

[전문가로부터 배우는 알레르기질환 약물 사용법]

천식 흡입기를 사용할 수 없을 때 사용할 수 있는 약물은? 경구 약물로도 치료가 가능합니다.

김경원

연세의대 소아과학교실, 세브란스어린이병원

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 - 류코트리엔 조절제, 테오필린 등 크산틴계 약물, 그 외 기타 약물

천식 치료 약제

- 질병조절제: 천식 조절을 위해서 규칙적으로 사용하는 약제
 - 기도 염증, 천식 증상, 급성 악화와 폐기능 저하의 위험을 감소시킨다.
- 증상완화제: 천식 증상이 발생했을 때 증상 경감을 위하여 필요시 사용할 수 있는 약제
 - 운동 유발 천식을 예방하기 위해 운동 전에 사용할 수도 있다.
 - 증상완화제가 필요하지 않을 정도로 천식 조절상태를 잘 유지하는 것이 천식 치료의 목표이다.

한국 천식진료지침

천식 단계별 치료 (한국 천식진료지침)

6세 이상 소아, 청소년, 성인		5세 이하 소아	
<p>● 소년 청소년 단계별 ● 대처 가능 청증조제 ● 충상면제</p> <p>● 대처 가능 청증조제 ● 충상면제</p> <p>● 대처 가능 청증조제 ● 충상면제</p>	<p>● 단계1 ● 단계2 ● 단계3 ● 단계4</p> <p>● 단계1 ● 단계2 ● 단계3 ● 단계4</p> <p>● 단계1 ● 단계2 ● 단계3 ● 단계4</p>		
<p>● 대처 가능 청증조제 ● 충상면제</p> <p>● 대처 가능 청증조제 ● 충상면제</p> <p>● 대처 가능 청증조제 ● 충상면제</p>	<p>● 단계1 ● 단계2 ● 단계3 ● 단계4</p> <p>● 단계1 ● 단계2 ● 단계3 ● 단계4</p> <p>● 단계1 ● 단계2 ● 단계3 ● 단계4</p>		

ICS: 흡입 스퀘어或多孔吸入器, LABA: 바이신 흡입 배양 장치, “여기에서 디포보이트 사용 가능”

천식 단계별 치료 (GINA guidelines)

6세 이상 소아, 청소년, 성인		5세 이하 소아	
<p>● 대처 가능 청증조제 ● 충상면제</p> <p>● 대처 가능 청증조제 ● 충상면제</p> <p>● 대처 가능 청증조제 ● 충상면제</p>	<p>● 단계1 ● 단계2 ● 단계3 ● 단계4</p> <p>● 단계1 ● 단계2 ● 단계3 ● 단계4</p> <p>● 단계1 ● 단계2 ● 단계3 ● 단계4</p>	<p>● 대처 가능 청증조제 ● 충상면제</p> <p>● 대처 가능 청증조제 ● 충상면제</p> <p>● 대처 가능 청증조제 ● 충상면제</p>	<p>● 단계1 ● 단계2 ● 단계3 ● 단계4</p> <p>● 단계1 ● 단계2 ● 단계3 ● 단계4</p> <p>● 단계1 ● 단계2 ● 단계3 ● 단계4</p>

● 대처 가능 청증조제
● 충상면제

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● 대처 가능 청증조제
● 충상면제

성인 천식 단계별 치료 (Japanese guidelines)

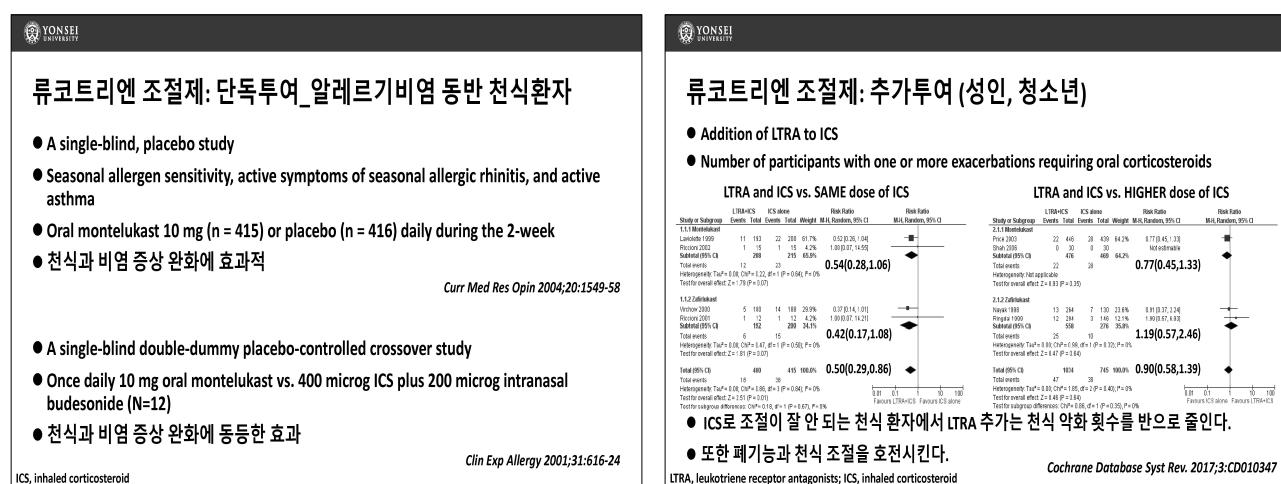
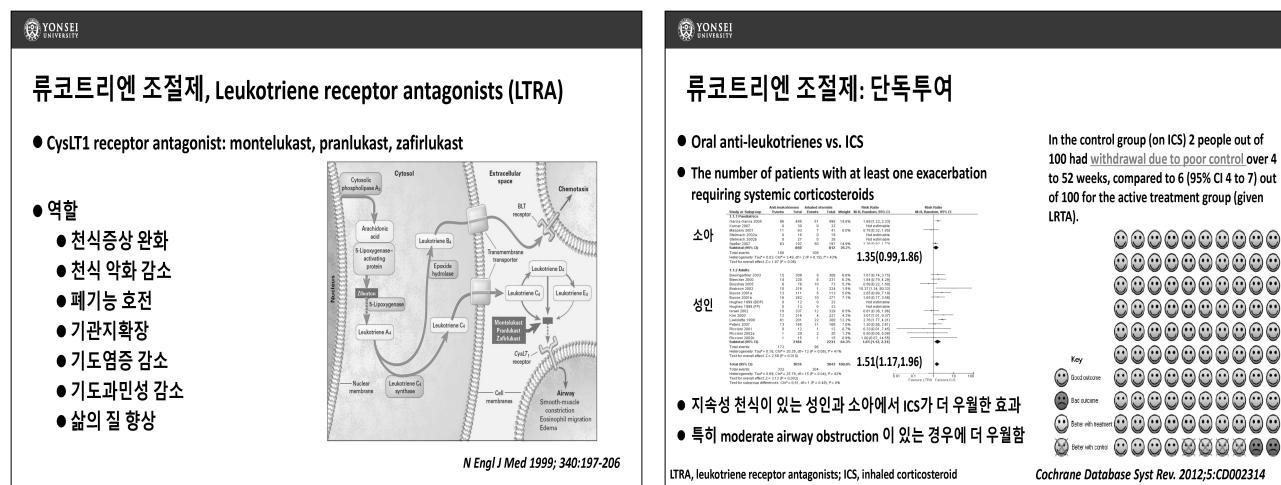
	Treatment step 1	Treatment step 2	Treatment step 3	Treatment step 4
Long-term management agents	Basic treatment Inhaled corticosteroid (low dose)	Inhaled corticosteroid (low to medium doses)	Inhaled corticosteroid (medium to high doses)	Inhaled corticosteroid (high dose)
	If the above agent cannot be used, use one of the following agents: • LABA • LTRA • Theophylline sustained-release preparation (unnecessary for rare symptoms)	If the above agent is ineffective, concomitantly use one or more of the agents below: • LABA (a compounding agent can be used) • LTRA • Theophylline sustained-release preparation • LAMA	Concomitantly use one or more of the agents below: • LABA (a compounding agent can be used) • LTRA • Theophylline sustained-release preparation • LAMA • Anti-IgE antibody • Oral corticosteroid	Concomitantly use multiple agents of those below: • LABA (a compounding agent can be used) • LTRA • Theophylline sustained-release preparation • LAMA • Anti-IgE antibody • Oral corticosteroid
Additional treatment	Anti-allergics other than LTRA	Anti-allergics other than LTRA	Anti-allergics other than LTRA	Anti-allergics other than LTRA
Exacerbation treatment [†]	Inhaled SABA	Inhaled SABA	Inhaled SABA	Inhaled SABA

LTRA, leukotriene receptor antagonists; LABA, long-acting β_2 agonist; SABA, short-acting β_2 agonist; LAMA, long-acting muscarinic antagonist. Anti-allergics refer to mediator anti-releasers, histamine H1 antagonists, thromboxane A2 inhibitors, and Th2 cytokine inhibitors.

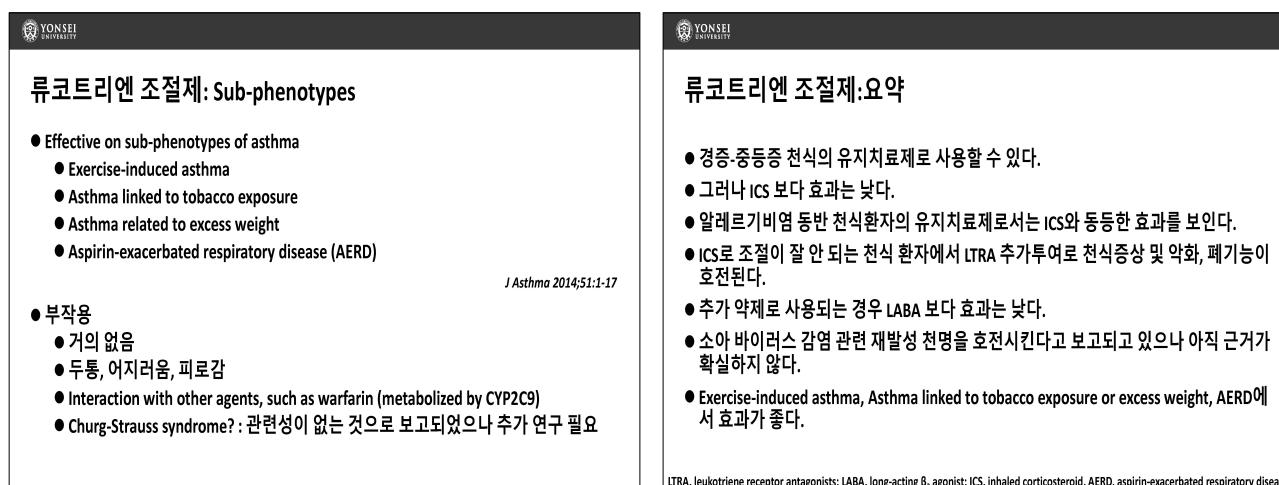
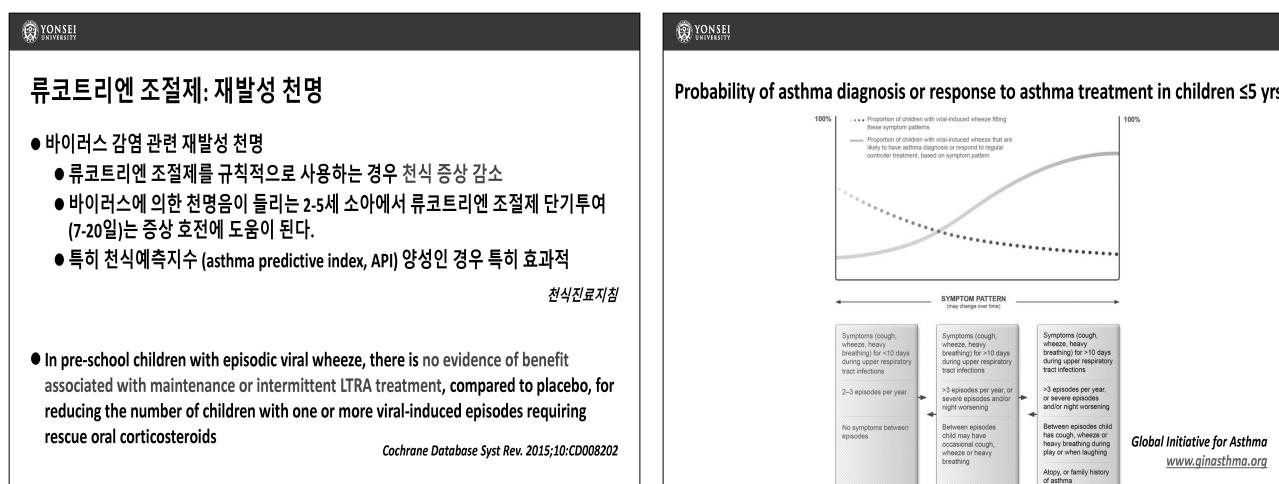
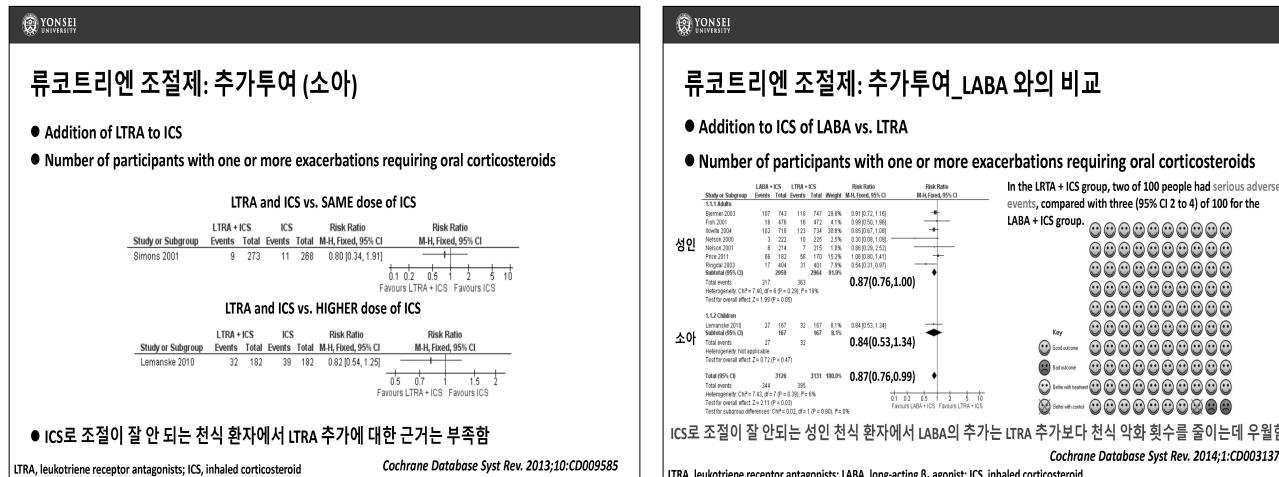
소아 천식 단계별 치료 (Japanese guidelines)

2세 미만	Step 1	Step 2	Step 3	Step 4
Basal therapy	SABA as needed	LTRA and/or DSCG	ICS (medium dose)	ICS (high dose) possibly add LTRA
Additional therapy	LTRA and/or DSCG	ICS (low dose)	LTRA LABA (p.o. or adhesive skin patch)	LABA (p.o. or adhesive skin patch) Theophylline (maintain at 5–10 mg/mL in blood conc.) can be considered
2-5세	Step 1	Step 2	Step 3	Step 4
Basal therapy	SABA as needed	LTRA and/or DSCG and/or ICS (low dose)	ICS (medium dose)	ICS (high dose) + possibly add one or more of the following drugs: LTRA Theophylline LABA or SFC
Additional therapy	LTRA and/or DSCG	LTRA	LABA or SFC Theophylline (consider)	Consider the following: Increase ICS/SFC to higher doses or p.o. steroid
6-15세	Step 1	Step 2	Step 3	Step 4
Basal therapy	SABA as needed	ICS (low dose) and/or LTRA and/or DSCG	ICS (medium dose)	ICS (high dose) – possibly add one or more of the following drugs: LTRA Theophylline LABA or SFC
Additional therapy	LTRA and/or DSCG	Theophylline (consider)	LTRA Theophylline LABA or SFC	Consider the following: Increase ICS/SFC to higher doses or p.o. steroid

LTRA, leukotriene receptor antagonist;
ICS, inhaled corticosteroid;
DSCG, disodium cromoglycate;
LABA, long-acting β_2 agonist;
SFC, salmeterol/ fluticasone combined drug



김경원 천식 흡입기를 사용할 수 없을 때 사용할 수 있는 약물은? 경구 약물로도 치료가 가능합니다.



테오필린 등 크산틴계 약물, Sustained-release theophylline

- Long-acting bronchodilator with anti-inflammatory effects
- 역할
 - 기관지확장제
 - 저용량: 항염증 작용
- 부작용
 - 구역, 구토 등의 위장관 증상, 무른변, 부정맥, 경련발작, 사망
 - 발열, 임신, 항결핵제는 테오필린 혈증농도 감소
 - 간질환, 심부전, 씨메티딘, 쿠비론계 일부, 마크롤라이드 일부는 부작용 위험 증가
 - 저용량의 테오필린은 부작용이 적다

테오필린 등 크산틴계 약물: 단독투여

- Budesonide 800 mg bd, budesonide 200 mg bd, or theophylline (Theo-Durs[®]) 300mg bd
- Double-blind, double-dummy, and randomized, in a parallel group design for 9 months

Percentage change in FEV₁

Budesonide 800 mg bd
Budesonide 200 mg bd
Theophylline 300 mg bd

The differences in asthma symptom score

Budesonide 800 mg bd
Budesonide 200 mg bd
Theophylline 300 mg bd

The efficacy of ICS was superior to oral theophylline

Respir Med 2002;96:432-8

ICS, inhaled corticosteroid

테오필린 등 크산틴계 약물: 단독투여

- A randomized, double-masked, placebo controlled trial in 489 participants with poorly controlled asthma randomly assigned to placebo, theophylline (300 mg/d), or montelukast (10 mg/d).

CHANGE IN ASTHMA SYMPTOM SCORES BY TREATMENT ASSIGNMENT			
	No. Participants	Treatment Assignment, mean (95% CI)	
AQoQ score	408	0.7 (0.4, 0.9) 0.8 (0.6, 1.0) 0.8 (0.6, 1.0)	
ASU score	462	0.10 (0.0, 0.2) 0.10 (0.0, 0.2) 0.10 (0.0, 0.2)	
ACQ	462	-0.7 (-0.8, -0.6) -0.7 (-0.8, -0.6) -0.7 (-0.8, -0.5)	

Definition of abbreviations: AQoQ = Asthma Control Questionnaire; AQoQ = Asthma Quality-of-Life Questionnaire; ASU = Asthma Symptom Utility Index; CI = confidence interval.

For the AQoQ and ASU scores, a positive value indicates improvement. For the ACQ, a negative value indicates improvement. p values for treatment effects, mean questionnaire scores, and 95% confidence intervals were estimated from linear regression models with robust variance estimation and adjusted for sex, where appropriate (i.e., for repeated measures of ASU and ACQ). Note: the means were significantly different from placebo at week 0.

Low dose theophylline was beneficial in those patients who had not been prescribed ICS.

ICS, inhaled corticosteroid

Am J Respir Crit Care Med 2007;175:235-42

테오필린 등 크산틴계 약물: 추가투여

- Patients with moderate asthma and persistent symptoms (N=62)
- In a double-blind, placebo-controlled trial for 3 months
- 400 mg of inhaled budesonide (low-dose) with 250 or 375 mg of theophylline (depending on body weight) or 800 mg of inhaled budesonide (high-dose)

Change in Predicted FEV₁ (%)

...● Theophylline —▲— Montelukast ●—● Placebo

Median Daily Symptom Scores

Week 0 Week 3 Week 6 Week 9 Week 12

P = 0.002 P = 0.03 P = 0.20 P = 0.05 P = 0.08

Median No. of Puffs of β_2 -Agonists Daily

Daytime Nighttime

High-dose budesonide Low-dose budesonide plus theophylline Placebo

P = 0.001 P = 0.009 P = 0.012 P = 0.05

N Engl J Med 1997;337:1412-8

테오필린 등 크산틴계 약물: 추가투여

- Multicentre, randomised, double-blind, double-dummy, parallel-group study
- Salmeterol/fluticasone propionate combination (SFC) 50 mg/250 mg+1 placebo tablet vs. fluticasone propionate 250 mg+1 sustained release theophylline 200 mg (SR-T+FP), twice daily for 8 weeks
- LABA was associated with greater improvements in lung function than theophylline.
- A LTRA (N=33) and a sustained released theophylline (Theo, N=34), with a moderate dose of ICS for 4 weeks
- The effects of both medications were comparable.
- For asthmatic patients even on a moderate dose of ICS, the addition of either LTRA or sustained released theophylline does not improve asthma-related symptoms but significantly and equally increases PEF.

Res Med 2008;102:1055-64

Allergy Asthma Proc 2005;26:287-91

LTRA, leukotriene receptor antagonists; LABA, long-acting β_2 agonist; ICS, inhaled corticosteroid; PEF, peak inspiratory flow

테오필린 등 크산틴계 약물: 요약

- 경증·중등증 천식의 유지 치료제로 사용할 수 있다. 그러나 ICS 보다 효과는 낮다.
- ICS 보다 효과는 약하므로 ICS를 사용하기 어려운 경우 사용하는 것이 좋다.
- ICS로 잘 조절되지 않는 천식에서 테오필린을 추가 약제로 사용할 수 있다.
- 추가 약제로 사용되는 경우 LABA 보다 효과는 낮다.
- 추가 약제로 사용되는 경우 LTRA와 효과는 비슷하다.
- 경증·중등증 소아 천식의 유지 치료제로 사용할 수 있다.(일본)
- 경증·중등증 소아 천식의 유지 치료제로 권장하지 않는다.(한국 천식진료지침 및 GINA guidelines)
- Step 4 소아 천식의 추가 약제로서 사용한다.(일본)
- Step 4 소아 천식의 추가 약제로서 사용하지 않는다.(한국 천식진료지침 및 GINA guidelines)

Cochrane Database Syst Rev 2006;1:CD002885

LTRA, leukotriene receptor antagonist; LABA, long-acting β_2 agonist; ICS, inhaled corticosteroid

Cromones (nedocromil sodium and sodium cromoglycate, SCG)

- 경증-중등증 소아 천식의 유지 치료제로 사용할 수 있다.

Cochrane Database Syst Rev. 2006;3:CD004108

- 소아와 성인의 지속성 천식에서 유지치료제로 사용할 수 있다.
- 소아와 성인 천식에서 폐기능 호전과 천식 조절에 ICS가 SCG보다 우월하다.

Cochrane Database Syst Rev. 2006;2:CD003558

Other oral medications from Japanese guidelines (adult asthma)

1. Corticosteroids	4. Leukotriene receptor antagonists
1) Inhaled corticosteroids	1) Pranlukast hydrate
ii) Fluticasone propionate	2) Montelukast sodium
iii) Budesonide	5. Theophylline sustained-release preparation
iv) Ciclesonide	6. Long-acting muscarinic receptor antagonist
v) Mometasone furoate	Tiotropium bromide hydrate
2) Oral corticosteroids	7. Anti-IgE
2) Long-acting β_2 -agonists	Anti-body Omalizumab
1) Inhalants	8. Anti-allergics other than leukotriene receptor antagonists
Salmeterol xinafoate	1) Mediator antireleasers Sodium cromoglicate, trinalast, amlexanox, reprimast, ibadilast, tazarotest, and pemolinol potassium
2) Patch	2) Histamine H ₁ receptor antagonists Ketotifen fumarate, azelastine hydrochloride, oxatolazine, and epinephrine hydrochloride
Tulobuterol	3) Thromboxane A ₂ synthesis inhibitor Ozogatril hydrochloride
3) Oral medicines	ii) Thromboxane A ₂ receptor antagonist Serevent
Proterterol hydrochloride	4) Thrombin inhibitor Sifelazide tosylate
Clenbuterol hydrochloride	9. Other agents and therapies (Chinese medicines, specific immunotherapy, and non-specific immunotherapy)
Formoterol fumarate	<i>Allergol Int 2017;66:163-89</i>
Tulobuterol hydrochloride	
Mabuterol hydrochloride	
3. Combination inhaler of corticosteroid/long-acting β_2 -agonist	
1) Combination inhaler of fluticasone propionate/salmeterol xinafoate	
2) Combination inhaler of budesonide/formoterol fumarate	
3) Combination inhaler of fluticasone propionate/formoterol fumarate	
4) Combination inhaler of fluticasone propionate/vilanterol tifentate	

Choosing between controller options for population-level decisions

- Choosing between treatment options at a population level
- The 'preferred treatment' at each step is based on:
 - Efficacy
 - Effectiveness
 - Safety
- Availability and cost at the population level

Global Initiative for Asthma www.ginasthma.org

Choosing between controller options for individual patients

- Use shared decision-making with the patient/parent/carer to discuss the following:

1. Preferred treatment for symptom control and for risk reduction
2. Patient characteristics (phenotype)
 - Does the patient have any known predictors of risk or response?
(e.g. smoker, history of exacerbations, blood eosinophilia)
3. Patient preference
 - What are the patient's goals and concerns for their asthma?
4. Practical issues
 - Inhaler technique - can the patient use the device correctly after training?
 - Adherence: how often is the patient likely to take the medication?
 - Cost: can the patient afford the medication?

Global Initiative for Asthma www.ginasthma.org