2020 On-line asthma school

# Year in review: Severe asthma

강남세브란스병원 박혜정

# CONTENTS

# Introduction of severe asthma

**Table 1.** Published definitions of severe asthma

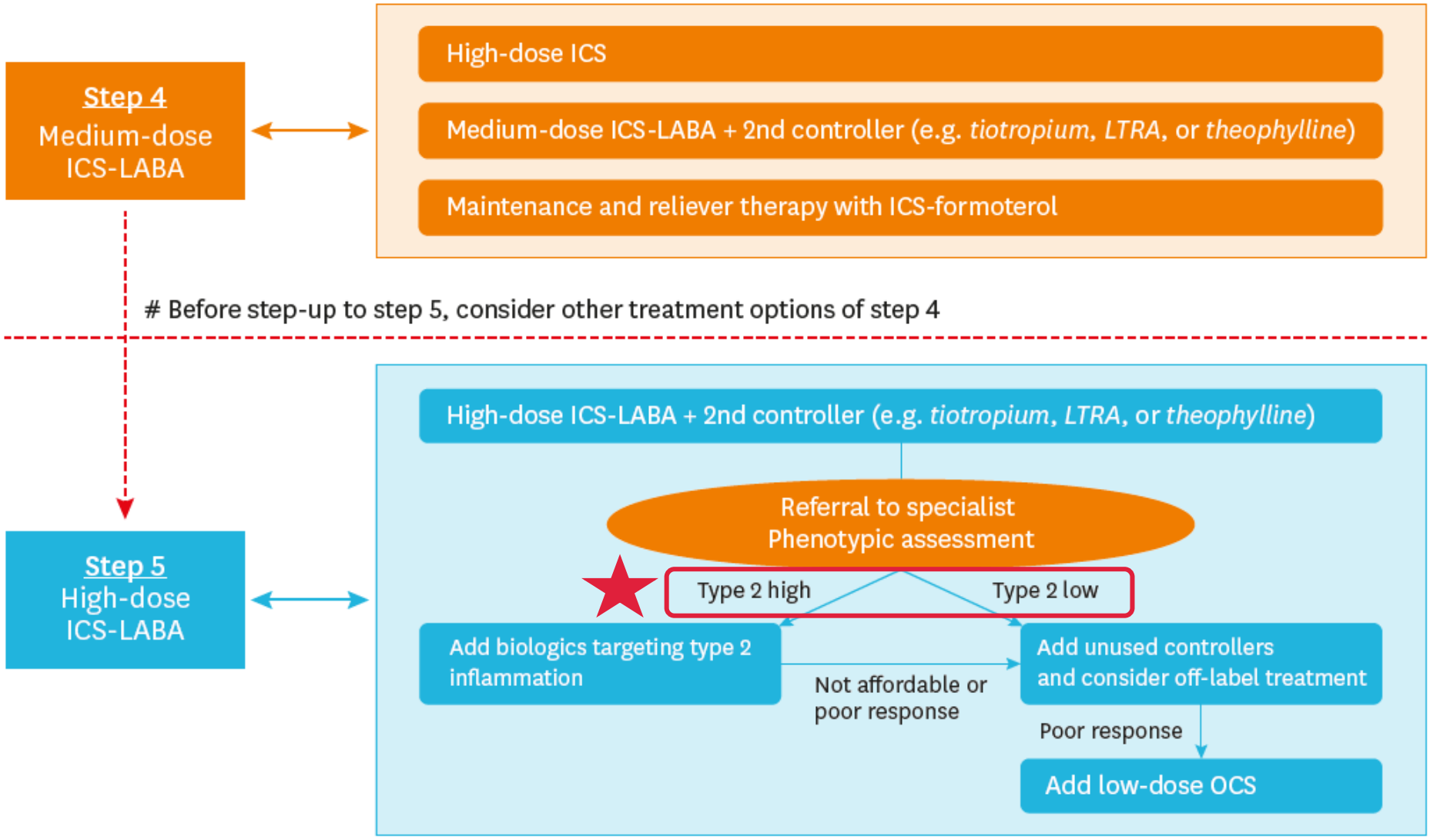
| Guidelines | Definition | Required medications | Additional details |
|---|---|---|---|
| ATS (2000) | • Refractory asthma requires 1 or both major criteria and 2 minor criteria | • Major criteria<br>1) Continuous or near-continuous (≥ 50% of the year) OCS<br>2) High-dose ICS | • Minor criteria; at least 2 of following categories<br>1) Requirement for daily treatment with additional controller<br>2) Requirement for short-acting inhaled ⊠2-agonist<br>3) Persistent airway obstruction<br>4) 1 or more urgent care visits for asthma per year<br>5) 3 or more oral steroid "bursts" per year<br>6) Prompt deterioration with ≤ 25% reduction in oral or ICS dose<br>7) Near-fatal asthma event in the past |
| WHO (2009) | • Treatment-resistant severe asthma<br>1) "Control" is not achieved despite highest level treatment<br>2) "Control" maintained only with highest level treatment | • High-dose ICS or a high-dose ICS–LABA combination<br>• Frequent or chronic use of SCS | • Level of control assessed based on following categories:<br>1) Daytime symptoms<br>2) Limitations on activities<br>3) Nocturnal symptoms/awakenings<br>4) Need for short-acting inhaled ⊠2-agonist<br>5) Lung function<br>6) Exacerbations |
| IMI (2011) | • Refractory asthma despite high-intensity treatment | • High-dose ICS with or without SCS | • Uncontrolled and/or frequent (≥ 2/year) exacerbations |
| ERS/ATS (2014) | • Asthma that requires high-intensity medication to prevent it becoming "uncontrolled" or that remains "uncontrolled" despite therapy<br>• Controlled asthma that worsens on tapering of these high doses of ICS or SCS (or additional biologics) | • Medications for GINA steps 4–5 asthma for the previous year or<br>• SCS for ≥ 50% of the previous year | • Uncontrolled asthma; at least 1 of the following:<br>1) Poor symptom control<br>2) Frequent severe exacerbations<br>3) Serious exacerbations<br>4) Airflow limitation |
| GINA (2019) | • Uncontrolled asthma despite adherence to maximal optimized therapy and treatment contributory factors<br>• Asthma worsens when high-dose treatment is decreased | • Medications for GINA steps 4–5 asthma | • Uncontrolled asthma; at least 1 of the following categories:<br>1) Poor symptom control<br>2) Frequent or serious exacerbations<br>• Good adherence and inhaler technique |

ATS, American Thoracic Society; WHO, World Health Organization; IMI, Innovative Medicine Initiative; ERS, European Respiratory Society; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; LABA, long-acting β2-agonists; OCS, oral corticosteroids; SCS, systemic corticosteroids.

"**GINA step 4-5** 에서, 적절한 약물/비약물 치료 및 위험인자 조절에도 **uncontrolled인 천식**"

**다양한 '중증 천식' 의 정의 존재**

*Kim et al.*
*Allergy Asthma Immunol Res 2020;12:910-33*




**'중증 천식' 의 치료 방향**

*Kim et al.*
*Allergy Asthma Immunol Res 2020;12:910-33*

# Type 2 inflammation in GINA

*Assess the severe asthma phenotype during high dose ICS treatment (or lowest possible dose of OCS)*

| Type 2 inflammation | |
|---|---|
| *Could patient have Type 2 airway inflammation?* | • Blood eosinophils ≥150/μl and/or<br>• FeNO ≥20 ppb and/or<br>• Sputum eosinophils ≥2%, and/or<br>• Asthma is clinically allergen-driven and/or<br>• Need for maintenance OCS<br>(Repeat blood eosinophils and FeNO up to 3x, on lowest possible OCS dose) |
| *Note: these are not the criteria for add-on biologic therapy (see* **6b**) | |

**Type 2 inflammation 의 지표들 (GINA version)**

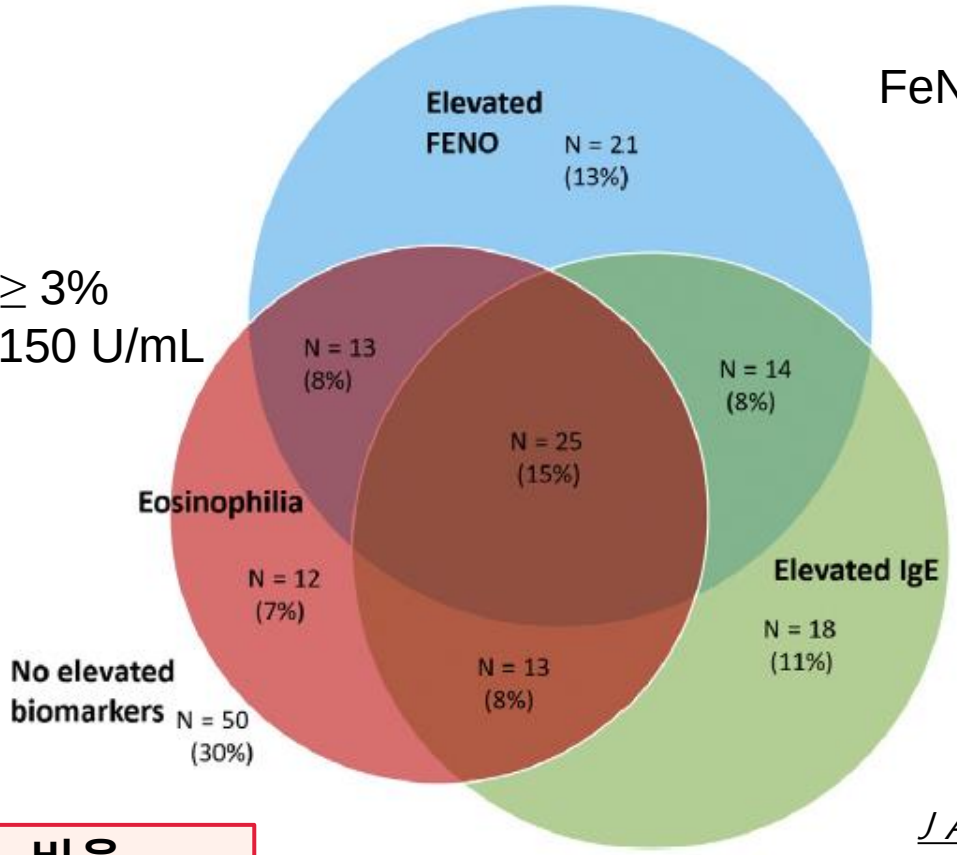
*2020 GINA Reports*

# The prevalence of subtypes of Type 2 inflammation

- In 166 severe asthma, 116 (70%) had at least 1 T2 biomarker elevated.

FeNO ≥ 25 ppb

Sputum eosinophil ≥ 3%
Blood eosinophil ≥ 150 U/mL




IgE ≥ 150 UmL

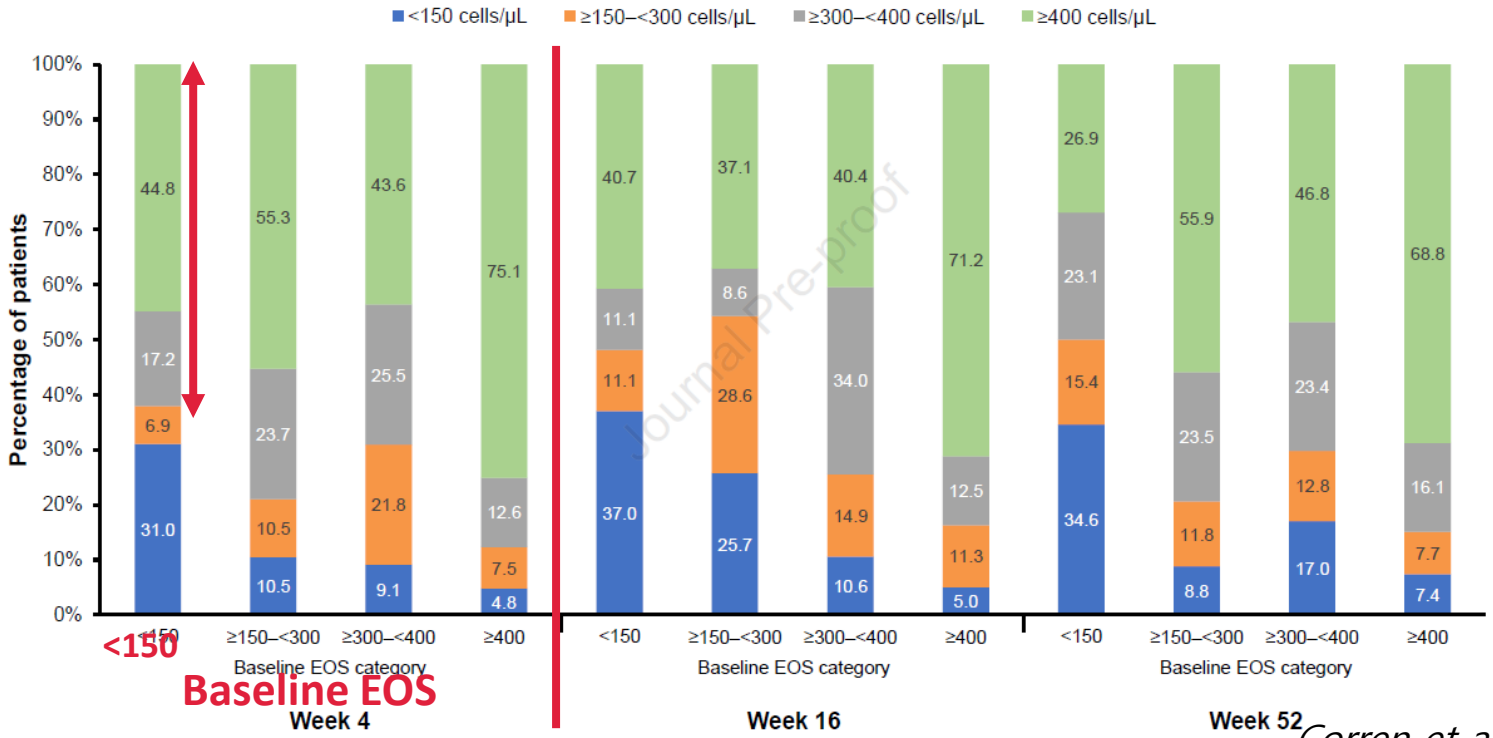
*Frossing et al.*
*J Allergy Clin Immunol Pract*
*E-pub*

**Type 2 inflammation 비율**

# Variability in blood eosinophil counts

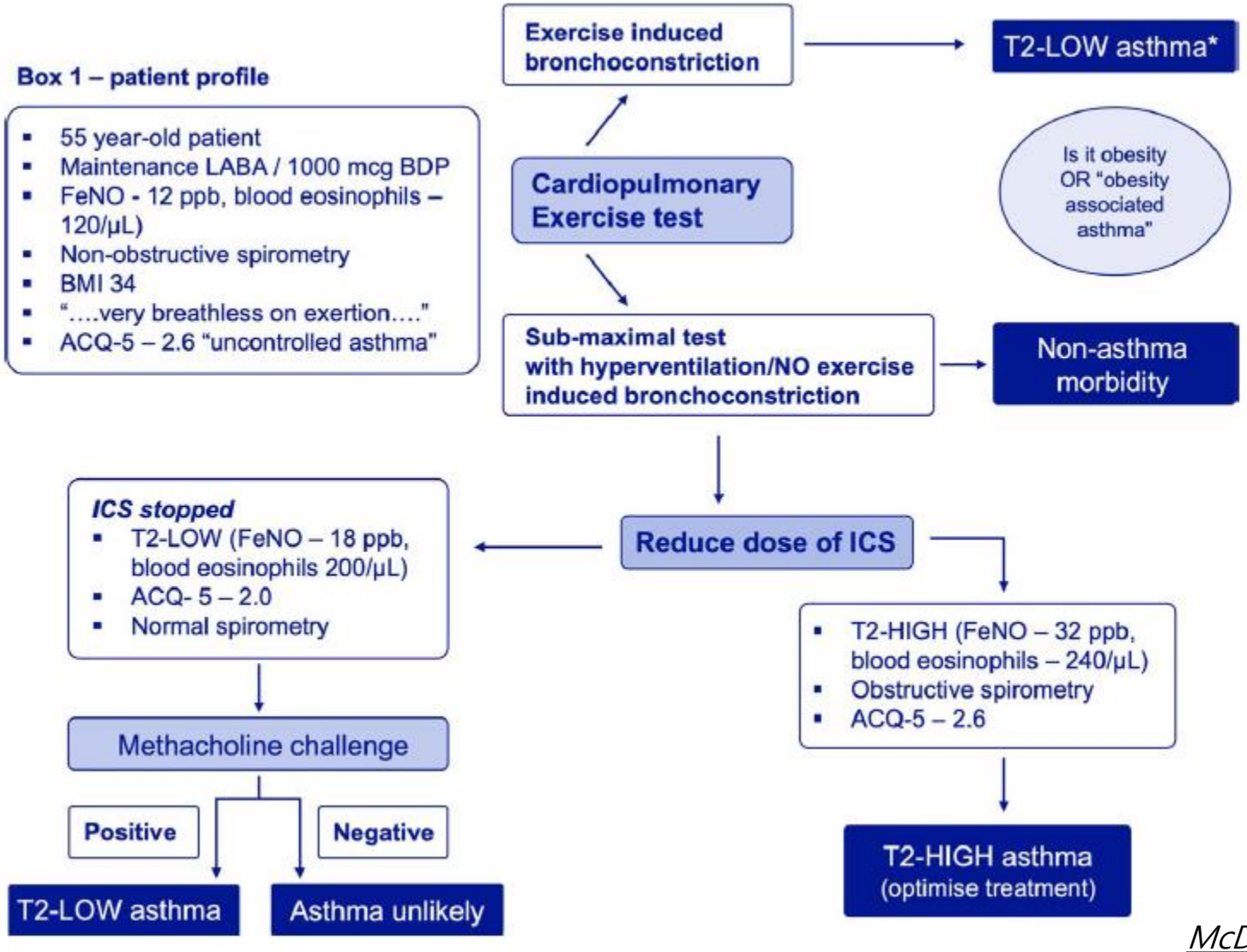
- Pooled data from study participants receiving placebo (previously randomized 1:1To receive reslizumab or placebo)

**Baselinle EOS**가 **150 미만**이었던 대상자들 중 **62% 가 한 달 뒤 EOS 가 300 이상**임




**EOS의 변동성**

*Corren et al. J Allergy Clin Immunol Pract E-pub*



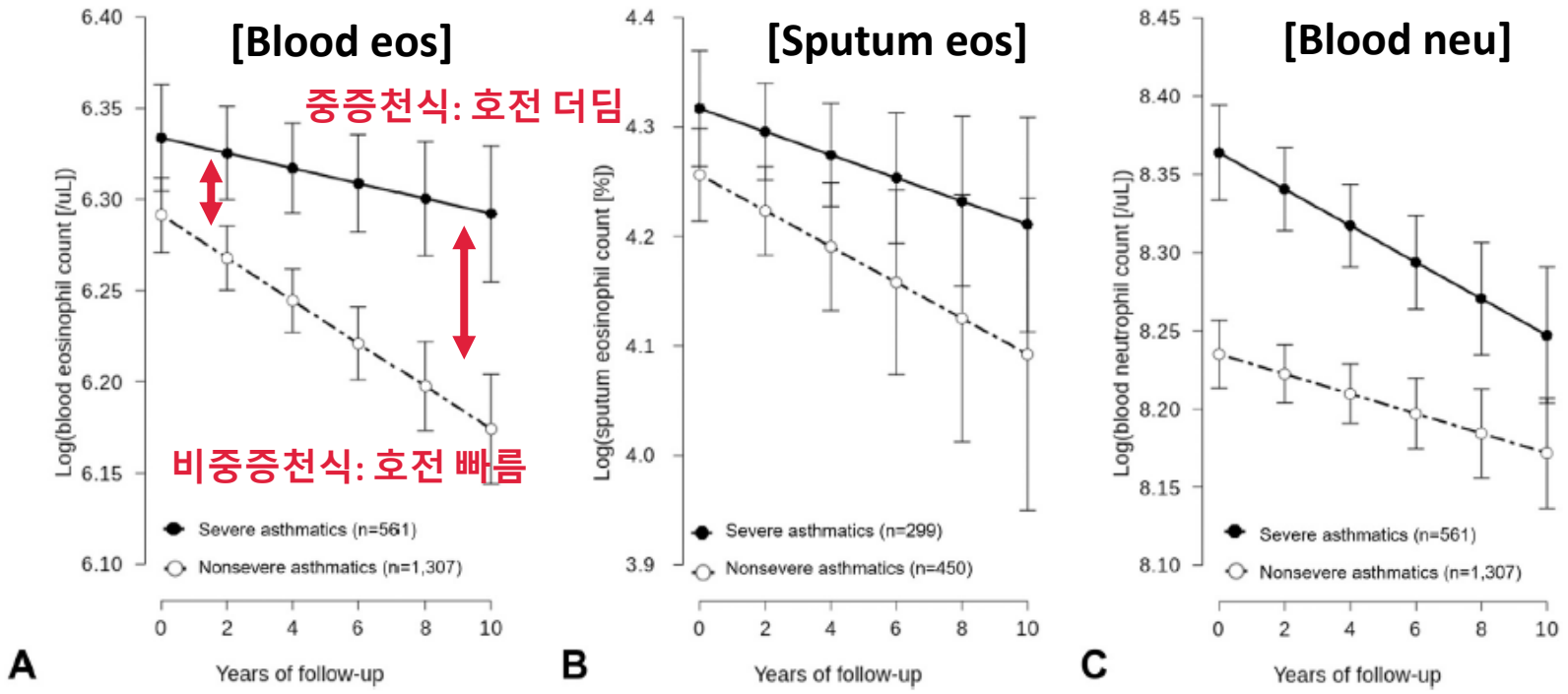

**'T2-low 중증 천식' 의 진단/치료 방향**

McDowell et al. Allergy 2020;75:302-10

# Characteristics of severe asthma

# Longitudinal outcomes of severe asthma

- Severe asthmatics (n=567) vs. non-severe asthmatics (n=1,337): **ICARUS**



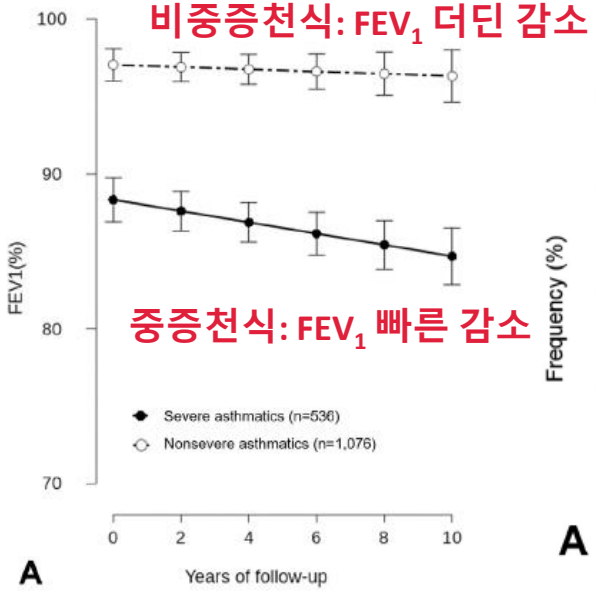

Lee et al.
J Allergy Clin Immunol Pract
E-pub

# Longitudinal outcomes of severe asthma

**[$FEV_1$]**

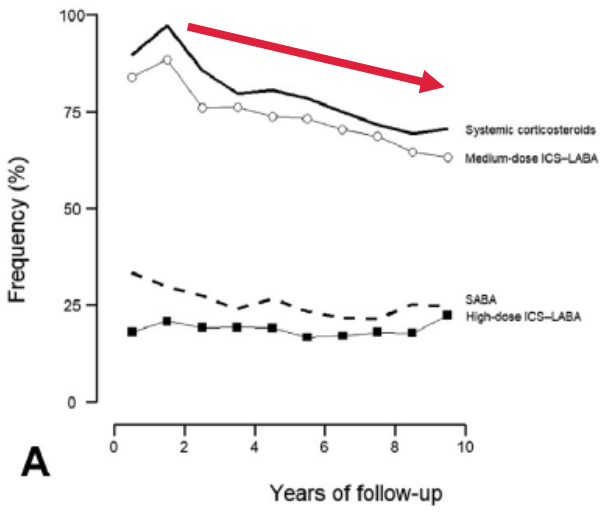
비중증천식: $FEV_1$ 더딘 감소

중증천식: $FEV_1$ 빠른 감소



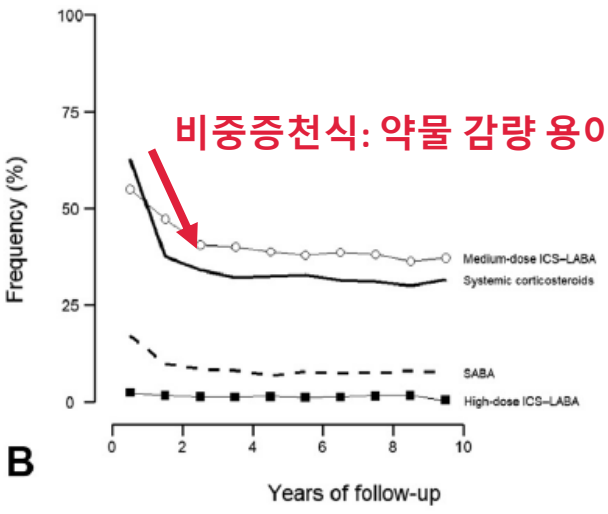

**[Asthma medication in severe asthma]**

중증천식: 약물 감량 어려움




**[Asthma medication in non-severe asthma]**

비중증천식: 약물 감량 용이

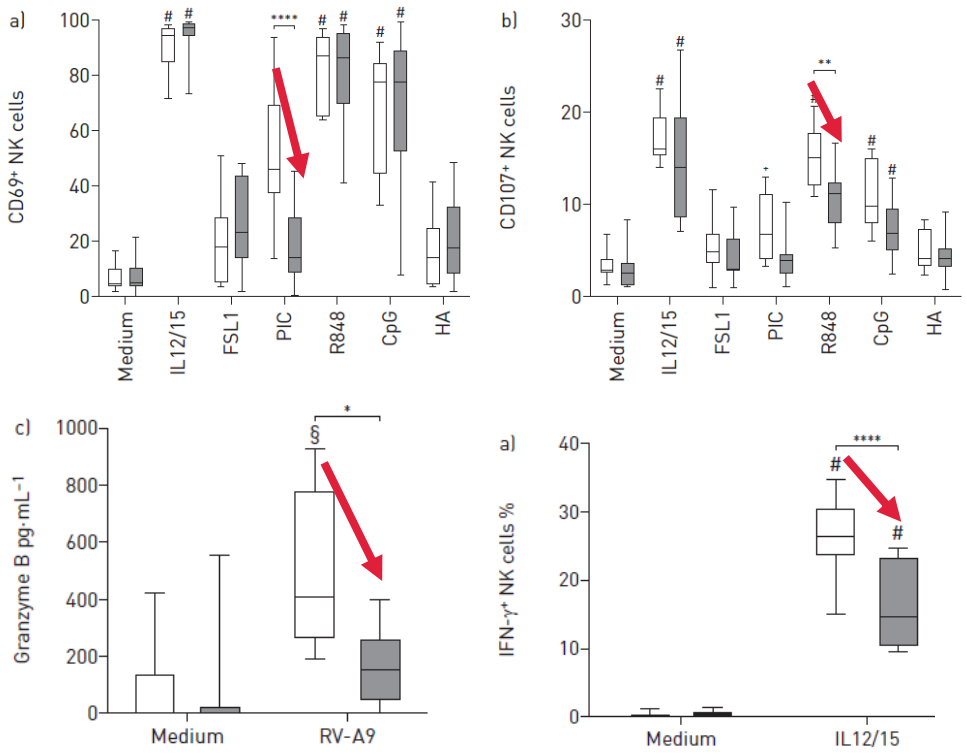



**중증 천식 특징 1.** 치료 반응 및 예후가 좋지 않다.

*Lee et al.*
*J Allergy Clin Immunol Pract*
*E-pub*

# Aberrant anti-viral response of NK cells

- PBMCs from severe asthma (n=31) and healthy donors (n=11)




중증천식에서,
건강인에 비해,
**Virus 침입에 대한**
**NK cell의 반응저하**
가 관찰됨

**중증 천식 특징 2.** 바이러스에 대한 면역 반응 떨어짐

*Devulder et al.*
*Eur Respir J*
*2020;55:1802422*

# Increased capsaicin sensitivity with poor outcome

- 122 patients with severe asthma

**Table 4.** Risk Factors for Clinical Features of Severe Asthma

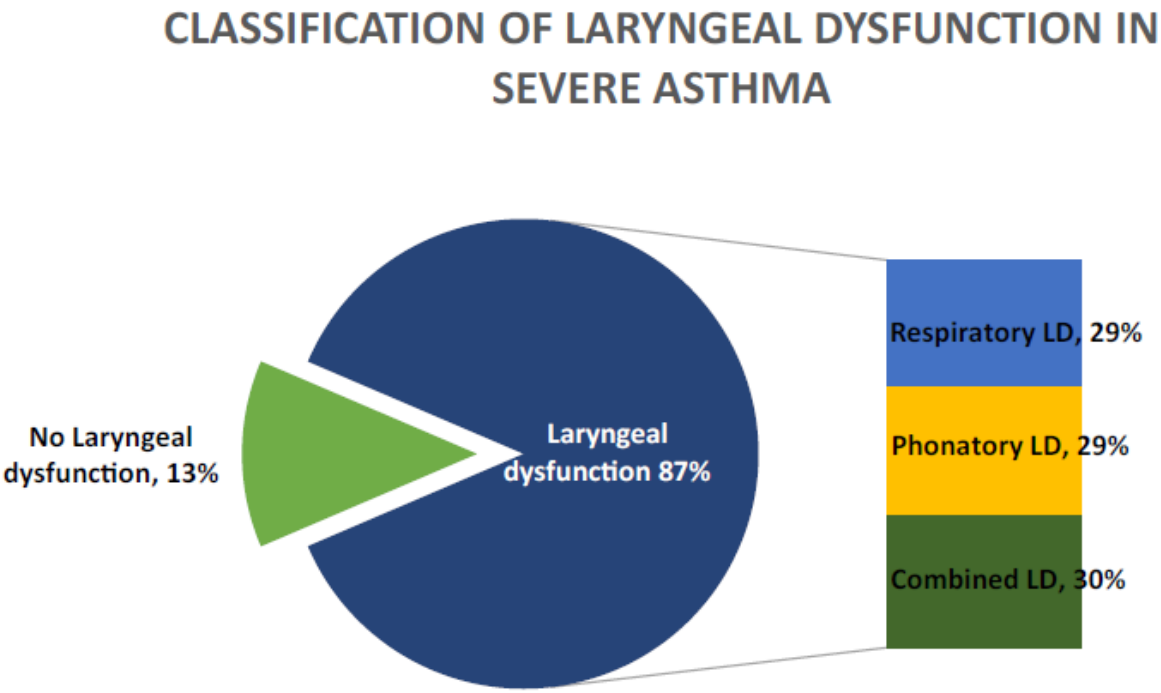
| | Asthma Control (*ACT* Score < 20) ($R^2$ = 0.31) | | | Exacerbations (≥2/yr) ($R^2$ = 0.26) | | | Admissions (≥1/yr) ($R^2$ = 0.36) | | | Airflow Limitation ($FEV_1$% Predicted < 80%) ($R^2$ = 0.24) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | *P* Value | OR | 95% CI | *P* Value | OR | 95% CI | *P* Value | OR | 95% CI | *P* Value |
| General factors | | | | | | | | | | | | |
| Sex, F | — | — | — | 3.34 | 0.95–11.7 | 0.06 | — | — | — | 0.51 | 0.19–1.34 | 0.17 |
| BMI ≥ 25 kg/$m^2$ | — | — | — | 1.79 | 0.65–4.94 | 0.26 | — | — | — | — | — | — |
| Nonatopic | 2.15 | 0.97–4.71 | 0.06 | — | — | — | 3.13 | 0.91–10.7 | 0.07 | — | — | — |
| Ex-smoking status | 2.16 | 0.95–4.91 | 0.07 | — | — | — | 6.52 | 1.89–22.4 | 0.003 | 2.07 | 0.79–5.40 | 0.14 |
| Biomarkers and $FEV_1$% predicted | | | | | | | | | | | | |
| C5 ≤ 2.44 μM | 4.83 | 1.97–10.4 | 0.0004 | 2.83 | 1.04–7.71 | 0.04 | 3.43 | 0.91–12.9 | 0.07 | — | — | — |
| ANC ≥ 5,000/μl | 3.62 | 0.87–15.1 | 0.08 | 2.86 | 0.74–11.1 | 0.13 | 4.55 | 0.86–24.1 | 0.07 | — | — | — |
| $FE_{NO}$ ≥ 25 ppb | — | — | — | — | — | — | — | — | — | 1.58 | 0.63–3.96 | 0.33 |
| $FEV_1$% predicted < 80% | 2.99 | 1.13–7.94 | 0.03 | 5.42 | 1.77–16.6 | 0.003 | 3.89 | 0.996–15.2 | 0.051 | N/A | N/A | — |
| Comorbidities, presence | | | | | | | | | | | | |
| Chronic rhinosinusitis | — | — | — | — | — | — | — | — | — | 2.78 | 1.04–7.43 | 0.04 |
| GERD | — | — | — | 2.45 | 0.91–6.54 | 0.07 | — | — | — | — | — | — |
| Diabetes mellitus | 2.03 | 0.58–7.09 | 0.27 | 0.69 | 0.15–3.11 | 0.63 | 1.69 | 0.37–7.65 | 0.50 | 7.17 | 2.25–22.8 | 0.0009 |

**중증 천식 특징 3.** Capsaicin sensitivity가 poor outcome 반영

*Kanemitsu et al.*
*Am J Respir Crit Care Med*
*2020;201:1068-77*

# Laryngeal dysfunction

- 53 severe asthma patients




**중증 천식 특징 4.** laryngeal dysfunction 비율이 높다.

*Vertigan et al. J Allergy Clin Immunol Pract E-pub*

# Laryngeal dysfunction

- After 4-week course of speech pathology treatment in 12 participants with mod-severe laryngeal dysfunction in the severe asthma group

**TABLE V.** Pre- and post-treatment results

| Outcome measures | Pretreatment M (SD) | Post-treatment M (SD) | Change M (SD) | *P* value |
|---|---|---|---|---|
| Questionnaire scores | | | | |
| Laryngeal Hypersensitivity Questionnaire | 12.7 (3.9) | 15.1 (4.4) | 2.4 (2.5) | .005 |
| Leicester Cough Questionnaire | 12.3 (4.3) | 14.6 (4.8) | 2.3 (2.4) | .005 |
| Voice Handicap Index | 32.8 (14.4) | 27.2 (19.5) | 5.6 (15.6) | .218 |
| Asthma Control Questionnaire | 2.5 (1.0) | 2.0 (0.8) | 0.5 (0.7) | .020 |
| Objective measures | | | | |
| Maximum phonation time | 9.9 (5.7) | 9.2 (3.0) | 0.7 (5.9) | .697 |
| CAPE-V | 30.6 (13.4) | 22.5 (11.8) | 8.0 (0.54) | .054 |
| Harmonic to noise ratio | 9.9 (6.0) | 15.7 (4.8) | 5.9 (7.1) | .028 |
| Cough frequency | 9.4 (5.3) | 8.8 (4.0) | 0.5 (7.3) | .864 |

*CAPE-V*, Consensus Auditory Perceptual Evaluation-Voice; *M*, mean; *SD*, standard deviation.

**Table 2** Examples of strategies in the treatment programme

| Component | Example |
|---|---|
| Education | No physiological benefit from cough; capacity for voluntary cough control |
| Strategies to reduce cough | Identify warning signs for cough and replace with modified swallow technique, pursed lip breathing exercise, or relaxed throat breath |
| Reduce laryngeal irritation | Increase hydration, decrease exposure to irritating stimuli |
| Psycho-educational counselling | Internalising locus of control; acceptance that treatment is hard work; setting realistic goals |

**중증 천식 특징 4.**
Speech pathology treatment가 laryngeal dysfunction 및 천식 조절에 도움된다.

*Vertigan et al.*
*J Allergy Clin Immunol Pract E-pub*

# Treatment I:  Pharmacotherapy

# Oral corticosteroids

**Table 1** Prevalence of OCS-related comorbidities in patients with severe asthma

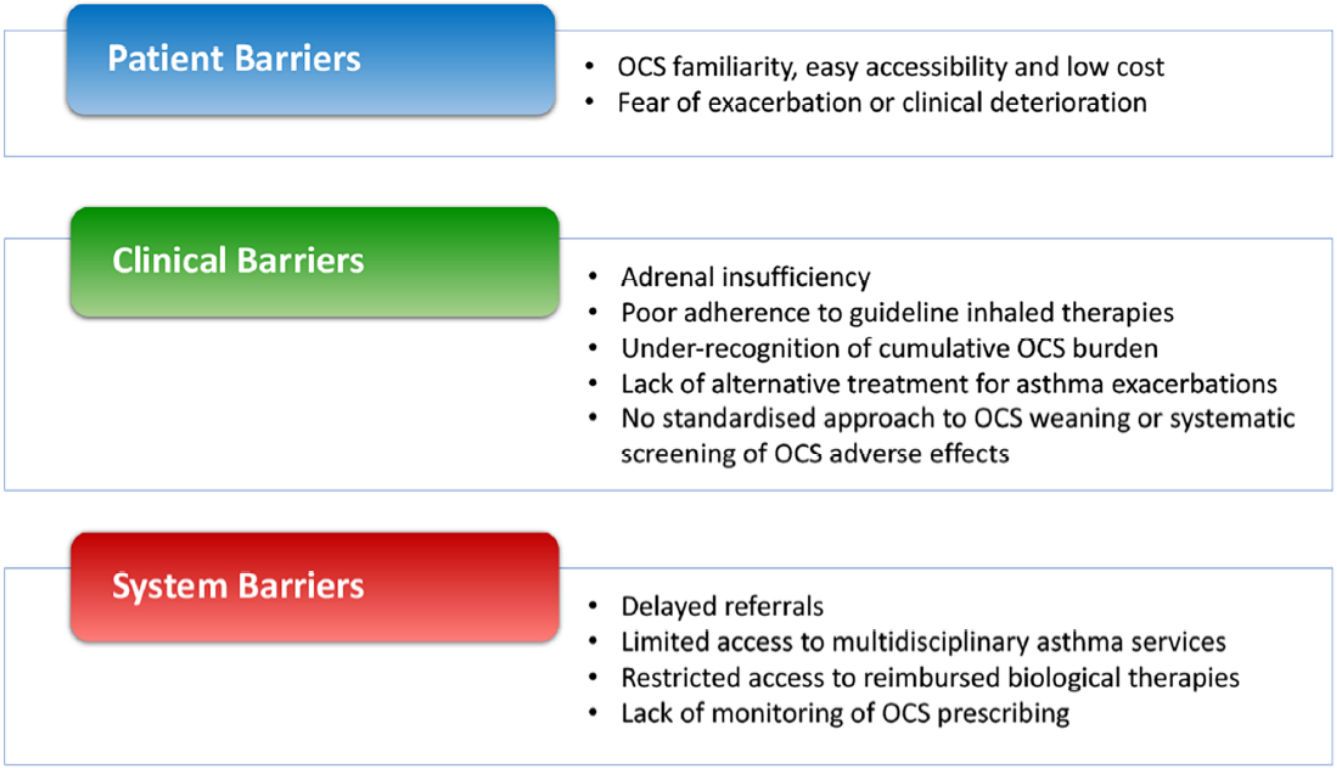
| OCS-related comorbidities | Prevalence (%) |
|---|---|
| Dyspeptic disorders | 65 |
| Obesity (body mass index >30) | 42 |
| Psychiatric disorders | 38 |
| Hypertension | 34 |
| Osteoporosis | 16 |
| Hypercholesterolaemia | 15 |
| Type 2 diabetes | 10 |
| Osteopenia | 10 |
| Cardiovascular disease | 10 |
| Cataract | 9 |
| Fracture | 5 |
| Glaucoma | 4 |
| Sleep disorder | 4 |

Prevalence data from the cross-sectional Optimum Patient Care Research Database and the British Thoracic Society Difficult Asthma registry ($n = 808$) (Adapted from Sweeney *et al.*[7]).

**중증 천식 치료 1**. OCS의 부작용

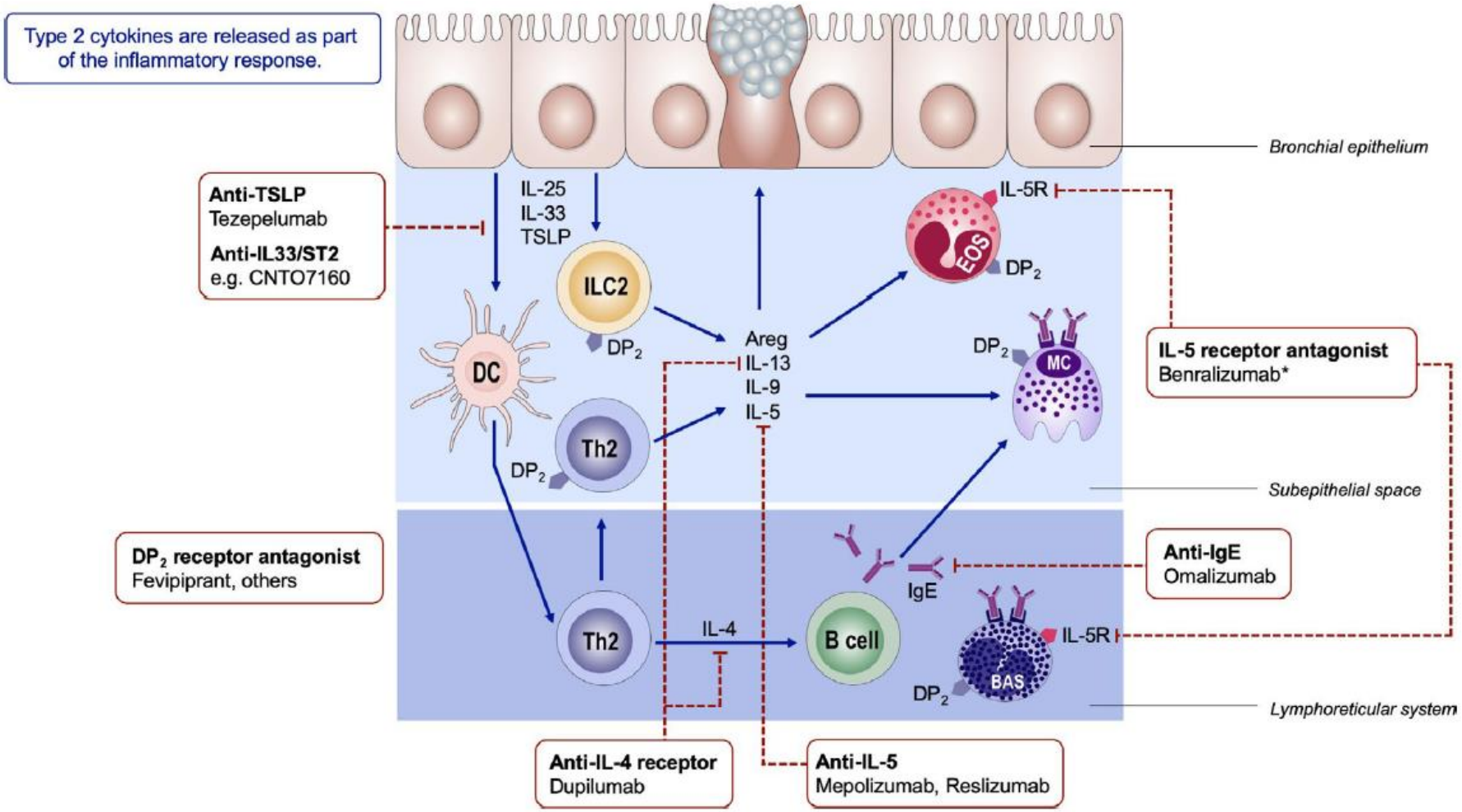
*Chung et al. Respirology 2020;25:161-72*

# Barriers of OCS-sparing strategies




**중증 천식 치료 1.** OCS-sparing strategies의 어려움

*Chung et al. Respirology 2020;25:161-72*




**중증 천식 치료 2.** Biologics

*McDowell et al. Allergy 2020;75:302-10*

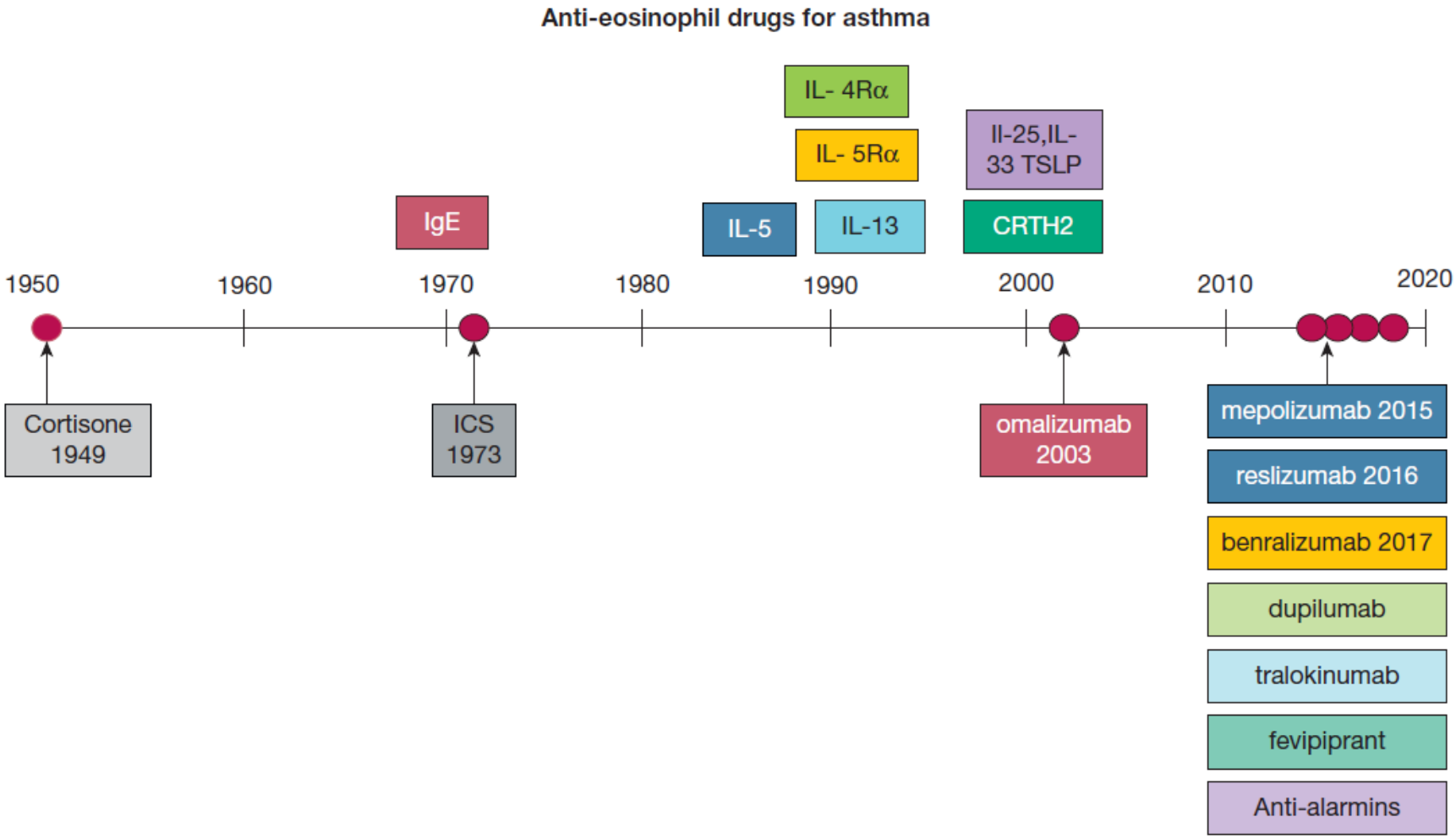



Figure 2 – *Anti-eosinophil drugs for asthma. See Figure 1 legend for expansion of abbreviations.*

Bel et al. Chest 2017;152:1276-82

# ERS/ATS guidelines

ERS OFFICIAL DOCUMENTS
ERS/ATS GUIDELINES


**Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline**

**[The ERS/ATS task force makes recommendations ]**

- Biologics
- Antimuscarinic agents
- Macrolides
- Biomarkers for predicting treatment response

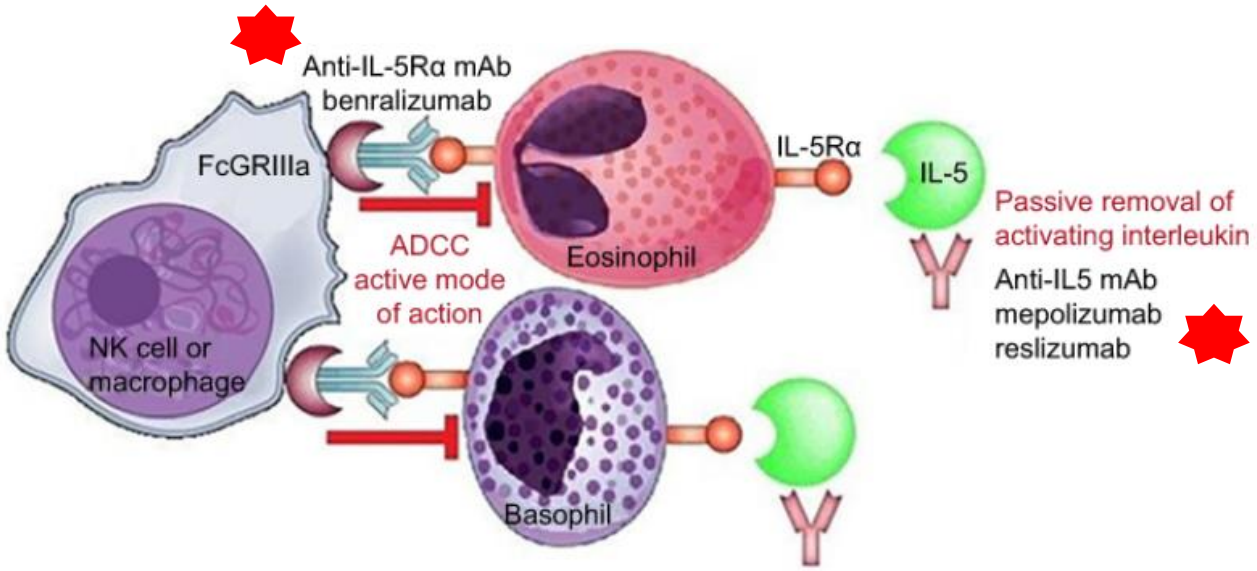
**중증 천식 치료 2.** Biologics recommendations – ERS/ATS guideline

*Holguin et al. Eur Respir J 2020;55:1900588*

# ERS/ATS guidelines

**[Question 1. Should a monoclonal anti-IL-5 antibody be used in adults and children with severe asthma?]**

- Mepolizumab
- Reslizumab
- Benralizumab




Holguin et al.
Eur Respir J
2020;55:1900588

# ERS/ATS guidelines

**[Mepolizumab-I]**

- 135 severe asthma (≥6-month history of **glucocorticoids**) with eosinophilia (≥ 300/μL before screening or 150/μL during optimization phase)
- 100 mg mepolizumab SC every 4 wk

**Table 2. Primary and Secondary Outcomes.**

| Outcome | Placebo (N = 66) | Mepolizumab (N = 69) | Odds Ratio (95% CI)* | P Value |
|---|---|---|---|---|
| Reduction in oral glucocorticoid dose at 20 to 24 wk: primary outcome — no. (%)† | | | 2.39 (1.25–4.56) | 0.008 |
| 90 to 100% | 7 (11) | 16 (23) | | |
| 75 to <90% | 5 (8) | 12 (17) | | |
| 50 to <75% | 10 (15) | 9 (13) | | |
| >0 to <50% | 7 (11) | 7 (10) | | |
| No decrease in oral glucocorticoid dose, a lack of asthma control, or withdrawal from treatment | 37 (56) | 25 (36) | | |

The median percentage reduction of GC was **50%**

*Bel et al. N Engl J Med* ***2014***;371:1189-97

# ERS/ATS guidelines

## [Mepolizumab-II]

- 576 severe asthma (**≥2 exacerbation** during the previous year) with **eosinophilia** (≥ 300/μL before screening or 150/μL during optimization phase)
- 75 mg IV or 100 mg mepolizumab SC every 4 wk

**Table 2. Summary of Efficacy Outcomes.***

| Outcome | Placebo (N=191) | Intravenous Mepolizumab (N=191) | Difference from Placebo (95% CI) | P Value | Subcutaneous Mepolizumab (N=194) | Difference from Placebo (95% CI) | P Value |
|---|---|---|---|---|---|---|---|
| Mean rate of clinically significant exacerbations | 1.74 | 0.93 | 47 (28 to 60)† | <0.001 | 0.83 | 53 (36 to 65)† | <0.001 |
| Mean rate of exacerbations requiring hospitalization or emergency department visit | 0.20 | 0.14 | 32 (−41 to 67)† | 0.30 | 0.08 | 61 (17 to 82)† | 0.02 |
| Mean rate of exacerbations requiring hospitalization | 0.10 | 0.06 | 39 (−66 to 77)† | 0.33 | 0.03 | 69 (9 to 89)† | 0.03 |
| Change from baseline in $FEV_1$ — ml | | | | | | | |
| Before bronchodilation | 86±31 | 186±32 | 100 (13 to 187) | 0.02 | 183±31 | 98 (11 to 184) | 0.03 |
| After bronchodilation | 30±34 | 176±34 | 146 (50 to 242) | 0.003 | 167±33 | 138 (43 to 232) | 0.004 |
| Change from baseline in score on Asthma Control Questionnaire | −0.50±0.07 | −0.92±0.07 | −0.42 (−0.61 to −0.23) | <0.001 | −0.94±0.07 | −0.44 (−0.63 to −0.25) | <0.001 |
| Change from baseline in score on St. George's Respiratory Questionnaire | −9.0±1.2 | −15.4±1.2 | −6.4 (−9.7 to −3.2) | <0.001 | −16.0±1.1 | −7.0 (−10.2 to −3.8) | <0.001 |

The rate of exacerbations was reduced by **47% (IV)** and **53% (SC).**

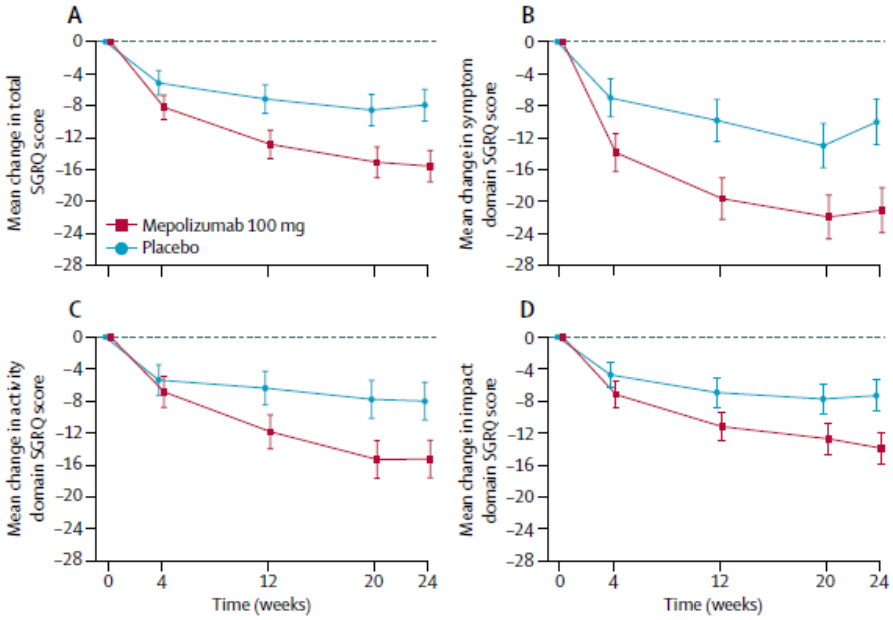
*Ortega et al. N Engl J Med 2014;371:1198-207*

# ERS/ATS guidelines

**MUSCA study**

**[Mepolizumab-III]**

- 274 severe asthma (≥2 exacerbation during the previous year) with eosinophilia (≥ 300/μL before screening or 150/μL during optimization phase)
- 100 mg mepolizumab SC every 4 wk



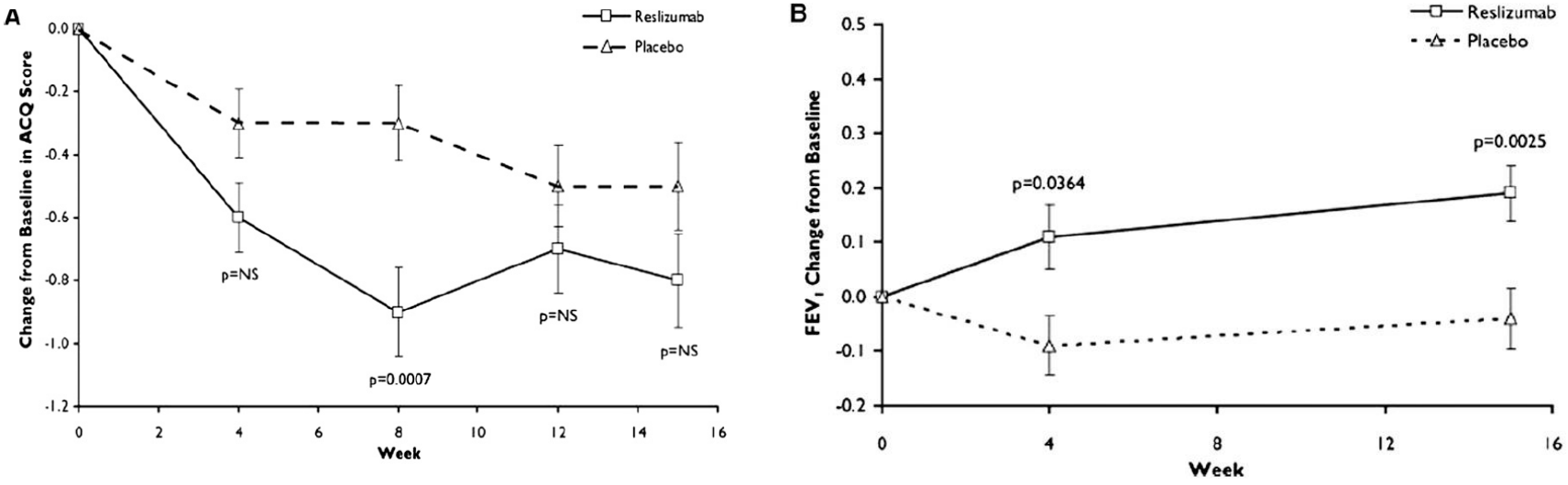

Mepolizumab showed significant improvement in **SGRQ** total score (-15.6 vs. -7.9), and reduced exacerbation rate (**58%**).

*Chupp et al. Lancet Respir Med 2017;5:390-400*

# ERS/ATS guidelines

**[Reslizumab-I]**

- 106 severe asthma with eosinophilia (≥ **3% sputum** eosinophil)
- **0.3 or 3.0 mg/kg** reslizumab IVF every 4 wk



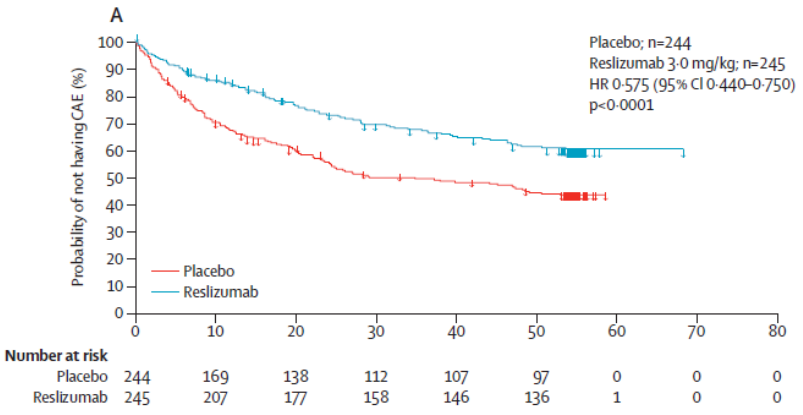

Reslizumab improved asthma **symptom, $FEV_1$,** symptoms, and reduced sputum eosinophils.

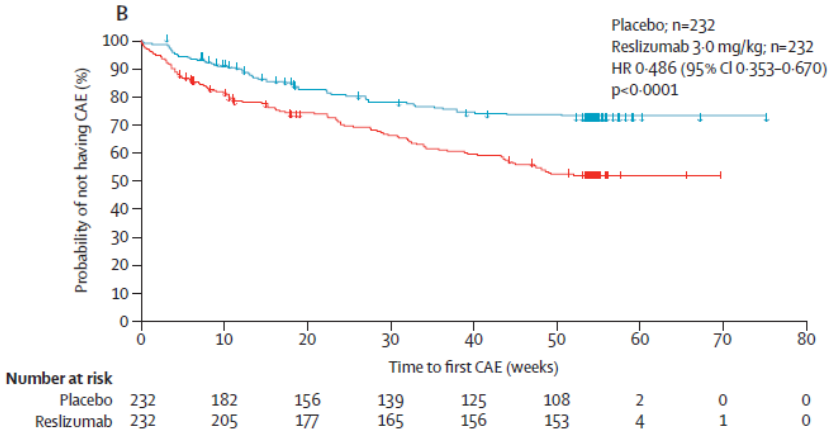
*Castro et al.*
*Am J Respir Crit Care Med* ***2011***;184:1125-32

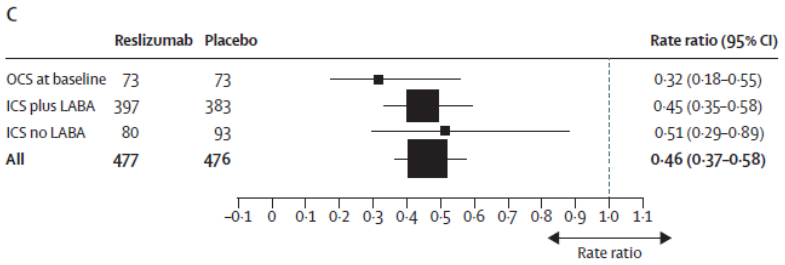
# ERS/ATS guidelines

**[Reslizumab-II]**

- 489 and 464 severe asthma with **eosinophilia (≥ 400/μL** during screening period) and at least one of exacerbation history in previous year
- **3.0 mg/kg reslizumab** IVF every 4 wk



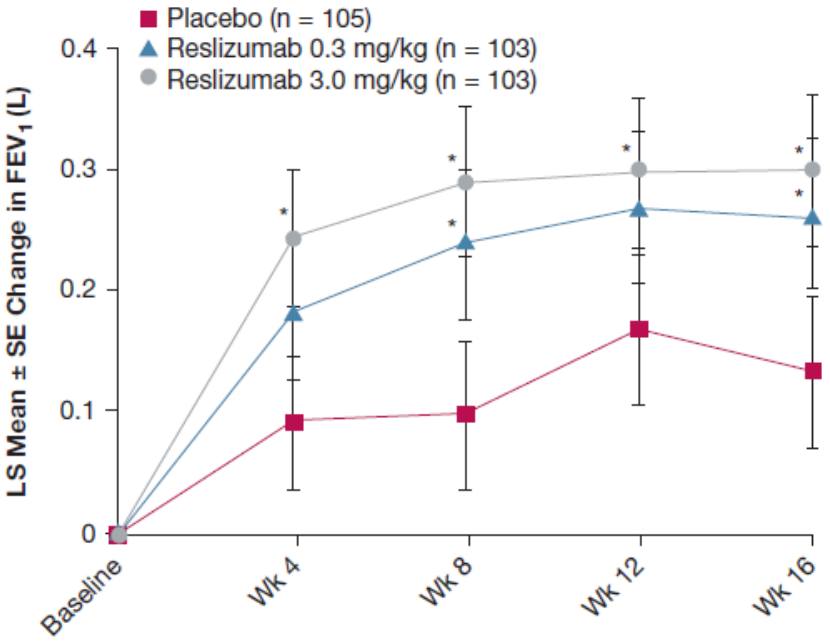

Reslizumab reduced **exacerbation rate** by 50%.

*Castro et al. Lancet Respir Med **2015**;3:355-66*

# ERS/ATS guidelines

**[Reslizumab-III]**

- 315 severe asthma with eosinophilia (≥ 400/μL during screening period)
- 0.3 or 3.0 mg/kg reslizumab IVF every 4 wk



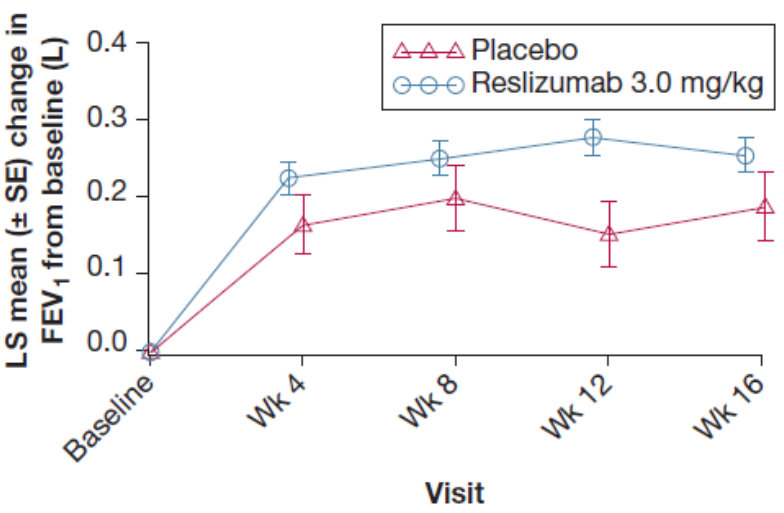

Reslizumab **improved $FEV_1$,** symptoms, and QOL.

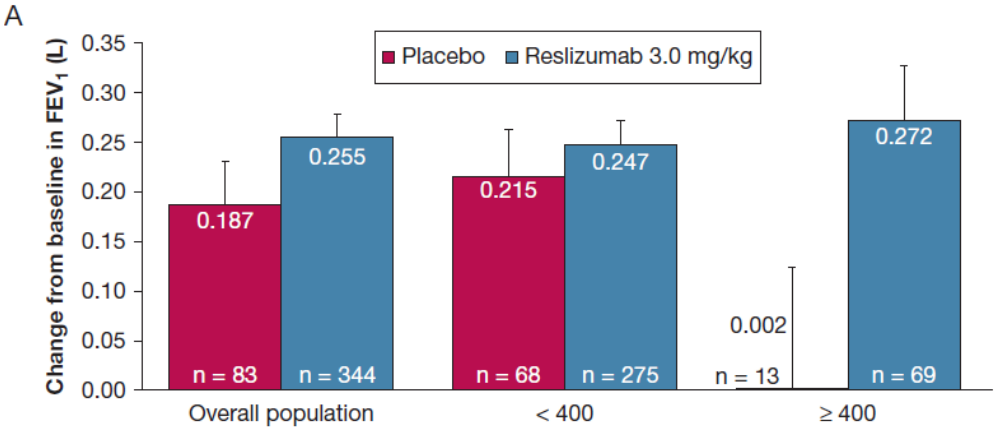
*Bjermer et al. Chest 2016;150:789-98*

# ERS/ATS guidelines

**[Reslizumab-IV]**

- 492 severe asthma (Regardless of eosinophilia)
- 3.0 mg/kg reslizumab IVF every 4 wk



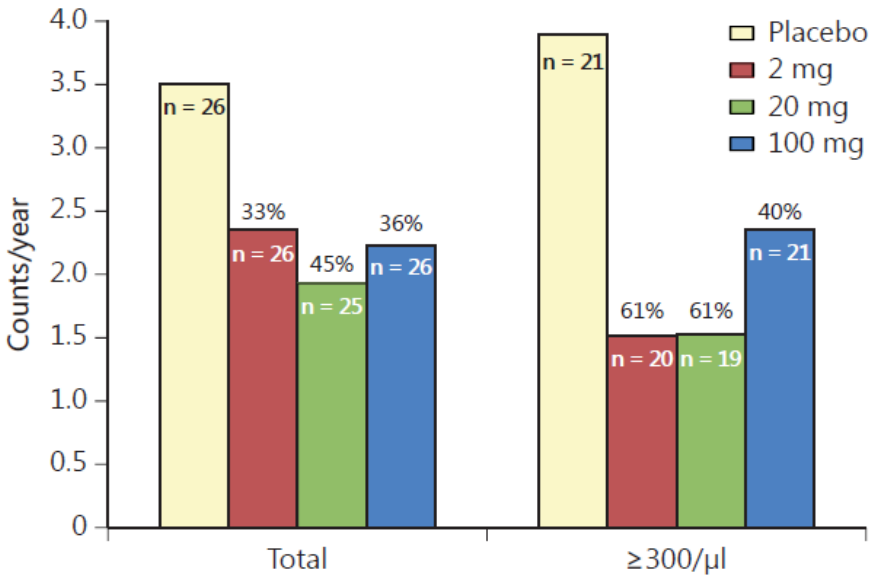

Reslizumab did not improve asthma, but it did in patients with eosinophilia (≥ 400/μL )

*Corren et al. Chest 2016;150:799-810*

# ERS/ATS guidelines

**[Reslizumab-V]**

- 106 severe asthma with eosinophilia (≥ 2% sputum eosinophil or ≥ 50 ppb FeNO) in South **Korea and Japan**
- **2 mg, 20 mg, 100 mg** reslizumab IVF every 4 wk



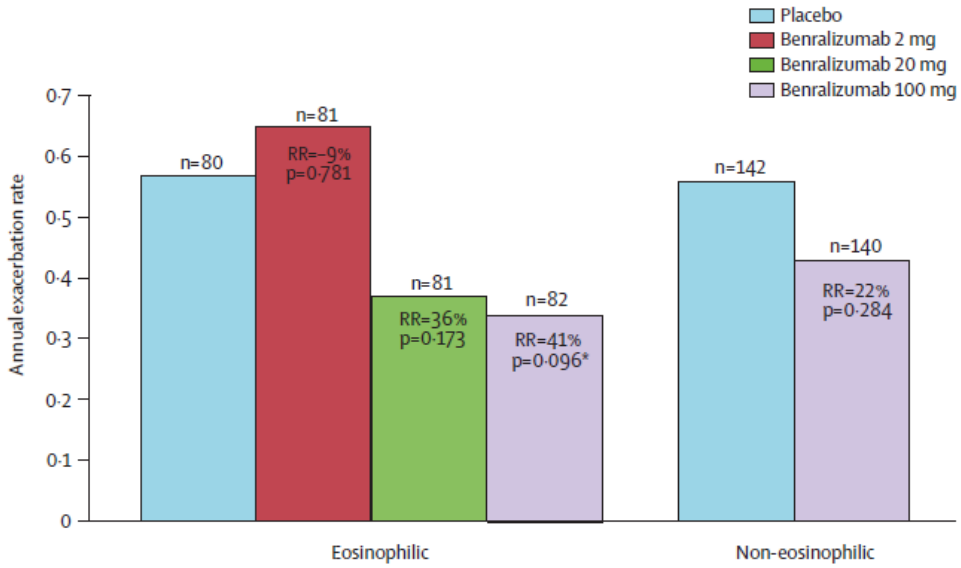

Reslizumab reduced asthma exacerbation rate by **33, 45, 36%.**

*Park et al.*
*Int Arch Allergy Immunol*
*2016;169:135-45*

# ERS/ATS guidelines

**[Benralizumab-I]**

- 324 severe asthma (**GINA 4-5**) with **at least two** of exacerbation history in previous year (stratified by eosinophil status: ≥ 2% sputum eosinophil or ≥ 50 ppb FeNO )
- **2 mg, 20 mg, 100 mg** benralizumab IVF every 4 wk




Benralizumab (100 mg) reduced asthma exacerbation rate by **41%** (**eosinophilic**) **and 22%** (non-eosinophilic)

*Castro et al. Lancet Respir Med 2014;2:878-90*

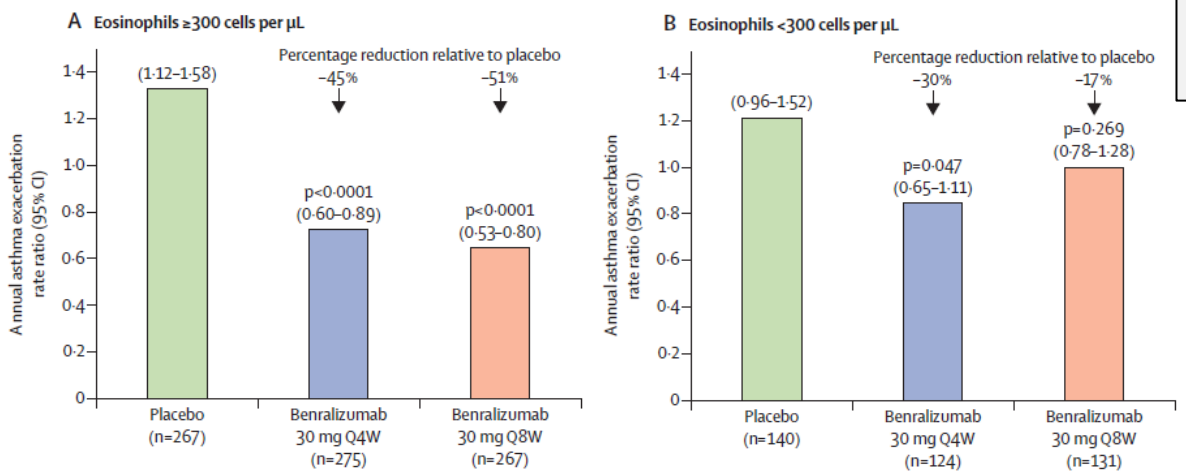
# ERS/ATS guidelines

**SIROCCO study**

**[Benralizumab-II]**

- 1,205 severe asthma (**GINA 4-5**) with **at least one** of exacerbation history in previous study (regardless of eosinophil)
- 30 mg Benralizumab IVF every 4 or 8 wk

Eos ≥ 300
: -45%, -51%




Eos <300
: -30%, -17%

Benralizumab reduced exacerbation rate.

*Bleecker et al. Lancet 2016;388:2115-27*

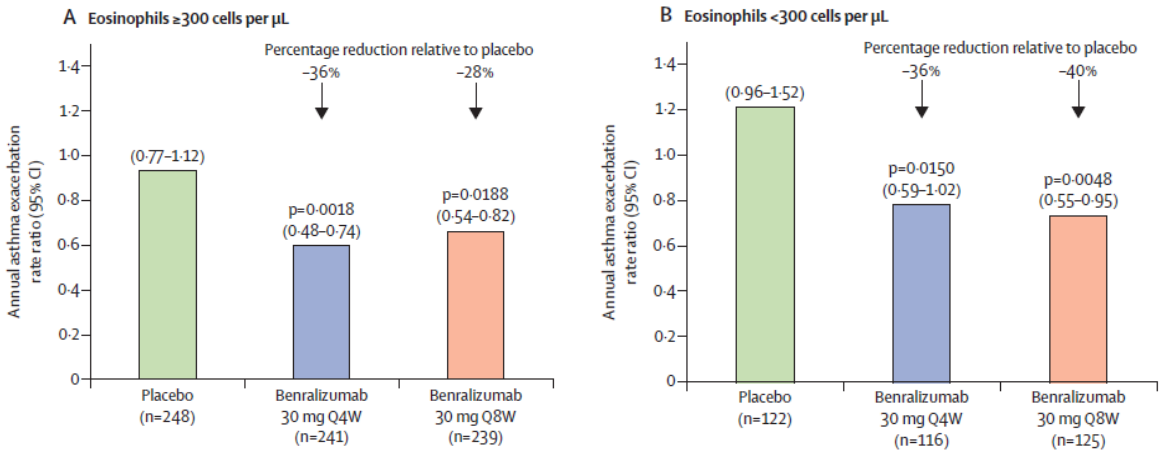
# ERS/ATS guidelines

**CALIMA study**

**[Benralizumab-III]**

- 1,306 severe asthma (**GINA 4-5**) with **at least two** of exacerbation history in previous year (stratified by eosinophil 300)
- 30 mg benralizumab IVF every 4 or 8 wk

Eos ≥ 300
: -36%, -28%




Eos <300
: -36%, -40%

Benralizumab reduced asthma exacerbation rate.

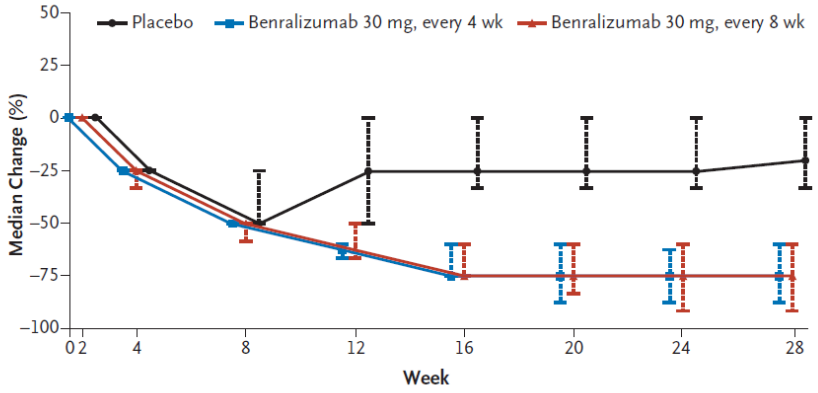
*FitzGerald et al. Lancet 2016;388:2128-41*

# ERS/ATS guidelines

**[Benralizumab-IV]**

- 220 severe asthma treated continuously with **oral glucocorticoids** for 6 months or more (regardless of eosinophil)
- 30 mg benralizumab IVF every 4 wks or 8 wks

A Change from Baseline in Oral Glucocorticoid Dose




| No. at Risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Benralizumab 30 mg, every 4 wk | 72 | 70 | 70 | 69 | 69 | 68 | 66 | 68 |
| Benralizumab 30 mg, every 8 wk | 70 | 72 | 67 | 69 | 69 | 66 | 69 | 68 |
| Placebo | 74 | 75 | 73 | 74 | 74 | 73 | 73 | 72 |

Reslizumab reduced oral glucocorticoid (OR **4.09-4.12**), and exacerbation rate (**55% and 70%**).

*Nair et al. N Engl J Med 2017;376:2448-58*

# ERS/ATS guidelines

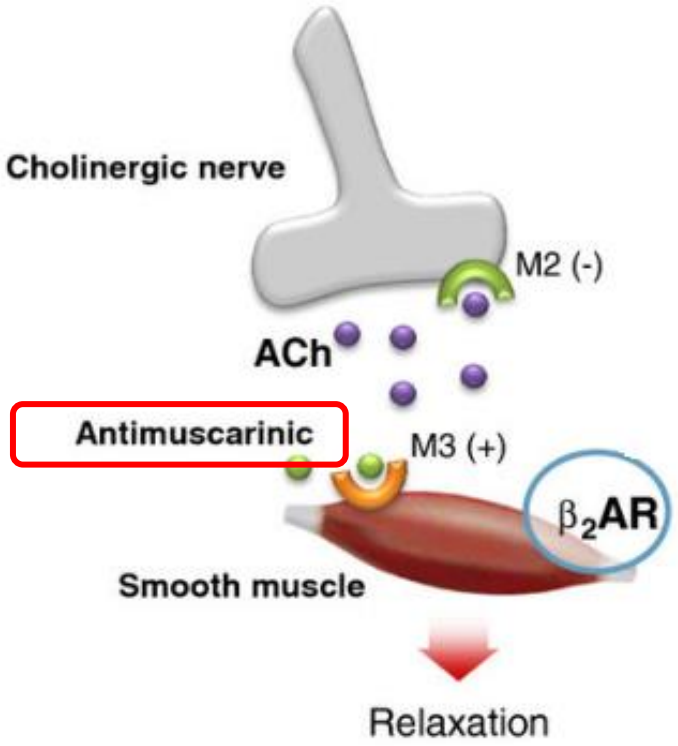
**[Question 1. Should a monoclonal anti-IL-5 antibody be used in adults and children with severe asthma?]**

- We suggest an **anti-IL-5 strategy** as **add-on therapy** for adult patients with severe uncontrolled asthma with an **eosinophilic phenotype** and for those with severe **corticosteroid-dependent asthma** (the Task Force gave this a conditional recommendation because inclusion criteria across studies did not consistently align with the ERS/ATS severe asthma definition).

*Holguin et al.*
*Eur Respir J*
*2020;55:1900588*

# ERS/ATS guidelines

**[Question 4. Should a long-acting inhaled muscarinic antagonist be used in adults and children with severe asthma?**

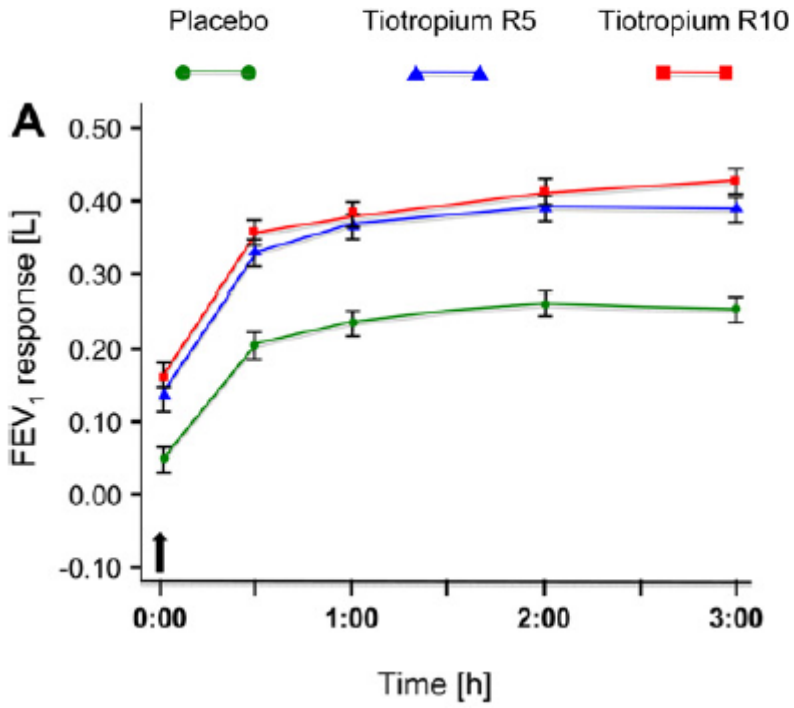



*Holguin et al. Eur Respir J 2020;55:1900588*

# ERS/ATS guidelines

**[Tiotropoium-I]**

- 107 severe asthma (**absolutely excluded COPD**)
- Tiotropium **5 or 10 μg** every for 8 wks



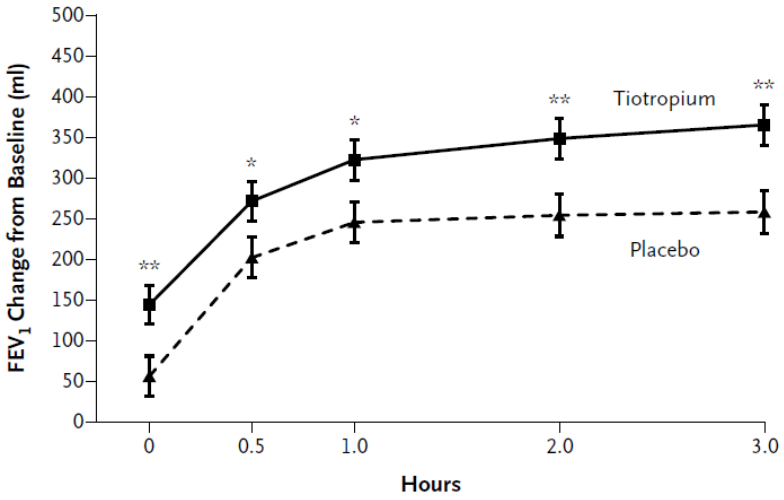

Tiotropium improved **lung function** over 24 hrs

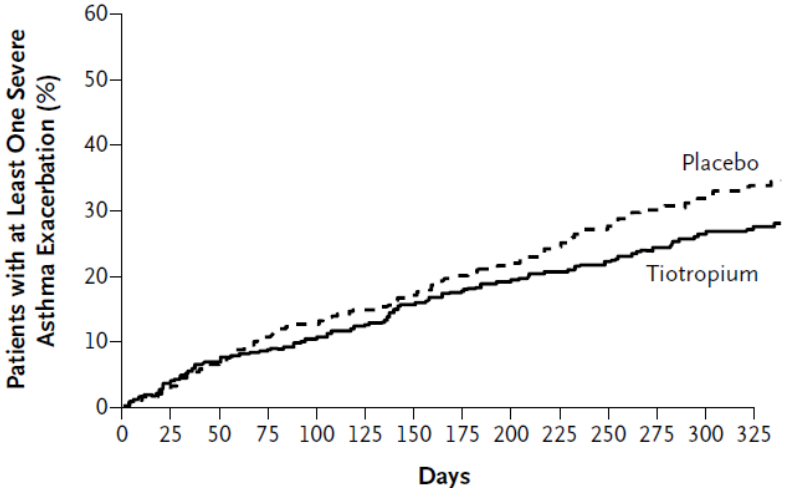
*Kerstjens et al.*
*J Allergy Clin Immunol*
*2011;128:308-14*

# ERS/ATS guidelines

**[Tiotropoium-II]**

- 912 severe asthma (**GINA 4-5**) with at least once acute exacerbation in the previous year (absolutely excluded COPD)
- Tiotropium **5 μg** every for **48 wks**



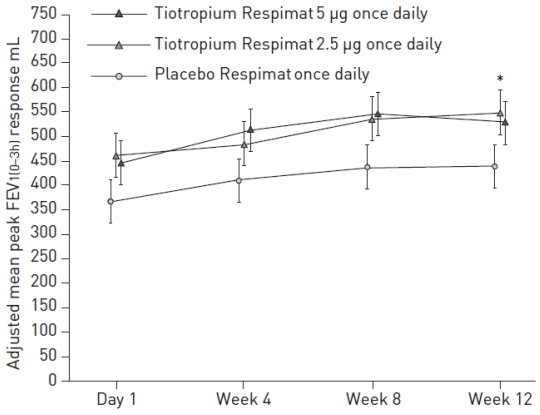

Tiotropium reduced risk of **severe exacerbation** and provided modest sustained bronchodilation

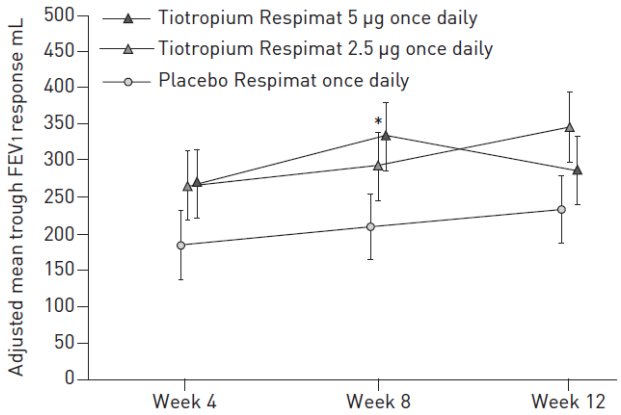
*Kerstjens et al. N Engl J Med 2012;367:1198-207*

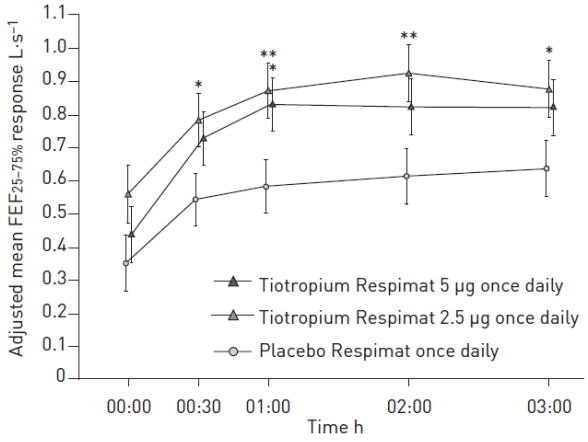
# ERS/ATS guidelines

**[Tiotropoium-III]**

- 392 severe (**GINA 4-5**) asthma
- Tiotropium **2.5** or 5 μg every for **12 wks**




Although **primary end-point efficacy was not met**, positive trends for improvements in lung function and asthma control were observed.

*Hamelmann et al. Eur Respir J 2017;49:1601100*

# ERS/ATS guidelines

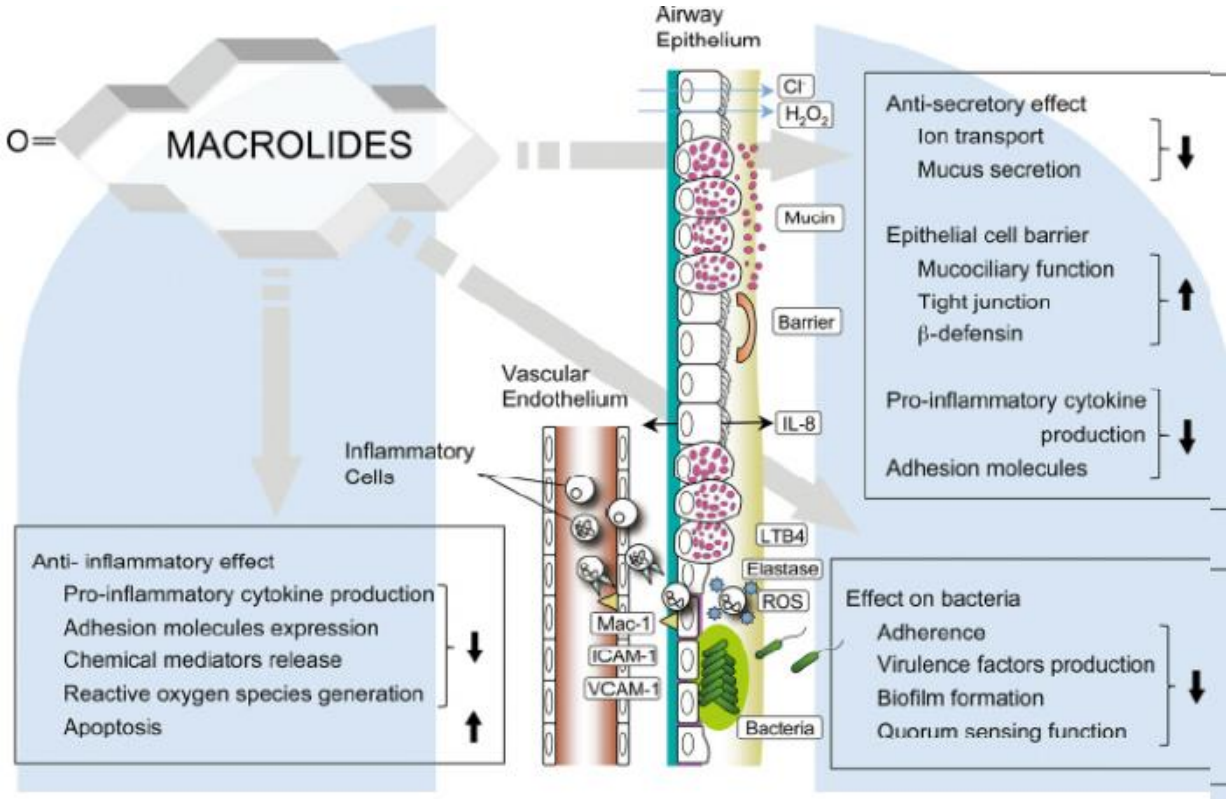
**[Question 4. Should a long-acting inhaled muscarinic antagonist be used in adults and children with severe asthma?**

- Adults with severe asthma uncontrolled despite GINA step 4–5 or NAEPP step 5 therapies, we recommend the addition of tiotropium (**strong recommendation**, moderate quality of evidence).

*Holguin et al.*
*Eur Respir J*
*2020;55:1900588*

# ERS/ATS guidelines

**[Question 5. Should a macrolide (i.e. azithromycin, clarithromycin) be used in adults and children with severe asthma?]**

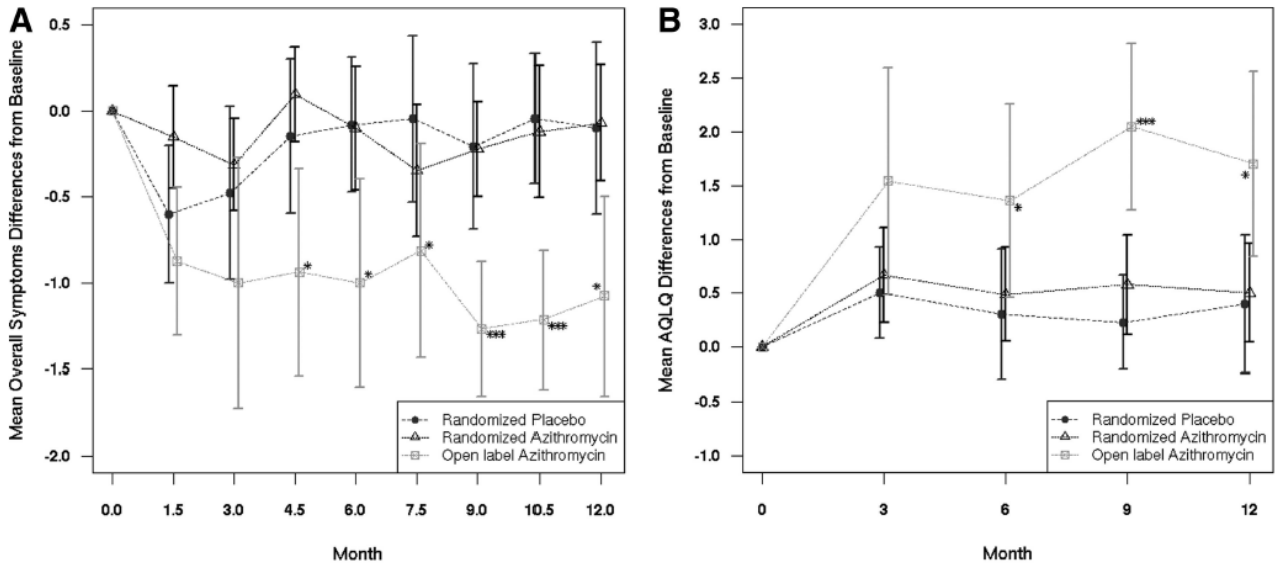



Holguin et al. Eur Respir J 2020;55:1900588

# ERS/ATS guidelines

**[Macrolide-I]**

- 97 **mild**-to-severe asthma
- **600 mg** azithromycin 1 tablet **weekly** for 11 wks (← after 3 days daily)




Azithromycin **did not** show significant improvement in asthma outcomes

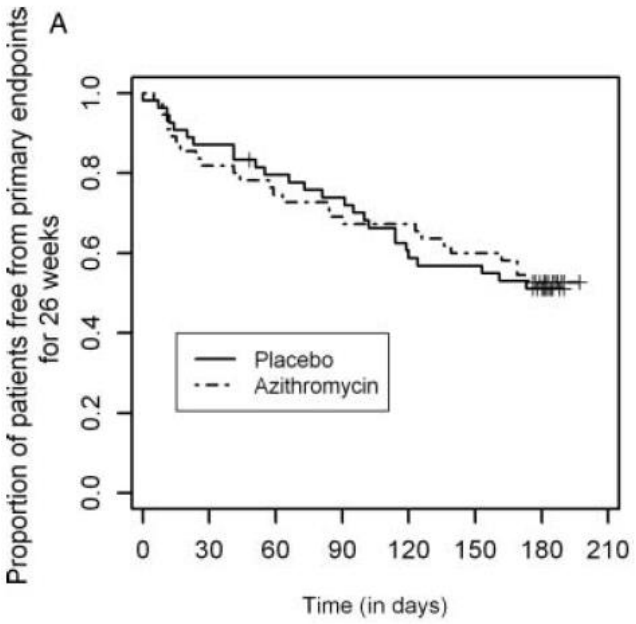
*Habn et al.*
*J Am Board Fam Med*
*2012;25:422-59*

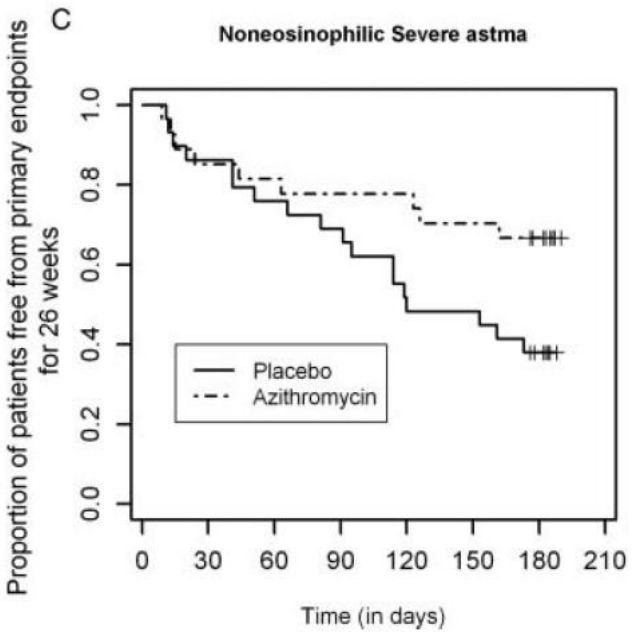
# ERS/ATS guidelines

**AZISAST study**

**[Macrolide-II]**

- 104 severe asthma with at least once severe exacerbation (normal FeNO)
- **250 mg** azithromycin **three times** a week (← after 5 days)




Azithromycin only reduced the rate of severe exacerbation in non-eosinophilic severe asthma (Normal FeNO & eosinophil < 200/μL).

*Brusselle et al. Thorax 2013;68:322-9*

# ERS/ATS guidelines

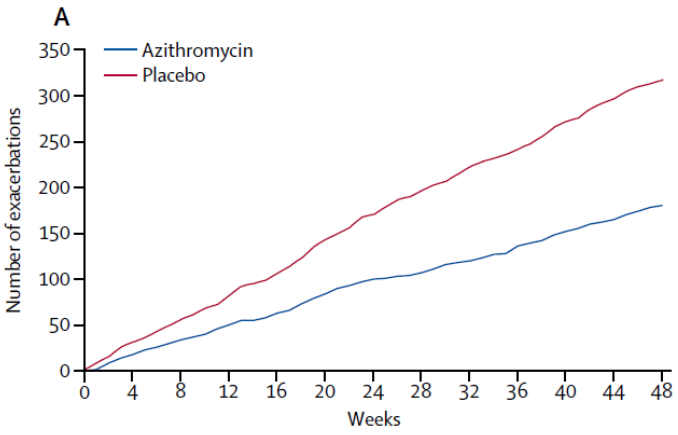
**AMAZES study**

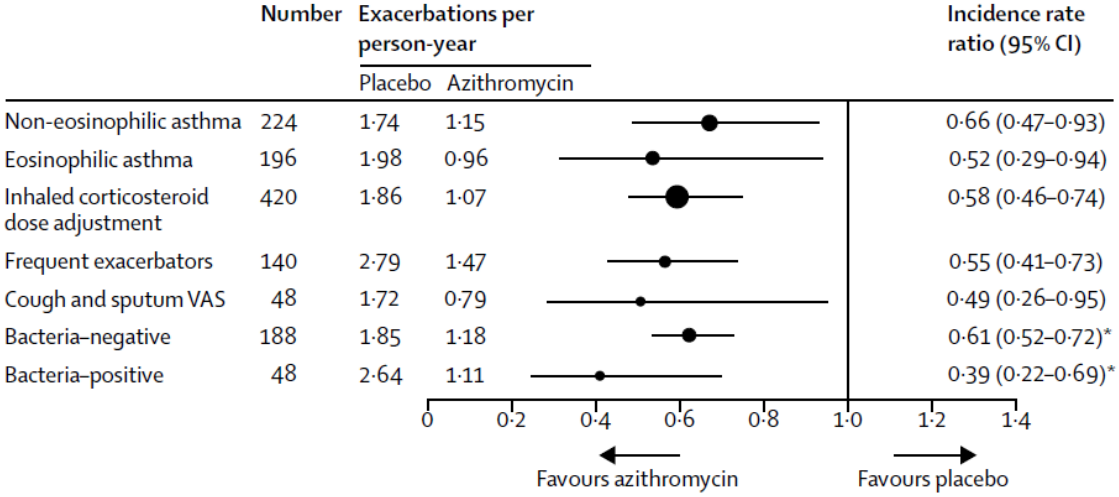
**[Macrolide-III]**

- 420 **mod**-to-severe asthma (no hearing impairment or abnormal QT interval)

  , however, severe asthma was predominant (>80%)

- **500 mg** azithromycin **three times** per week for 48 wks




Azithromycin reduced asthma exacerbation by **41%** and improved QOL. **Diarrhea** was common side effect.

*Gibson et al. Lancet 2017;390:659-68*

# ERS/ATS guidelines

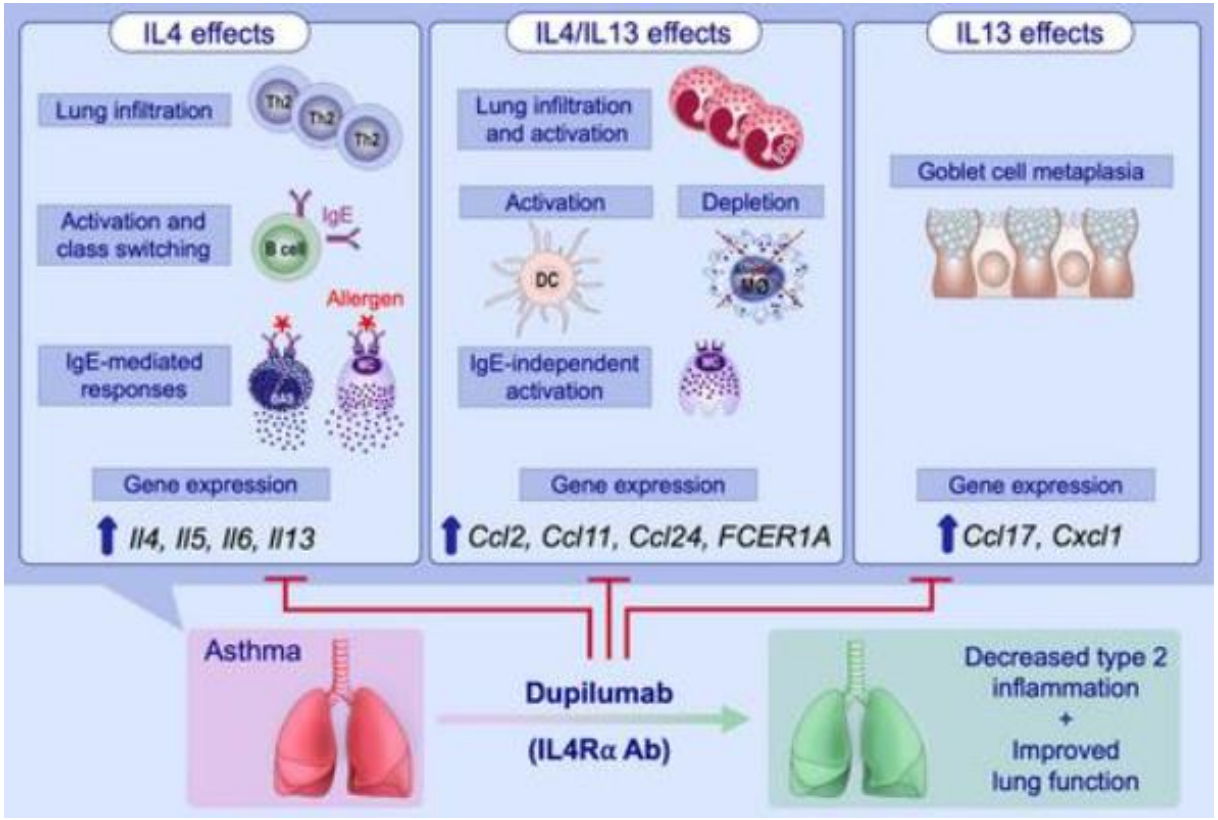
**[Question 5. Should a macrolide (i.e. azithromycin, clarithromycin) be used in adults and children with severe asthma?]**

- We suggest a **trial of macrolide** treatment to reduce asthma exacerbations in adult asthma subjects on GINA/NAEPP step 5 therapy that remain persistently symptomatic or uncontrolled (**conditional** recommendation, low quality of evidence)
- We suggest against the use of chronic macrolide treatment in children and adolescents with severe uncontrolled asthma (conditional recommendation, low quality of evidence).

*Holguin et al.*
*Eur Respir J*
*2020;55:1900588*

# ERS/ATS guidelines

**[Question 6. Should a monoclonal anti-IL-4Rα be used in adults and children with severe asthma?]**

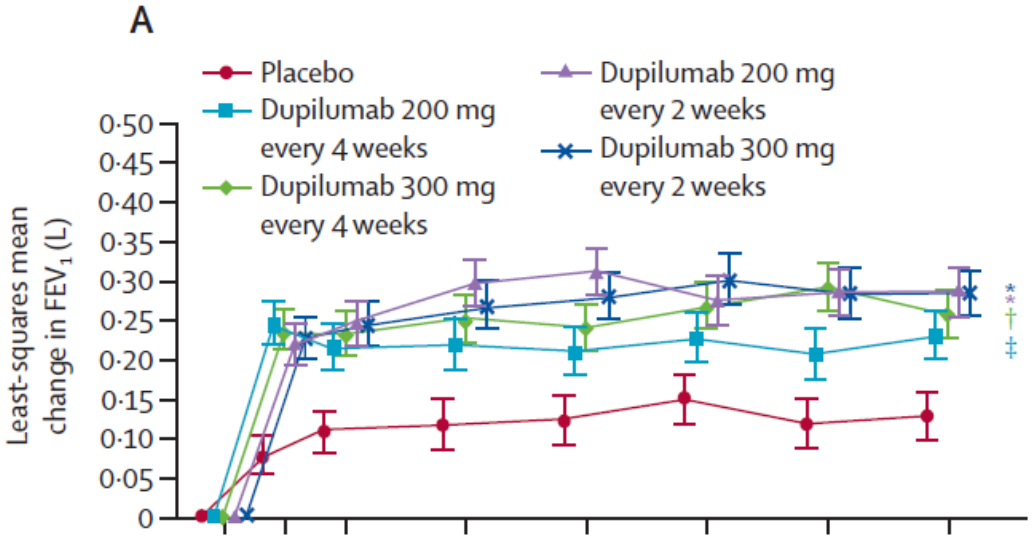



Holguin et al. Eur Respir J 2020;55:1900588

# ERS/ATS guidelines

**[Dupilumab-I]**

- 769 severe asthma (**GINA 4-5**) with at least two of exacerbation history in previous year (regardless of eosinophil)
- 200 or 300 mg dupilumab SQ every 2 wks or 4 wks



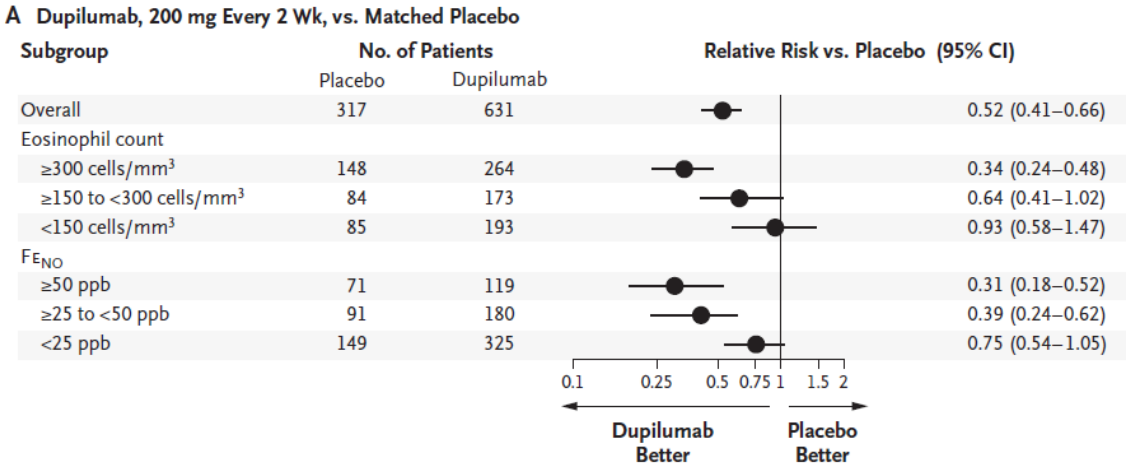

Dupilumab increased lung function (**100-200 mL**) and reduced severe exacerbation (**OR, 6.97-8.75**) irrespective of baseline eosinophil count.

*Castro et al. Lancet 2016;388:31-44*

# ERS/ATS guidelines

**[Dupilumab-II]**

- 1,902 severe asthma (**GINA 4-5**) with at least two of exacerbation history in previous year (regardless of eosinophil)
- 200 or 300 mg dupilumab SQ every 2 wks



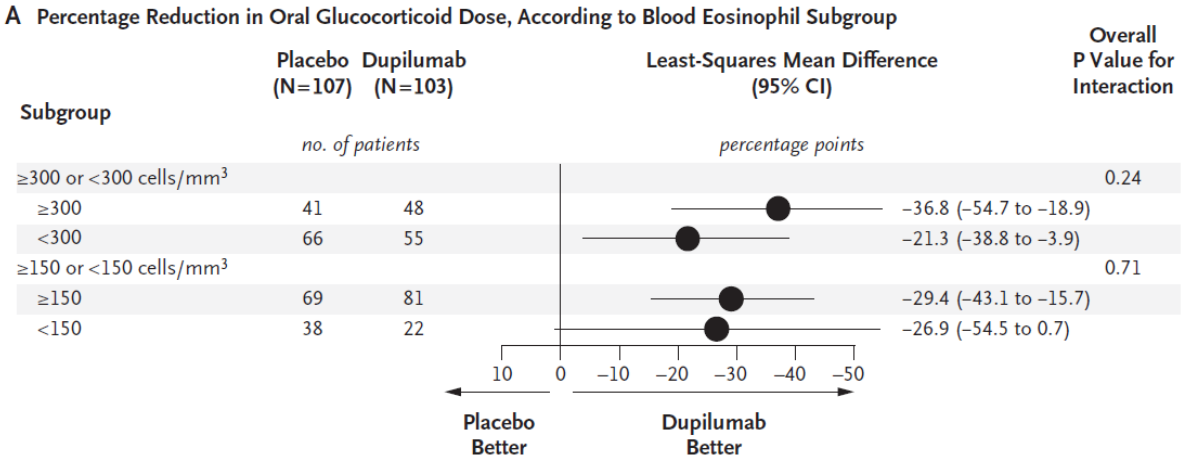

Dupilumab had lower rates of severe asthma exacerbation **(OR, 0.52),** as well as better lung function and asthma control. Greater benefits were seen in patients with higher baseline levels of eosinophils.

*Castro et al. N Engl J Med 2018;378:2486-96*

# ERS/ATS guidelines

**[Dupilumab-III]**

- 210 severe asthma (**GINA 4-5**) treated regular with oral glucocorticoids for 6 months or more (regardless of eosinophil)
- 300 mg dupilumab SQ every 2 wks




Dupilumab reduced oral glucocorticoid use (**70% vs. 42%**) while decreasing the rate of severe exacerbations and increasing the $FEV_1$.

*Rabe et al. N Engl J Med 2018;378:2475-85*

# ERS/ATS guidelines

**[Question 6. Should a monoclonal anti-IL-4Rα be used in adults and children with severe asthma?]**

- We suggest dupilumab as add-on therapy for adult patients with **severe eosinophilic asthma** and for those with **severe corticosteroid-dependent** asthma regardless of eosinophil levels (conditional recommendation).

# The END

*Holguin et al. Eur Respir J 2020;55:1900588*

| | Anti-IgE | Anti-IL-5/anti-IL5R | Anti-IL-4R |
|---|---|---|---|
| **Eligibility in GINA** | Sensitization or sIgE<br>Total IgE & weight<br>Exacerbation in last year | Exacerbation in last year<br>BEC≥300/μL | Exacerbation in last year<br>BEC≥150/μL or FeNO >25 ppb<br>or need for maintenance OCS |
| **Good response recommended in GINA** | BEC≥260/μL<br>FeNO≥20ppb<br>Allergen-driven symptom<br>Childhood-onset asthma | High BEC<br>More exacerbation in previous year<br>Adult-onset of asthma<br>Nasal polyposis | High BEC<br>High FeNO<br>(+moderate/severe AD, nasal polyposis) |
| **Insurance/permission** | In High-dose ICS/LABA+LAMA<br>1)) IgE≥76IU/mL<br>2) Sensitization or sIgE to perennial allergen<br>3) FEV1 <80%<br>4) ≥ 2 exerbation requiring systemic steroid in last 12 months<br>**(+LAMA)** | **Nucala**: uncontrolled severe eosinophilic asthma (**BEC≥150/μL in initial or BEC≥300/μL in last 12 m**)<br>**Cinqair**: **BEC≥400/μL** in initial<br>**Fasenra**: uncontrolled severe eosinophilic asthma | **BEC≥150/μL, FeNO≥25ppb, OCS dependent** |
| **Cost (won/1 vial)** | 270,000 (real: 162,000) (150 mg) | **Nucala:** 2,000,000 (100 mg)<br>**Cinqair**: 560,000 (100 mg)<br>**Fasenra**: 3,000,000 (30 mg) | 680,000 |
| **Dose** | Total IgE*weight<br>(usual: 150-600 mg sc 4w) | **Nucala:** 100 mg sc q4w<br>**Cinqair:** 3 mg/kg IVF q4w<br>**Fasenra**: 30 mg sc q4w for 3 times -> 30 mg sc q8w | 2 vial (initial) + 1 vial sc q2w |
| **Cost (won/1 month)** | 162,000~648,000 | **Nucala:** 2,000,000<br>**Cinqair:** 1,120,000<br>**Fasenra:** 3,000,000 -> 1,500,000 | 1,360,000 |

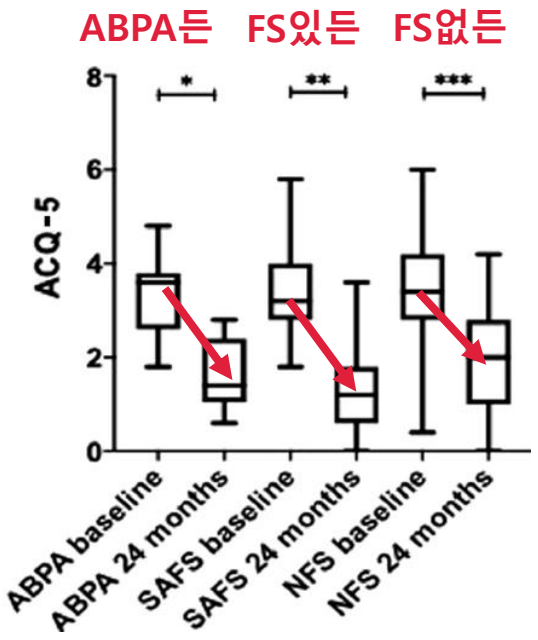
# Omalizumab in SA with fungal sensitization (or ABPA)

- 62 (with FS including 11 ABPA) vs. 156 (without FS) severe asthma (≥2 exacerbation during the previous year)

TABLE II. Response to treatment with omalizumab

| | ASAFS baseline | ASAFS 24 mo | Mean change/adjusted mean change (95% CI), *P* value | Difference (SAFS − NFS) in change over time (95% CI), *P* value |
|---|---|---|---|---|
| No. of subjects | 62 | 42 | | |
| ACQ-5, mean ± SD | 3.39 ± 0.74 | 1.31 ± 0.88 | −2.1 (−2.54 to −1.67), <.001<br>−1.60 (−1.85 to −1.35), <.001 | −0.30 (−0.82 to 0.22) *P* = .25 |
| Exacerbations, mean ± SD | 1.11 ± 0.51 | 0.35 ± 0.65 | IRR = 0.35 (0.16 to 0.73), .005<br>IRR = 0.40 (0.17 to 0.91), .029 | IRR = 0.51 (0.22 to 1.12), *P* = .11 |
| OCS dose (mg/d), median (IQR) | 10 (10 to 20) | 0 (0 to 0) | OR = 0.06 (0.16 to 0.22), <.001<br>OR = 0.09 (0.02 to 0.38), .001 | OR = 1.32 (0.30 to 0.59), .71 |

*IQR*, Interquartile range; *IRR*, incident rate ratio; *OR*, odds ratio.

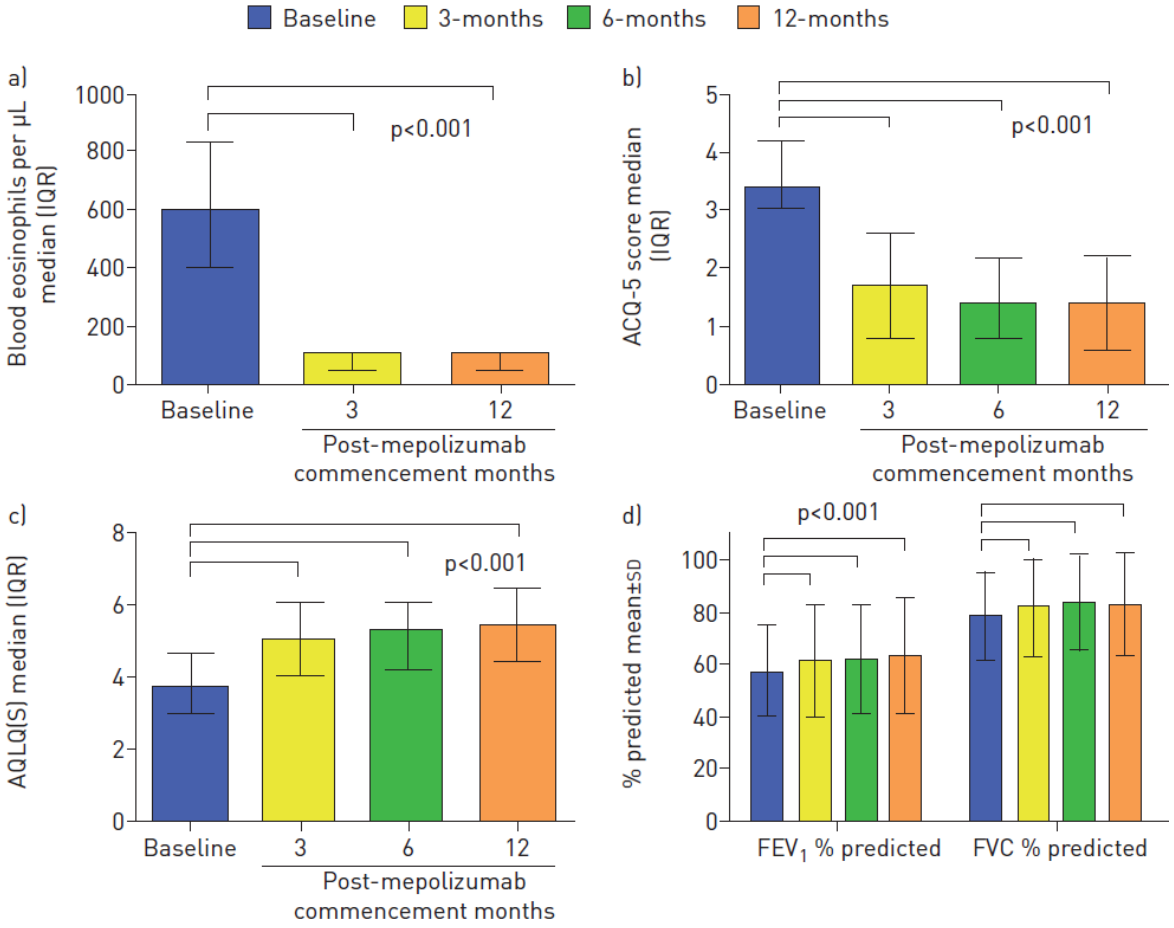



**중증 천식 치료 2-1.** Omalizumab – FS/ABPA 상관없이 효과적

*Peter et al.*
*J Allergy Clin Immunol Pract E-pub*

# Real-world study of mepolizumab

- 309 severe eosinophilic asthma in real-world observational data: **AMR**



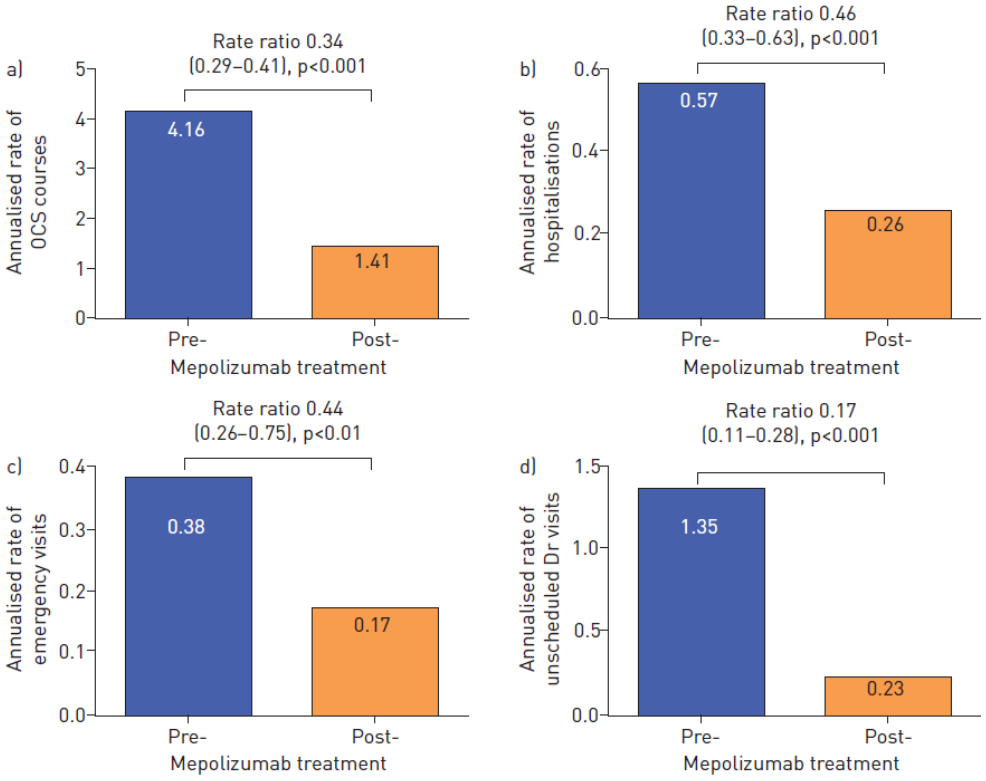

Real-world에서 **mepolizumab**은 blood eosinophil, ACQ-5 score, AQLQ, 및 $FEV_1$에 **효과적**

* Eosinophilic asthma: ≥300 cell/mL in the previous 12 m
* AMR: Australian Mepolizumab Registry

*Hary et al. Eur Respir J 2020;55:1902420*

# Real-world study of mepolizumab

- 309 severe eosinophilic asthma in real-world observational data: **AMR**




Real-world에서 **mepolizumab**은 OCS사용, 입원, 응급실 방문, 외래 방문 감소에 **효과적**

**중증 천식 치료 2-2.** Mepolizumab – real-world에서 효과적

*Hary et al. Eur Respir J 2020;55:1902420*

# Real-world study of mepolizumab

- 309 severe eosinophilic asthma in real-world observational data: **AMR**

TABLE 4 Adverse drug-related reactions in patients treated with mepolizumab

| | |
|---|---|
| **Patients n** | **309** |
| **Total mepolizumab administration events n#** | **2374 (n=308)** |
| **Adverse drug reaction reported¶** | **57/304 (18.8%)** |
| Reaction type | |
| Anaphylaxis | 0/304 (0%) |
| Urticaria | 7 (2.3%) |
| Angioedema | 1 (0.3%) |
| Rash | 10 (3.3%) |
| Bronchospasm | 0 (0%) |
| Hypotension | 0 (0%) |
| Headache | 30 (9.9%) |
| Local site reaction | 10 (3.3%) |
| Other | 30 (9.9%) |
| **Mepolizumab ceased due to adverse drug reaction** | **6/309 (1.9%)** |
| Reaction | |
| Severe headache | 2 |
| Persistent eczematous reaction involving face, trunk and upper limbs | 1 |
| Arthralgia | 1 |
| Pruritus | 1 |
| Middle back pain | 1 |

Data are presented as n (%), n/N (%) or n, unless otherwise stated. #: Administration event missing for one patient; ¶: adverse drug reaction data missing for five patients.

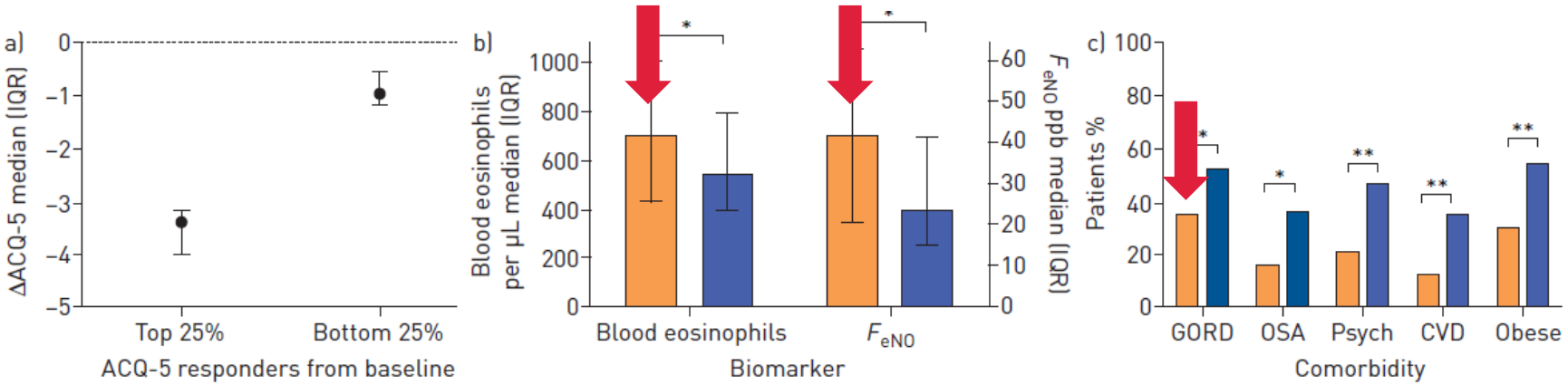
Real-world에서 **mepolizumab**은 비교적 **안전**

*Hary et al. Eur Respir J 2020;55:1902420*

**중증 천식 치료 2-2.** Mepolizumab – real-world에서 안전

# Real-world study of mepolizumab

- 309 severe eosinophilic asthma in real-world observational data: **AMR**




**Super-responder**는 blood eosinophil이 높고, FeNO가 높고, GERD, OSA, Psychiatric, CVD, and obesity등의 동반질환이 적은 **특징이 있음**.

*Hary et al.*
*Eur Respir J*
*2020;55:1902420*

**중증 천식 치료 2-2.** Mepolizumab – Super-responder 특징

# Long-term safety of reslizumab

- 1,028 reslizumab-treated patients (pooled-analysis of 6 trials)
- 3.0 mg/kg IV for 12-24 months

| Patients | Placebo (n = 730) | Reslizumab 3.0 mg/kg (n = 1028) | RR (95% CI) |
|---|---|---|---|
| AEs by system organ class | | | |
| Infections and infestations | 386 (53) | 420 (41) | 0.77 (0.70-0.85) |
| Respiratory, thoracic, and mediastinal disorders | 352 (48) | 320 (31) | 0.65 (0.57-0.73) |
| Nervous system disorders | 113 (15) | 123 (12) | 0.77 (0.61-0.98) |
| Gastrointestinal disorders | 108 (15) | 109 (11) | 0.72 (0.56-0.92) |
| Musculoskeletal and connective tissue disorders | 83 (11) | 106 (10) | 0.91 (0.69-1.18) |
| General disorders and administration-site conditions | 80 (11) | 77 (7) | 0.68 (0.51-0.92) |
| Investigations | 59 (8) | 73 (7) | 0.89 (0.63-1.22) |
| Skin and subcutaneous tissue disorders | 70 (10) | 71 (7) | 0.72 (0.53-0.99) |
| Injury, poisoning, and procedural complications | 62 (8) | 69 (7) | 0.79 (0.57-1.10) |
| Metabolism and nutrition disorders | 33 (5) | 37 (4) | 0.80 (0.50-1.26) |
| Vascular disorders | 19 (3) | 32 (3) | 1.20 (0.68-2.09) |
| Psychiatric disorders | 21 (3) | 21 (2) | 0.71 (0.39-1.29) |
| Eye disorders | 25 (3) | 19 (2) | 0.55 (0.30-0.98) |
| Cardiac disorders | 37 (5) | 18 (2) | 0.35 (0.20-0.60) |
| Immune system disorders | 16 (2) | 17 (2) | 0.75 (0.38-1.48) |
| Ear and labyrinth disorders | 11 (2) | 16 (2) | 1.03 (0.48-2.21) |
| AEs by preferred term | | | |
| Asthma | 289 (40) | 232 (23) | 0.57 (0.49-0.66) |
| Nasopharyngitis | 103 (14) | 103 (10) | 0.71 (0.55-0.92) |
| Upper respiratory tract infection | 69 (9) | 96 (9) | 0.99 (0.74-1.33) |
| Headache | 62 (8) | 78 (8) | 0.89 (0.65-1.22) |
| Sinusitis | 51 (7) | 57 (6) | 0.79 (0.55-1.14) |
| Bronchitis | 52 (7) | 34 (3) | 0.46 (0.30-0.71) |
| Urinary tract infection | 24 (3) | 34 (3) | 1.00 (0.60-1.69) |
| Back pain | 25 (3) | 33 (3) | 0.94 (0.56-1.56) |
| Influenza | 37 (5) | 33 (3) | 0.63 (0.40-1.00) |
| Rhinitis allergic | 22 (3) | 28 (3) | 0.90 (0.52-1.57) |
| Oropharyngeal pain | 16 (2) | 27 (3) | 1.20 (0.65-2.21) |
| Pharyngitis | 25 (3) | 23 (2) | 0.65 (0.37-1.14) |

2% 이상 흔히 발생한 부작용들 중, placebo에 비해 reslizumab에서 유의하게 부작용이 흔하게 발생한 것은 없었음.

*Virchow et al. J Allergy Clin Immunol Pract. 2020;8:540-8*

# Long-term safety of reslizumab

- 1,028 reslizumab-treated patients (pooled-analysis of 6 trials)
- 3.0 mg/kg IV for 12-24 months

TABLE V. AEs in patients with >12 mo of exposure to reslizumab—comparison with data for ≤12 mo

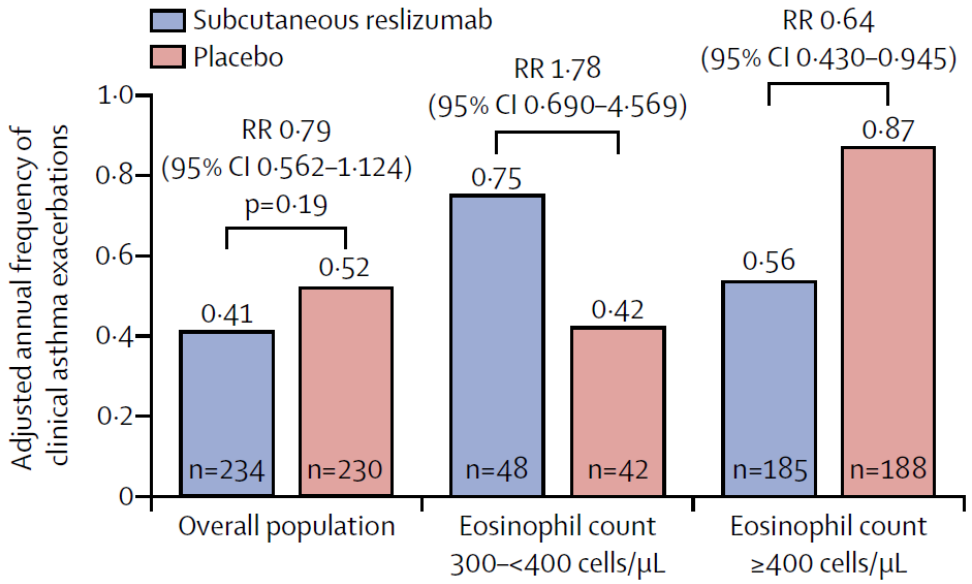
| | Reslizumab 3.0 mg/kg (exposure >12 mo)* (n = 756; 1262 patient-years) | | Placebo-controlled trials (≤52 wk) | | | |
|---|---|---|---|---|---|---|
| | | | Placebo (n = 730; 517 patient-years) | | Reslizumab 3.0 mg/kg (n = 1028; 612 patient-years) | |
| Patients | n (%) | Event rate (/100 patient-years) | n (%) | Event rate (/100 patient -years) | n (%) | Event rate (/100 patient-years) |
| Patients with ≥1 AEs | 651 (86) | 367 | 589 (81) | 588 | 690 (67) | 434 |
| Common AEs (>5% incidence) | | | | | | |
| Asthma | 320 (42) | 58.1 | 289 (40) | 147 | 232 (23) | 69.9 |
| Nasopharyngitis | 169 (22) | 24.4 | 103 (14) | 29.2 | 103 (10) | 25.0 |
| Upper respiratory tract infection | 123 (16) | 14.6 | 69 (9) | 19.5 | 96 (9) | 20.9 |
| Headache | 104 (14) | 12.8 | 62 (8) | 17.2 | 78 (8) | 18.9 |
| Sinusitis | 78 (10) | 11.4 | 51 (7) | 15.9 | 57 (6) | 12.7 |
| Bronchitis | 64 (8) | 6.42 | 52 (7) | 12.8 | 34 (3) | 6.20 |
| Influenza | 54 (7) | 6.10 | 37 (5) | 9.87 | 33 (3) | 6.86 |
| Patients with ≥1 SAEs | 87 (12) | 11.8 | 66 (9) | 21.1 | 65 (6) | 17.0 |
| AEs leading to discontinuation | 8 (1) | 0.871 | 40 (5) | 11.61 | 48 (5) | 8.65 |
| AEs of special interest | | | | | | |
| Infections and infestations | 506 (67) | 121 | 386 (53) | 163 | 420 (41) | 130 |
| Anaphylactic reaction | 1 (<1)† | 0.079 | 0 | 0 | 5 (<1)‡ | 0.816 |
| Malignancy | 12 (2) | 1.188 | 2 (<1) | 0.387 | 6 (<1) | 1.143 |
| Myalgia | 10 (1) | 0.792 | 4 (<1) | 1.16 | 10 (<1) | 1.63 |

*Virchow et al.*
*J Allergy Clin Immunol Pract. 2020;8:540-8*

**중증 천식 치료 2-3.** Reslizumab – 안전

# Fixed-dose of SC (110 mg) of reslizumab

- 468 + 177 reslizumab-treated patients (pooled-analysis of 2 trials)
- Fixed dose of 110 mg SC




Eosinophil 300-400 cell/mL인 경우, 급성악화, 폐기능, 증상 조절에 **효과 없음**.

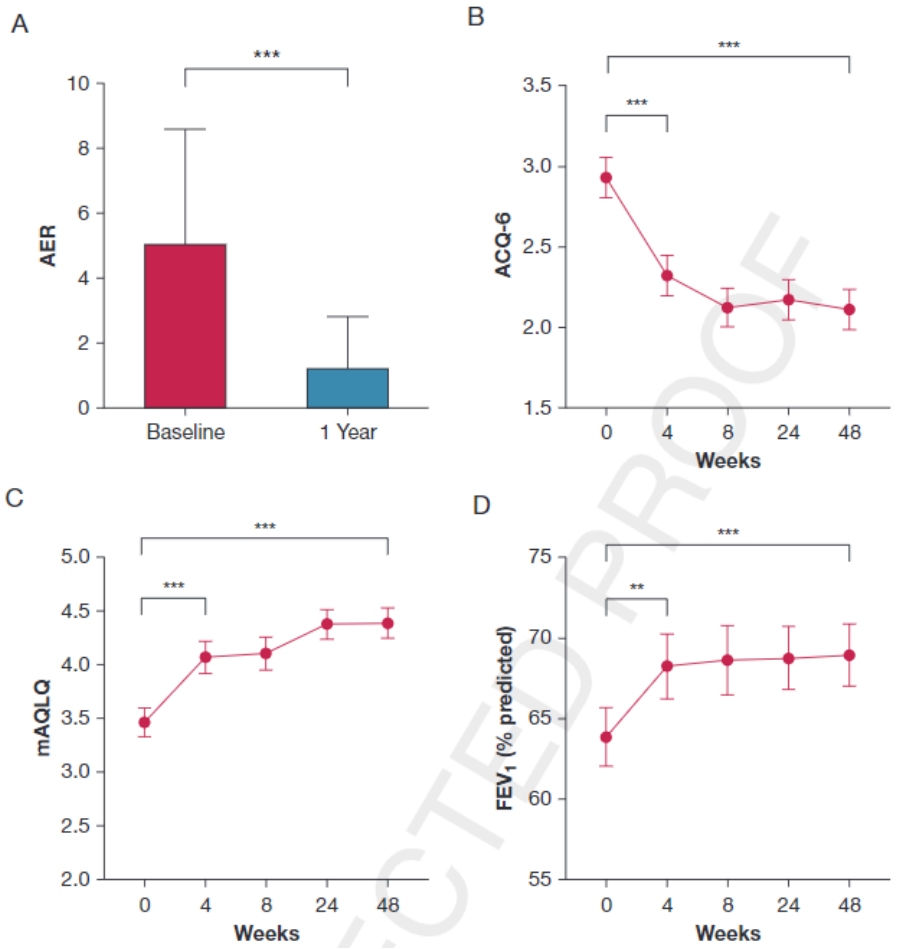
Fixed dose of 110 mg SC보다 높은 **충분한 용량의 reslizumab이 필요**할 것으로 사료됨.

*Bernstein et al. Lancet Respir Med 2020;8:461-74*

**중증 천식 치료 2-3.** Reslizumab – 충분한 용량 필요

# Real-world study of benralizumab

- 130 severe eosinophilic asthma with benralizumab

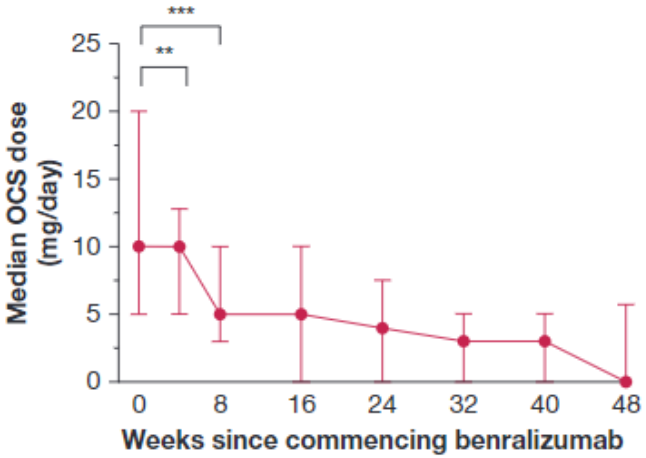


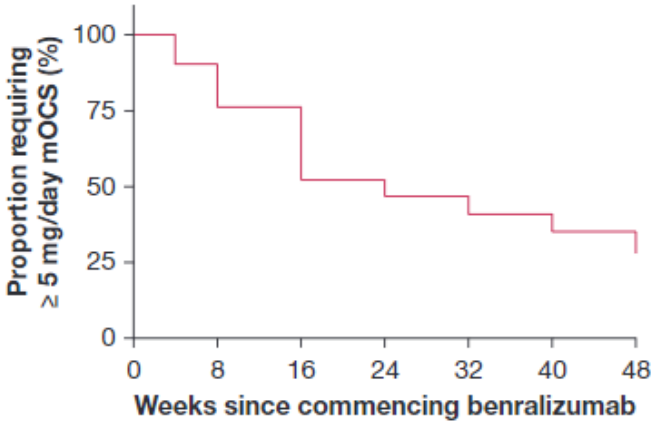

Benralizumab은 real-world에서 천식 조절 (**악화율 감소, 증상 및 삶의 질 개선, 폐기능 향상**) 효과 있음.

*Kavanagh et al. Chest In Press*

# Real-world study of benralizumab

- 130 severe eosinophilic asthma with benralizumab



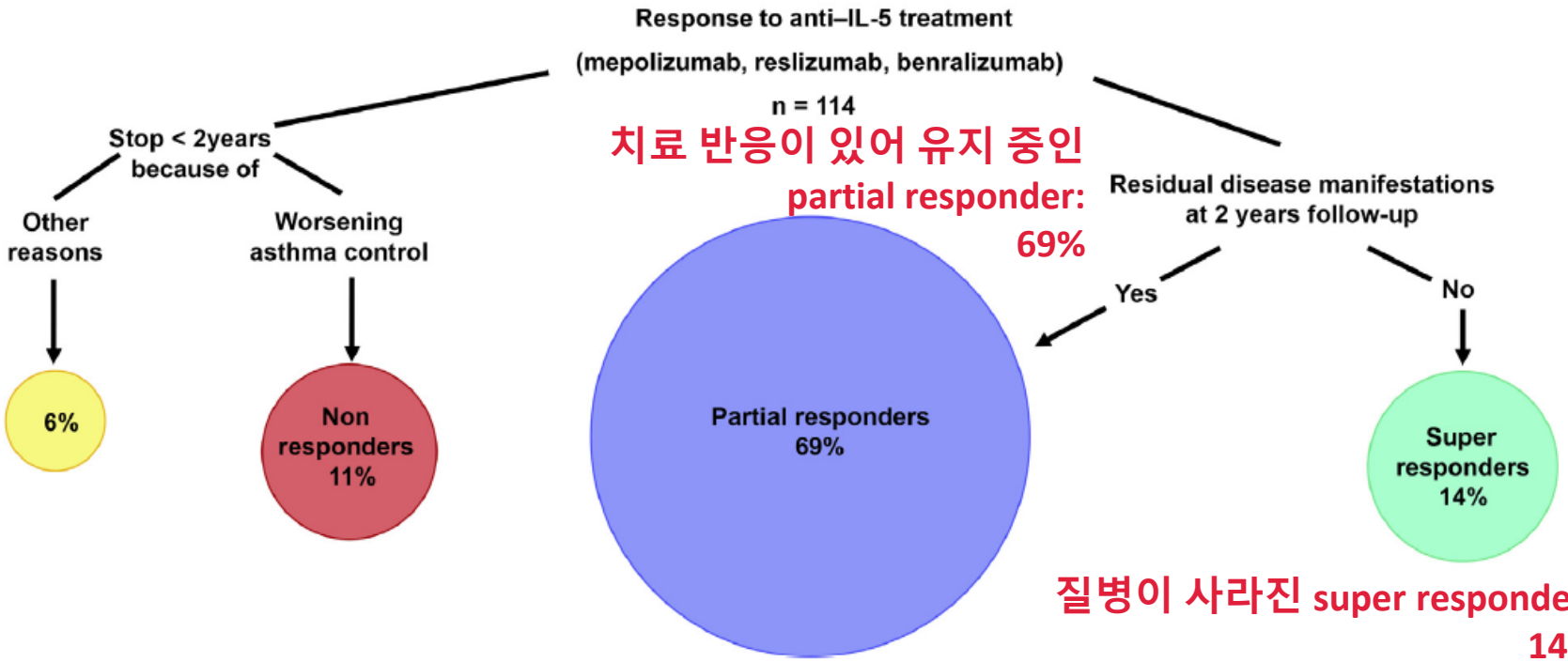

Benralizumab은 real-world에서 **스테로이드 감량**에 효과적임.

**중증 천식 치료 2-4.**
Benralizumab
– real-world에서도 효과적

*Kavanagh et al.*
*Chest*
*In Press*

# Long-term therapy response to anti-IL-5 biologics

- Real-life data after 2-year follow-up




치료 반응이 있어 유지 중인 partial responder: 69%

질병이 사라진 super responder: 14%

**중증 천식 치료.** Anti-IL-5 biologics의 long-term response

*Eger et al.*
*J Allergy Clin Immunol Pract*
*E-pub*

# Long-term therapy response to anti-IL-5 biologics

- Real-life data after 2-year follow-up

**TABLE II.** Predictors of super response to long-term anti–IL-5 biologics

| Predictor | Adjusted OR* | 95% CI | *P* value |
|---|---|---|---|
| Asthma onset ≥18 y | 5.961 | 0.706-50.311 | .101 |
| Absence of NPs | 5.950 | 0.721-49.082 | .098 |
| FEV ≥80% predicted | 3.708 | 1.120-12.284 | .032 |
| Asthma duration <10 y | 3.572 | 1.093-11.673 | .035 |
| BMI <25 | 2.675 | 0.820-8.719 | .103 |

*BMI*, Body mass index; *OR*, odds ratio.
*OR adjusted for age and sex.

**중증 천식 치료.** Anti-IL-5 biologics의 super-responder

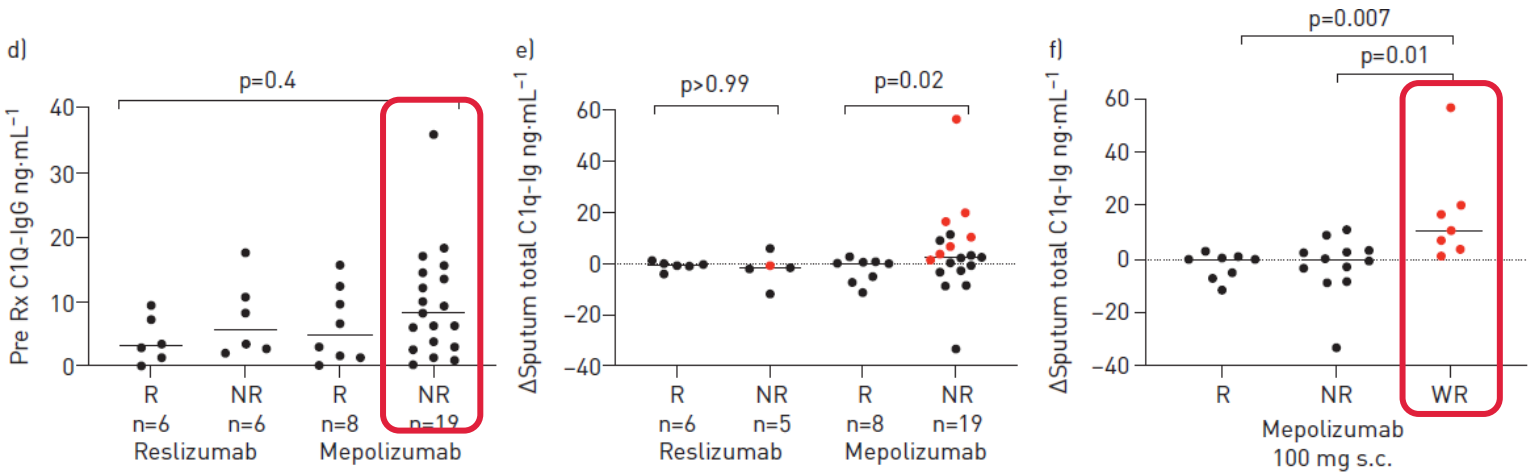
*Eger et al.*
*J Allergy Clin Immunol Pract*
*E-pub*

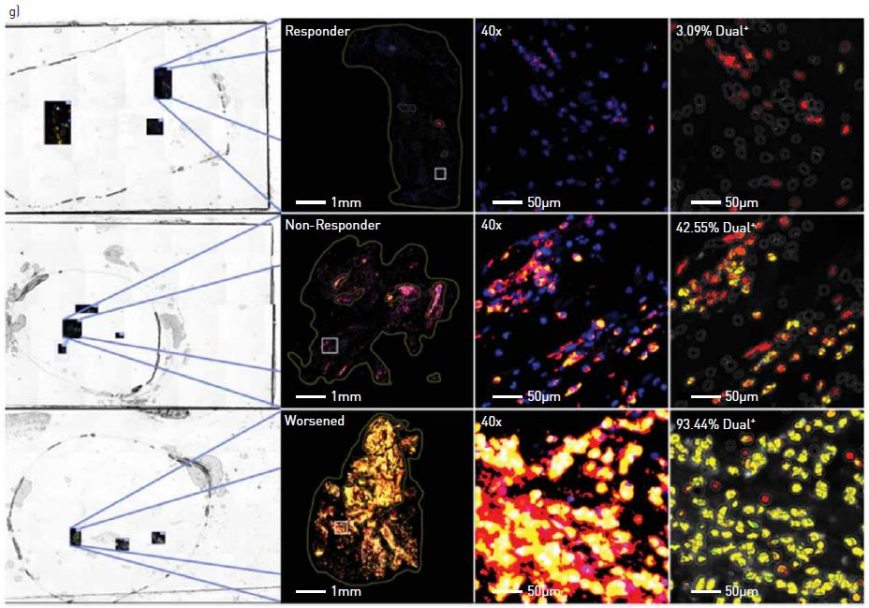
# Suboptimal treatment response to anti-IL-5 antibodies

- 250 mod-to-severe asthma with anti-IL-5 mAbs (mepolizumab/reslizumab)
- In 4 Canadian academic centers
- Non-responder (any of 3): <50% reduction of CS, ACQ-5<1.5, <50% reduction of exacerbation ➔ **42.8%** (OCS-dependent: 28.4%, others: 14.4%)

*Mukherjee et al.*
*Eur Respir J*
*2020;56:2000117*

# Suboptimal treatment response to anti-IL-5 antibodies




Mepolizumab은 **Immune-complex mediated complement activation**이 일어난 환자들에서는 반응이 떨어짐

**"Autoimmune phenomenon"**

**중증 천식 치료.** Anti-IL-5 biologics의 Non-responder

← **C1q-bound/IL-5-bound IgG**

*Mukherjee et al. Eur Respir J 2020;56:2000117*

# Dupilumab in real-world study

- 64 severe asthma patients with dupilumab in real-world study

TABLE 2 Summary of main asthma control outcomes for patients with severe asthma during treatment in the nATU programme at each follow-up visit

| | Asthma Control Test score | Number of exacerbations | FEV1 (mL) | FEV1 (%) | OCS dose[a] | ICS dose[a] |
|---|---|---|---|---|---|---|
| Analysis at 3 mo (N = 64) | | | | | | |
| N | 30 | / | 32 | 34 | 49 | 60 |
| Baseline | 11 [7-15] | | 1690 [1030-2115] | 53 [42-71] | 20 [10-30] | 800 [800-1600] |
| 3 mo | 19 [13-22] | | 1864 [1205-2490] | 67 [45-81] | 10 [7-15] | 800 [400-800] |
| Difference | 7 [1-11] | | 230 [10-610] | 8 [1-18] | −5 [−18 to 0] | 0 [−360 to 0] |
| *P*-value | *P* < .001 | | *P* < .001 | *P* < .001 | *P* < .001 | *P* < .001 |
| Analysis at 6 mo (N = 61) | | | | | | |
| N | 39 | / | 43 | 45 | 45 | 57 |
| Baseline | 11 [6-16] | | 1550 [1010-2250] | 55 [45-76] | 20 [10-30] | 800 [800-1600] |
| 6 mo | 20 [12-22] | | 2060 [1290-2490] | 66 [53-92] | 7 [0-15] | 800 [600-800] |
| Difference | 6 [2-9] | | 180 [−30 to 530] | 9 [2-17] | −10 [−20 to −5] | 0 [−320 to 0] |
| *P*-value | *P* < .001 | | *P* < .001 | *P* < .001 | *P* < .001 | *P* < .001 |
| Analysis at 12 mo (N = 51) | | | | | | |
| N | 32 | 41 | 39 | 42 | 37 | 47 |
| Baseline | 14 [7-16] | 4 [2-7] | 1780 [1190-2170] | 58 [47-76] | 20 [10-30] | 800 [800-1600] |
| 12 mo | 22 [17-24] | 1 [0-2] | 1940 [1250-2670] | 68 [58-88] | 5 [0-7] | 800 [400-800] |
| Difference | 9 [5-12] | −3 [−5 to −2] | 200 [−30 to 620] | 10 [1-19] | −13 [−20 to −5] | 0 [−800 to 0] |
| *P*-value | *P* < .001 | *P* < .001 | *P* < .001 | *P* < .001 | *P* < .001 | *P* < .001 |

Dupilumab 사용 1년 뒤,
**$FEV_1$ 200 mL (10%) 호전**
**OCS 13 mg 감량**

*Dupin et al. Clin Exp Allergy 2020;50:789-98*

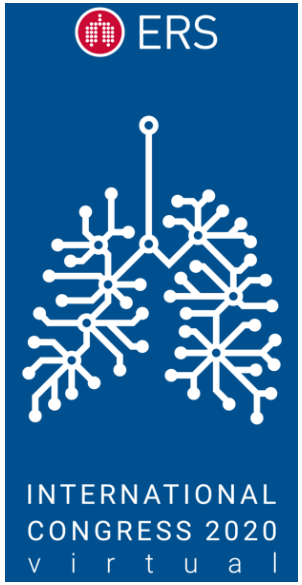
**중증 천식 치료 2-5.** Dupilumab – real-world에서 효과적

# Dupilumab in long-term safety and efficacy

- Long-term safety data in 2,930 patients (48-96 wks)
- **LIVERTY Asthma TRAVERSE open-label extension study**
- **3 studies** (P3 QUEST, P2a EXPEDITION, P3 VENTURE)

## SAFETY

- The most common TEAEs occurring in any treatment group during OLE were **nasopharyngitis** and **injection-site erythema**, **9–13% of patients experienced SAEs**, the number of patients with TEAE leading to **permanent discontinuation (<5%)** was low and **4 deaths** occurred (metastatic lung cancer, adenocarcinoma gastric, craniocerebral injury, and respiratory failure)




**중증 천식 치료 2-5.** Dupilumab – long-term에서 안전

*Wechsler et al. In ERS conference*

# Dupilumab in long-term safety and efficacy

➢ **Efficacy** in annualized severe exacertbation rate

- At parent study baseline for P2b and QUEST, mean number of exacerbations in the past year across treatment groups in the overall ITT populations were **1.85–2.37 and 2.02–2.31**, respectively[5,6]

Exacerbation rate 감소

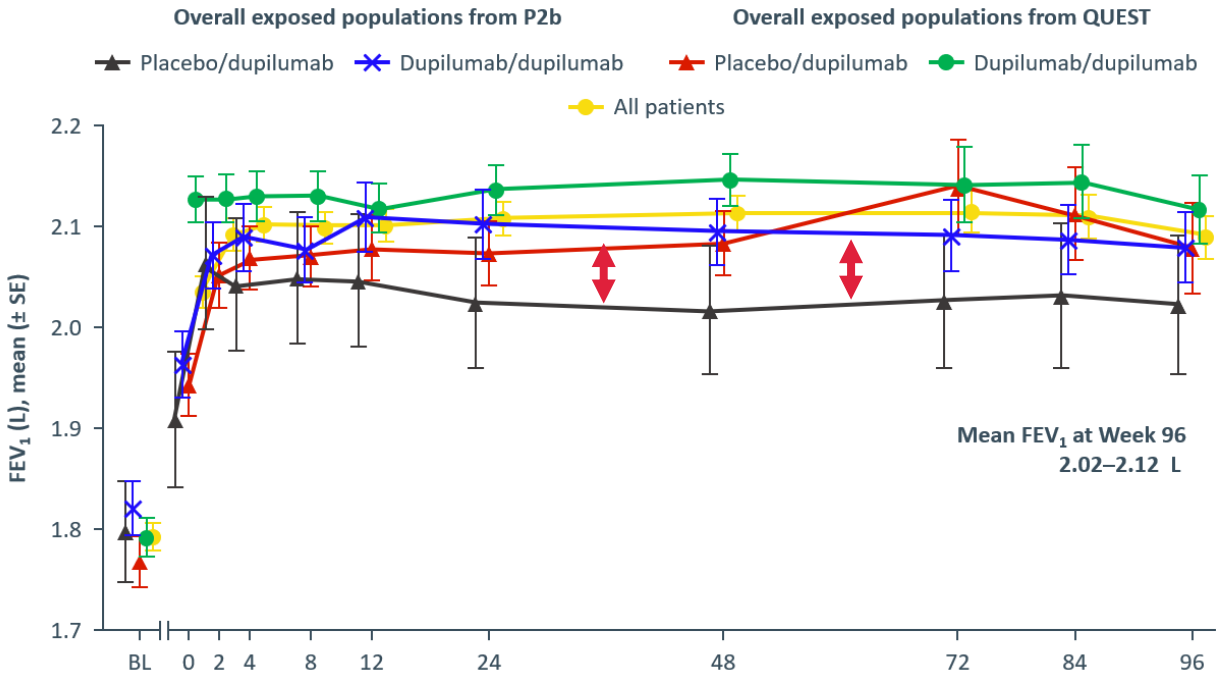
- At end of parent study treatment, unadjusted AER for placebo- and dupilumab-treated patients were 1.07 and **0.31–0.69** for P2b and 0.98–1.09 and **0.48–0.56** for QUEST, respectively
- During the OLE, unadjusted AER ranged from **0.31–0.35** in the non-OCS dependent population

**중증 천식 치료 2-5.** Dupilumab – long-term에서 효과적

*Wechsler et al. In ERS conference*

# Dupilumab in long-term safety and efficacy

- **Efficacy** in lung function



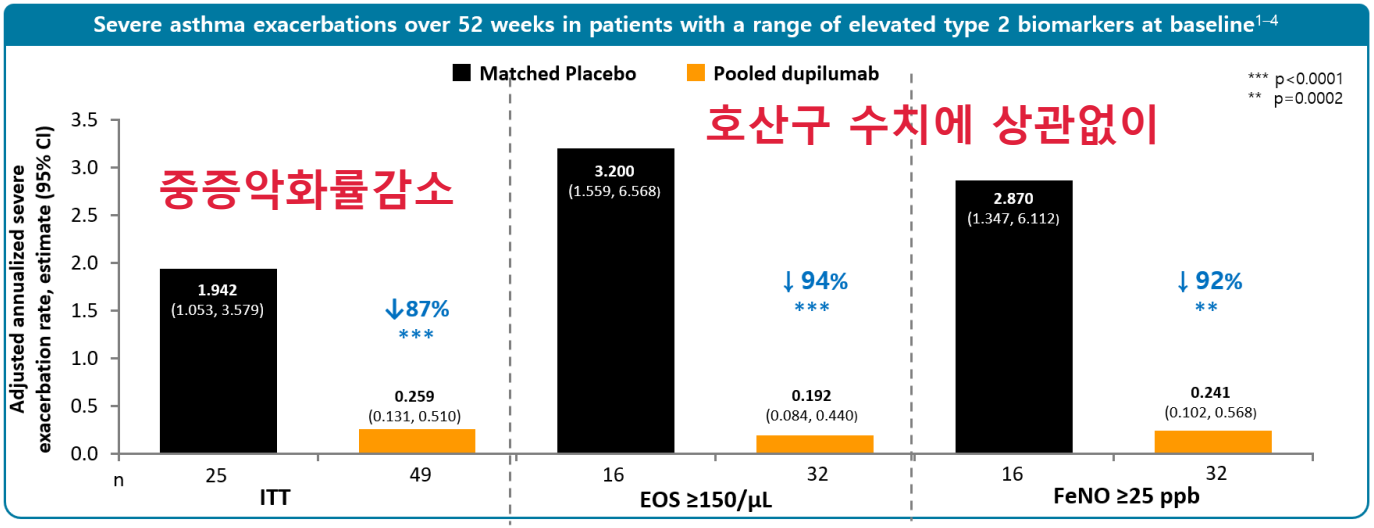

**중증 천식 치료 2-5.** Dupilumab – long-term에서 효과적

*Wechsler et al.*
*In ERS conference*

# Dupilumab in Korean

- Mod-to-severe asthma (≥1 exacerbation during the previous year)
- Sub-group analysis **(74 Korean - 4% of total) of LIVERTY ASTHMA Quest study**
- **200 or 300 mg SC q2w**

Breathe together, Think together
KATRD Virtual Conference
International Conference 2020

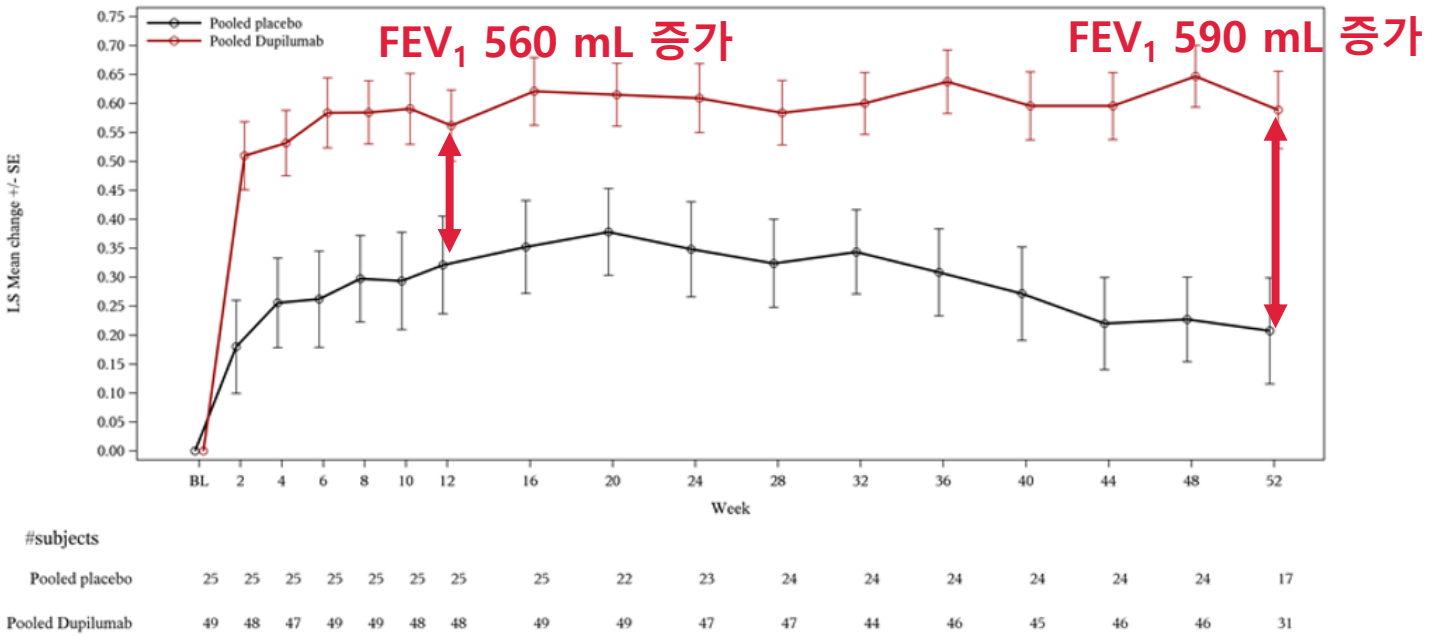



**중증 천식 치료 2-5.** Dupilumab – 한국인에서도 효과적

*Rhee et al. In KATRDIC*

# Dupilumab in Korean

- Mod-to-severe asthma (≥1 exacerbation during the previous year)
- Sub-group analysis **(Korean) of LIVERTY ASTHMA Quest study**




**중증 천식 치료 2-5.** Dupilumab – 한국인에서도 효과적

*Rhee et al.*
*In KATRDIC*

# Dupilumab in Korean

- Mod-to-severe asthma (≥1 exacerbation during the previous year)
- Sub-group analysis **(Korean) of LIVERTY ASTHMA Quest study**

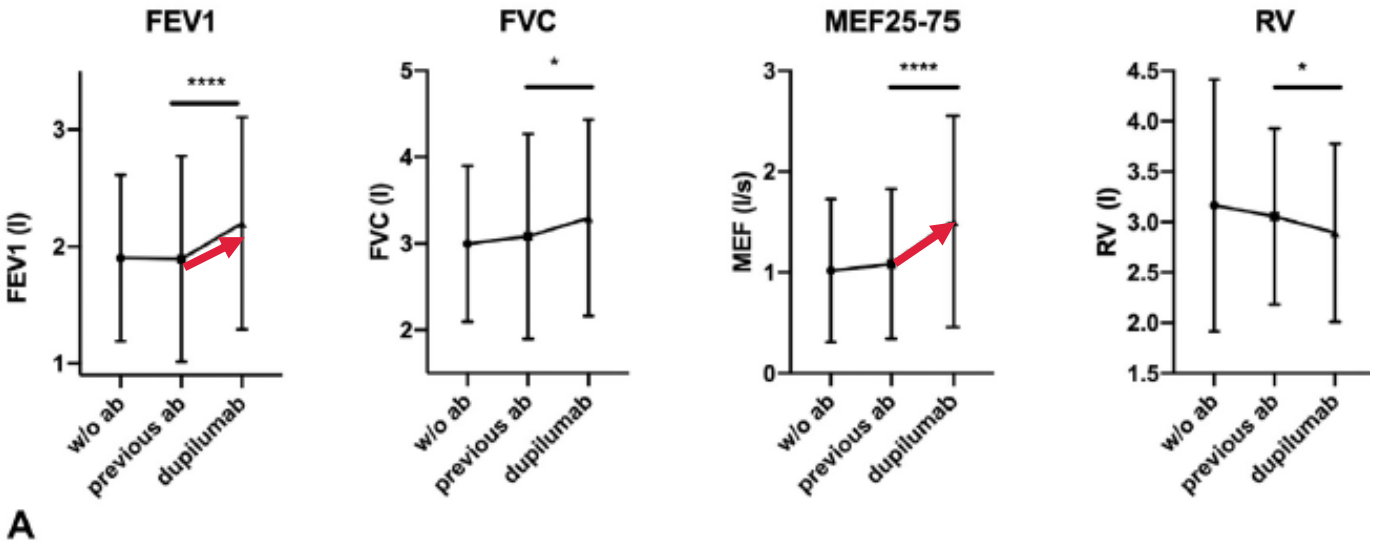
| n (%) | Placebo (n=25) | Dupilumab (n=49) |
|---|---|---|
| Any TEAE | 22 (88.0%) | 44 (89.8%) |
| Any treatment-emergent SAE | 3 (12.0%) | 5 (10.2%) |
| Any TEAE leading to death | 0 | 0 |
| Any AE leading to permanent treatment discontinuation | 0 | 4 (8.2%) |

**중증 천식 치료 2-5.** Dupilumab – 한국인에서도 안전

*Rhee et al. In KATRDIC*

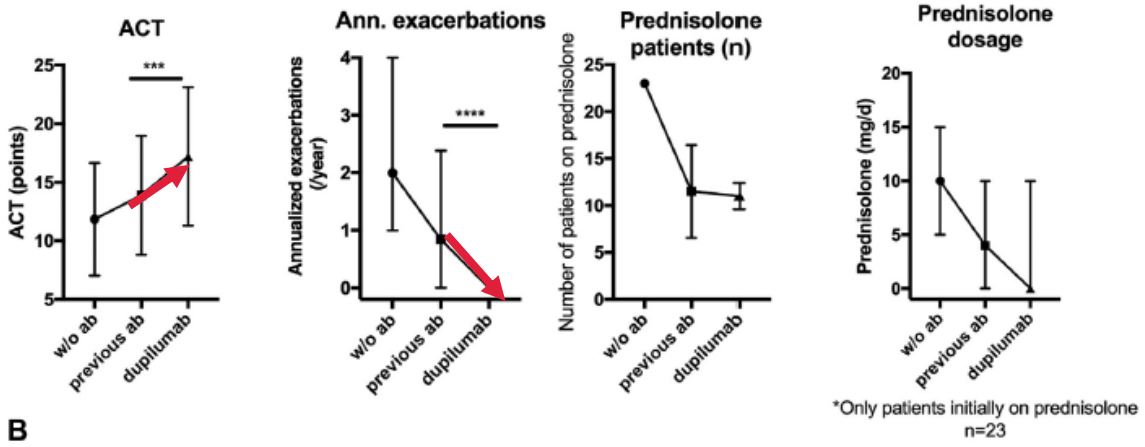
# Switching to dupilumab

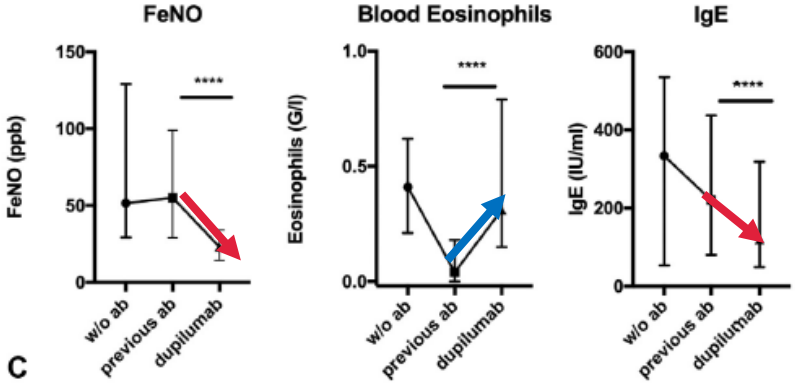
- 38 patients switched to dupilumab from a previous anti-IgE or anti-IL5/IL-5 receptor medication because of insufficient outcome (retrospective)




*Mummler et al.*
*J Allergy Clin Immunol Pract*
*E-pub*

# Switching to dupilumab

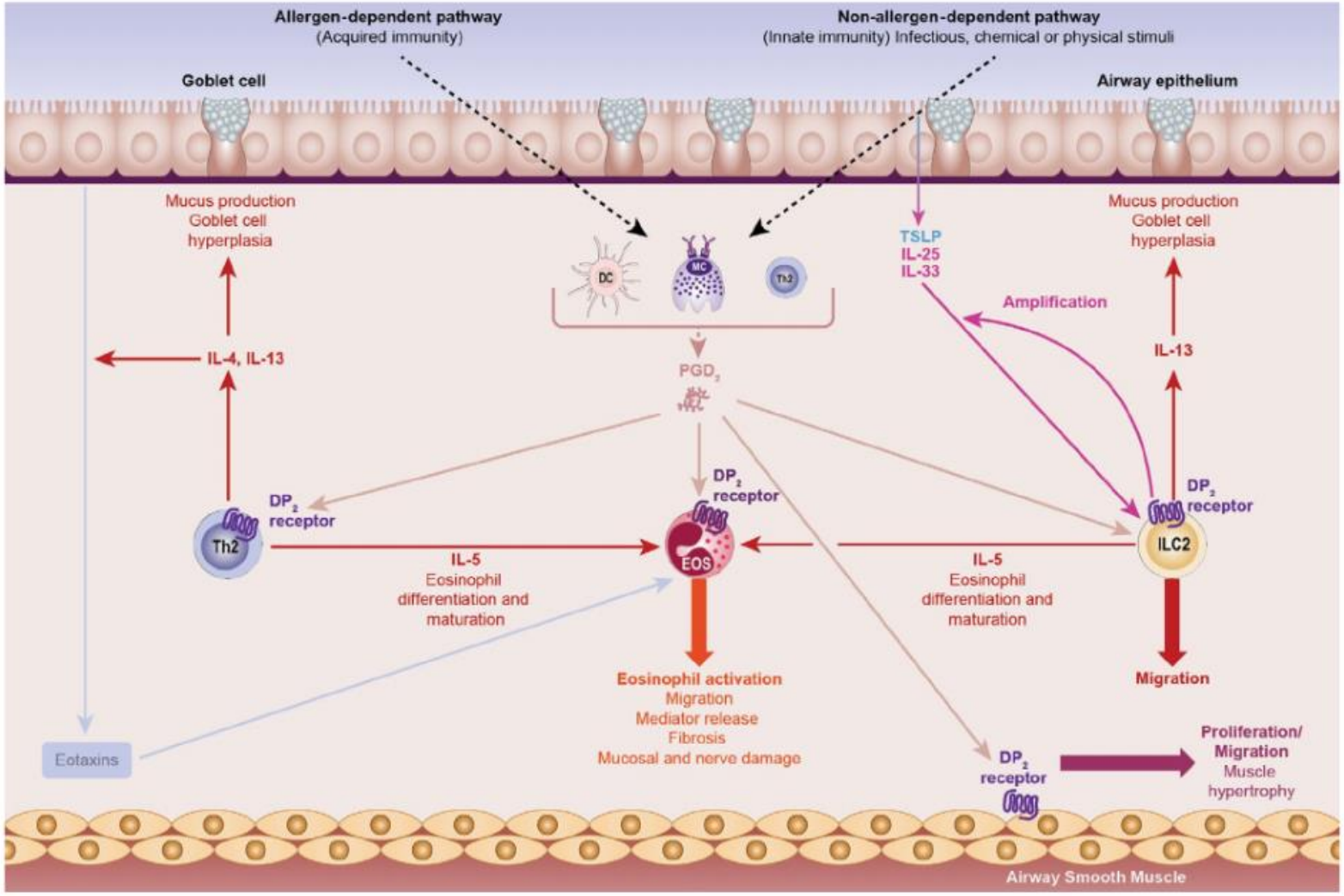



**중증 천식 치료 2-5.** Dupilumab – 다른 제재에 효과가 불충분할 경우 대체 고려 가능

*Mummler et al.*
*J Allergy Clin Immunol Pract*
*E-pub*

# **Fevipiprant** (antagonist of the **prostaglandin D2** receptor 2)

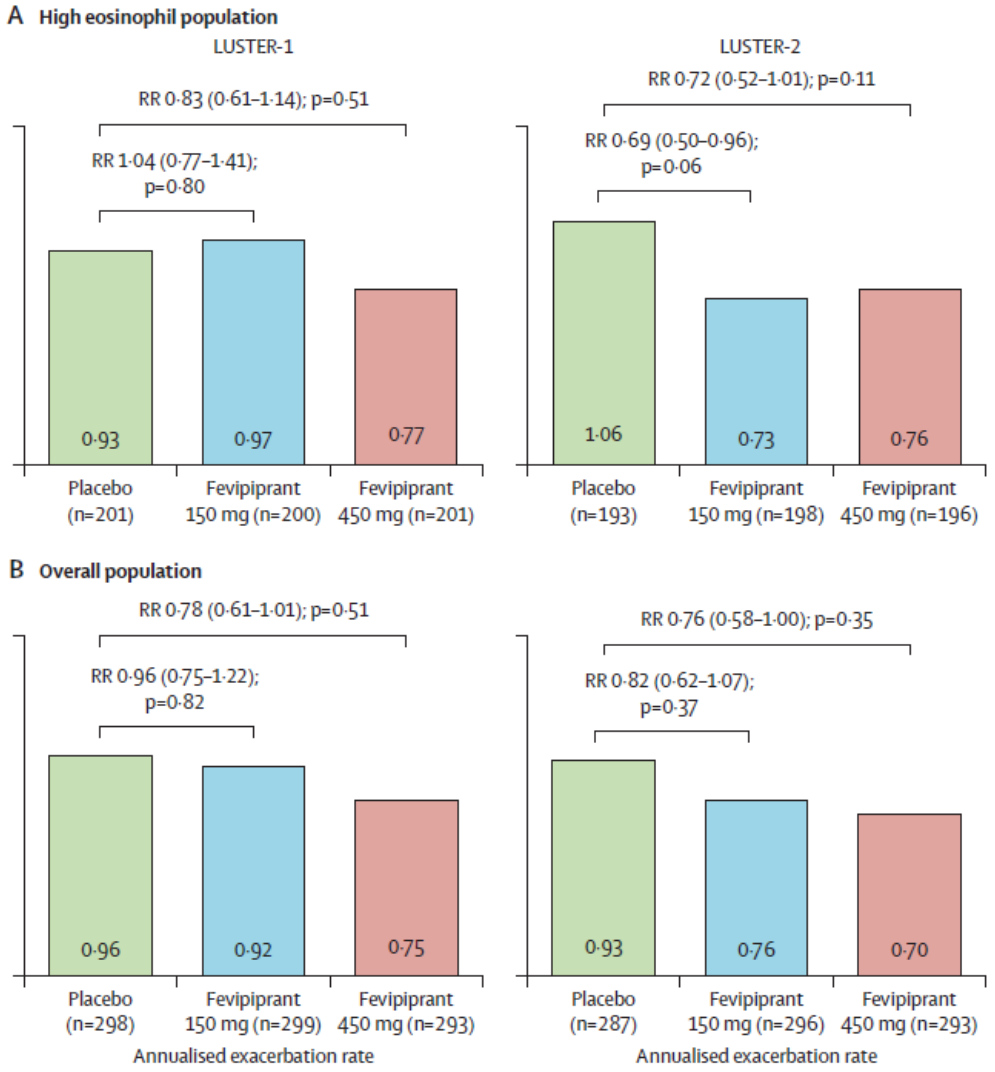



*Brightling et al. Allergy 2020;75:761-8*

# Fevipiprant

- 1,771 severe asthma (**GINA 4-5**)

Mod-to-severe 악화률에 의미있는 **차이는 없었으나**, 감소 경향을 보임

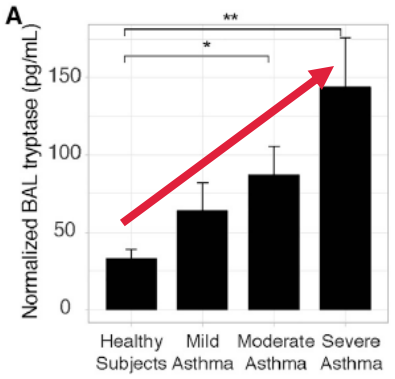


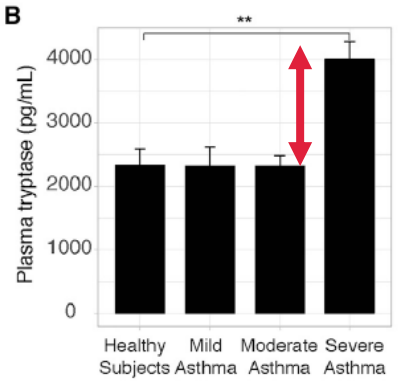

*Peter et al. J Allergy Clin Immunol Pract E-pub*

**중증 천식 치료 2-6. Fevipiprant의 equivocal한 효과**

# Anti-tryptase antibody in mast cell-mediated SA

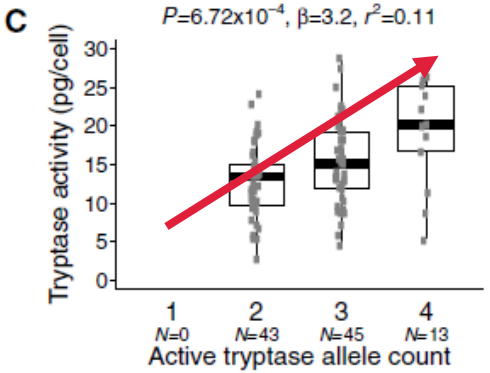
- Increased mast cell tryptase levels are associated with asthma severity in dependent of type 2 inflammation.

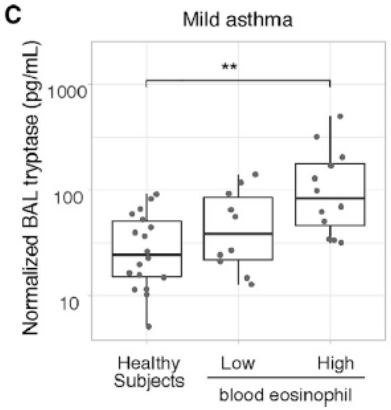


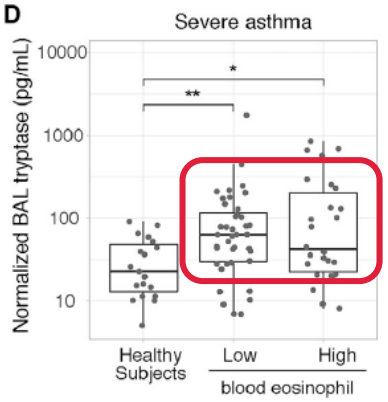



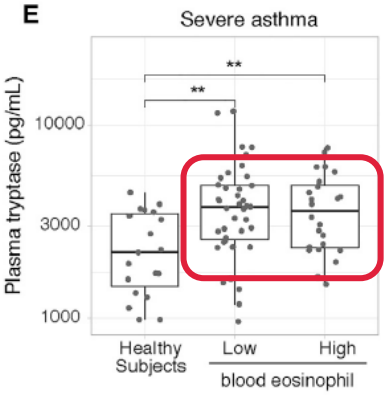

천식의 **중증도에 따른 tryptase level**

**Tryptase allele 개수에 따른 tryptase activity 증가**



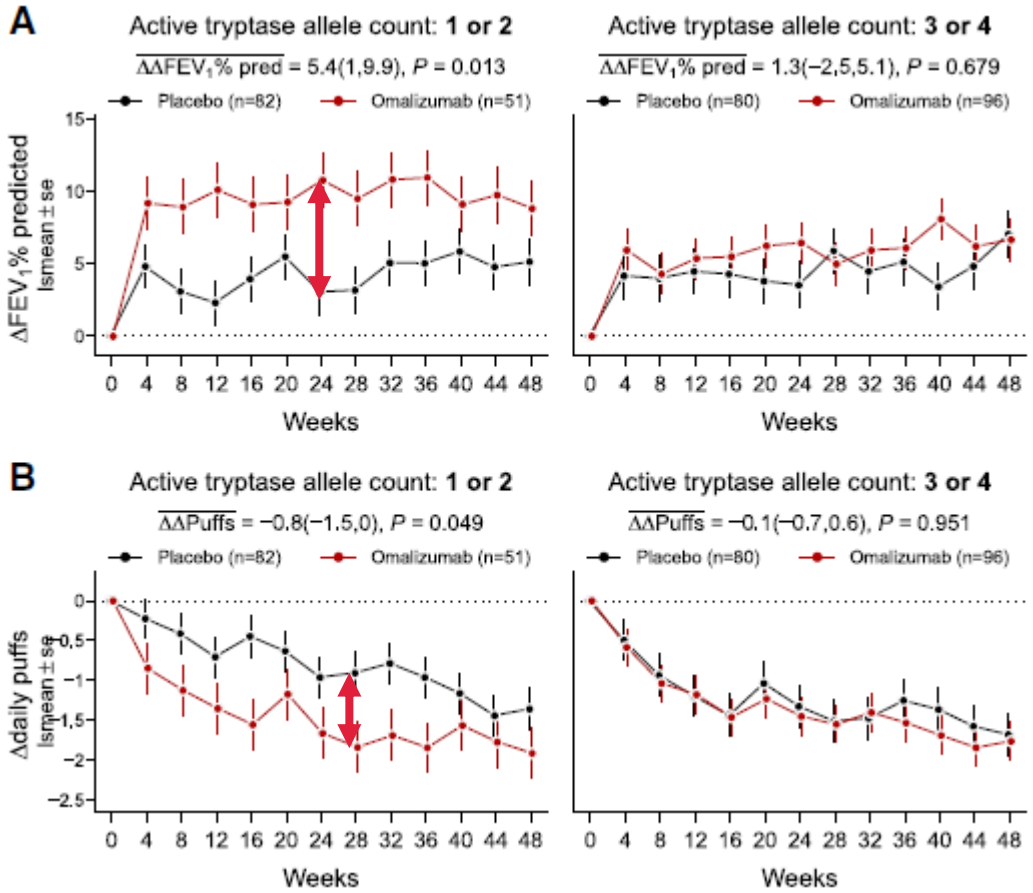




**중증 천식**에서는 eosinophil 상관없이 **tryptase level 증가**

*Maun et al. Cell 2019;179:417-31*

# Anti-tryptase antibody in mast cell-mediated SA

- Increased active tryptase alleles are associated with decreased clinical responses to anti-IgE treatment

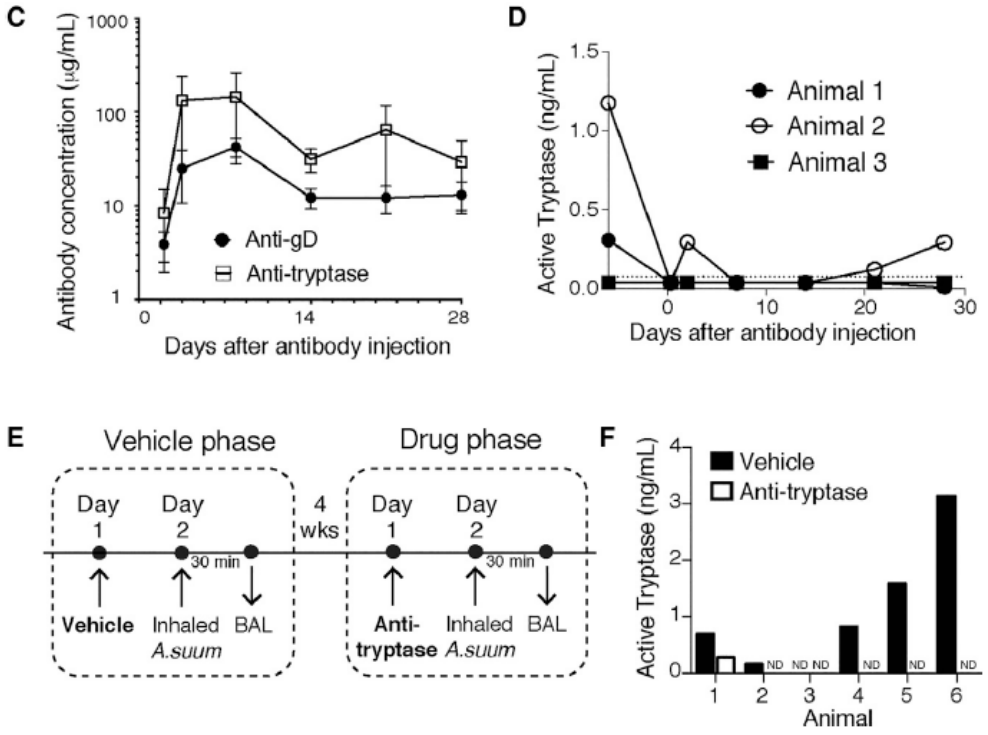



**Omalizumab의 치료 효과**가 active tryptase allele count가 1 or 2 인 사람에게만 나타나며, 3 or 4인 사람에게는 없음.

*Maun et al. Cell 2019;179:417-31*

# Anti-tryptase antibody in mast cell-mediated SA

- They generated a anti-tryptase antibody, as a clinical candidate for severe asthma treatment




*in mouse & monkey model*

**중증 천식 치료 2-7. Anti-tryptase antibody의 가능성**

Maun et al. Cell 2019;179:417-31

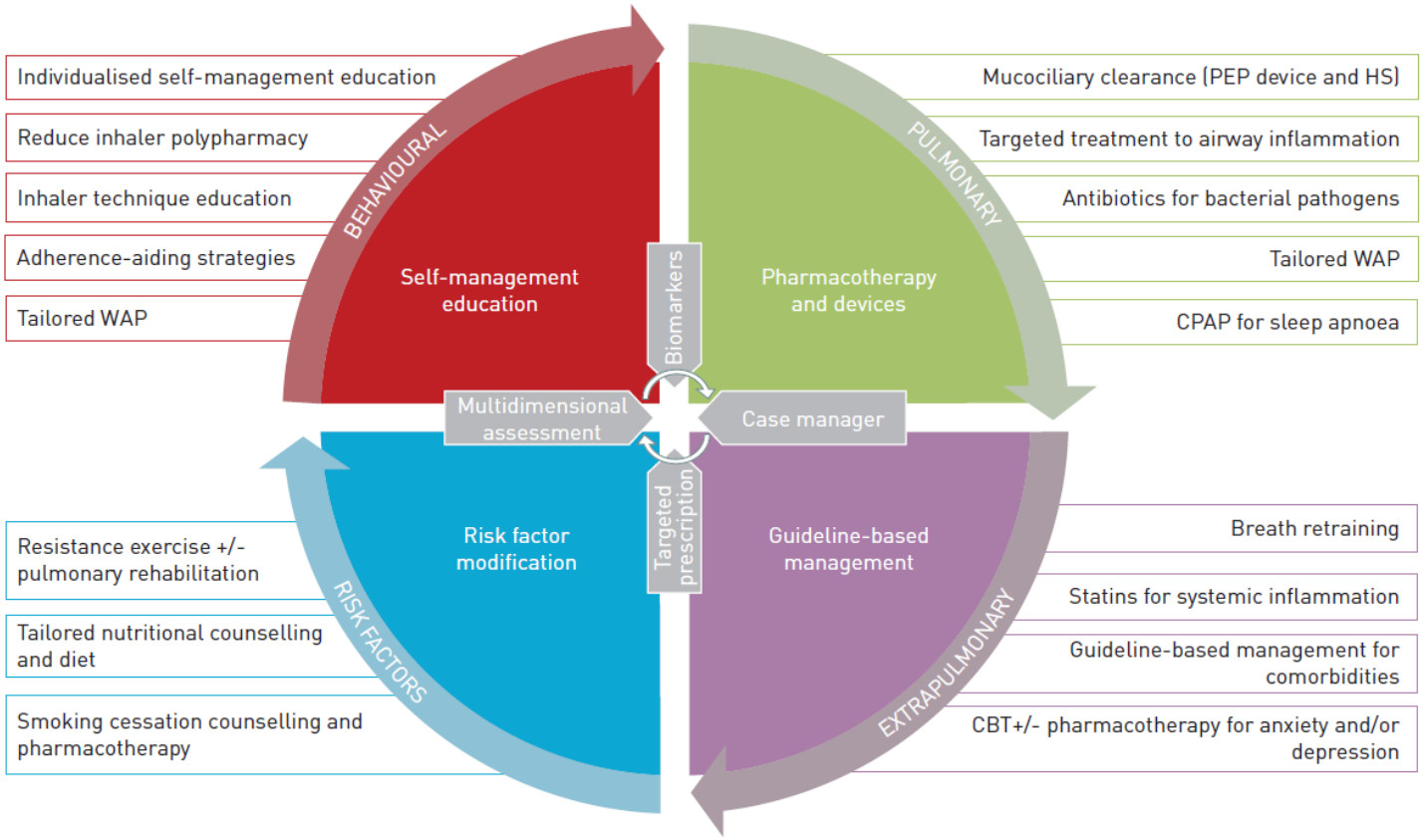
# Issues in biologics

- Select candidates who will be good responder
- Duration of treatment (tapering?)
- Efficacy after stop
- Insurance coverage and cost-effectiveness
- Modified protocol in real-clinics
- Efficacy in sub-optimal dose
- Long-term safety

# Treatment II: Others

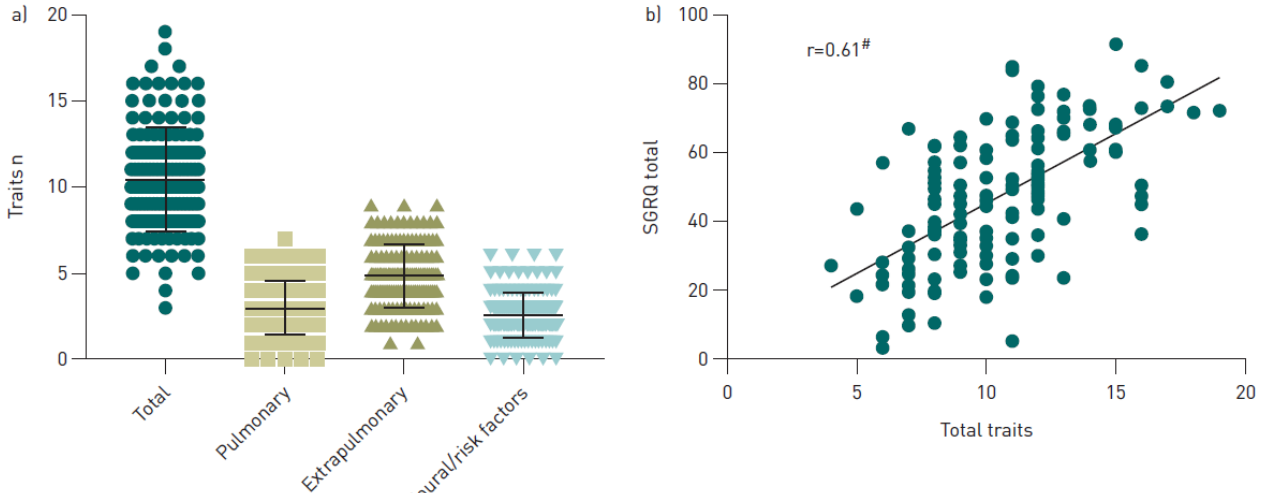
# Targeting treatable traits

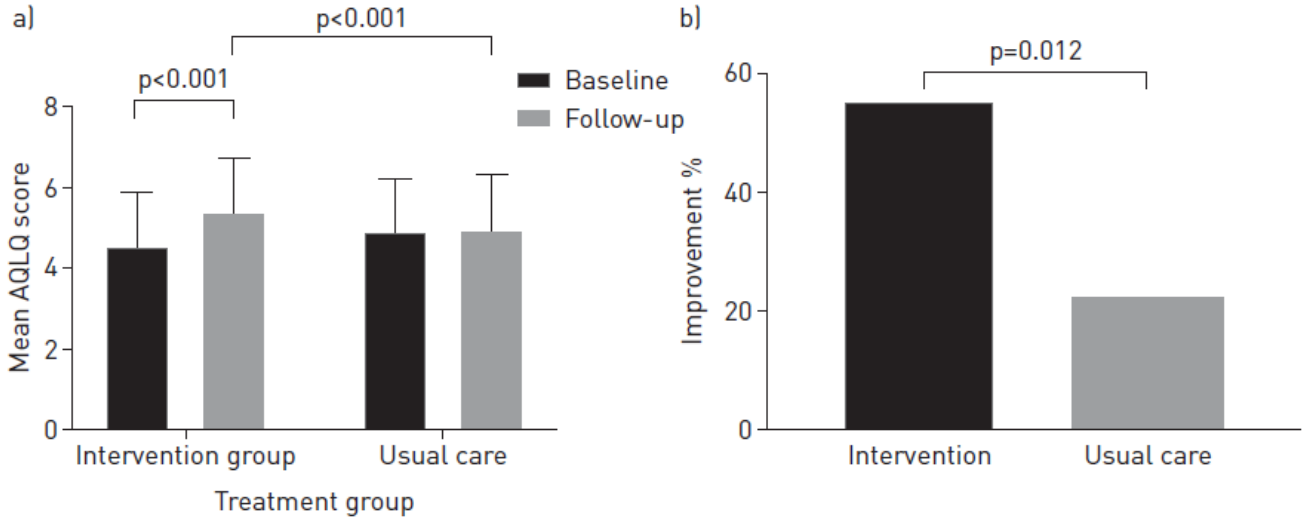
- 55 participants with severe asthma
- Management targeted to predefined treatable traits vs. usual care (RCT)




McDonald et al. Eur Respir J 2020;55:1901509

# Targeting treatable traits




**중증 천식 치료 3-1.**
Treatable trait 교정은 삶의 질 향상

*McDonald et al. Eur Respir J 2020;55:1901509*

# Bronchial thermoplasty

- 40 Severe asthma (20 immediate BT vs. 20 delayed BT - RCT)

| | Immediate treatment group (n=18) | | | Delayed BT control group (n=20) | | | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | **At inclusion** | **6 months after BT** | **Change** | **At inclusion** | **After 6 months standard care** | **Change** | **P-value** |
| **ACQ-6 score** | 2.97 ± 0.62 | 2.13 ± 1.13 | -0.79 (-1.61; 0.02) | 2.53 ± 0.66 | 2.86 ± 0.92 | 0.09 (-0.25; 1.17) | 0.006* |
| **AQLQ score** | 3.74 ± 0.91 | 4.63 ± 1.05 | 0.83 (-0.15; 1.69) | 4.18 ± 1.0 | 4.06 ± 0.96 | -0.02 (-0.77; 0.75) | 0.04* |
| **Dose of LABA (µg/d salmeterol equivalents)** | 127.7 ± 56.0 | 127.7 ± 56.0 | - | 143.4 ± 57.1 | 140.9 ± 50.6 | 0 (0; 0) | - |
| **Dose of ICS (µg/d fluticasone equivalents)** | 1069 ± 629 | 1097 ± 613 | 0 (0; 0) | 1209 ± 660 | 1209 ± 660 | - | - |
| **No. of patients on maintenance use of OCS (dose in mg/d)** | 3 (9.2 ± 1.4) | 2 (8.8 ± 1.8) | 0 (0; 0) | 6 (15.0 ± 6.3) | 7 (14.3 ± 6.1) | 0 (0; 0) | 0.17 |
| **Pre-bronchodilator $FEV_1$ (% predicted)** | 80.9 ± 20.1 | 82.1 ± 23.4 | 4.5 (-2.0; 8.0) | 85.5 ± 27 (n=19) | 86.0 ± 26 (n=19) | -1.0 (-7.25; 7.25) (n=19) | 0.26 |
| **Reversibility $FEV_1$ (%)** | 8.5 (4.0;12.8) | 3.0 (2.0;13.5) | -2.0 (-7.75;1.25) | 12.0 (7;23) (n=19) | 13.0 (4;21) (n=19) | 1.0 (-5.25; 9.25) (n=19) | 0.19 |
| **PC20 (mg/ml)†** | 0.24 (0.03;2.91) | 1.33 (0.06;4.0) | 0.18 (0.0;0.85) | 0.20 (0.03;2.83) (n=18) | 0.09 (0.03;2.60) (n=18) | 0.0 (-0.03; 0.43) (n=18) | 0.08 |
| **FeNO (ppb)** | 14.5 (9.5;59.5) (n=14) | 18.0 (11.3;40.0) (n=14) | -0.50 (-3.38;7.38) (n=14) | 23.8 (13.5;45.0) (n=12) | 25.0 (15.3;46.5) (n=12) | 1.75 (-5.38; 12.0) (n=12) | 0.60 |

*Goorsenberg et al.*
*Am J Resp Crit Care Med.*
*In Press*

# Bronchial thermoplasty

- Treatment response was associated with serum IgE and eosinophil levels

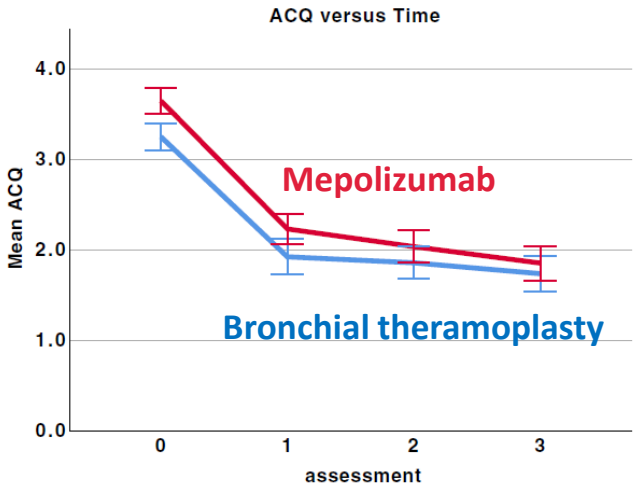
| | ACQ-6 change | | AQLQ change | |
|---|---|---|---|---|
| | rho | p-value | rho | p-value |
| Asthma age of onset | -0.20 | 0.25 | 0.30 | 0.08 |
| Total IgE† | -0.53 | 0.001* | 0.24 | 0.17 |
| Blood eosinophils x$10^9$/L† | -0.46 | 0.006* | 0.48 | 0.004* |
| Pre-SABA $FEV_1$% predicted‡ | -0.02 | 0.89 | 0.20 | 0.26 |
| Reversibility $FEV_1$‡ | -0.13 | 0.48 | 0.21 | 0.25 |
| PC20 (mg/ml)§ | 0.30 | 0.08 | -0.09 | 0.61 |
| FeNO (ppb)ǁ | -0.28 | 0.19 | 0.21 | 0.33 |
| ASM mass (%) desmin | 0.07 | 0.69 | -0.009 | 0.96 |
| ASM mass (%) α-SMA | 0.18 | 0.29 | -0.05 | 0.79 |

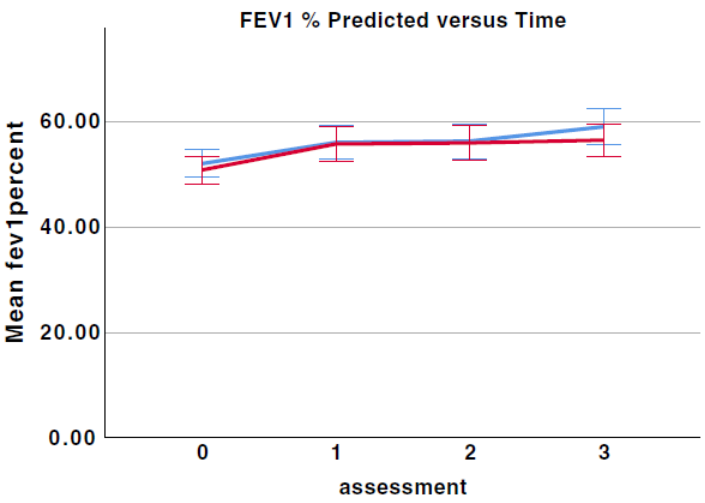
*Goorsenberg et al.*
*Am J Resp Crit Care Med.*
*In Press*

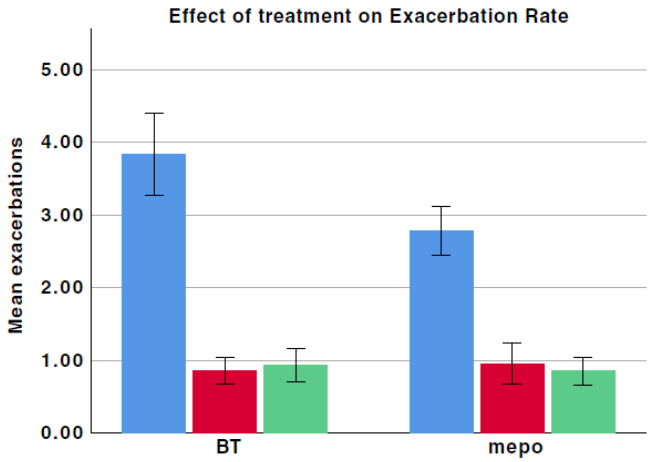
**중증 천식 치료 3-2.** 기관지 열성형술-효과적(IgE, eosinophil)

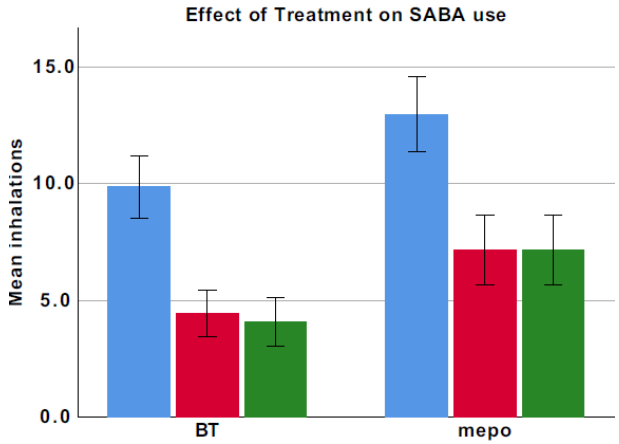
# Bronchial thermoplasty (vs. mepolizumab)

- Severe asthma (44 BT vs. 44 mepolizumab – observation [not RCT])




Bronchial thermoplasty는 **mepolizumab과,** 천식 증상 조절, 폐기능 및 악화율에 **동일한 효과**를 보임

*Langton et al. Respirology In Press*

# Bronchial thermoplasty (vs. mepolizumab)

- Severe asthma (44 BT vs. 44 mepolizumab – observation [not RCT])

**Table 2** Outcomes following BT in patients defined by baseline blood eosinophils

| | Baseline blood eosinophils <300 (cells/μL) | Baseline blood eosinophils ≥300 (cells/μL) |
|---|---|---|
| *n* | 26 | 18 |
| Eosinophil count (cells/μL) | 92 ± 16 | 550 ± 61* |
| Age (years) | 58.1 ± 14.0 | 53.7 ± 11.9 |
| BMI (kg/m$^2$) | 30.5 ± 7.5 | 28.5 ± 5.8 |
| ACQ baseline | 3.3 ± 0.9 | 3.2 ± 1.1 |
| ACQ 6 months | 1.9 ± 1.1 | 1.9 ± 1.5 |
| ACQ 12 months | 1.7 ± 1.2 | 1.8 ± 1.5 |
| $FEV_1$ baseline (% predicted) | 52.7 ± 20.8 | 51.0 ± 11.7 |
| $FEV_1$ 6 months (% predicted) | 56.0 ± 21.1 | 57.2 ± 21.2 |
| $FEV_1$ 12 months (% predicted) | 58.0 ± 21.9 | 60.4 ± 21.4 |
| Exacerbations base (per 6 months) | 3.5 ± 2.7 | 5.6 ± 9.0 |
| Exacerbations 6 months (per 6 months) | 0.7 ± 1.0 | 1.1 ± 1.5 |
| Exacerbations 12 months (per 6 months) | 0.7 ± 1.0 | 1.2 ± 2.0 |
| OCS (mg/day) | 9.3 ± 11.8 | 5.9 ± 10.4 |
| OCS (mg/day) | 5.0 ± 7.2 | 3.9 ± 7.3 |
| OCS (mg/day) | 3.4 ± 5.8 | 5.8 ± 9.1 |
| SABA base (puffs/day) | 10.6 ± 9.6 | 8.8 ± 7.8 |
| SABA 6 months (puffs/day) | 4.6 ± 6.1 | 4.1 ± 7.6 |
| SABA 12 months (puffs/day) | 4.1 ± 5.2 | 4.3 ± 7.7 |

호산구 수치에 상관없이, **ACQ 호전**

호산구 수치에 상관없이, **악화율 감소**

호산구 수치에 상관없이, **OCS, SABA 사용 감소**

**중증 천식 치료 3-2.** 기관지 열성형술-효과적 (mepolizumab 만큼)

*Langton et al. Respirology In Press*

# Rehabilitation

- Severe asthma

**12주 (3달) 간** 재활치료 프로그램 진행

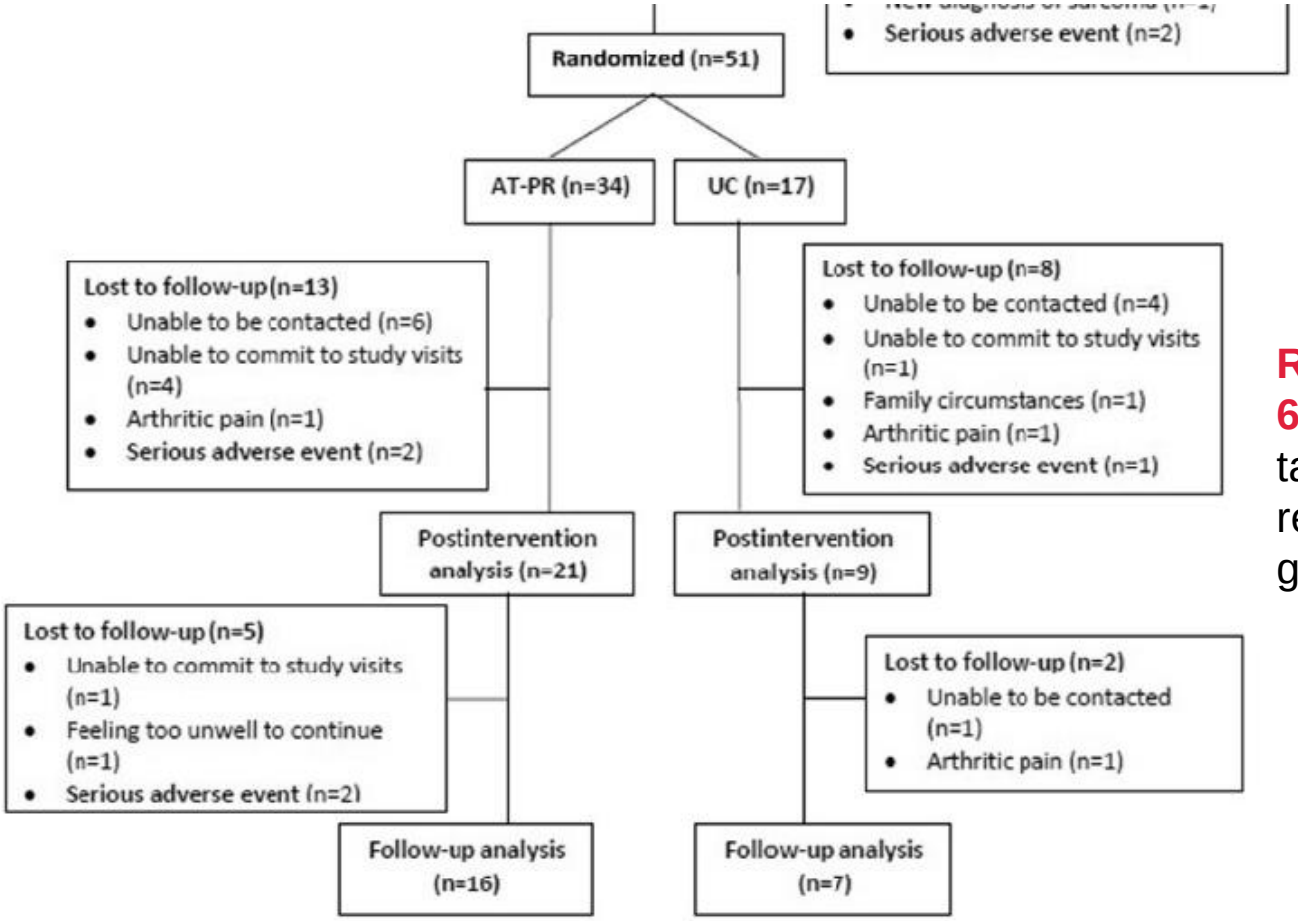
TABLE I. Exercise component for 12-wk AT-PR

| Variable | Supervised | Unsupervised |
|---|---|---|
| Aerobic training | | |
| Frequency | Twice weekly | Minimum 1 additional session at home but daily walk encouraged when not in class and diary kept |
| Intensity | 85% $VO_{2pk}$ derived from the ISWT distance, 60%-80% $VO_{2pk}$ for treadmill walking or additional cycling | As per supervised |
| Time | 20-30 min | As per supervised |
| Type | Predominantly continuous endurance training with ground walking | Ground walking |
| | Treadmill walking and cycling also used | |
| Strength training | | |
| Frequency | Twice weekly | One additional session at home |
| Intensity | 80% 1-RM progressed using ratings of perceived exertion (Borg Scale) | As per supervised |
| Time | Two sets of 6-12 repetitions | As per supervised |
| Type | Knee extensors and flexors using gym equipment | As per supervised for upper limb exercises |
| | Elbow flexion and extension using free weights | Lower limb strengthening exercise such as sit to stand and step-ups |

*1-RM*, One repetition maximum; *ISWT*, incremental shuttle walk test; $VO_{2pk}$, peak oxygen uptake.

*Majd et al.*
*J Allergy Clin Immunol Pract.*
*In Press*

# Rehabilitation




**Retention rate was 62%** for the asthma-tailored pulmonary rehabilitation (AT-PR) group

*Majd et al.*
*J Allergy Clin Immunol Pract.*
*In Press*

# Rehabilitation

TABLE IV. Comparison of the secondary outcome measures between AT-PR and UC at 12 wk

| | AT-PR | | UC | | AT-PR vs UC |
|---|---|---|---|---|---|
| Measure | Before | After | Before | After | Change |
| ITM $VO_{2pk}$ (mL/kg/min) | 22.5 ± 6.2 | 23.2 ± 7.6 | 22.9 ± 3.9 | 22.3 ± 2.4 | 1.4 (−1.1 to 3.8) |
| EIB on ITM (%) | | | | | |
| Mild | 7 ± 33 | 8 ± 38 | 1 ± 12.5 | 3 ± 37.5 | |
| Moderate | 2 ± 10 | 3 ± 14 | 1 ± 12.5 | 1 ± 12.5 | |
| Severe | 2 ± 10 | 0 ± 0 | 0 ± 0 | 0 ± 0 | NA |
| ICE $VO_{2pk}$ (mL/kg/min) | 17.5 ± 6.0 | 18.8 ± 6.9 | 16.9 ± 4.3 | 16.1 ± 2.8 | 2.0 (−0.3 to 4.2) |
| EIB on ICE (%) | | | | | |
| Mild | 3 ± 17 | 5 ± 28 | 0 ± 0 | 1 ± 17 | |
| Moderate | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | |
| Severe | 0 ± 0 | 0 ± 0 | 0 ± 0 | 0 ± 0 | NA |
| ISWT distance (m) | 418 ± 172 | 450 ± 199 | 443 ± 121 | 403 ± 104 | 74 (25 to 124) |
| QMVC (Newton) | 103 ± 53 | 116 ± 64 | 113 ± 35 | 110 ± 28 | 22 (4 to 41) |
| Sputum eosinophil (%) | −0.46 ± 1.01 | 0.26 ± 1.07 | 0.30 ± 0.49 | −0.01 ± 0.18 | NA |
| FENO (ppb), median (IQR) | 28.5 (13.5 to 37.0) | 25.0 (19.0 to 35.0) | 28.5 (18.5 to 53.3) | 37.5 (21.3 to 51.8) | NA |
| ACQ | 2.1 ± 0.8 | 1.9 ± 0.8 | 1.5 ± 0.9 | 1.9 ± 1.0 | −0.4 (−0.9 to 0.1) |
| CRQ-D | 3.1 ± 1.2 | 4.1 ± 1.3 | 3.7 ± 1.5 | 3.6 ± 1.1 | 0.9 (0 to 1.8) |
| CRQ-F | 3.7 ± 1.8 | 4.7 ± 1.2 | 4.7 ± 1.7 | 4.4 ± 1.6 | 0.9 (−0.1 to 1.8) |
| CRQ-EF* | 5.1 ± 1.4 | 5.4 ± 1.1 | 6.1 ± 0.7 | 6.1 ± 0.8 | −0.1 (−0.6 to 0.5) |
| CRQ-M* | 4.7 ± 1.3 | 5.4 ± 1.1 | 6.1 ± 1.0 | 6.0 ± 0.8 | 0.2 (−0.5 to 0.9) |
| AQLQ* | 19.0 ± 4.5 | 19.7 ± 4.0 | 22.2 ± 3.0 | 21.7 ± 2.6 | −0.2 (−2.7 to 2.3) |
| AQLQ-S | 4.9 ± 1.2 | 5.1 ± 1.1 | 5.6 ± 0.9 | 5.6 ± 0.9 | −0.1 (−0.7 to 0.6) |
| AQLQ-AL | 4.8 ± 1.3 | 5.0 ± 1.1 | 5.3 ± 0.8 | 5.1 ± 0.9 | 0.2 (−0.5 to 0.8) |
| AQLQ-EF* | 4.6 ± 1.4 | 4.9 ± 1.2 | 6.0 ± 0.8 | 5.7 ± 1.1 | 0.1 (−0.7 to 0.9) |
| AQLQ-ES | 4.6 ± 1.4 | 4.6 ± 1.5 | 5.3 ± 1.1 | 5.2 ± 0.7 | −0.2 (−1.2 to 0.8) |
| HADS-A* | 6.3 ± 4.4 | 5.1 ± 3.7 | 3.2 ± 2.5 | 2.4 ± 2.8 | 0.4 (−1.3 to 2.1) |
| HADS-D* | 4.8 ± 2.7 | 3.5 ± 2.8 | 2.8 ± 1.6 | 2.4 ± 1.0 | −0.3 (−1.9 to 1.3) |
| EQ-5D VAS score | 68.0 ± 14.2 | 73.4 ± 13.2 | 82.8 ± 16.4 | 72.8 ± 26.1 | 15.4 (1.7 to 29.1) |
| EQ-5D index score | 0.85 ± 0.14 | 0.85 ± 0.13 | 0.94 ± 0.10 | 0.88 ± 0.14 | 0.05 (−0.05 to 0.15) |

**Improvement** in exercise performance, health-related QOL, and asthma control

*Majd et al.*
*J Allergy Clin Immunol Pract.*
*In Press*

**중증 천식 치료 3-3.** 재활치료 – 효과적이나 유지 어려움

# Special issues: COVID-19

# Severe asthma case during COVID-19 pandemic

- Case report: 52-year-old allergic severe asthma patients

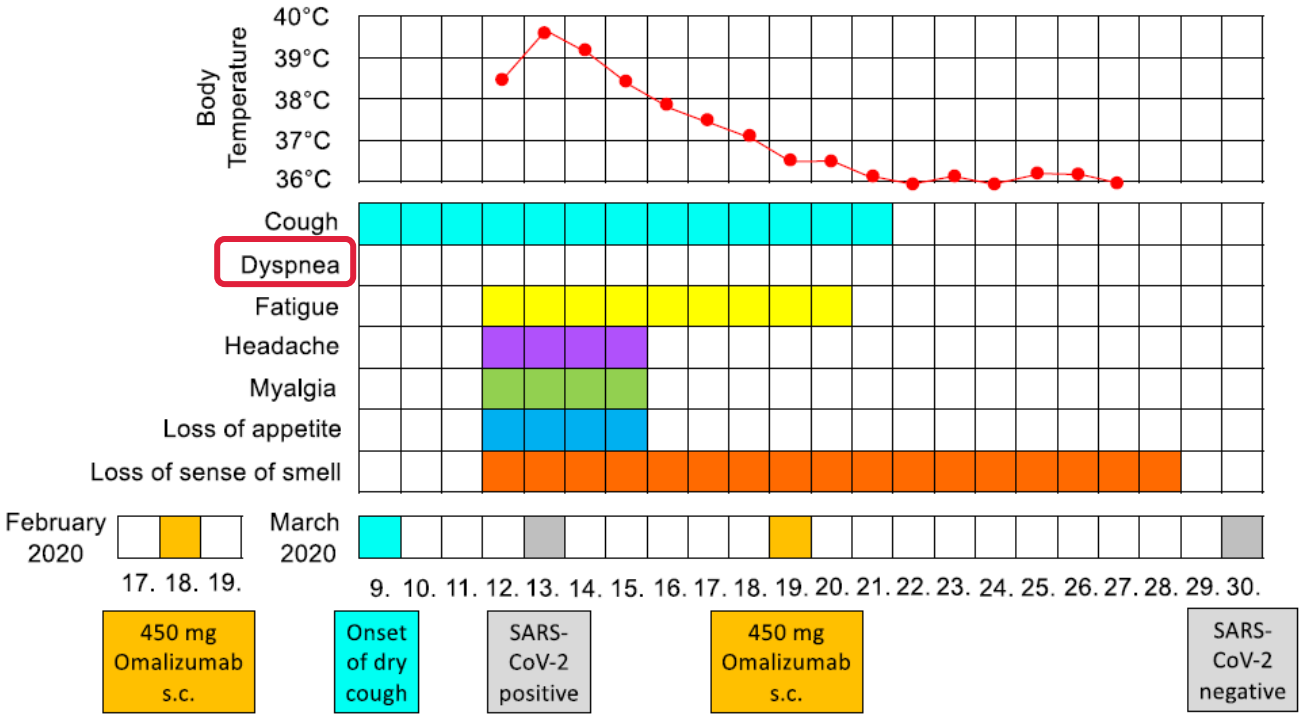


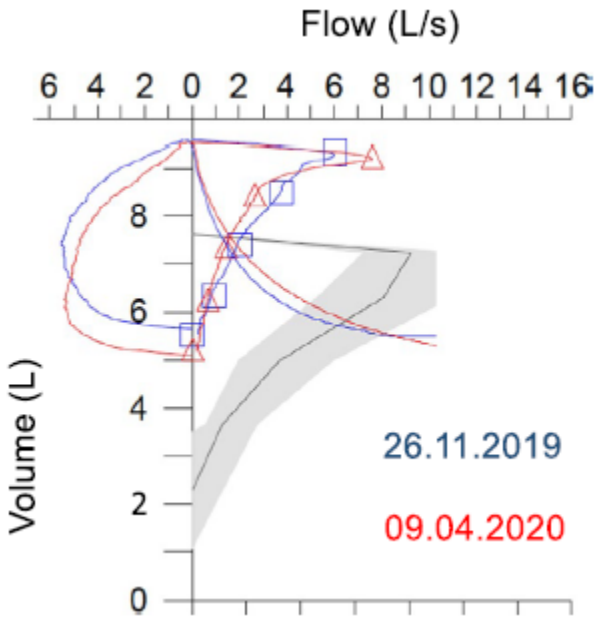

FIGURE 2 Timeline of symptoms and events before and during the SARS-CoV-2 infection

*Lommatzsch et al. Allergy 2020;E-pub*

# Severe asthma case during COVID-19 pandemic

- Case report: 52-year-old allergic severe asthma patients

| | Before COVID-19 | After COVID-19 |
|---|---|---|
| | 26.11.2019 | 09.04.2020 |
| **ACT** | 20 points | 21 points |
| **$FEV_1$** | 2.7 l (65 %) | 2.4 l (58 %) |
| **RV** | 5.3 l (226 %) | 5.2 l (221 %) |
| **FeNO** | 13 ppb | 8 ppb |
| **Eos** | 160 cells/µL | 180 cells/µL |




**중증 천식 환자에서 COVID-19 감염:** 이전-이후 차이 없음

*Lommatzsch et al. Allergy 2020;E-pub*

# Severe asthma case series during COVID-19 pandemic

## Severe asthma in adults does not significantly affect the outcome of COVID-19 disease: Results from the Italian Severe Asthma Registry

| | | | Asthma treatment | | | | |
|---|---|---|---|---|---|---|---|
| Bronchiectasis | GERD | Comorbidities (n.) | Treatment | ICS, daily dose (μg) | Add-on biologic drug | COVID-19 severity | ICU |
| No | No | 1 (Obesity) | ICS + LABA | FP, 1000 | Omalizumab | Home care | - |
| No | No | 1 | ICS + LABA + OCS | FP, 1000 | Omalizumab | Hospitalized | No |
| Yes | No | 2 | ICS + LABA + LAMA | Bu, 960 | Mepolizumab | Home care | - |
| Yes | No | 2 | ICS + LABA + LAMA | Be, 800 | Omalizumab | Home care | - |
| Yes | No | 3 | ICS + LABA + LAMA | FF, 184 | Mepolizumab | Hospitalized | No |
| No | Yes | 1 | ICS + LABA + LAMA | FF, 184 | Mepolizumab | Home care | - |
| No | No | 1 | ICS + LABA | FF, 94 | Mepolizumab | Home care | - |
| - | - | 1.6 | - | - | - | - | |
| - | - | 0.7 | - | - | - | - | |

**중증 천식 환자에서 COVID-19 감염:** 예후에 차이 없음

*Antonicelli et al. Allergy 2020;E-pub*

# COVID-19 infection in severe asthma

Table 1. Clinical characteristics and prognosis of COVID-19 patients

| Parameters | COVID-19 patients without underlying asthma | COVID-19 patients with underlying asthma | *P*-value | COVID-19 patients with underlying asthma | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Step 1 | Step 2 | Step 3 | Step 4 | Step 5 | *P*-value |
| **Age (years);** N (%) | | | | | | | | | |
| 0–9 | 62 (0.8%) | 20 (9.2%) | <0.001** | 2 (3.9%) | 0 (0.0%) | 0 (0.0%) | 18 (19.2%) | 0 (0.0%) | 0.058 |
| 10–19 | 343 (4.7%) | 6 (2.8%) | | 1 (2.0%) | 0 (0.0%) | 1 (4.2%) | 4 (4.3%) | 0 (0.0%) | |
| 20–29 | 1,833 (24.9%) | 19 (8.7%) | | 8 (15.7%) | 3 (6.7%) | 3 (12.5%) | 5 (5.3%) | 0 (0.0%) | |
| 30–39 | 758 (10.3%) | 18 (8.2%) | | 4 (7.8%) | 3 (6.7%) | 1 (4.2%) | 10 (10.6%) | 0 (0.0%) | |
| 40–49 | 983 (13.3%) | 25 (11.5%) | | 7 (13.7%) | 5 (11.1%) | 4 (16.7%) | 8 (8.5%) | 1 (25.0%) | |
| 50–59 | 1,468 (19.9%) | 34 (15.6%) | | 10 (19.6%) | 6 (13.3%) | 5 (20.8%) | 13 (13.8%) | 0 (0.0%) | |
| 60–69 | 1,020 (13.8%) | 36 (16.5%) | | 7 (13.7%) | 12 (26.7%) | 4 (16.7%) | 13 (13.8%) | 0 (0.0%) | |
| 70– | 846 (11.5%) | 60 (27.5%) | | 12 (23.5%) | 16 (35.6%) | 6 (25.0%) | 23 (24.5%) | 3 (75.0%) | |
| **Sex;** N (%) | | | | | | | | | |
| Male | 3,000 (40.7%) | 95 (43.6%) | 0.393 | 23 (45.1%) | 20 (44.4%) | 12 (50.0%) | 38 (40.4%) | 2 (50.0%) | 0.923 |
| Female | 4,372 (59.3%) | 123 (56.4%) | | 28 (54.9%) | 25 (55.6%) | 12 (50.0%) | 56 (59.6%) | 2 (50.0%) | |
| **Charlson comorbidity index;** N (%) | | | | | | | | | |
| 0 | 2,029 (27.5%) | 0 (0.0%) | <0.001** | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0.017* |
| 1 | 1,726 (23.4%) | 48 (22.0%) | | 12 (23.5%) | 3 (6.7%) | 5 (20.8%) | 28 (29.8%) | 0 (0.0%) | |
| 2 | 1,179 (16.0%) | 40 (18.4%) | | 11 (21.6%) | 5 (11.1%) | 7 (29.2%) | 17 (18.1%) | 0 (0.0%) | |
| ≥3 | 2,438 (33.1%) | 130 (59.6%) | | 28 (54.9%) | 37 (82.2%) | 12 (50.0%) | 49 (52.1%) | 4 (100%) | |
| **Prognosis;** N (%) or mean ± standard deviation) | | | | | | | | | |
| Mortality | 210 (2.8%) | 17 (7.8%) | <0.001** | 5 (9.8%) | 2 (4.4%) | 1 (4.2%) | 9 (9.6%) | 0 (0.0%) | 0.703 |
| Admission to ICU | 208 (2.8%) | 7 (3.2%) | 0.733 | 3 (5.9%) | 1 (2.2%) | 0 (0.0%) | 3 (3.2%) | 0 (0.0%) | 0.691 |
| Duration of admission (days) | 20.1 ± 12.2 | 21.0 ± 13.5 | 0.285 | 18.7 ± 12.0 | 23.7 ± 15.7 | 22.7 ± 13.0 | 19.9 ± 12.6 | 38.3 ± 16.4 | 0.026* |
| Total medical cost (USD) | 4,261.0 ± 5,354.0 | 5,388.1 ± 10,135.3 | 0.003* | 4403.5 ± 4992.1 | 6242.7 ± 9180.5 | 4694.6 ± 3815.9 | 5669.8 ± 13470.9 | 5868.4 ± 2789.8 | 0.912 |
| **Total** | 7,372 (97.1%) | 218 (2.9%) | | 51 (23.4%) | 45 (20.6%) | 24 (11.0%) | 94 (43.1%) | 4 (1.8%) | |

*Choi & Park et al.*
*Eur Resp J*
*2020;early view*

**중증 천식 환자에서 COVID-19 감염:** 입원기간 연장에만 영향

# COVID-19 infection in severe asthma

Table 5. Significant factors affecting the admission duration (days)

| | | Univariate | | | Multivariate | | | VIF |
|---|---|---|---|---|---|---|---|---|
| | | $\beta$ coefficient | 95% CI | *P*-value | $\beta$ coefficient | 95% CI | *P*-value | |
| **Among all COVID-19 patients†** | | | | | | | | |
| Asthma | | 0.947 | -0.693–2.587 | 0.258 | -0.342 | -1.993–1.309 | 0.685 | |
| **Among asthma patients‡** | | | | | | | | |
| ICS alone | Last one year | -1.385 | -5.306–2.537 | 0.487 | -1.083 | -6.096–3.929 | 0.670 | 1.630 |
| | Last two months | -2.805 | -6.869–1.260 | 0.175 | -3.579 | -9.083–1.925 | 0.201 | 1.822 |
| ICS-LABA | Last one year | 0.611 | -3.094–4.316 | 0.746 | -0.794 | -5.220–3.631 | 0.724 | 1.425 |
| | Last two months | 0.055 | -3.707–3.818 | 0.977 | -1.994 | -6.675–2.688 | 0.402 | 1.551 |
| Oral LABA | Last one year | -3.899 | -7.636–-0.162 | 0.041* | -3.503 | -7.703–0.696 | 0.102 | 1.238 |
| | Last two months | -4.248 | -8.070–-0.428 | 0.030* | -3.744 | -8.214–0.726 | 0.100 | 1.341 |
| Patch LABA | Last one year | 0.520 | -4.095–5.135 | 0.825 | 4.516 | -1.292–10.324 | 0.127 | 1.583 |
| | Last two months | -0.948 | -5.804–3.908 | 0.701 | 3.302 | -3.208–9.811 | 0.318 | 1.799 |
| LTRA | Last one year | -0.273 | -4.354–3.809 | 0.895 | 0.662 | -3.952–5.277 | 0.777 | 1.278 |
| | Last two months | -1.812 | -5.626–2.002 | 0.350 | -0.620 | -5.184–3.944 | 0.789 | 1.428 |
| Inhaled SABA | Last one year | -0.573 | -4.286–3.141 | 0.762 | 1.076 | -3.748–5.900 | 0.661 | 1.686 |
| | Last two months | 0.100 | -3.697–3.896 | 0.959 | 3.915 | -1.347–9.177 | 0.144 | 1.924 |
| Oral SABA | Last one year | 4.088 | -1.119–9.295 | 0.123 | 5.734 | 0.014–11.453 | 0.049* | 1.193 |
| | Last two months | 3.149 | -2.225–8.523 | 0.249 | 4.893 | -1.210–10.997 | 0.115 | 1.284 |
| Xanthine | Last one year | 1.036 | -2.569–4.641 | 0.572 | -0.129 | -4.095–3.836 | 0.949 | 1.208 |
| | Last two months | 0.682 | -2.937–4.300 | 0.711 | -0.225 | -4.327–3.878 | 0.914 | 1.287 |
| Inhaled LAMA | Last one year | 0.450 | -5.210–6.111 | 0.876 | -3.046 | -10.192–4.099 | 0.402 | 1.593 |
| | Last two months | 0.450 | -5.210–6.111 | 0.876 | -2.431 | -9.623–4.760 | 0.506 | 1.617 |
| Severity of asthma (Reference Step 1) | Step 2 | 5.044 | -0.301–10.390 | 0.064 | 4.565 | -1.127–10.258 | 0.115 | 1.668 |
| | Step 3 | 4.000 | -2.470–10.470 | 0.224 | 2.739 | -3.998–9.475 | 0.424 | 1.397 |
| | Step 4 | 1.238 | -3.308–5.783 | 0.592 | 0.976 | -3.802–5.753 | 0.688 | 1.759 |
| | Step 5 | 19.583 | 6.011–33.155 | 0.005* | 18.414 | 4.031–32.796 | 0.012* | 1.171 |

†Adjusted for age, sex, and underlying diseases

‡Adjusted for age, sex, underlying disease, and asthma medications/severity

CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-acting $\beta_2$-agonists; LAMA, long-acting muscarine antagonists; LTRA, leukotriene receptor antagonists; SABA, short-acting $\beta_2$-agonists; VIF, variance inflation factor

*Choi & Park et al.*
*Eur Resp J*
*2020;early view*

**중증 천식 환자에서 COVID-19 감염:** 입원기간 연장에만 영향

# SUMMARY

## ➢ Introduction of severe asthma

: GINA step 4-5 에서, 여러 인자/약물 조절해도 uncontrolled인 천식
: Type 2 inflammation (IgE, eosinophil, FeNO, OCS 등)이 多

## ➢ Characteristics of severe asthma

**:** 치료 반응 및 예후가 좋지 않음
: 바이러스에 대한 면역력 떨어질 수 있음
: Capsaicin sensitivity가 poor outcome 반영
: laryngeal dysfunction 동반 많으며, 이에 대한 치료가 도움 됨

## ➢ Treatment I: Pharmacotherapy

: OCS < Biologics (ATS/ERS guideline…- LAMA, macrolide)
: Omalizumab, mepolizumab, reslizumab, benralizumap, dupilumap, fevipiprant, anti-tryptase Ab

## ➢ Treatment II: Others

: Targeting treatable traits, Bronchial thermoplasty, rehabilitation…

## ➢ Special issues: COVID-19


Thank you
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Severance