T2 Low asthma 치료해보기

Hyun Lee
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Contents

- Disease spectrum
- Assessment
- Current treatment recommendation
- Potential therapeutics
- Summary

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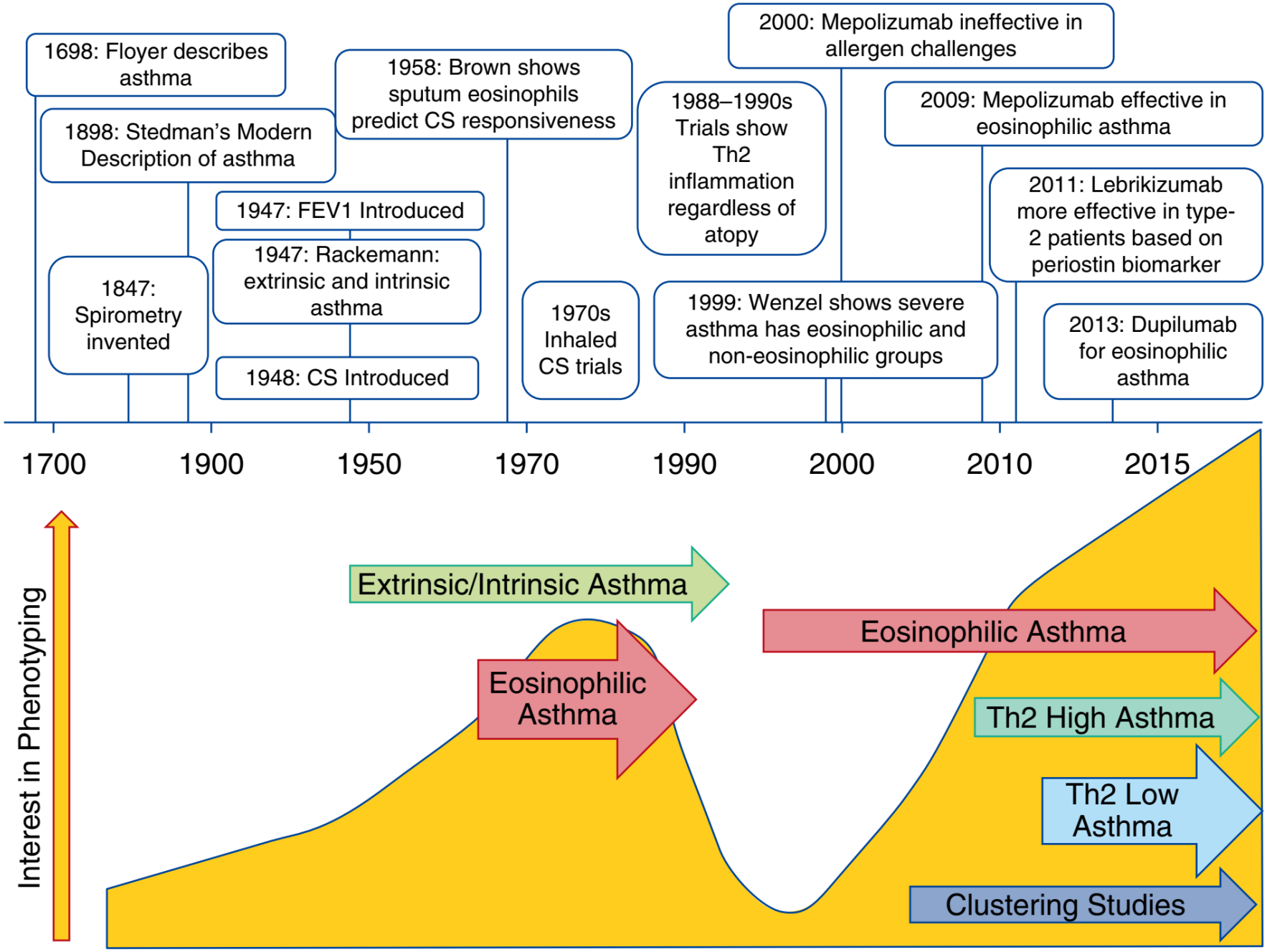
- Summary



Gauthier et al., Am J Respir Crit Care Med 2015;192:660-8.

T2-low vs. high asthma

TABLE 1 Differential diagnostic characteristics of type 2 (T2)-low *versus* T2-high asthma

	T2-low asthma	T2-high asthma
Onset	Late	Early
Symptoms	Mostly significant	May be significant
Obesity	Often present	May be present
Smoking	Often present	May be present
Response to inhaled corticosteroids	Often poor	Usually good
Severity of asthma	Often difficult to treat	Mild to severe
Asthma control	Often poor	Variable
Sputum eosinophils	Absent	Normal or high levels
Sputum neutrophils	Frequently present	May be present
Exhaled nitric oxide	Usually normal	Elevated or normal
Airways	Often present	May be present

Kyriakopoulos et al. ERJ open research 2021;7: 00309-2020.

Identification of Type 2 inflammation

- Blood eosinophil 》150 ul
- FeNO 》 20 ppb
- Sputum eosinophils 》 2%
- Asthma clinically allergy driven

- Repeat tests
  - Blood eosinophils and FeNO up to 3x
  - At least 1-2 weeks after OCS or on lowest possible OCS dose

Usefulness of Inflammatory phenotype

Mild-to-moderate asthma

<

Difficult-to-treat and severe Asthma

TIOT vs. Momentasone

ORIGINAL ARTICLE

Mometasone or Tiotropium in Mild Asthma with a Low Sputum Eosinophil Level

S.C. Lazarus, J.A. Krishnan, T.S. King, J.E. Lang, K.V. Blake, R. Covar, N. Lugogo, S. Wenzel, V.M. Chinchilli, D.T. Mauger, A.-M. Dyer, H.A. Boushey, J.V. Fahy, P.G. Woodruff, L.B. Bacharier, M.D. Cabana, J.C. Cardet, M. Castro, J. Chmiel, L. Denlinger, E. DiMango, A.M. Fitzpatrick, D. Gentile, A. Hastie, F. Holguin, E. Israel, D. Jackson, M. Kraft, C. LaForce, R.F. Lemanske, Jr., F.D. Martinez, W. Moore, W.J. Morgan, J.N. Moy, R. Myers, S.P. Peters, W. Phipatanakul, J.A. Pongracic, L. Que, K. Ross, L. Smith, S.J. Szefler, M.E. Wechsler, and C.A. Sorkness, for the National Heart, Lung, and Blood Institute AsthmaNet*

Inclusion: Patients with mild, persistent asthma 》12 yrs of age

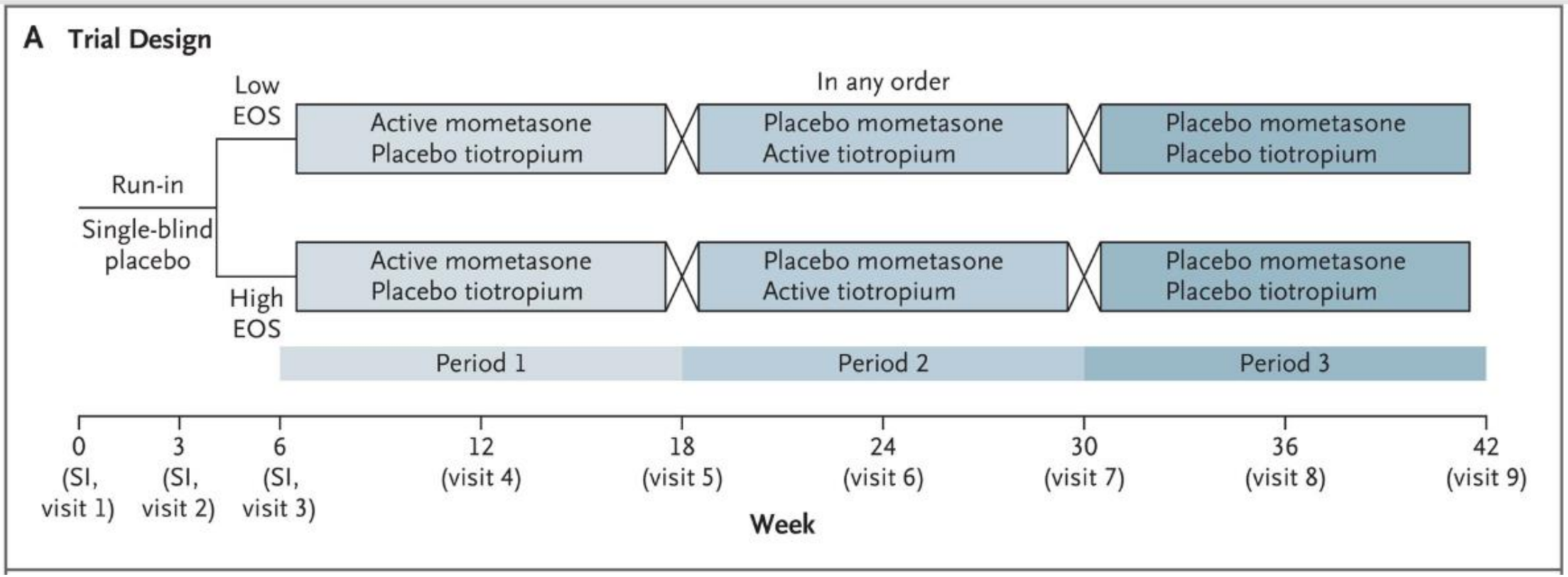
Exposure: TIOT vs. Momentasone
Sputum eosinophil count

Primary outcome: Treatment response
(Composite outcome: treatment failure, asthma control days, and FEV_1)

Lazarus et al., N Engl J Med 2019;380:2009-19

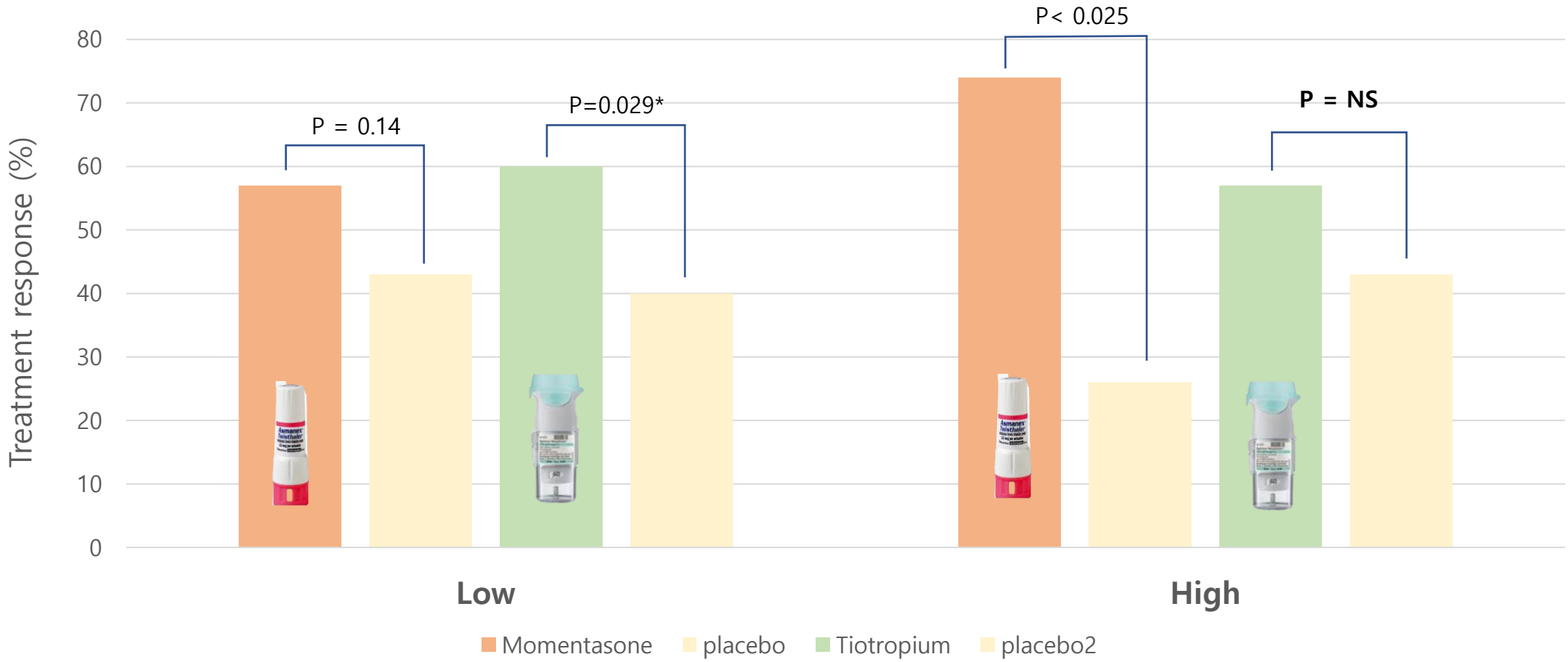
TIOT vs. Momentasone

Sputum eosinophil (EOS) level (<2% or ≥2%)



Lazarus et al., N Engl J Med 2019;380:2009-19

TIOT is not better than momentasone when sputum eos < 2%



*P < 0.025 is significant

Lazarus et al., N Engl J Med 2019;380:2009-19

Usefulness of Inflammatory phenotype

Mild-to-moderate asthma

Difficult-to-treat and severe Asthma

LAMA vs. LAMA/ICS

	Treatment exposure periods (n = 329) considering mixed patients (n = 74) only		
	Relative Risk	95% CI	p-value
Mono therapy	**5.72**	**1.39-23.62**	**0.016**
Dual therapy	Ref	Ref	–
Triple therapy	N/A	N/A	N/A
Female sex	0.77	0.22-2.69	0.677
Age	0.95	0.89-1.00	0.065
History of exacerbations	2.14	0.92-5.01	0.079
Allergic rhinitis	0.86	0.27-2.70	0.793
Sinusitis	0.00	0.00-∞	1.00
Depression	**5.09**	**1.27-20.35**	**0.021**
Lower respiratory tract infection	**6.04**	**1.53- 23.90**	**0.011**
Smoking: never	ref		
Smoking: current	0.24	0.048-1.20	0.083
Smoking: past	0.00	0.00-∞	1.000
Smoking: unknown	0.00	0.00-∞	1.000

Baan et al., Pulmonary Pharmacology & Therapeutics 2021;71:102074.

Clinical phenotypes of T2 low asthma

- Mild to severe asthma in nonsmokers or ex-smokers (both co ntrolled and uncontrolled)
- Smokers with asthma
- High body mass index (obesity)
- Occupational or work-exacerbated asthma
- Factors associated with higher neutrophil counts
  - Older age
  - Exposure to environmental pollution
  - Respiratory infections

Thomson NC, Ther Adv Respir Dis 2016;10:211-34.

Contents

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  - Confirm diagnosis
  - Inflammatory phenotyping
- Current treatment recommendation
- Potential therapeutics
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Case

- 75세/여자

- 개인력: Never-smoker
- 과거력: AD(-) AR(-) 천식(-) 결핵(-)

- 3개월 전부터 쌕쌕거리고 약간 숨이 차서 동네 의원 내원

- 고용량 ICS/LABA 치료에도 호전 없어 전원

표 3-7. 한국어판 천식조절검사(Asthma control test: ACT)

1	2	3	4	5
지난 4 주 동안, 당신은 천식으로 인해 얼마나 많은 시간을 직장이나 학교나 집에서 평소에 했던 만큼 일하고 공부하고 활동하는데 지장을 받았습니까?				
항상 그랬다	대부분의 시간 동안 그랬다	**다소의 시간 동안 그랬다**	아주 약간의 시간 동안 그랬다	전혀 그렇지 않았다
지난 4 주 동안, 당신은 얼마나 자주 숨을 헐떡였거나 / 숨을 쉬기가 어려웠습니까?				
하루에 두번 이상 그랬다	**하루에 한번 그랬다**	일주일에 3-6번 그랬다	일주일에 1-2번 그랬다	전혀 그렇지 않았다
지난 4 주 동안, 당신은 천식증상(쌕쌕거리는 소리, 기침, 숨가쁨, 가슴답답함이나 통증) 으로 인해 얼마나 자주 밤에 잠을 깨거나 아침에 평소보다 일찍 일어났습니까 ?				
일주일에 4일 밤 이상을 그랬다	**일주일에 2-3일 밤을 그랬다**	일주일에 한번 그랬다	한 두번 그랬다	전혀 그렇지 않았다
지난 4주 동안, 당신은 응급약물(예를 들면 살부타몰, 페노테롤, 벤토린®, 베로텍® 등)을 얼마나 자주 사용했습니까 ?				
하루에 3번 이상 사용했다	하루에 1-2번 사용했다	일주일에 2-3번 사용했다	일주일에 한 번 이하로 사용했다	**전혀 사용하지 않았다**
당신은 지난 4주 동안 천식을 얼마나 잘 조절했다고 평가하겠습니까?				
전혀 조절하지 못했다	잘 조절하지 못했다	다소 조절했다	잘 조절했다	완벽하게 조절했다

What is your next plan?

SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

Assess and treat severe asthma phenotypes

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities, non-pharmacologic strategies)

5 *Investigate* further and provide *patient support*

- Investigate for comorbidities/differential diagnoses and treat/refer as appropriate
  - Consider: CBC, CRP, IgG, IgA, IgM, IgE, fungal precipitins; CXR and/or HRCT chest; DLCO; DEXA scan
  - Skin prick testing or specific IgE for relevant allergens, if not already done
  - Consider screening for adrenal insufficiency in patients taking maintenance OCS or high dose ICS
  - If blood eosinophils ≥300/µl, look for and treat non-asthma causes, including parasites (e.g. Strongyloides serology, or stool examination)
  - If hypereosinophilia e.g. ≥1500/µl, consider causes such as EGPA
  - Other directed testing (e.g. ANCA, CT sinuses, BNP, echocardiogram) based on clinical suspicion
- Consider need for social/psychological support
- Involve multidisciplinary team care (if available)
- Invite patient to enroll in registry (if available) or clinical trial (if appropriate)

6 Assess the *severe asthma phenotype*

Could patient have Type 2 airway inflammation?

yes

Type 2 inflammation

- Blood eosinophils ≥150/µl and/or
- FeNO ≥20 ppb and/or
- Sputum eosinophils ≥2%, and/or
- Asthma is clinically allergen-driven

(Repeat blood eosinophils and FeNO up to 3x, at least 1-2 weeks after OCS or on lowest possible OCS dose)

*Note: these are **not** the criteria for add-on biologic therapy (see **8**)*

no

No evidence of Type 2 airway inflammation

- Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects
- Avoid exposures (tobacco smoke, allergens, irritants)
- Consider investigations (if available and not done)
  - Sputum induction
  - High resolution chest CT
  - Bronchoscopy for alternative/additional diagnoses
- Consider trial of add-on treatments (if available and not already tried)
  - LAMA
  - Low dose azithromycin
  - Anti-IL4R* if taking maintenance OCS
  - Anti-TSLP* (but insufficient evidence in patients on maintenance OCS)
  - As last resort, consider add-on low dose OCS, but implement strategies to minimize side-effects
- Consider bronchial thermoplasty (+ registry)
- Stop ineffective add-on therapies

** Check local eligibility criteria for specific biologic therapies as these may vary from those listed*

7 Consider *other* treatments

Type 2 airway inflammation

- Consider adherence tests
- Consider increasing the ICS dose for 3-6 months
- Consider add-on non-biologic treatment for specific Type 2 clinical phenotypes, e.g. AERD, ABPA, chronic rhinosinusitis, nasal polyposis, atopic dermatitis

Is add-on Type 2 biologic therapy available/ affordable?

yes

no

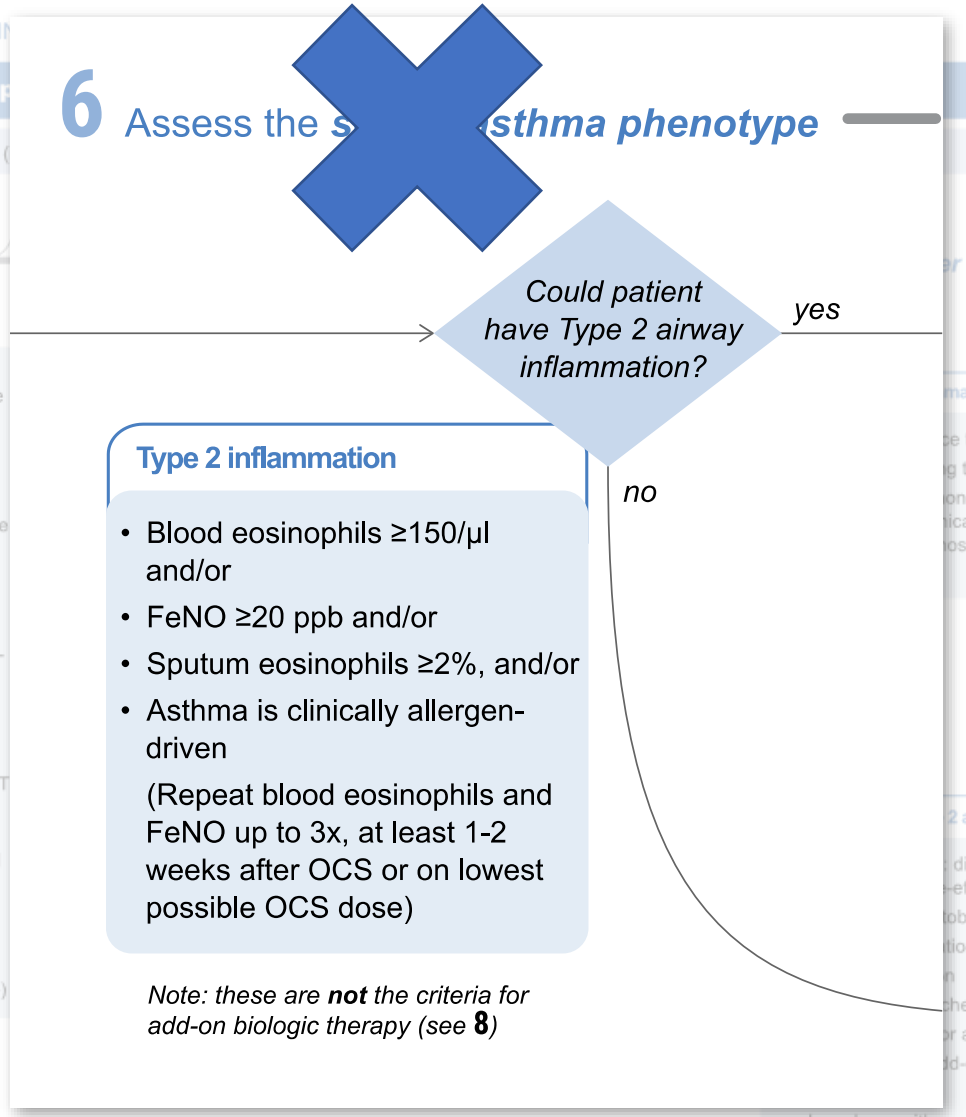
If add-on Type 2-targeted biologic therapy is NOT available/affordable

- Consider higher dose ICS, if not used
- Consider other add-on therapy (e.g. LAMA, LM/LTRA, low dose azithromycin)
- As last resort, consider add-on low dose OCS, but implement strategies to minimize side-effects
- Stop ineffective add-on therapies

Go to section **10**

Not currently eligible for T2-targeted biologic therapy

Go to section **10**


6 Assess the s sthma phenotype
Could patient have Type 2 airway inflammation?
yes
no
Type 2 inflammation
• Blood eosinophils ≥150/µl and/or
• FeNO ≥20 ppb and/or
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• Asthma is clinically allergen-driven
(Repeat blood eosinophils and FeNO up to 3x, at least 1-2 weeks after OCS or on lowest possible OCS dose)
Note: these are **not** the criteria for add-on biologic therapy (see **8**)

GP OR SPECIALIST CARE

Investigate and manage difficult-to-treat asthma in adults and adolescents

Consider referring to specialist or [illegible] clinic at any stage

DIAGNOSIS: *"Difficult-to-treat asthma"*

For adolescents and adults with symptoms and/or exacerbations despite medium or high dose ICS-LABA, or taking maintenance OCS

1 Confirm the diagnosis (asthma/differential diagnoses)

2 Look for factors contributing to symptoms, exacerbations and poor quality of life:

- Incorrect inhaler technique
- Suboptimal adherence
- Comorbidities including obesity, GERD, chronic rhinosinusitis, OSA
- Modifiable risk factors and triggers at home or work, including smoking, environmental exposures, allergen exposure (if sensitized); medications such as beta-blockers and NSAIDs
- Overuse of SABA relievers
- Medication side effects
- Anxiety, depression and social difficulties

3 Optimize management, including:

- Asthma education
- Optimize treatment (e.g. check and correct inhaler technique and adherence; switch to ICS-formoterol maintenance and reliever therapy, if available)
- Consider non-pharmacological interventions (e.g. smoking cessation, exercise, weight loss, mucus clearance, influenza and COVID-19 vaccination)
- Treat comorbidities and modifiable risk factors
- Consider non-biologic add-on therapy (e.g. LABA, LAMA, LM/LTRA, if not used)
- Consider trial of high dose ICS-LABA, if not used

4 Review response after ~3-6 months

Is asthma still uncontrolled?

yes → DIAGNOSIS: *"Severe asthma"* → If not done by now, refer to a specialist, if possible

no → Consider stepping down treatment, OCS first (if used)

Does asthma become uncontrolled when treatment is stepped down?

yes → Restore previous dose

no → Continue optimizing management

Key

- decision, filters
- intervention, treatment
- diagnosis, confirmation

GP OR SPECIALIST CARE

Investigate and manage difficult-to-treat asthma in adults and adolescents

Consider referring to specialist or severe asthma clinic at any stage

DIAGNOSIS: *"Difficult-to-treat asthma"*

1 **Confirm** the diagnosis (asthma/differential diagnoses)

3 **Optimize management,** including:

4 Review **response after ~3-6 months**

1 **Confirm** the diagnosis (asthma/differential diagnoses)

- smoking, environmental exposures, allergen exposure (if sensitized); medications such as beta-blockers and NSAIDs
- Overuse of SABA relievers
- Medication side effects
- Anxiety, depression and social difficulties

modifiable risk factors

- Consider non-biologic add-on therapy (e.g. LABA, LAMA, LM/LTRA, if not used)
- Consider trial of high dose ICS-LABA, if not used

Is asthma still uncontrolled?

yes

DIAGNOSIS: *"Severe asthma"*

If not done by now, refer to a specialist, if possible

no

Consider stepping down treatment, OCS first (if used)

Restore previous dose

Does asthma become uncontrolled when treatment is stepped down?

yes

no

Continue optimizing management

Key

decision, filters

intervention, treatment

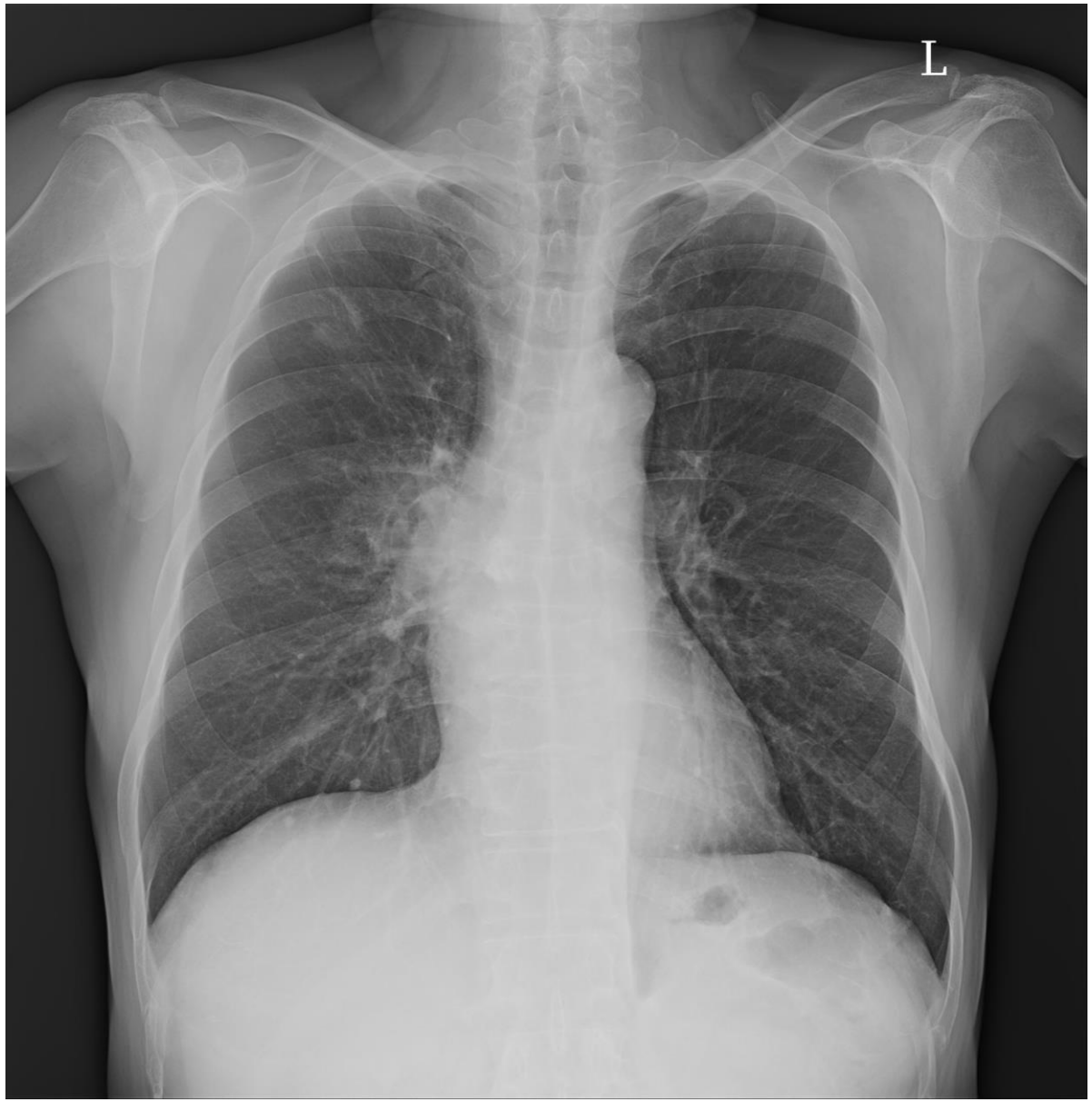
diagnosis, confirmation

The First thing we should do

- Wrong diagnosis in 12-50% of subjects assumed to have severe asthma

Symptoms	Differential diagnosis
Dyspnea	**Obesity, COPD**, Cardiac disease, deconditioning
Cough	VCD, UACS, GERD, **bronchiectasis**, ACEi
Wheeze	**Obesity, COPD**, Tracheobronchomalacia, VCD

Hashimoto et al., Clin Exp Allergy 2012;42:693-705.
GINA 2022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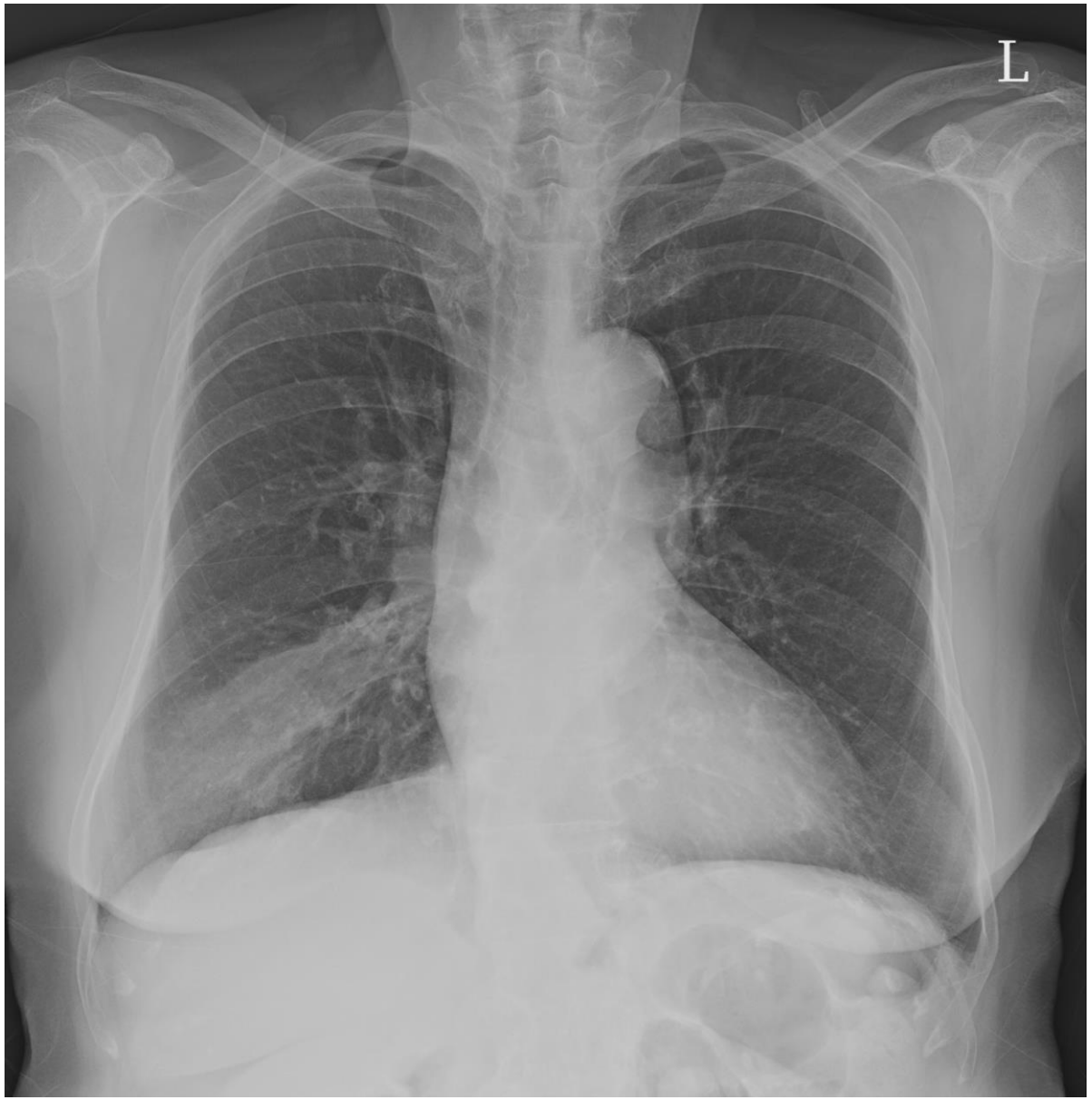
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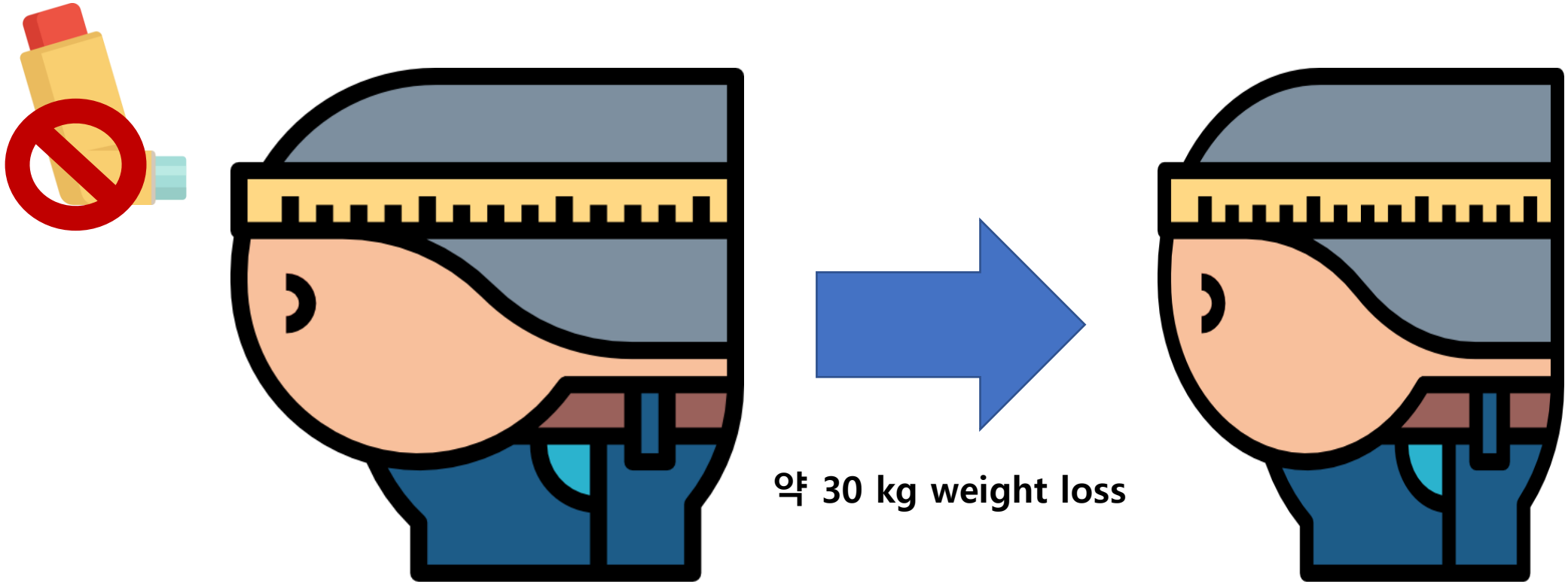
Case

- 42세/M
- 170cm/120kg
- 2014년 호흡곤란으로 내원 당시 신체검진 상 wheezing (+)
- Never smoker, Allergy (-) Pulm TB (-)

- CXR/Chest CT - Normal
- PFT – BDR (-) MBPT test (-) FENO 20
- Blood eos – 100

- High-dose ICS/LABA 추적관찰 → f/u loss

2017년 pre-op risk assessment로 내원



"저 천식이 아니었던 것 같아요!"

Confirm the correct diagnosis

- **Careful history & physical examination**
- **Differential diagnosis**

Box 1-5 (continued). Differential diagnosis of asthma in adults, adolescents and children 6–11 years

Age	Symptoms	Condition
12–39 years	Sneezing, itching, blocked nose, throat-clearing	Chronic upper airway cough syndrome
	Dyspnea, inspiratory wheezing (stridor)	Inducible laryngeal obstruction
	Dizziness, paresthesia, sighing	Hyperventilation, dysfunctional breathing
	Productive cough, recurrent infections	Bronchiectasis
	Excessive cough and mucus production	Cystic fibrosis
	Cardiac murmurs	Congenital heart disease
	Shortness of breath, family history of early emphysema	$Alpha_1$-antitrypsin deficiency
	Sudden onset of symptoms	Inhaled foreign body
40+ years	Dyspnea, inspiratory wheezing (stridor)	Inducible laryngeal obstruction
	Dizziness, paresthesia, sighing	Hyperventilation, dysfunctional breathing
	Cough, sputum, dyspnea on exertion, smoking or noxious exposure	COPD*
	Productive cough, recurrent infections	Bronchiectasis
	Dyspnea with exertion, nocturnal symptoms, ankle edema	Cardiac failure
	Treatment with angiotensin converting enzyme (ACE) inhibitor	Medication-related cough
	Dyspnea with exertion, non-productive cough, finger clubbing	Parenchymal lung disease
	Sudden onset of dyspnea, chest pain	Pulmonary embolism
	Dyspnea, unresponsive to bronchodilators	Central airway obstruction
All ages	Chronic cough, hemoptysis, dyspnea; and/or fatigue, fever, (night) sweats, anorexia, weight loss	Tuberculosis

*For more detail, see Chapter 5 (p.141). Any of the above conditions may also contribute to respiratory symptoms in patients with confirmed asthma.

Confirm the correct diagnosis.

- **Perform spirometry**

Box 1-3. Steps for confirming the diagnosis of asthma in a patient already taking controller treatment

Current status	Steps to confirm the diagnosis of asthma
Variable respiratory symptoms and variable airflow limitation	Diagnosis of asthma is confirmed. Assess the level of asthma control (Box 2-2, p.36) and review controller treatment (Box 3-5, p.61).
Variable respiratory symptoms but no variable airflow limitation	Consider repeating spirometry after withholding BD (4 hrs for SABA, 24 hrs for twice-daily ICS-LABA, 36hrs for once-daily ICS-LABA) or during symptoms. Check between-visit variability of FEV_1, and bronchodilator responsiveness. If still normal, consider other diagnoses (Box 1-5, p.27). *If FEV_1 is >70% predicted*: consider stepping down controller treatment (see Box 1-5) and reassess in 2–4 weeks, then consider bronchial provocation test or repeating BD responsiveness. *If FEV_1 is <70% predicted*: consider stepping up controller treatment for 3 months (Box 3-5), then reassess symptoms and lung function. If no response, resume previous treatment and refer patient for diagnosis and investigation.
Few respiratory symptoms, normal lung function, and no variable airflow limitation	Consider repeating BD responsiveness test again after withholding BD as above or during symptoms. If normal, consider alternative diagnoses (Box 1-5, p.27). Consider stepping down controller treatment (see Box 1-5): • *If symptoms emerge and lung function falls*: asthma is confirmed. Step up controller treatment to previous lowest effective dose. • *If no change in symptoms or lung function at lowest controller step*: consider ceasing controller, and monitor patient closely for at least 12 months (Box 3-7).
Persistent shortness of breath and persistent airflow limitation	Consider stepping up controller treatment for 3 months (Box 3-5, p.61), then reassess symptoms and lung function. If no response, resume previous treatment and refer patient for diagnosis and investigation. Consider asthma–COPD overlap (Chapter 5, p.141).

BD: bronchodilator; LABA: long-acting $beta_2$-agonist; SABA: short-acting $beta_2$-agonist. 'Variable airflow limitation' refers to expiratory airflow.

Contents

- Disease spectrum
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- Potential therapeutics
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SPECIALIST CARE; SEVERE ASTHMA CLINIC IF AVAILABLE

Assess and treat severe asthma phenotypes

Continue to optimize management as in section **3** (including inhaler technique, adherence, comorbidities, non-pharmacologic strategies)

5 *Investigate* further and provide *patient support*

- Investigate for comorbidities/differential diagnoses and treat/refer as appropriate
  - Consider: CBC, CRP, IgG, IgA, IgM, IgE, fungal precipitins; CXR and/or HRCT chest; DLCO; DEXA scan
  - Skin prick testing or specific IgE for relevant allergens, if not already done
  - Consider screening for adrenal insufficiency in patients taking maintenance OCS or high dose ICS
  - If blood eosinophils ≥300/µl, look for and treat non-asthma causes, including parasites (e.g. Strongyloides serology, or stool examination)
  - If hypereosinophilia e.g. ≥1500/µl, consider causes such as EGPA
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- Involve multidisciplinary team care (if available)
- Invite patient to enroll in registry (if available) or clinical trial (if appropriate)

6 Assess the *severe asthma phenotype*

Could patient have Type 2 airway inflammation?

yes

Type 2 inflammation

- Blood eosinophils ≥150/µl and/or
- FeNO ≥20 ppb and/or
- Sputum eosinophils ≥2%, and/or
- Asthma is clinically allergen-driven

(Repeat blood eosinophils and FeNO up to 3x, at least 1-2 weeks after OCS or on lowest possible OCS dose)

*Note: these are **not** the criteria for add-on biologic therapy (see **8**)*

no

No evidence of Type 2 airway inflammation

- Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects
- Avoid exposures (tobacco smoke, allergens, irritants)
- Consider investigations (if available and not done)
  - Sputum induction
  - High resolution chest CT
  - Bronchoscopy for alternative/additional diagnoses
- Consider trial of add-on treatments (if available and not already tried)
  - LAMA
  - Low dose azithromycin
  - Anti-IL4R* if taking maintenance OCS
  - Anti-TSLP* (but insufficient evidence in patients on maintenance OCS)
  - As last resort, consider add-on low dose OCS, but implement strategies to minimize side-effects
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** Check local eligibility criteria for specific biologic therapies as these may vary from those listed*

7 Consider *other* treatments

Type 2 airway inflammation

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- Consider increasing the ICS dose for 3-6 months
- Consider add-on non-biologic treatment for specific Type 2 clinical phenotypes, e.g. AERD, ABPA, chronic rhinosinusitis, nasal polyposis, atopic dermatitis

Is add-on Type 2 biologic therapy available/ affordable?

yes

no

If add-on Type 2-targeted biologic therapy is NOT available/affordable

- Consider higher dose ICS, if not used
- Consider other add-on therapy (e.g. LAMA, LM/LTRA, low dose azithromycin)
- As last resort, consider add-on low dose OCS, but implement strategies to minimize side-effects
- Stop ineffective add-on therapies

Go to section **10**

Not currently eligible for T2-targeted biologic therapy

Go to section **10**

Key changes to GINA severe asthma guide in 2022

Contents

- Disease spectrum
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- Current treatment recommendation
  - LAMA
  - Azithromycin
  - Anti-IL4R if taking maintenance OCS
  - Anti-TSLP (insufficient evidence in pts on maintenance OCS)
  - Consider bronchial thermoplasty
- Potential therapeutics

No evidence of Type 2 airway inflammation

- Review the basics: differential diagnosis, inhaler technique, adherence, comorbidities, side-effects
- Avoid exposures (tobacco smoke, allergens, irritants)
- Consider investigations (if available and not done)
  - Sputum induction
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- Consider bronchial thermoplasty (+ registry)
- Stop ineffective add-on therapies

LAMA

JAMA | Original Investigation

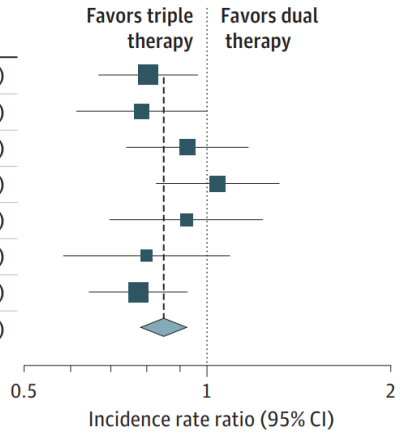
Triple vs Dual Inhaler Therapy and Asthma Outcomes in Moderate to Severe Asthma
A Systematic Review and Meta-analysis

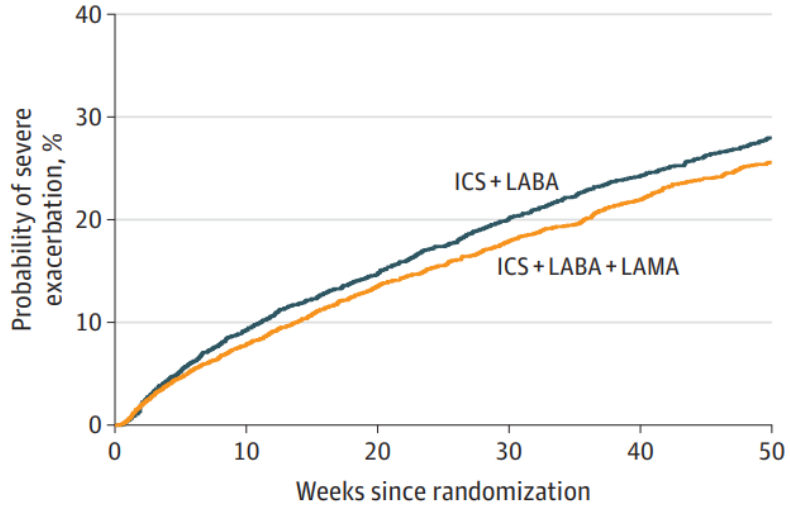
Lisa H. Y. Kim, MD; Carol Saleh, MD; Anna Whalen-Browne, MD; Paul M. O'Byrne, MB; Derek K. Chu, MD, PhD

18 RCTs – Moderate to severe asthma using Triple vs. ICS/LABA
LAMA - tiotropium, glycopyrrolate, glycopyrronium, and umeclidinium

A Incidence rate ratio of exacerbations

Source	Mean annualized exacerbation rate[a] Triple	Dual	Incidence rate ratio (95% CI)	Weight, %
Kerstjens et al,[46] 2012	0.53	0.66	0.80 (0.66-0.96)	21
Kerstjens et al,[55] 2020[b]	0.26	0.33	0.78 (0.61-1.00)	12
Kerstjens et al,[55] 2020[b]	0.38	0.41	0.93 (0.74-1.17)	14
Lee et al,[56] 2020[b]	0.38	0.41	1.04 (0.82-1.31)	14
Lee et al,[56] 2020[b]	0.39	0.38	0.92 (0.69-1.23)	9
Pearl Therapeutics,[57] 2017	0.44	0.55	0.79 (0.58-1.09)	8
Virchow et al,[45] 2019	0.27	0.35	0.77 (0.64-0.93)	22
Overall: $I^2 = 0\%$			0.85 (0.78-0.92)	100





No. at risk						
ICS + LABA	4137	3650	3320	2922	2540	1760
ICS + LABA + LAMA	4159	3774	3396	2871	2332	1475
No. of studies	6	6	6	6	6	4

Reduced risk of AE

Kim et al., JAMA 2021;325:2466-2479

LAMA

JAMA | Original Investigation

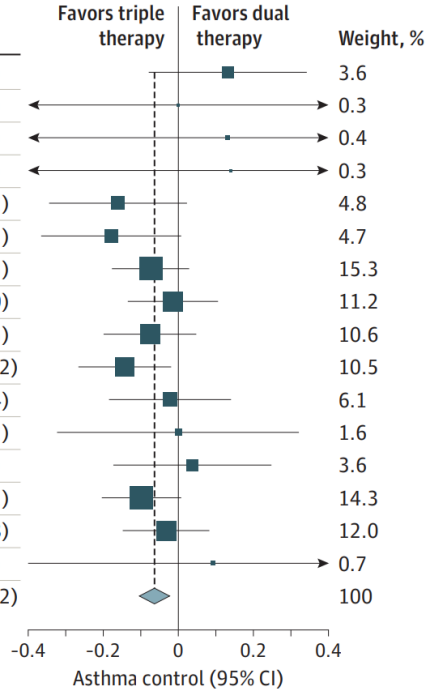
Triple vs Dual Inhaler Therapy and Asthma Outcomes in Moderate to Severe Asthma

A Systematic Review and Meta-analysis

Lisa H. Y. Kim, MD; Carol Saleh, MD; Anna Whalen-Browne, MD; Paul M. O'Byrne, MB; Derek K. Chu, MD, PhD

A Asthma control

Source	Scale[a]	Triple therapy No.	Triple therapy Mean (SD)	Dual therapy No.	Dual therapy Mean (SD)	Standardized mean difference (95% CI)	Weight, %
Hamelmann et al,[50] 2017	ACQ-7	256	-0.87 (0.82)	132	-0.97 (0.57)	0.13 (-0.08 to 0.34)	3.6
Ishiura et al,[52] 2019	ACT	17	0.40 (6.20)	17	0.40 (6.20)	0.00 (-0.67 to 0.67)	0.3
Ishiura et al,[53] 2020	ACQ-5	19	-0.40 (4.60)	19	-1.00 (4.60)	0.13 (-0.51 to 0.77)	0.4
Jabbal et al,[47] 2017	ACQ-7	14	-0.22 (0.44)	14	-0.28 (0.41)	0.14 (-0.60 to 0.88)	0.3
Kerstjens et al,[46] 2012[b]	ACQ-7	237	-0.71 (0.75)	222	-0.59 (0.75)	-0.16 (-0.34 to 0.02)	4.8
Kerstjens et al,[46] 2012[b]	ACQ-7	216	-0.57 (0.73)	232	-0.44 (0.74)	-0.18 (-0.36 to 0.01)	4.7
Kerstjens et al,[55] 2020[b]	ACQ-7	552	-1.09 (0.70)	1094	-1.05 (0.45)	-0.07 (-0.18 to 0.03)	15.3
Kerstjens et al,[55] 2020[b]	ACQ-7	537	-0.96 (0.67)	536	-0.96 (0.66)	-0.02 (-0.13 to 0.10)	11.2
Lee et al,[56] 2020[b]	ACQ-7	790	-0.77 (0.66)	374	-0.72 (0.66)	-0.08 (-0.20 to 0.05)	10.6
Lee et al,[56] 2020[b]	ACQ-7	784	-0.73 (0.67)	371	-0.64 (0.66)	-0.14 (-0.27 to -0.02)	10.5
Pearl Therapeutics,[57] 2017	ACQ-7	665	-0.86 (2.90)	187	-0.80 (0.77)	-0.02 (-0.18 to 0.14)	6.1
Singh et al,[59] 2014	ACQ-6	152	-0.19 (1.45)	49	-0.19 (0.55)	-0.00 (-0.32 to 0.32)	1.6
Szefler et al,[49] 2017	ACQ-7	262	-0.95 (0.73)	130	-0.97 (0.54)	0.04 (-0.17 to 0.25)	3.6
Virchow et al,[45] 2019[b]	ACQ-7	858	-0.82 (1.26)	571	-0.71 (0.73)	-0.10 (-0.20 to 0.01)	14.3
Virchow et al,[45] 2019[b]	ACQ-7	575	-0.74 (0.69)	574	-0.72 (0.70)	-0.03 (-0.15 to 0.08)	12.0
Wang et al,[60] 2015	ACT	30	-5.77 (7.87)	33	-6.38 (5.34)	0.09 (-0.40 to 0.59)	0.7
Overall: I^2=0%		5964		4555		-0.06 (-0.10 to -0.02)	100



Better asthma control

Kim et al., JAMA 2021;325:2466-2479

LAMA

JAMA | Original Investigation

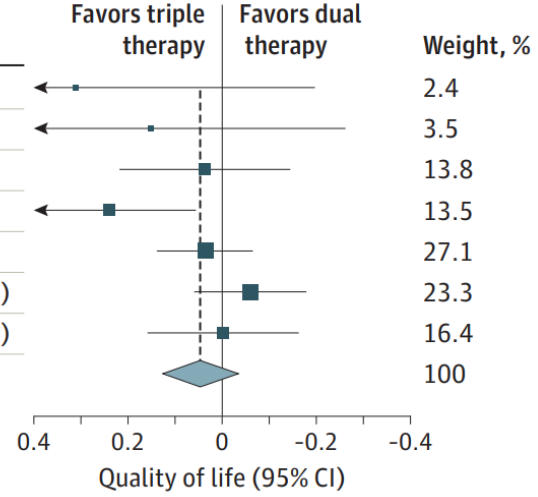
Triple vs Dual Inhaler Therapy and Asthma Outcomes in Moderate to Severe Asthma

A Systematic Review and Meta-analysis

Lisa H. Y. Kim, MD; Carol Saleh, MD; Anna Whalen-Browne, MD; Paul M. O'Byrne, MB; Derek K. Chu, MD, PhD

B Quality of life

Source	Scale[a]	Triple therapy No.	Triple therapy Mean (SD)	Dual therapy No.	Dual therapy Mean (SD)	Standardized mean difference (95% CI)	Weight, %
Hoshino et al,[51] 2018	AQLQ	29	0.50 (1.00)	30	0.20 (0.90)	0.31 (-0.20 to 0.83)	2.4
Kerstjens et al,[48] 2011	Mini-AQLQ	67	0.21 (0.69)	33	0.11 (0.49)	0.15 (-0.26 to 0.57)	3.5
Kerstjens et al,[46] 2012[b]	AQLQ	237	0.55 (1.01)	222	0.51 (1.01)	0.04 (-0.15 to 0.22)	13.8
Kerstjens et al,[46] 2012[b]	AQLQ	216	0.48 (0.96)	232	0.24 (1.02)	0.24 (0.06 to 0.43)	13.5
Kerstjens et al,[55] 2020[b]	AQLQ	552	0.87 (0.82)	1093	0.83 (1.19)	0.04 (-0.07 to 0.14)	27.1
Kerstjens et al,[55] 2020[b]	AQLQ	535	0.76 (0.83)	536	0.81 (0.83)	-0.06 (-0.18 to 0.06)	23.3
Pearl Therapeutics,[57] 2017	AQLQ	667	0.95 (4.94)	188	0.96 (1.01)	-0.00 (-0.16 to 0.16)	16.4
Overall: I^2 = 32%		2303		2334		0.05 (-0.03 to 0.13)	100



No difference in QoL

Kim et al., JAMA 2021;325:2466-2479

LAMA

JAMA | Original Investigation

Triple vs Dual Inhaler Therapy and Asthma Outcomes in Moderate to Severe Asthma

A Systematic Review and Meta-analysis

Lisa H. Y. Kim, MD; Carol Saleh, MD; Anna Whalen-Browne, MD; Paul M. O'Byrne, MB; Derek K. Chu, MD, PhD

	Severe AE	FEV1
T2-Low	**0.85 (0.76 to 0.95)**	MD 0.09 (0.06 to 0.12)
T2-High	0.86 (0.74 to 1.01)	MD 0.08 (0.01 to 0.09)
P for interaction	0.88	0.09

Kim et al., JAMA 2021;325:2466-2479 Supplement

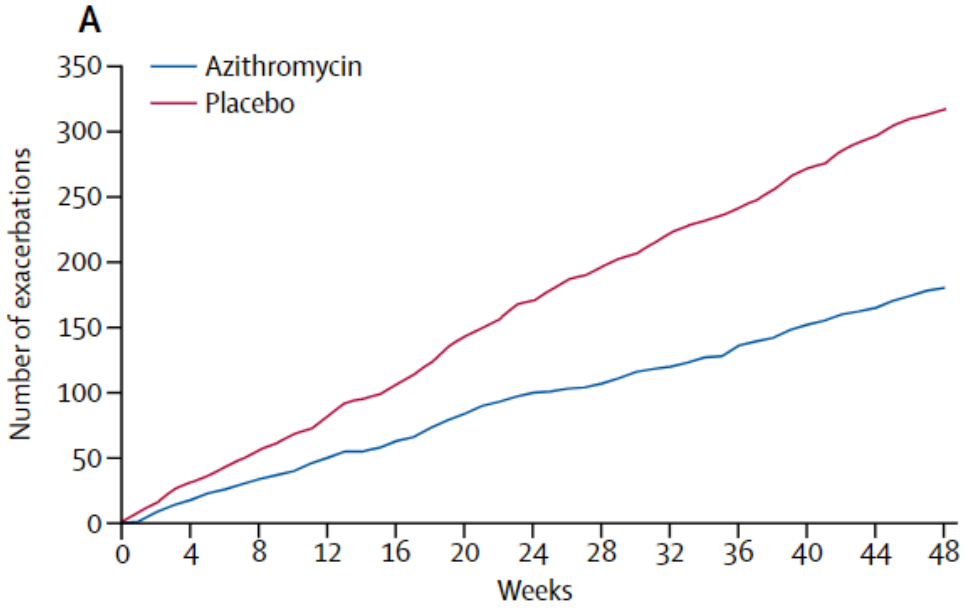
Azithromycin

Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial

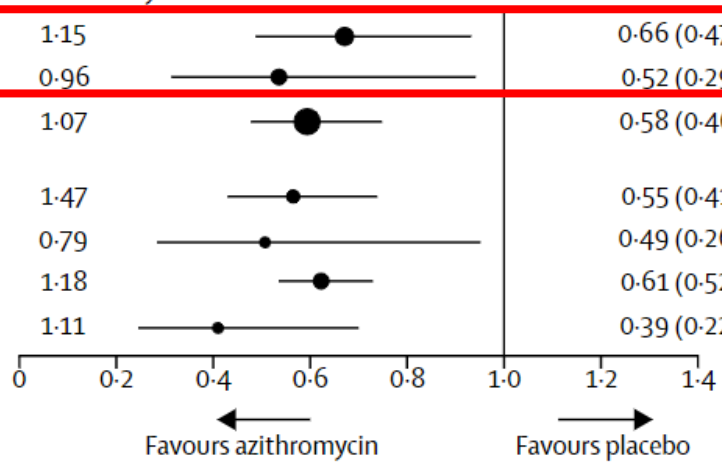
Peter G Gibson, Ian A Yang, John W Upham, Paul N Reynolds, Sandra Hodge, Alan L James, Christine Jenkins, Matthew J Peters, Guy B Marks, Melissa Baraket, Heather Powell, Steven L Taylor, Lex E X Leong, Geraint B Rogers, Jodie L Simpson

Inclusion: Adults with asthma 18 yrs using ICS/LABA
but symptomatic with at least partial loss of asthma control (ACQ5 ≥ 0.75)

Exposure: Azithromycin vs. placebo
Primary outcome: AE over 48 wks



	Number	Exacerbations per person-year		Incidence rate ratio (95% CI)
		Placebo	Azithromycin	
Non-eosinophilic asthma	224	1·74	1·15	0·66 (0·47–0·93)
Eosinophilic asthma	196	1·98	0·96	0·52 (0·29–0·94)
Inhaled corticosteroid dose adjustment	420	1·86	1·07	0·58 (0·46–0·74)
Frequent exacerbators	140	2·79	1·47	0·55 (0·41–0·73)
Cough and sputum VAS	48	1·72	0·79	0·49 (0·26–0·95)
Bacteria–negative	188	1·85	1·18	0·61 (0·52–0·72)*
Bacteria–positive	48	2·64	1·11	0·39 (0·22–0·69)*



Gibson et al., Lancet 2017;390(10095):659-668.

Biologics ?

Class	Name	Age*	Asthma indication*	Other indications*
Anti-IgE	Omalizumab (SC)	≥6 years	Severe allergic asthma	Nasal polyposis, chronic spontaneous urticaria
Anti-IL5 Anti-IL5R	Mepolizumab (SC) Reslizumab (IV) Benralizumab (SC)	≥6 years ≥18 years ≥12 years	Severe eosinophilic/Type 2 asthma	Mepolizumab: EGPA, CRSwNP, hypere osinophilic syndrome
Anti-IL4R	Dupilumab (SC)	≥6 years	Severe eosinophilic/Type 2 asthma, or **maintenance OCS**	Moderate-severe atopic dermatitis, CR SwNP
Anti-TSLP	Tezepelumab (SC)	≥12 years	**Severe asthma regardless of Type 2**	

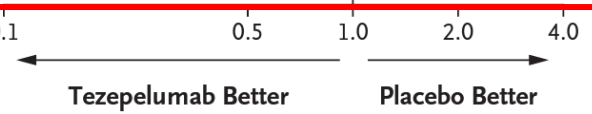
Key changes to GINA severe asthma guide in 2022

Tezepelumab

Inclusion:
Subjects with asthma (12-80 yrs) using high-dose ICS + one controller at least 12 months w/wo OCS

Exposure: Tezepelumab vs. placebo
Primary outcome: annualized rate of asthma exacerbations over 52 wks

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



Menzies-Gow et al., N Engl J Med 2021;384:1800-9

OCS-sparing effect of Tezepelumab

Evaluation of the oral corticosteroid-sparing effect of tezepelumab in adults with oral corticosteroid-dependent asthma (SOURCE): a randomised, placebo-controlled, phase 3 study

*Michael E Wechsler, Andrew Menzies-Gow, Christopher E Brightling, Piotr Kuna, Stephanie Korn, Tobias Welte, Janet M Griffiths, Kinga Sałapa, Åsa Hellqvist, Gun Almqvist, Harbans Lal, Primal Kaur, Tor Skärby, Gene Colice, on behalf of the SOURCE study group**

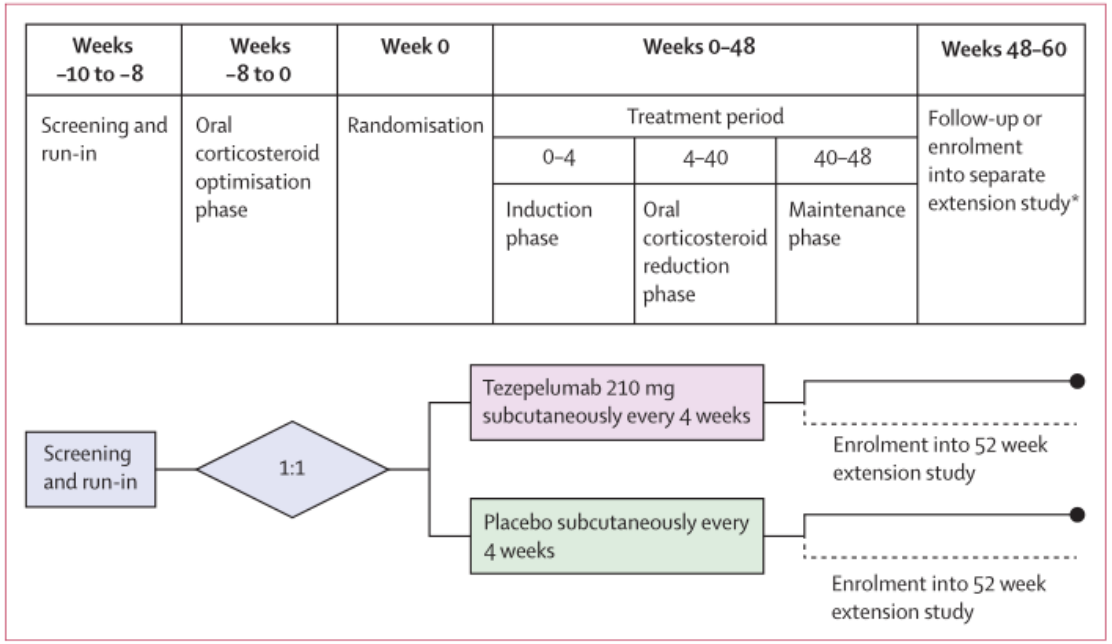


***Figure 1*: Study design**
Figure reproduced from Wechsler and colleagues.[19] *Participants who enrolled in a long-term extension study on the same day as the end-of-treatment visit in SOURCE did not attend follow-up visits at week 54 and week 60.

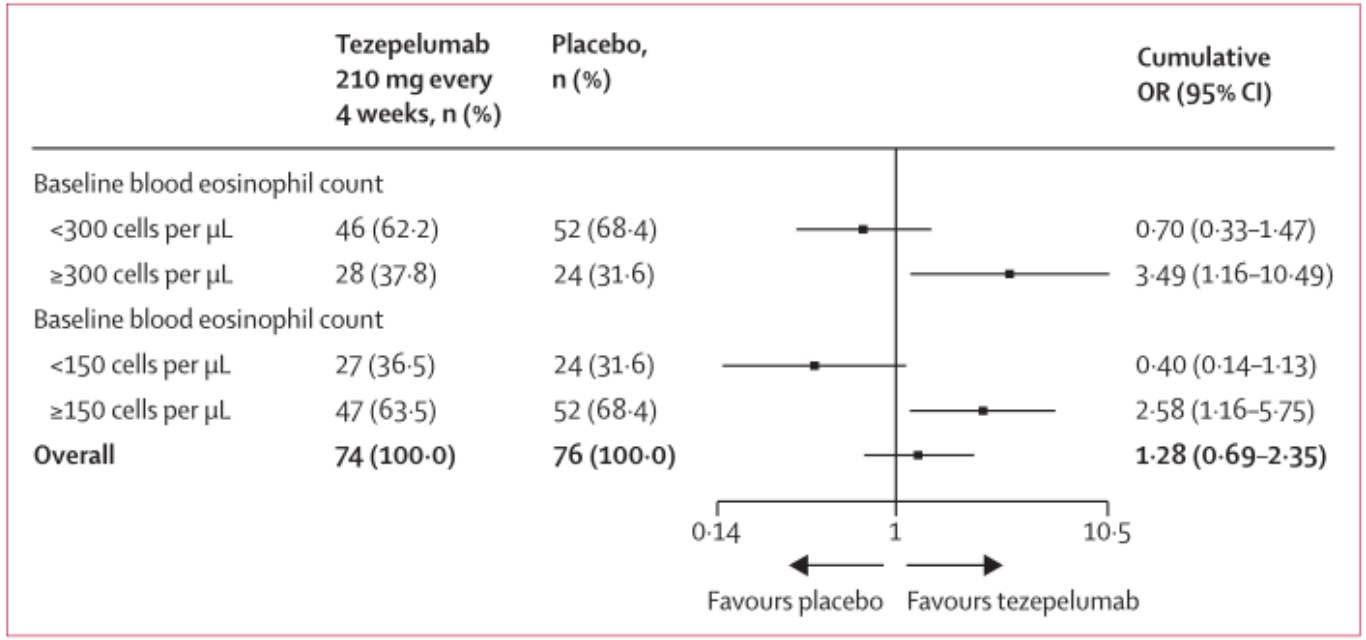


***Figure 3*: Categorised percentage reduction from baseline in maintenance daily oral corticosteroid dose at week 48 in the overall population and in participants grouped by baseline blood eosinophil count**
Cumulative ORs were estimated on the basis of a proportional odds model with the ordered percentage reduction category number (1–5) at week 48 as the response variable. Treatment, region, baseline oral corticosteroid dose, eosinophil subgroup, and treatment-by-eosinophil subgroup interaction were included in the model as covariates. OR=odds ratio.

Wechsler et al., The Lancet Respiratory medicine 2022;10:650-660.

Bronchial Thermoplasty

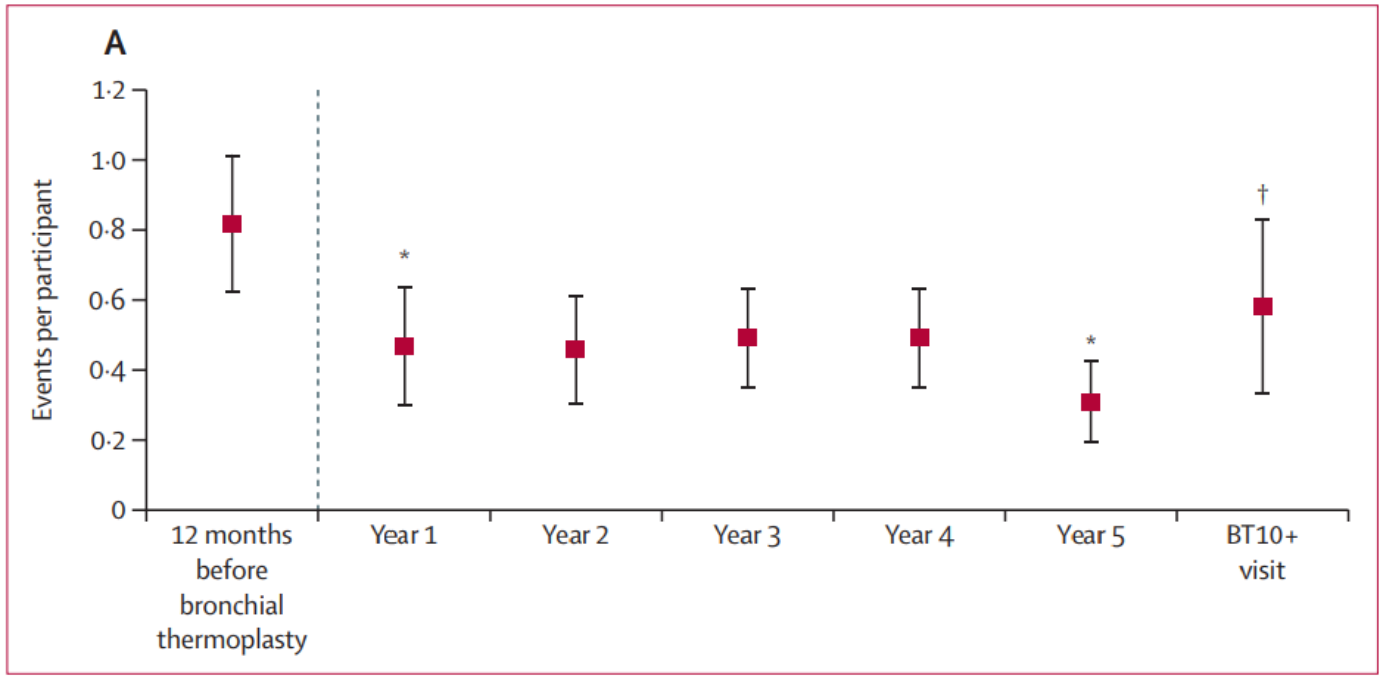
Safety and effectiveness of bronchial thermoplasty after 10 years in patients with persistent asthma (BT10+): a follow-up of three randomised controlled trials

*Rekha Chaudhuri, Adalberto Rubin, Kaharu Sumino, Jose Roberto Lapa e Silva, Robert Niven, Salman Siddiqui, Karin Klooster, Charlene McEvoy, Pallav L Shah, Michael Simoff, Sumita Khatri, Richard Barbers, G Mark Grubb, Edmund A McMullen, Jennifer L Olson, Michel Laviolette, on behalf of the BT10+ Study Group**

Study population: 1
92 (45%) of the 429 enrolled
in the AIR, RISA, and AIR2 trials

Primary outcome:
1) Effectiveness endpoint
: Severe AE
(Use of systemic CS or increase of systemic CS)

2) Safety endpoint:
: Post-treatment respiratory image changes
(Bronchiectasis or bronchial stenosis)



Chaudhuri et al., Lancet Respir Med 2021;9:457-466.

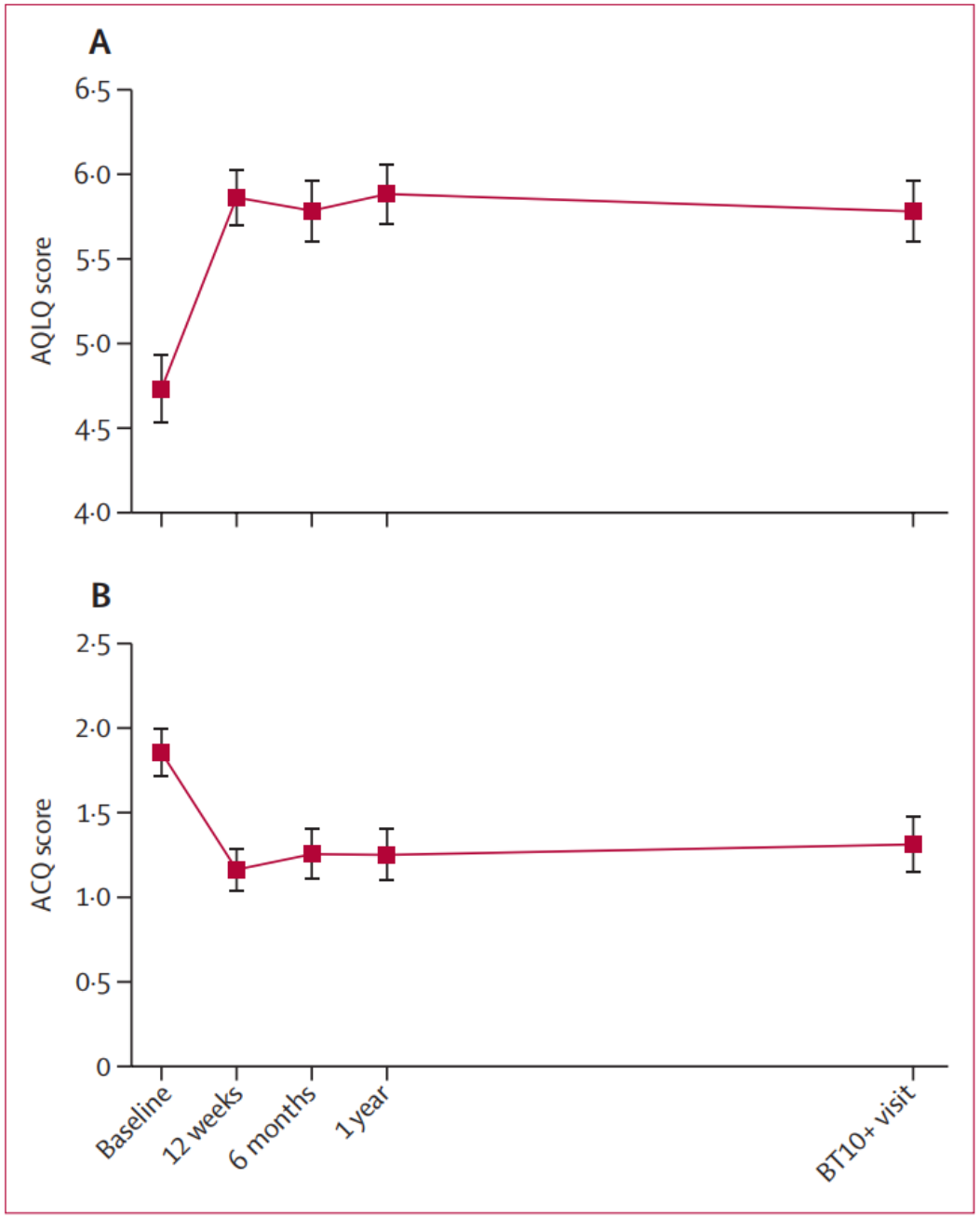


***Figure 3*: AQLQ (A) and ACQ (B) scores over time in participants treated with bronchial thermoplasty**

	Sham (n=24)	Bronchial thermoplasty (n=99)
Bronchiectasis observed at baseline	3/21 (14%; 3·0–36·3)	7/96 (7%; 3·0–14·4)
Bronchiectasis observed at BT10+ visit	2/21 (10%; 1·2–30·4)	13/97 (13%; 7·3–21·8)
Bronchiectasis observed at BT10+ visit and not baseline	0/18 (0; 0–18·5)	6/89 (7%; 2·5–14·1)

Data are n/N (%; 95% CI). Sham participants receiving bronchial thermoplasty after participation in the AIR2 study were excluded. Baseline high-resolution CT information for one AIR2 bronchial thermoplasty participant was missing but this participant had a high-resolution CT at the BT10+ study visit.

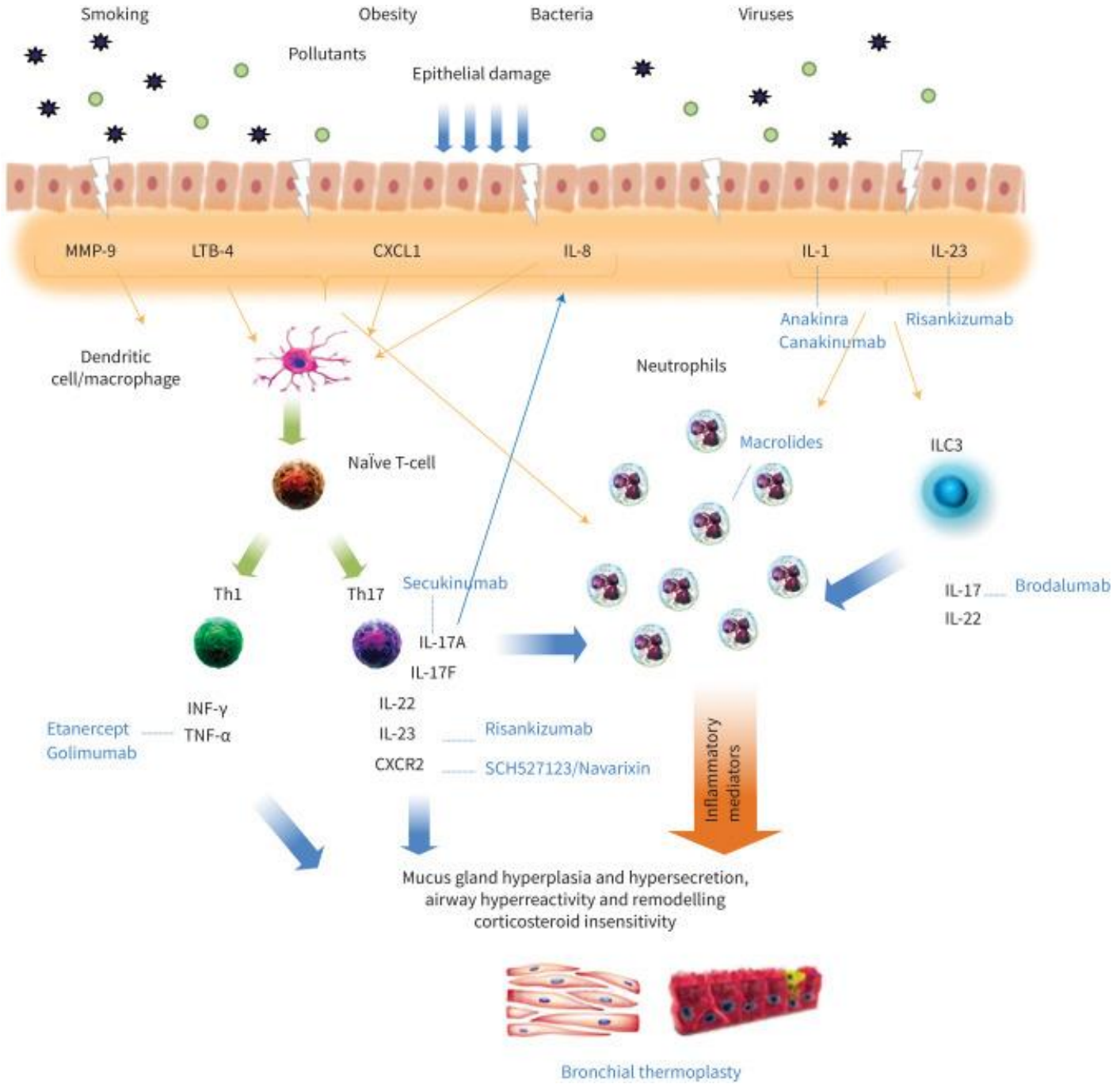
***Table 2*: Results of high-resolution pulmonary CT at the BT10+ study visit (AIR2 participants only)**

Chaudhuri et al., Lancet Respir Med 2021;9:457-466.

Contents

- Disease spectrum
- Assessment
- Current treatment recommendation
- Potential therapeutics
- Summary

Type 2-low asthma pathways and potential therapeutic targets



Kyriakopoulos et al., ERJ open research 2021;7: 00309-2020.

TABLE 2 Overview of the major biologic approaches currently in development for type 2 low asthma management

	Studied biomarker	Biologic	Drug type	Sponsor	Main effects	[Ref.]
Add-on therapy in severe uncontrolled neutrophilic asthma	IL-8	SCH527123/ navarixin	CXCR2 antagonist	AstraZeneca	Reduction in sputum neutrophils and in blood neutrophils No improvement in clinical outcomes and exacerbation rates	[81–83]
Add-on therapy in uncontrolled moderate-to-severe asthma	IL-17	Brodalumab	Human anti-IL-17 receptor A monoclonal antibody	Leo Pharma	Did not improve ACQ score, lung function or asthma symptoms	[84]
Add-on therapy in severe uncontrolled neutrophilic asthma	PDE4	PRL-554 CHF6001 (inhaled)	Dual phosphodiesterase PDE3 and PDE4 inhibitors	Verona Pharma, Chiesi Farmaceutici	Bronchodilatatory and anti-inflammatory effect	[85, 86]
Severe and mild asthma **Severe, refractory, or steroid-resistant asthma**	TNF-α	Etanercept, golimumab	Human monoclonal antibody against TNF-α	Pfizer, Janssen Biologics	Treatment was associated with substantial adverse reactions such as infections and malignancies	[87, 88]

Kyriakopoulos et al., ERJ open research 2021;7: 00309-2020.

TABLE 2 Overview of the major biologic approaches currently in development for type 2 low asthma management

	Studied biomarker	Biologic	Drug type	Sponsor	Main effects	[Ref.]
Add-on therapy in severe uncontrolled neutrophilic asthma	IL-1	Anakinra	Human IL-1 receptor antagonist	Swedish Orphan Biovitrum	Reduced neutrophilic airway inflammation and sputum levels of IL-1β, IL-6 and IL-8	[89]
Severe neutrophilic asthma	p38 MAPK tyrosine kinase	Losmapimod, AZD7624, masitinib, imatinib	Protein kinase inhibitors, MAPK inhibitors, tyrosine kinase inhibitors	GlaxoSmithKline, AstraZeneca, AB Science, Novartis	Reduced exacerbations Reduced inflammatory biomarkers from blood (IL-6, neutrophil percentage and CRP) and sputum (IL-6 and IL-8)	[90–92]
Severe uncontrolled asthma **Severe neutrophilic asthma**	PI3-kinase	Nemiralisib, IPI-145, RV-1729 (duvelisib)	PI3-kinase inhibitors	GlaxoSmithKline	Improved asthma control No discernible difference in trough FEV_1 and ACT score Attenuation of airway inflammation, promotion of bronchodilation and reversal of β_2-adrenoreceptor tachyphylaxis	[93–96]

Kyriakopoulos et al., ERJ open research 2021;7: 00309-2020.

Box 3-9. Non-pharmacological interventions - summary

Intervention	Advice/recommendation (continued on next page)	Evidence
Cessation of smoking and ETS exposure	• At every visit, strongly encourage people with asthma who smoke to quit. Provide access to counseling and smoking cessation programs (if available).	A
	• Advise parents/carers of children with asthma not to smoke and not to allow smoking in rooms or cars that their children use.	A
	• Strongly encourage people with asthma to avoid environmental smoke exposure.	B
	• Assess smokers/ex-smokers for COPD or overlapping features of asthma and COPD (asthma–COPD overlap, ACO, Chapter 5, p.141), as additional treatment strategies may be required.	D
Physical activity	• Encourage people with asthma to engage in regular physical activity for its general health benefits.	A
	• Provide advice about prevention of exercise-induced bronchoconstriction with regular ICS.	A
	• Provide advice about prevention of breakthrough exercise-induced bronchoconstriction with ○ warm-up before exercise ○ SABA before exercise ○ low dose ICS-formoterol before exercise.	 A A B
	• Regular physical activity improves cardiopulmonary fitness, and can have a small benefit for asthma control and lung function, including with swimming in young people with asthma.	B
	• There is little evidence to recommend one form of physical activity over another.	D
Avoidance of occupational exposures	• Ask all patients with adult-onset asthma about their work history and other exposures.	D
	• In management of occupational asthma, identify and eliminate occupational sensitizers as soon as possible, and remove sensitized patients from any further exposure to these agents.	A
	• Patients with suspected or confirmed occupational asthma should be referred for expert assessment and advice, if available.	A
Avoidance of medications that may make asthma worse	• Always ask about asthma before prescribing NSAIDs, and advise patients to stop using them if asthma worsens.	D
	• Always ask people with asthma about concomitant medications.	D
	• Aspirin and NSAIDs (non-steroidal anti-inflammatory drugs) are not generally contraindicated unless there is a history of previous reactions to these agents (see p.102).	A
	• Decide about prescription of oral or ophthalmic beta-blockers on a case-by-case basis. Initiate treatment under close medical supervision by a specialist.	D
	• If cardioselective beta-blockers are indicated for acute coronary events, asthma is not an absolute contra-indication, but the relative risks/benefits should be considered.	D
Healthy diet	• Encourage patients with asthma to consume a diet high in fruit and vegetables for its general health benefits.	A

Box 3-9 (continued) Non-pharmacological interventions – Summary

Intervention	Advice/recommendation	Evidence
Avoidance of indoor allergens	• Allergen avoidance is not recommended as a general strategy in asthma.	A
	• For sensitized patients, there is limited evidence of clinical benefit for asthma in most circumstances with single-strategy indoor allergen avoidance.	A
	• Remediation of dampness or mold in homes reduces asthma symptoms and medication use in adults.	A
	• For patients sensitized to house dust mite and/or pets, there is limited evidence of clinical benefit for asthma with avoidance strategies (only in children) .	B
	• Allergen avoidance strategies are often complicated and expensive, and there are no validated methods for identifying those who are likely to benefit.	D
Weight reduction	• Include weight reduction in the treatment plan for obese patients with asthma. • For obese adults with asthma a weight reduction program plus twice-weekly aerobic and strength exercises is more effective for symptom control than weight reduction alone.	B B
Breathing exercises	• Breathing exercises may be a useful supplement to asthma pharmacotherapy for symptoms and quality of life, but they do not reduce exacerbation risk or have consistent effects on lung function.	A
Avoidance of indoor air pollution	• Encourage people with asthma to use non-polluting heating and cooking sources, and for sources of pollutants to be vented outdoors where possible.	B
Avoidance of outdoor allergens	• For sensitized patients, when pollen and mold counts are highest, closing windows and doors, remaining indoors, and using air conditioning may reduce exposure to outdoor allergens.	D
Dealing with emotional stress	• Encourage patients to identify goals and strategies to deal with emotional stress if it makes their asthma worse.	D
	• There is insufficient evidence to support one stress-reduction strategy over another, but relaxation strategies and breathing exercises may be helpful.	B
	• Arrange a mental health assessment for patients with symptoms of anxiety or depression.	D
Avoidance of outdoor air pollutants/weather conditions	• During unfavorable environmental conditions (very cold weather or high air pollution) it may be helpful to stay indoors in a climate-controlled environment, and to avoid strenuous outdoor physical activity; and to avoid polluted environments during viral infections, if feasible.	D
Avoidance of foods and food chemicals	• Food avoidance should not be recommended unless an allergy or food chemical sensitivity has been clearly demonstrated, usually by carefully supervised oral challenges.	D
	• For confirmed food allergy, food allergen avoidance may reduce asthma exacerbations.	D
	• If food chemical sensitivity is confirmed, complete avoidance is not usually necessary, and sensitivity often decreases when asthma control improves.	D

NSAID: non-steroidal anti-inflammatory drugs; SABA: short-acting beta$_2$-agonist.
Interventions with highest level evidence are shown first.

Weight loss

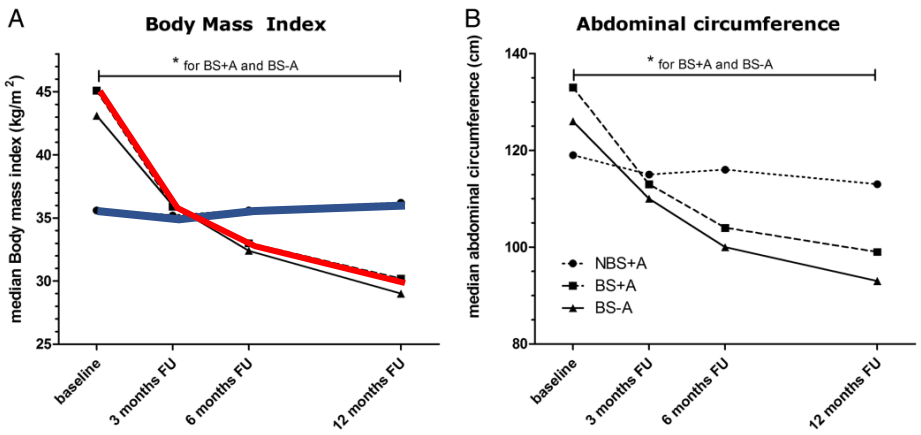
Weight reduction for obese patients

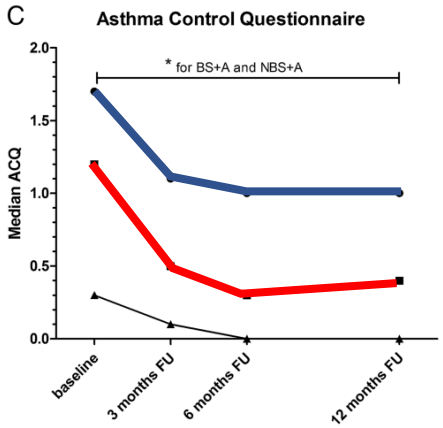
Asthma can be more difficult to control in obese patients,[388-390] the risk of exacerbations is greater,[100,101] and response to ICS may be reduced.[391] There is limited evidence about the effect of weight loss on asthma control. Studies have ranged from dietary restriction to multifactorial interventions with exercise training and cognitive behavioral therapy, but populations have generally been small, and interventions and results have been heterogeneous.[392] In some studies, weight loss has improved asthma control, lung function and health status, and reduced medication needs in obese patients with asthma.[393,394] The most striking results have been observed after bariatric surgery,[395,396] but even 5–10% weight loss with diet, with or without exercise, can lead to improved asthma control and quality of life.[397]

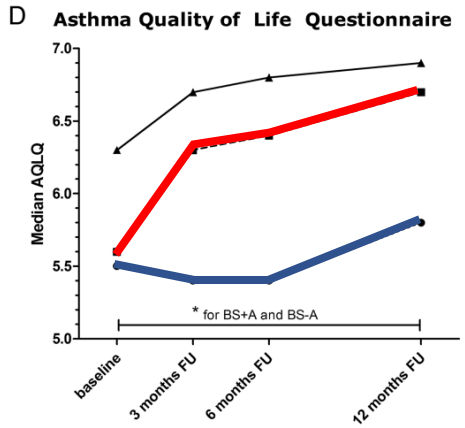
Advice

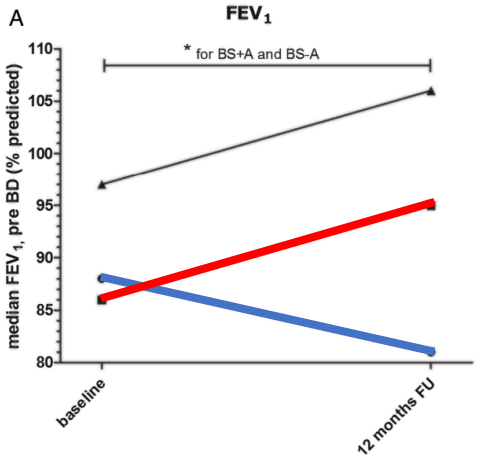
- Include weight reduction in the treatment plan for obese patients with asthma (Evidence B). Increased exercise alone appears to be insufficient (Evidence B).

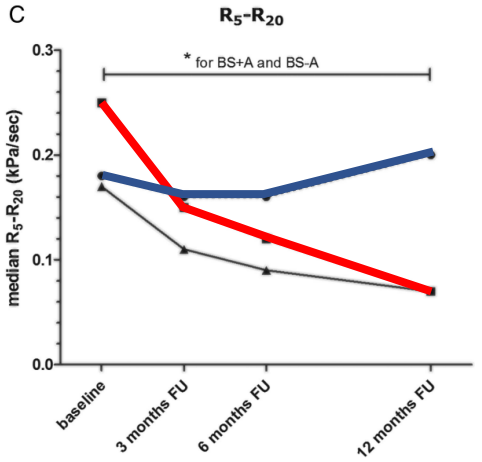
Effect of bariatric surgery on asthma











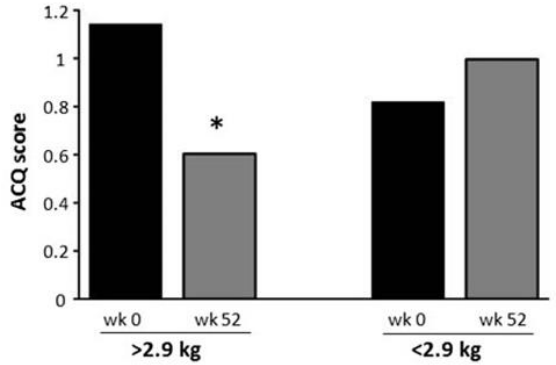
van Huisstede et al., Thorax 2015;70:659-667

GLP-1R agonist → weight loss → asthma

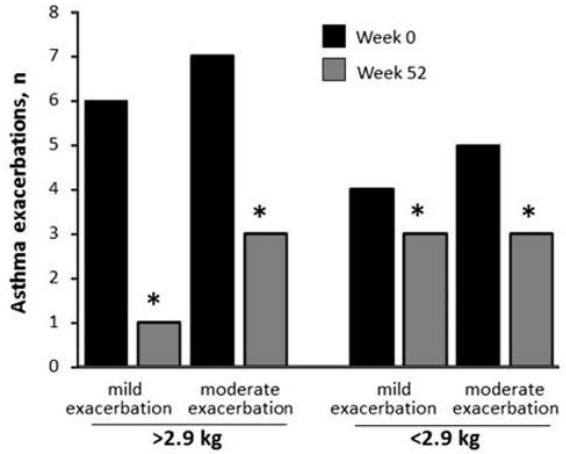
Table 1. Baseline demographic and other clinical variables among T2DM participants with concomitant asthma completing 52 weeks of follow up

Parameter	Value
N	9
Gender (male/female)	4/5
Age (yr)	61.9 ± 2.3
Smoking status (never/former/current)	9/0/0
Family history of asthma (yes/no)	3/6
Asthma onset (youth onset/late onset	5/4
Weight (kg)	88 ± 5
BMI[a] (kg/m^2)	32.3 ± 2.5
Asthma acute exacerbation rate (annual)	2.6 ± 0.62
Asthma controllers, *n* on any ICS[b]	8
GINA[c] treatment step (step 1/2/3/4/5)	1/1/3/4/0
ACQ[d] score	1.03 ± 0.1
AQLQ[e] overall score	5.59 ± 0.2
AQLQ symptom score	5.80 ± 0.2
AQLQ activity score	5.57 ± 0.3
AQLQ emotional score	5.56 ± 0.4
AQLQ environmental stimuli score	5.06 ± 0.3
Severe asthma (*n*)[f]	4
FVC[g] (post-bronchodilator) L	3.5 ± 0.3
FEV1[h] (post-bronchodilator)L	2.34 ± 0.2
% FEV1/FVC (post-bronchodilator)	67.8 ± 3
HbA1c[i] (<48 mmol/mol)	57.0 ± 1.7

A Mean ACQ score versus median weight loss with liraglutide therapy



B Mild and moderate asthma exacerbations versus median weight loss with liraglutide therapy



Khan et al., QJM 2017;110:853–854.

GLP-1R agonist → metabolism change → asthma

Study design:
Population:
- **4,373 patients with asthma and DM**
- **New initiation of GLP-1R, SGLT-2i, DDP-4i, sulfonylurea, or basal insulin**

- **Mean (SD) BMI - 39.5 (8.6)**

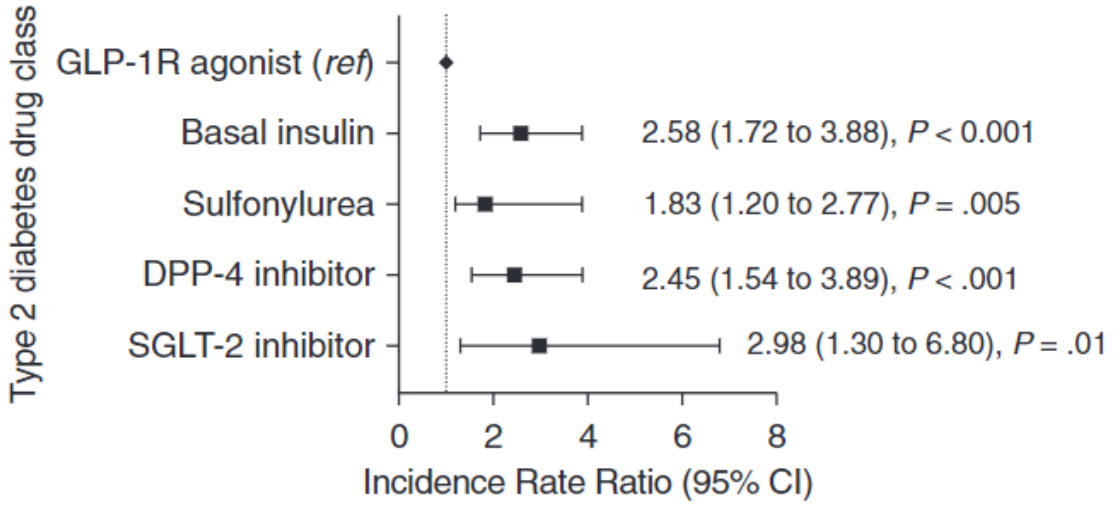


Table 3. Sensitivity Analysis for Asthma Exacerbations Outcome, Inclusive of Baseline and Change in HbA_{1c} and BMI

Treatment Groups*	Asthma Exacerbations		
	Incidence Rate Ratio	95% CI	*P* Value
GLP-1R ($n = 271$)	ref	—	—
SGLT-2 inhibitor ($n = 74$)	2.95	1.19–7.31	0.02
DPP-4 inhibitor ($n = 224$)	2.11	1.14–3.91	0.02
Sulfonylurea ($n = 1,007$)	1.97	1.14–3.41	0.02
Basal insulin ($n = 1,015$)	2.44	1.42–4.19	0.001

Foer et al., Am J Respir Crit Care Med 2021;203:831-840.

Summary

- T2 low severe asthma가 의심되는 경우
  - 정말 **Asthma**일지 확인

- T2 low asthma의 치료
  - LAMA
  - Azithromycin
  - Anti-IL4R if taking maintenance OCS
  - Anti-TSLP (insufficient evidence in pts on maintenance OCS)
  - Consider bronchial thermoplasty
  - Lifestyle modification (stop smoking, physical activity, weight loss)
  - Roflumilast

- Potential future therapeutics

doi: 10.1111/cea.12670

Clinical & Experimental Allergy, **46**, 754–763

ORIGINAL ARTICLE **Experimental Models of Allergic Disease**

Effect of roflumilast on airway remodelling in a murine model of chronic asthma

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Cite this as: S. W. .Kim, J. H. Kim., C. K. Park, T. J. Kim, S. Y. Lee, Y. K. Kim,

Summary

Background Airway remodelling is associated with irreversible, or partially reversible, airflow obstruction and ultimately unresponsiveness to asthma therapies such as corticosteroids. Roflumilast is a selective phosphodiesterase-4 inhibitor that has an anti-inflammatory effect in chronic obstructive pulmonary disease (COPD).

Objective The objective of this study was to study the effect of roflumilast on airway inflammation and remodelling in a murine model of chronic asthma.

Methods BALB/c mice sensitized to ovalbumin (OVA) were chronically exposed to intranasal OVA administration twice a week for additional 3 months. Roflumilast was administered orally during the intranasal OVA challenge. A lung fibroblast cell line was used in the proliferation assay.

Results Compared with control mice, mice chronically exposed to OVA developed eosinophilic airway inflammation, airway hyper-responsiveness (AHR), and exhibited features of airway remodelling. Administration of roflumilast significantly inhibited airway inflammation and AHR. Roflumilast also significantly decreased goblet cell hyperplasia and pulmonary fibrosis, which are parameters of airway remodelling. The levels of interleukin (IL)-4, IL-5, and IL-13 in the bronchoalveolar lavage (BAL) fluids were significantly lower in the roflumilast group. *In vitro*, roflumilast significantly inhibited stem cell factor (SCF)-induced cell proliferation of fibroblasts. The SCF concentration and mRNA expression in a murine model also significantly decreased with roflumilast treatment.

Conclusions These results suggest that the administration of roflumilast regulates airway inflammation, AHR, and airway remodelling in a model of chronic asthma. The beneficial effects from roflumilast may be related to the SCF/c-kit pathway.

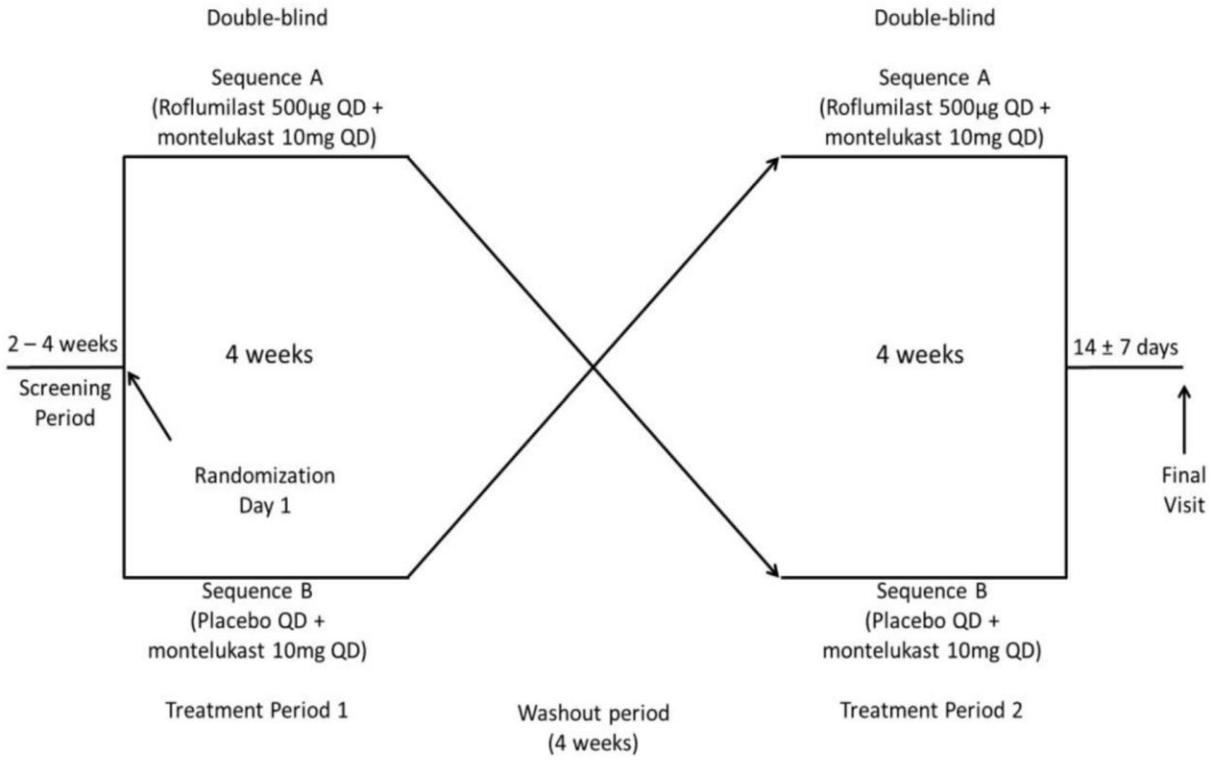
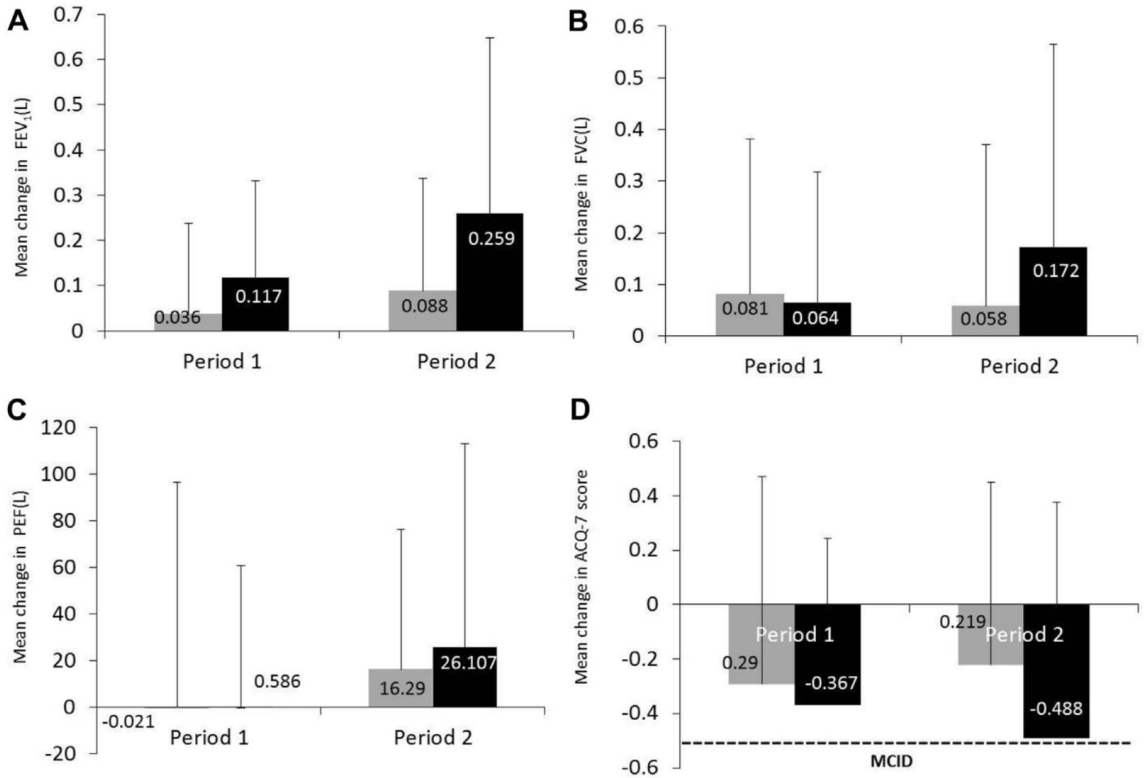


FIG 1. Schematic of the crossover study design: 2- to 4-week screening period, followed by two 4-week double-blind treatment periods separated by a washout period of 4 weeks. A final visit took place 7 to 21 days after the second treatment period. *QD*, Once daily.



Bateman et al., JACI 2016;138:142-149.e8.