at least 2, 92 (63%) for at least 3, and 45 (31%) were responders for all 4 efficacy outcomes.

Liu MC et al. Respir Res 2021;22:144.

Case 2

- 56/F
- C.C: cough, chest discomfort
- Asthma (10 years), nasal polyp op. (2nd)
- Total IgE: 221 IU/mL

  MAST: all negative

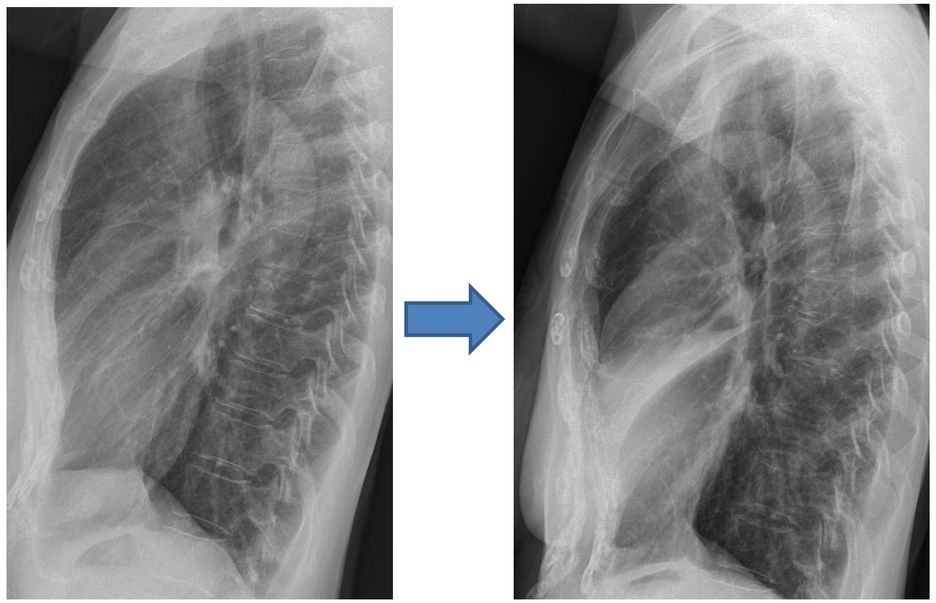
  Blood eosinophils: 790/μL

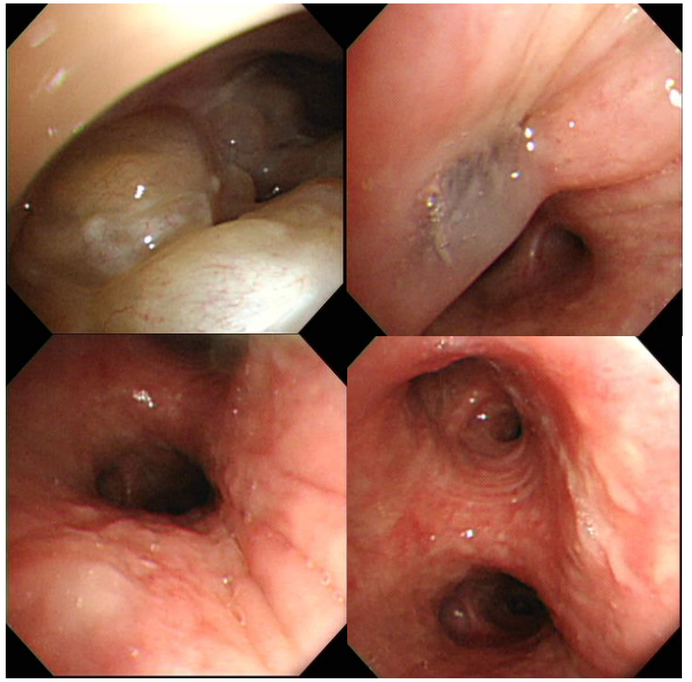
  FeNO: 73 ppb
- Asthma with CRSwNP

  : Eosinophilic + nonatopic + comorbidity

Case 2

Spirometry	(BTPS)	PRED	PRE-RX BEST	PRE-RX %PRED	POST-RX BEST	POST-RX %PRED
FVC	Liters	3.19	3.08	97	3.29	103
FEV1	Liters	2.38	2.17	91	2.49	105
FEV1/FVC	%	74	71		76	





- Recurrent respiratory symptoms and anosmia shortly after OCS

Chronic inflammation with many eosinophilic infiltration.

Case 2

- **Reslizumab** for 2month
  - Targeting eosinophils
  - Partly controlled respiratory symptoms, persistent anosmia

- Switching to **dupilumab**

  “**냄새가 좀 난다**” (1month)

  “냄새를 맡을 수 있어서 이제 좀 살 것 같다. 숨쉬는 것도 편하다” (2month)

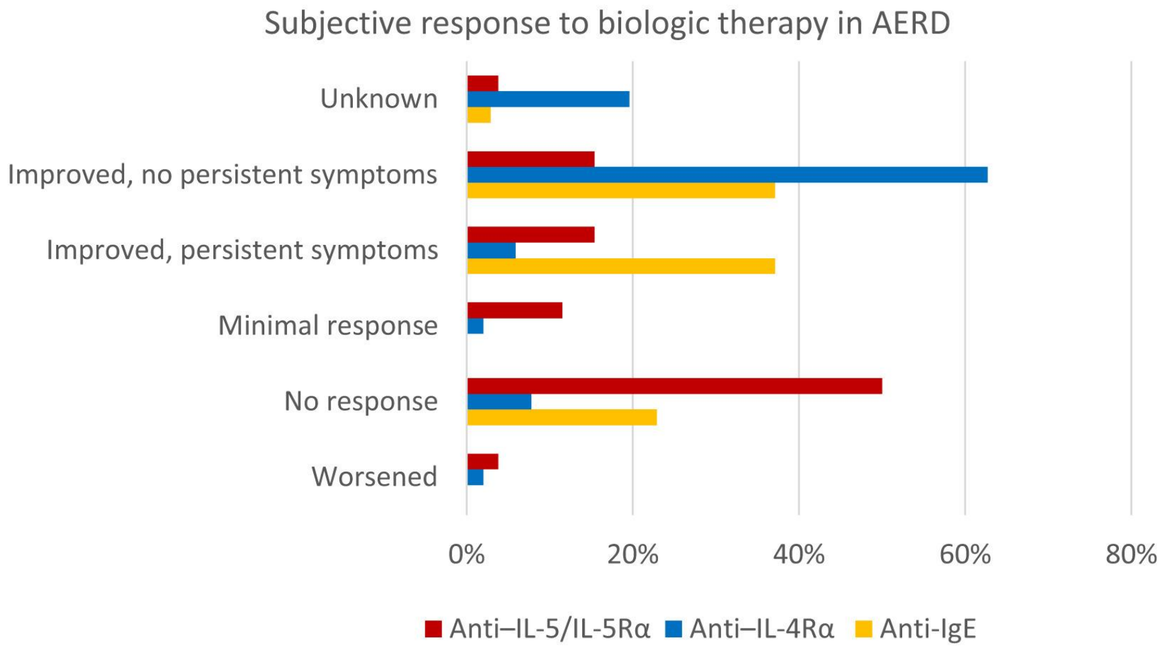
  “주사 맞고 6주 동안은 편하지만 이후에 냄새를 다시 못 맡는다”

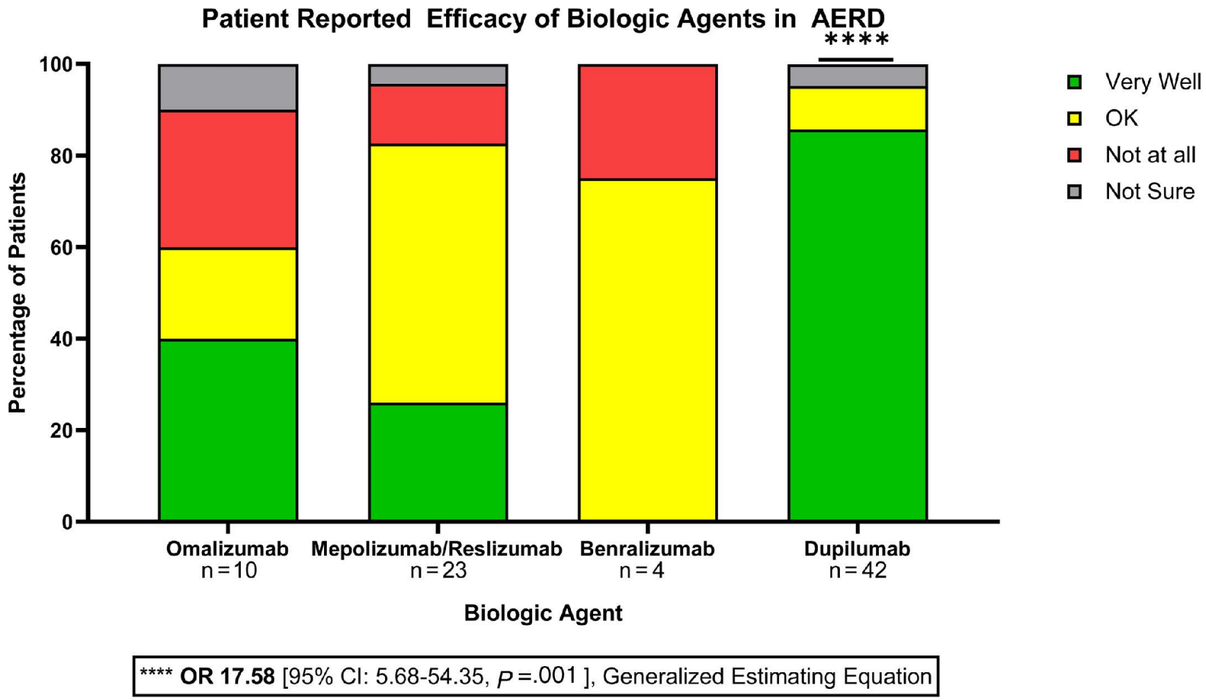
  – 현재 dupilumab 2개월 간격 유지 중

  – “이제는 이 주사가 없으면 안될 것 같아요”

Biologics for AERD

- *Aspirin-exacerbated respiratory disease (AERD)*





✓ Anti-IL-4Rα: significant reduction in SNOT-22 scores, corticosteroid bursts, antibiotics use

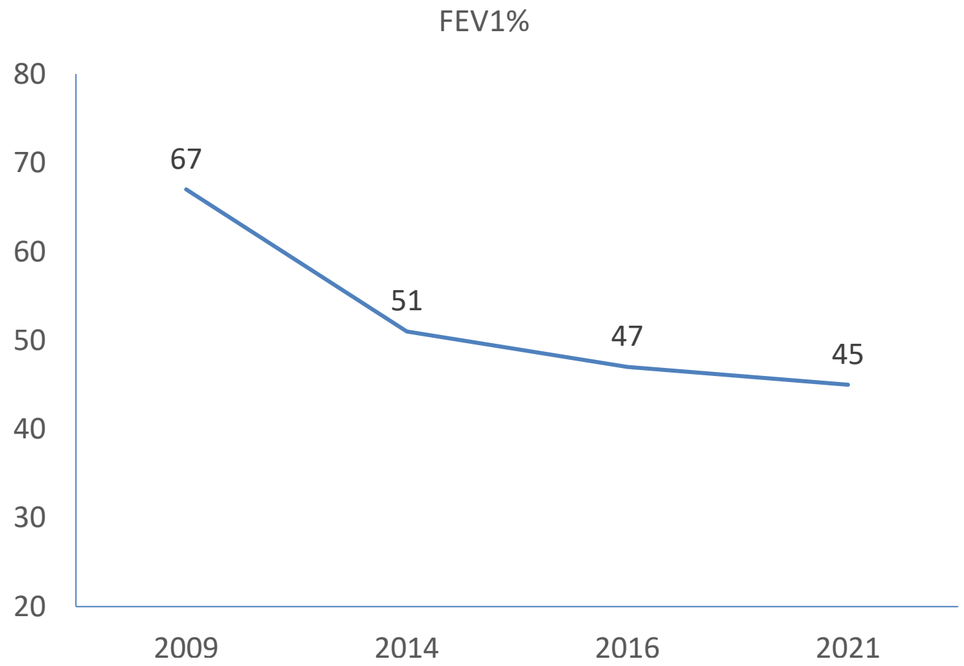
✓ Dupilumab worked “very well” (OR 17.58)

Wangberg H et al. J Allergy Clin Immunol Pract 2022;10:478-484.
Mullur J et al. Ann Allergy Asthma Immunol 2022;128:575-582.

Case 3

- 50/F
- Asthma (20 years); recurrent admission for asthma AE
- Stable since triple therapy for 3 years

  : 평지 걸을 때는 문제 없으나, 조금만 뛰거나 경사진 곳 오를 때 숨이 참.
- Refer for biologics treatment



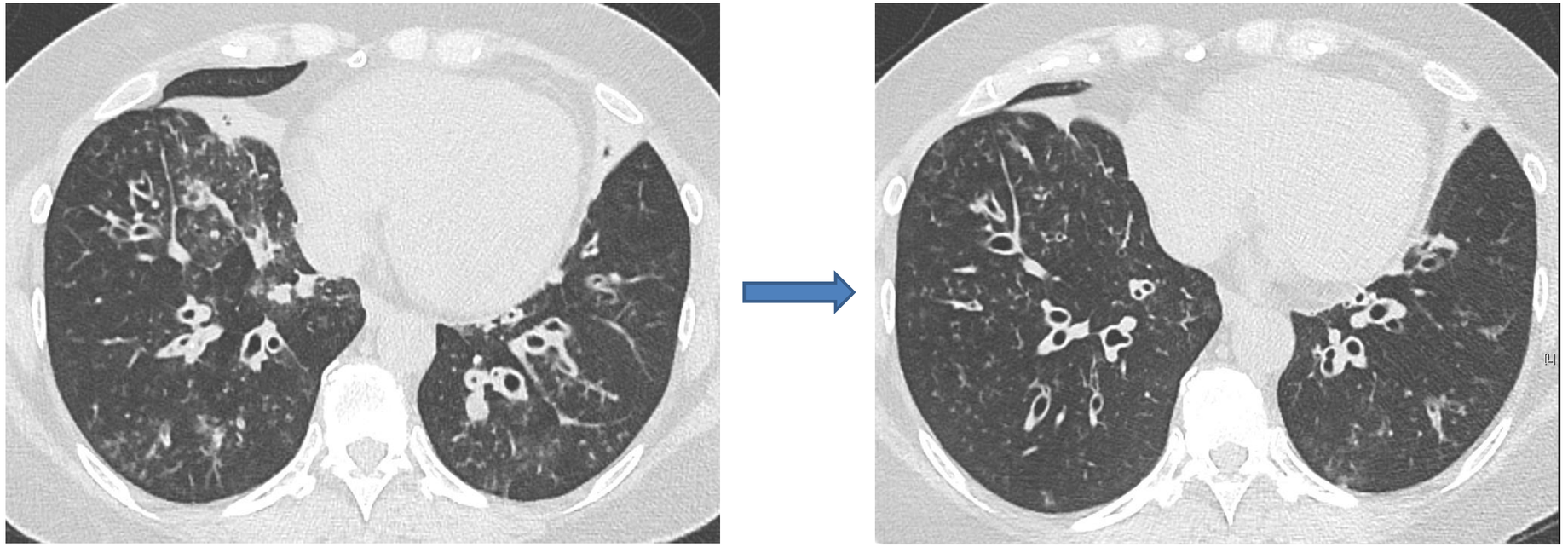
Case 3

Variable	Result
Blood eosinophil	1,490 (cells/μL)
Total IgE	2,385 (IU/mL)
Aspergillus fumigatus IgE	23.2 (KU/L)
Aspergillus fumigatus IgG	> 200 (U/mL)
Sputum AFB culture	Negative

→ **ABPA**

Case 3

- Discontinuation of OCS because of side effects
- Omalizumab 450mg for 2month, followed by dupilumab 300mg for 6months (monthly administered)
- FEV1 (%): 45 → 46
- “아이들이랑 뛰어 다녀도 숨이 차지 않고 (유치원 교사), 경사진 곳에 오를 때 더 이상 숨이 안차요“
  “똑바로 누워서 자도 가래가 거의 나오지 않아요”



Biologic treatment of ABPA

Use of monoclonal antibodies for allergic bronchopulmonary aspergillosis in patients with asthma and cystic fibrosis: literature review

- 32 studies (30 studies with asthma), 161 patients (median age 50.3 years, 1:1 F:M)
- Omalizumab: 17 studies (104 patients), Mepolizumab: 9 studies (32 patients)

  Dupilumab: 2 studies (21 patients), Benralizumab: 2 studies (2 patients)
- ABPA using the diagnostic criteria either by Patterson or the ISHAM.
- All patients had failed to respond adequately to steroids and antifungal therapies.
- Biologics improved acute exacerbations, ACT scores, pulmonary function, total IgE, and OCS requirement.
- Evidence comes mainly from case series or case report (no RCT).

Eraso IC et al. Ther Adv Respir Dis 2020;14:1753466620961648.

Biologic treatment of ABPA

Table 3. Treatment with Omalizumab in patients with ABPA and asthma.

					Pre-treatment clinical variables					Post-treatment clinical variables						
Study ID	**Type of study**	**Sample**	**Gender**	**Age**	**Blood Eosinophils (Absolute count (cells/μL) or percentage)**	**Total IgE (IU/mL)**	**FEV1 (%predicted or L)**	**Frequency of acute exacerbations**	**Antifungal treatment**	**Follow-up time**	**Total eosinophil count (cell/μL)**	**Total IgE (IU/mL)**	**FEV1 (% predicted or L)**	**Frequency of acute exacerbations**	**Systemic steroids**	**Antifungal treatment**
Koutsokera *et al.*[36]	Case series	11	5M6F	27.8 (21.8–37.7)	430 cells/μL (180–560)	889 (715.5–2991.5)	39.5% (33–59)	NI	NI	**1 yr**	NI	NI	NI	NI	No change	NI
Unal[16]	Case series	15	9M6F	48.26 (SD +–9.92[a]	692 cells/μL (SD +–346)[b]	1380 (647 –3339)[b]	42.51% (SD +–12.94)[a]	NI	Itraconazole	**3 yr**	NI	NI	54.11% (SD +–17.18)[a]	Reduced	Suspended	NI
Cunha *et al.*[9]	Case report	1	F	53	NI	NI	24%	NI	NI	**1 yr**	108	477	35.6%	Reduced	Suspended	NI
Aguiar *et al.*[10]	Case report	1	M	45	570 cells/μL	2674	58%	NI	No	**6 mo** 12 mo **18 mo**	200 160 90	1683 1600 1950	68% 78%	Reduced	Reduced Suspended	N.A.
Homma *et al.*[17]	Case report	1	M	51	1358 cells/μL	1500	58%	NI	Itraconazole	**4 mo 12 mo**	988 964	972 609	55.9% 54.7%	Reduced	Reduced by 50%	Discontinued (toxicity)
Aydin *et al.*[34]	Case series	14	7M7F	44.2 (SD +–13.01)	7.35% (SD +–2.15)	1056.93 (SD +–555.62)	59% (SD +–19.40)	2.7 (SD+– 1.5)	Itraconazole	**1 yr**	NI	769 (456–2030)[bc] to 1616 (1348–1808)[bd]	71%	Reduced	Reduced	NI
Evans *et al.*[15]	Case report	1	F	32	NI	22,893	NI		Itraconazole	**1 yr**	NI	NI	60%	Reduced	Suspended	NI
Voskamp *et al.*[18]	Randomized, double blinded, cross over trial	13	4M9F	59	500 cells/μL	2314 (376–7860)	73.2% (47–136)	NI	Itraconazole	**4 mo**	NI	NI	72% (SD +–22.5)	Reduced	NI	NI

Eraso IC et al. Ther Adv Respir Dis 2020;14:1753466620961648.

Biologic treatment of ABPA

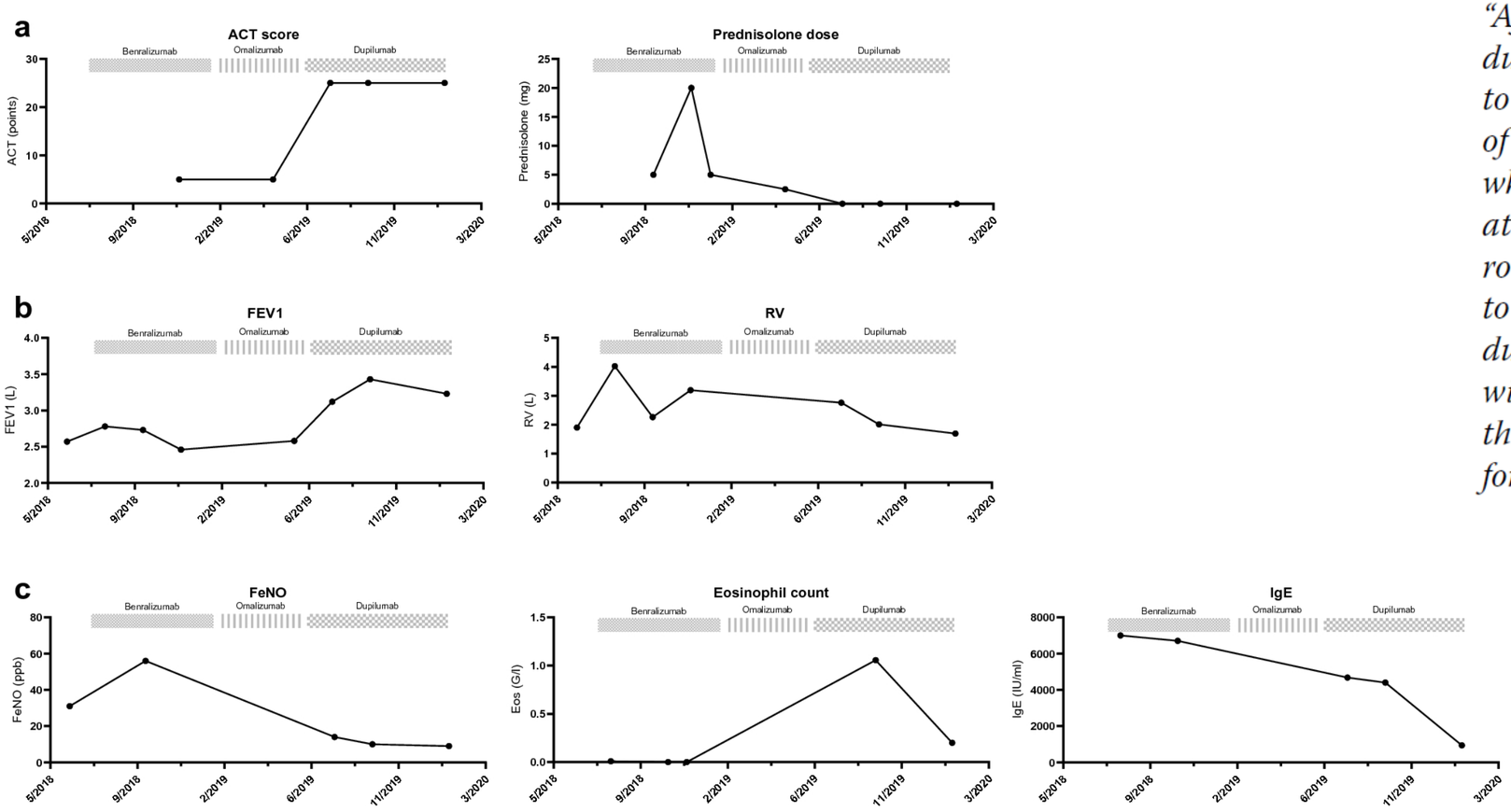
Table 5. Treatment with dupilumab in patients with ABPA and asthma.

					Pre-treatment clinical variables						Post-treatment clinical variables							
Study ID	**Type of study**	**Sample**	**Gender**	**Age**	**Previous biologic treatment**	**Absolute eosinophil count (cell/μL)**	**Total IgE (IU/mL)**	**FEV1 (% predicted or L)**	**Frequency of acute exacerbations or asthma control test**	**Antifungal treatment**	**Follow-up time**	**Total eosinophil count (cell/μL)**	**Total IgE (IU/mL)**	**FEV1 (%predicted)**	**Frequency of acute exacerbations or asthma control test**	**Systemic steroids**	**Antifungal treatment**	**Adverse effects**
Ramonell *et al.*[30]	Case series	3	F	60	Omalizumab and Mepolizumab	1620	561	1.51 L (58%)	NI	NI	**6 months**	1090 (4 mo)	380 (3 mo)	2.18 L (99%)	Improved	Discontinued	NI	hypereosinophilia
			F	51	Mepolizumab	1040	>2000	2.75 L (95%)	NI	Itraconazole	**3 months**	160	384	2.82 L (97%)	Improved	Discontinued	NI	No
			M	33	No	1750	11.290	1.97 L (37%)	NI	Voriconazole	**3 months**	690	1637	2.33 L (56%)	Asthma exacerbation after onset dupilumab	NI	NI	Hypereosinophilia
Corren *et al.*[31]	Post Hoc analysis of an RCT[f] (35)	18	NI	NI	NI	NI	3383 (1480–5000[b]	2.00 L (68%)[a]	2.28 (1.53)[a,d]	NI	**13 months**	NI	691,5 (323–2617)[b]	24 w 2.26 52 w 2.33[c]	Improved	NI	NI	Injection-site reaction

Eraso IC et al. Ther Adv Respir Dis 2020;14:1753466620961648.

Biologic treatment of ABPA

- Case report: 49/F with ABPA



Patient perspective

"After nearly 50 years of breathlessness, therapy with dupilumab changed my life from one day to the next: to breathe without resistance is really a new quality of life! Perhaps there are two things in my case, which are special to this success. First, I am doing at minimum one hour of sport each day (bicycling, rowing) since 35 years, even when this was hard to practice. And second: I lost, after starting with dupilumab and stopping cortisone, 17 kg of weight within three months with a fasting cure. Altogether, this is giving me a reliable and hopeful perspective for my future."

✓ Switching to dupilumab: complete resolution of pulmonary symptoms, exacerbations and withdrawal of OCS.

Mummler C et al. Allergy Asthma Clin Immunol 2020;16:55.

Case 4

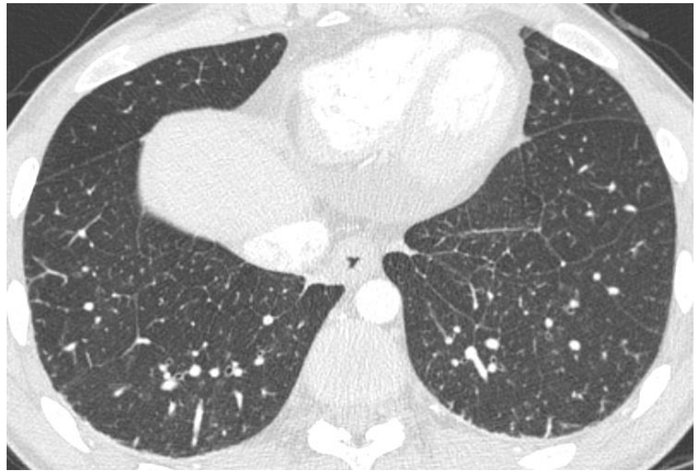
- 23/M
- Asthma (7 years), nasal polyp op (2nd)
- C.C: Tingling sense, gait disturbance (1 week)
- **NCV: suggestive of mononeuritis multiplex**.

  Blood eosinophils: 21,890/μL

  PNS: sinusitis

  Chest CT: septal thickening with multiple lung nodule

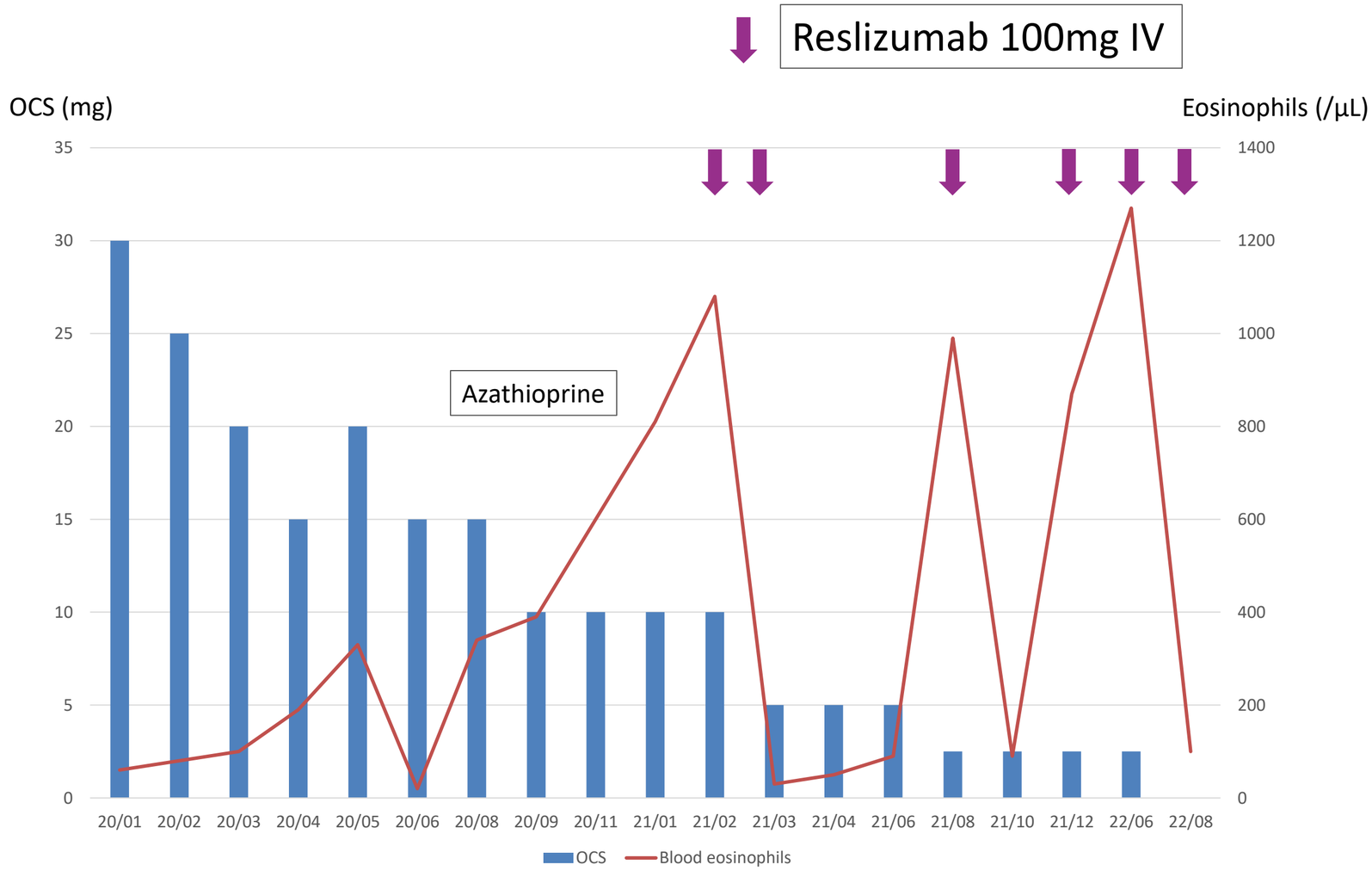
  pANCA: negative



- Diagnosis: **Eosinophilic granulomatosis with polyangiitis (EGPA)**
- Remission induction: steroid + cyclophosphamide pulse (4th) with PO

Case 4

- OCS maintenance and tapering



Biologic treatment of EGPA

- Relapsing or refractory EGPA taking a stable dose of OCS

RCT (300mg) (n=136)

CLINICAL BENEFIT: DEFINITION 1

Remission (BVAS 0 and ≤4 mg/d GC)
or
≥50% reduction in GC dose
or
relapse-free

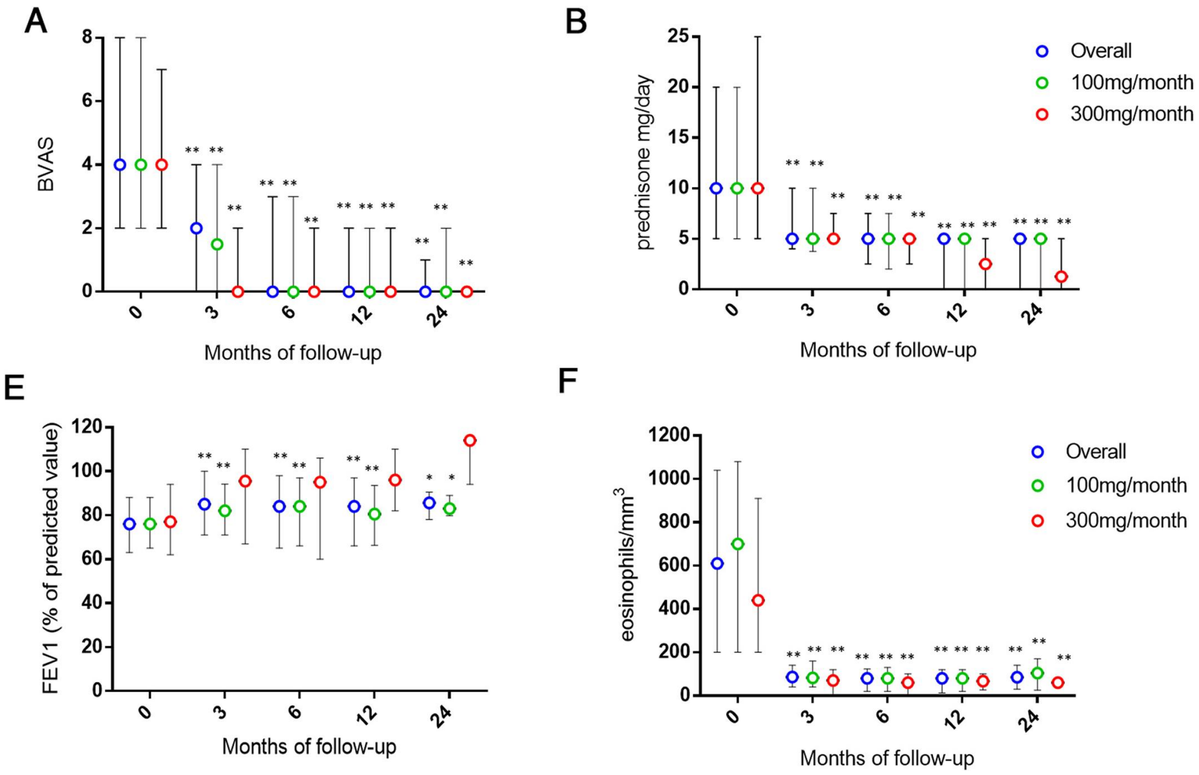
78% MEPOLIZUMAB vs 32% PLACEBO

CLINICAL BENEFIT: DEFINITION 2

Remission (BVAS 0 and ≤7.5 mg/d GC)
or
≥50% reduction in GC dose
or
relapse-free

87% MEPOLIZUMAB vs 53% PLACEBO

Multicenter observational study (n=203)



✓ Mepolizumab 100mg is also effective.

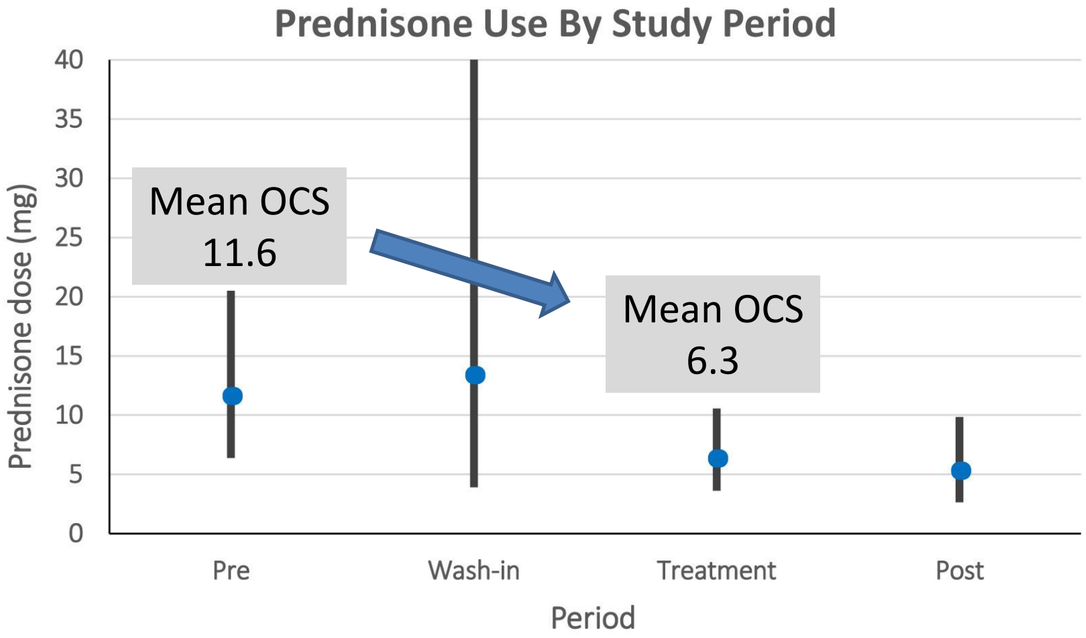
Steinfeld J et al. J Allergy Clin Immunol 2019;143:2170-2177.
Bettiol A et al. Arthritis Rheumatol 2022;74:295-306.

Biologic treatment of EGPA

- Steroid sparing effects from reslizumab (n=8) and benralizumab (n=10)

Means of Outcome Variables at Start and End of Trial Participation (N = 8)

Outcome variable	Start of trial (week 0)[a]	EOT[a]	One-tailed test (week 0-EOT),[a]
			P values
Prednisone (mg)	17.5	8.12	.049
Absolute eosinophils (cells/μL)	187.5	87.5	.19[b]
FEV_1 (% predicted)	81.47	76.06	.17
FeNO (ppb)	33.37	56.37	.32[b]
AQLQ	5.97	5.74	.16
ACQ-7	1.23	1.32	.35
BVAS	8.25	4.24	.04
IgE (kU/L)	504.85	550.05	.23[b]



✓ 5 patients: withdrawal OCS

Manka LA et al. Ann Allergy Asthma Immunol 2021126:696-701.
Guntur BP et al. J Allergy Clin Immunol Pract 2021;9:1186-93.

Summary

- Understanding disease and treatment burden of severe asthma
- Assessment of severe asthma: phenotype and biomarker
- Set individual treatment goal
- Selection of biologics depending on phenotype, biomarker, and goal (± cost)
- Switching biologics when ineffective
- Application of biologics to ABPA, CRSwNP (AERD), and EGPA

경청해 주셔서 감사합니다