Semana de Congresos y Jornadas Nacionales

Sociedad Argentina de Pediatría

Dirección de Congresos y Eventos

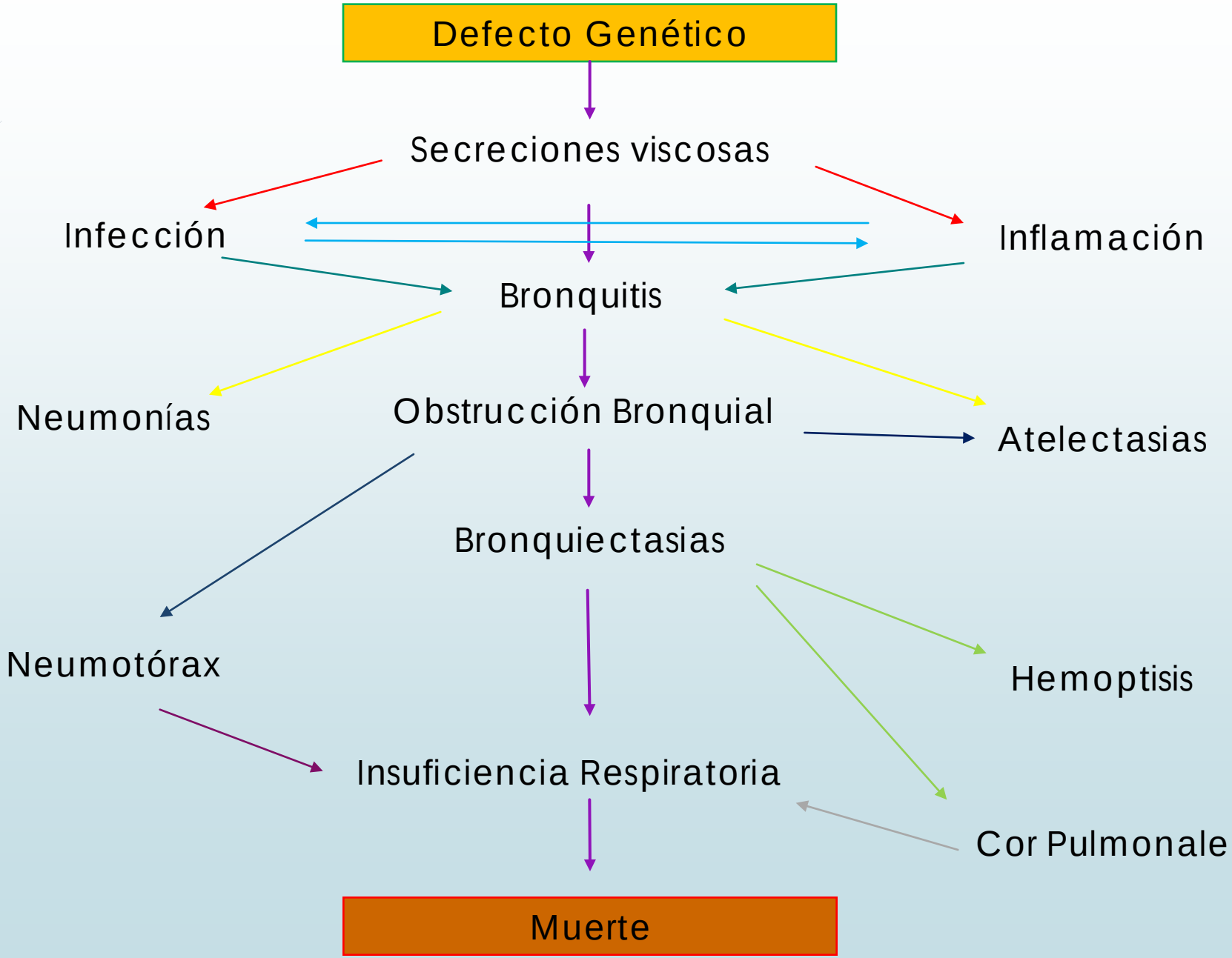
Por un niño sano en un mundo mejor

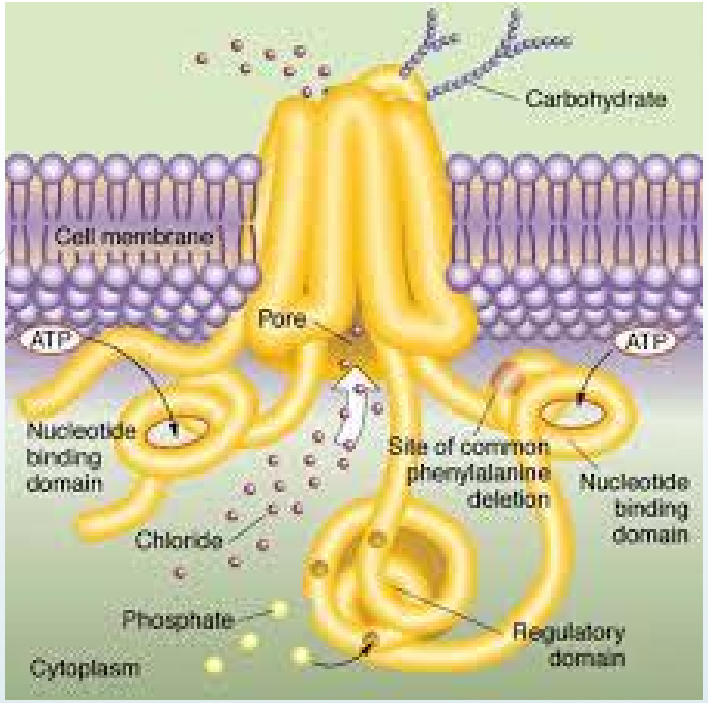
NUEVAS ESTRATEGIAS TERAPÉUTICAS EN FIBROSIS QUÍSTICA

Dra Virginia D'Alessandro
Pediatra Neumonóloga
Servicio de Neumonología
Htal de Niños "Sor María Ludovica"

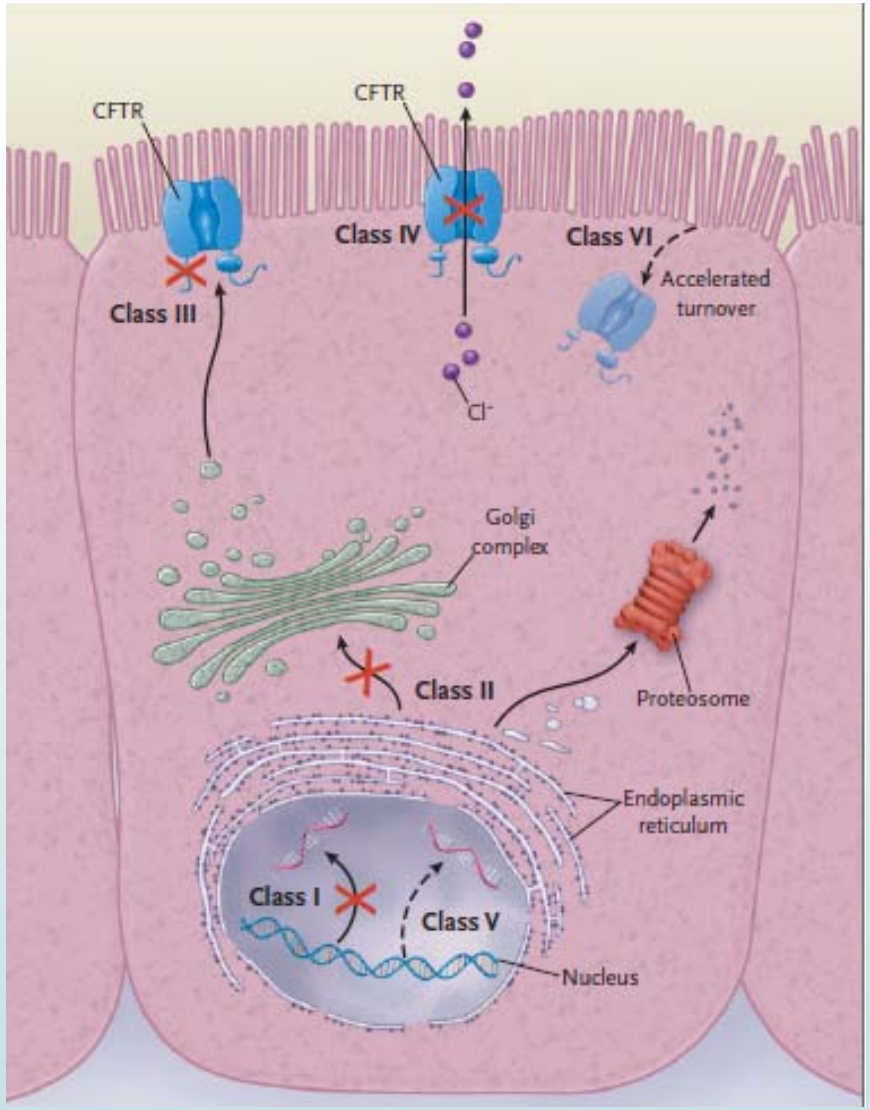
Objetivos

- Revisar conceptos generales de la Fibrosis Quística (FQ)
- Analizar los avances terapéuticos en las distintas áreas respiratorias en FQ


Defecto Genético
Secreciones viscosas
Infección
Inflamación
Bronquitis
Neumonías
Obstrucción Bronquial
Atelectasias
Bronquiectasias
Neumotórax
Hemoptisis
Insuficiencia Respiratoria
Cor Pulmonale
Muerte



CFTR es una proteína quinasa A que permite el paso de Cl^- a través de la membrana celular de células epiteliales secretoras



Categorías de las CFTR mutaciones

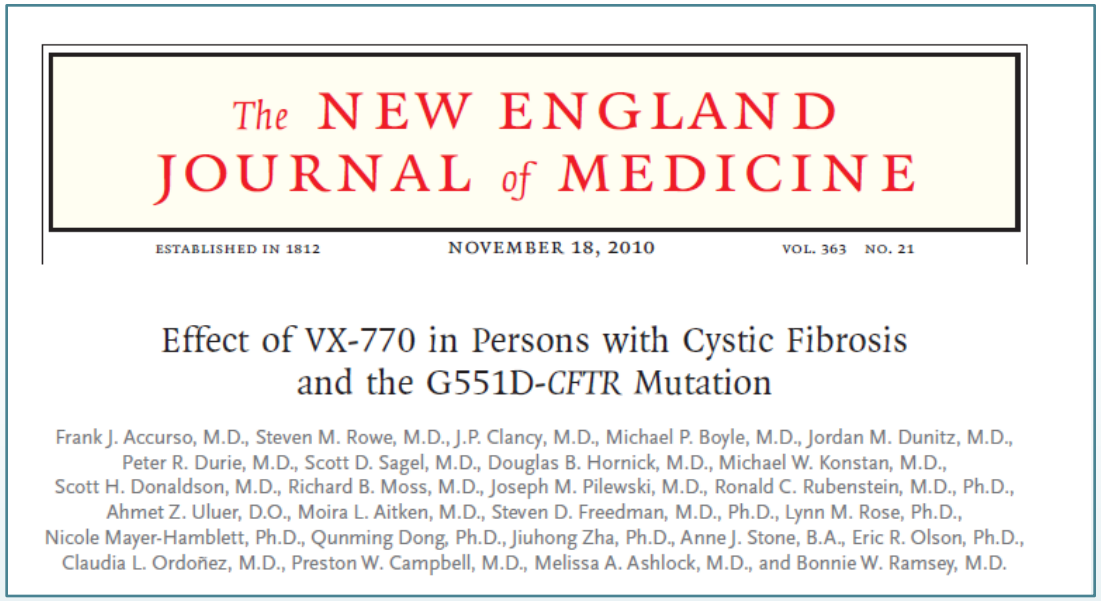
Potenciadores/Correctores

Potenciadores: Incrementan el tiempo de actividad del CFTR (Clase III y IV)

Correctores: Ayudan a “corregir” el defecto del CFTR

G551D: Clase III

- Sustitución de glicina por ácido aspártico en el Aa 551
- 4-5% de pacientes con FQ
- Importancia del registro FQ



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 18, 2010 VOL. 363 NO. 21

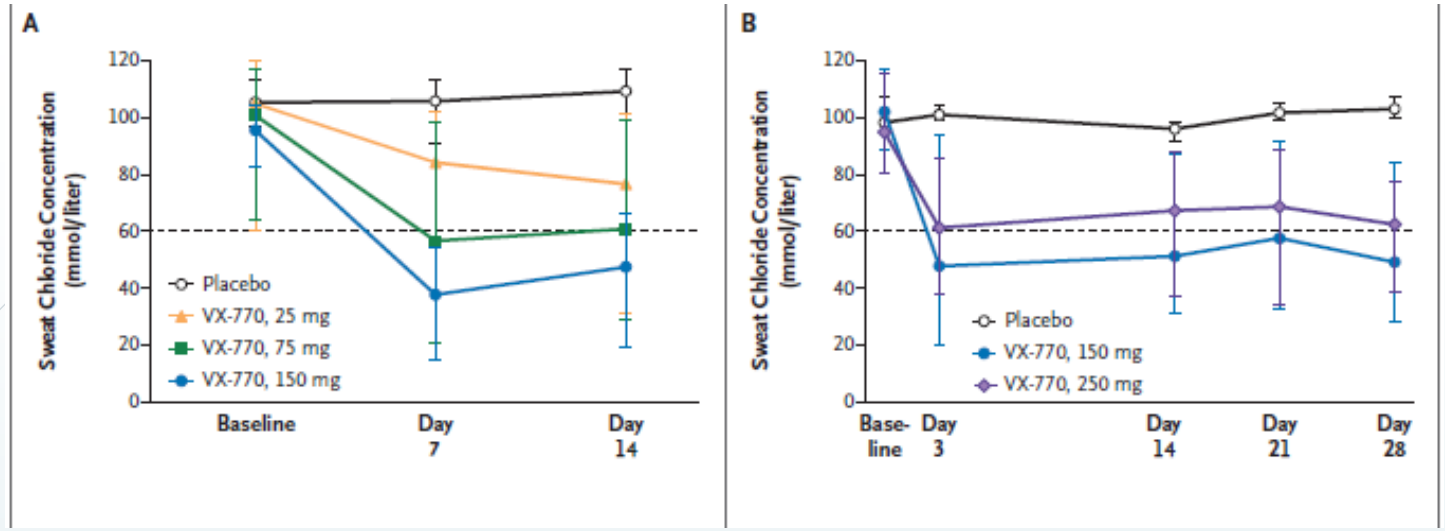
Effect of VX-770 in Persons with Cystic Fibrosis and the G551D-*CFTR* Mutation

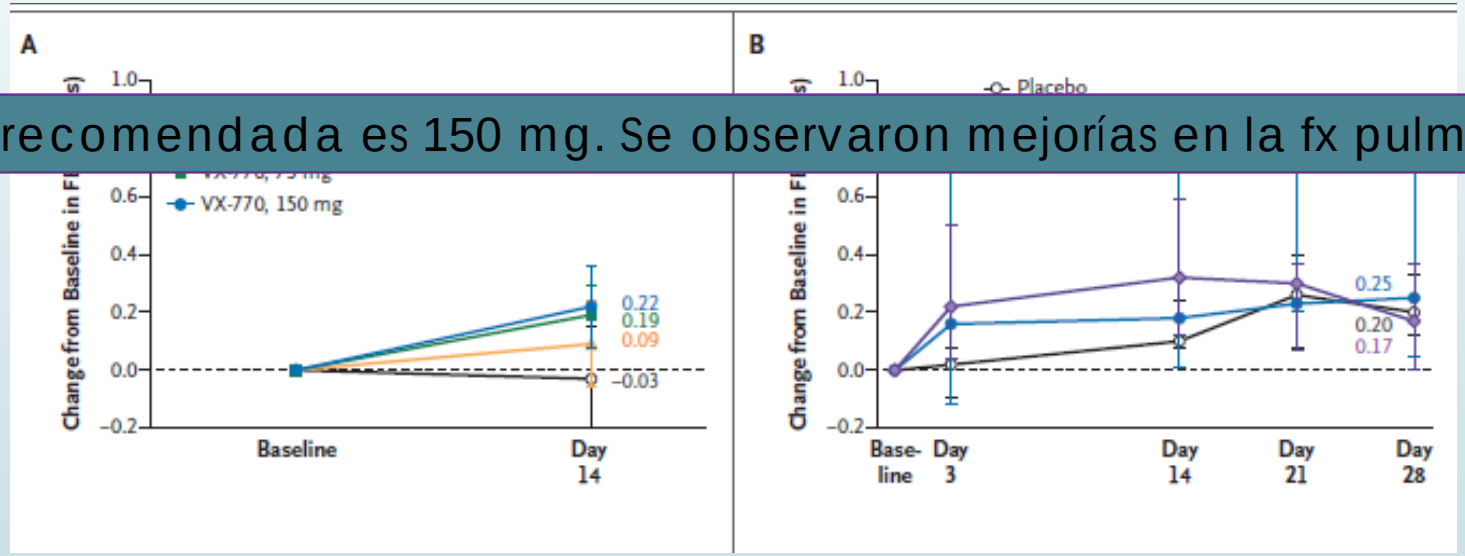
Frank J. Accurso, M.D., Steven M. Rowe, M.D., J.P. Clancy, M.D., Michael P. Boyle, M.D., Jordan M. Dunitz, M.D., Peter R. Durie, M.D., Scott D. Sagel, M.D., Douglas B. Hornick, M.D., Michael W. Konstan, M.D., Scott H. Donaldson, M.D., Richard B. Moss, M.D., Joseph M. Pilewski, M.D., Ronald C. Rubenstein, M.D., Ph.D., Ahmet Z. Uluer, D.O., Moira L. Aitken, M.D., Steven D. Freedman, M.D., Ph.D., Lynn M. Rose, Ph.D., Nicole Mayer-Hamblett, Ph.D., Qunming Dong, Ph.D., Jiuhong Zha, Ph.D., Anne J. Stone, B.A., Eric R. Olson, Ph.D., Claudia L. Ordoñez, M.D., Preston W. Campbell, M.D., Melissa A. Ashlock, M.D., and Bonnie W. Ramsey, M.D.

- Estudio randomizado, placebo control, doble ciego y multicéntrico
- Dos fases: VX-770 cada 12hs (25,75 y 150 mg) por 14 días

  VX-770 cada 12hs(150 y 250 mg) por 28 días
- 39 adultos
- Cambios en el potencial transmembrana, test del sudor , función pulmonar y efectos adversos

N Engl J Med 2010;363:1991-2003.



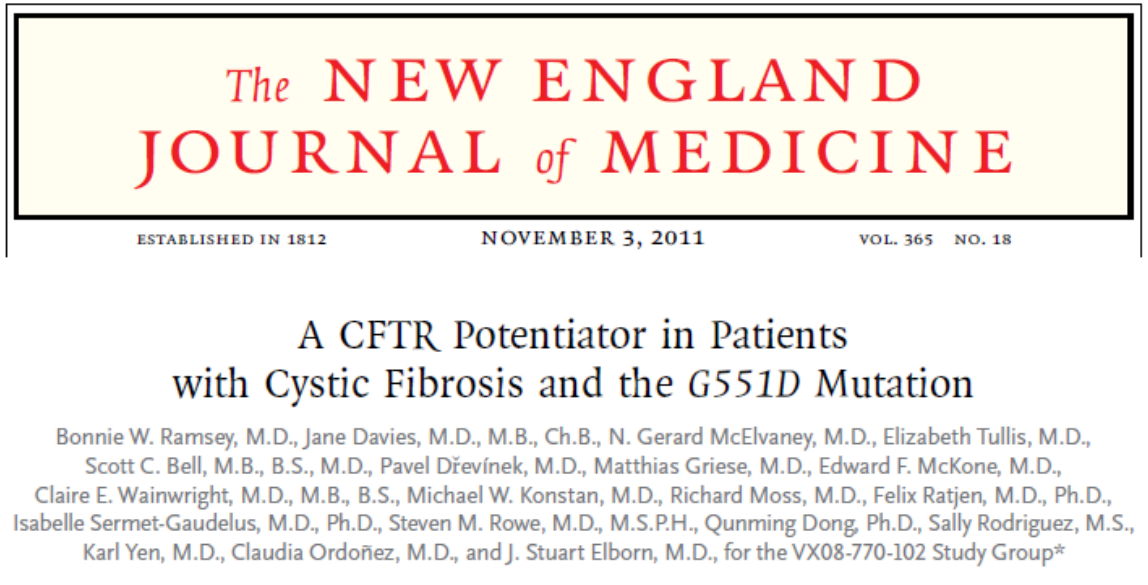


Conclusión: Dosis recomendada es 150 mg. Se observaron mejorías en la fx pulmonar

- RESULTADOS: Cambios en el potencial transmembrana, disminución de valores del test del sudor en 59.5 mmol/l (150 MG)

  X de cambio en 8.7 % en el VEF_1 (150 MG)

N Engl J Med 2010;363:1991-2003.



The NEW ENGLAND JOURNAL of MEDICINE

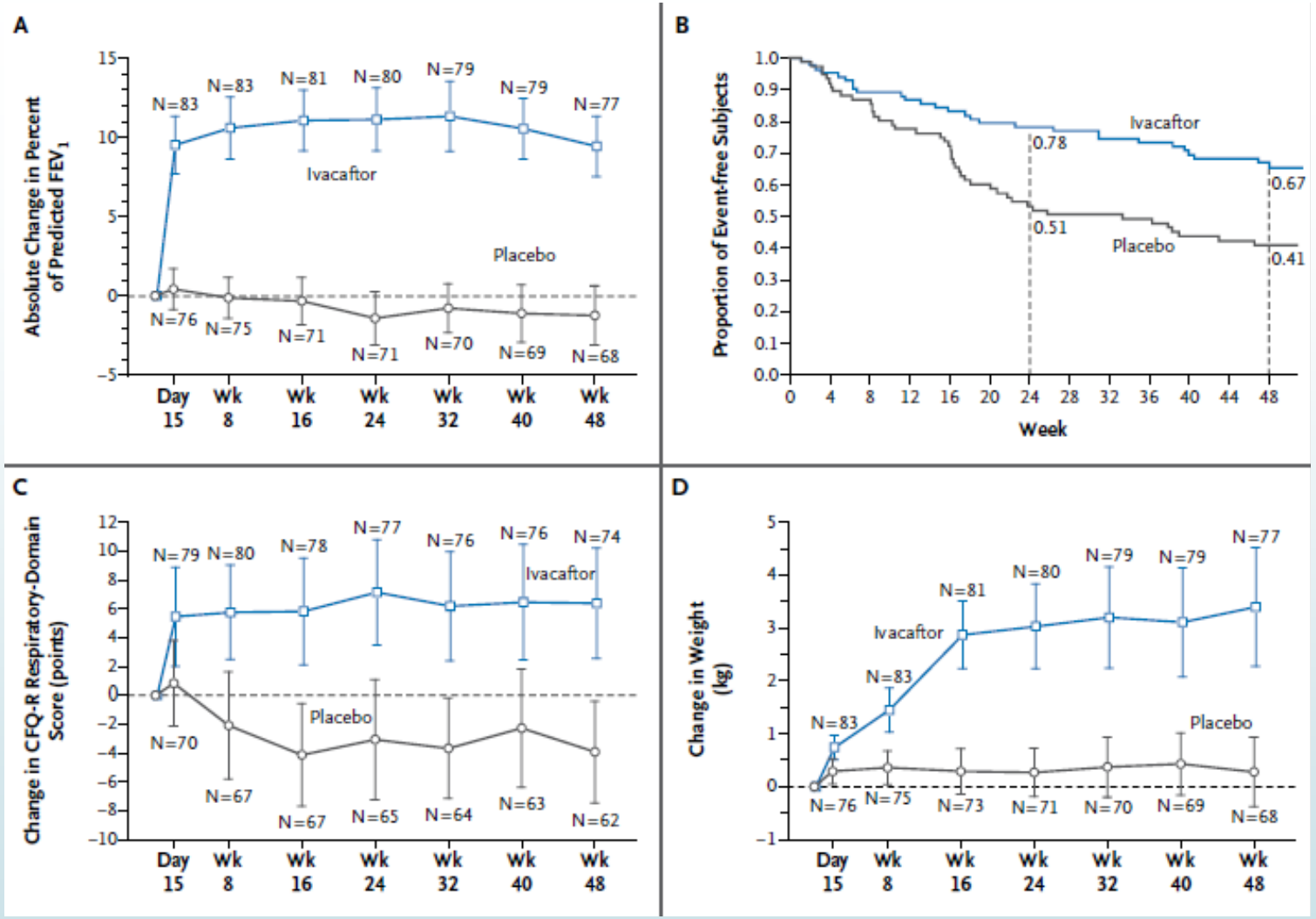
ESTABLISHED IN 1812 NOVEMBER 3, 2011 VOL. 365 NO. 18

A CFTR Potentiator in Patients with Cystic Fibrosis and the *G551D* Mutation

Bonnie W. Ramsey, M.D., Jane Davies, M.D., M.B., Ch.B., N. Gerard McElvaney, M.D., Elizabeth Tullis, M.D., Scott C. Bell, M.B., B.S., M.D., Pavel Dřevínek, M.D., Matthias Griese, M.D., Edward F. McKone, M.D., Claire E. Wainwright, M.D., M.B., B.S., Michael W. Konstan, M.D., Richard Moss, M.D., Felix Ratjen, M.D., Ph.D., Isabelle Sermet-Gaudelus, M.D., Ph.D., Steven M. Rowe, M.D., M.S.P.H., Qunming Dong, Ph.D., Sally Rodriguez, M.S., Karl Yen, M.D., Claudia Ordoñez, M.D., and J. Stuart Elborn, M.D., for the VX08-770-102 Study Group*

- Estudio randomizado, doble ciego, en FQ mayores de 12 años
- G551D
- VX-770 cada 12 hs por 48 semanas
- VEF_1 a las 24 semanas

N Engl J Med 2011;365:1663-72.



Conclusiones: Mejorías en la fx pulmonar a las 2 semanas y sostenidas hasta la semana 48.

Menor número de exacerbaciones pulmonares

Aumento en el peso, y disminución de síntomas respiratorios

N Engl J Med 2011;365:1663-72.

Efficacy and Safety of Ivacaftor in Patients Aged 6 to 11 Years with Cystic Fibrosis with a *G551D* Mutation

Jane C. Davies[1,2], Claire E. Wainwright[3], Gerard J. Canny[4], Mark A. Chilvers[5], Michelle S. Howenstine[6], Anne Munck[7], Jochen G. Mainz[8], Sally Rodriguez[9], Haihong Li[9], Karl Yen[9], Claudia L. Ordoñez[9], and Richard Ahrens[10]; on behalf of the VX08-770-103 (ENVISION) Study Group

Am J Respir Crit Care Med Vol 187, Iss. 11, pp 1219–1225, Jun 1, 2013

ENVISION: Cambio del 10% en VEF_1 y + 2,8 kg

ORIGINAL ARTICLE

Clinical Mechanism of the Cystic Fibrosis Transmembrane Conductance Regulator Potentiator Ivacaftor in G551D-mediated Cystic Fibrosis

Steven M. Rowe[1], Sonya L. Heltshe[2,3], Tanja Gonska[4], Scott H. Donaldson[5], Drucy Borowitz[6], Daniel Gelfond[6], Scott D. Sagel[7], Umer Khan[3], Nicole Mayer-Hamblett[2,3], Jill M. Van Dalfsen[3], Elizabeth Joseloff[8], and Bonnie W. Ramsey[2,3]; on behalf of the GOAL Investigators of the Cystic Fibrosis Foundation Therapeutics Development Network

Am J Respir Crit Care Med Vol 190, Iss 2, pp 175–184, Jul 15, 2014

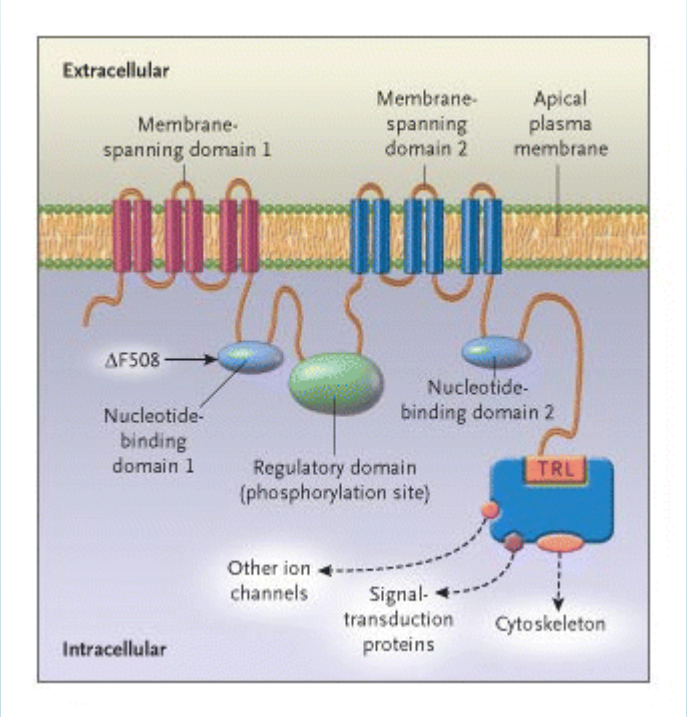
GOAL: Fase 4

VEF_1 del 6,7% y IMC 0.8 K/m^2

Menor número de hospitalizaciones y carga de *Pseudomonas*

ΔF508:Clase II

- Pérdida de la fenilalanina en la posición 508 que lleva a la inestabilidad del nucleótido dominio 1 (NBD1)
- NBD1 interacciona de manera no efectiva con dominio 2 (MSD2)



Registro Nacional(RENAFQ)/ Registro Pcial BsAs

- Registro Nacional: ΔF508/ ΔF508 ~ 70%

  http://www.anlis.gov.ar

- Registro Pcial BsAs: ΔF508/ ΔF508 35%

  http://www.registrofqprovinciabuenosaires.org/

Lumacaftor: VX-809

- Estabilizar el interdominio NBD-MSD y reducir el no procesamiento
- El efecto en el transporte de Cl^- es en un cuarto a un tercio del observado con ivacaftor en G551D
- Combinación de VX809-VX770 logra de un 50 a 100% de fx del CFTR
- La asociación es todavía inferior al logrado del ivacaftor como monoterapia

ORIGINAL ARTICLE

Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del *CFTR*

C.E. Wainwright, J.S. Elborn, B.W. Ramsey, G. Marigowda, X. Huang, M. Cipolli, C. Colombo, J.C. Davies, K. De Boeck, P.A. Flume, M.W. Konstan, S.A. McColley, K. McCoy, E.F. McKone, A. Munck, F. Ratjen, S.M. Rowe, D. Waltz, and M.P. Boyle, for the TRAFFIC and TRANSPORT Study Groups*

N Engl J Med 2015;373:220-31.

- Estudio randomizado, doble ciego, en FQ mayores de 12 años (TRAFFIC y TRANSPORT)
- Homocigotas ΔF508
- Lumacaftor a 600 mg/día o 400mg cada 12 hs combinado con ivacaftor 250mg dos veces por día
- Incluyeron 1108 pacientes con una media de VEF_1 de 61%
- 24 semanas

Conclusiones: Combinación bien tolerada. Los efectos adversos más significativos fueron el aumento de enzimas hepáticas, creatinina, hemoptisis y disnea

Los resultados son modestos en comparación con los obtenidos con ivacaftor para clase III

Todos los cambios observados en el porcentaje del VEF_1, IMC y disminución de las exacerbaciones fueron observados mientras los pacientes recibían su terapia habitual, por lo tanto la mejoría clínica esperada de la combinación Lumacaftor-Ivacaftor se produce cuando se usan en forma concomitante con la terapia habitual de la FQ.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 23, 2017 VOL. 377 NO. 21

Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del

Jennifer L. Taylor-Cousar, M.D., Anne Munck, M.D., Edward F. McKone, M.D., Cornelis K. van der Ent, M.D., Ph.D., Alexander Moeller, M.D., Christopher Simard, M.D., Linda T. Wang, M.D., Edward P. Ingenito, M.D., Ph.D., Charlotte McKee, M.D., Yimeng Lu, Ph.D., Julie Lekstrom-Himes, M.D., and J. Stuart Elborn, M.D.

- 509 p mayores de 12 años (TZF-IVF vs Placebo)
- 475 p completaron las 24 semanas
- Objetivo primario: Cambio del VEF1% (24 sem)
- Objetivos secundarios: IMC, exacerbación respiratoria
- Fase 3: EEUU, Canadá y Europa desde enero 2015 a enero 2017

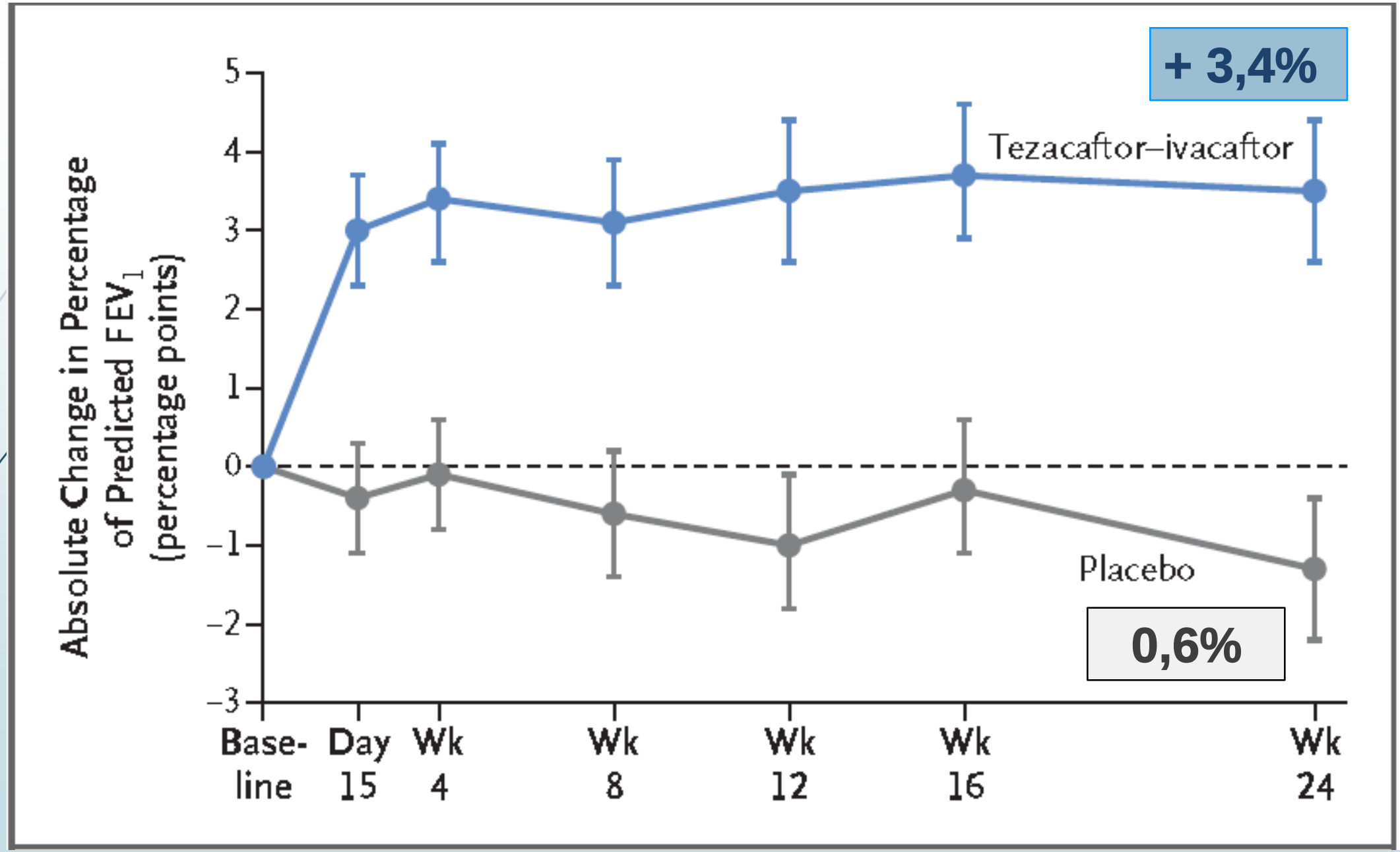
Table 1. Demographic and Clinical Characteristics at Baseline.*

Characteristic	Placebo Group (N = 256)	Tezacaftor–Ivacaftor Group (N = 248)
Female sex — no. (%)	125 (48.8)	121 (48.8)
Age at screening		
Mean — yr	25.7±9.5	26.9±11.2
Distribution — no. (%)		
<18 yr	58 (22.7)	58 (23.4)
≥18 yr	198 (77.3)	190 (76.6)
Geographic region — no. (%)		
North America	68 (26.6)	59 (23.8)
Europe	188 (73.4)	189 (76.2)
Percentage of predicted FEV_1		
Mean value	60.4±15.7	59.6±14.7
Distribution — no. (%)		
<40%	24 (9.4)	23 (9.3)
≥40% to <70%	152 (59.4)	157 (63.3)
≥70% to ≤90%	73 (28.5)	65 (26.2)
>90%	7 (2.7)	2 (0.8)
Missing data	0	1 (0.4)
Body-mass index†	21.12±2.88	20.96±2.95
Sweat chloride — mmol/liter	100.5±10.2	101.3±10.9
CFQ-R respiratory domain score‡	69.9±16.6	70.1±16.8
Pseudomonas aeruginosa–positive — no. (%)	182 (71.1)	185 (74.6)

Tezacaftor
100 mg día

más

Ivacaftor
150 mg dos veces por día


+ 3,4%
Absolute Change in Percentage of Predicted FEV1 (percentage points)
5
4
3
2
1
0
−1
−2
−3
Tezacaftor–ivacaftor
Placebo
0,6%
Base-line
Day 15
Wk 4
Wk 8
Wk 12
Wk 16
Wk 24

Resultados (más)

- Disminución del número de exacerbaciones

Table 2. Primary and Secondary Efficacy End Points.*

End Point	Placebo Group (N = 256)	Tezacaftor–Ivacaftor Group (N = 248)	Difference (95% CI)	P Value
Primary end point				
Absolute change from baseline in percentage of predicted FEV_1 through wk 24 (95% CI) — percentage points	–0.6 (–1.3 to 0.0)	3.4 (2.7 to 4.0)	4.0 (3.1 to 4.8)	<0.001
Key secondary end points				
Relative change from baseline in percentage of predicted FEV_1 through wk 24 (95% CI) — %	–0.5 (–1.7 to 0.6)	6.3 (5.1 to 7.4)	6.8 (5.3 to 8.3)	<0.001
Pulmonary exacerbation through wk 24 — no. of events (annualized estimated event rate)	122 (0.99)	78 (0.64)	0.65 (0.48 to 0.88) †	0.005
Absolute change from baseline in BMI at wk 24 (95% CI)	0.12 (0.03 to 0.22)	0.18 (0.08 to 0.28)	0.06 (–0.08 to 0.19)	0.41
Absolute change from baseline in CFQ-R respiratory domain score through wk 24 (95% CI)	–0.1 (–1.6 to 1.4)	5.0 (3.5 to 6.5)	5.1 (3.2 to 7.0)	—
Other secondary end points				
Absolute change from baseline in BMI-for-age z score from baseline at wk 24 (95% CI) ‡	–0.02 (–0.10 to 0.06)	–0.06 (–0.14 to 0.02)	–0.04 (–0.15 to 0.07)	—
Absolute change from baseline in sweat chloride concentration through wk 24 (95% CI) — mmol/liter	0.2 (–0.8 to 1.2)	–9.9 (–10.9 to –8.9)	–10.1 (–11.4 to –8.8)	—

Conclusiones

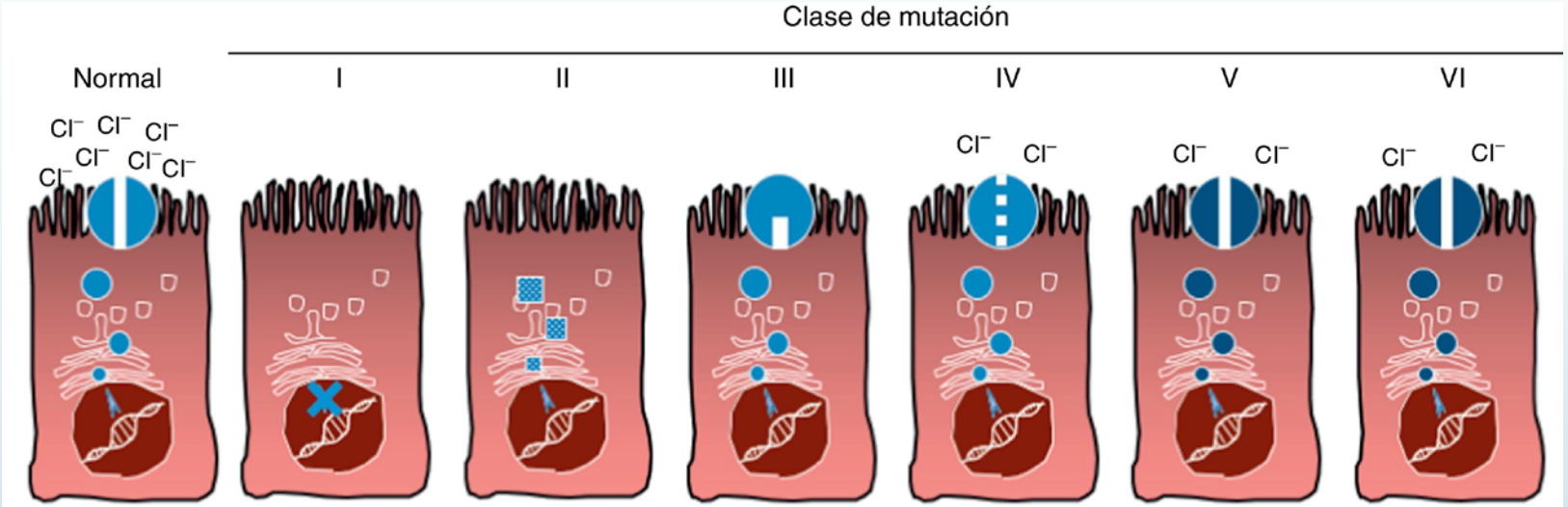
- TZF/IVF fue una terapia bien tolerada.
- Cómo seguimos?????

Alternativas en estudio: ΔF508

- Riociguat es un estimulador de la guanilato ciclasa en la vía de ON (Fase 2a)(1)(Se discontinuó)
- Inhibidores de fosfodiesterasa (sildenafil y valdanafil)(2)

1. Blonder JP y col. A novel GSNOR inhibitor with potent bronchodilator effetcs and CFTR potentiation activity. *Peds Pulm 2013, Supl* . 36
2. Robert R y col. Structural analog of sildenafil identified as a novel corrector of the F508del-CFTR trafficking defect. *Mol Pharmacol 2008;73:478-489*

Mutaciones CLASE I: G542X



Defecto molecular	No síntesis	Bloqueo procesamiento	Bloqueo de regulación	Reducción de conducción	Síntesis reducida	Vida media reducida
Alteración funcional	No se sintetiza proteína	Defecto de plegamiento	Defecto de apertura canal	Defecto transporte iones	Descenso síntesis proteína	Descenso vida media proteína
Principales mutaciones	Gly542X Trp128X Arg553X 621+1G→T	Phe508del Asn1303Lys Ile507del Arg560Thr	Gly551Asp Gly178Arg Gly551Ser Ser549Asn	Arg117His Arg347Pro Arg117Cys Arg334Trp	3849+10kbC→T 2789+5G→A 3120+1G→A 5T	4326delTC Gln1412X 4279insA

ATALUREN: PTC124

- Mutaciones sin sentido o “stop codón”
- Ataluren anula la señal y permite la síntesis proteica
- 10% pacientes con FQ
- Estudios publicados desde 2008, 2011

Año 2016 en fase 3 se suspendió por no cumplir con los objetivos primarios y secundarios

Table 4 Ataluren (PTC124) Clinical Trials

Reference *Design*	*CFTR* Mutation	Population	Treatment *Duration*	Results
Kerem (2008)[25] *Randomized*	Nonsense mutation (class I mutations)	Age 18–56 years Cycle 1: N = 23 Cycle 2: N = 21 $FEV_1 \geq 40\%$	Cycle 1: ATA 4 mg/kg at breakfast, 4 mg/kg at lunch, 8 mg/kg with dinner Cycle 2: ATA 10 mg/kg at breakfast, 10 mg/kg at lunch, 20 mg/kg with dinner *For each cycle: 14 days on treatment, then 14 days off treatment*	• Patients with NPD within normal range: ◦ Cycle 1: 13 (57%) ($P = 0.0003$) ◦ Cycle 2: 9 (43%) ($P = 0.02$) • Mean change in NPD chloride transport from baseline to day 14: ◦ Cycle 1: –7.1 mV ± 7 ($P < 0.0001$) ◦ Cycle 2: –3.7 mV ± 7.3 ($P = 0.032$) • Weight change from baseline: ◦ Cycle 1: 0.6 kg ± 0.6 ($P < 0.001$) ◦ Cycle 2: Maintained
Sermet-Gaudelus (2010)[64] *Randomized, crossover*	Class I mutations	Age 6–18 years N = 30 $FEV_1 \geq 40\%$	ATA 4 mg/kg at breakfast, 4 mg/kg at lunch, 8 mg/kg with dinner ATA 10 mg/kg at breakfast, 10 mg/kg at lunch, 20 mg/kg with dinner *14 days of treatment → 14 day WO period → 14 days of treatment (groups traded treatments after WO)*	• Mean change in chloride transport from baseline to end of cycle 2: ◦ Low-to-high dosing: –4.6 mV ($P = 0.037$) ◦ High-to-low dosing: –3.9 mV ($P = 0.046$) • Number of patients with NPD changes of at least –5 mV at the end of cycle 2: ◦ Low-to-high dosing: 8 (53%) (95% CI, 30 to 76; $P < 0.0001$) ◦ High-to-low dosing: 7 (47%) (95% CI, 24 to 70, $P = 0.0003$)
Wilschanski (2011)[65] *Randomized*	Class I mutations	Age 19–57 years N = 19 $FEV_1 \geq 40\%$	ATA 4 mg/kg at breakfast, 4 mg/kg at lunch, 8 mg/kg with dinner ATA 10 mg/kg at breakfast, 10 mg/kg at lunch, 20 mg/kg with dinner *12 wks*	• Mean change in chloride transport from baseline to 12 wks: ◦ Low dose: –6.8 mV ($P = 0.004$) ◦ High dose: –3.4 mV ($P = 0.025$) ◦ Combined groups: –5.4 mV ($P < 0.001$) • Number of patients with NPD change of at least –5 mV at 12 wks: ◦ Low dose: 7 (64%) (95% CI, 35 to 86; $P < 0.001$) ◦ High dose: 4 (57%) (95% CI, 23 to 87; ($P < 0.001$) ◦ Combined groups: 11 (61%) (95% CI, 39 to 80; ($P < 0.001$)
Rowe (2012)[66] *Randomized, double-blind, placebo-controlled*	Class I mutations	Age ≥ 6 years N = 238 FEV_1 40–90%	ATA 10 mg/kg at breakfast, 10 mg/kg at lunch, 20 mg/kg with dinner PBO *48 wks*	• Relative mean FEV_1 percent predicted at 48 wks ($P = 0.124$): ATA, –2.5%; PBO, –5.5% • Pulmonary exacerbation rate ($P = 0.099$): ATA, 23% lower than PBO • Patient not treated with chronic inhaled antibiotics, relative change in percent FEV_1 predicted at 48 wks compared with PBO ($P = 0.015$): ATA, 6.7%

ATA = ataluren; *CFTR* = cystic fibrosis transmembrane conductance regulator gene; FEV_1 = forced expiratory volume in 1 second; mV = millivolt; CI = confidence interval; NPD = nasal potential difference

- Todavía no está aprobado por la FDA
- Interacciona con la tobramicina

MICROORGANISMOS

- *Pseudomonas aeruginosa*
- *Sthaphylococcus aureus meticilino resistente (SAMR)*
- *ABPA*

Pseudomonas aeruginosa(Pa)
Primo infección

- Una **nueva infección por Pa** lleva a infección crónica con un deterioro de la fx pulmonar, de aspectos nutricionales, más número de exacerbaciones y alta mortalidad
- No hay evidencia de qué rápido hay que tratarla **PERO SE RECOMIENDA NO RETRASARSE MÁS DE 4 SEMANAS**
- Opciones terapéuticas: Tobramicina nebulizada por 28 días o Colistina por 3 meses Asociada a ciprofloxacina vía oral

Journal of Cystic Fibrosis 13 (2014) S23 – S42

Guías de diagnóstico y tratamiento de FQ: Ciprofloxacina más colistina nebulizada por 3 meses

Pseudomonas aeruginosa(Pa)
Infección Crónica

- Guía americanas recomiendan TOBRAMICINA en mayores de 6 años (6 meses alternos)
- **TOBRAMICINA**: Disponible en nebulización o Polvo seco
- **AZTREONAM**: Prolonga el tiempo para la realización del tratamiento endovenoso, mejora la calidad de vida

1. Smith A y col. *J of Cystic Fibrosis 2014;13:23-42*
2. McCoy KS y col. Inhaled aztreonam lysine for chronic aiway Pseudomonas aeruginosa in cystic fibrosis. *Am J Resp Crit Care Med 2008; 178:921-928*
3. Oerman CM y col. An 18 month study of the safety and efficacy of repeated courses of inhaled aztreonam lysine in cystic fibrosis. *Pediatr Pulmonol 2010; 45:1121-1134*

ELSEVIER

Journal of Cystic Fibrosis 12 (2013) 130–140

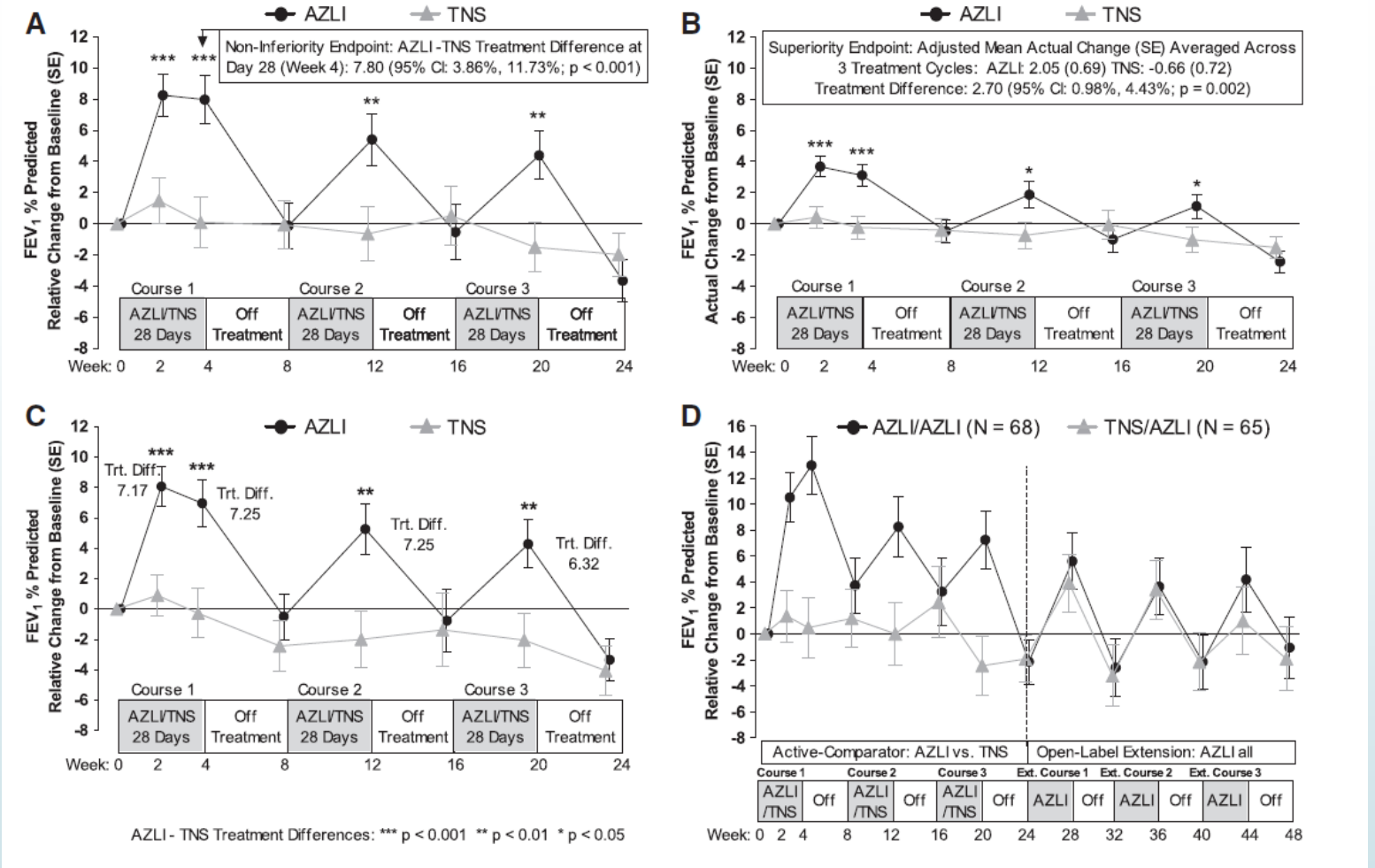
Journal of Cystic Fibrosis
www.elsevier.com/locate/jcf

Original Article

Inhaled aztreonam lysine vs. inhaled tobramycin in cystic fibrosis: A comparative efficacy trial☆

Baroukh M. Assael [a,*], Tacjana Pressler [b], Diana Bilton [c], Michael Fayon [d], Rainald Fischer [e], Raphael Chiron [f], Mario LaRosa [g], Christiane Knoop [h], Noel McElvaney [i], Sandra A. Lewis [j], Mark Bresnik [k], A. Bruce Montgomery [j], Christopher M. Oermann [l]
For the AZLI Active Comparator Study Group [l]

- AZT (75 mg 3 veces por día) vs TB (300 mg dos veces por día)
- Mayores de 6 años
- 3 meses alternos, y luego finalizaron todos con AZT (3 meses alternos)



Conclusiones: AZT demostró mejorar la fx pulmonar, disminuir las exacerbaciones , mejorar los síntomas respiratorios.

ELSEVIER

Journal of Cystic Fibrosis 14 (2015) 507 – 514

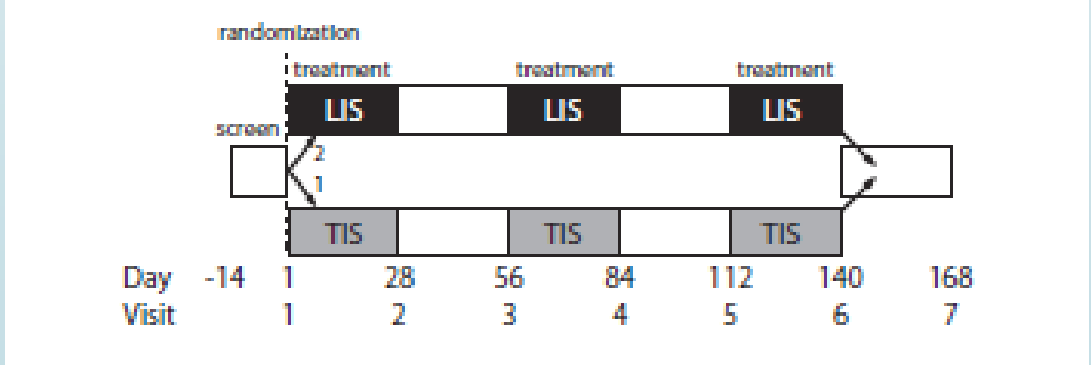
Journal of Cystic Fibrosis
www.elsevier.com/locate/jcf

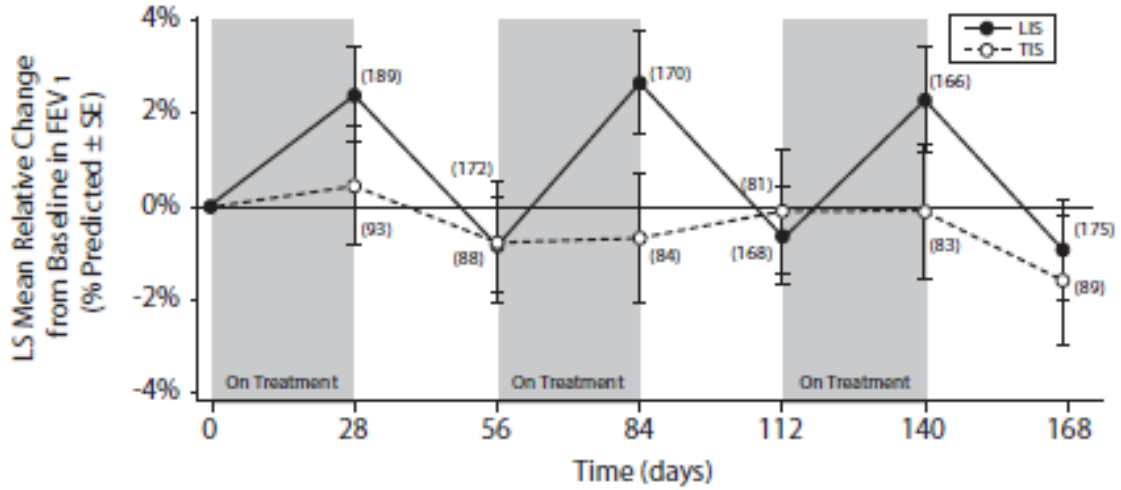
Original Article

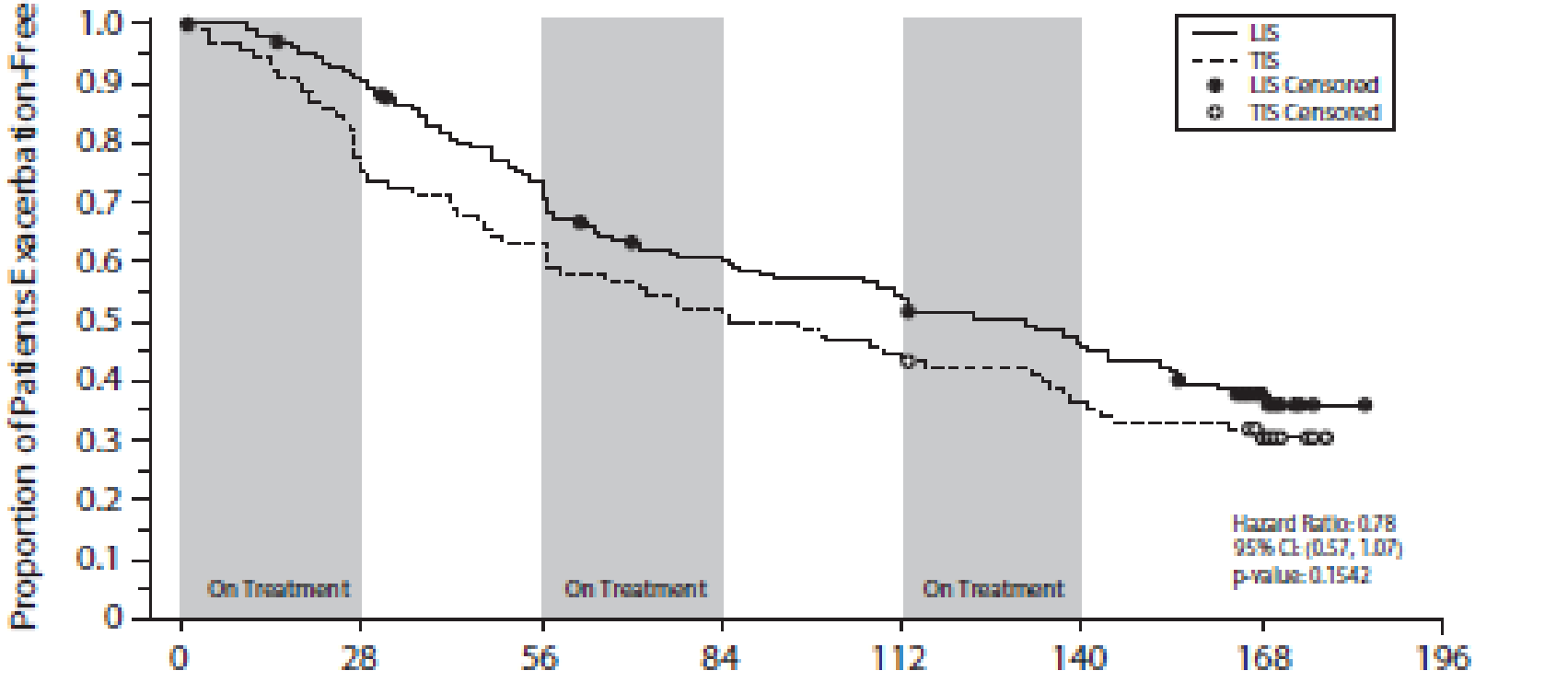
A phase 3, open-label, randomized trial to evaluate the safety and efficacy of levofloxacin inhalation solution (APT-1026) versus tobramycin inhalation solution in stable cystic fibrosis patients☆

J. Stuart Elborn [a], David E. Geller [b], Douglas Conrad [c], Shawn D. Aaron [d], Alan R. Smyth [e], Rainald Fischer [f], Eitan Kerem [g], Scott C. Bell [h,i], Jeffery S. Loutit [j], Michael N. Dudley [j], Elizabeth E. Morgan [j], Donald R. VanDevanter [k], Patrick A. Flume [l,m,*]

- Estudio mulitcéntrico, randomizado que compara la eficacia y seguridad de LIS vs TB en pacientes con FQ e infección crónica con Pa
- Mayores de 12 años




LS Mean Relative Change from Baseline in FEV 1 (% Predicted ± SE)
4%
2%
0%
-2%
-4%
LIS
TIS
(189)
(93)
(172)
(88)
(170)
(84)
(81)
(168)
(166)
(83)
(175)
(89)
On Treatment
On Treatment
On Treatment
0
28
56
84
112
140
168
Time (days)
Mean change from Baseline in P. aeruginosa sputum density (log10 CFU/g ± SE)
0
-0.5
-1.0
-1.5
(146)
(71)
(161)
(79)
(140)
(67)
(136)
(67)
(151)
(74)
LIS
TIS
On Treatment
On Treatment
On Treatment
0
28
56
84
112
140
168
Time (days)



Conclusiones: LIS demostró no ser inferior a la TB en el tto de pacientes con infección crónica por Pa

LIS estuvo asociado a una mejoría en el score clínico y disminución de la tasa de hospitalizaciones por exacerbaciones respiratorias

Es segura y efectiva y ofrece ser una alternativa de tratamiento

Sthapylococcus aureus (SAMR)

Trial record **1 of 1** for: nct01594827

Previous Study | Return to List | Next Study

Persistent Methicillin Resistant Staphylococcus Aureus Eradication Protocol (PMEP)

This study is currently recruiting participants. (see Contacts and Locations)

Verified March 2015 by Johns Hopkins University

Sponsor:
Michael Boyle

Collaborators:
Case Western Reserve University
Cystic Fibrosis Foundation Therapeutics

Information provided by (Responsible Party):
Michael Boyle, Johns Hopkins University

ClinicalTrials.gov Identifier:
NCT01594827

First received: May 7, 2012
Last updated: March 30, 2015
Last verified: March 2015
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

The prevalence of methicillin resistant Staphylococcus aureus (MRSA) respiratory infection in Cystic Fibrosis (CF) has increased dramatically over the last decade. Evidence suggests that persistent infection with MRSA may result in an increased rate of decline in FEV1 and shortened survival. Currently there are no conclusive studies demonstrating an effective aggressive treatment protocol for persistent MRSA respiratory infection in CF. Data demonstrating an effective and safe method of clearing persistent MRSA infection are needed.

The purpose of this study is to evaluate the safety and efficacy of a 28-day course of vancomycin for inhalation, 250 mg twice a day, (in combination with oral antibiotics) in eliminating MRSA from the respiratory tract of individuals with CF and persistent MRSA infection. Subjects will be assigned in a 1:1 ratio to either vancomycin for inhalation (250 mg twice a day) or taste matched placebo and will be followed for 3 additional months. In addition, both groups will receive oral rifampin, a second oral antibiotic (TMP-SMX or doxycycline, protocol determined), mupirocin intranasal cream and chlorhexidine body washes. Forty patients with persistent respiratory tract MRSA infection will be enrolled in this trial.

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Trial record 1 of 1 for: nct01537666
Previous Study | Return to List | Next Study

Inhaled Vancomycin Tolerability, Safety and Pharmacokinetics

This study has been completed.

Sponsor:
Savara Inc.

Collaborator:
INC Research Limited

Information provided by (Responsible Party):
Savara Inc.

ClinicalTrials.gov Identifier:
NCT01537666

First received: February 17, 2012
Last updated: March 3, 2014
Last verified: March 2014
History of Changes

Full Text View | Tabular View | Study Results | Disclaimer | How to Read a Study Record

Purpose

The study is carried out to evaluate the safety, tolerability and pharmacokinetics of AeroVanc inhalation powder in healthy volunteers, and in patients with cystic fibrosis.

Condition	Intervention	Phase
Healthy Cystic Fibrosis	Drug: AeroVanc Drug: IV vancomycin hydrochloride	Phase 1

Study Type: Interventional
Study Design: Allocation: Non-Randomized
Endpoint Classification: Safety Study
Intervention Model: Parallel Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: Phase I, Reference-controlled, Dose Escalating Study to Examine the Pharmacokinetics and Safety of AeroVanc Inhalation Powder.

Vancomicina nebulizada: Aerovanc

ABPA

UK Guidelines

Corticoides (CO) usar en las exacerbaciones por ABPA

Itraconazol: Incorporar cuando hay pobre o no respuesta a los CO

Voriconazol agregar cuando no hay rta al itraconazol

No hay evidencia suficiente para el **uso de anfotericina B**

CFF Guidelines

Corticoides (CO) usar en las exacerbaciones por ABPA

Itraconazol: Incorporar cuando hay pobre o no respuesta a los CO

Voriconazol , omalizumab y anfotericina B no recomendar

Pero las guías de FQ Royal Brompton 2017: POSACONAZOL (2DA LÍNEA)

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Trial record 1 of 1 for: nct01222273
Previous Study | Return to List | Next Study

Open-label Vitamin D Trial for Patients With Cystic Fibrosis and Allergic Bronchopulmonary Aspergillosis

The recruitment status of this study is unknown because the information has not been verified recently.

Verified October 2010 by University of Pittsburgh.
Recruitment status was Recruiting

Sponsor:
University of Pittsburgh

Collaborator:
National Heart, Lung, and Blood Institute (NHLBI)

Information provided by:
University of Pittsburgh

ClinicalTrials.gov Identifier:
NCT01222273

First received: October 14, 2010
Last updated: NA
Last verified: October 2010
History: No changes posted

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

The purpose of this study is to see if giving people with CF and ABPA enough vitamin D to make their blood levels of the vitamin higher, will reduce the allergic response in their body and make the symptoms caused by ABPA better.

Condition	Intervention	Phase
Cystic Fibrosis Allergic Bronchopulmonary Aspergillosis A. Fumigatus	Dietary Supplement: cholecalciferol (Vitamin D3)	Phase 1 Phase 2

Study Type: Interventional
Study Design: Allocation: Non-Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: Open-label Vitamin D Trial for Patients With Cystic Fibrosis and Allergic Bronchopulmonary Aspergillosis

Terapia Antiinflamatoria

AZITROMICINA

- Azitromicina en mayores de 6 años con FQ e infección crónica por Pa
- Tiene propiedades inmunomoduladoras y antiinflamatorias
- Estudios publicados: Demostraron efectos en el peso, disminución del uso de ATB orales, mejoría en la fx pulmonar y menor número de exacerbaciones

Saiman L. Azitromycin in patients with cystic fibrosis chronically infected with Pseudomonas aeruginosa: a randomized controlled trial. *JAMA 2003; 290:1749-1756*

Otros……en estudio…..

- Ibuprofeno
- Alfa 1 anti-tripsina (NCT 01684410) Fase 2, 30 participantes
- Glutation : Estudio randomizado en mayores de 8 años no demostró mejorar la Fx Pulmonar (Fase 2)
- CXCR2 antagonistas
- Inhibidores de leucotrienos: LTB4 debió suspenderse por los efectos adversos

MICROBIOME - EXACERBACIÓN PULMONAR

- Las investigaciones en microbiome pulmonar han demostrado como las comunidades bacteriológicas cambian con el tiempo, especialmente con la progresión de la enfermedad pulmonar y respuesta al tratamiento antibiótico
- La diversidad bacteriana parece aumentar durante la primer década, pero luego disminuye en la edad adulta asociada a declinación de la fx pulmonar
- Las exacerbaciones respiratorias pueden no estar dadas por los microrganismos habituales

MICROBIOME - EXACERBACIÓN PULMONAR

- Asociación entre disminución de la diversidad bacteriana y aumento de la resistencia no está del todo claro, pero el USO REPETIDO DE ATB juega un rol importante.(1)
- Papel de los ANAEROBIOS en la enfermedad pulmonar queda por definirse (*Prevotella y Veillonella*)

1. Sibley CD. Culture enriched molecular profiling of the cystic fibrosis airway microbiome. *PLOS ONE 2011;6:e22702*

PLOS | ONE

Inflammation and Airway Microbiota during Cystic Fibrosis Pulmonary Exacerbations

Edith T. Zemanick , J. Kirk Harris, Brandie D. Wagner, Charles E. Robertson, Scott D. Sagel, Mark J. Stevens, Frank J. Accurso, Theresa A. Laguna

Published: April 30, 2013 • DOI: 10.1371/journal.pone.0062917

Abstract

Background

Pulmonary exacerbations (PEx), frequently associated with airway infection and inflammation, are the leading cause of morbidity in cystic fibrosis (CF). Molecular microbiologic approaches detect complex microbiota from CF airway samples taken during PEx. The relationship between airway microbiota, inflammation, and lung function during CF PEx is not well understood.

Objective

To determine the relationships between airway microbiota, inflammation, and lung function in CF subjects treated for PEx.

Methods

Expectorated sputum and blood were collected and lung function testing performed in CF subjects during early (0–3d.) and late treatment (>7d.) for PEx. Sputum was analyzed by culture, pyrosequencing of 16S rRNA amplicons, and quantitative PCR for total and specific bacteria. Sputum IL-8 and neutrophil elastase (NE); and circulating C-reactive protein (CRP) were measured.

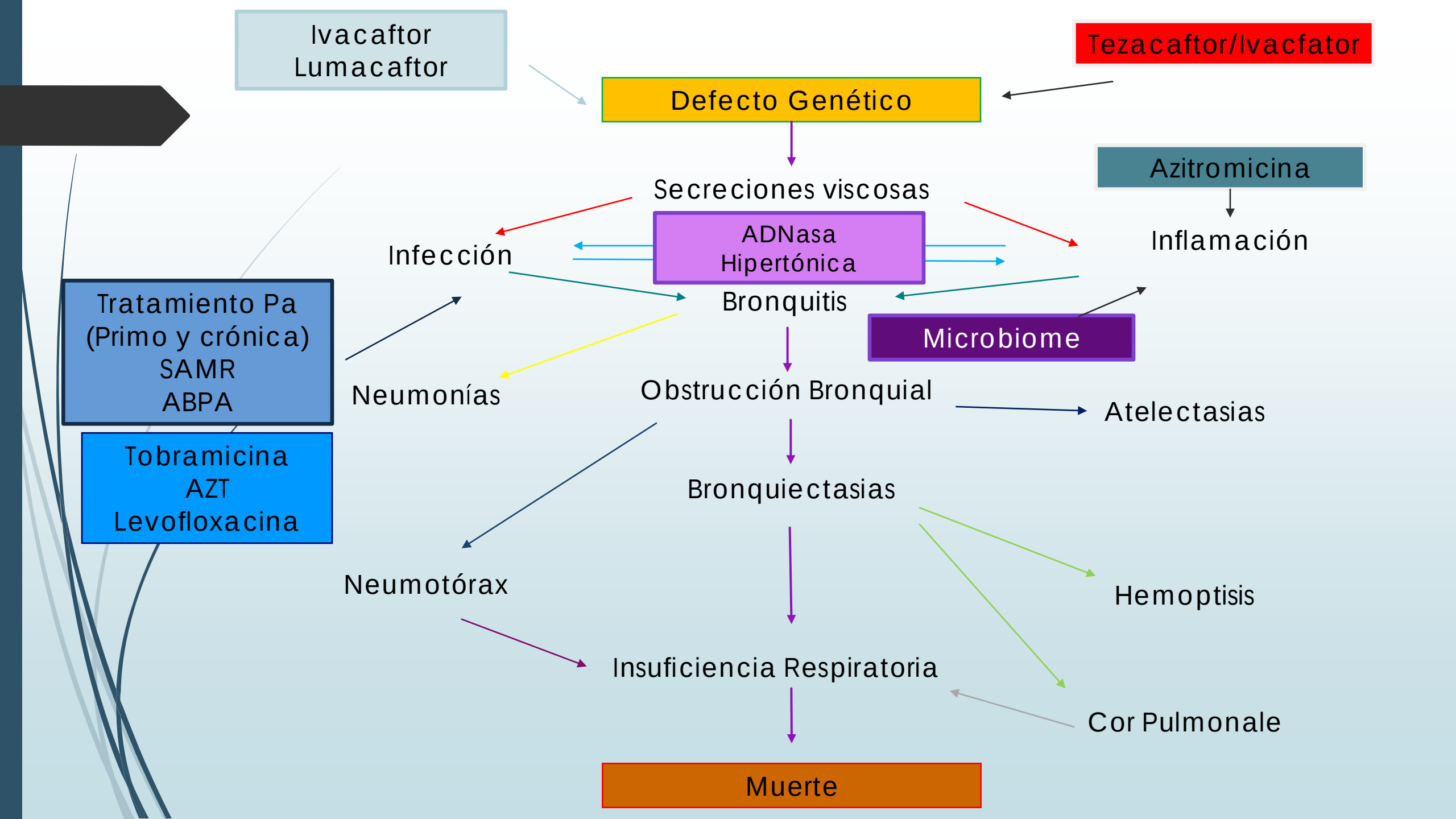
Results

Thirty-seven sputum samples were collected from 21 CF subjects. At early treatment, lower diversity was associated with high

Preguntas: Cuál es la relación entre disminución de la diversidad bacteriana y enfermedad avanzada?

Rol de los anaerobios?

El uso de biomarcadores para la exacerbación pulmonar?


Ivacaftor
Lumacaftor
Tezacaftor/Ivacfator
Defecto Genético
Secreciones viscosas
ADNasa
Hipertónica
Azitromicina
Inflamación
Infección
Bronquitis
Tratamiento Pa
(Primo y crónica)
SAMR
ABPA
Microbiome
Neumonías
Obstrucción Bronquial
Atelectasias
Tobramicina
AZT
Levofloxacina
Bronquiectasias
Neumotórax
Hemoptisis
Insuficiencia Respiratoria
Cor Pulmonale
Muerte

GRACIAS!!