NOVETATS en el DIAGNÒSTIC i TRACTAMENT de la TUBERCULOSI

Actualització en el tractament

Malú De Souza Galvão
Unitat de Tuberculosi
Vall d'Hebron-Drassanes
Barcelona
msouza@vhebron.net

Fàrmacs per el tractament de la TB

GRUP	FÀRMAC
1. Orals de 1ª línia	Isoniacida, Rifampicina, Pirazinamida, Etambutol
2. Inyectables	Estreptomicina, Kanamicina, Amikacina, Capreomicina
3. Fluoroquinolones	Moxifloxacino, Gatifloxacino, Levofloxacino
4. Bacteriostàticos orals de 2ª línia	Protionamida, Etionamida, Cicloserina, PAS
5. Potencialment útils, eficàcia no demostrada	Clofacimina, Linezolid, Claritromicina, Tiazetazona

TB-MDR: Resistència a Rifampicina e Isoniacida

TB-XDR: MDR + fluoroquinolones + Inyectables

Tractament de la Tuberculosi

3-5 comp/d

2RHZE

Tractament de la Tuberculosi

2 comp/d

4RH

MICROBIOLOGIA

ESTUDI BACTERIOLÒGIC

SOCA BACTERIANA

Soca tramesa

Finalitzat: **No**

Correspon a micobacteris en cultiu pur

Mycobacterium tuberculosis

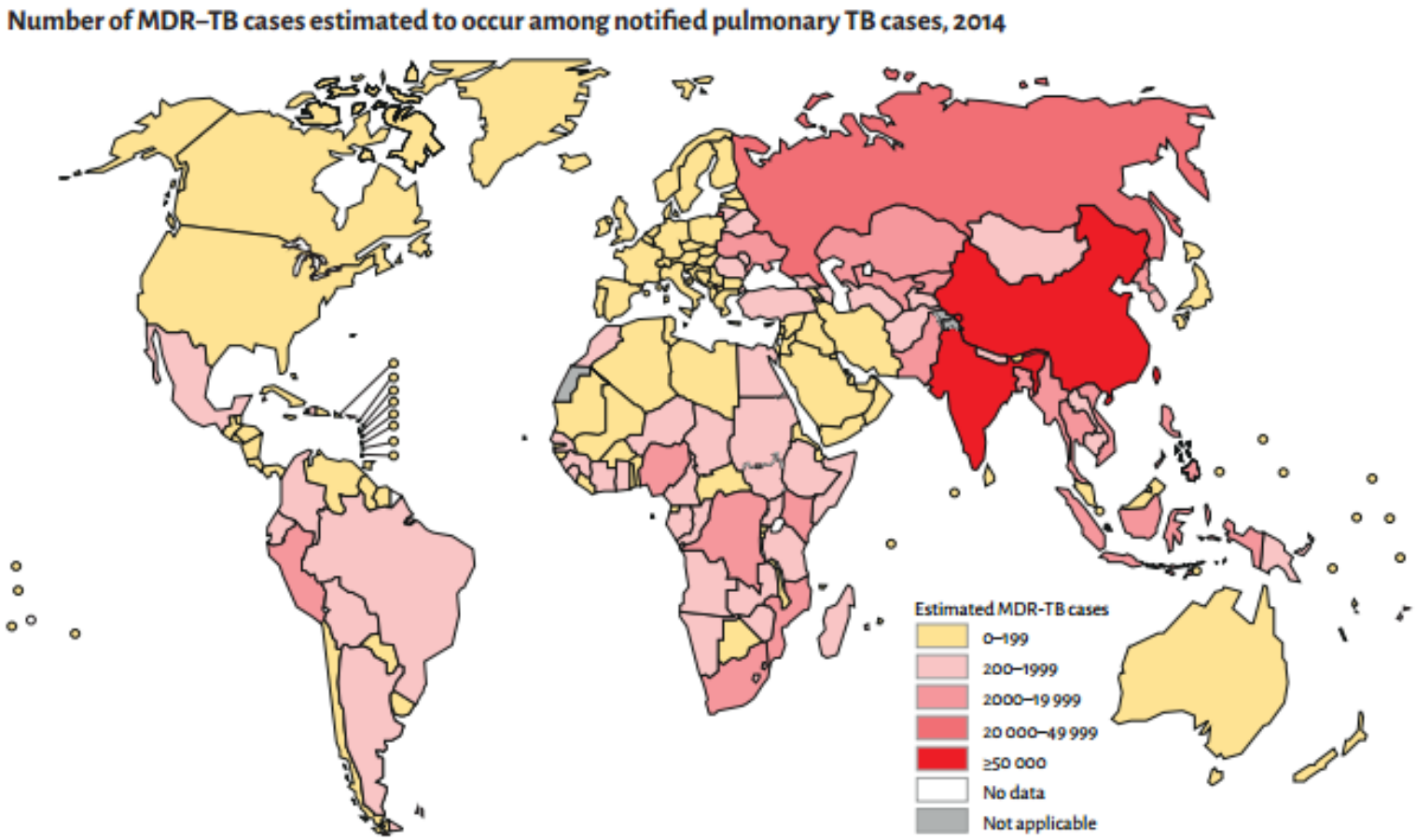
	Mycobacterium tuberculosis µg/ml		
Rifampicina BK	R		
Isoniacida BK	R		
Estreptomicina BK	R		
Etambutol BK	R		
Pirazinamida BK	R		
Amikacina BK	R		
Capreomicina BK	R		
Etionamida BK	R		
Ofloxacina BK	S		
Moxifloxacino BK	R		

Detecció de M. tuberculosis complex i de gens de resistència a fàrmacs de primera línia. **Positiu. Resistent a Rifampicina. Resistent a Isoniacida.**

Taula 50. Resum de la TBC a Catalunya l'any 2014

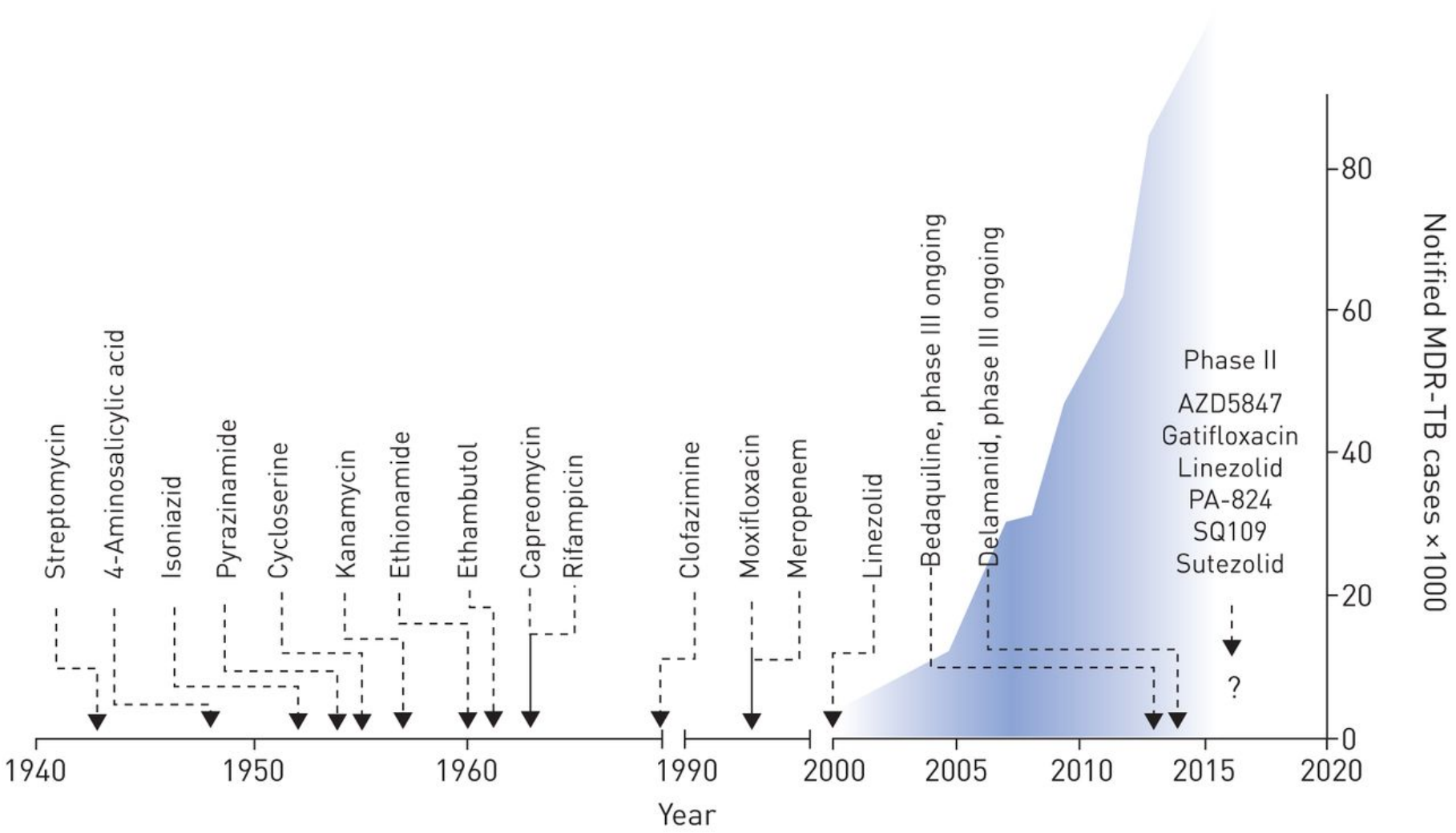
Indicadors	Catalunya 2014
Nombre total de casos notificats	1.135
Taxa de TBC per 10^5 habitants	15,1
Percentatge anual de canvi en la taxa de notificació	–1,9%
Proporció de casos nascuts a l'estranger	46,4%
Raó home/dona	1,4
Proporció de casos amb TBC pulmonar	68,5%
Taxa de TBC pulmonar per 10^5 habitants	10,3
Taxa de TBC pulmonar amb bacil·loscòpia d'esput positiva per 10^5 habitants	4,5
Taxa de TBC extrapulmonar per 10^5 habitants	4,7
Taxa de TBC en infants menors de 5 anys	12,4
Proporció de casos nous	95%
Proporció de casos de TBC infectats pel VIH	3,9%
Proporció de TBC MDR en els casos nous	0,7%
Proporció de TBC MDR en el total de casos	1,1%
Conclusió del tractament en els casos de TBC pulmonar confirmats (2013):	
- Curació o tractament complet	87,9%
- Defunció	7,6%
- Tractament prolongat	1,5%
- Seguiment perdut, traslladat o desconegut	3,0%

Casos de Tuberculosi MDR



WHO Global Tuberculosis Report 2015

Anti-tuberculosis drug development and the increase in number of notified multidrug-resistant tuberculosis (MDR-TB) cases worldwide.



Ioana Diana Olaru et al. Eur Respir J 2015;45:1119-1131

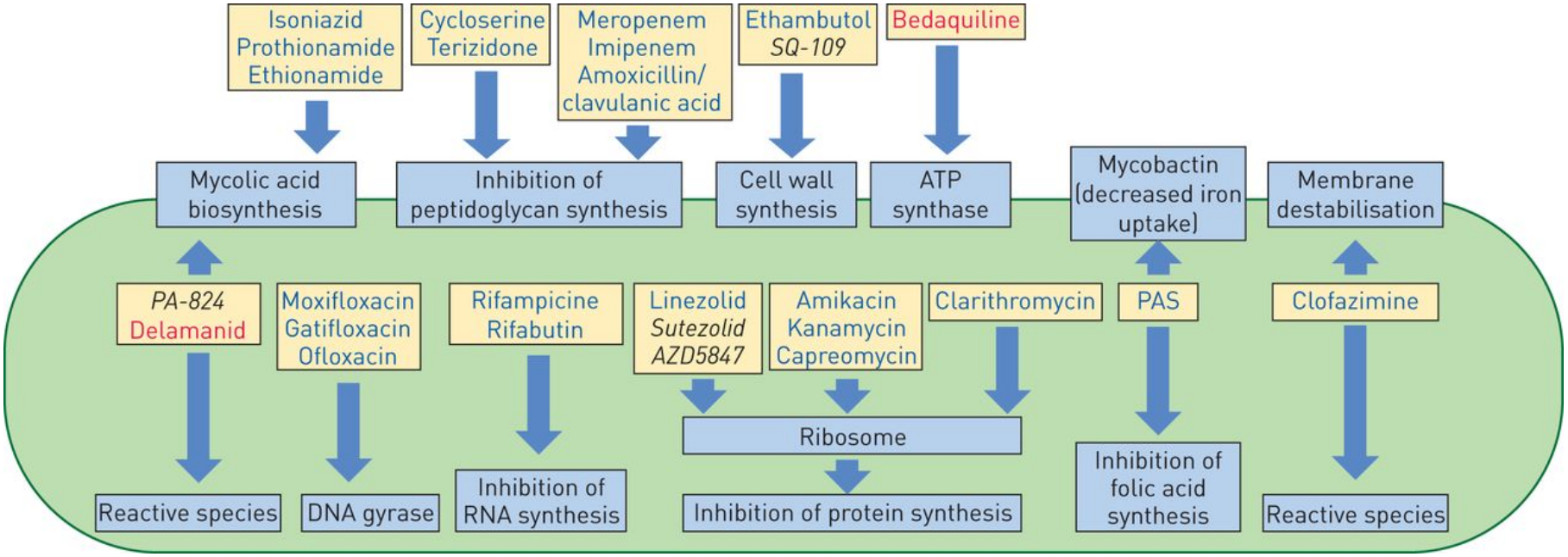
Limitacions

- Llarga durada
- Gran quantitat de pastilles
- Toxicitat significativa
- Importants interaccions farmacocinètiques
- Manca d'eficàcia enfront la TB MDR

Fàrmacs ideals

- Fàrmacs potents amb **efecte bactericida** per a evitar el desenvolupament de resistències
- **Vida mitja llarga** i similar de tots els components que permeti dosificacions 1 o 2 cops a la setmana (facilitar la teràpia directament observada (TDO)
- Activitat enfront **microorganismes latents** o en fase no replicativa que permeti escurçar el tractament
- Activitat enfront microorganismes **MDR**
- **Perfil farmacocinètic** que permeti combinacions amb altres fàrmacs (de 1ª linea, anti-retrovirals, etc)

Mecanismes d'acció dels fàrmacs anti-TB



Ioana Diana Olaru et al. Eur Respir J 2015;45:1119-1131

Global TB Drug Pipeline [1]

Preclinical Development | **Clinical Development**

Early Stage Development	GLP Tox.	Phase I	Phase II	Phase III
Riminophenazine TBI-166	PBTZ169*	TBA-354	Sutezolid (PNU-100480)	Bedaquiline (TMC-207) with OBR[2] for MDR-TB
Caprazene nucleoside CPZEN-45*	BTZ-043*	Q203*	SQ109*	Delamanid (OPC-67683) with OBR for MDR-TB
Capuramycin SQ641*			Rifapentine for DS-TB	Pretomanid-Moxifloxacin-Pyrazinamide Regimen
Spectinamide 1599*			High Dose Rifampicin for DS-TB	
Macrolide SEQ-9*			Bedaquiline-Pretomanid-Pyrazinamide Regimen	
			Levofloxacin with OBR for MDR-TB	

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone , imidazopyridine amide, New chemical class*

[1] Details for projects listed can be found at http://www.newtbdrugs.org/pipeline.php and ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php.

[2] OBR = Optimized Background Regimen

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: September 2015

Global TB Drug Discovery Pipeline [1]

Hit-to-Lead

Phenotype Hit-to-Lead (Vertex Pharmaceuticals)
Actinomycete Metabolites (U ILL Chicago, Myongii U)
Novel Hit-to-Lead Programs (Lilly DDi) GATB
Adamantanids (U ILL Chicago)
Whole-Cell Hit-to-Lead (GSK, GATB)
Malate Synthase Inhibitors (GSK, TAMU, GATB)
Menaquinone Synthase Inhibitors (CSU)
M. tb Energy Metabolism Inhibitors (UPenn, GATB)
Isoprenoid Biosynthesis Inhibitors (Lilly DDi)
Whole-Cell Hit-to-Lead (GATB, Sanofi)
RNA Polymerase Inhibitors (GATB, Rutgers U)
ATP Synthesis Inhibitors (GATB, Calibr)

Lead Optimization

Diarylquinolines (GATB, U Auckland, Janssen)
InhA Inhibitors (GSK)
LeuRS Inhibitors (Anacor Pharmaceuticals, GSK)
Pyrazinamide Analogs (GATB, Yonsei U)
Translocase-1 Inhibitors (Sequella)
DprE Inhibitors Azaindoles (GATB, Calibr)
Ureas (Sanofi, GATB)
Ruthenium(II)phosphine/picolinate Complexes (FAPESP/Brazil)
Spectinamides (St. Jude, U Tenn, CSU, UZ, Microbiotix)
Indazoles (GATB, GSK)
Macrolides (GATB, Sanofi)
Cyclopeptides (GATB, Sanofi)
DrpE Inhibitros (GATB)
SPR-113 (Gates Foundation)

[1] Details for projects listed can be found at http://www.newtbdrugs.org/pipeline-discovery.php and clinical development projects can be viewed at http://www.newtbdrugs.org/pipeline.php.

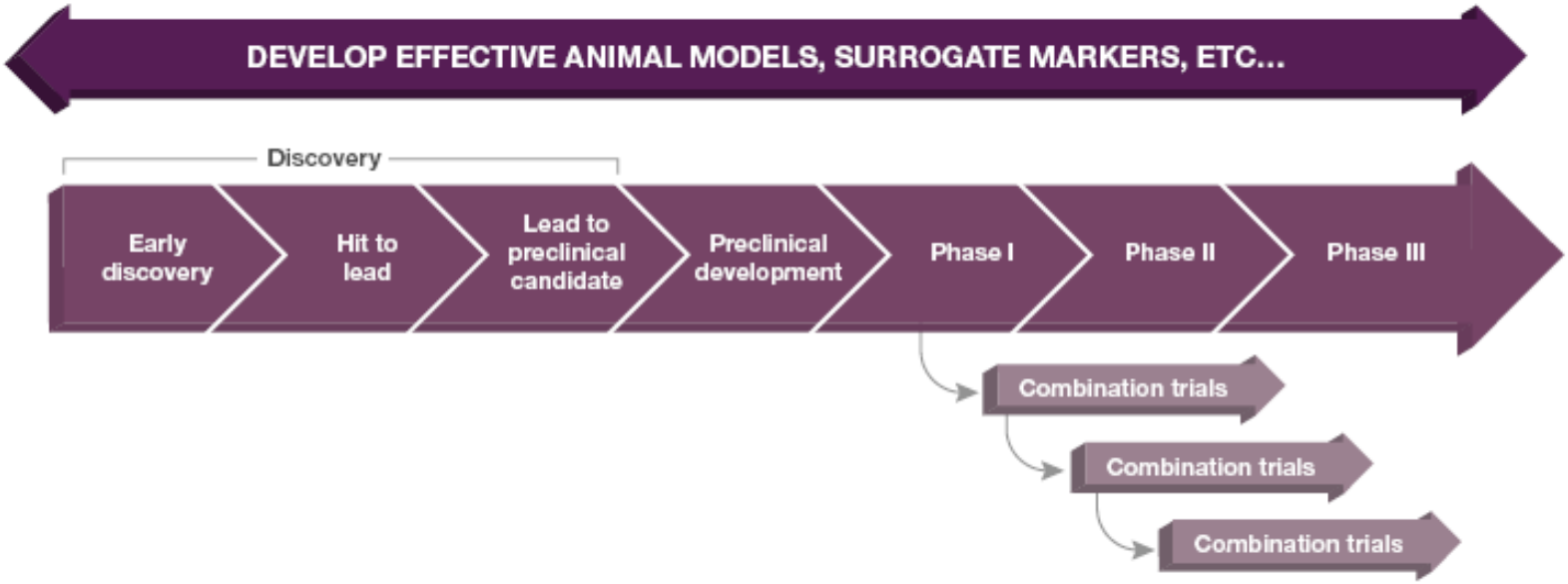
Abbreviations of Developers: **CSU**-Colorado State University; **FAPESP**-São Paulo Research Foundation; **GATB**-Global Alliance for TB Drug Development (TB Alliance); **GSK**-GlaxoSmithKline; **Lilly DDi**-Lilly TB Drug Discovery Initiative; **RI**-Research Institute; **St. Jude**-St. Jude Children's Research Hospital; **TAMU**-Texas A&M University; **U**-University; **U ILL**-University of Illinois; **UPenn**-University of Pennsylvania; **U Tenn**-University of Tennessee; **UZ**-University of Zurich

WORKING GROUP ON NEW TB DRUGS
www.newtbdrugs.org

Updated: September 2015

Fàrmacs en projecte

FIGURE 35: TB DRUG DEVELOPMENT PIPELINE



8 A 12 ANYS

OLD DOG, NEW TRICKS

NOUS ASSAIGS; VELLS FÀRMACS

RIFAPENTINA:

- Rifamicina sintetitzada l'any **1965**
- **1998** aprovada per la FDA pel tractament de la **TB pulmonar**; però no a Europa
- Vida mitja llarga que permet **dosi setmanal**
- EUA: aprovada pauta **RPT+H setmanal en la fase de continuació** (no cavitaris , HIV negatius)

American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of Tuberculosis

TABLE 2. DRUG REGIMENS FOR CULTURE-POSITIVE PULMONARY TUBERCULOSIS CAUSED BY DRUG-SUSCEPTIBLE ORGANISMS

Initial Phase			Continuation Phase				Rating* (Evidence)†	
Regimen	Drugs	Interval and Doses‡ (*minimal duration*)	Regimen	Drugs	Interval and Doses‡,§ (*minimal duration*)	Range of Total Doses (*minimal duration*)	HIV⁻	HIV⁺
1	INH RIF PZA EMB	Seven days per week for 56 doses (8 wk) *or* 5 d/wk for 40 doses (8 wk)‖	1a	INH/RIF	Seven days per week for 126 doses (18 wk) *or* 5 d/wk for 90 doses (18 wk)‖	182–130 (26 wk)	A (I)	A (II)
			1b	INH/RIF	Twice weekly for 36 doses (18 wk)	92–76 (26 wk)	A (I)	A (II)#
			1c**	INH/RPT	Once weekly for 18 doses (18 wk)	74–58 (26 wk)	B (I)	E (I)
2	INH RIF PZA EMB	Seven days per week for 14 doses (2 wk), *then* twice weekly for 12 doses (6 wk) *or* 5 d/wk for 10 doses (2 wk),‖ *then* twice weekly for 12 doses (6 wk)	2a	INH/RIF	Twice weekly for 36 doses (18 wk)	62–58 (26 wk)	A (II)	B (II)#
			2b**	INH/RPT	Once weekly for 18 doses (18 wk)	44–40 (26 wk)	B (I)	E (I) *
3	INH RIF PZA EMB	Three times weekly for 24 doses (8 wk)	3a	INH/RIF	Three times weekly for 54 doses (18 wk)	78 (26 wk)	B (I)	B (II)
4	INH RIF EMB	Seven days per week for 56 doses (8 wk) *or* 5 d/wk for 40 doses (8 wk)‖	4a	INH/RIF	Seven days per week for 217 doses (31 wk) *or* 5 d/wk for 155 doses (31 wk)‖	273–195 (39 wk)	C (I)	C (II)
			4b	INH/RIF	Twice weekly for 62 doses (31 wk)	118–102 (39 wk)	C (I)	C (II)

***Increment de recidives en cavitaris i monoresistencia a R als HIV**

RIFAPENTINA:

- Rifamicina sintetitzada l'any 1965
- 1998 aprovada per la FDA pel tractament de la **TB pulmonar**; però no a Europa
- Vida mitja llarga que permet **dosi setmanal**
- EUA: aprovada pauta **RPT+H setmanal en la fase de continuació** (no cavitaris , HIV negatius)
- **Study 29: P a 10mg/kg diària x 10mg/kg R diària**
  Negativització cultiu al 2n mes en TB pulmonar BK+ (no superior a la pauta estàndar amb R)

Substitution of Rifapentine for Rifampin During Intensive Phase Treatment of Pulmonary Tuberculosis: Study 29 of the Tuberculosis Trials Consortium

Susan E. Dorman,[1] Stefan Goldberg,[2] Jason E. Stout,[3] Grace Muzanyi,[4] John L. Johnson,[4,5] Marc Weiner,[6] Lorna Bozeman,[2] Charles M. Heilig,[2] Pei-Jean Feng,[2] Ruth Moro,[2] Masahiro Narita,[7] Payam Nahid,[8] Susan Ray,[9] Edward Bates,[10] Betial Haile,[11] Eric L. Nuermberger,[1] Andrew Vernon,[2] Neil W. Schluger,[12] and the Tuberculosis Trials Consortium

Background. Rifapentine administered 5 days per week has potent activity in mouse models of antituberculosis chemotherapy, but efficacy and safety data are limited in humans. We compared the antimicrobial activity and safety of rifapentine vs rifampin during the first 8 weeks of pulmonary tuberculosis treatment.

Methods. In total, 531 adults with sputum smear-positive pulmonary tuberculosis were randomized to rifapentine 10 mg/kg/dose or rifampin 10 mg/kg/dose, administered 5 days per week for 8 weeks (intensive phase), with isoniazid, pyrazinamide, and ethambutol. Coprimary outcomes were negative sputum culture on liquid and on solid media at completion of intensive phase.

Results. Negative cultures on solid media occurred in 145 of 174 participants (83.3%) in the rifampin group and 171 of 198 participants (86.4%) in the rifapentine group (difference, 3.0%; 95% confidence interval [CI]: −4.3, 10.5); negative cultures in liquid media occurred in 110 of 169 (65.1%) in the rifampin group and 133 of 196 (67.9%) in the rifapentine group (difference, 2.8%; 95% CI: −6.9, 12.4). Among 529 participants who received study therapy, 40 of 254 participants (15.7%) in the rifampin group and 40 of 275 participants (14.5%) in the rifapentine group prematurely discontinued treatment ($P = .79$).

Conclusions. The rifapentine regimen was safe but not significantly more active than a standard rifampin regimen, by the surrogate endpoint of culture status at completion of intensive phase. Assessment of higher exposures to rifapentine for tuberculosis treatment is warranted.

Clinical Trials registration. NCT00694629.

Am J Respir Crit Care Med. 2015 Feb 1;191(3):333-43

RIFAPENTINA:

- Rifamicina sintetitzada l'any 1965
- Comercialitzada als EUA, però no aprovada a Europa
- Vida mitja llarga que permet **dosi setmanal**
- EUA: aprovada pauta **RPT+H setmanal en la fase de continuació** (no cavitaris , HIV negatius)
- **Study 29: P a 10mg/kg diària x R 10mg/kg diària** Negativització cultiu al 2n mes en TB pulmonar BK+ (no superior a la pauta estàndar amb R)
- **Estudis amb dosificacions superiors a 10mg/kg**

Daily Rifapentine for Treatment of Pulmonary Tuberculosis

A Randomized, Dose-Ranging Trial

Susan E. Dorman[1], Radojka M. Savic[2], Stefan Goldberg[3], Jason E. Stout[4], Neil Schluger[5], Grace Muzanyi[6], John L. Johnson[6,7], Payam Nahid[2], Emily J. Hecker[4], Charles M. Heilig[3], Lorna Bozeman[3], Pei-Jean I. Feng[3], Ruth N. Moro[3,8], William MacKenzie[3], Kelly E. Dooley[1], Eric L. Nuermberger[1], Andrew Vernon[3], Marc Weiner[9], and the Tuberculosis Trials Consortium

[1]Johns Hopkins University School of Medicine, Baltimore, Maryland; [2]University of California, San Francisco, San Francisco, California; [3]Centers for Disease Control and Prevention, Atlanta, Georgia; [4]Duke University School of Medicine, Durham, North Carolina; [5]Columbia University Medical Center, New York, New York; [6]Uganda–Case Western Reserve University Research Collaboration, Kampala, Uganda; [7]Case Western Reserve University School of Medicine, Cleveland, Ohio; [8]CDC Foundation Research Collaboration, Atlanta, Georgia; and [9]University of Texas Health Science Center at San Antonio and the South Texas VAMC, San Antonio, Texas

Abstract

Rationale: Rifapentine has potent activity in mouse models of tuberculosis chemotherapy but its optimal dose and exposure in humans are unknown.

Objectives: We conducted a randomized, partially blinded dose-ranging study to determine tolerability, safety, and antimicrobial activity of daily rifapentine for pulmonary tuberculosis treatment.

Methods: Adults with sputum smear-positive pulmonary tuberculosis were assigned rifapentine 10, 15, or 20 mg/kg or rifampin 10 mg/kg daily for 8 weeks (intensive phase), with isoniazid, pyrazinamide, and ethambutol. The primary tolerability end point was treatment discontinuation. The primary efficacy end point was negative sputum cultures at completion of intensive phase.

Measurements and Main Results: A total of 334 participants were enrolled. At completion of intensive phase, cultures on solid media were negative in 81.3% of participants in the rifampin group versus 92.5% ($P = 0.097$), 89.4% ($P = 0.29$), and 94.7% ($P = 0.049$) in the rifapentine 10, 15, and 20 mg/kg groups. Liquid cultures were negative in 56.3% (rifampin group) versus 74.6% ($P = 0.042$), 69.7% ($P = 0.16$), and 82.5% ($P = 0.004$), respectively. Compared with the rifampin group, the proportion negative at the end of intensive phase was higher among rifapentine recipients who had high rifapentine areas under the concentration–time curve. Percentages of participants discontinuing assigned treatment for reasons other than microbiologic ineligibility were similar across groups (rifampin, 8.2%; rifapentine 10, 15, or 20 mg/kg, 3.4, 2.5, and 7.4%, respectively).

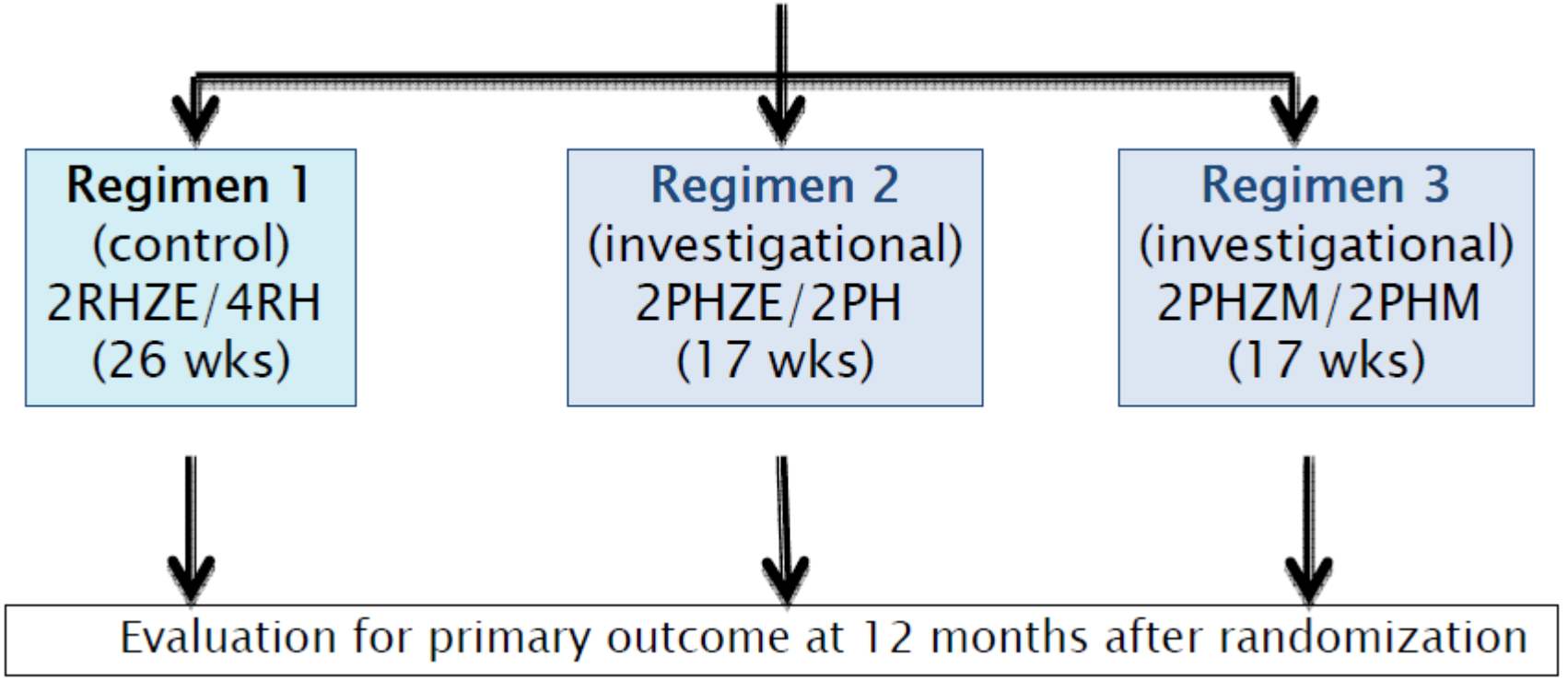
Conclusions: Daily rifapentine was well-tolerated and safe. High rifapentine exposures were associated with high levels of sputum sterilization at completion of intensive phase. Further studies are warranted to determine if regimens that deliver high rifapentine exposures can shorten treatment duration to less than 6 months.

Clinical trial registered with www.clinicaltrials.gov (NCT 00694629).

Keywords: mycobacterium; rifamycins; rifapentine; therapeutics; tuberculosis

TBTC Study 31 / ACTG A5349

Rifapentine-containing treatment shortening regimens for pulmonary tuberculosis: A randomized, open-label, controlled phase 3 clinical trial



P: 1200 mg; H: 300 mg; Z: 1000 mg a 2000 mg; Moxifloxacin: 400 mg

Reduir tractament de la TB a 4 mesos

RIFAPENTINA:

- Rifamicina sintetitzada l'any 1965
- Comercialitzada als EUA, però no aprovada a Europa
- Vida mitja llarga que permet **dosi setmanal**
- EUA: aprovada pauta **RPT+H setmanal en la fase de continuació** (no cavitaris , HIV negatius)
- **Study 29:** negativització cultiu al 2n mes en TB pulmonar BK+ (no superior a la pauta estàndar amb R)
- Estudis amb dosificacions superiors a 10mg/kg
- **EUA: aprovada pel tractament de la infecció TB latent RPT+H setmanals x 12 setmanes.**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 8, 2011 VOL. 365 NO. 23

Three Months of Rifapentine and Isoniazid for Latent Tuberculosis Infection

Timothy R. Sterling, M.D., M. Elsa Villarino, M.D., M.P.H., Andrey S. Borisov, M.D., M.P.H., Nong Shang, Ph.D., Fred Gordin, M.D., Erin Bliven-Sizemore, M.P.H., Judith Hackman, R.N., Carol Dukes Hamilton, M.D., Dick Menzies, M.D., Amy Kerrigan, R.N., M.S.N., Stephen E. Weis, D.O., Marc Weiner, M.D., Diane Wing, R.N., Marcus B. Conde, M.D., Lorna Bozeman, M.S., C. Robert Horsburgh, Jr., M.D., Richard E. Chaisson, M.D., for the TB Trials Consortium PREVENT TB Study Team*

ABSTRACT

BACKGROUND

Treatment of latent *Mycobacterium tuberculosis* infection is an essential component of tuberculosis control and elimination. The current standard regimen of isoniazid for 9 months is efficacious but is limited by toxicity and low rates of treatment completion.

METHODS

We conducted an open-label, randomized noninferiority trial comparing 3 months of directly observed once-weekly therapy with rifapentine (900 mg) plus isoniazid (900 mg) (combination-therapy group) with 9 months of self-administered daily isoniazid (300 mg) (isoniazid-only group) in subjects at high risk for tuberculosis. Subjects were enrolled from the United States, Canada, Brazil, and Spain and followed for 33 months. The primary end point was confirmed tuberculosis, and the noninferiority margin was 0.75%.

RESULTS

In the modified intention-to-treat analysis, tuberculosis developed in 7 of 3986 subjects in the combination-therapy group (cumulative rate, 0.19%) and in 15 of 3745 subjects in the isoniazid-only group (cumulative rate, 0.43%), for a difference of 0.24 percentage points. Rates of treatment completion were 82.1% in the combination-therapy group and 69.0% in the isoniazid-only group (P<0.001). Rates of permanent drug discontinuation owing to an adverse event were 4.9% in the combination-therapy group and 3.7% in the isoniazid-only group (P=0.009). Rates of investigator-assessed drug-related hepatotoxicity were 0.4% and 2.7%, respectively (P<0.001).

CONCLUSIONS

The use of rifapentine plus isoniazid for 3 months was as effective as 9 months of isoniazid alone in preventing tuberculosis and had a higher treatment-completion rate. Long-term safety monitoring will be important. (Funded by the Centers for Disease Control and Prevention; PREVENT TB ClinicalTrials.gov number, NCT00023452.)

From the Vanderbilt University School of Medicine, Nashville (T.R.S., A.K.); the Centers for Disease Control and Prevention, Atlanta (M.E.V., A.S.B., N.S., E.B.-S., L.B.); the Washington DC Veterans Affairs Medical Center and George Washington University — both in Washington, DC (F.G.); the Johns Hopkins University School of Medicine, Baltimore (J.H., R.E.C.); Family Health International and Duke University — both in Durham, NC (C.D.H.); Montreal Chest Institute, McGill University, Montreal (D.M.); the University of North Texas Health Science Center at Fort Worth, Fort Worth (S.E.W.); the South Texas Veterans Health Care System and University of Texas Health Science Center at San Antonio — both in San Antonio (M.W.); and the South Texas Consortium, Harlingen (D.W.); the Federal University of Rio de Janeiro, Rio de Janeiro (M.B.C.); and Boston University School of Medicine, Boston (C.R.H.). Address reprint requests to Dr. Sterling at A2209 Medical Center North, 1161 21st Ave. S., Nashville, TN 37232, or at timothy.sterling@vanderbilt.edu.

Drs. Horsburgh and Chaisson contributed equally to this article.

*Investigators participating in the PREVENT TB study are listed in the Supplementary Appendix, available at NEJM.org.

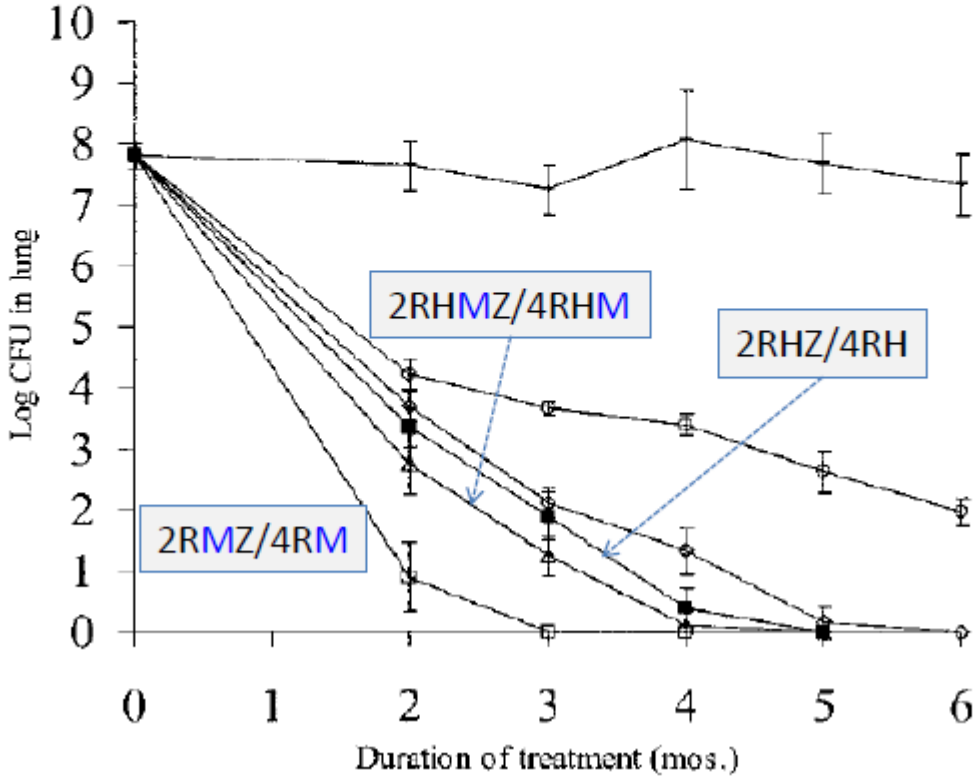
N Engl J Med 2011;365:2155-66.

Fluoroquinolones:

- **Moxifloxacino**, Sparfloxacino, Gatifloxacino, **Levofloxacino** > Ofloxacino
- Les mès potents i eficaces "*in vitro*" i "*in vivo*"
- Bactericides. Activitat intra i extracel·lular
- **Principal pilar del tractament de la TB MDR**
- Baixa toxicitat i poca interacció farmacològica
- **Moxifloxacino vs Levofloxacino:**
  - Moxi > Levo (capacitat esterilitzant model animal)
  - Estudi de Koh: no diferències en la conversió de l'esput als 3 m **750mgLevo** x **400mgMoxi**
  - 1000mg Levo à major poder bactericida

Moxifloxacin-containing Regimen Greatly Reduces Time to Culture Conversion in Murine Tuberculosis

Eric L. Nuermberger, Tetsuyuki Yoshimatsu, Sandeep Tyagi, Richard J. O'Brien, Andrew N. Vernon, Richard E. Chaisson, William R. Bishai, and Jacques H. Grosset



Am J Respir Crit Care Med. 2004 Feb 1;169(3):421-6.

Substitution of Moxifloxacin for Isoniazid during Intensive Phase Treatment of Pulmonary Tuberculosis

- TBTC Study 28: Estudi multicèntric, aleatoritzat, doble cec
- **RHZE**(+Moxi placebo) x **RZEMox**i (+placebo H)
- End point: cultiu d'esput negatiu a les 8 setmanes

TABLE 2. PERCENTAGES OF PARTICIPANTS WITH NEGATIVE SPUTUM CULTURES AT COMPLETION OF WEEK 8, BY TREATMENT GROUP, FOR THE PROTOCOL CORRECT ANALYSIS GROUP

	Overall, n		Isoniazid, n		Moxifloxacin, n		Difference (95% CI)	*P* Value
Primary analysis	57.6	189/328	54.9	90/164	60.4	99/164	5.5 (−5.8, 16.8)	0.37
Post-hoc analyses								
African sites*	48.4	103/213	43.0	43/100	53.1	60/113	10.1 (−4.2, 24.4)	0.18
Non-African sites	74.8	86/115	73.4	47/64	76.5	39/51	3.0 (−14.6, 20.7)	0.88
Liquid medium†	57.0	187/328	53.7	88/164	60.4	99/164	6.7 (−4.6, 18.0)	0.26
Solid medium	89.3	292/328	87.2	143/164	91.5	150/164	4.3 (−3.0, 11.5)	0.28

* $P < 0.01$ for comparison of overall results for African sites versus non-African sites.
† $P < 0.01$ for comparison of overall results for liquid versus solid medium.

In conclusion, replacement of isoniazid with moxifloxacin during the first 2 months of pulmonary TB treatment resulted in a small but statistically nonsignificant increase in the percentage of participants with negative cultures at Week 8. Additional studies are ongoing to determine the optimal role of moxifloxacin in pulmonary TB treatment.

Estudis amb fluorquinolones

	REMoxTB[1] (n= 1.548)	OFLOTUB[2] (n= 1.692)	RIFAQUIN[3] (n= 593)
Diseño	Aletorizado, doble ciego, no inferioridad	Aleatorizado, abierto, no inferioridad	Aleatorizado, abierto, no inferioridad
Pautas	**-2RHZE/4RH** -RHZMox17se./RHZPla9se. -RMoxZE17se./RPlaZE9se.	**-2RHZE/4RH** -2RHZGati/2RHGati	**-2RHZE/4RH** **-2REZMox/2P(900)Mox 2/se.** **-2REZMox/4P(900)Mox 2/se.**
Análisis	Fracaso/Recaída (18 m. postto.)	Fracaso/Recaída/ Muerte (24 m. postto.)	Fracaso/Recaída (12-18 m. postto.)

Cap dels estudis ha pogut provar la NO inferioritat de la pauta amb quinolona per escurçar el tractament de la TB a 4 mesos

1 N Engl J Med 2014;371:1577-87. 2 N Engl J Med 2014;371:1588-98. 3 N Engl J Med 2014;371:1599-608.

Clofacimina:

- Fàrmac utilitzat en el tractament de la **lepra (1950)**
- Classificada en el grup 5 de la classificació de l'OMS
- Recuperada pel tractament de la TB MDR en la **"pauta de Bangladesh"**
- **87,9% curació** en 206 pacients **TB MDR** amb **9m de ttm**
- **9m GATI+CLOFA+E+Z** prèvia fase intensiva de **4 mesos** amb **PTH+Kana+H** altes dosis

Short, Highly Effective, and Inexpensive Standardized Treatment of Multidrug-resistant Tuberculosis

Armand Van Deun[1,2], Aung Kya Jai Maug[3], Md Abdul Hamid Salim[3], Pankaj Kumar Das[3], Mihir Ranjan Sarker[3], Paul Daru[3], and Hans L. Rieder[1,4]

[1]International Union Against Tuberculosis and Lung Disease, Paris, France; [2]Mycobacteriology Unit, Institute of Tropical Medicine, Antwerp, Belgium; [3]Damien Foundation Bangladesh, Dhaka, Bangladesh; and [4]Institute of Social and Preventive Medicine, University of Zurich, Switzerland

Linezolid:

- Oxazolidiononones: inhibidors de la síntesi proteica
- **Actiu enfront de Gram positius,** presenta bona activitat *in vitro* enfront a MTB
- Tractament de la TB MDR i XDR (**Grup 5**)
- **Toxicitat elevada:** mielossupressió (anèmia, leucopènia, trombocitopènia), neuropatia perifèrica
  - Dosi depenent (?) 600mg/d à 1200mg/d
  - Temps d'exposició (?) 315 (178-540 dies)
- Preu elevat

Linezolid: an effective, safe and cheap drug for patients failing multidrug-resistant tuberculosis treatment in India

R. Singla*, J.A. Caminero[#,¶], A. Jaiswal*, N. Singla[+], S. Gupta*, R.K. Bali* and D. Behera*

29 pacients, 89.7% conversión BK i cultiu
72.4% curació 10.3% retirada per efectes adversos

=

Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis

Giovanni Sotgiu, Rosella Centis, Lia D'Ambrosio, Jan-William C. Alffenaar,

Systematic review and meta-analysis of the efficacy and safety of therapy with linezolid containing regimens in the treatment of multidrug-resistant and extensively drug-resistant tuberculosis

Xin Zhang[1,2], Matthew E. Falagas[3], Konstantinos Z. Vardakas[3], Rui Wang[4], Rong Qin[4], Jin Wang[3], Youning Liu[1]

- **Excel·lent eficàcia**
- Necessitat **d'estreta monitorització d'efectes secundaris**
- Reservat a pacients amb **TB-MDR i TB-XDR**
- Es requereixen estudis per **determinar les dosis i duració** del tractament

Carbapenems:

- Imipenem, Meropenem, Ertapenem
- Estudis publicats entre 2005 i 2016
- Curació: 57%
- **Molt bona seguretat i tolerabilitat**
- < 15% efectes adversos
- Intravenós/ 12 h , catèter central
- En estudi: Doripenem, Biapenem, Panipenem, Faropenem

Review

Carbapenems to Treat Multidrug and Extensively Drug-Resistant Tuberculosis: A Systematic Review

Giovanni Sotgiu [1,†], Lia D'Ambrosio [2,3,†], Rosella Centis [2,†], Simon Tiberi [4], Susanna Esposito [5], Simone Dore [1], Antonio Spanevello [6,7] and Giovanni Battista Migliori [2,*]

¿Que hay de nuevo, viejo?

Sirturo™
bedaquiline
100mg tablets

2013

- Multi-drug Resistant TB
- About SIRTURO™
- SIRTURO™ Clinical Trials
- SIRTURO™ Appropriate Use

900-30.000 $ Tractament de 6m

SIRTURO™ Is the First Anti-Tuberculosis (TB) Medication With a Novel Mechanism of Action in Over 40 Years

Indications

- SIRTURO™ (bedaquiline) is a diarylquinoline antimycobacterial drug indicated as part of combination therapy in adults (≥18 years) with pulmonary multi-drug resistant tuberculosis (MDR-TB).
- Reserve SIRTURO™ for use when an effective treatment regimen cannot otherwise be provided.
- SIRTURO™ should be administered by directly observed therapy (DOT).
- This indication is based on analysis of time to sputum culture conversion from two controlled Phase 2 trials in patients with pulmonary MDR-TB.

Limitations of Use

Use of SIRTURO™ in these settings is not recommended:

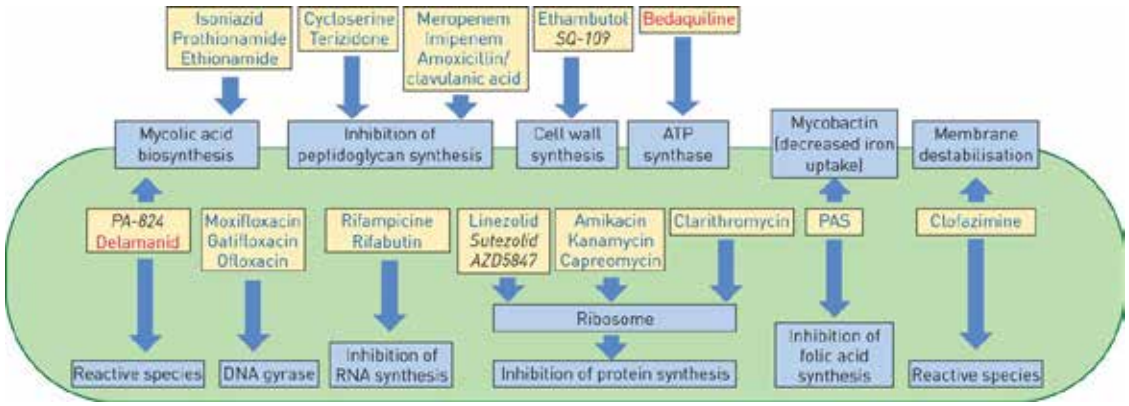
- The safety and efficacy of SIRTURO™ for the treatment of drug-sensitive TB (DS-TB) and latent infection due to *Mycobacterium tuberculosis* has not been established.
- There are no data on the treatment with SIRTURO™ of extrapulmonary TB (e.g., central nervous system).

Mechanism of Action

- SIRTURO™ is the first anti-TB drug to interfere with bacterial energy metabolism.
  - SIRTURO™ specifically inhibits mycobacterial ATP (adenosine 5'-triphosphate) synthase, an enzyme that is essential for the generation of energy in *Mycobacterium tuberculosis*.

Bedaquilina

- Diarylquinolines
- Primer fàrmac anti-TB comercialitzat en els últims 50 anys **(Sirturo** ®)
- Mecanisme d'acció totalment nou
- **Inhibeix la bomba de protons de l'ATP sintetasa** de *Mycobacterium tuberculosis* **(MTB)**
- **No resistència creuada** amb els altres antituberculosos



Bedaquilina

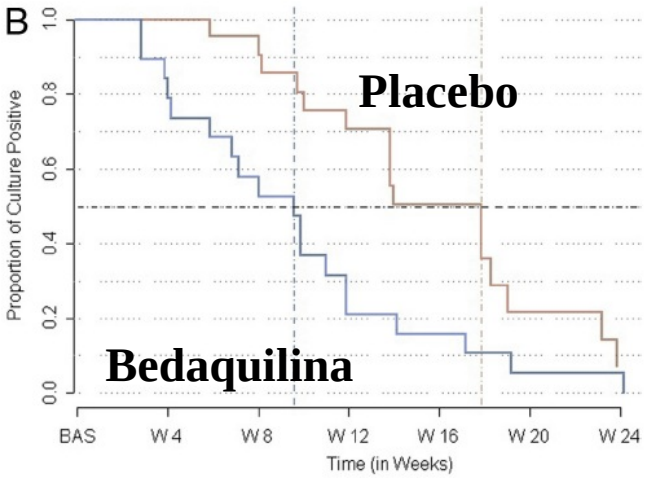
- Metabolizada per l'enzim CYP3A4
- Contraindicada amb **inductors** (Rifamicines) – risc de fracàs i **inhibidors** (Ketoconazol) risc de toxicitat
- **Toxicitat hepàtica;** requereix control transaminases, evitació d'alcohol i d'altres fàrmacs.
- **Arritmia: allargament de l'interval QT. Control ECG.**
- **Dosis:** (+ mínim 3 fàrmacs amb sensibilitat confirmada)
  - 400 mg/d 2 setmanes + 200mg 3 cops/set 22 setmanes
- Administrat amb **el menjar**

AAC
Journals.ASM.org

Randomized Pilot Trial of Eight Weeks of Bedaquiline (TMC207) Treatment for Multidrug-Resistant Tuberculosis: Long-Term Outcome, Tolerability, and Effect on Emergence of Drug Resistance

A. H. Diacon,[a] P. R. Donald,[a] A. Pym,[b] M. Grobusch,[c] R. F. Patientia,[a] R. Mahanyele,[b] N. Bantubani,[c] R. Narasimooloo,[c] T. De Marez,[d] R. van Heeswijk,[e] N. Lounis,[e] P. Meyvisch,[e] K. Andries,[e] and D. F. McNeeley[d]

Faculty of Health Sciences, Stellenbosch University, Tygerberg, South Africa[a]; Medical Research Council, Durban, South Africa[b]; Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa[c]; Tibotec, Inc., Yardley, Pennsylvania, USA[d]; and Tibotec BVBA, Mechelen, Belgium[e]



- 2 estudis controlats en fase 2 en pacientes con TB-MDR (conversió de l'esput als 2m)
- Increment del **risc de mort**:

  9/79 (**11.4%**) x placebo (2/81, **2.5%**)

Bedaquiline and multidrug-resistant tuberculosis: a systematic and critical analysis of the evidence

Emanuele Pontali[1,5], Giovanni Sotgiu[2,5], Lia D'Ambrosio[3,4], Rosella Centis[3] and Giovanni Battista Migliori[3]

- Conversió de l'esput més ràpida
- **Efectes adversos més frequents lleus / moderats:** nàusees, vòmits, artralgies, alteració lleu de transaminases
- **Increment del QT sense rellevància clínica** (relacionat amb tractament amb Clofacimina)
- Mortalitat relacionada amb IRC o TB evolucionada
- **Bon fàrmac per el tractament de la TB MDR**

Eur Respir J. 2016 Feb;47(2):394-402.

1 TABLET 100 mg = 500€

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 7, 2012 VOL. 366 NO. 23

Delamanid for Multidrug-Resistant Pulmonary Tuberculosis

Maria Tarcela Gler, M.D., Vija Skripconoka, M.D., Epifanio Sanchez-Garavito, M.D., Heping Xiao, M.D., Jose L. Cabrera-Rivero, M.D., Dante E. Vargas-Vasquez, M.D., Mengqiu Gao, M.D., Ph.D., Mohamed Awad, M.B., B.Ch., M.D., Seung-Kyu Park, M.D., Ph.D., Tae Sun Shim, M.D., Ph.D., Gee Young Suh, M.D., Manfred Danilovits, M.D., Hideo Ogata, M.D., Anu Kurve, M.D., Joon Chang, M.D., Ph.D., Katsuhiro Suzuki, M.D., Thelma Tupasi, M.D., Won-Jung Koh, M.D., Barbara Seaworth, M.D., Lawrence J. Geiter, Ph.D., and Charles D. Wells, M.D.

ABSTRACT

BACKGROUND

Delamanid (OPC-67683), a nitro-dihydro-imidazooxazole derivative, is a new antituberculosis medication that inhibits mycolic acid synthesis and has shown potent in vitro and in vivo activity against drug-resistant strains of *Mycobacterium tuberculosis*.

METHODS

In this randomized, placebo-controlled, multinational clinical trial, we assigned 481 patients (nearly all of whom were negative for the human immunodeficiency virus) with pulmonary multidrug-resistant tuberculosis to receive delamanid, at a dose of 100 mg twice daily (161 patients) or 200 mg twice daily (160 patients), or placebo (160 patients) for 2 months in combination with a background drug regimen developed according to World Health Organization guidelines. Sputum cultures were assessed weekly with the use of both liquid broth and solid medium; sputum-culture conversion was defined as a series of five or more consecutive cultures that were negative for growth of *M. tuberculosis*. The primary efficacy end point was the proportion of patients with sputum-culture conversion in liquid broth medium at 2 months.

RESULTS

Among patients who received a background drug regimen plus 100 mg of delamanid twice daily, 45.4% had sputum-culture conversion in liquid broth at 2 months, as compared with 29.6% of patients who received a background drug regimen plus placebo (P=0.008). Likewise, as compared with the placebo group, the group that received the background drug regimen plus 200 mg of delamanid twice daily had a higher proportion of patients with sputum-culture conversion (41.9%, P=0.04). The findings were similar with assessment of sputum-culture conversion in solid medium. Most adverse events were mild to moderate in severity and were evenly distributed across groups. Although no clinical events due to QT prolongation on electrocardiography were observed, QT prolongation was reported significantly more frequently in the groups that received delamanid.

CONCLUSIONS

Delamanid was associated with an increase in sputum-culture conversion at 2 months among patients with multidrug-resistant tuberculosis. This finding suggests that delamanid could enhance treatment options for multidrug-resistant tuberculosis. (Funded by Otsuka Pharmaceutical Development and Commercialization; ClinicalTrials.gov number, NCT00685360.)

From the Makati Medical Center, Manila (M.T.G.), and the Tropical Disease Foundation, Makati City (M.T.G., T.T.) — both in the Philippines; the State Agency of Tuberculosis and Lung Diseases, Riga, Latvia (V.S.); Hospital Nacional Sergio E. Bernales (E.S.-G.), Unidad de Investigacion, Hospital Nacional Daniel A. Carrión (J.L.C.-R.), and Hospital Nacional Hipólito Unanue (D.E.V.-V.) — all in Lima, Peru; Shanghai Pulmonary Hospital, Shanghai (H.X.), and Beijing Chest Hospital, Beijing (M.G.) — both in China; Sadr Abassia Hospital, Cairo (M.A.); National Masan Hospital, Masan (S.-K.P.), Asan Medical Center, Seoul (T.S.S.), Samsung Medical Center, Seoul (G.Y.S., W.-J.K.), and Yonsei University Medical Center, Severance Hospital, Seoul (J.C.) — all in South Korea; Tartu University Lung Hospital, Tartu (M.D.), and North Estonian Medical Center Foundation, Center of Pulmonology, Tallinn (A.K.) — both in Estonia; Fukujuji Hospital, Tokyo (H.O.), and National Hospital Organization Kinki-Chuo Chest Medical Center, Osaka (K.S.) — both in Japan; the University of Texas Health Center at Tyler, Tyler (B.S.); and Otsuka Pharmaceutical Development and Commercialization, Rockville, MD (L.J.G., C.D.W.). Address reprint requests to Dr. Geiter at Otsuka Novel Products/OPDC, 2440 Research Blvd., Rockville, MD 20850, or at lawrence.geiter@otsuka-us.com.

N Engl J Med 2012;366:2151-60.

DELAMANID

- Dihidroimidazoxazol: **inhibeix síntesi de l'àcid ketomicòlic** un cop és activat per MTB
- Selectiu enfront a MTB en estat actiu i en fase **latent**
- **No resistència creuada** amb cap fàrmac de 1ª linia
- **Absorció augmentada amb aliments rics en greix**
- No interacció amb enzims hepàtics
- Prolongació de **l'intèrval QT**

Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis

Vija Skripconoka*, Manfred Danilovits#, Lea Pehme#, Tarmo Tomson¶, Girts Skenders*, Tiina Kummik#, Andra Cirule*, Vaira Leimane*, Anu Kurve¶, Klavdia Levina¶, Lawrence J. Geiter+, Davide Manissero§ and Charles D. Wells+

- **DELAMANID ≥ 6m** x ≤ 2m (seguiment **à** 24m)
  - **100 o 200mg/d 2m + 100 o 200mg 2d x setm 6m**
  - **Millors resultats: 74.5%** x 55%
  - **Disminució de la mortalitat 1,0%** x 8,3% (p>0.001)
  - Benificis també en pacients amb **TB XDR**

This analysis suggests that treatment with delamanid for 6 months in combination with an optimised background regimen can improve outcomes and reduce mortality among patients with both multidrug-resistant and extensively drug-resistant TB.

Altres fàrmacs en estudi:

PA-824: **PRETOMANID: nou nitroimidazol**

- Inhibeix la síntesi **d'àcids micòlics** de la paret cel·lular
- Bactericida i esterilizante

SQ109: derivat no anàleg de l'Etambutol

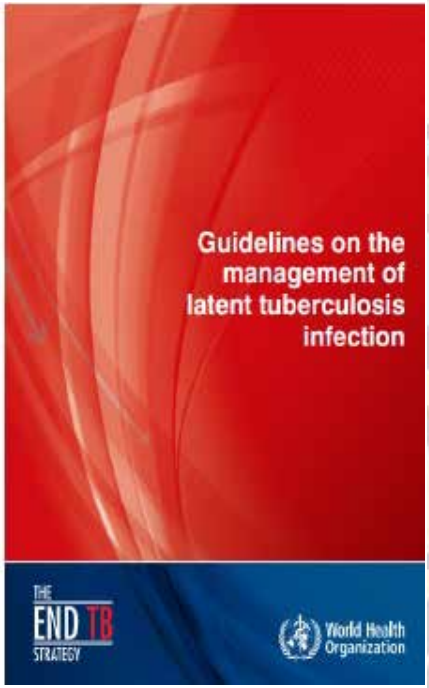
- Inhibeix la síntesi de la **paret cel·lular** amb una diana distinta. Bactericida. No resistència creuada amb E

PNU100480 (SUTEZOLID):

- Activitat bactericida superior al linezolid; **menor toxicitat**

Tractament de la infecció latent: (WHO)

- ü **6 a 9 mesos de ISONIACIDA**
- ü **3-4 RIFAMPICINA+ISONIACIDA**
- ü **3-4 RIFAMPICINA**
- ü **3 ISONIACIDA + RIFAPENTINA (setmanal)**



Conclusions:

- Identificació de **noves dianes farmacològiques**, augment de les inversions i de l' interès en el desenvolupament de nous fàrmacs antiTB
- Moltes **noves molècules** en diferents fases d' estudi i molts **assatjos amb fàrmacs ja coneguts**
- **No s'ha pogut escurçar el tractament de la TB a 4m amb pautes amb quinolones**
- **Rifapentina en dosis altas** para intentar escurçar el ttm
- **Bedaquilina i Delamanid** ja comercialitzats en EUA per TB-MDR
- En els propers anys probablement tindrem **nous fàrmacs** comercialitzats i **nous esquemes terapèutics**

GRÀCIES per la vostra ATENCIÓ

Malú De Souza Galvão
Unitat de Tuberculosi
Vall d'Hebron-Drassanes
Barcelona
msouza@vhebron.net