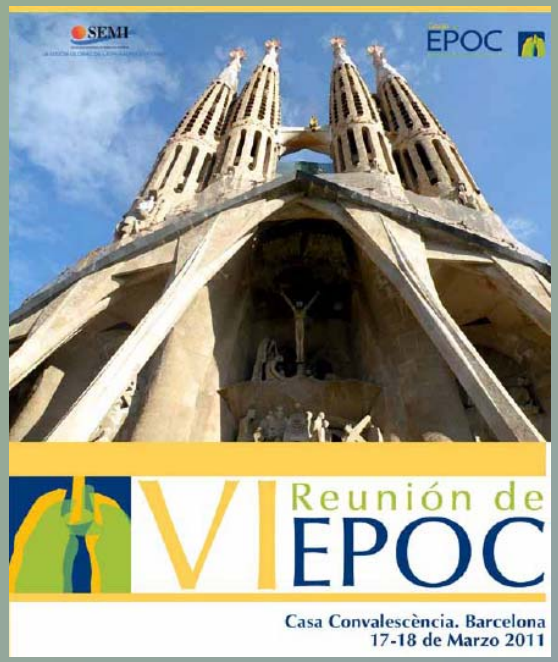


VI REUNION DE EPOC-SEMI

Barcelona, 18 marzo 2011

NUEVOS TRATAMIENTOS EN LA EPOC.

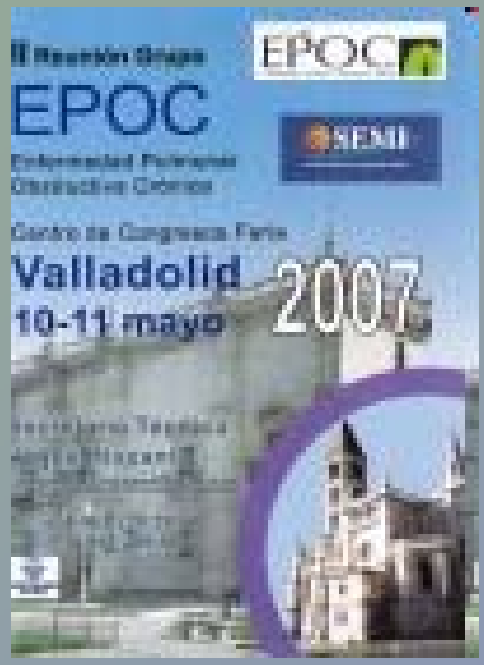
José Manuel Varela
Servicio de Medicina Interna,
Hospital Virgen del Rocío, Sevilla.
CIBER Epidemiología y Salud Pública
Instituto de Biomedicina de Sevilla

IBIS INSTITUTODEBIOMEDICINADESEVILLA

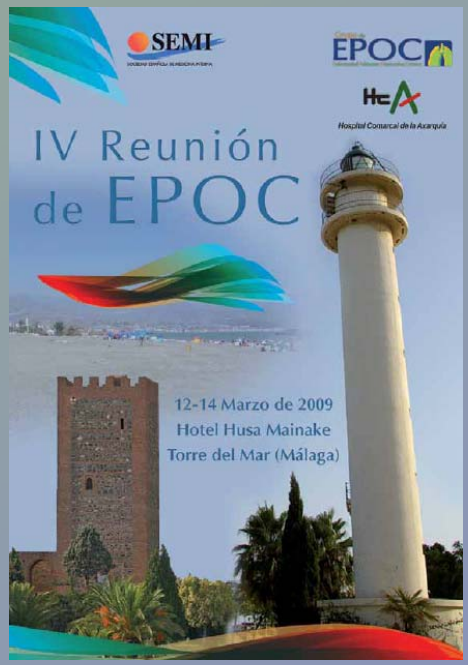
HOSPITAL UNIVERSITARIO VIRGEN DEL ROCÍO

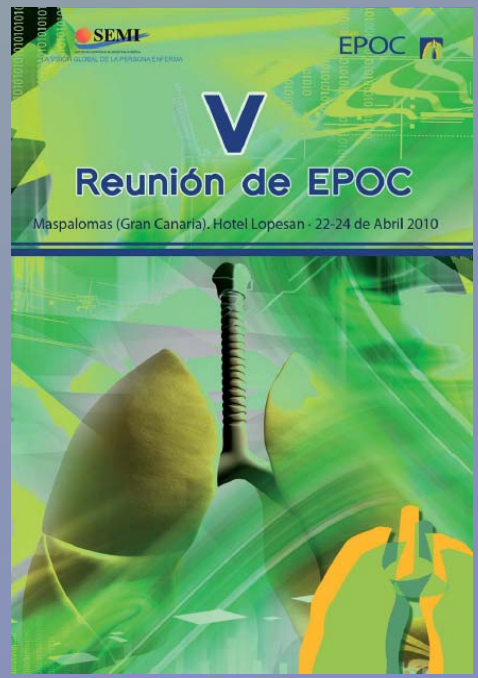
ciberesp Centro de Investigación Biomédica en red Epidemiología y Salud Pública

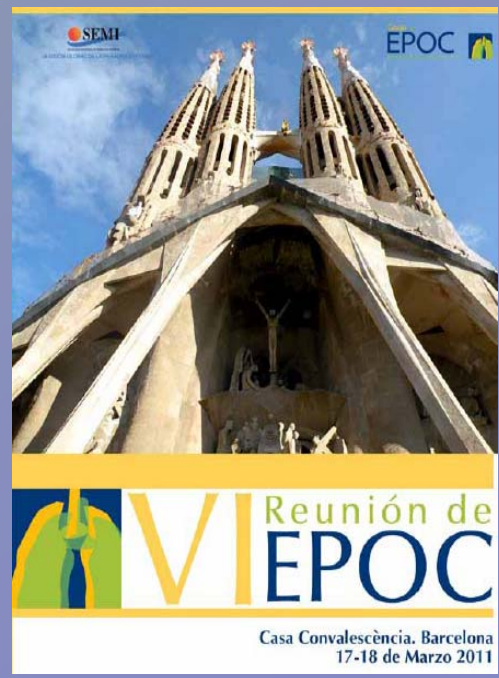

I Reunión de
EPOC
Enfermedad Pulmonar Obstructiva Crónica
Hotel Meliá Alicante, 12-13 mayo 2006
SEMI


EPOC
Valladolid 2007
10-11 mayo


SEMI
III Reunión
EPOC
Enfermedad Pulmonar Obstructiva Crónica
Hotel Guadiana · 3-5 Abril 2008 · CIUDAD REAL


SEMI
EPOC
IV Reunión de EPOC
12-14 Marzo de 2009
Hotel Husa Mainake
Torre del Mar (Málaga)


SEMI
EPOC
V
Reunión de EPOC
Maspalomas (Gran Canaria). Hotel Lopesan · 22-24 de Abril 2010


SEMI
EPOC
VI Reunión de EPOC
Casa Convalescència. Barcelona
17-18 de Marzo 2011

NUEVOS TRATAMIENTOS EPOC
DIFICULTADES

- **Mecanismos celulares y moleculares.**
- **Necesidad de nuevos modelos animales.**
- **Incertidumbre parámetro para testar utilidad del fármaco.**
- **Diversidad de fenotipos.**
- **Comorbilidad – EPOC**
- **Variables subrogadas – Poca información (pe. Biomarcadores).**

Nuevos tratamientos de la EPOC

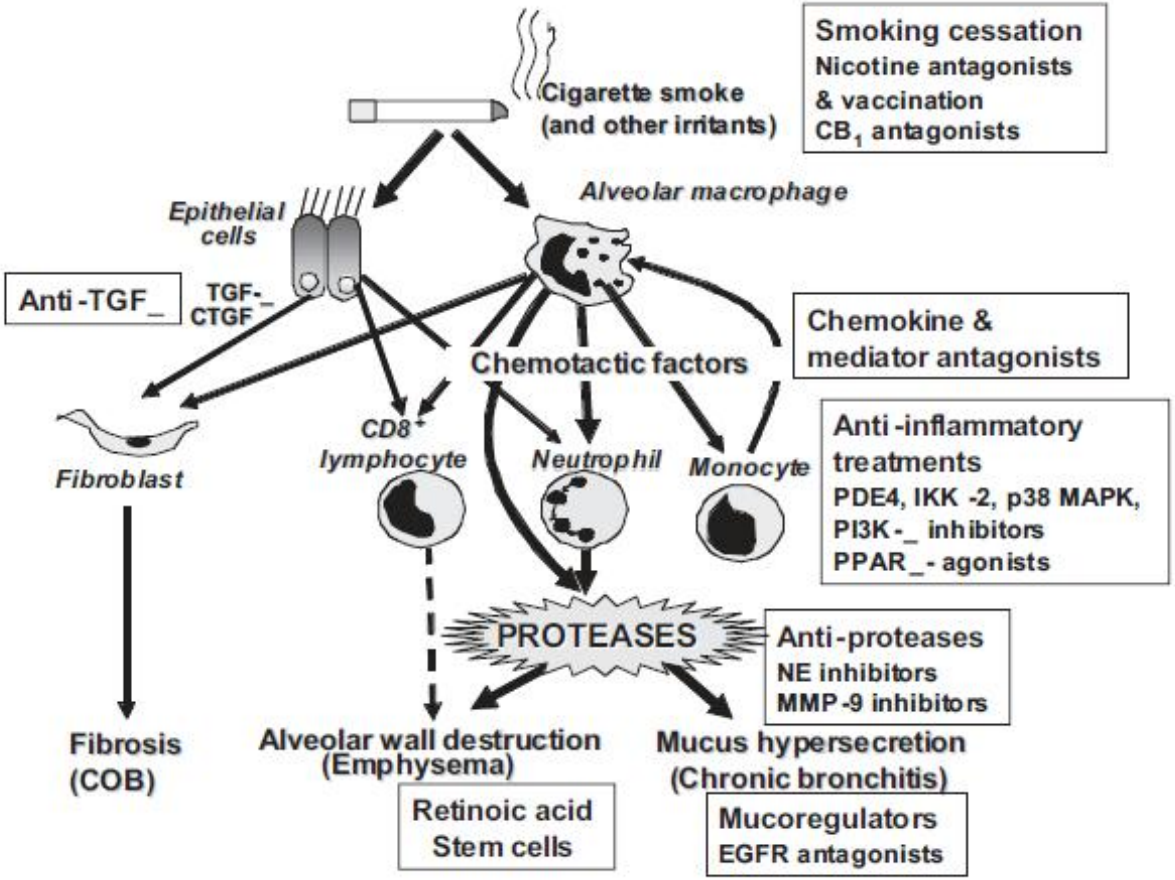
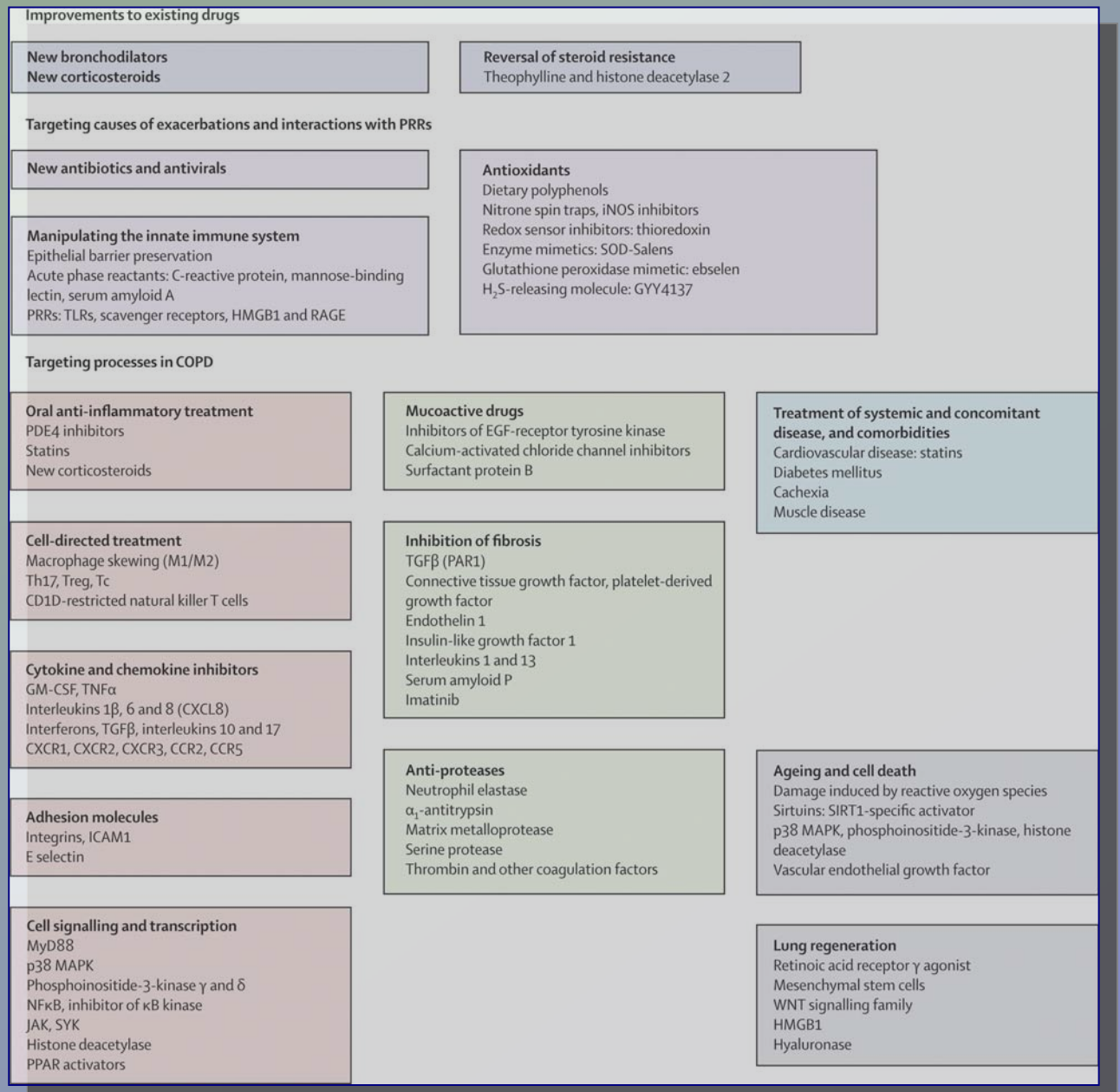


FIGURE 1. Cigarette smoke (and other irritants) activate macrophages in the respiratory tract that release multiple chemotactic factors attracting neutrophils, monocytes, and T lymphocytes (particularly CD8+ cells). Several cells also release proteases, such as neutrophil elastase (NE) and MMP-9, which the break down connective tissue in the lung parenchyma (emphysema) and also stimulate mucus hypersecretion (*ie*, chronic bronchitis). CD8+ cells may also be involved in alveolar wall destruction. TGF-β and connective tissue growth factor (CTGF) released from inflammatory cells may mediate small airway fibrosis. The inflammatory process may be inhibited at several stages (shown in the boxes). COB = chronic obstructive bronchitis; CB = cannabinoid; EGFR = epithelial growth factor receptor.

Barnes PJ. Emerging pharmacotherapies for COPD. Chest 2008;134:1278-86.

Dianas terapéuticas en EPOC

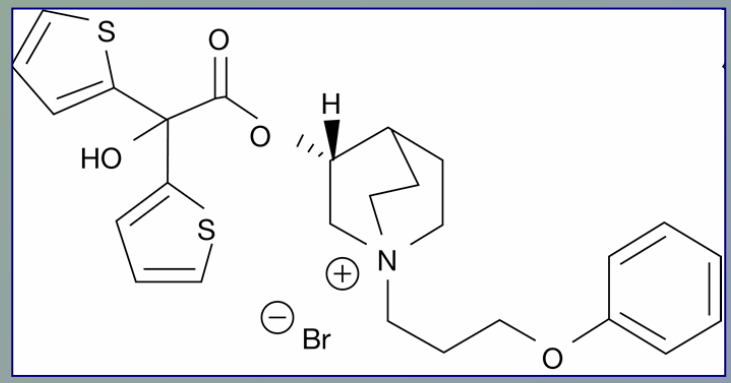


Hansel TT, Barnes PJ. Lancet 2009;374:744-55.

NUEVOS TRATAMIENTOS DE LA EPOC

- **Mejorar los tratamientos existentes: nuevos LAMA, ultra-LABA y corticoides. Nuevas asociaciones.**

Bromuro de ACLIDINIO



- **Es un nuevo broncodilatador muscarínico inhalado, de larga duración, que se une de forma prolongada sobre los receptores M3.**
- **Genuair® sistema de polvo seco de dosis múltiples, con diseño intuitivo a través de una ventana coloreada y un ´'clic' audible.**
- **Actualmente en desarrollo clínico con estudios en fase III. 15 ensayos registrados (13 completos).**
- **Registro previsto 2011.**

Bromuro de ACLIDINIO

NTC00435760

Clinical Trial to Assess Rate of Onset of Bronchodilator Action in Severe Stable Chronic Obstructive Pulmonary Disease (COPD) Patients

- **Diseño: Cruzado, doble ciego, double-dummy, multicéntrico.**
- **Intervención: Aclidinio (200 mcg/d; Genuair®) vs tiotropio (18 mcg/d; Handihaler®) vs placebo.**
- **Duración: Dosis única.**
- **Pacientes: 115 pt (EPOC moderado-severo).**
- **Variables principal: efecto broncodilatador tras dosis única. Porcentaje de pacientes con un incremento del VEMS > 10% del nivel basal a las 3 horas post-dosis.**
  - **Aclidinio: 49.5%**
  - **Tiotropio: 51.8%**
  - **Placebo: 13.8%**

p<0.0001

- **Variables secundarias: Modificación del VEMS (%) a los 30' post-dosis respecto al basal.**
  - **Aclidinio: 12%**
  - **Tiotropio: 11%**
  - **Placebo: 3%**

p<0.0001

Vestbo J et al. Fast onset effect of aclidinium bromide, a novel long-acting antimuscarinic, in patients with COPD. Viena, ESR Congress 2009. Thorax 2009; 64 (Suppl 4): A167.

Bromuro de ACLIDINIO

NCT00868231

Efficacy of Aclidinium Bromide Administered in Chronic Obstructive Pulmonary Disease (COPD) Patients. Fase II.

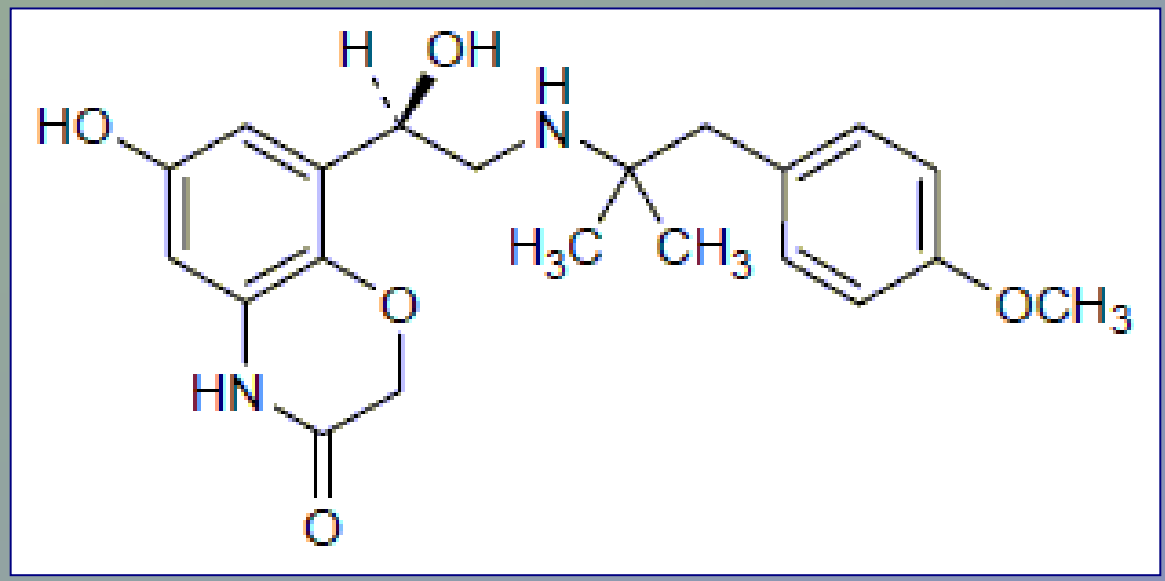
- **Objetivo: Evaluar la eficacia de aclidinio en múltiples dosis en pacientes con EPOC moderado-severo.**
- **Intervención: Aclidinio (400 mcg/12h) vs tiotropio (18 mcg/d) vs placebo.**
- **Duración: 15 días.**
- **Pacientes: 30 pt.**
- **Variables principal: modificación del VEMS a los 15 días de la intervención.**

NCT0089462- ACCORD COPD I

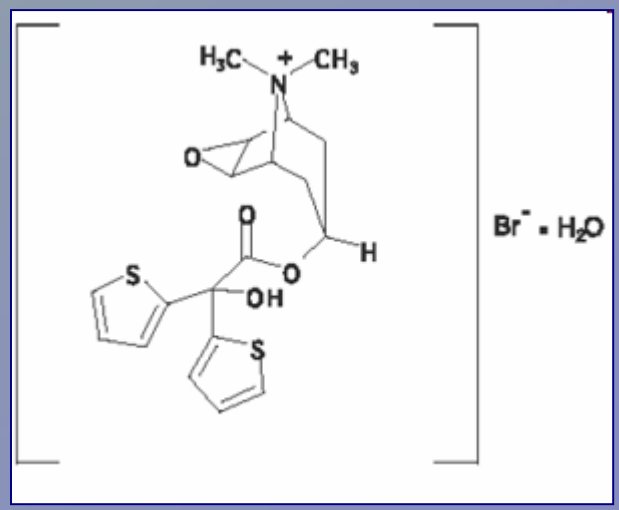
Efficacy and Safety of Aclidinium Bromide for Treatment of Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD). Fase III.

- **Objetivo: Evaluar la eficacia de aclidinio en múltiples dosis en pacientes con EPOC moderado-severo.**
- **Intervención: Aclidinio (200 mcg/12h) vs aclidinio (400 mcg/12h) vs placebo.**
- **Duración: 3 meses.**
- **Variables principal: modificación del VEMS a los 3 meses de la intervención.**

OLODATEROL



TIOTROPIO



OLODATEROL + TIOTROPIO

Bronchodilators in airways disease

5557

Four weeks once daily treatment with tiotropium+olodaterol (BI 1744) fixed dose combination compared with tiotropium in COPD patients

Place a comment or grade

F. Maltais, E. Beck, D. Webster, M. R. Maleki-Yazdi, J. V. Seibt, A. Arnoux, A. Hamilton
(Toronto, Burlington, Canada; Rüdersdorf, Germany; Killeen, United States Of America; Reims, France)

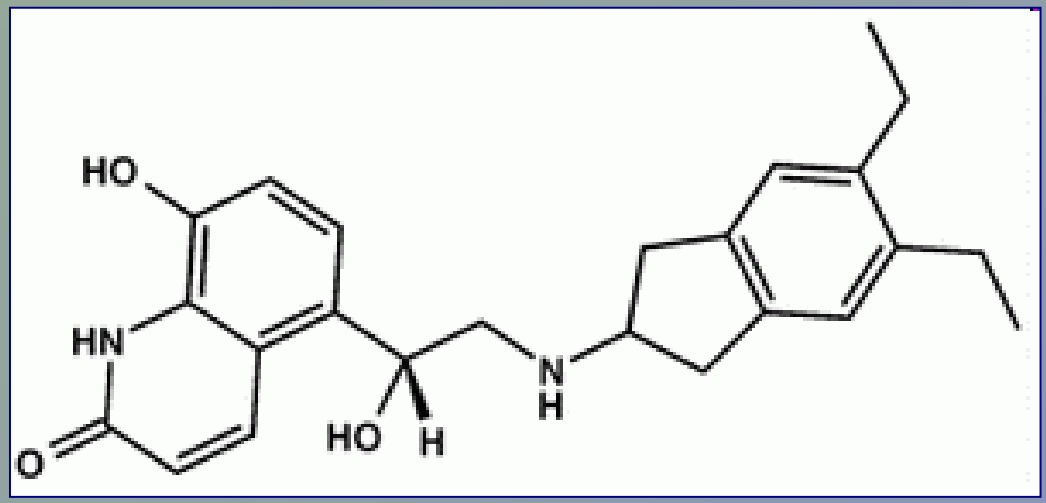
Background Tiotropium, a muscarinic receptor antagonist, and olodaterol, a novel long-acting ß$_2$-agonis
studies. Combining tiotropium and olodaterol in a single inhaler provides the potential for superior bronc
Objective To investigate the bronchodilator efficacy of tiotropium+olodaterol (T+O) fixed dose combinatio
both administered using the Respimat® soft mist™ inhaler, in COPD patients.
Methods In a randomized, double-blind, parallel group design, 360 (196 M, 164 F) COPD patients inhale
baseline post-bronchodilator FEV$_1$ was 1.46 L (0.51) (53% predicted); mean age was 63 (9) yrs; mean s
reversibility was 17 (15) %. FEV$_1$ was measured pre-dose (trough) and up to 6h post-dose.
Results Peak FEV$_1$ response from baseline was significantly increased for all doses of T+O FDC compa
significantly increased for T+O (5/10µg) FDC compared with T. No safety or tolerability concerns were ide

			Peak FEV1 response (mL)		Trou	
		N	Mean (SE)	p-value	Mean (SE)	p-value
T 5µg		90	266 (24)		110 (20)	
T+O FDC	5/2µg	89	353 (24)	0.008	134 (21)	0.38
	5/5µg	93	348 (24)	0.012	143 (20)	0.22
	5/10µg	88	410 (24)	<0.0001	168 (21)	0.034

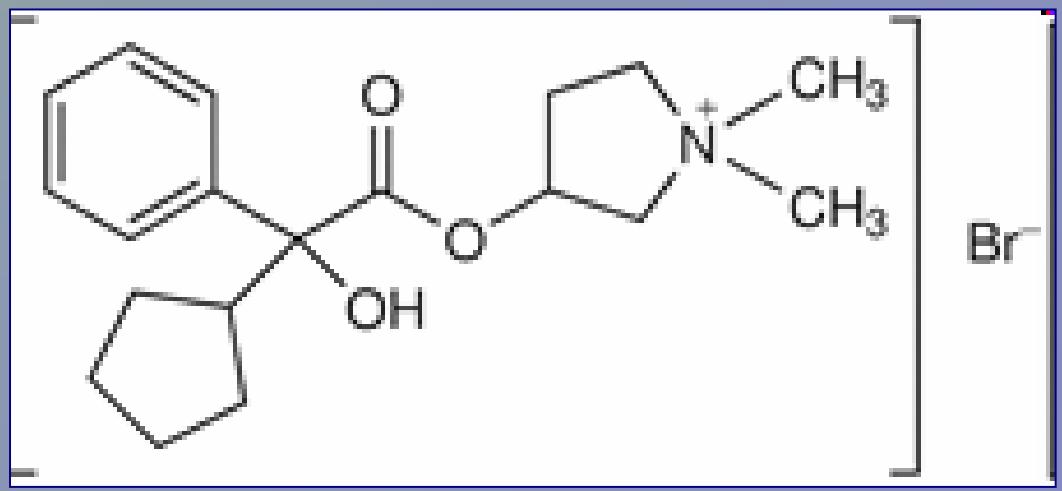
Conclusion T+O (5/10µg) FDC is more effective than T 5µg in COPD patients, with superior bronchodilation over 24h following 4 wks once daily dosing.

ERS 2010 (Barcelona 18-22 septiembre 2010).

INDACATEROL



GLICOPIRRONIO



QVA149 demonstrates superior bronchodilation compared with indacaterol or placebo in patients with chronic obstructive pulmonary disease

Jan A van Noord,[1] Roland Buhl,[2] Craig LaForce,[3] Carmen Martin,[4] Francis Jones.[4] Michael Dolker,[5] Tim Overend[4]

Thorax 2010;**65**:1086–1091.

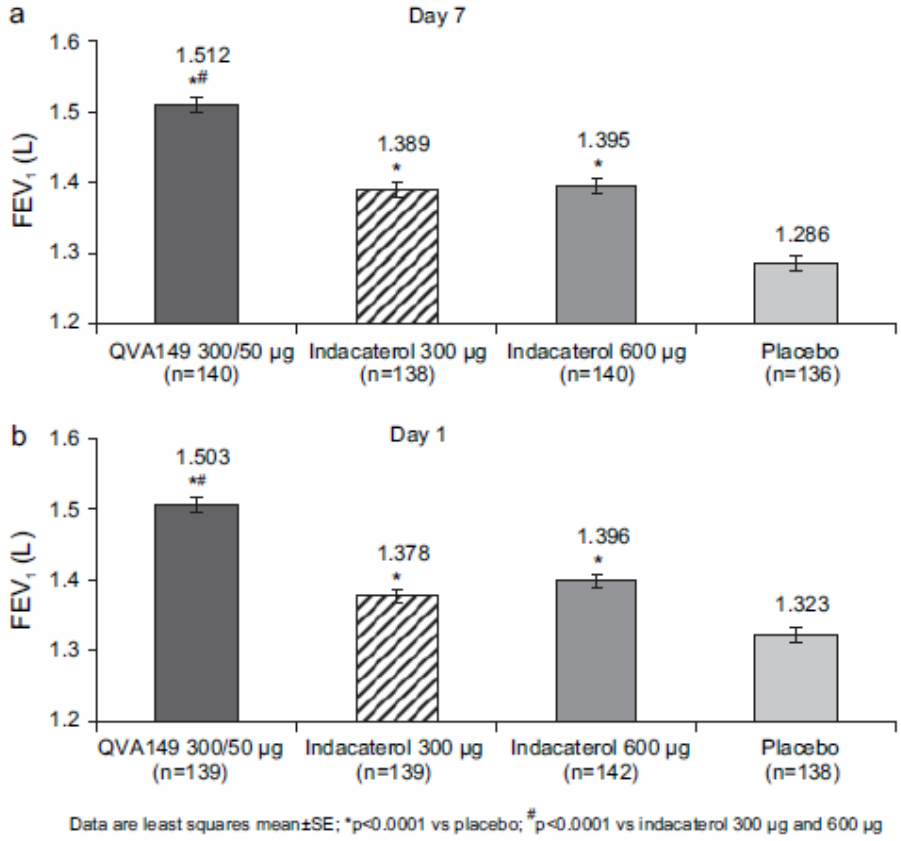
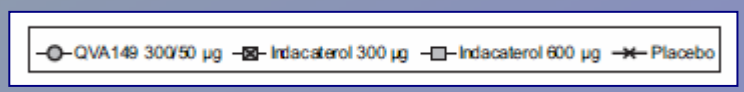


Figure 2 Trough forced expiratory volume in 1 s (FEV_1) on (A) day 7 (B) day 1.

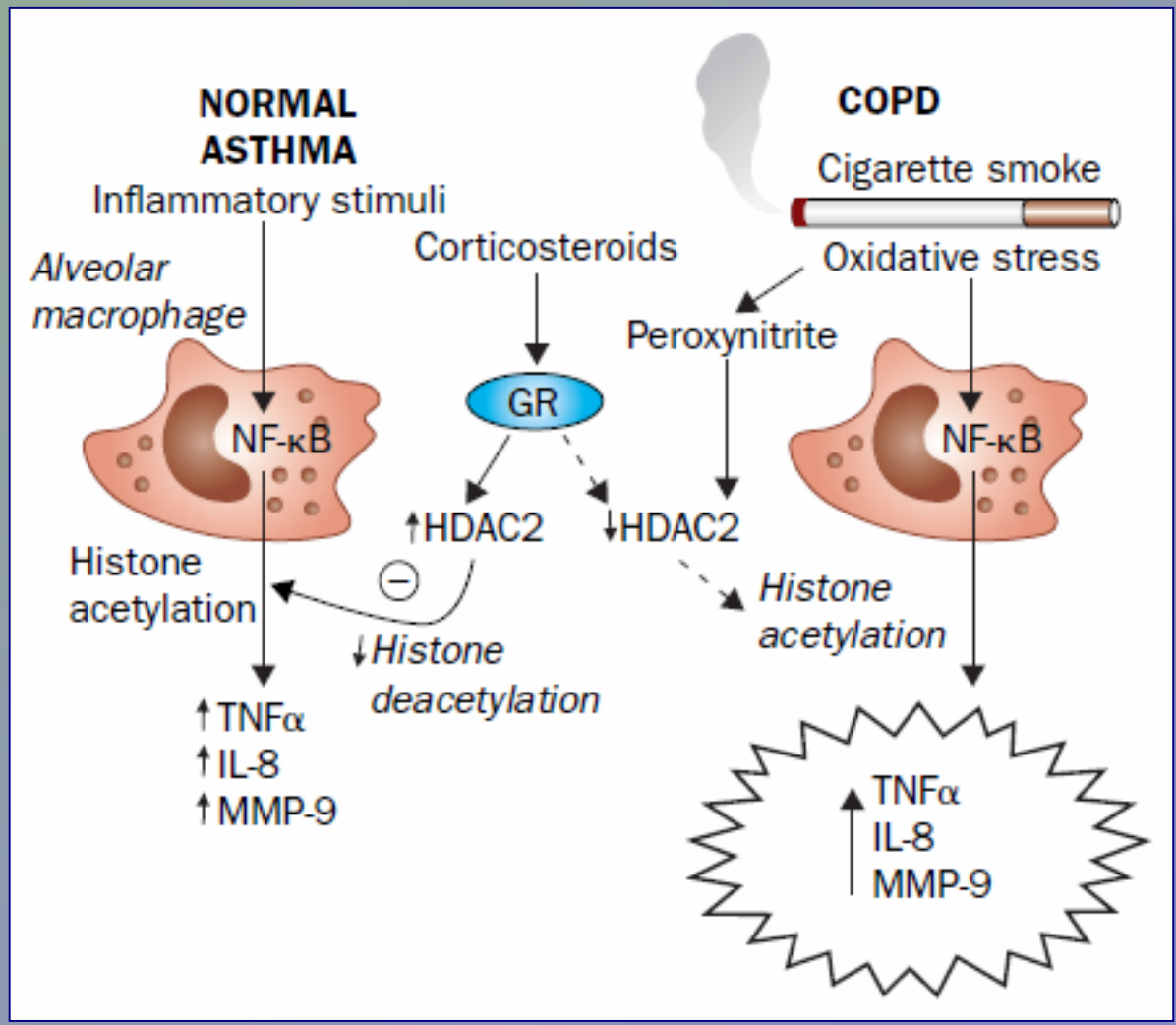
Figure 3 Forced expiratory volume in 1 s (FEV_1) at all time points on (A) day 7 (B) day 1.



NUEVOS TRATAMIENTOS DE LA EPOC

- **Mejorar los tratamientos existentes: nuevos LAMA, ultra-LABA y corticoides. Nuevas asociaciones.**
- **Mejorar la resistencia a los esteroides: teofilinas.**

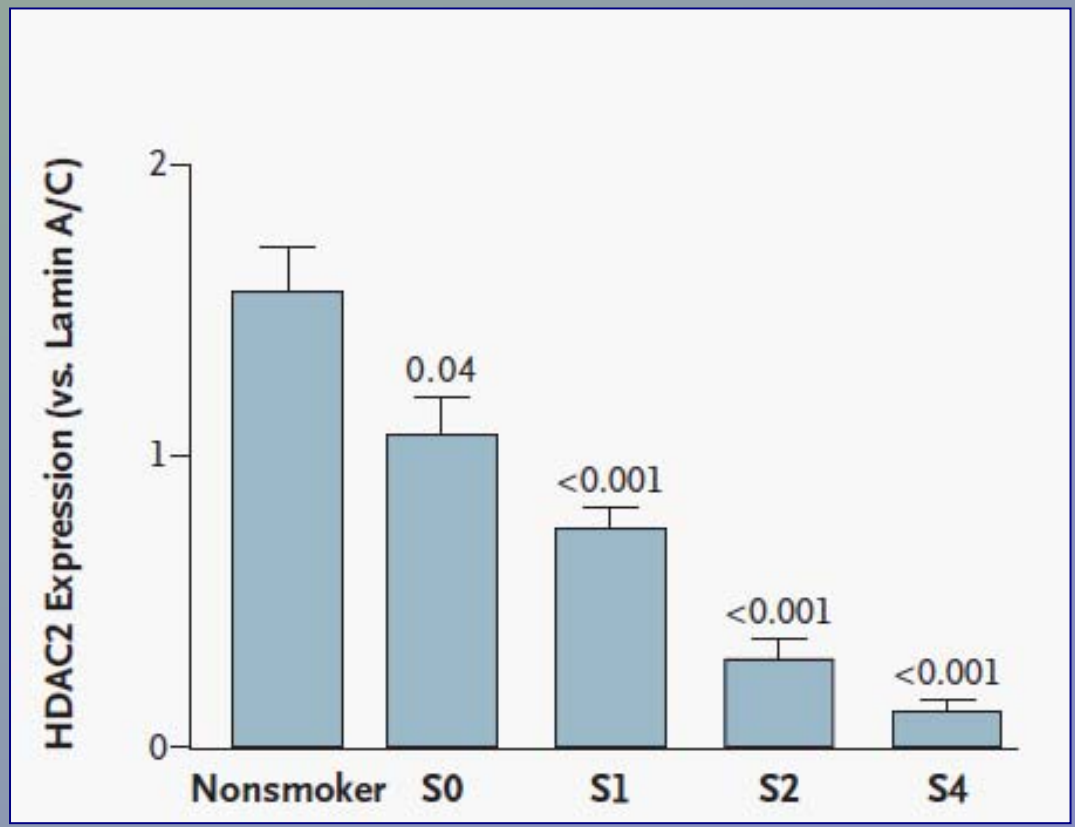
La expresión reducida de HDAC puede promover inflamación y menor respuesta a los CIs en la EPOC



Decreased Histone Deacetylase Activity in Chronic Obstructive Pulmonary Disease

N ENGL J MED 352;19 WWW.NEJM.ORG MAY 12, 2005

Kazuhiro Ito, Ph.D., Misako Ito, B.A., W. Mark Elliott, Ph.D., Borja Cosio, M.D., Gaetano Caramori, Ph.D., Onn Min Kon, M.D., Adam Barczyk, M.D., Shizu Hayashi, Ph.D., Ian M. Adcock, Ph.D., James C. Hogg, M.D., and Peter J. Barnes, D.M., D.Sc.

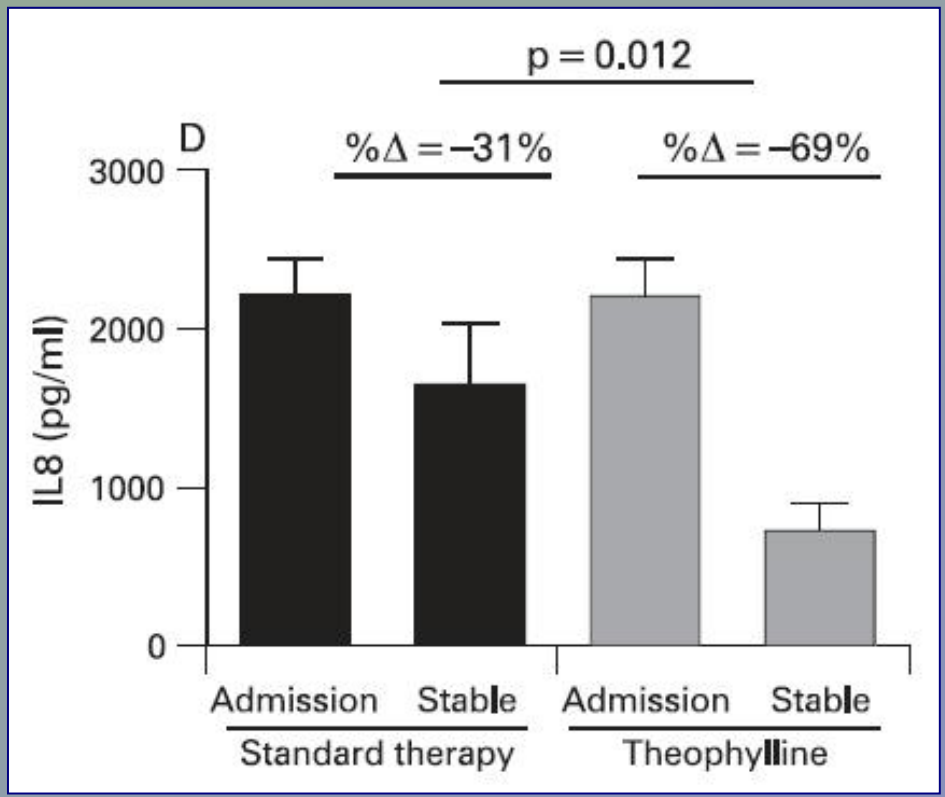


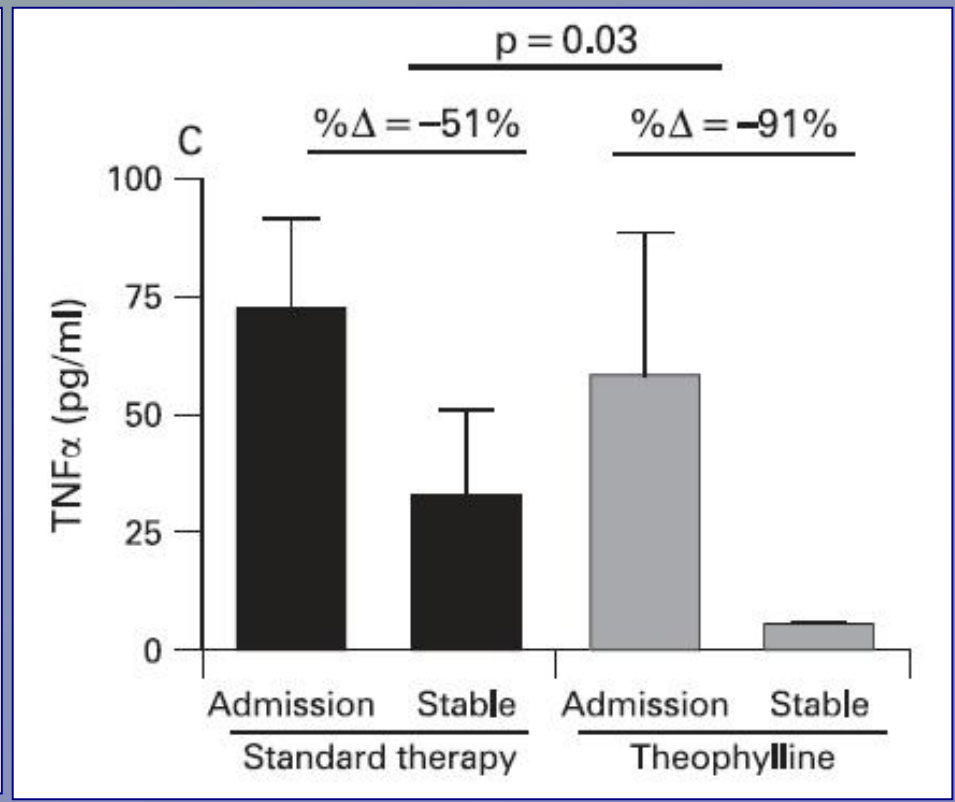
Histone Deacetylase (HDAC) Expression in Peripheral Lung Tissue.

Low-dose theophylline enhances the anti-inflammatory effects of steroids during exacerbations of COPD

B G Cosio,[1,2,3] A Iglesias,[2] A Rios,[3] A Noguera,[1,2,3] E Sala,[1,2,3] K Ito,[4] P J Barnes,[4] A Agusti[1,2,3]

Thorax 2009;**64**:424–429. doi:10.1136/thx.2008.103432





N=35 pt. Teofilina 100 mg/12 h vs placebo x 3 meses

Treatment Effects of Low-Dose Theophylline Combined With an Inhaled Corticosteroid in COPD

CHEST 2010; 137(6):1338–1344

Paul A. Ford, PhD; Andrew L. Durham, PhD; Richard E. K. Russell, PhD; Fabiana Gordon, PhD; Ian M. Adcock, PhD; and Peter J. Barnes, DM, FCCP

Theophylline Improves Steroid Sensitivity in Acute Alcoholic Hepatitis

Stuart F. W. Kendrick, Elsbeth Henderson, Jeremy Palmer, David E. J. Jones, and Chris P. Day

(HEPATOLOGY 2010;52:126-131)

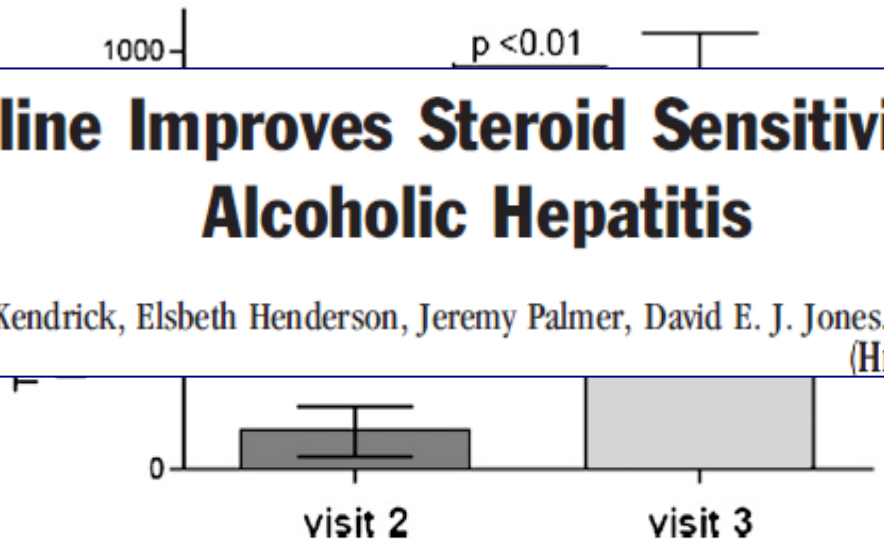


FIGURE 2. The effect of treatment with inhaled fluticasone propionate and theophylline on total HDAC activity in peripheral blood mononuclear cells from seven patients with COPD. Data are presented with means ± 95% CI and compare visit 2 with visit 3 from the open-label trial extension of arm 2. HDAC = histone deacetylase.

Fluticasona 500 mcg/12 h + Teofilina 250 mg/12 h x 4 semanas

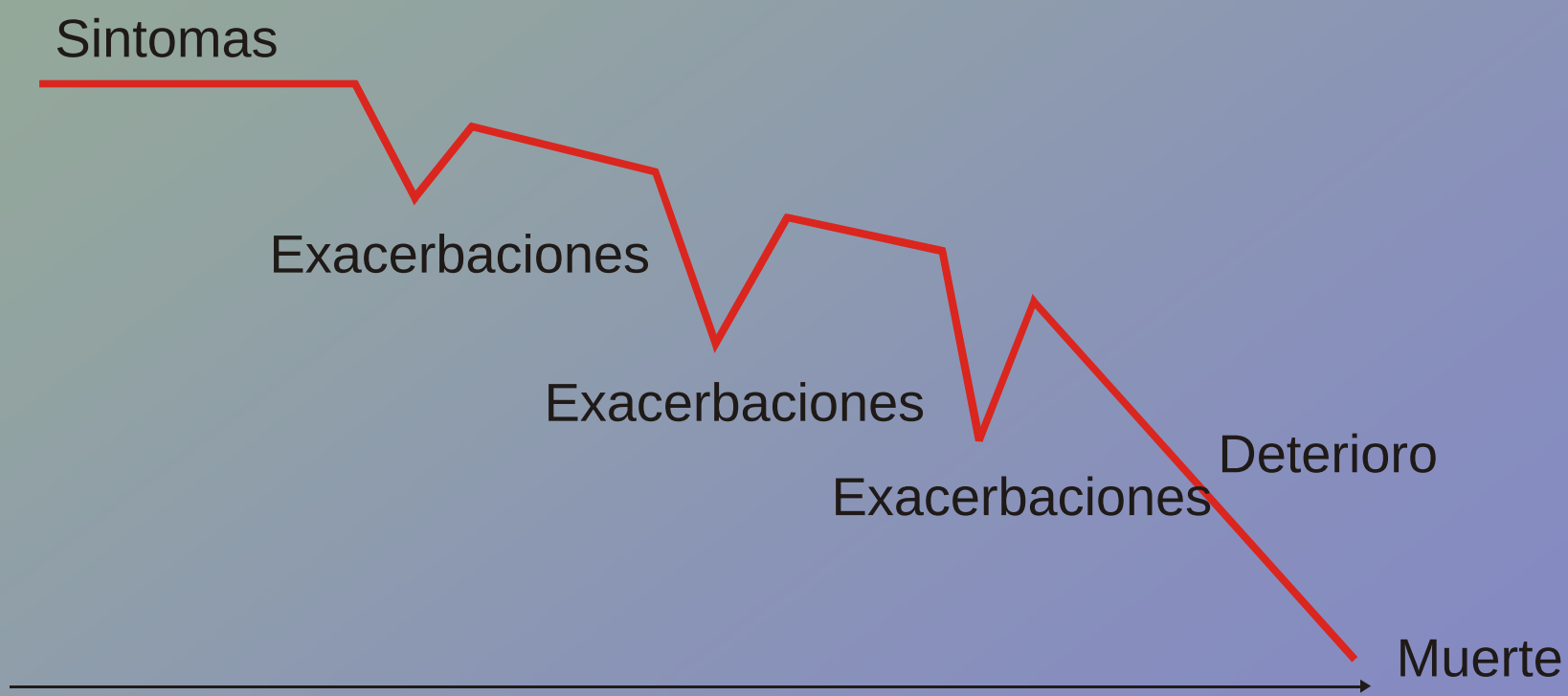
NUEVOS TRATAMIENTOS DE LA EPOC

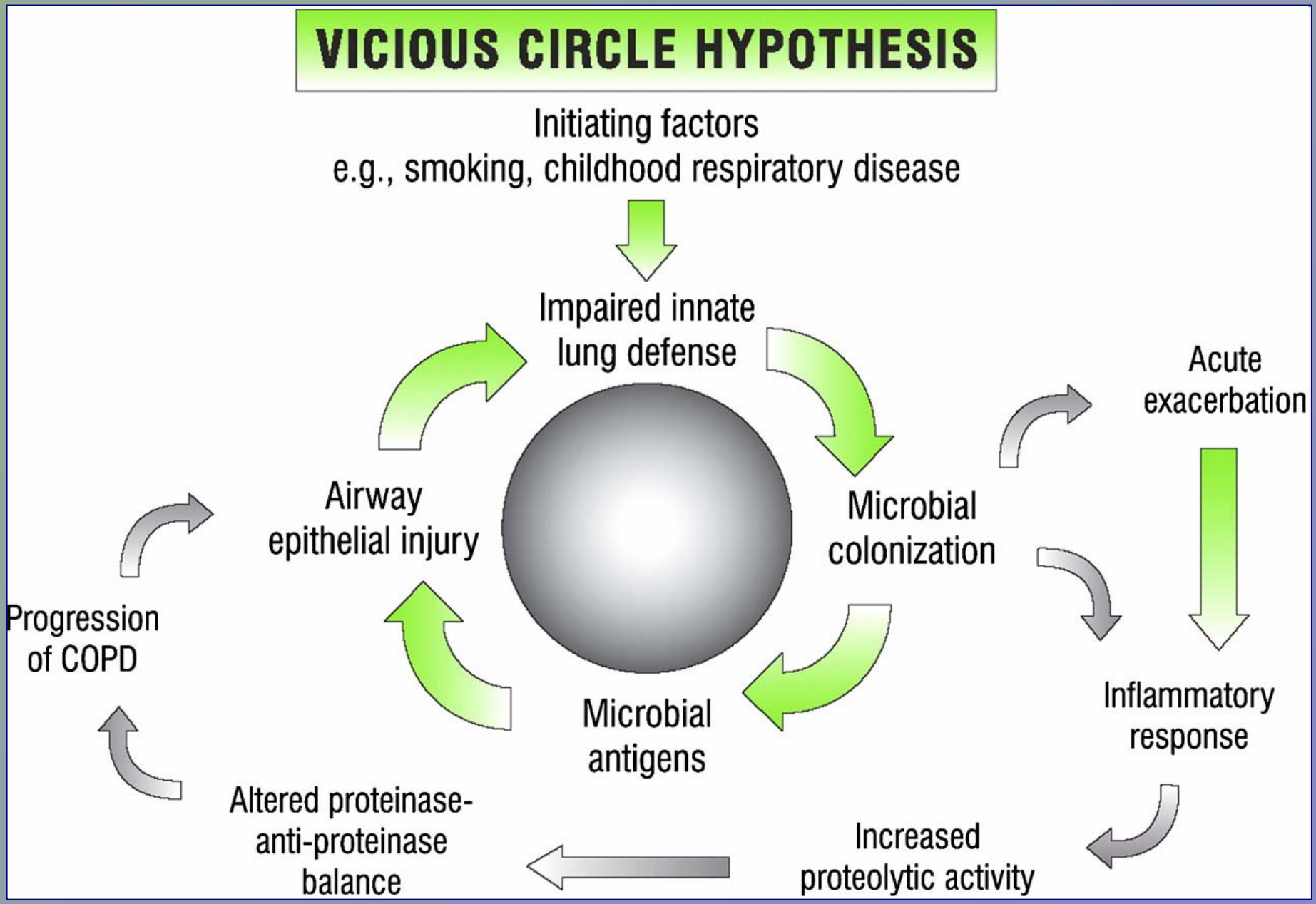
- **Mejorar los tratamientos existentes: nuevos LAMA, ultra-LABA y corticoides. Nuevas asociaciones.**
- **Mejorar la resistencia a los esteroides: teofilinas.**
- **Reducir las exacerbaciones:**
  - **Antibióticos: quinolonas y macrólidos.**
  - **Nuevos antiinflamatorios: roflumilast.**

Consecuencias de las exacerbaciones de la EPOC

- Exacerbaciones son responsables del 50% de los costes sanitarios directos (IBERPOC).

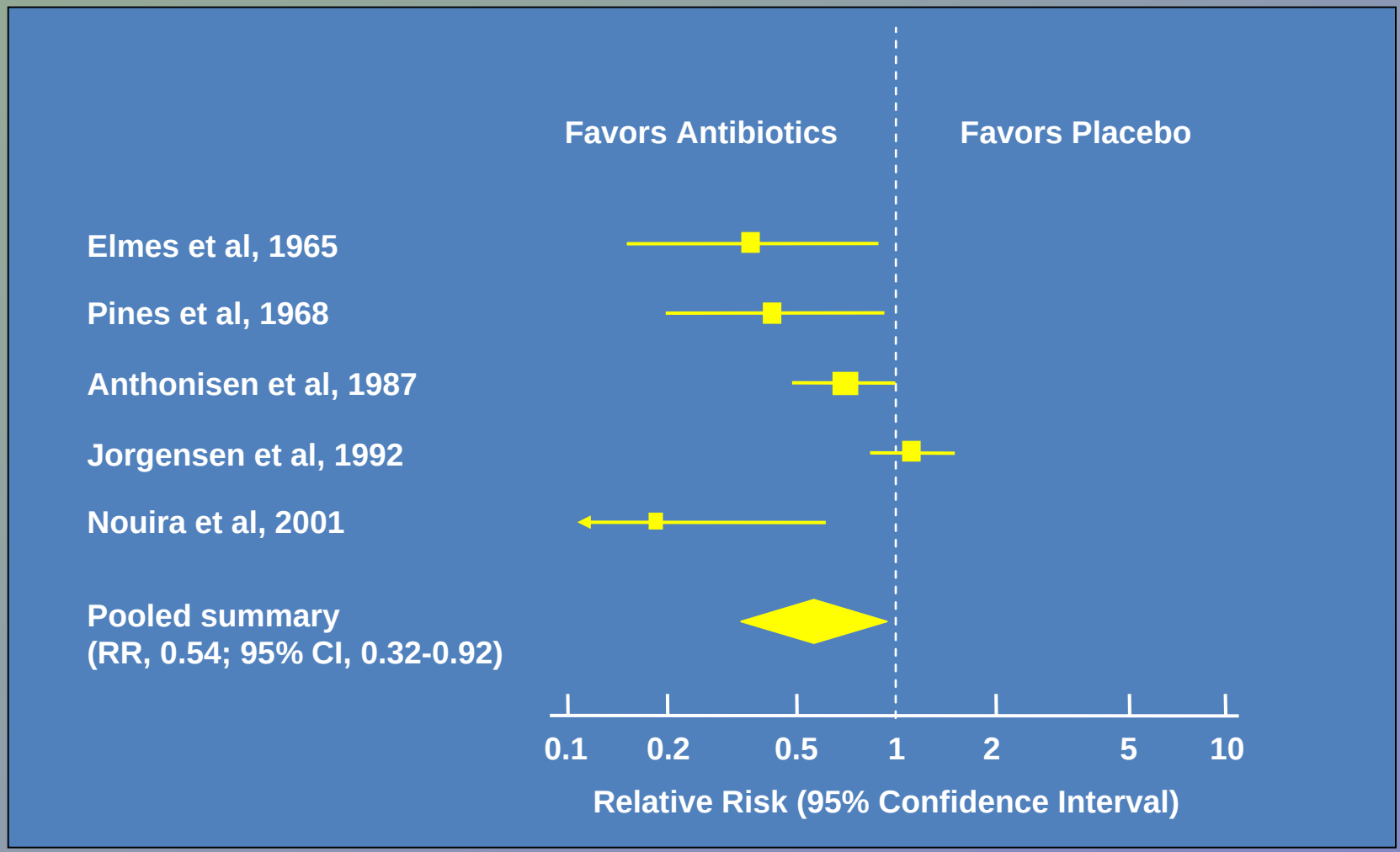
Historia natural de un paciente con EPOC





Sethi S. N Engl J Med 2008;359:2355-6

Meta-analysis of Efficacy: Antibiotic Therapy and Risk for Treatment Failure



Quon BS et al. Contemporary Management of Acute Exacerbations of COPD. Chest 2008; 133:756-66

Long-term Erythromycin Therapy Is Associated with Decreased Chronic Obstructive Pulmonary Disease Exacerbations

Terence A. R. Seemungal[1,2*], Tom M. A. Wilkinson[2*], John R. Hurst[2], Wayomi R. Perera[2], Ray J. Sapsford[2], and Jadwiga A. Wedzicha[2]

Am J Respir Crit Care Med Vol 178. pp 1139–1147, 2008

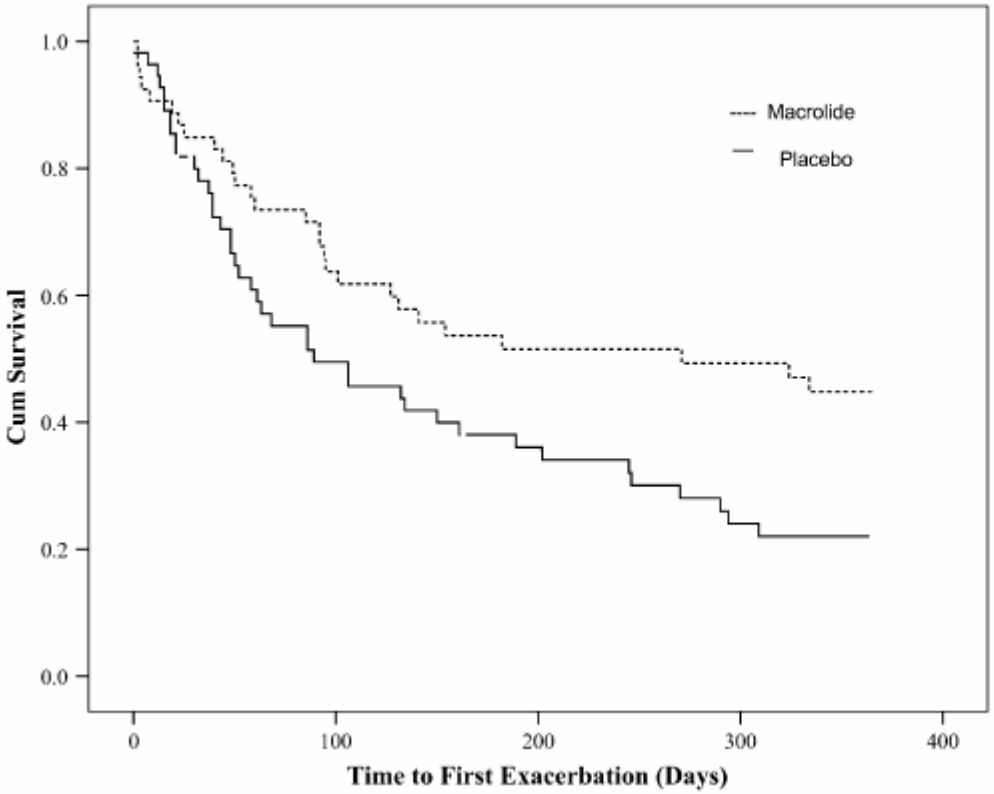


Figure 3. Kaplan-Meier curves showing the proportion of patients without an exacerbation (Cum Survival axis) versus time to the first exacerbation between macrolide and placebo arms of the study. Patients in the macrolide arm were less likely to have a first exacerbation than those in the placebo arm ($P = 0.02$).

Eritromicina 250 mg/12 h vs placebo x 12 meses

Sethi *et al. Respiratory Research* 2010, **11**:10
http://respiratory-research.com/content/11/1/10

RESPIRATORY RESEARCH

RESEARCH **Open Access**

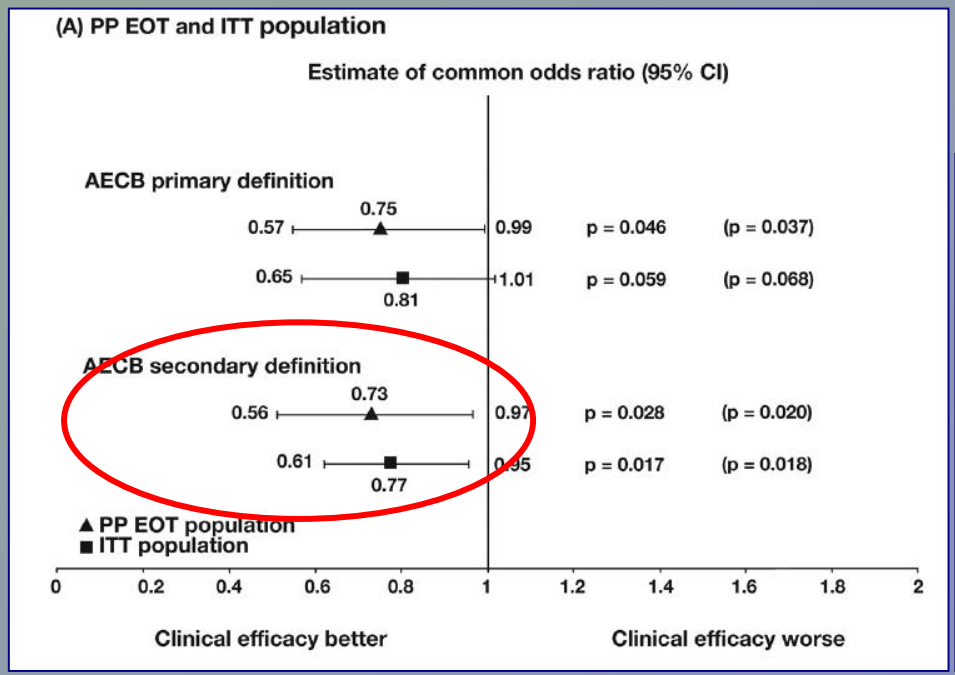
Pulsed moxifloxacin for the prevention of exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial

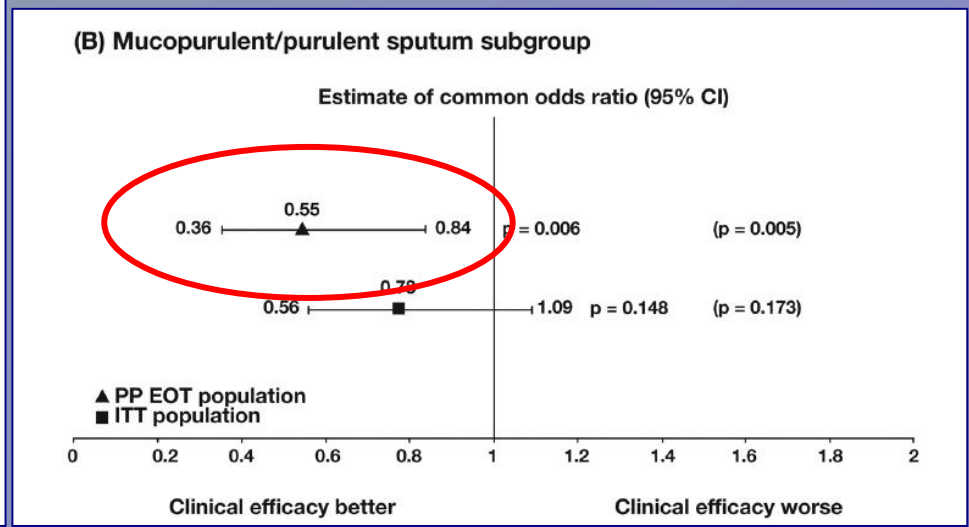
Sanjay Sethi[1*], Paul W Jones[2], Marlize Schmitt Theron[3], Marc Miravitlles[4], Ethan Rubinstein[5], Jadwiga A Wedzicha[6], Robert Wilson[7], the PULSE Study group

Moxifloxacino 400 mg/d x 5 d vs placebo

n: 573 vs n: 584

Duración: 48 semanas





Efectividad Macrólidos *vs* Quinolonas en AEPOC.

Comparative Effectiveness of Macrolides and Quinolones for Patients Hospitalized With Acute Exacerbations of Chronic Obstructive Pulmonary Disease (AECOPD)

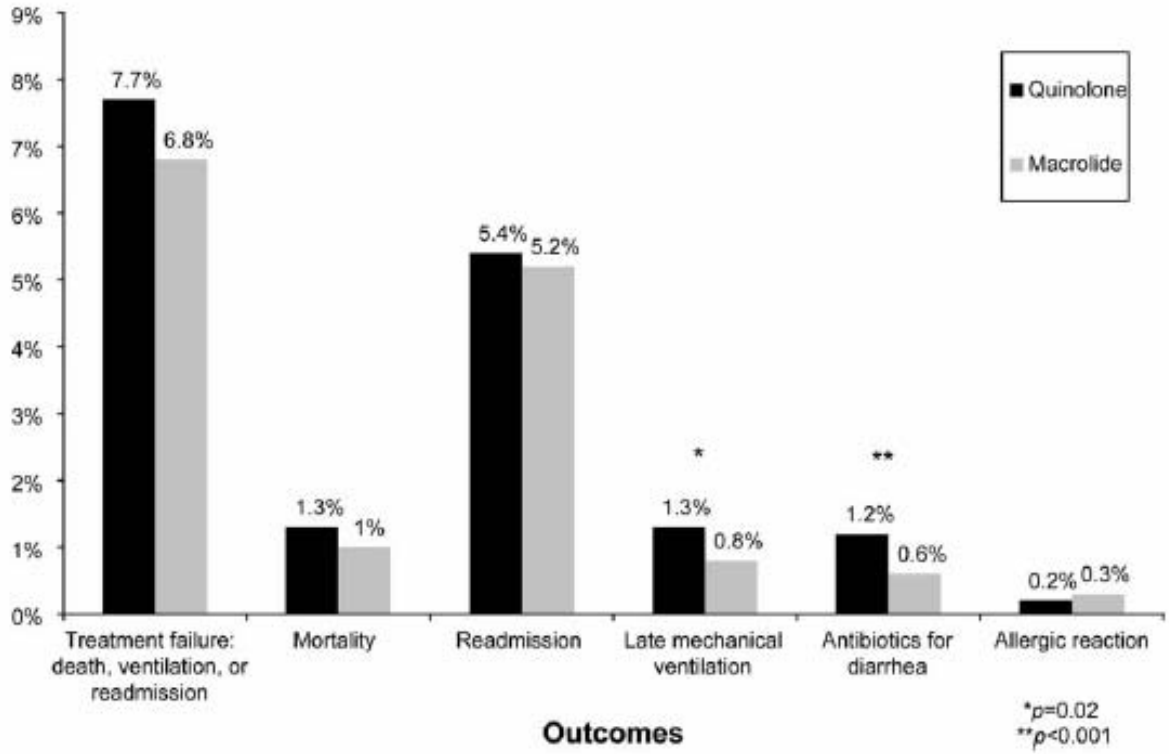


FIGURE 1. Outcomes of quinolone-treated and macrolide-treated patients in the sample matched by propensity score.

Rothberg MB et al. J Hosp Med 2010; 5:261-7.

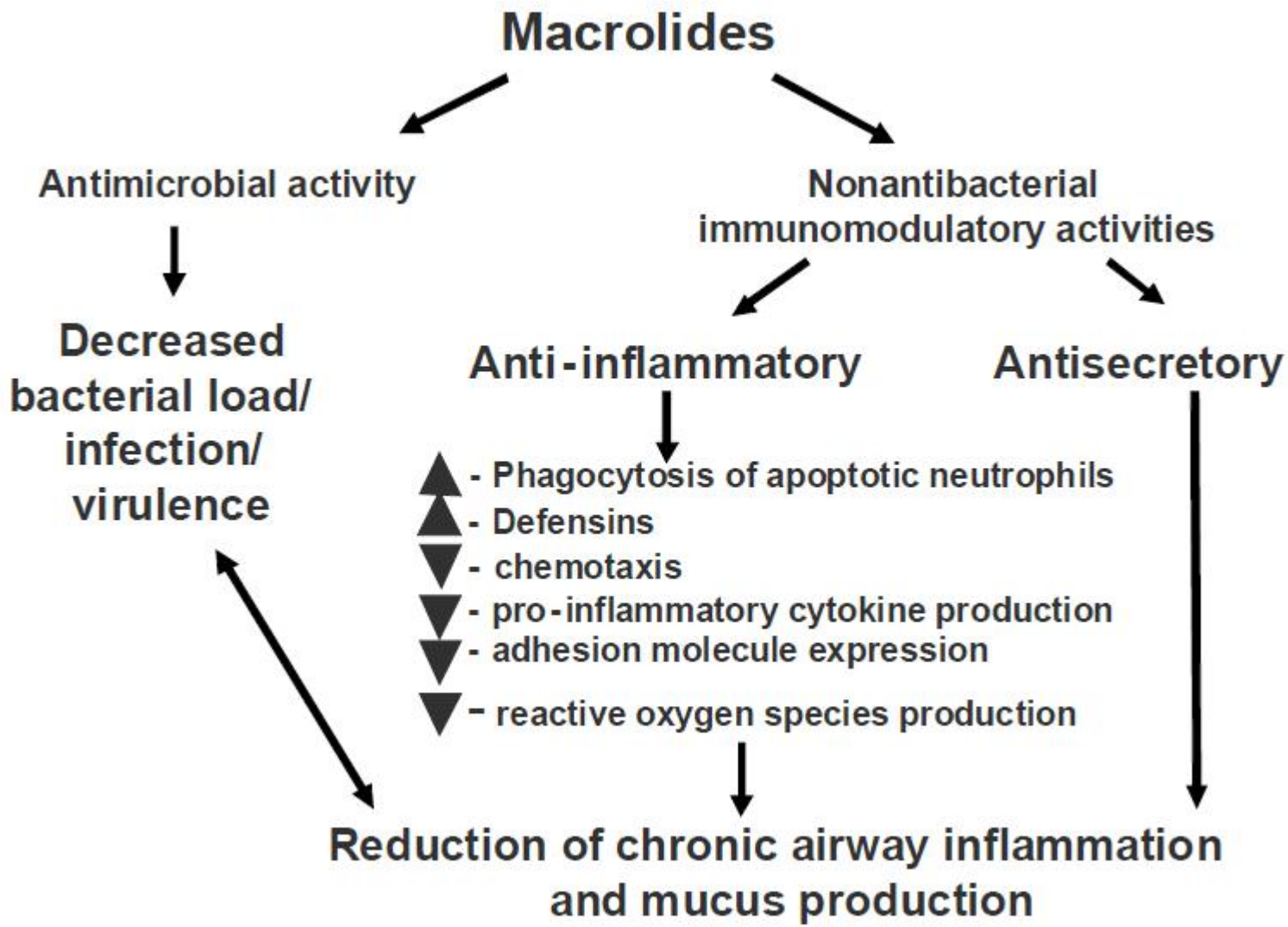


Figure 3 Potential beneficial effects of macrolides in COPD patient.

Effect of 6 Months of Erythromycin Treatment on Inflammatory Cells in Induced Sputum and Exacerbations in Chronic Obstructive Pulmonary Disease

Respiration 2010;80:445–452

Zhi-Yi He[a] Li-Mei Ou[b] Jian-Quan Zhang[a] Jing Bai[a] Guang-Nan Liu[a]
Mei-Hua Li[a] Jing-Min Deng[a] William MacNee[c] Xiao-Ning Zhong[a]

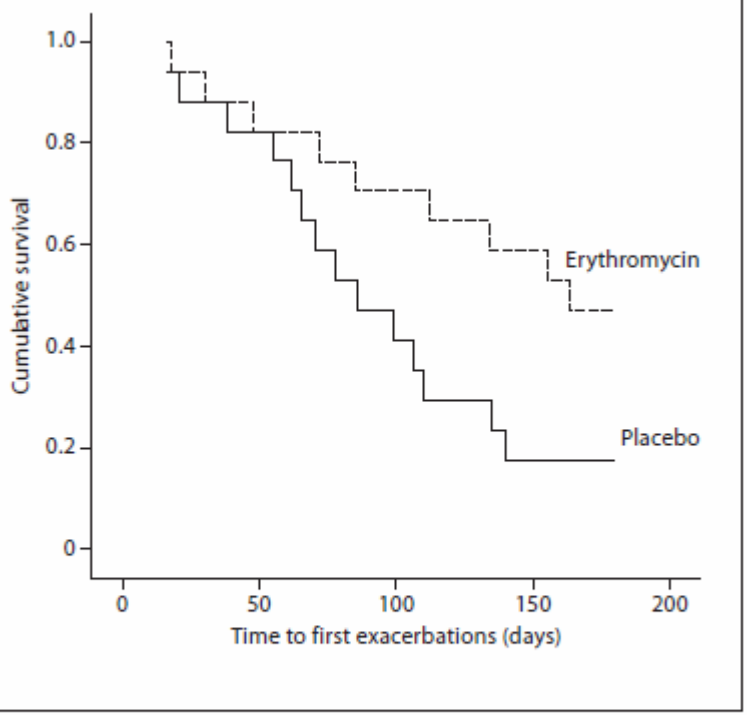


Fig. 3. Kaplan-Meier curves showing the proportion of patients without an exacerbation (cumulative survival analysis) versus time to the first exacerbation for the placebo and erythromycin groups (p = 0.032).

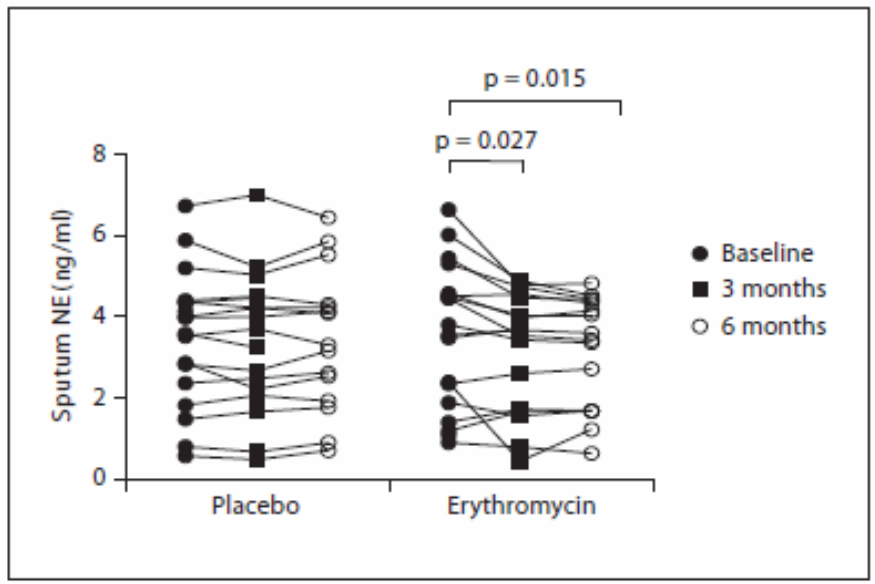


Fig. 2. Effect of erythromycin on induced sputum NE concentration (ng/ml) in COPD patients at baseline and after 3 and 6 months of treatment (p = 0.024, erythromycin vs. placebo after 6 months of treatment).

The Effect of Clarithromycin on Inflammatory Markers in Chronic Obstructive Pulmonary Disease: Preliminary Data

Ann Pharmacother 2004;38:1400-5.

Ilknur Basyigit, Fusun Yildiz, Sevgiye Kacar Ozkara, Elif Yildirim, Hasim Boyaci, and Ahmet Ilgazli

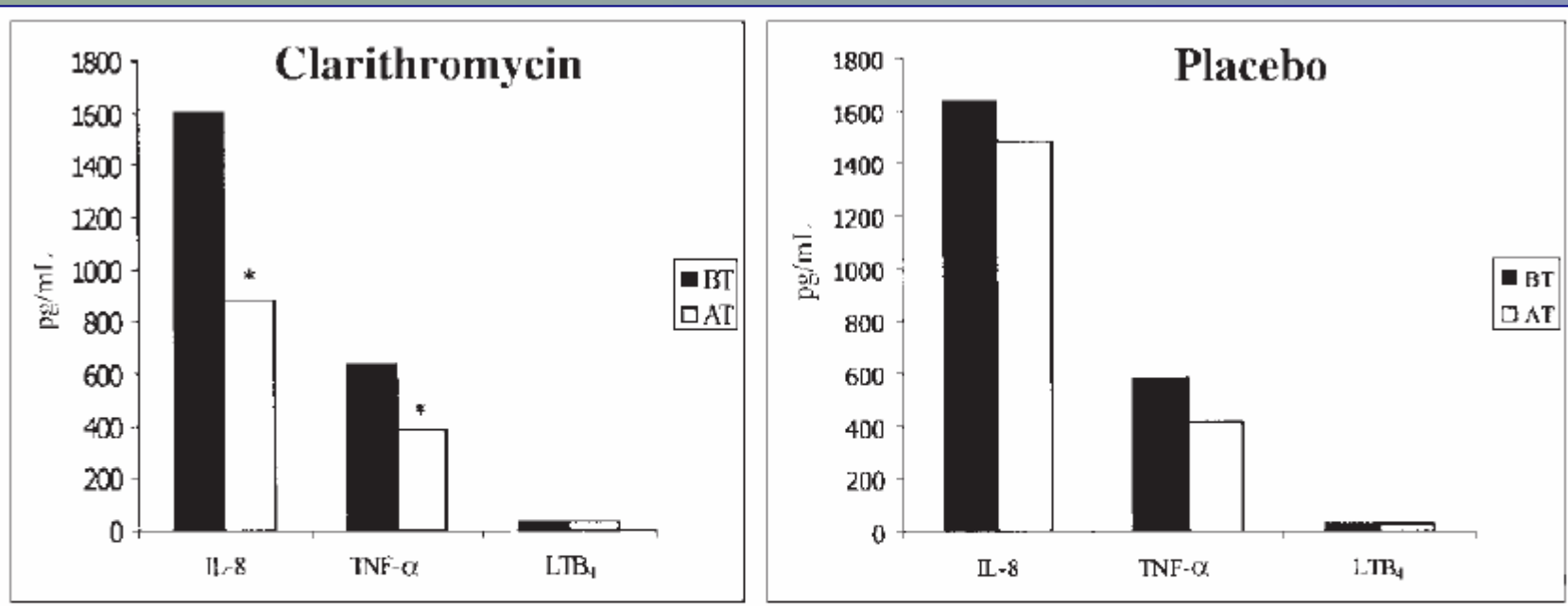


Figure 1. Levels of induced-sputum inflammatory markers in the clarithromycin and placebo groups before and after treatment. AT = after treatment; BT = before treatment; IL-8 = interleukin-8; LTB_4 = leukotriene B_4; TNF-α = tumor necrosis factor-α. *$p < 0.05$ before versus after treatment.

Clarithromycin Prevents Smoke-induced Emphysema in Mice

Yutaka Nakanishi[1,2], Dale Kobayashi[3], Yasuo Asano[1], Takanobu Sakurai[1], Masato Kashimura[1], Shigeru Okuyama[1], Yukio Yoneda[2], Steven D. Shapiro[4], and Kiyoshi Takayama[1,5*]

Am J Respir Crit Care Med Vol 179. pp 271–278, 2009

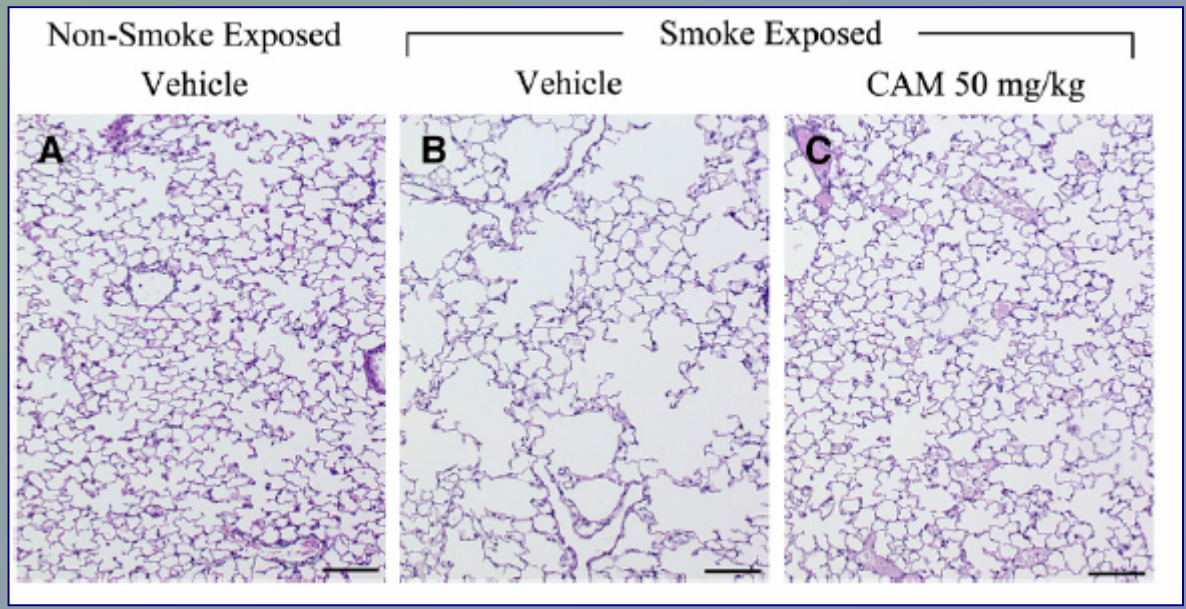


Figure 1. Clarithromycin (CAM) protects against emphysema induced by cigarette smoke in mice. The lungs were inflated using neutral-buffered 10% formalin and embedded. Hematoxylin and eosin (H&E) staining was used for the morphologic analysis. Representative H&E sections are presented for non-smoke–exposed mice (*A*), mice exposed to smoke for 6 months (*B*), and smoke-exposed mice treated with CAM at 50 mg/kg (*C*). *Scale bar*, 100 μm.

REFLEXIONES

- **LAMA y LABA representan la piedra angular del tratamiento de la EPOC.**

- **El futuro inmediato serán las asociaciones de LAMA + ultraLABA.**

- **Hay información preliminar para sugerir la utilización de teofilinas a dosis bajas en caso de resistencia a corticoides.**

- **¿Recuperar la utilización de ciclos de antibióticos? ¿macrólidos?.**

Muchas gracias por su atención.