Uso Racional de Fármacos del Grupo 5 en el Tratamiento de la TB-XDR y Nuevos Fármacos en el Tratamiento de la TBC

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Clasificación Racional de Fármacos anti-TB

Adaptada de Caminero JA. Lancet Inf Dis 2010; 10; 621-629

Grupo 1: Fármacos de Primera Línea, Vía Oral

H,R,E,Z → Todos los Posibles

Grupo 2: Quinolonas: Altas dosis Lfx, o Mx → Sólo 1

Grupo 3: Inyectables S.L: Km, Ak, Cm → Sólo 1

Grupo 4: Otras Drogas de Segunda Línea:

Eth/Pth, Cs/Tz, PAS → Hasta completar 4

Grupo 5: Posibles Drogas de Refuerzo:

Linezolid, Clofaz., Carbapenem, Amoxi/Clav. → Si < 4

Clasificación Racional de Fármacos anti-TB

Adaptada de Caminero JA. Lancet Inf Dis 2010; 10; 621-629

Grupo 1: ***Drogas Primera Línea, Oral*** → **Todos los Posibles**

- H, R (Esenciales)

- E, Z (Acompañantes)

Grupo 2: ***Quinolonas (Esenciales): Altas dosis Lfx, o Mx*** → **Sólo 1**

Grupo 3: ***Inyectables S.L (Esenciales):*** ***Km, Ak, Cm*** → **Sólo 1**

Grupo 4: ***Otras Drogas de Segunda Línea:***

Eth/Pth, Cs/Tz, PAS → **Hasta completar 4**

Grupo 5: ***Posibles Drogas de Refuerzo:*** → **Si < 4**

- Esenciales: Linezolid, Bedaquilina ?, Delamanid ?

- Acompañantes: Clofaz., Carbapenem, Amoxi/Clav.

Clasificación Racional de Fármacos anti-TB

¿ Deberíamos pensar en una re-clasificación de estos Grupos basado en la experiencia acumulada en los últimos años respecto del Grupo 5 ?

Clasificación Racional de Fármacos anti-TB

Caminero JA. Int J Tuberc Lung Dis 2006, 10: 829-837

Grupo 5: Posibles Drogas de Refuerzo:

- ***Esenciales: Linezolid, Bedaquilina ?, Delamanid ?*** → ***Si < 4***
- ***Acompañantes: Clofaz., Carbapenem, Amoxi/Clav***

Pensando sobre todo en la XDR-TB, es necesario re-evaluar el Papel de estas Drogas

El Grupo 5 de Drogas Anti-TB

- ***Basado en su Eficacia, posibles Efectos Adversos y Costo, la secuencia de introduccion de las Drogas de este Grupo debería ser:***

1. ***Clofazimine (Cfz)***
2. ***Amoxicillin-clavulanate (Amx/Clv).***
3. ***Linezolid (Lzd)***
4. ***Carbapenems (imipenem / meropenem)***
5. ***Clarithromycine***
6. ***Thioacetazone***

Caminero JA, et al. Lancet Infect Dis 2010; 10: 621–29

El Grupo 5 de Drogas Anti-TB

- ***Basado en su Eficacia y no coniderando el COSTO y posibles Efectos Adversos, la secuencia de introduccion de las Drogas de este Grupo debería ser:***

1. ***Linezolid (Lzd)***
2. ***Bedaquiline ?***
3. ***Delamanid ?***
4. ***Clofazimine (Cfz)***
5. ***Carbapenems (imipenem / meropenem)***
6. ***Amoxicillin-clavulanate (Amx/Clv).***

El Grupo 5 de Drogas Anti-TB

- Ba… …D y pos… intr… …ser:

Mucha gente es muy contraria a recomendar estas drogas porque la evidencia es muy Escasa

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Smith GSC, Pell J. *BMJ*. 2003

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

What is already known about this topic

Parachutes are widely used to prevent death and major injury after gravitational challenge

Parachute use is associated with adverse effects due to failure of the intervention and iatrogenic injury

Studies of free fall do not show 100% mortality

What this study adds

No randomised controlled trials of parachute use have been undertaken

The basis for parachute use is purely observational, and its apparent efficacy could potentially be explained by a "healthy cohort" effect

Individuals who insist that all interventions need to be validated by a randomised controlled trial need to come down to earth with a bump

Linezolid

Oxazolidinonas

- ***Nueva (1987) clase de antibióticos orales de amplio espectro***
- ***Linezolid ha sido el primero registrado por la FDA***
- ***Inhibe la Síntesis Temprana de las proteínas***
- ***Otros miembros con excelente actividad "in vitro" contra M. Tb (Sutezolid > linezolid > eperezolid)***
- ***La actividad "in vivo" de Sutezolid es similar a H y R***

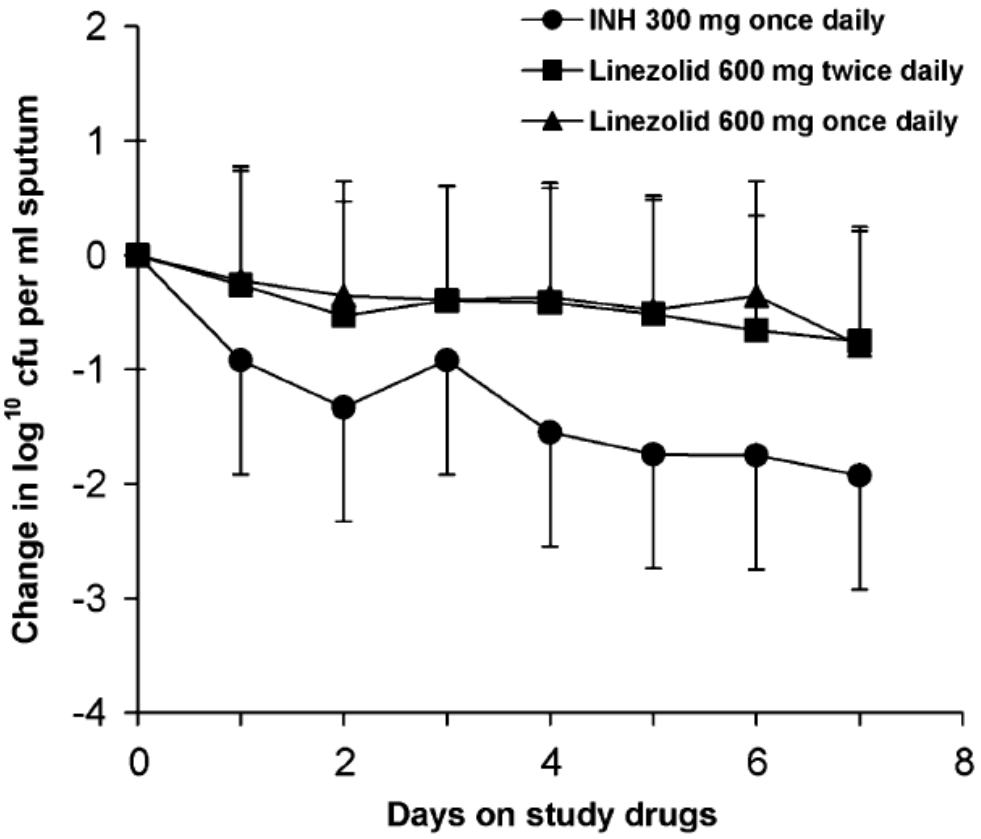
Barbachnyn MR, et al. J Med Chem 1996; 39:680-685

Cynamon MH, et al. Antimicrob Agent Chemother 1999;43:1189-91

Early and Extended Early Bactericidal Activity of Linezolid in Pulmonary Tuberculosis

Reynaldo Dietze[1], David Jamil Hadad[1], Bryan McGee[2,3], Lucilia Pereira Dutra Molino[1], Ethel Leonor Noia Maciel[1], Charles A. Peloquin[2,3], Denise F. Johnson[4], Sara M. Debanne[5], Kathleen Eisenach[6], W. Henry Boom[4], Moises Palaci[1], and John L. Johnson[4]

Am J Respir Crit Care Med Vol 178. pp 1180–1185, 2008



Linezolid has modest early bactericidal activity against rapidly dividing tubercle bacilli in patients with cavitary pulmonary TB during the first 2 days of administration, but little extended early bactericidal activity.

Early and Extended Early Bactericidal Activity of Linezolid in Pulmonary Tuberculosis

Reynaldo Dietze[1], David Jamil Hadad[1], Bryan McGee[2,3], Lucilia Pereira Dutra Molino[1], Ethel Leonor Noia Maciel[1], Charles A. Peloquin[2,3], Denise F. Johnson[4], Sara M. Debanne[5], Kathleen Eisenach[6], W. Henry Boom[4], Moises Palaci[1], and John L. Johnson[4]

Am J Respir Crit Care Med Vol 178. pp 1180–1185, 2008

TABLE 5. MEDIAN PHARMACODYNAMIC PARAMETERS (RANGE) ADJUSTED FOR FREE DRUG CONCENTRATIONS AFTER 5 DAYS OF DAILY MONOTHERAPY WITH STUDY DRUGS

Drug	n	C_{max} ($\mu g/ml$)*	AUC_{0-12} ($\mu g \cdot h/ml$)*	AUC_{0-24} ($\mu g \cdot h/ml$)*	C_{max}/MIC† (IQR)	AUC_{0-12}/MIC† (IQR)	AUC_{0-24}/MIC† (IQR)	Percent Dosing Interval above MIC†,‡ (IQR)
INH, 300 mg once daily	10	3.1 (2.5–4.8)	15.3 (5.8–24.2)	17.2 (5.8–26.1)	62.7 (51.0–77.3)	306.7 (229.3–405.2)	344.6 (249.4–449.2)	95.5 (over 24 h) (76.4–100)
Linezolid, 600 mg twice daily	9§	13.4 (8.1–17.2)	80.3 (34.8–136.1)	160.7 (134.4–225.8)	16.2 (14.3–23.0)	121.6 (79.8–141.6)	243.2 (159.7–283.2)	100.0 (over 12 h) (100–100)
Linezolid, 600 mg once daily	10	10.3 (8.2–14.7)	60.1 (32.8–82.3)	66.8 (33.0–99.2)	20.0 (10.2–21.9)	107.8 (63.4–126.3)	116.2 (71.0–138.4)	62.8 (over 24 h) (54.6–77.0)

Definition of abbreviation: AUC_{0-12} and AUC_{0-24} = area under the curve during the first 12 and 24 hours after dosing, respectively; C_{max} = plasma maximal drug concentration; IQR = interquartile range; INH = isoniazid; MIC = minimal inhibitory concentration.

* C_{max} and AUC versus time curve for unbound (free) drug in plasma. Linezolid and INH were assumed to be 31 and 10% protein bound, respectively.

† C_{max}/MIC, AUC_{0-12}/MIC, AUC_{0-24}/MIC, and percent dosing interval above MIC were calculated using the published MIC_{90} for INH of 0.05 μg/ml (28) and the measured MIC against linezolid for a pretreatment sputum *M. tuberculosis* isolate from each patient.

‡ Determined by linear extrapolation of concentration-versus-time curve to intersection with MIC.

§ One patient in the linezolid twice-daily arm withdrew from the study after randomization before receiving any doses of study drug.

INT J TUBERC LUNG DIS 16(4):447–454

http://dx.doi.org/10.5588/ijtld.11.0451
Published online 8 February 2012

REVIEW ARTICLE

Linezolid for the treatment of complicated drug-resistant tuberculosis: a systematic review and meta-analysis

H. Cox,*† N. Ford‡§

*Médecins Sans Frontières, Khayelitsha, Cape Town, South Africa; †Monash University, Melbourne, Victoria, Australia; ‡Médecins Sans Frontières, London, UK; §Centre for Infectious Disease Epidemiology and Research, University of Cape Town, Cape Town, South Africa

- **11 studies → 148 patients.**
- **Treatment success was 67.99%**
- **There were no significant differences in success comparing daily linezolid dose (⩽600 vs. >600 mg) and mean linezolid duration (⩽7 vs. >7 months).**
- **The pooled estimate for the frequency of any adverse events was 61.48% (95%CI 40.15–82.80), with 36.23% (95%CI 20.67–51.79) discontinuing linezolid due to adverse events.**

Eur Respir J 2012; 40: 1430–1442
DOI: 10.1183/09031936.00022912

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, Holly A. Anger, Jose A. Caminero, Paolo Castiglia, Saverio De Lorenzo, Giovanni Ferrara, Won-Jung Koh, Giesela F. Schecter, Tae S. Shim, Rupak Singla, Alena Skrahina, Antonio Spanevello, Zarir F. Udwadia, Miquel Villar, Elisabetta Zampogna, Jean-Pierre Zellweger, Alimuddin Zumla and Giovanni Battista Migliori

- **Twelve studies (11 countries; three continents) → 121 patients**
- **Most MDR-TB cases achieved sputum smear (86/93, 92.5%) and culture (100/107, 93.5%) conversion after treatment with individualized Lz regimens**
- **Median time to smear and culture conversion being 43.5 (21-90) and 61 (29-119) days, respectively.**
- **99/121 (81.8%) were successfully treated.**
- **No significant differences were detected regarding dosage ≤ 600 mg vs. > 600 mg**

Eur Respir J 2012; 40: 1430–1442
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- ***Adverse events were observed in 58.9%* (63/107) of which 68.4% (54/79) were major, including anaemia (38.1%), peripheral neuropathy (47.1%), gastro-intestinal disorders (16.7%), *optic neuritis (13.2%)* and thrombocytopenia (11.8%).**
- ***The proportion of AEs was significantly higher when the linezolid daily dosage exceeded 600 mg*.**

Chang KC, Yew WW, Tam CM, Leung CC. WHO Group 5 drugs and difficult multidrug-resistant tuberculosis: a systematic review with cohort analysis and meta-analysis. Antimicrob Agents Chemother. 2013 Jun 17.

- ***A cohort of 194 patients was assembled from 20 articles involving 12 geographical regions.***

- ***In descending order of frequency, linezolid was used in 162 (84%), macrolides in 84 (43%), clofazimine in 65 (34%), amoxicillin with clavulanate in 56 (29%), thioridazine in 18 (9%), carbapenem in 16 (8%), and high-dose isoniazid in 16 (8%).***

- ***Linezolid use significantly increased the probability (95% confidence interval) of favorable outcome by 55-57%***

Chang KC, Yew WW, Tam CM, Leung CC. WHO Group 5 drugs and difficult multidrug-resistant tuberculosis: a systematic review with cohort analysis and meta-analysis. Antimicrob Agents Chemother. 2013 Jun 17.

- ***Any significant add-on benefit from the use of other Group 5 drugs on outcome of patients treated with linezolid, although selection bias might have underestimated their effects.***

- ***Our findings substantiated use of linezolid in the treatment of XDR-TB or fluoroquinolone-resistant MDR-TB, and calls for further studies to evaluate the roles of other Group 5 drugs.***

INT J TUBERC LUNG DIS 16(12):1588–1593

http://dx.doi.org/10.5588/ijtld.12.0322
E-published ahead of print 2 October 2012

Linezolid-containing regimens for the treatment of drug-resistant tuberculosis in South African children

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*Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Health Sciences, Stellenbosch University, Cape Town, Tygerberg, †Department of Paediatrics and Child Health, Faculty of Health Sciences, Free State University, Bloemfontein, ‡Department of Paediatrics, Pelonomi Hospital, Bloemfontein, South Africa; §Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, UK; ¶Tygerberg Children's Hospital, Cape Town, Tygerberg, South Africa

- Seven children (three human immunodeficiency virus [HIV] infected) received a linezolidc ontaining regimen → All had culture-confirmed DR-TB; five had previously failed second-line anti-tuberculosis treatment.
- **Four children were cured and three were still receiving anti-tuberculosis treatment, but had culture converted.**
- **None of the non-HIV-infected children experienced adverse events while receiving linezolid.**
- Three HIV-infected children had adverse events, one of which was life-threatening; linezolid was permanently discontinued in this case.
- Adverse events included lactic acidosis (*n* = 1), pancreatitis (*n* = 2), peripheral neuropathy (*n* = 1) and asymptomatic bone marrow hypoplasia (*n* = 1).

Oxazolidinonas. Problemas

- ***LINEZOLID***

  – ***Alto Perfil de Toxicidad (Toxicidad Hematológica y poli-neuritis) cuando se da más de 6-8 semanas***

  – ***Muy Caro (50 US$ / día)***

EXCELENTE Droga Anti-TB

Eur Respir J 2012; 39: 956–962
DOI: 10.1183/09031936.00076811

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

1 US$ /día

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

- *29 MDR-TB treatment failure patients (sixteen had laboratory proven XDR-TB, and rest 13 had MDR-TB with resistance to any quinolone but sensitive to injectables)*
- *All patients received daily unsupervised therapy with linezolid, one injectable agent, one fluoroquinolone and two or more other drugs.*
- *Out of total 29 patients, 89.7% patients achieved sputum smear and culture conversion; **72.4% showed interim favorable outcome**; 10.3% died, 6.8% failed and 10.3% patients defaulted.*
- *Linezolid had to be stopped in 3 (10.3%) patients due to adverse reactions.*
- *The outcome of treatment of 16 XDR-TB patients was comparable to the other 13.*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

N Engl J Med 2012; 367:1508-1518

Linezolid for Treatment of Chronic Extensively Drug-Resistant Tuberculosis

Myungsun Lee, M.D., Jongseok Lee, Ph.D., Matthew W. Carroll, M.D.,

- 41 XDR-TB with response to any available chemotherapeutic option during the previous 6 months → Randomly assigned to linezolid therapy that started immediately or after 2 months, at a dose of 600 mg per day, without a change in their background regimen.

- By 4 months, 15 of the 19 patients (79%) in the immediate-start group and 7 of the 20 (35%) in the delayed-start group had culture conversion (P=0.001).

- Most patients (34 of 39 [87%]) had a negative sputum culture within 6 months after linezolid had been added to their drug regimen.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

N Engl J Med 2012; 367:1508-1518

Linezolid for Treatment of Chronic Extensively Drug-Resistant Tuberculosis

Myungsun Lee, M.D., Jongseok Lee, Ph.D., Matthew W. Carroll, M.D.,

- Of the 38 patients with exposure to linezolid, 31 (82%) had clinically significant adverse events that were possibly or probably related to linezolid.

- Patients who received 300 mg per day after the second randomization had fewer adverse events than those who continued taking 600 mg per day.

- Thirteen patients completed therapy and have not had a relapse. Four cases of acquired resistance to linezolid have been observed.

Chang KC, et al. Can Intermittent Dosing Optimize Prolonged Linezolid Treatment of Difficult Multidrug-Resistant Tuberculosis? *Antimicrob Agents Chemother. 2013 Jun 17*

- ***Treatment with linezolid, dosed at 800 mg once daily for 1 to 4 months as guided by sputum culture status and tolerance and then at 1,200 mg thrice weekly until ≥1 year after culture conversion, in addition to individually optimized regimens among 10 consecutive patients with extensively drug-resistant tuberculosis or fluoroquinolone-resistant multidrug-resistant tuberculosis.***

- ***All achieved stable cure, with anemia corrected and neuropathy stabilized, ameliorated, or avoided after switching to intermittent dosing. Serum linezolid profiles appeared better optimized.***

J Antimicrob Chemother
doi:10.1093/jac/dks078

Antimicrobial Chemotherapy

Daily 300 mg dose of linezolid for multidrug-resistant and extensively drug-resistant tuberculosis: updated analysis of 51 patients

Won-Jung Koh[1]†, Yeh Rim Kang[1]†, Kyeonman Jeon[1], O. Jung Kwon[1], Jiwon Lyu[2], Woo Sung Kim[2] and Tae Sun Shim[2]*

[1]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University Schoo of Medicine, Irwon-ro 81, Gangnam-gu, Seoul, Korea; [2]Division of Pulmonary and Critical Care Medicine, University of Ulsan College of Medicine, Asan Medical Center, 88 Olympic-ro 43-gil, Songpa-gu, Seoul, Korea

*Corresponding author. Tel: +82-2-3010-3892; Fax: +82-2-3010-6968; E-mail: shimts@amc.seoul.kr
†These authors contributed equally to this work.

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Objectives: Linezolid may be an effective treatment for multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB). The objective was to evaluate the efficacy, tolerability and adverse events of a 300 mg daily dose of linezolid in the treatment of MDR/XDR-TB.

Patients and methods: We retrospectively reviewed the medical records of 51 MDR-TB patients, including 26 patients (51%) with XDR-TB, to evaluate the safety, tolerability and efficacy of therapy with 300 mg/day linezolid. All patients had failed previous treatments with second-line anti-TB drugs.

Results: Patients were treated with linezolid for a median of 413 days (IQR 237–622 days). Favourable treatment outcome (treatment success or still on treatment after culture conversion) was achieved in 40 patients (78%) with culture conversion at a median of 55 days (IQR 41–91 days) from the start of linezolid therapy. Eleven patients (22%) had unfavourable outcomes (treatment failure or death) and 14 (27%) discontinued treatment due to neurotoxicity (peripheral or optic neuropathy) after a median of 278 days (IQR 174–412 days).

Conclusions: Our findings suggest that linezolid at a daily dose of 300 mg is effective against intractable MDR/XDR-TB, and may be associated with fewer neuropathic side effects than a daily dose of 600 or 1200 mg.

Bedaquilina

FDA aprueba Bedaquilina

- **A finales de Diciembre 2012, la FDA aprobó Interinamente Bedaquilina para el tratamiento de la TB-MDR.**

- **Es la Primera droga anti-TB aprobada en 40 años.**

TMC 207 (R207910, Bedaquiline o J)

- ***Descubierta por Janssen, en desarrollo por TIBOTEC y TB Alliance***

- ***Inhibe la bomba de protones de la Sintasa de ATP de Mycobacterium tuberculosis***

- ***Activa contra cepas sensibles y resistentes a drogas anti TB convencionales***

CIM de la Diarylquinioline *R207910* frente a Micobacterias

Andries et al. Science 2005; 307:223-7

Mycobacterial species	Number of strains	Range of MICs for multiple strains (µg/ml)	Median MIC (µg/ml)
M. tuberculosis, H37Rv	1	—	0.030
M. tuberculosis, fully susceptible clinical isolates	6	0.030–0.120	0.060
M. tuberculosis resistant to isoniazid	7	0.003–0.060	0.010
M. tuberculosis resistant to rifampin	1	—	0.030
M. tuberculosis resistant to isoniazid and rifampin	2	0.030–0.030	0.030
M. tuberculosis resistant to isoniazid and streptomycin	1	—	0.010
M. tuberculosis resistant to ethambutol	1	—	0.010
M. tuberculosis resistant to pyrazinamide	1	—	0.030
M. tuberculosis resistant to fluoroquinolone	2	0.060–0.120	0.090
M. bovis	1	—	0.003
M. avium/M. intracellulare (MAC)	7	0.007–0.010	0.010
M. kansasii	1	—	0.003
M. marinum	1	—	0.003
M. fortuitum	5	0.007–0.010	0.010
M. abscessus	1	—	0.250
M. smegmatis	7	0.003–0.010	0.007
M. ulcerans	1	—	0.500

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 4, 2009 VOL. 360 NO. 23

The Diarylquinoline TMC207 for Multidrug-Resistant Tuberculosis

Andreas H. Diacon, M.D., Ph.D., Alexander Pym, M.D., Ph.D., Martin Grobusch, M.D., D.T.M.&H., Ramonde Patientia, M.D., Roxana Rustomjee, M.D., Ph.D., Liesl Page-Shipp, M.D., Christoffel Pistorius, M.D., Rene Krause, M.D., Mampedi Bogoshi, M.D., Gavin Churchyard, M.B., Ch.B., Amour Venter, Nat.Dip.Med.Tech.(Micro), Jenny Allen, B.Sc., Juan Carlos Palomino, Ph.D., Tine De Marez, Ph.D., Rolf P.G. van Heeswijk, Pharm.D., Ph.D., Nacer Lounis, Ph.D., Paul Meyvisch, M.Sc., Johan Verbeeck, D.V.M., Ph.D., Wim Parys, M.D., Karel de Beule, Pharm.D., Koen Andries, D.V.M., Ph.D., and David F. Mc Neeley, M.D., M.P.H.T.M.

- ***Estudio Fase IIb en MDR-TB***
- ***TMC207 + régimen de 2da línea vs placebo + régimen de 2da línea por 8 semanas, esterilizó el esputo en 48% de los pacientes vs 9% en el caso del placebo.***
- ***Al cabo de 2 años de tratamiento, se curaron 81% de los pacientes que recibieron TMC207 + régimen estándar vs 57% de los que recibieron solo el régimen estandar***

- In a randomized placebo controlled study of 47 patients with MDR-TB, **bedaquiline** increased the proportion of patients with conversion (48% vs. 9%) (1) and reduced the time to culture conversion over 24 weeks of observation (2).
- In addition, none of the patients who received bedaquiline acquired resistance to ofloxacin compared with 22% of those on placebo.

1. *Diacon AH, Pym A, Grobusch M, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. N Engl J Med 2009;360:2397-405.*

2. Diacon AH, Donald PR, Pym A, et al. 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. Antimicrob Agents Chemother 2012;56:3271-6.

TMC 207 (R207910, Bedaquiline o J)

- ***La combinación TMC207/H/Z y TMC207/R/Z cura la TB en el modelo murino en 2 meses. Es sinergista con pirazinamida***
- ***Actividad Bactericida Precoz (EBA) inicial menor que H y R, pero la iguala a los 14 días.***
- ***Puede tener interacciones desfavorables con RIF, aunque parece que no pierde actividad bactericida.***

Burman WJ: Clin Inf Dis 2010; 50(S3): S165-S170

14-day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial

www.thelancet.com Published online July 23, 2012

Andreas H Diacon, Rodney Dawson, Florian von Groote-Bidlingmaier, Gregory Symons, Amour Venter, Peter R Donald, Christo van Niekerk, Daniel Everitt, Helen Winter, Piet Becker, Carl M Mendel, Melvin K Spigelman

- **The mean 14-day EBA of PA-824-moxifloxacin-pyrazinamide (n=13; 0·233 [SD 0·128]) was significantly higher than that of bedaquiline (14; 0·061 [0·068]), bedaquiline- pyrazinamide (15; 0·131 [0·102]), bedaquiline-PA-824 (14; 0·114 [0·050]), but not PA-824-pyrazinamide (14; 0·154 [0·040]), and comparable with that of standard treatment (ten; 0·140 [0·094]).**
- **Treatments were well tolerated and appeared safe. One patient on PA-824-moxifloxacin-pyrazinamide was withdrawn because of corrected QT interval changes exceeding criteria prespecified in the protocol.**
- **Interpretation: PA-824-moxifloxacin-pyrazinamide is potentially suitable for treating drug-sensitive and multidrugresistant tuberculosis.**

The use of bedaquiline in the treatment of multidrug-resistant tuberculosis

Interim policy guidance

World Health Organization

WHO/HTM/TB/2013.6

The use of Bedaquiline in the treatment of MDR-TB

WHO Interim policy guidance, June 2013

Table 1. Summary of evidence for the efficacy of bedaquiline in the treatment of MDR-TB

Parameters	Bedaquiline	Placebo	p value
Median time to sputum conversion	83 days (95% CI: 56,97)	125 days (95% CI: 98,168)	<0.0001
Proportion of patients with culture conversion			
Week 24	78.8 %	57.6%	0.008
Week 72	71.2%	56.1%	0.069
Week 120	62.1%	43.9%	0.035
Proportion cured	57.6% (38/66)	31.8% (21/66)	0.003

The use of Bedaquiline in the treatment of MDR-TB

WHO Interim policy guidance, June 2013

Table 2. Summary of adverse events of interest

	Bedaquiline/BR N=79 (%)	Placebo/BR N=81 (%)
Musculoskeletal and connective tissue	39 *(49.4)*	40 *(49.4)*
Myalgia	*6 (7.6)*	*7 (8.6)*
Musculoskeletal pain	*4 (5.1)*	*4 (4.9)*
Rhabdomyolysis/Myopathy	*0*	*0*
Gastrointestinal disorders	53 (67.1)	53 (65.4)
Pancreatitis	*1 (1.3)*	*0*
Increased amylase	*2 (2.5)*	*1 (1.2)*
Nausea	*32 (40.5)*	*30 (37.0)*
Vomiting	*23 (29.1)*	*22 (27.2)*
Upper abdominal pain	*10 (12.7)*	*7 (8.6)*
Gastritis	*7 (8.9)*	*16 (19.8)*

The use of Bedaquiline in the treatment of MDR-TB

WHO Interim policy guidance, June 2013

- **Dose**: 400mg daily for the first two weeks, followed by 200mg three times per week at least 48 hours apart, for a total maximum duration of 24 weeks.

- Available data suggest better uptake of bedaquiline when administered **with food**.

- Laboratory testing of the minimal inhibitory concentration (**MIC**) of bedaquiline seems to suggest a **breakpoint** for susceptibility **at <0.5µg/ml in agar medium**; however, until a specific DST assay for bedaquiline is developed, clinicians will not be able to be guided by MIC values or DST results when composing a regimen

The use of Bedaquiline in the treatment of MDR-TB

WHO Interim policy guidance, June 2013

- ***To be used as one of the 4 effective drugs in:***

1. ***MDR-TB with***
   a. ***known adverse drug reactions, poor tolerance, or contraindication to any component of the combination regimen; or***
   b. ***unavailability or lack of a guaranteed supply of a drug***

2. ***Pre-XDR-TB***

3. ***XDR-TB*** ***(Janssen does not give the Drug for failures to the Standarized MDR-TB regimen)***

The use of Bedaquiline in the treatment of MDR-TB

WHO Interim policy guidance, June 2013

- ***The current recommendation for the use of bedaquiline applies to adults (≥18yrs) with pulmonary disease.***
- ***Special caution is needed when bedaquiline is used in people aged 65 years and older, and in adults living with HIV, as data on efficacy and safety are extremely limited.***
- ***Use of the drug in pregnant women and children is not advised due to a lack of evidence on safety and efficacy.***
- ***While patients with exclusive extrapulmonary disease were not included in the bedaquiline trial, the use of the drug in extrapulmonary TB patients may be considered, extrapolating from the data in patients with pulmonary TB.***

AAC Accepts, published online ahead of print on 3 March 2014
Antimicrob. Agents Chemother. doi:10.1128/AAC.00037-14

Cross-resistance between Clofazimine and Bedaquiline through Up-regulation of MmpL5 in *Mycobacterium tuberculosis*

Ruben C. Hartkoorn, Swapna Upekar°, Stewart T. Cole*

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Nuevos Fármacos Anti-TB de Interés

1. *Fluoroquinolonas*
2. *Rifamicinas*
3. *Oxizolidinonas*
4. ***Nitroimidazoles***
5. *Diarylquinolines (R207910)*
6. *Diamine SQ109*
7. *Pyrrole (LL3858)*

Ma Z, et al. Lancet 2010; 375: 2100–09

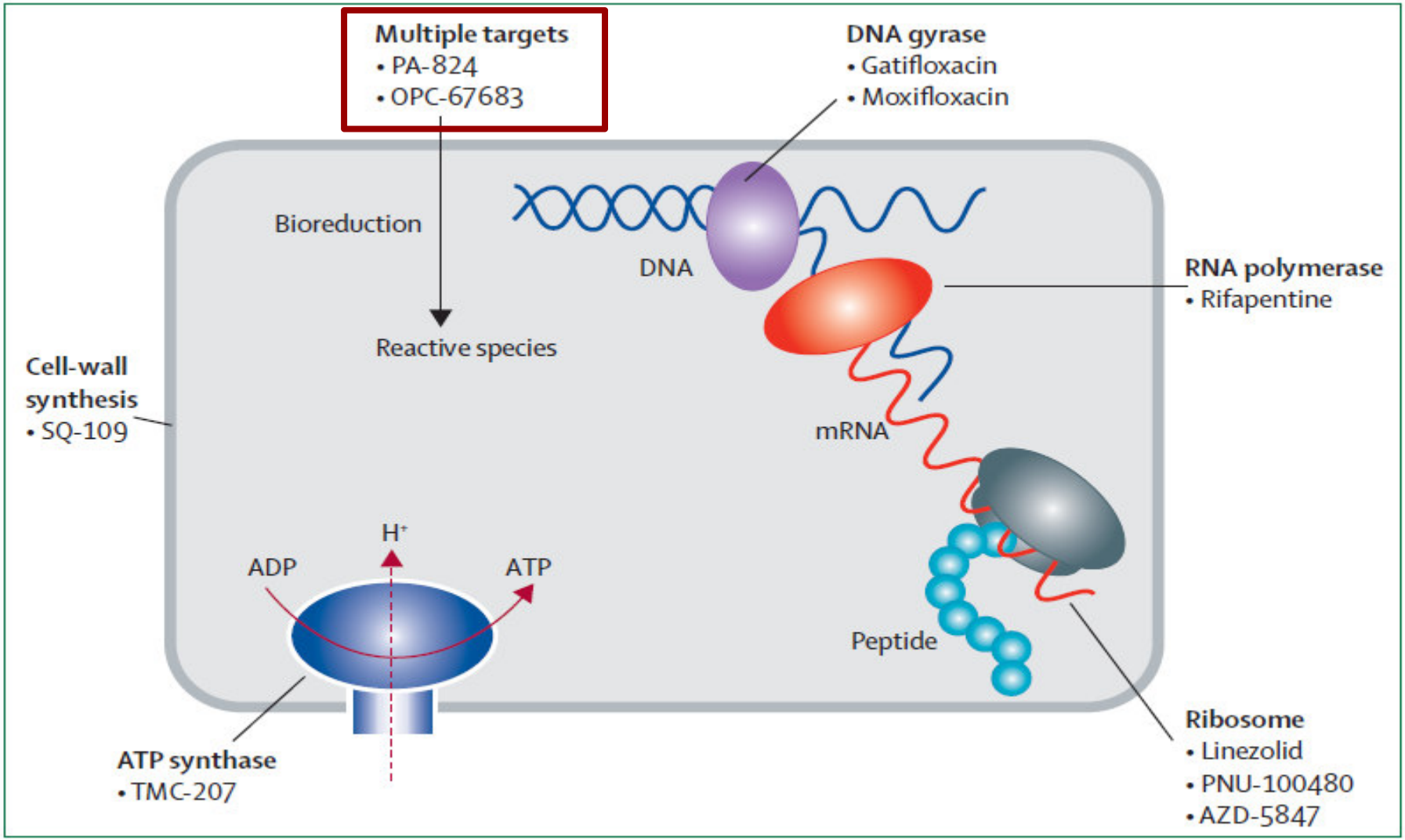

Figure 3: **Mechanisms of action of new compounds in clinical development for tuberculosis**

Nitroimidazoles

- ***Dos Nitroimidazoles están en desarrrollo clínico:***
  - ***PA-824** es un miembro de la familia nitroimidazo-oxazine.*
  - ***Delamanid** es un miembro de la familia nitroimidazo-oxazole.*

PA-824 y Delamanid

- ***Compuestos bactericidas potentes con***
  - ✓ ***actividad antituberculosa. Inhiben la síntesis proteica y la biosíntesis de los ácidos micólicos de la pared celular***
  - ✓ ***blanco de acción reducido (alta especificidad para TB)***
- ***Eficacia potencial***
  - ✓ ***Modelo murino: absorción oral. Actividad a los 10 días comparable a INH***
  - ✓ ***actividad contra las cepas MDR-TB estudiadas***

PA-824 y Delamanid

- ***Actividad en bacilos en fase latente***
  - ✓ *modelo de cultivo anaerobico estático*
  - ✓ *Estructura relacionada con metronidazol*
- ***Actividad y biodisponibilidad por vía oral***
- ***Sin mutagenidad o toxicidad en estudios prelim.***
- ***Candidatos para la nueva etapa de investigación (Estudios Fase III)***

14-day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial

www.thelancet.com Published online July 23, 2012

Andreas H Diacon, Rodney Dawson, Florian von Groote-Bidlingmaier, Gregory Symons, Amour Venter, Peter R Donald, Christo van Niekerk, Daniel Everitt, Helen Winter, Piet Becker, Carl M Mendel, Melvin K Spigelman

- **The mean 14-day EBA of PA-824-moxifloxacin-pyrazinamide (n=13; 0·233 [SD 0·128]) was significantly higher than that of bedaquiline (14; 0·061 [0·068]), bedaquiline-pyrazinamide (15; 0·131 [0·102]), bedaquiline-PA-824 (14; 0·114 [0·050]), but not PA-824-pyrazinamide (14; 0·154 [0·040]), and comparable with that of standard treatment (ten; 0·140 [0·094]).**
- **Treatments were well tolerated and appeared safe. One patient on PA-824-moxifloxacin-pyrazinamide was withdrawn because of corrected QT interval changes exceeding criteria prespecified in the protocol.**
- **Interpretation: PA-824-moxifloxacin-pyrazinamide is potentially suitable for treating drug-sensitive and multidrugresistant tuberculosis.**

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.

- Delamanid (OPC-67683) is a nitro-dihydro-imidazooxazole derivative that inhibits mycolic acid synthesis.
- In a recently published randomized placebo-controlled multinational clinical trial, 481 patients were assigned to receive delamanid 100 mg twice daily, delamanid 200 mg twice daily, or placebo for 2 months in combination with an optimized background regimen.
- Culture conversion at 2 months in a liquid culture system was more likely in patients who received **delamanid 100 mg twice daily** (45.4%, p = 0.0008)) or **delaminid 200 mg twice daily** (41.9%, p=0.04) than placebo.
- Similarly with solid media, conversion occurred in 53.8%, 65.2% and 33.6%, respectively.
- Adverse events were distributed relatively equally across the three groups except that QT prolongation was more common in the delamanid group.

Gler MT, Skripconoka V, Sanchez-Garavito E, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. N Engl J Med 2012;366:2151-60.

Eur Respir J 2013; 41: 1393–1400
DOI: 10.1183/09031936.00125812

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+

- **Favourable outcomes were observed in 143/192 patients (74.5%) who received delamanid ≥6 months, compared to 126/229 patients (55.0%) who received delamanid for ≤2 months.**
- **Mortality was reduced to 1.0% among those receiving long-term delamanid, versus short-term/no delamanid (8.3%), p<0.001.**
- **Treatment benefit was also seen among patients with XDR-TB**
- **Conclusion: This analysis suggests that treatment with delamanid for 6 months in combination with an optimized background regimen can improve outcomes and reduce mortality among M/XDR-TB**

Eur Respir J 2013; 41: 1393–1400
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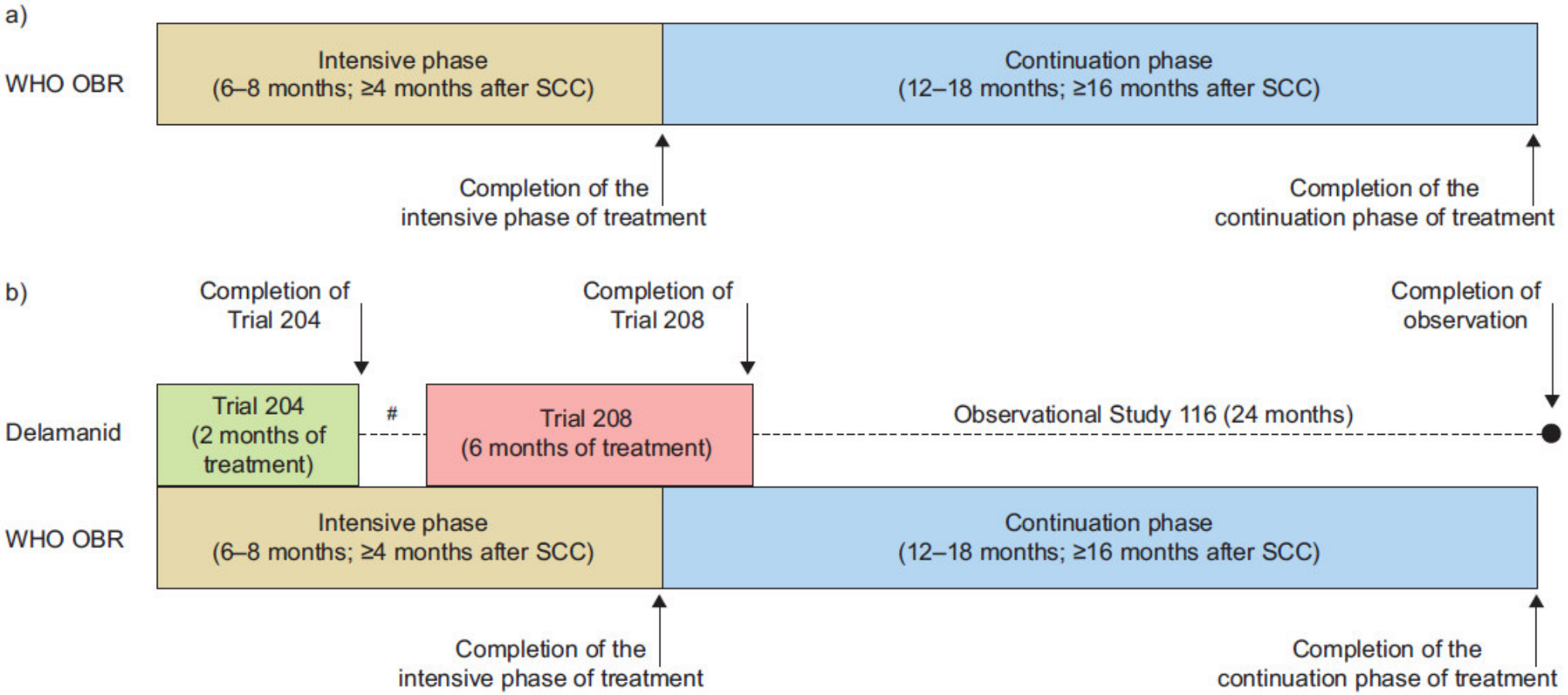

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MDR-TB and XDR-TB

TABLE 2 Long-term (24 month) treatment outcomes after treatment with delamanid in combination with an optimised background treatment regimen: MDR- and XDR-TB patients

Treatment outcome	Long-term treatment#	Short-term treatment¶	All patients+
Favourable	143 (74.5; 67.7–80.5)§	126 (55.0; 48.3–61.6)§	269 (63.9; 59.1–68.5)
Cured	110 (57.3; 50.0–64.4)	111 (48.5; 41.8–55.1)	221 (52.5; 47.6–57.4)
Completed	33 (17.2; 12.1–23.3)§	15 (6.6; 3.7–10.6)§	48 (11.4; 8.5–14.8)
Unfavourable	49 (25.5; 19.5–32.3)§	103 (45.0; 38.4–51.7)§	152 (36.1; 31.5–40.9)
Died	2 (1.0; 0.1–3.7)§	19 (8.3; 5.1–12.7)§	21 (5.0; 3.1–7.5)
Failed	32 (16.7; 11.7–22.7)	26 (11.4; 7.6–16.2)	58 (13.8; 10.6–17.4)
Defaulted	15 (7.8; 4.4–12.6)§	58 (25.3; 19.8–31.5)§	73 (17.3; 13.8–21.3)

Eur Respir J 2013; 41: 1393–1400
DOI: 10.1183/09031936.00125812

Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis

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Just XDR-TB

TABLE 3 Long-term (24 month) treatment outcomes after treatment with delamanid in combination with an optimised background treatment regimen: XDR-TB patients only

Treatment outcome	Long-term treatment#	Short-term treatment¶	All Patients+
Favourable	27 (61.4; 45.5–75.6)	6 (50.0; 21.1–78.9)	33 (58.9; 45.0–71.9)
Cured	11 (25.0; 13.2–40.3)	5 (41.7; 15.2–72.3)	16 (28.6; 17.3–42.2)
Completed	16 (36.4; 22.4–52.2)	1 (8.3; 0.2–38.5)	17 (30.4; 18.8–44.1)
Unfavourable	17 (38.6; 24.4–54.5)	6 (50.0; 21.1–78.9)	23 (41.1; 28.1–55.0)
Died	0 (0.0)§	3 (25.0; 5.5–57.2)§	3 (5.4; 1.1–14.9)
Failed	14 (31.8; 18.6–47.6)	3 (25.0; 5.5–57.2)	17 (30.4; 18.8–44.1)
Defaulted	3 (6.8; 1.4–18.7)	0.0 (0.0)	3 (5.4; 1.1–14.9)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 July 2013
EMA/446276/2013
EMEA/H/C/002552

Questions and answers

Refusal of the marketing authorisation for Delamanid (delamanid)

What were the CHMP's main concerns that led to the refusal? (1)

- ***The CHMP's main concern was that the benefits of Delamanid in the treatment of MDR-TB had not been sufficiently shown.***

- ***The CHMP considered that the duration of treatment in the main study (two months) was too short to establish the effectiveness of delamanid in treating TB when added to other anti-TB medicines.***

- ***As Delamanid was to be used for at least six months the data from two months' treatment could not be used to predict the effectiveness of delamanid when given for six months.***

What were the CHMP's main concerns that led to the refusal? (2)

- ***In addition, the results of the extension and follow-up studies could not be used to support the longer term use of Delamanid as the studies included only those patients who had agreed to take part and who might therefore not be representative of the patients as a whole.***
- ***Finally, the CHMP was of the view that it was not possible from the data submitted to determine the most appropriate dosing for Delamanid.***
- ***Therefore, at that point in time, the CHMP was of the opinion that the benefits of Delamanid did not outweigh its risks and recommended that it be refused marketing authorisation***

Clofazimine

Nature **179**, 1013-1015 (18 May 1957) | doi:10.1038/1791013a0

A New Series of Phenazines (Rimino-Compounds) With High Antituberculosis Activity

VINCENT C. BARRY, J. G. BELTON, MICHAEL L. CONALTY, JOAN M. DENNENY, DEIRDRE W. EDWARD, J. F. O'SULLIVAN, DERMOT TWOMEY & FRANK WINDER

1. Laboratories of the Medical Research Council of Ireland, Trinity College, Dublin

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Clofazimine is a riminophenazine antibiotic that was synthesized in 1954 for the treatment of tuberculosis

INT J TUBERC LUNG DIS 16(8):1119–1125

http://dx.doi.org/10.5588/ijtld.11.0752
E-published ahead of print 12 June 2012

In vitro and in vivo activity of clofazimine against *Mycobacterium tuberculosis* persisters

J. Xu,* Y. Lu,* L. Fu,* H. Zhu,* B. Wang,* K. Mdluli,† A. M. Upton,† H. Jin,* M. Zheng,* W. Zhao,* P. Li*

*Department of Pharmacology, Beijing Tuberculosis and Thoracic Tumour Research Institute, Beijing Chest Hospital, Capital Medical University, Beijing, China; †The Global Alliance for TB Drug Development, New York, New York, USA

- CFZ showed significant bactericidal activity in the mouse model over the wide dose range of 2–200 mg/kg.
- CFZ activity was dose-dependent. The bacilli were eradicated in the CFZ 200 mg/kg group after treatment for 60 days, and in the CFZ 20 mg/kg group after 90 days of treatment

Clofazimine had dose-dependent, sustained bactericidal activity against M. tuberculosis persisters in a mouse model of chronic TB

INT J TUBERC LUNG DIS 17(8):1001–1007

http://dx.doi.org/10.5588/ijtld.12.0144
E-published ahead of print 25 March 2013

REVIEW ARTICLE

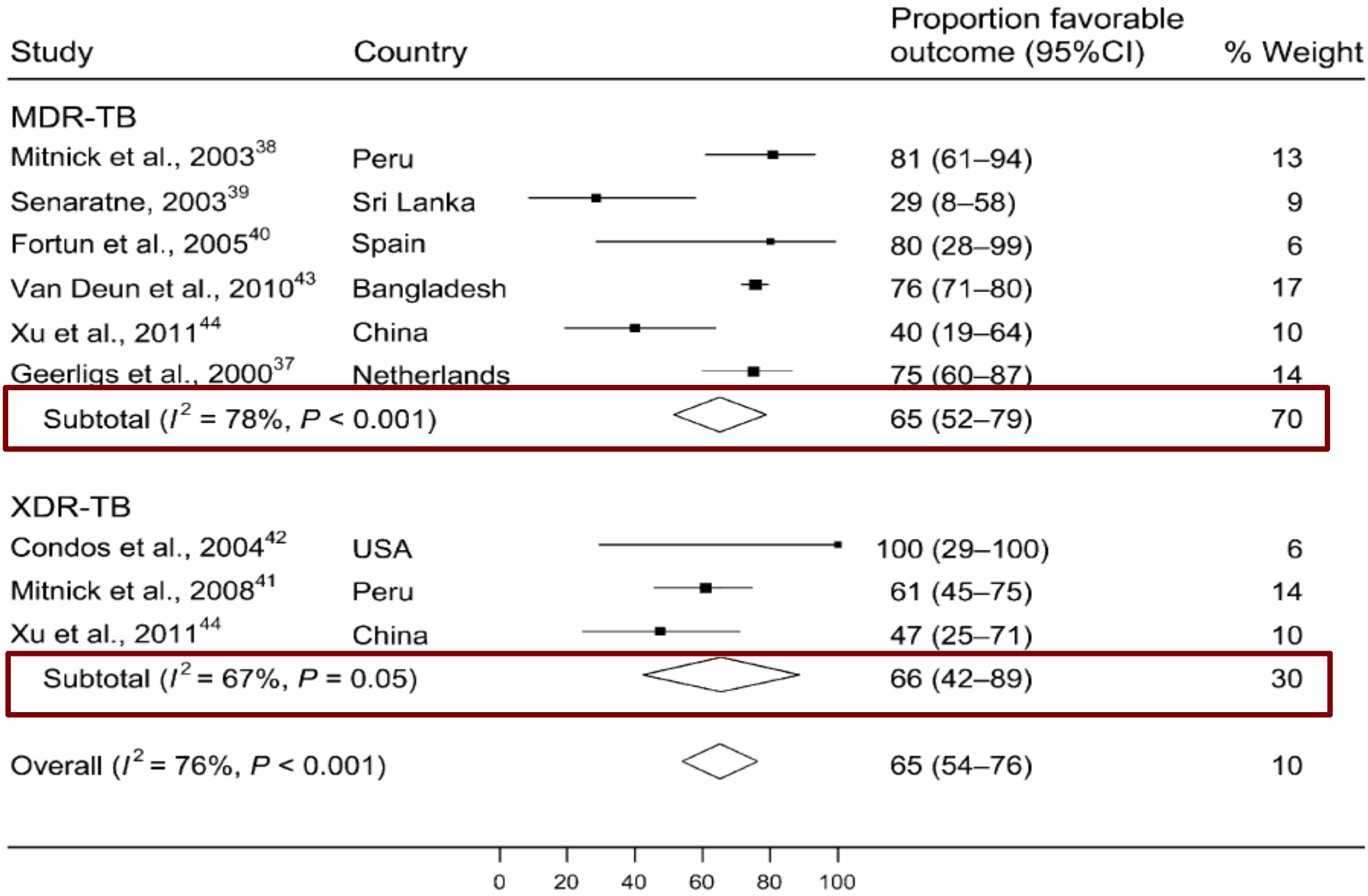
Systematic review of clofazimine for the treatment of drug-resistant tuberculosis

M. Gopal,* N. Padayatchi,† J. Z. Metcalfe,‡ M. R. O'Donnell*†

*Division of Pulmonary Medicine, Albert Einstein College of Medicine, Bronx, NY, USA; †Centre for AIDS Programme of Research in South Africa, Durban, South Africa; ‡Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital, and Francis J Curry International Tuberculosis Center, University of California, San Francisco, California, USA

- Nueve estudios observacionales (seis sobre TB-MDR y tres sobre TBXDR).
- En general, el 65% de los pacientes alcanzó un desenlace favorable (IC95% 54–76)
- Mediante un meta-análisis de efectos aleatorios, se encontró que 65% de los pacientes con TB-MDR (IC95% 52–79) y 66% de los pacientes con TB-XDR (IC95% 42–89) lograron un desenlace terapéutico favorable.

Clofazimine and MDR-TB. Gopal el at. Int J Tuberc Lung Dis 2013



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REVIEW ARTICLE

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*Division of Pulmonary Medicine, Albert Einstein College of Medicine, Bronx, NY, USA; †Centre for AIDS Programme of Research in South Africa, Durban, South Africa; ‡Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital, and Francis J Curry International Tuberculosis Center, University of California, San Francisco, California, USA

Table Summary of cohort studies utilizing CFZ for drug-resistant TB

Author, year, reference	Study location	Study years	Sample size/ patients treated with CFZ	HIV-positive patients/ total no. tested	Age, years mean (±SD)	Female %	Median no. of drugs (range)	Dose mg	Patients with favorable outcome/ no. treated (%)
MDR-TB									
Geerligs et al., 2000[37]	Netherlands	1985–1998	44/39	0/39	33	29.5	6 (4–9)	Not known	33/44
Mitnick et al., 2003[38]	Peru	1996–1999	75/26	1/65	26.8 (±15)	51	6 (5–9)	Not known	21/26 (83)
Senaratne, 2003[39]	Sri Lanka	1997–2002	14/14	Not available	50 (±26)	21.4	5–7	Not known	4/14 (28.5)
Fortun et al., 2005[40]	Spain	1999–2004	5/5	1/5	~26	20	~4	100	4/5 (80)
Van Deun et al., 2010[43]	Bangladesh	1997–2007	427/427 in intensive and 244/427 in consolidative	Not tested	33.8 (±1.1)	25	~5	50–100	323/427 (75.6)
Xu et al., 2011[44]	China	2008–2011	20/20	Not tested	38 (±18)	34.4	6 (4–7)	100	8/20 (40)
MDR-TB favorable outcome									65% (95%CI 52–79)
XDR-TB									
Condos et al., 2004[42]	USA	2000–2005	7/3	1/7	~31	85.7	~7	Not known	3/3 (100)
Mitnick et al., 2008[41]	Peru	1999–2002	48/46	0	32.0 (±9.9)	35.4	5.3 (4–7)	200–300	28/46 (60.8)
Xu et al., 2011[44]	China	2008–2011	19/19	Not tested	38 (±16)	34.4	6 (4–7)	100	9/19 (47.3)
XDR-TB favorable outcome									66% (95%CI 42–89)
Overall favorable outcome									65% (95%CI 54–76)

Carbapenems

Carbapenems in the Treatment of MDR/XDR-TB

- Following the rational invoked for the Amx/Clv, the carbapenems offer a second approach to overcoming the b-lactam resistance of M. tuberculosis.

- They are poor substrates for both class A and class C b-lactamases and two carbapenems, meropenem and imipenem, are active in vitro against M. tuberculosis.

- Effectiveness has been demonstrated in some reports on MDR-TB patients treated with imipenem and meropenem combined to clavulanic acid.

- In any case, the limited experience, the unknown long-term toxicity and the high costs relegate carbapenems to a group to be used only in extreme situations.

Caminero JA, et al. Lancet Infect Dis 2010; 10: 621–29

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 2005, p. 2816–2821 Vol. 49, No. 7
0066-4804/05/$08.00+0 doi:10.1128/AAC.49.7.2816–2821.2005

Imipenem for Treatment of Tuberculosis in Mice and Humans

Henry F. Chambers,* Joan Turner, Gisela F. Schecter, Masae Kawamura, and Philip C. Hopewell

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Received 22 December 2004/Returned for modification 24 January 2005/Accepted 23 March 2005

Chemotherapy of tuberculosis caused by multiple-drug-resistant (MDR) strains is problematic because of choices limited to relatively inefficacious and toxic drugs. Some beta-lactam antibiotics are active against *Mycobacterium tuberculosis* in vitro. We investigated the efficacy of imipenem in a mouse model of tuberculosis and in humans with MDR tuberculosis. Mice infected with *M. tuberculosis* strain H37Rv were treated with isoniazid or imipenem. Residual organisms in lung and spleen and survival of imipenem-treated mice were compared to those of untreated or isoniazid-treated mice. Ten patients with MDR tuberculosis also were treated with imipenem in combination with other first- or second-line agents; elimination of *M. tuberculosis* from sputum samples was measured by quantitative culture. Although it was less effective than isoniazid, imipenem significantly reduced the numbers of *M. tuberculosis* organisms in lungs and spleens and improved survival of mice. Eight of 10 patients with numerous risk factors for poor outcomes responded to imipenem combination therapy with conversion of cultures to negative. Seven remained culture-negative off of therapy. There were two deaths, one of which was due to active tuberculosis. Organisms were eliminated from the sputa of responders at a rate of 0.35 $\log_{10}$ CFU/ml/week. Relapse upon withdrawal of imipenem and development of resistance to imipenem in a nonresponder suggest that imipenem exerts antimycobacterial activity in humans infected with *M. tuberculosis*. Imipenem had antimycobacterial activity both in a mouse model and in humans at high risk for failure of treatment for MDR tuberculosis.

Hugonnet J, et al. Meropenem-clavulanate is effective against extensively drug-resistant Mycobacterium tuberculosis. Science 2009;323:1215-8.

- Meropenem-clavulanate → Potent activity against M. tuberculosis (MIC < 1 mg/ml)

-Inhibitory activity against anaerobically grown cultures ("persistent“)

- Inhibited the growth of 13 XDR-TB and in 4 drug-susceptible strains

Eur Respir J 2013; 41: 1386–1392
DOI: 10.1183/09031936.00124312

Efficacy and safety of meropenem–clavulanate added to linezolid-containing regimens in the treatment of MDR-/XDR-TB

Saverio De Lorenzo*,, Jan Wilem Alffenaar#,**, Giovanni Sotgiu¶, Rosella Centis+, Lia D'Ambrosio+, Simon Tiberi*, Mathieu S. Bolhuis#, Richard van Altena§, Piero Viggiani*, Andrea Piana¶, Antonio Spanevello*,ƒ and Giovanni Battista Migliori+**

A case-control study of **meropenem and clavunate plus linezolid** containing MDR-TB regimens was reported to be associated with a smear conversion rate at 3 months of **87.5% vs 56%** (p =0.02) in controls

Eur Respir J 2013; 41: 1386–1392
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- 37 Cases with MDR/XDR-TB were prescribed MC (daily dose: 3 g) in addition to a linezolid-containing regimen (dosage range: 300-1,200 mg·day, designed according to international guidelines, which was prescribed to controls (61).
- The clinical severity of cases was worse than that of controls (DST profile; % Sm+, % of re-treatment cases).
- **The group of cases yielded a higher proportion of sputum smear converters (28/32, 87.5% VS. 9/16, 56.3%; p-value: 0.02) and culture converters (31/37, 83.8% VS. 15/24, 62.5%; p-value: 0.06).**
- Excluding XDR-TB patients (11/98, 11.2%), cases scored a significantly higher proportion of culture converters than controls (p-value: 0.03).

Amoxicillin-Clavulanate

Amoxicillin-Clavulanate in the Treatment of MDR/XDR-TB

- M. tuberculosis is naturally resistant b-lactams antibiotics → mediated by a class A b-lactamase which hydrolyses penicillins and cephalosporins

- Resistance may be overcome by two means:

- Inhibition of the b-lactamase (+Clavulanate) or
- The use of an antibiotic that is not a substrate for it (carbapenems).

Amoxicillin-Clavulanate in the Treatment of MDR/XDR-TB

-Amx/Clv is active in vitro (1) and has early bactericidal activity in patients with pulmonary TB (2).

-Anecdotally, Amx/Clv combined with other second-line agents has been successfully used in selected patients infected with MDR strains (3).

-This approach has met considerable scepticism, and the role, if any, of Amx/Clv remains unclear

- In any case, the lack of effective drugs for the treatment of MDR-TB and XDR-TB cases, the good tolerance and the low toxicity profile of this drug have made Amx/Clv a drug of choice from group 5

1 Cynamon MH. Antimicrob Agents Chemother 1983;24:429-31.

2. Chambers HF. Clin Infect Dis 1998;26:874-7. *3. Nadler JP. Chest 1991;99:1025-6*.

Journal of Infectious Diseases Advance Access published August 30, 2012

REVIEW ARTICLE

World Health Organization Group 5 Drugs for the Treatment of Drug-Resistant Tuberculosis: Unclear Efficacy or Untapped Potential?

Kelly E. Dooley,[1] Ekwaro A. Obuku,[2] Nadza Durakovic,[3] Vera Belitsky,[3] Carole Mitnick,[4] and Eric L. Nuermberger[1] on behalf of the Efficacy Subgroup, RESIST-TB

[1]Johns Hopkins University School of Medicine, Baltimore, Maryland; [2]Institute of Human Virology, University of Maryland School of Medicine, AIDS Relief Programme and Joint Clinical Research Centre, Kampala, Uganda; [3]Partners In Health, Boston, Massachusetts; and [4]Harvard Medical School, Boston, Massachusetts

- Administration of amoxicillin using divided doses was shown to have better EBA activity than single daily dosing and new formulations of amox/clav (2000/125 mg) may be safely administered 2-3 times per day achieving 50% T/MIC target against isolates for which AMX/CLAV MICS are 4-8 mcg/ml

Rational Classification of Anti-TB Drugs.

A proposal for a Near Future

Group 1: ***First Line Drugs, Oral*** ***(H,R,E,Z)***

Group 2: ***Quinolones:*** ***High dose Lfx, or Mox***

Group 3: ***Linezolid, Bedaquiline?, Delamanid?***

Group 4: ***SL Injectables:*** ***Km, Ak, Cm***

Group 5: ***Eth/Pth, Clofazimine, Carbapenems?***

Group 6: ***Cs/Tz, PAS, Am/Cl***