«Η νέα εποχή στην θεραπεία του σοβαρού άσθματος – παλαιά φάρμακα με νέες θεωρήσεις»

LAMA – LTRAs – antibiotics: ποια η θέση τους στην εξατομικευμένη προσέγγιση;

Ελένη Καρέτση
Πνευμονολόγος
Επιμελήτρια Α΄
Πνευμονολογική Κλινική Πανεπιστημίου Θεσσαλίας

Severe asthma-definition

- Severe asthma is asthma that requires Step 4 or 5 treatment, to prevent it from becoming 'uncontrolled', or asthma that remains 'uncontrolled' despite this treatment.

- ERS/ATS: severe asthma should be reserved for patients with **refractory asthma** and those in whom response to treatment of comorbidities is incomplete.

Chung KF, et al. International ERS/ATS Guidelines on Definition, Evaluation and Treatment of Severe Asthma. Eur Respir J 2014

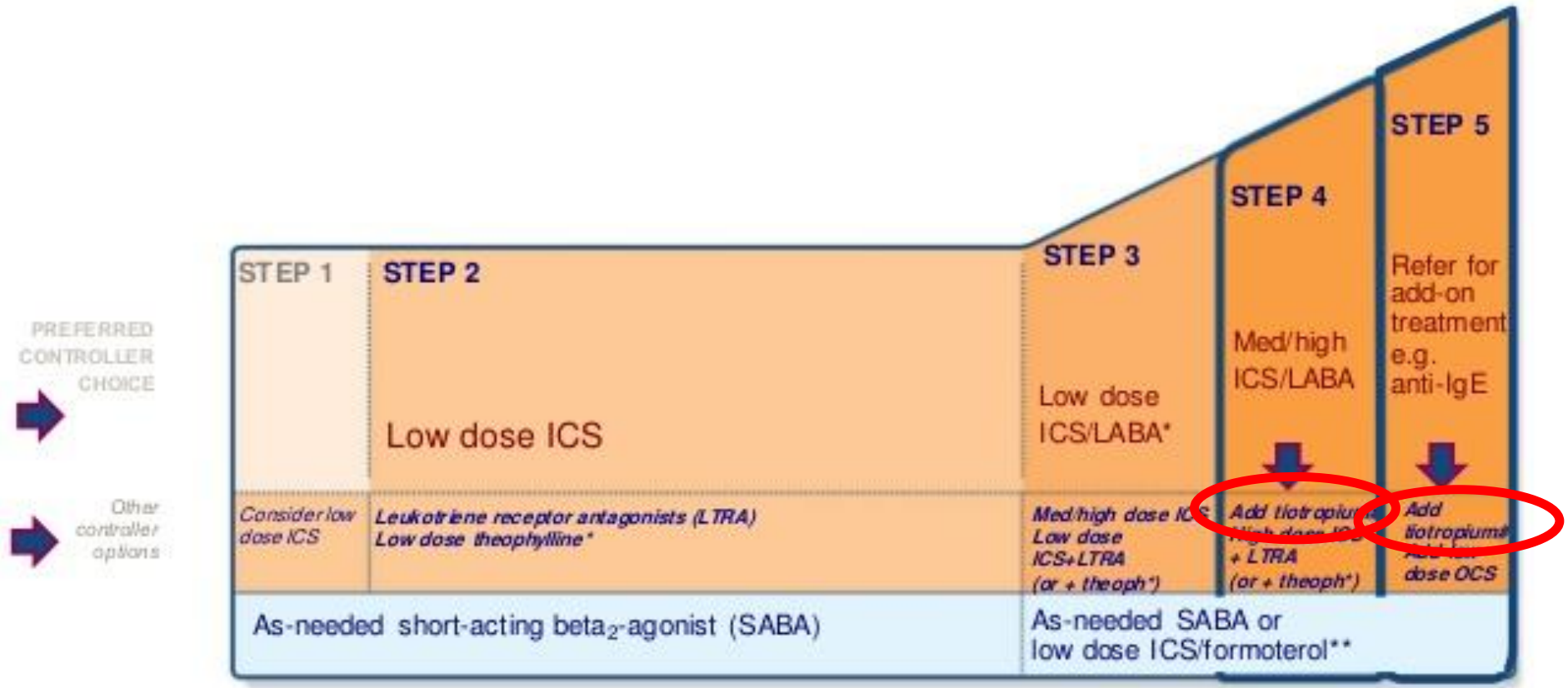
Η νέα εποχή στην θεραπεία του σοβαρού άσθματος – ***παλαιά φάρμακα με νέες θεωρήσεις***

- **LAMA**
- **LTRAs**
- **Antibiotics**

Η νέα εποχή στην θεραπεία του σοβαρού άσθματος – ***παλαιά φάρμακα με νέες θεωρήσεις***

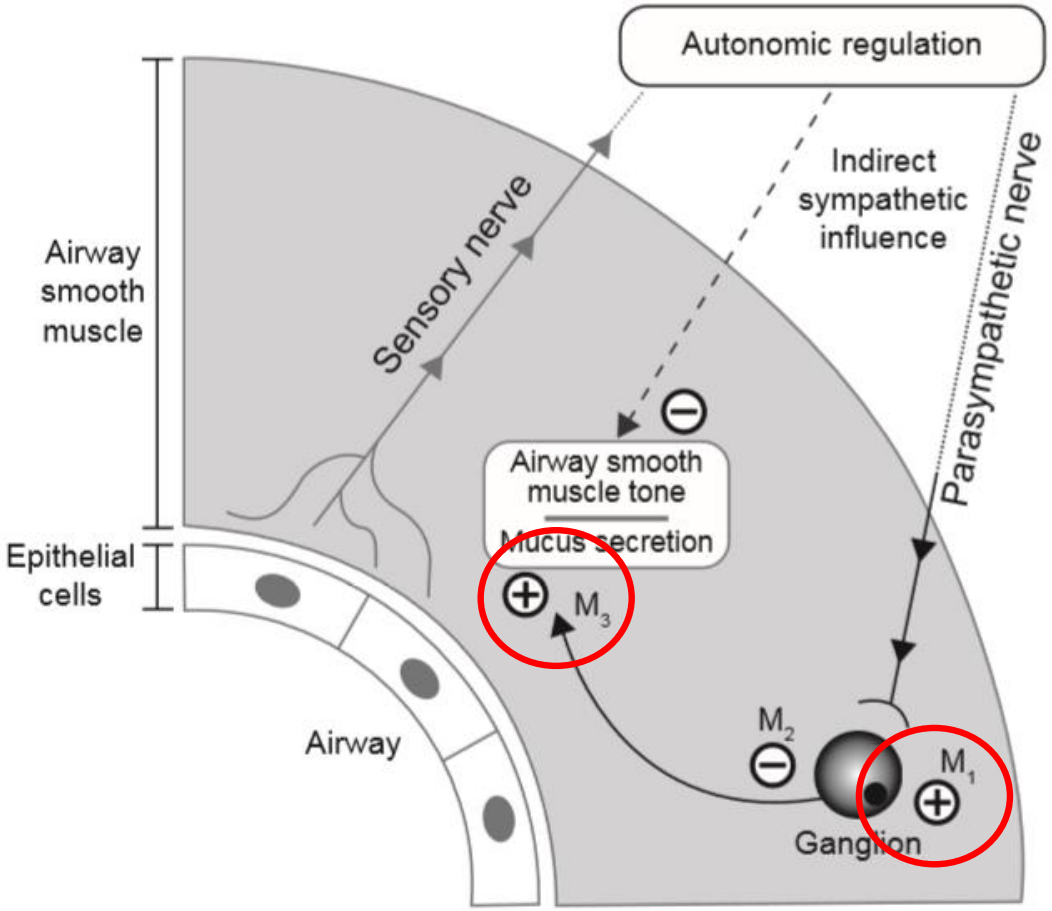
- **LAMA**
- **LTRAs**
- **Antibiotics**

GINA 2015 – changes to Steps 4 and 5



*For children 6-11 years, theophylline is not recommended, and preferred Step 3 is medium dose ICS
**For patients prescribed BDP/formoterol or BUD/formoterol maintenance and reliever therapy
Tiotropium by soft-mist inhaler is indicated as add-on treatment for patients with a history of exacerbations; it is not indicated in children <18 years.

GINA 2015



airway tone

airway smooth muscle contraction

mucus secretion

vasodilation

Table 1. Expression of muscarinic receptors on airway cells and their major effects[a]

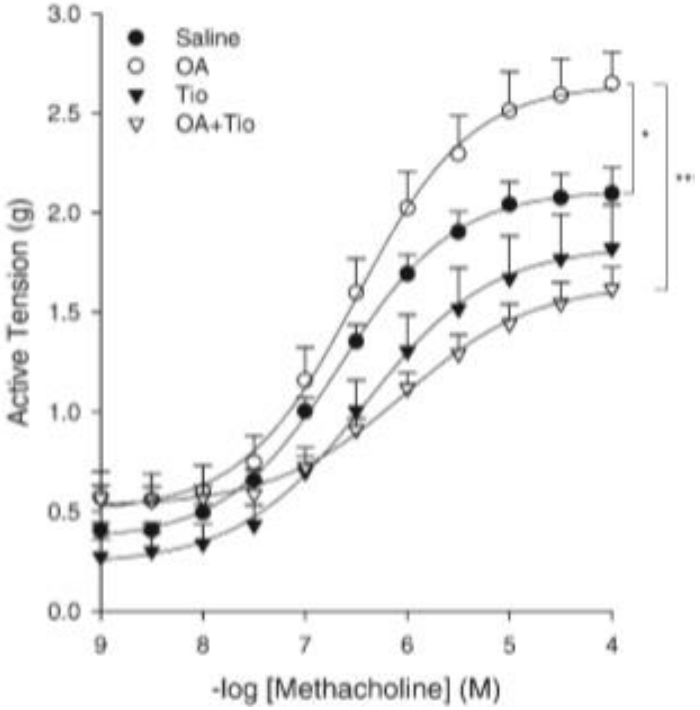
Cell	Muscarinic receptor expression	Functional effect
Neuron	M_1, M_2	Neurotransmission
Airway smooth muscle cell	M_2, M_3	Bronchoconstriction via M_3
Epithelial cell	M_1, M_2, M_3	Mucus secretion via M_3
Submucosal gland	M_1, M_3	Mucus secretion via M_3
Fibroblast	M_1, M_2, M_3	Proliferation, extracellular matrix production
Mast cell	M_1, M_3	Inhibition of histamine release
Macrophage	M_1, M_2, M_3	Cytokine production
Lymphocyte	M_1, M_2, M_3	Cytokine production
Neutrophil	M_1, M_2, M_3	Cytokine production
Eosinophil	M_1, M_2, M_3	Unknown

Protective Effects of Tiotropium Bromide in the Progression of Airway Smooth Muscle Remodeling

Reinoud Gosens, I. Sophie T. Bos, Johan Zaagsma, and Herman Meurs

Department of Molecular Pharmacology, University Centre for Pharmacy, University of Groningen, Groningen, The Netherlands

Am J Respir Crit Care Med. 2005



- 12 weekly repeated allergen challenges (in a guinea pig model of ongoing allergic asthma) induced an increase in airway smooth muscle mass in the noncartilaginous airways (not in cell size but in airway smooth muscle cell number).

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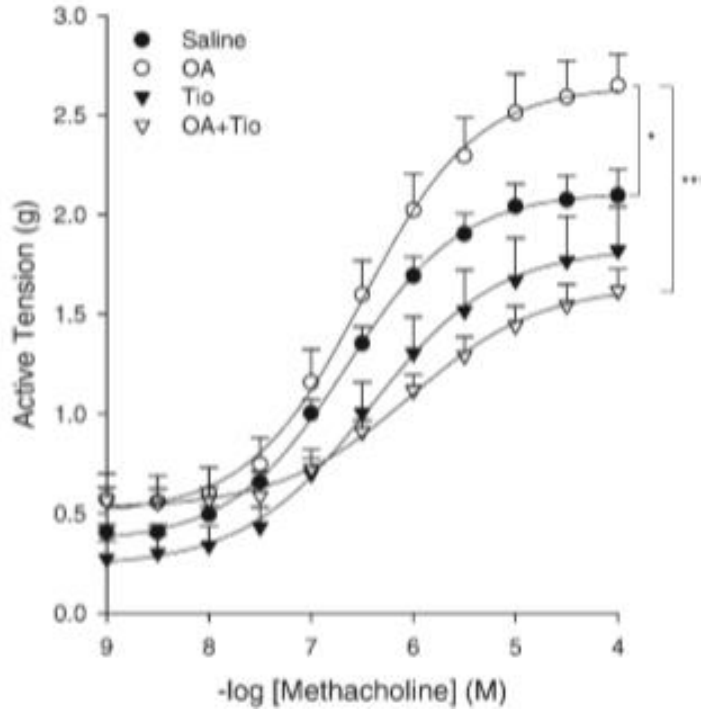

- **Treatment with inhaled tiotropium considerably inhibited the increase in airway smooth muscle mass, myosin expression, and contractility.**

Kistemaker et al. Respiratory Research (2016) 17:13
DOI 10.1186/s12931-016-0327-6

Respiratory Research

RESEARCH Open Access

Combination therapy of tiotropium and ciclesonide attenuates airway inflammation and remodeling in a guinea pig model of chronic asthma

Loes E. M. Kistemaker[1,2*], I. Sophie T. Bos[1,2], Mark H. Menzen[1,2], Harm Maarsingh[3], Herman Meurs[1,2] and Reinoud Gosens[1,2]

Combined treatment with tiotropium and ciclesonide did not inhibit acute allergen-induced inflammation, but **did inhibit chronic allergen-induced airway inflammation and remodeling** (airway eosinophilia and airway smooth muscle thickening).

Published in final edited form as:
N Engl J Med. 2010 October 28; 363(18): 1715–1726. doi:10.1056/NEJMoa1008770.

Tiotropium Bromide Step-Up Therapy for Adults with Uncontrolled Asthma

Stephen P. Peters, M.D., Ph.D., Susan J. Kunselman, M.A., Nikolina Icitovic, M.A.S., Wendy

210 patients

symptoms and lung function

Tiotropium improves lung function in patients with severe uncontrolled asthma: A randomized controlled trial

Huib A. M. Kerstjens, MD, PhD,[a] Bernd Disse, MD, PhD,[b] Winfried Schröder-Babo, MD,[c] Theo A. Bantje, MD,[d] Martina Gahlemann, MD,[b] Ralf Sigmund, Dipl-Math oec,[b] Michael Engel, MD,[b] and Jan A. van Noord, MD[e] *Groningen, Breda, and Heerlen, The Netherlands, and Biberach and Gelnhausen, Germany*

J Allergy Clin Immunol 2011;128:308-14

107 patients

dose of tiotropium

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Tiotropium in Asthma Poorly Controlled with Standard Combination Therapy

Huib A.M. Kerstjens, M.D., Michael Engel, M.D., Ronald Dahl, M.D., Pierluigi Paggiaro, M.D., Ekkehard Beck, M.D., Mark Vandewalker, M.D., Ralf Sigmund, Dipl.Math., Wolfgang Seibold, M.D., Petra Moroni-Zentgraf, M.D., and Eric D. Bateman, M.D.

N Engl J Med 2012;367:1198-207.
DOI: 10.1056/NEJMoa1208606

912 patients

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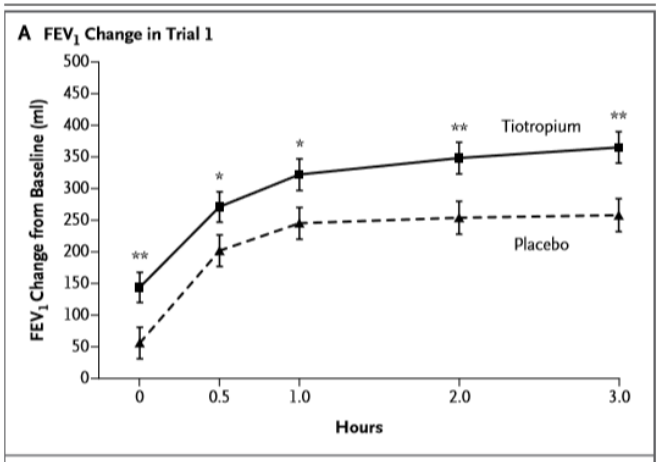
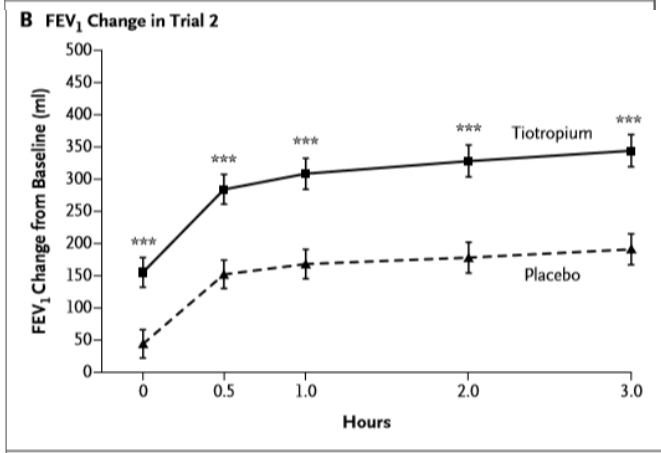
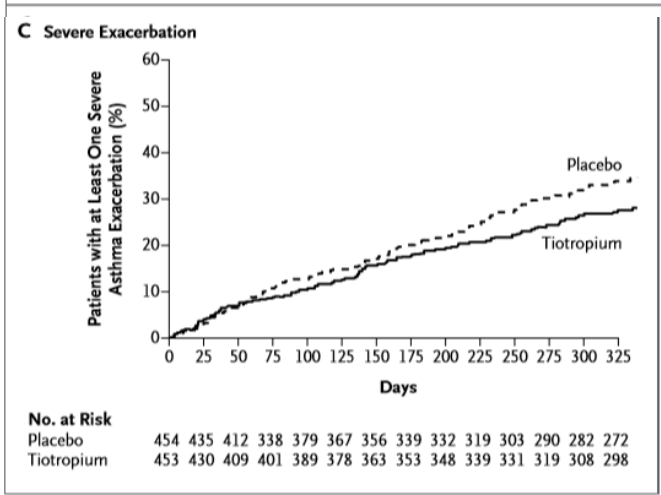
912 patients

Tiotropium Respimat significantly **increased the time to the first severe exacerbation** and **improved lung function**. However, improvements in Asthma Control Questionnaire (ACQ)-7 and Asthma Quality of Life Questionnaire (AQLQ) scores were small and inconsistent, and did not reach a clinically important difference.







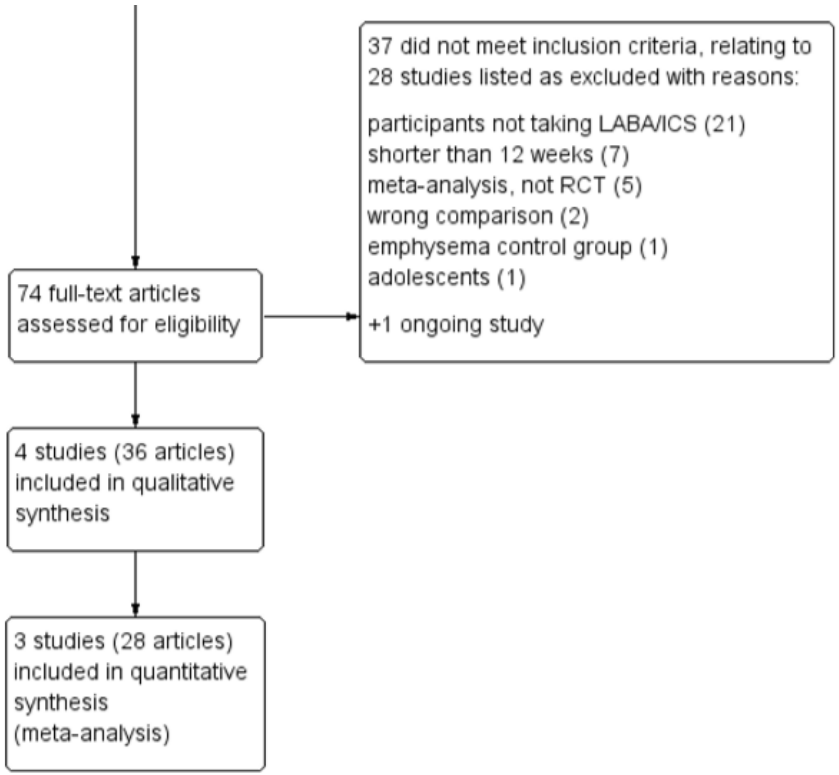
Cochrane Library

Cochrane Database of Systematic Reviews

Long-acting muscarinic antagonists (LAMA) added to combination long-acting beta$_2$-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma (Review)

Kew KM, Dahri K Cochrane Database of Systematic Reviews 2016

1197 patients with asthma, on ICS/LABA
mean FEV1 55%pred
48-52 weeks



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Kew KM, Dahri K Cochrane Database of Systematic Reviews 2016

Primary outcomes

- People randomised to take tiotropium add-on had **fewer exacerbations** requiring oral corticosteroids than those continuing to take LABA/ICS alone.
- **Quality of life**, as measured by the Asthma Quality of Life Questionnaire (AQLQ) was **no better** for those taking tiotropium add-on than for those taking LABA/ICS alone.

Cochrane Library

Cochrane Database of Systematic Reviews

Long-acting muscarinic antagonists (LAMA) added to combination long-acting beta$_2$-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma (Review)

Kew KM, Dahri K Cochrane Database of Systematic Reviews 2016

Secondary outcomes

- Exacerbations requiring hospital admission were too rare to tell whether tiotropium was beneficial over LABA/ICS alone.
- High quality evidence showing **benefits to lung function** (trough FEV1 and FVC) and potentially small benefits **to asthma control.** People taking tiotropium add-on were **less likely** to experience **non-serious adverse events.**

Respiratory Medicine 117 (2016) 198–206

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Tiotropium improves lung function, exacerbation rate, and asthma control, independent of baseline characteristics including age, degree of airway obstruction, and allergic status

Huib A.M. Kerstjens [a, *], Petra Moroni-Zentgraf [b], Donald P. Tashkin [c], Ronald Dahl [d], Pierluigi Paggiaro [e], Mark Vandewalker [f], Hendrik Schmidt [g], Michael Engel [b], Eric D. Bateman [h]

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- 456 tiotropium, 456 placebo (to ICS/LABA in patients with severe symptomatic asthma)

Tiotropium 5mg improved lung function, reduced the risk of asthma exacerbations and asthma worsening, and improved asthma symptom control, compared with placebo, independent of baseline characteristics including gender, age, body mass index, disease duration, age at asthma onset, FEV1 % predicted at screening and reversibility , IgE levels and eosinophils counts

Asthma management GINA 2018

- **STEP 4** (Other options)Tiotropium by mist inhaler may be used as add-on therapy for adult or adolescent patients with a history of exacerbations; it modestly improves lung function (Evidence A) and modestly increases the time to severe exacerbation.

- **STEP 5** Add-on tiotropium in patients aged ≥12 years whose asthma is not well-controlled with ICS/LABA. Add-on tiotropium by mist inhaler modestly improves lung function (Evidence A) and modestly increases the time to severe exacerbation requiring OCS (Evidence B).

Management of severe asthma

- Optimize dose of ICS/LABA
  - Complete resistance to ICS is rare
  - Consider therapeutic trial of higher dose
- Consider low dose maintenance oral corticosteroids
  - Monitor for and manage side-effects, including osteoporosis
- Add-on treatments without phenotyping
  - Tiotropium - reduces exacerbations (history of exacerbations, age ≥12 years)
  - Theophylline, LTRA – limited benefit
- Phenotype-guided treatment
  - Severe allergic asthma: add-on omalizumab (anti-IgE)
  - Severe eosinophilic asthma: add-on mepolizumab or reslizumab (anti-IL5)
  - Sputum-guided treatment to reduce exacerbations and/or steroid dose
  - Aspirin-exacerbated respiratory disease: consider add-on LTRA
- Non-pharmacological interventions
  - Consider bronchial thermoplasty for selected patients
  - Comprehensive adherence-promoting program

UPDATED 2018

Asthma–COPD overlap

- Asthma-COPD overlap (ACO) is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD.

- **fixed airway obstruction**
- **lower FEV1**
- **features of prominent remodelling changes**

Potential role of LAMA in elderly asthma patients

- The severity and mortality of asthma are reported to increase with age
- This population is partially excluded from randomized clinical trials due to age criteria and comorbidities.
- The number of medications for comorbidities, as well as functional status, determined by the higher physical functioning scale, are important parameters in assessing and predicting asthma control.

Ban GY. J Korean Med Sci 2015

- **As tiotropium has been shown to be efficacious and have a favorable safety profile in COPD patients who are generally older, it offers a good option for the treatment of elderly asthma patients, especially for those with comorbid conditions such as cardiovascular diseases.**

Glycopyrrolate/glycopyrronium in asthma

Published clinical asthma studies

- longer bronchodilation and protection against the MCT
- improved post exercise or cold air exposure FEV1
- prolonged improved FEV1 measures
- prolonged improved FEV1 measures in acute asthmatic patients (ED)

NIH U.S. National Library of Medicine

ClinicalTrials.gov

- *Unpublished clinical asthma studies (11 studies, 1 withdrawn)*

  Study of Efficacy and Safety of NVA237 in Patients With Poorly Controlled Asthma

Albertson TE, Expert Opinion on Investigational Drugs 2017

Umeclidinium in asthma

Published clinical asthma studies

- in healthy volunteers and focus on the pharmacokinetics and adverse effects of the drug
- dose–response effect on FEV1 efficacy
- improved FEV1 measures

NIH U.S. National Library of Medicine

ClinicalTrials.gov

(9 studies, 2 severe asthma)

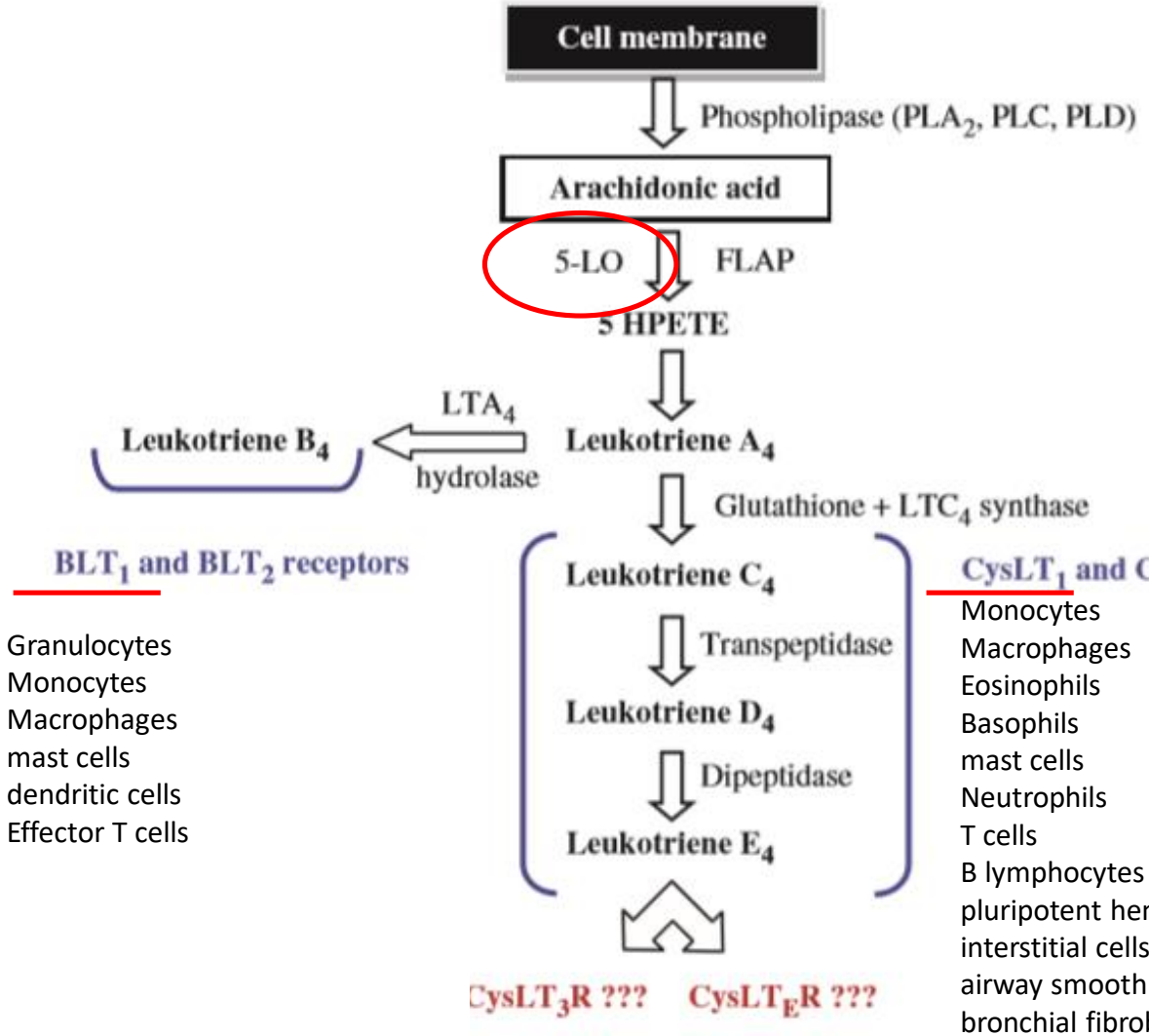
- Effectiveness of FF/UMEC/VI as Compared FP/SAL Plus TIO in Inadequately Controlled Asthma
- Comparing the Efficacy, Safety and Tolerability of FF/UMEC/VI With FF/VI in Subjects With Inadequately Controlled Asthma

Albertson TE, Expert Opinion on Investigational Drugs 2017

Η νέα εποχή στην θεραπεία του σοβαρού άσθματος – ***παλαιά φάρμακα με νέες θεωρήσεις***

- **LAMA**
- **LTRAs**
- **Antibiotics**

Biosynthesis of leukotrienes



BLT_1 and BLT_2 receptors

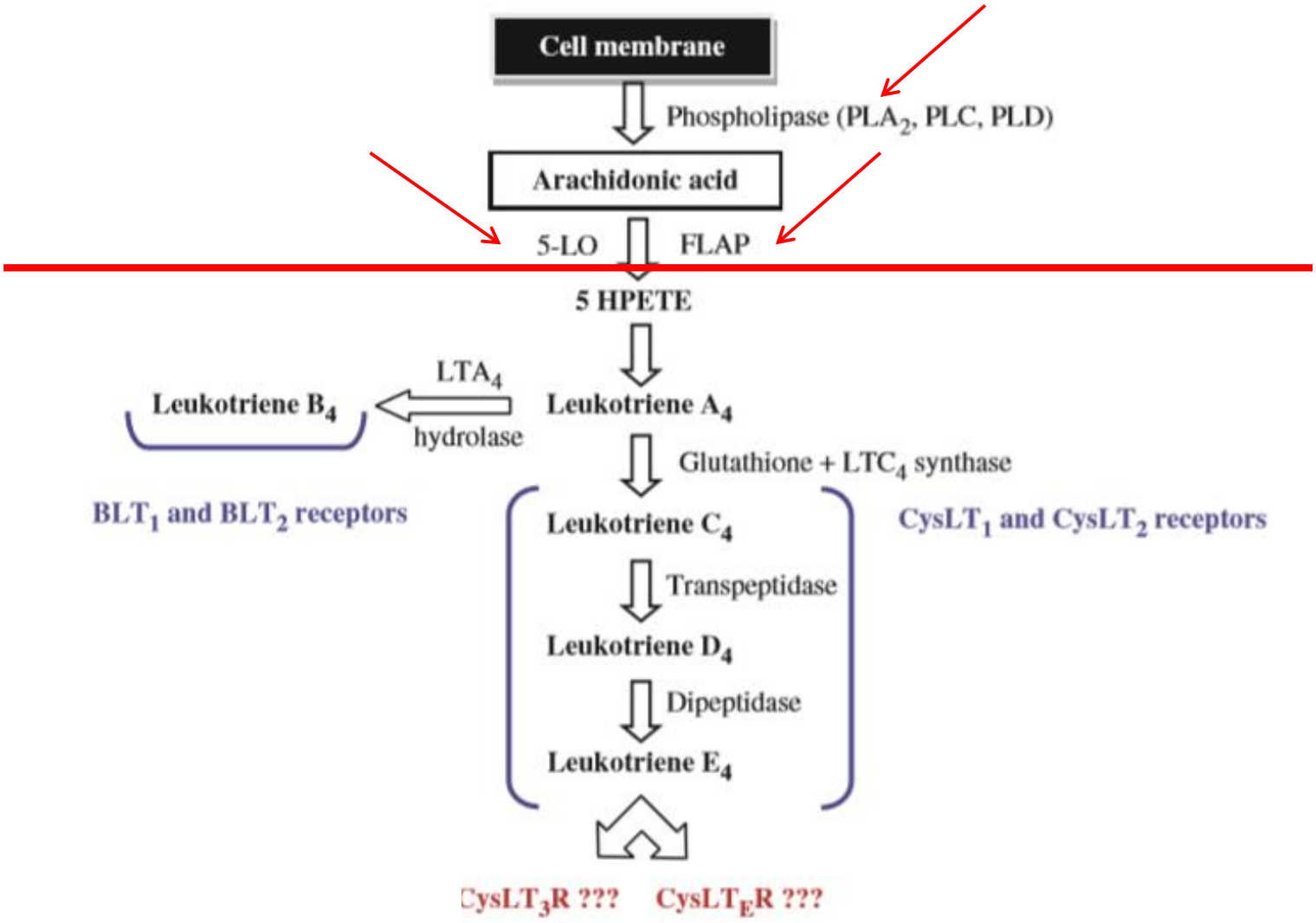
Granulocytes
Monocytes
Macrophages
mast cells
dendritic cells
Effector T cells

$CysLT_1$ and $CysLT_2$ receptors

Monocytes
Macrophages
Eosinophils
Basophils
mast cells
Neutrophils
T cells
B lymphocytes
pluripotent hematopoietic stem cells (CD34þ)
interstitial cells of the nasal mucosa,
airway smooth muscle cells
bronchial fibroblasts
vascular endothelial cells

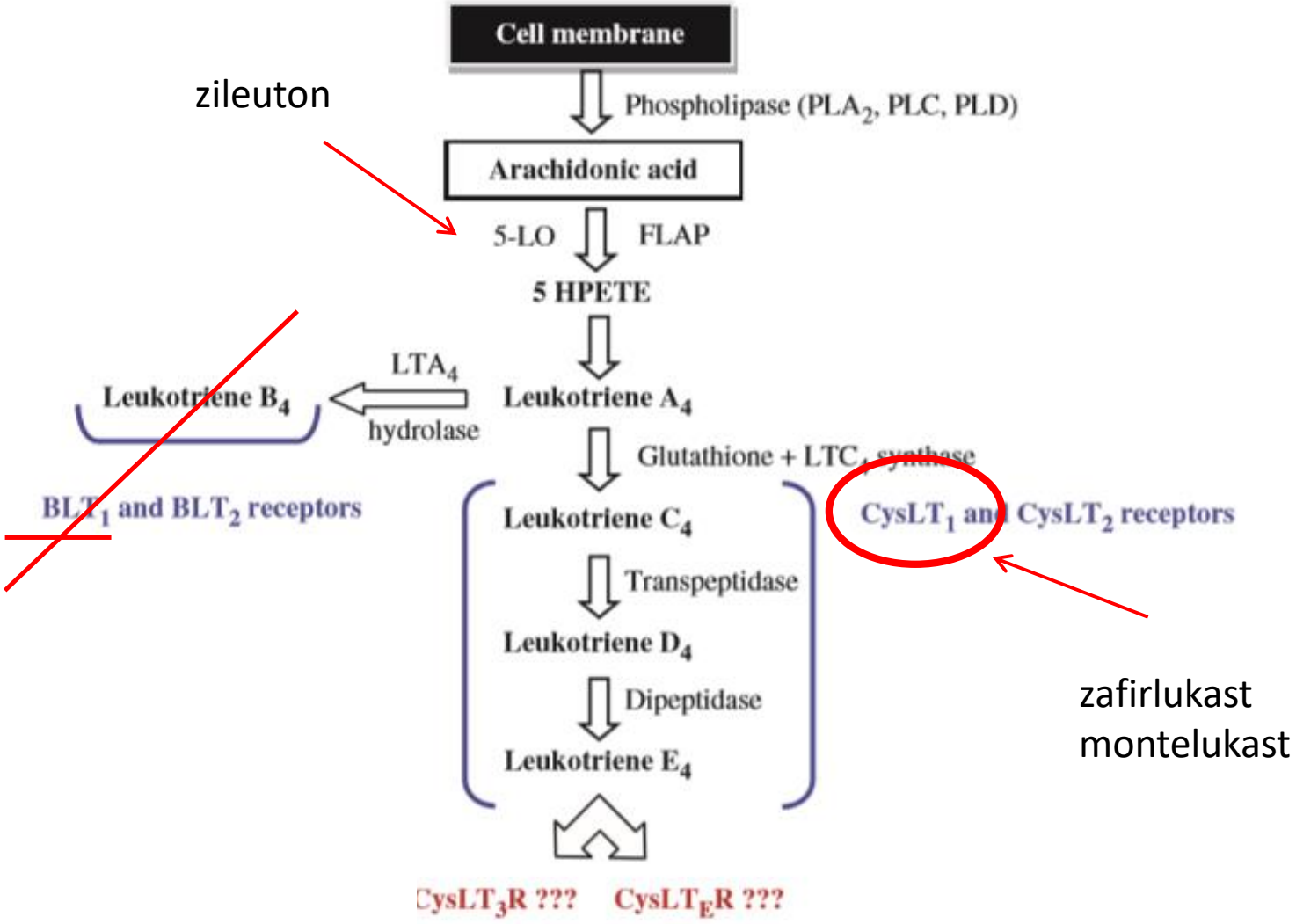
Singh RK, J Asthma 2013

Biosynthesis of leukotrienes



Singh RK, J Asthma 2013

Biosynthesis of leukotrienes



zileuton

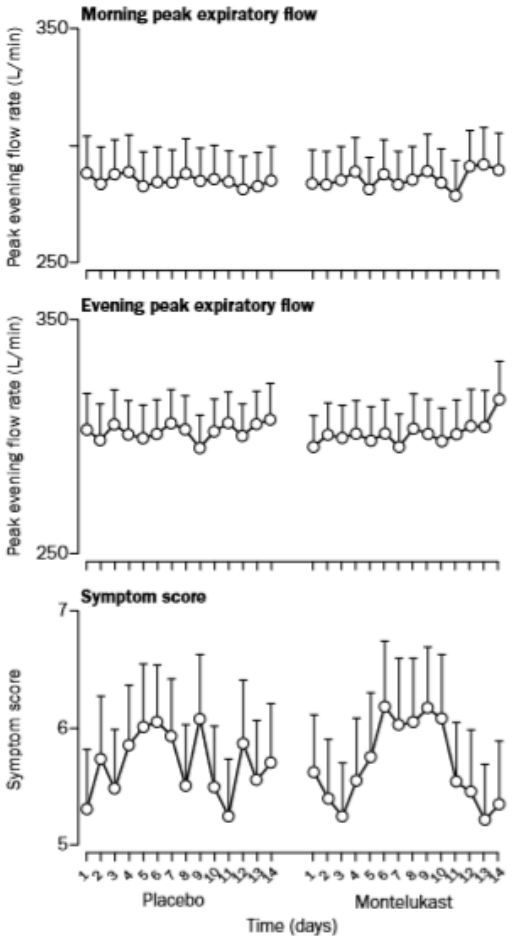
zafirlukast
montelukast

Singh RK, J Asthma 2013

Addition of leukotriene antagonists to therapy in chronic persistent asthma: a randomised double-blind placebo-controlled trial

- 100 patients high-dose ICS (+/- additional therapy
- 10 mg montelukast sodium for 14 days in an outpatient clinic setting
- Outcome measures were symptoms and peak flow diaries.

Montelukast did not provide additional benefit in lung function and symptoms in patients with moderate or severe asthma



Robinson DS, Lancet, 2001

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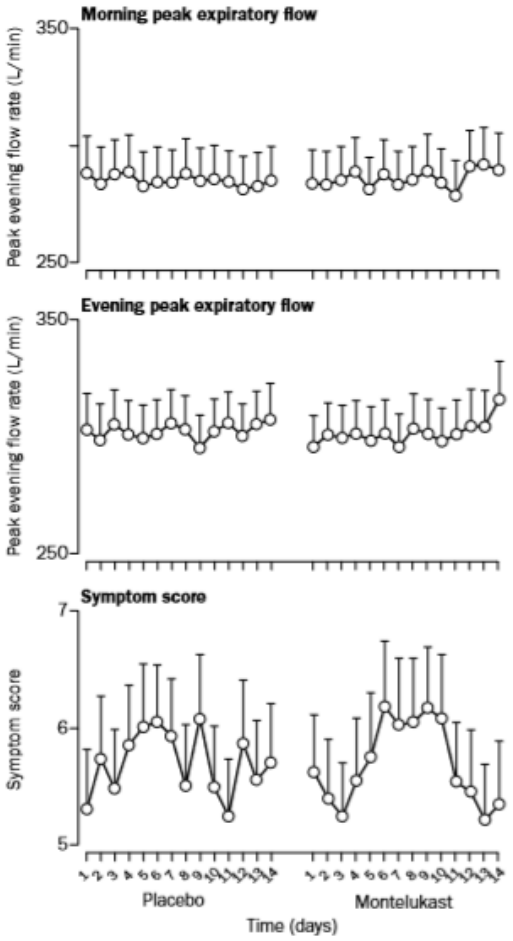


Robinson DS, Lancet, 2001

The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma

321 patients (163 severe , 158 with mild-to-moderate asthma)

Females (*F/M ratio 4.4:1 vs 1.6:1*)

Predominantly neutrophilic inflammation

Evidence of ongoing mediator release but less atopy

A potential risk factor for severe asthma that emerged from the ENFUMOSA study was exposure to aspirin.

Table 5. – Biomarkers of inflammation

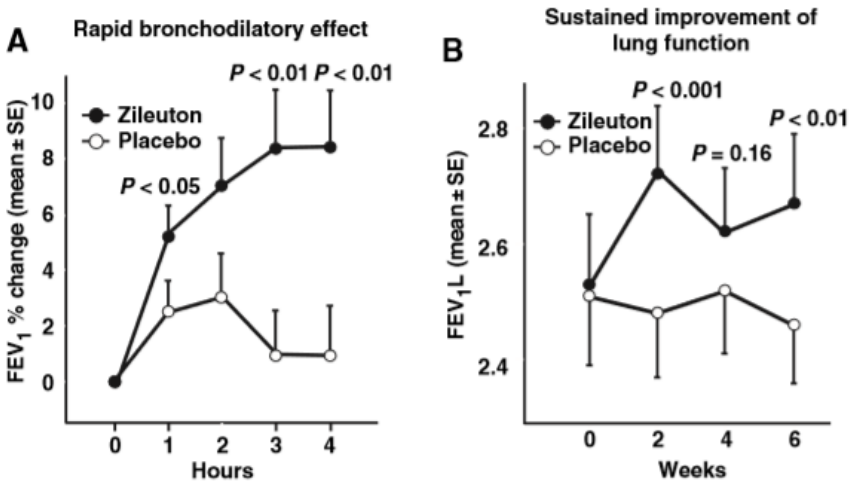
	Controlled asthma	Severe asthma	Controlled *versus* severe asthma
Peripheral WBC			
Subjects n	130	162	NS
Total count $\times 10^9 \cdot L^{-1}$	6.7±1.7	8.6±3.4	<0.05
Monocytes %	7.2±2.4	6.5±2.1	NS
Neutrophils %	57.3±8.3	61.2±12.1	<0.05
Lymphocytes %	30.4±7.1	27.1±9.3	NS
Eosinophils %	4.1±3.1	4.4±5.0	NS
Basophils %	0.7±0.8	0.7±0.8	NS
Urinary mediators			
Subjects n	136	153	
LTE_4 ng·mmol^{-1} creatinine	48±5.8	58±7.7$^{\#}$	<0.05
EPX µg·mmol^{-1} creatinine	45±4.6	62±9.3$^{\#}$	<0.05
Exhaled NO			
Subjects n	45	50	
Geometric mean ppb$^{\#}$ (95% CI)	9.2 (7.0–7.3)	9.8 (7.3–13.2)	NS

Data are presented as mean±SD unless otherwise indicated. WBC: white blood count; LTE_4: leukotriene E_4; EPX: eosinophil protein X; NO: nitric oxide; CI: confidence interval. $^{\#}$: age and sex adjusted.

Eur Respir J 2003

Benefits from Adding the 5-Lipoxygenase Inhibitor Zileuton to Conventional Therapy in Aspirin-intolerant Asthmatics

- double-blind placebo-controlled crossover study
- 40 subjects (aspirin-intolerant asthmatics)



Zileuton added to high doses of inhaled and/or oral steroids in well-controlled aspirin-intolerant asthmatics resulted in significant clinical improvements in both the upper and lower airways

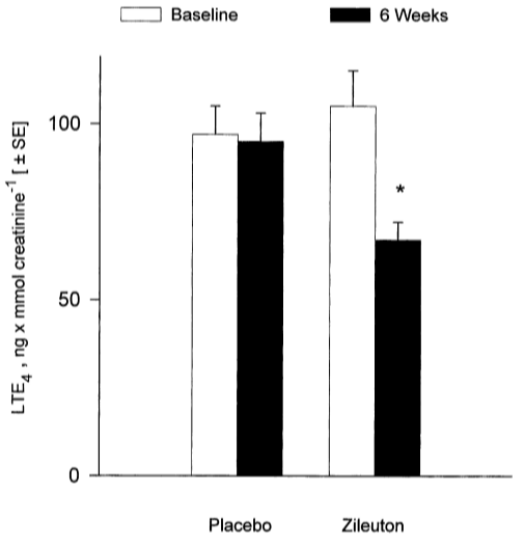


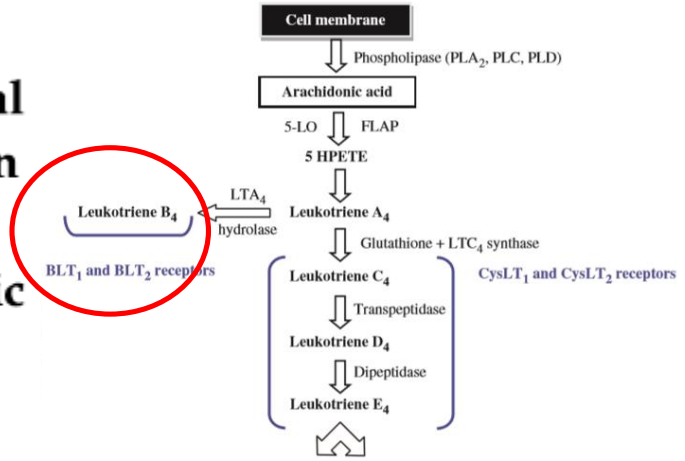
Figure 6. Basal excretion of LTE_4 in the urine was reduced by 36% after 6 wk of treatment with zileuton ($p < 0.01$).

Dahlén, AJRCCM 1998

American Journal of Therapeutics 20, 154–162 (2013)

A Randomized, Comparative, Multicentric Clinical Trial to Assess the Efficacy and Safety of Zileuton Extended-Release Tablets With Montelukast Sodium Tablets in Patients Suffering From Chronic Persistent Asthma

Amit H. Kubavat, MD,[1*] Narendra Khippal, MD,[2] Sandeep Tak, MD,[3] Puneet Rijhwani, MD,[4] Salil Bhargava, MD,[5] Tushar Patel, MD,[6] Nalin Shah, MD,[7] Rakeshkumar R. Kshatriya, M. Pharm,[1] and Ravindra Mittal, MD, DNB[1]



117 patients in group Zileuton ER, 110 patients in group Montelukast for 12 weeks

Peak expiratory flow rate (PEFR)
asthma symptoms were assessed on monthly scheduled out-patient visits.
Safety assessments by clinical and laboratory parameters

Thus, Zileuton ER seems to be more efficacious than Montelukast and well tolerated for the treatment of mild to moderate chronic persistent asthma in adult patient population.

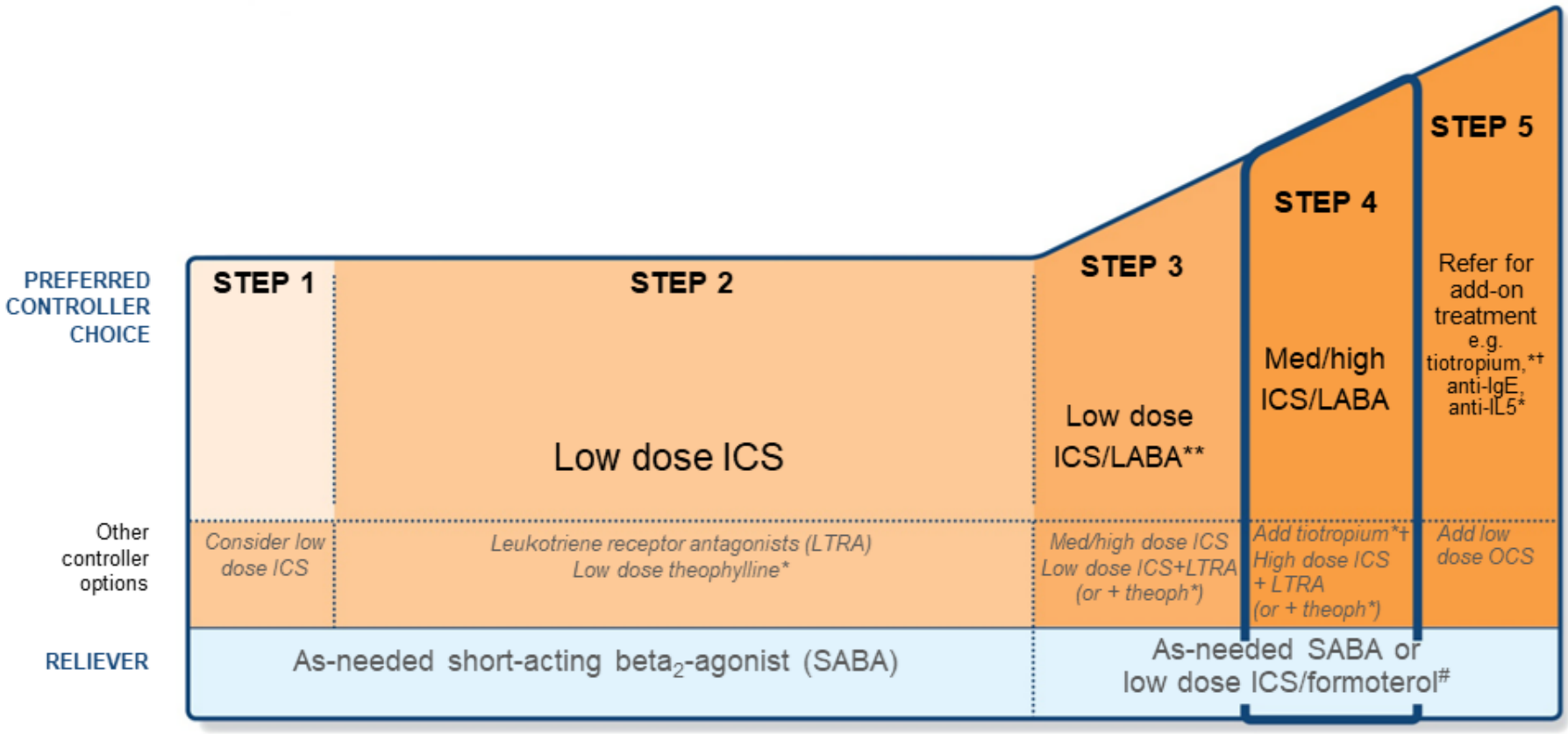
Montelukast as an Add-On Therapy to Inhaled Corticosteroids in the Treatment of Severe Asthma in Elderly Patients

- high or medium dose of ICS, and most (98%) also used LABA
- 12 months x 2
- 341 patients montelukast, 171 patients control

The significant **increase in the number of days without asthma symptoms**, the **reduction in the number of days of beta-agonist use**, and the **decrease in asthma exacerbation events** confirmed the efficacy of montelukast in elderly patients compared with the control group.

Bozek A, Journal of Asthma 2012

Step 4 – two or more controllers + as-needed inhaled reliever



*Not for children <12 years
**For children 6-11 years, the preferred Step 3 treatment is medium dose ICS
#For patients prescribed BDP/formoterol or BUD/ formoterol maintenance and reliever therapy
† Tiotropium by mist inhaler is an add-on treatment for patients ≥12 years with a history of exacerbations

Step 4 – two or more controllers + as-needed inhaled reliever

- Before considering step-up
  - Check inhaler technique and adherence
- Adults or adolescents: preferred option is combination low dose ICS/formoterol as maintenance and reliever regimen*, OR combination medium dose ICS/LABA with as-needed SABA
- Children 6–11 years: preferred option is to refer for expert advice
- Other options (adults or adolescents)
  - Tiotropium by mist inhaler may be used as add-on therapy for patients aged ≥12 years with a history of exacerbations
  - Adults: consider adding SLIT (see Non-pharmacological therapy)
  - Trial of high dose combination ICS/LABA, but little extra benefit and increased risk of side-effects
  - Increase dosing frequency (for budesonide-containing inhalers)
  - Add-on LTRA or low dose theophylline

*Approved only for low dose beclometasone/formoterol and low dose budesonide/formoterol

Management of severe asthma

- Optimize dose of ICS/LABA
  - Complete resistance to ICS is rare
  - Consider therapeutic trial of higher dose
- Consider low dose maintenance oral corticosteroids
  - Monitor for and manage side-effects, including osteoporosis
- Add-on treatments without phenotyping
  - Tiotropium - reduces exacerbations (history of exacerbations, age ≥12 years)
  - Theophylline, LTRA – limited benefit
- Phenotype-guided treatment
  - Severe allergic asthma: add-on omalizumab (anti-IgE)
  - Severe eosinophilic asthma: add-on mepolizumab or reslizumab (anti-IL5)
  - Sputum-guided treatment to reduce exacerbations and/or steroid dose
  - Aspirin-exacerbated respiratory disease: consider add-on LTRA
- Non-pharmacological interventions
  - Consider bronchial thermoplasty for selected patients
  - Comprehensive adherence-promoting program

UPDATED 2018

Η νέα εποχή στην θεραπεία του σοβαρού άσθματος – ***παλαιά φάρμακα με νέες θεωρήσεις***

- **LAMA**
- **LTRAs**
- **Antibiotics**

Macrolide antibiotics

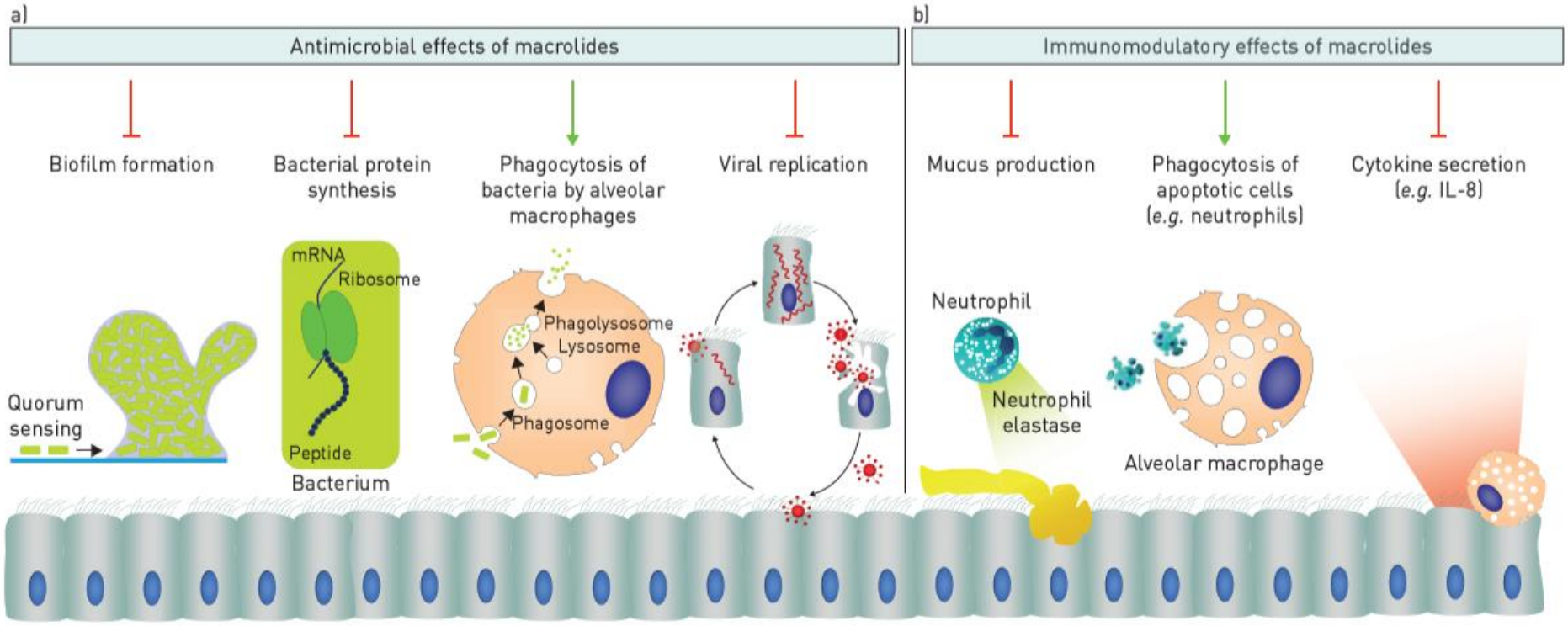
- Doxycycline
- Moxifloxacin
- Macrolides

immunomodulatory properties

Macrolide antibiotics

- A lactone ring attached to deoxy sugars
- Bacteriostatic (inhibit protein synnthesis of bacteria
- 14-membered lactone ring (erythromycin, clarithromycin and roxithromycin)
- 15-membered lactone ring azithromycin (also called an azalide)

Η αντιμικροβιακή και ανοσορρυθμιστική δράση των μακρολίδων

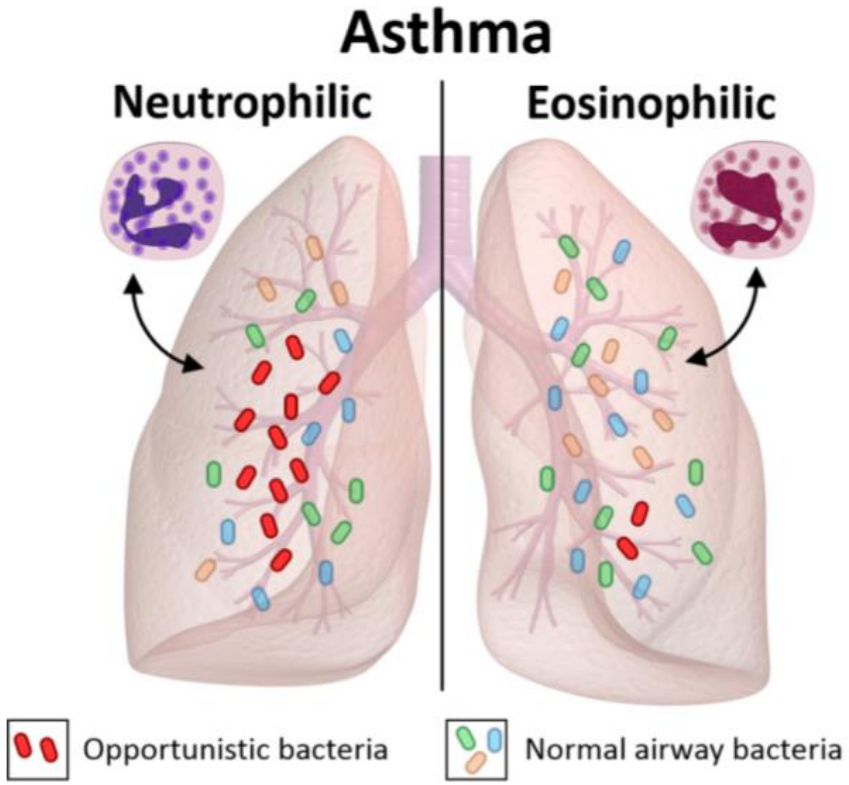


Infections and asthma

- As with respiratory viral infections, infection with and/or reactivation of atypical bacteria (Chlamydia pneumoniae, mycoplasma pneumoniae) has been associated with both asthma exacerbations and chronic severe asthma.

Cunningham AF, Eur Respir J 1998
Wark PAB, Eur Respir J 2002
Johnston SL, AJRCCM 2005

Sputum microbiota



- Sputum microbiota in severe asthma differs from healthy controls and non-severe asthmatics, and is characterized by the presence of *Streptococcus* spp with eosinophilia and Haemophilus, Moraxella in neutrophilic severe asthma

Taylor SL, JACI 2018

- Although a partial contribution of their bacteriostatic effects cannot be excluded, it is widely assumed that **the immunomodulatory properties** of macrolides are the predominant mechanism of action.

Essilfie A-T, Thorax 2015
Brusselle GG, Thorax 2015

Original articles

Efficacy of troleandomycin in outpatients with severe, corticosteroid-dependent asthma

J. ALLERGY CLIN. IMMUNOL.
DECEMBER 1980

Robert S. Zeiger, M.D., Ph.D., Michael Schatz, M.D., William Sperling, M.D., Ronald A. Simon, M.D., and Donald D. Stevenson, M.D.
San Diego and La Jolla, Calif.

16 severe, corticosteroid-dependent patients

Troleandomycin in the treatment of difficult asthma

J ALLERGY CLIN IMMUNOL
NOVEMBER 1993

Andrea Siracusa, MD, Giuliana Brugnami, MD, Tiziana Fiordi, MD, Stefano Areni, MD, Carla Severini, MD, and Alessandra Marabini, MD
Perugia, Italy

14 patients with severe steroid-dependent asthma

Macrolides for chronic asthma (Review)

Richeldi L, Ferrara G, Fabbri LM, Gibson PG

2005

- 7 studies
- 416 participants
- macrolide treatment > 4 weeks

- The results support an **anti-inflammatory effect** of this class of drugs in asthma, there were **no clear benefits to participants with asthma**. This may have been because the study design was not optimal. More research is needed to examine the role of macrolides in asthma therapy.

Other controller therapies.

Role in therapy -Various therapeutic regimens to reduce the dose of oral glucocorticosteroids required by patients with severe asthma have been proposed. These medications should be used only in selected patients under the supervision of an asthma specialist, as their potential steroid-sparing effects may not outweigh the risk of serious side effects. Two meta-analyses of the steroid-sparing effect of low-dose methotrexate showed a small overall benefit, but a relatively high frequency of adverse effects[102,103]. This small potential to reduce the impact of glucocorticosteroid side effects is probably insufficient to offset the adverse effects of methotrexate[104]. Cyclosporin[105] and gold[106,107] have also been shown to be effective in some patients. The macrolide, troleandomycin, has a small steroid-sparing effect when used with systemic methylprednisolone, but its effect may result from the macrolide decreasing metabolism of the glucocorticosteroid and therefore not improving safety. However, other effects of the long-term use of macrolides in asthma remain under study[108]. The use of intravenous immunoglobulin is not [111]. Data on a human monoclonal antibody ecrosis factor (TNF)-alpha suggest that the risk benefit equation does not favor the use of this class of treatments in severe asthma[216].

Side effects -Macrolide use is frequently associated with nausea, vomiting, and abdominal pain and occasionally liver toxicity. Methotrexate also causes gastrointestinal symptoms, and on rare occasions hepatic and diffuse pulmonary parenchymal disease, and hematological and

options, these benefits
of adverse effects and t
course of injection thera
wait required after each
should be considered o
avoidance and pharmac
inhaled glucocorticoster
patient's asthma[113]. The
specific immunotherapy
for asthma. The value o
allergens does not have
Side effects -Local and
conjunction with specific
Reactions localized to t
a minimal immediate wh
delayed allergic respons
anaphylactic reactions,
as well as severe exace
specific immunotherapy
severe asthma.

Reliever Medication

Reliever medications act
and its accompanying ac

Rapid-acting inhaled β

Role in therapy -Rapid-a
medications of choice fo
acute exacerbations of
of exercise-induced bro

ORIGINAL ARTICLE

Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial

Guy G Brusselle,[1] Christine VanderStichele,[1] Paul Jordens,[2] René Deman,[3]

Thorax 2013;68:322–329.

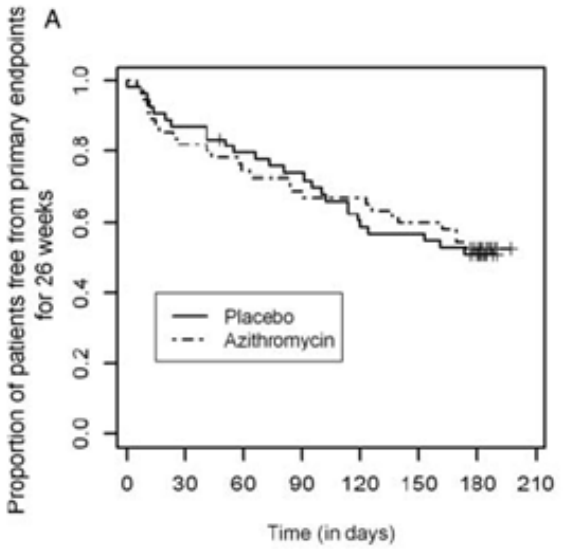
randomised double-blind placebo-controlled trial

109 patients, 250mg azithromycin/day for 5 days – 250mg 3/week (26 weeks)

Primary endpoint: severe exacerbations of asthma and LRTI requiring antibiotics

In patients with severe asthma, add-on treatment with low-dose azithromycin for 6 months **did not decrease the frequency of the primary endpoint** (severe exacerbations of asthma and LRTI requiring antibiotics)

0.75 PEPs (95% CI 0.55 to 1.01) per subject in the azithromycin group vs 0.81 PEPs (95% CI 0.61 to 1.09) in the placebo group (p=0.682).



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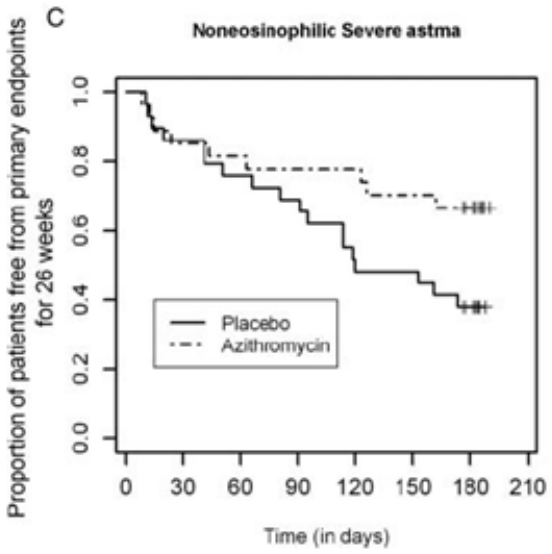
Primary endpoint: severe exacerbations of asthma and LRTI requiring antibiotics

In subjects with **severe non-eosinophilic asthma** (blood eosinophilia ≤200/ml) add-on treatment with azithromycin was associated with **a significant reduction in primary endpoints**

0.44 PEPs (95% CI 0.25 to 0.78) vs

1.03 PEPs (95% CI 0.72 to 1.48) (p=0.013).



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109 patients, 250mg azithromycin/day for 5 days – 250mg 3/week (26 weeks)

Primary endpoint: severe exacerbations of asthma and LRTI requiring antibiotics

Azithromycin significantly **improved the AQLQ score** but there were **no significant** between-group differences in **the ACQ score or lung function**.

Azithromycin was **well tolerated**, but was associated with **increased oropharyngeal carriage of macrolide-resistant streptococci**.

Cochrane Library

Cochrane Database of Systematic Reviews

Macrolides for chronic asthma (Review)

Kew KM, Undela K, Kotortsi I, Ferrara G

Cochrane Database of Systematic Reviews 2015, Issue 9. Art. No.: CD002997.

There is still **a need for additional high-quality** studies to confirm the possible benefit of macrolides in noneosinophilic severe asthma

Cochrane Library

Cochrane Database of Systematic Reviews

- 23 RCT (16new)
- 1513 ασθενείς

Macrolides for chronic asthma (Review)

Kew KM, Undela K, Kotortsi I, Ferrara G

Cochrane Database of Systematic Reviews 2015, Issue 9. Art. No.: CD002997.

Great variability in:

- type of patients (ranging from intermittent aspirin-induced asthma to severe asthma)
- interventions (different type of macrolides, administration scheme and doses in most of the studies)
- outcomes recorded

Median study duration was 8 weeks (range 4 to 52 weeks).

219: max number patient in

Data and analyses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbation requiring hospitalisation	2	143	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.13, 7.23]
2 'Severe' exacerbation - requiring at least OCS	5	290	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.43, 1.57]
3 Symptom scales	4	156	Std. Mean Difference (Fixed, 95% CI)	-0.35 [-0.67, -0.02]
4 Asthma Control	4	353	Std. Mean Difference (Fixed, 95% CI)	-0.05 [-0.26, 0.15]
5 Asthma Quality of Life Questionnaire (AQLQ)	5	389	Mean Difference (Fixed, 95% CI)	0.06 [-0.12, 0.24]
6 Rescue medication puffs/day	4	314	Mean Difference (Fixed, 95% CI)	-0.26 [-0.65, 0.12]
7 Morning PEF (L/min)	4	289	Mean Difference (Fixed, 95% CI)	2.22 [-9.73, 14.17]
8 Evening PEF (L/min)	3	212	Mean Difference (Fixed, 95% CI)	1.97 [-12.68, 16.62]
9 FEV_1 (L)	9	631	Mean Difference (Fixed, 95% CI)	0.08 [0.02, 0.14]
10 Bronchial hyperresponsiveness (BHR)			Other data	No numeric data
11 Oral corticosteroid dose	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12 Serious adverse events (incl mortality)	7	434	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.24, 2.68]
13 Withdrawal	9	563	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.59, 1.52]
14 Blood eosinophils	2		Mean Difference (Fixed, 95% CI)	-33.50 [-36.11, -30.90]
15 Sputum eosinophils	3		Mean Difference (Fixed, 95% CI)	Totals not selected
16 ECP in serum	2		Mean Difference (Fixed, 95% CI)	-12.84 [-15.67, -10.00]
17 ECP in sputum	2		Mean Difference (Fixed, 95% CI)	-1.45 [-1.78, -1.11]

Cochrane Database of Systematic Reviews 2015, Issue 9. Art. No.: CD002997.

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

www.thelancet.com **Published online July 4, 2017 http://dx.doi.org/10.1016/S0140-6736(17)31281-3**

- 420 patients (median age 60 years, 40% males)
- maintenance treatment with medium-to-high dose inhaled corticosteroids plus a long-acting bronchodilator (LABA, LAMA)
- azithromycin 500 mg or placebo three times per week for 48 weeks

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

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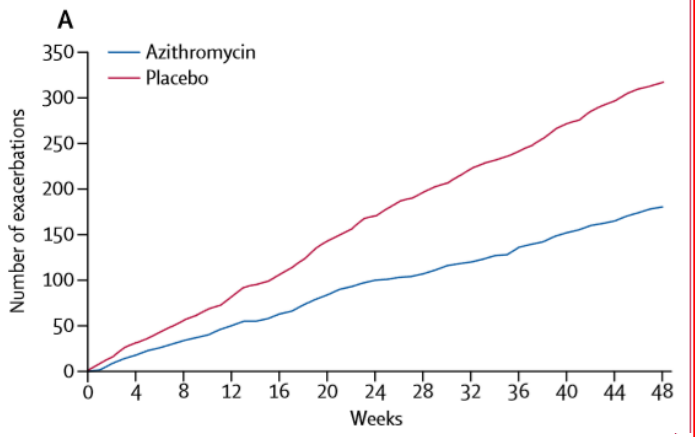

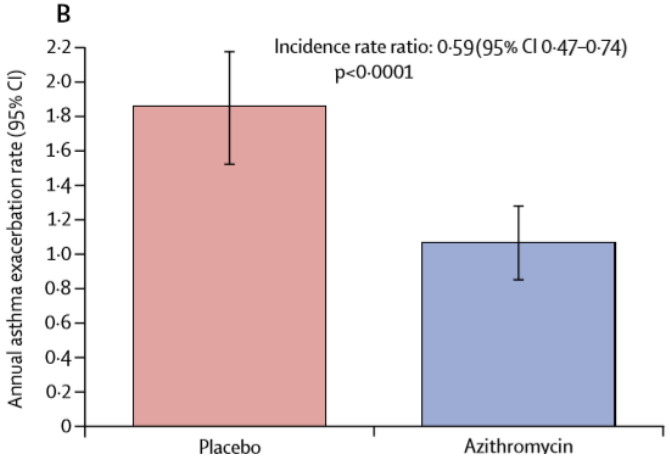

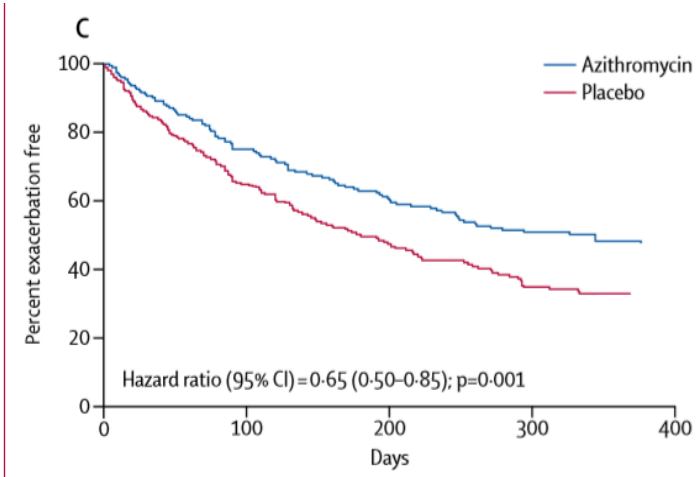

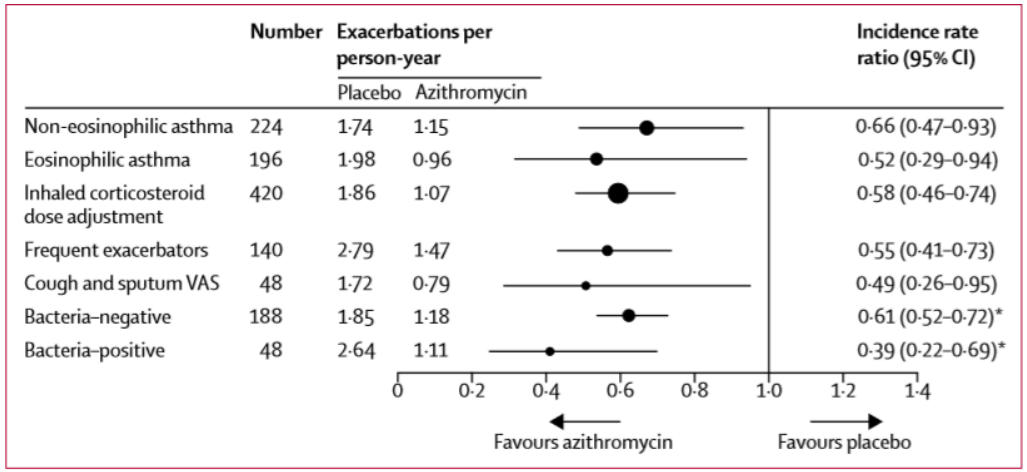

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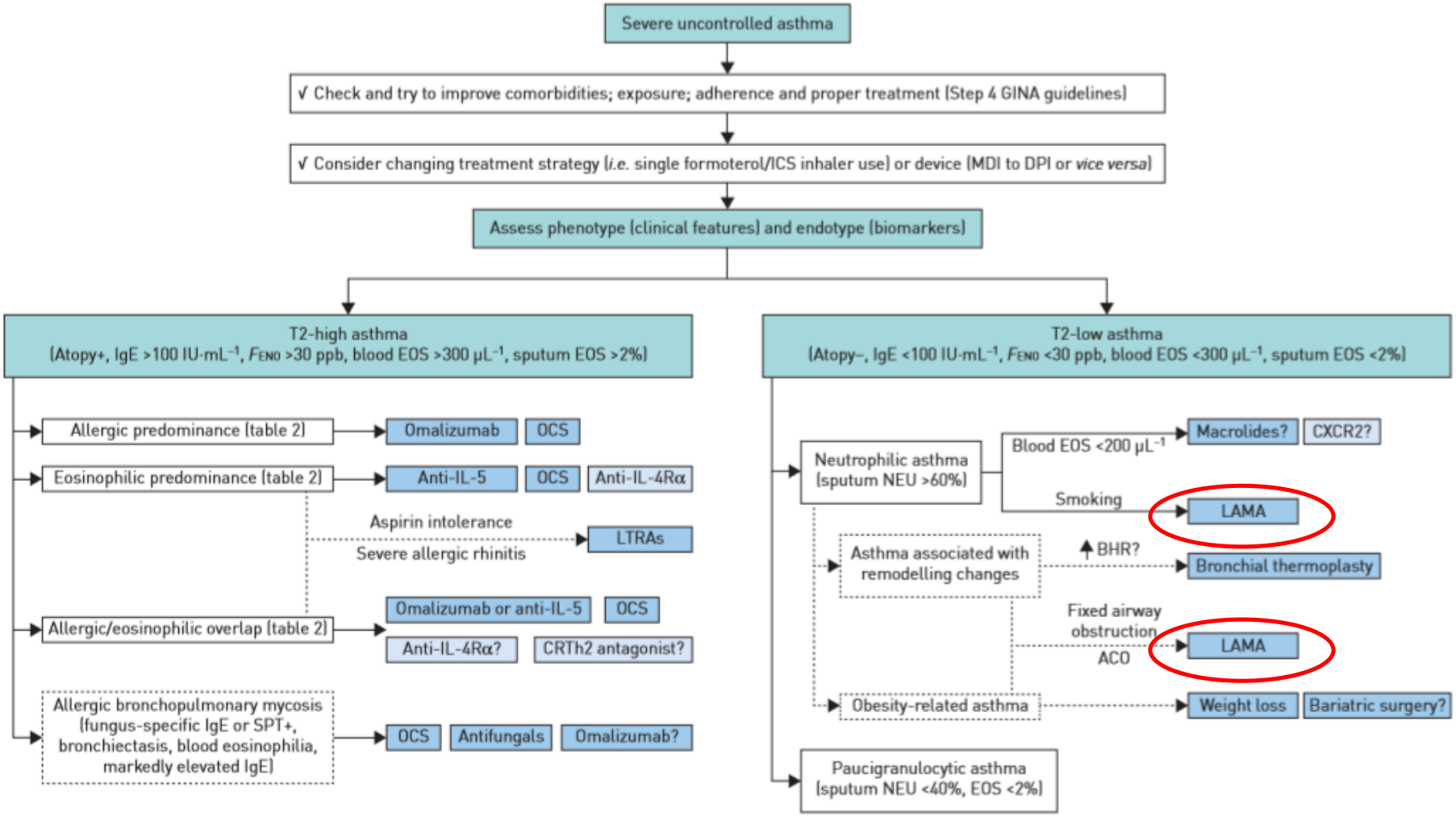
Interpretation Adults with persistent symptomatic asthma experience fewer asthma exacerbations and improved quality of life when treated with oral azithromycin for 48 weeks. Azithromycin might be a useful add-on therapy in persistent asthma.

Table 3. Recommendations for long-term macrolide treatment monitoring

Adverse events	Timing	Recommendation
Drug hypersensitivity	At start	Absence of known allergy to macrolides
Drug interactions	Any time	Verify concomitant medication
Hepatotoxicity	At start	Aminotransferase levels <3× upper limit of normal
	At 6 weeks	Monitor serum liver enzymes
	Yearly	Monitor liver enzymes (more frequently in risk groups)
Cardiotoxicity	At start	Perform electrocardiography to assess corrected QT interval (<450 ms)
	Any time	Repeat electrocardiography if new concomitant medication influencing QT duration
Ototoxicity	At start	Audiometric screening for pre-existing hearing loss in risk groups (*e.g.* elderly)
NTM infection	At start	Perform sputum samples to exclude pre-existing NTM infection
	6 monthly	Monitor sputum cultures for NTM (particularly in risk groups, *e.g.* cystic fibrosis)

Συνοψίζοντας…….

A stepwise therapeutic approach in severe uncontrolled asthmatic subjects



Zervas E et al, ERJ Open Res 2018

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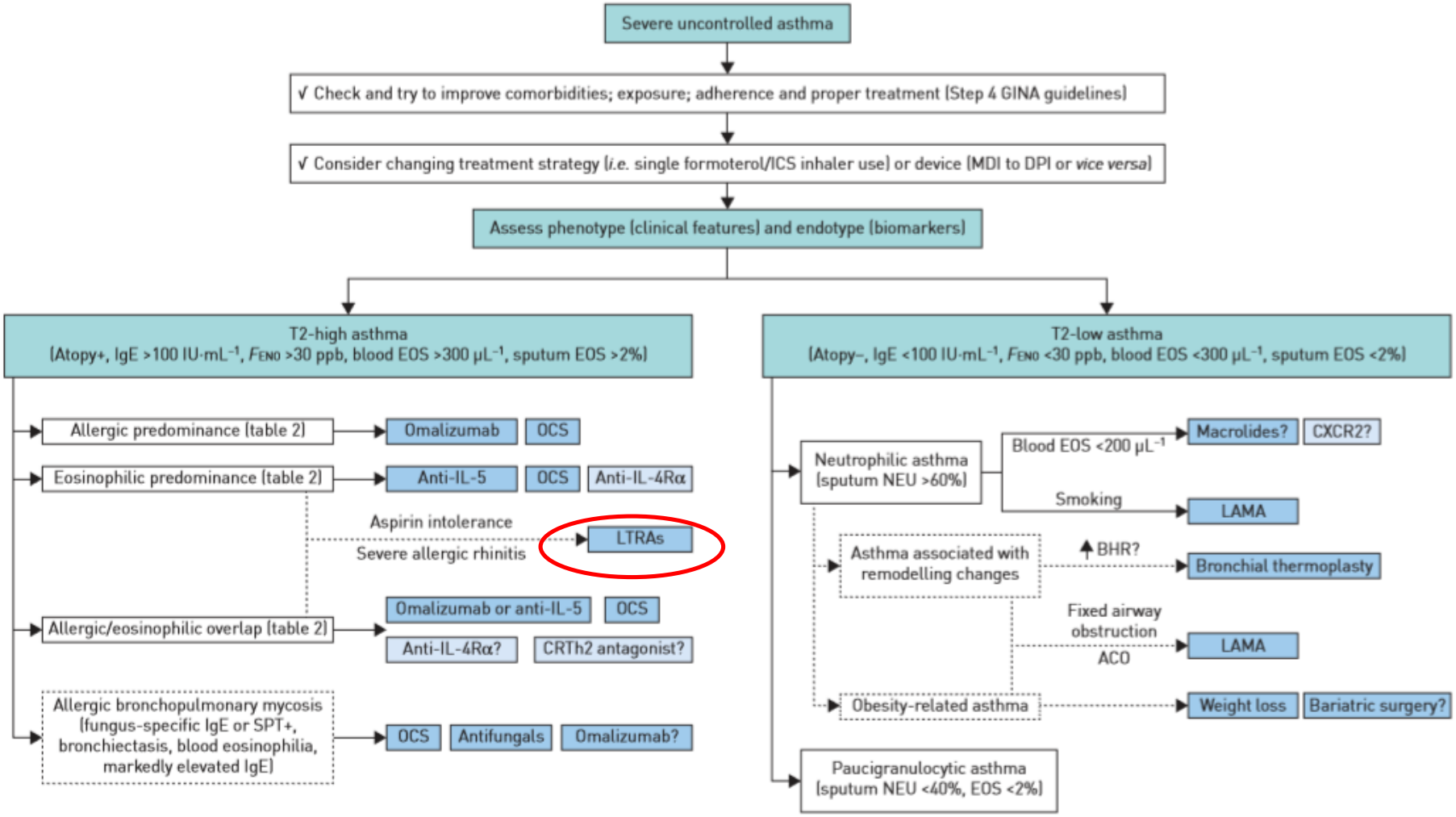

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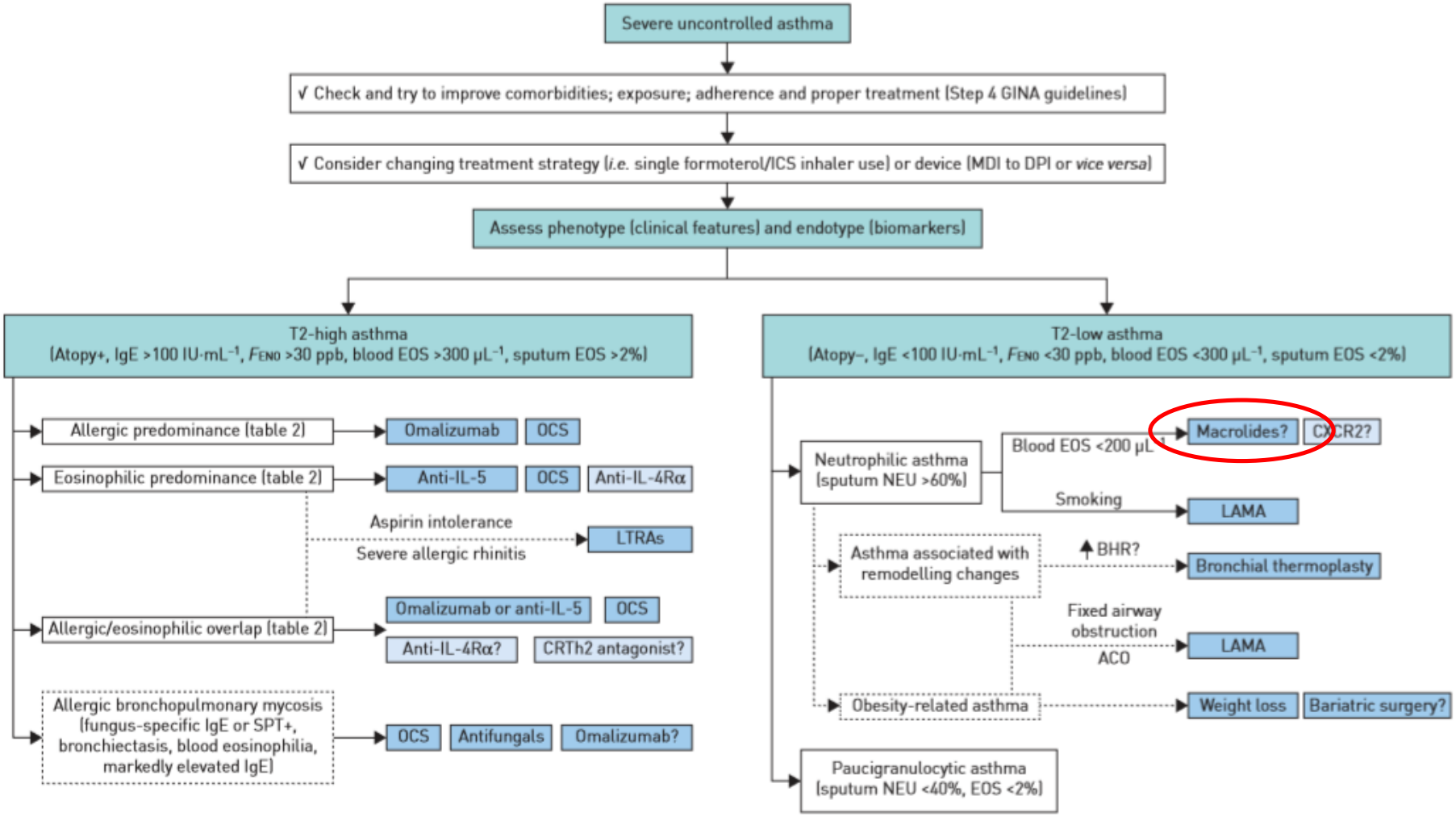

Zervas E et al, ERJ Open Res 2018

Dosing of macrolides

- **Azithromycin** : 500 mg three times weekly

or alternatively 250 mg daily

- **Roxithromycin:** 150 mg daily

- **Clarithromycin**: 500 mg twice daily

200 mg daily