Short Course Treatment is Possible in MDR-TB?

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고 원 중

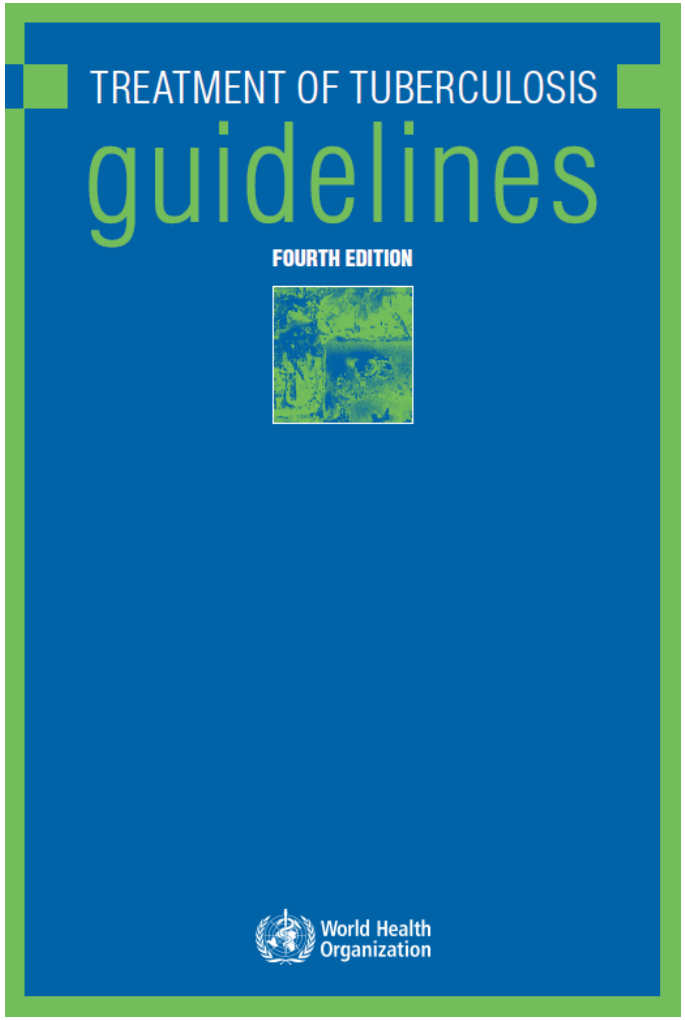
Declarations

- 본 발표 내용과 관련한 재정적 관계, 사적인 관계 등 이해관계(conflict of interest) 내용이 없습니다.

- 이 강의에 포함된 일부 주장은 제 생각과 달리 임재준 선생님의 생각일 수도 있습니다.

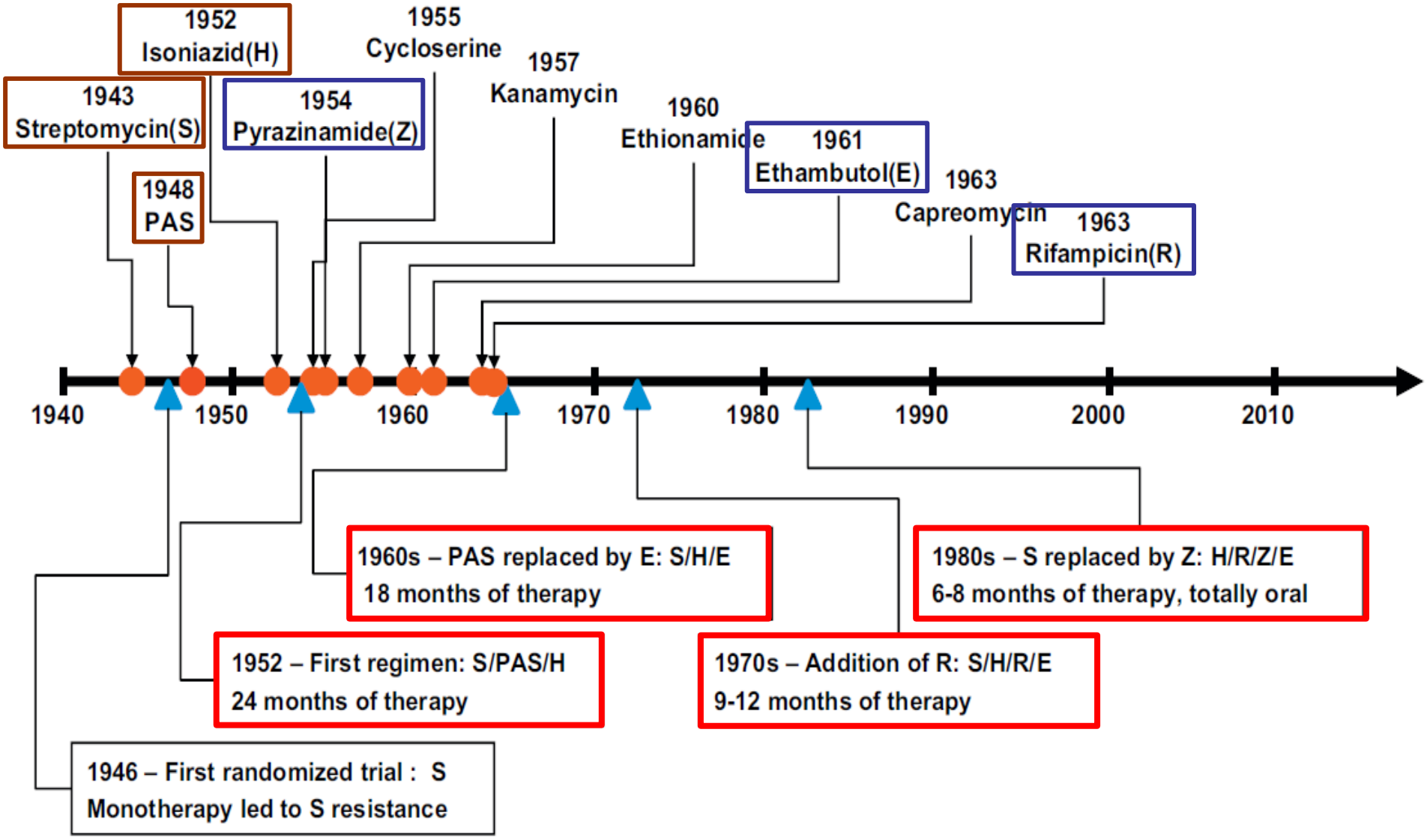
“단기”치료(“Short” Course)란?

WHO Guideline, 2009



Standard regimens
for new TB patients

- Intensive phase
  - 2 months of HRZE
- Continuation phase
  - 4 months of HR



Development of Regimens

폐결핵의 치료: 6개월 "단기"치료 확립

	약제	배양음전		실패	재발	추적 (개월)
		2개월	4개월			
Singapore	2HREZ/4HR	77%	99%	0	3.1%	36
/BMRC (1984)	2HRE/7HR	64%	98%	0	1.6%	
U.S.A.	2HRZ(E)/4HR	76%	95%	0	3.5%	24
(1990)	2HR(E)/7HR	68%	90%	0	2.8%	

(BTS. Br J Dis Chest 1984;78:330)
(Combs DL, et al. Ann Intern Med 1990;112:397)

현재 MDR-TB 치료성적은?

MDR-TB 치료성적 (메타분석결과)

- 33 retrospective observational cohort studies
- Overall Tx success 62% (95% CI, 58-67%)
- Regimen design
  - individualized 64% (95% CI, 59-68%)
  - standardized 54% (95% CI, 43-68%)
- Length of treatment
  - >18 months 66% (95% CI, 61-72%)
  - ≤18 months 56% (95% CI, 49-63%)

(Orenstein EW, et al. Lancet Infect Dis 2009;9:153)

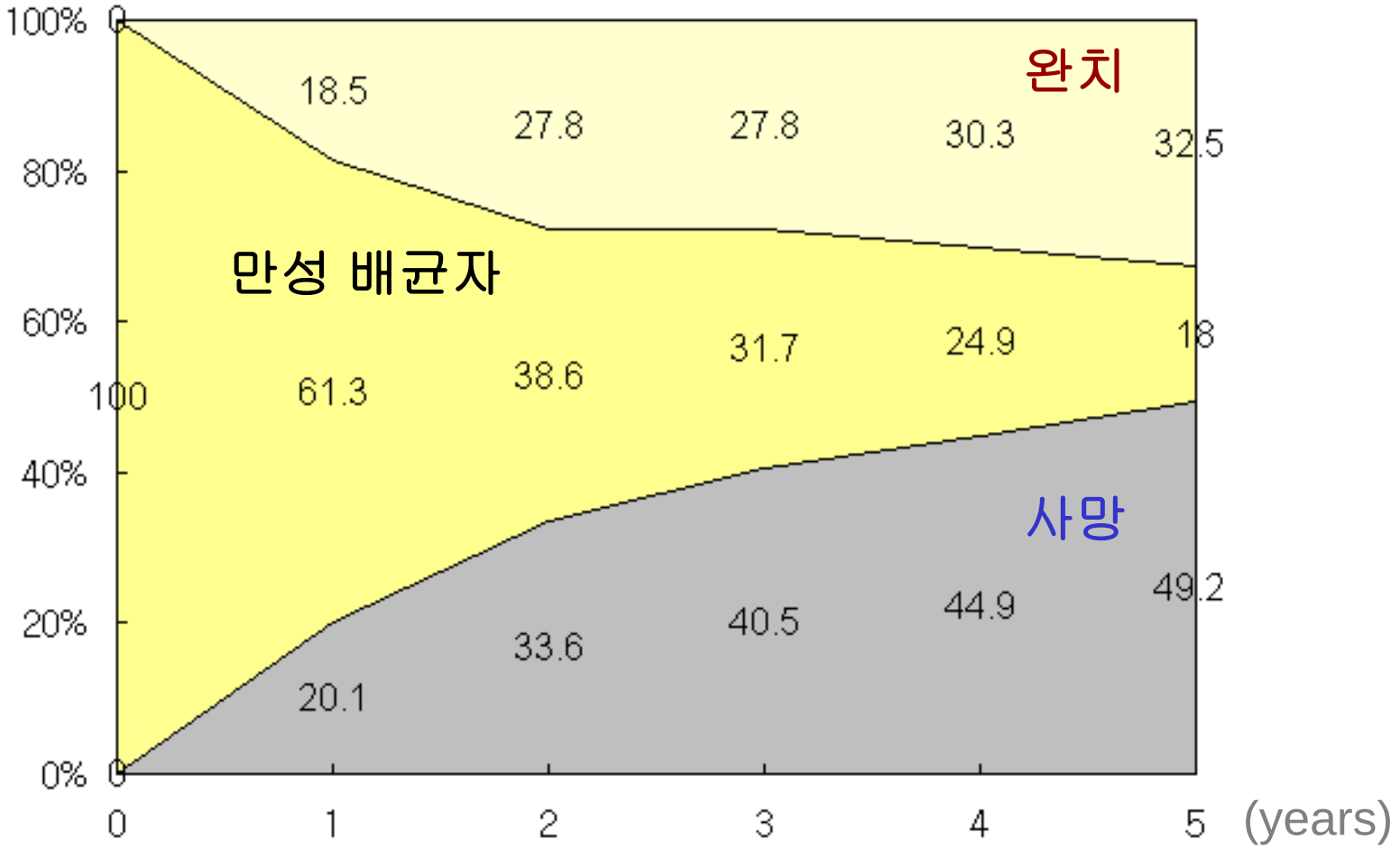
국내 MDR/XDR-TB 환자 치료성적

	XDR (n = 75)	Non-XDR (n = 1332)	Total (n = 1407)
Cure	9 (12%)	416 (31%)	425 (30%)
Tx completion	4 (5%)	89 (7%)	93 (7%)
Short-term Tx completion	9 (12%)	110 (8%)	119 (9%)
Failure	12 (16%)	53 (4%)	65 (5%)
Transfer out	9 (12%)	99 (7%)	108 (8%)
Default	12 (16%)	441 (33%)	453 (32%)
Death	20 (27%)	124 (9%)	144 (10%)
Tx success	22 (**29%**)	615 (**46%**)	637 (**45%**)
Relapse	3/22 (**14%**)	54/615 (**9%**)	57/637 (**9%**)

(Kim DH, et al. ARJCCM 2008;178:1075)

폐결핵의 자연 경과

AFB 도말 양성 폐결핵 환자를 치료 없이 5년간 추적관찰
인도 방갈로르(Bangalore), 1974



Guidelines for the programmatic management of drug-resistant tuberculosis

EMERGENCY UPDATE 2008

World Health Organization

Guidelines for the programmatic management of drug-resistant tuberculosis

2011 update

World Health Organization

4. Duration of second-line anti-tuberculosis regimens

Recommendations

4.1 In the treatment of patients with MDR-TB, an intensive phase of at least 8 months' duration is recommended (conditional recommendation, ⊕◯◯◯/ very low quality evidence).

4.2 In the treatment of patients with MDR-TB, a total treatment duration of at least 20 months is recommended in patients without any previous MDR-TB treatment (conditional recommendation, ⊕◯◯◯/very low quality evidence).

OPEN ACCESS Freely available online

PLOS | MEDICINE

Multidrug Resistant Pulmonary Tuberculosis Treatment Regimens and Patient Outcomes: An Individual Patient Data Meta-analysis of 9,153 Patients

Shama D. Ahuja[1], David Ashkin[2], Monika Avendano[3], Rita Banerjee[4], Melissa Bauer[5], Jamie N. Bayona[6], Mercedes C. Becerra[7,8], Andrea Benedetti[5], Marcos Burgos[9], Rosella Centis[10], Eward D. Chan[11], Chen-Yuan Chiang[12], Helen Cox[13], Lia D'Ambrosio[10], Kathy DeRiemer[14], Nguyen Huy Dung[15], Donald Enarson[16], Dennis Falzon[17], Katherine Flanagan[18], Jennifer Flood[19], Maria L. Garcia-Garcia[20], Neel Gandhi[21], Reuben M. Granich[17], Maria G. Hollm-Delgado[5], Timothy H. Holtz[22], Michael D. Iseman[23], Leah G. Jarlsberg[24], Salmaan Keshavjee[7], Hye-Ryoun Kim[25], Won-Jung Koh[26], Joey Lancaster[27], Christophe Lange[28], Wiel C. M. de Lange[29], Vaira Leimane[30], Chi Chiu Leung[31], Jiehui Li[32], Dick Menzies[5]*, Giovanni B. Migliori[10], Sergey P. Mishustin[33], Carole D. Mitnick[7], Masa Narita[34], Philly O'Riordan[35], Madhukar Pai[5], Domingo Palmero[36], Seung-kyu Park[37], Geoffrey Pasvol[38], Jose Peña[39], Carlos Pérez-Guzmán[40], Maria I. D. Quelapio[41], Alfredo Ponce-de-Leon[42], Vija Riekstina[30], Jerome Robert[43], Sarah Royce[24], H. Simon Schaaf[44], Kwonjune J. Seung[45], Lena Shah[5], Tae Sun Shim[46], Sonya S. Shin[45], Yuji Shiraishi[47], José Sifuentes-Osornio[48], Giovanni Sotgiu[49], Matthew J. Strand[23], Payam Tabarsi[50], Thelma E. Tupasi[41], Robert van Altena[29], Martie Van der Walt[27], Tjip S. Van der Werf[29], Mario H. Vargas[51], Pirett Viiklepp[52], Janice Westenhouse[53], Wing Wai Yew[54], Jae-Joon Yim[55], on behalf of the Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB[¶]

(Ahuja SD, et al. PLoS Med 2012;9:e1001300)

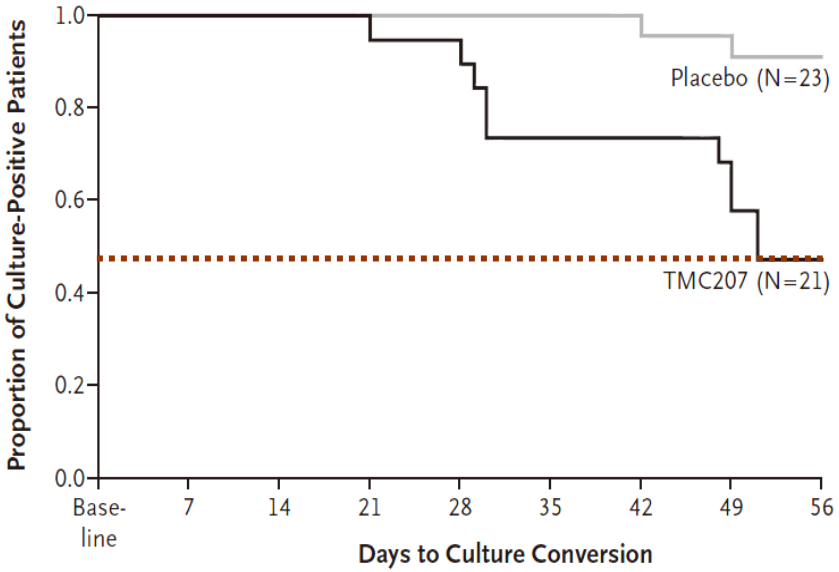
MDR-TB 치료기간: 성공 vs. 실패/재발 (과거 2차 약제 치료력 없는 경우)

Duration of Tx (mo)		N	Adjusted OR (95% CLs)
Initial	1.0-2.5	308	1.0 (reference)
	2.6-4.0	1406	1.2 (0.5-2.9)
	4.1-5.5	481	2.4 (1.3-4.3)
	5.6-7.0	377	3.7 (1.9-7.1)
	7.1-8.5	172	**5.1 (2.1-12.7)**
	8.6-20.0	792	2.2 (1.2-3.9)
Total	6.0-12.5	743	1.0 (reference)
	12.6-15.5	384	2.4 (1.5-3.6)
	15.6-18.5	1646	4.6 (2.0-10.4)
	18.6-21.5	612	**9.3 (5.8-15.0)**
	21.6-24.5	435	6.8 (4.2-11.1)
	24.6-27.5	207	8.2 (4.2-15.9)
	27.6-30.5	106	2.4 (1.2-5.0)
	30.6-36.0	48	1.3 (0.6-2.7)

(WHO, Guidelines for the programmatic management of drug-resistant tuberculosis 2011)

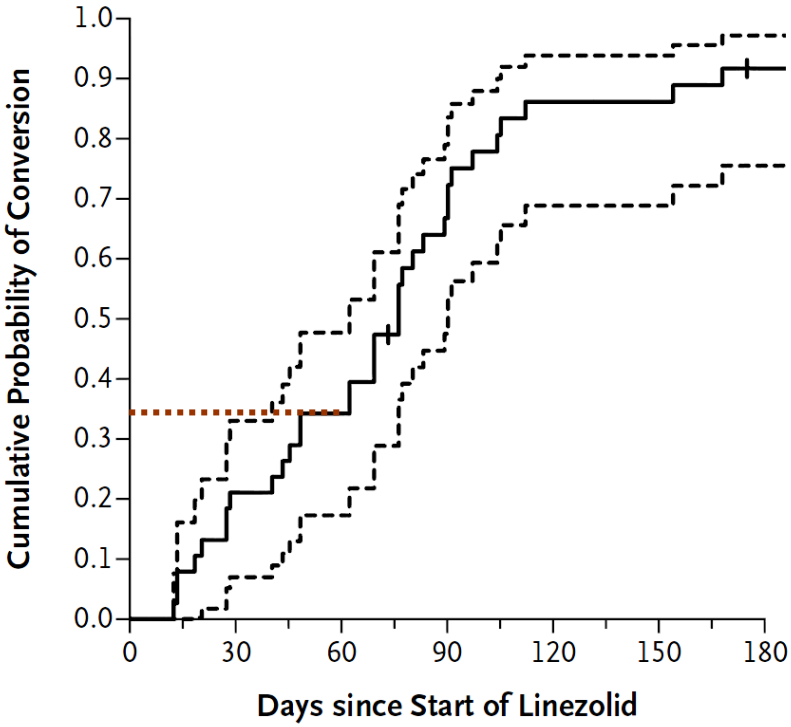
새로운 약제로 치료기간 단축이 가능한가?

Bedaquiline (TMC 207), NEJM 2009

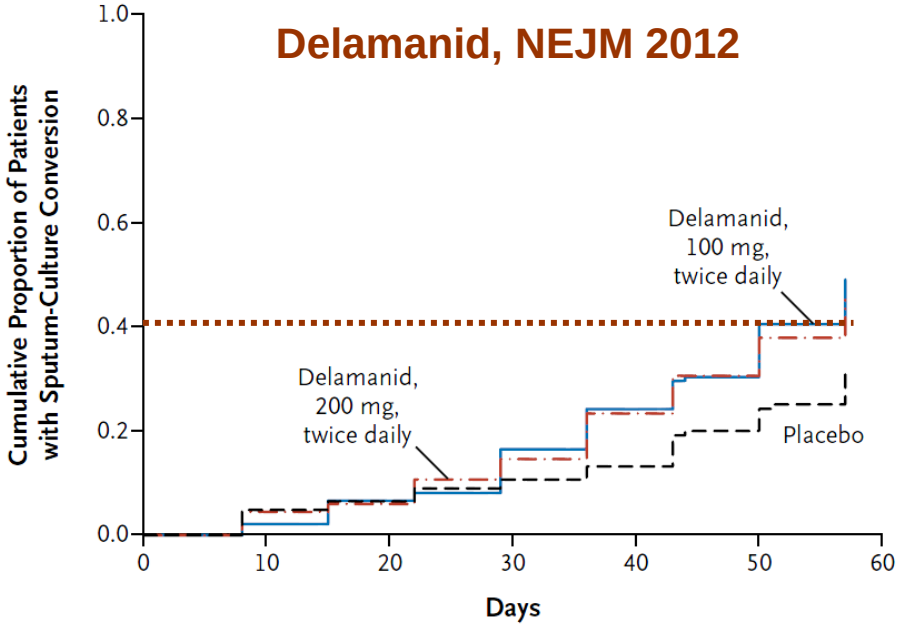


8주 치료 후 배양음전율

Linezolid, NEJM 2012



Delamanid, NEJM 2012



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(BTS. Br J Dis Chest 1984;78:330)
(Combs DL, et al. Ann Intern Med 1990;112:397)

MDR-TB 단기치료효과를 확인한 임상연구결과가 있는가?

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

- Exclusion: history of >1 mo of prior Tx with 2nd-line drugs
- Intensive phase (4 months)

  kanamycin, clofazimine, gatifloxacin, ethambutol, isoniazid, pyrazinamide, prothionamide (7 drugs)
- Continuation phase (5 months)

  clofazimine, gatifloxacin, ethambutol, pyrazinamide (4 drugs)
- Treatment outcomes

  - cure 82.5%, completion 5.3% (success 87.8%)

  - death 5.3%, default 5.8%, failure 0.5%, relapse 0.5%

(Van Deun A, et al. AJRCCM 2010;182:684)

1,359명 국내 MDR-TB 환자의 약제내성률

	과거 치료력 무 (n=385)	과거 1차약제 치료력 유 (n=791)	과거 2차약제 치료력 유 (n=183)
EMB	55%	52%	61%
PZA	32%	34%	44%
SM	23%	22%	31%
KM	11%	12%	24%
OFX	14%	12%	40%
PTH	16%	13%	34%
CS	5%	5%	14%
PAS	21%	16%	29%
CPM	0%	25%	86%

(Courtesy of Shim TS, MD)

치료기간과 재발과의 관계는?

MDR-TB 치료성공 후 재발

Country	Year	Relapse rate
Korea	2008	57/637 (8.9%)
Peru	2010	16/310 (5.2%)
Korea	2011	4/90 (4.4%)
Estonia	2012	11/129 (8.5%)

(Kim DH, et al. AJRCCM 2008;178:1075)
(Becerra MC, et al. CID 2010;51:709)
(Lee J, et al. IJTLD 2011;15:1331)
(Blöndal K, et al. IJTLD 2012;16:1228)

MDR-TB 재발 예측인자

- Retrospective cohort study in Peru (n = 402)
- median duration of follow-up: 40.5 months
- Predictors of recurrent TB

	Multivariable HR (95% CI)	P value
Aggressive regimen for >18 mo after sputum conversion	0.40 (0.17-0.96)	0.04
Diabetes mellitus	10.47 (2.17-50.60)	0.004

(Franke MF, et al. Clin Infect Dis. 2013;56:770)

Short Course Treatment is Possible in MDR-TB?

No

반론에 대한 재반론

Tuberculosis 2013: 2

Tuberculosis biomarkers discovery: developments, needs, and challenges

Robert S Wallis, Peter Kim, Stewart Cole, Debra Hanna, Bruno B Andrade, Markus Maeurer, Marco Schito, Alimuddin Zumla

Lancet Infect Dis 2013; 13: 362–72

Published Online March 24, 2013 http://dx.doi.org/10.1016/S1473-3099(13)70034-3

This is the second in a **Series** of six papers about tuberculosis

Specialty Care, Pfizer, Groton, CT, USA (Prof R S Wallis MD), **Departments of Medicine, Case Western Reserve University, Cleveland, OH, USA** (R S Wallis); **University of Medicine and Dentistry of New Jersey, Newark, NJ, USA** (R S Wallis);

Biomarkers are indispensable to the development of new tuberculosis therapeutics and vaccines. The most robust biomarkers measure factors that are essential to the underlying pathological process of the disease being treated, and thus can capture the full effects of many types of interventions on clinical outcomes in multiple prospective, randomised clinical trials. Many *Mycobacterium tuberculosis* and human biomarkers have been studied over the past decade. Present research focuses on three areas: biomarkers predicting treatment efficacy and cure of active tuberculosis, the reactivation of latent tuberculosis infection, and the induction of protective immune responses by vaccination. Many older, non-specific markers of inflammation, when considered in isolation, do not have sufficient predictive values for clinical use in tuberculosis. Although no new accurate, tuberculosis-specific biomarkers have yet been discovered, substantial progress has been made in some areas. However, the qualification of biomarkers as a surrogate for a clinical endpoint in tuberculosis is very challenging, and, for biomarkers that are non-culture-based, impossible to pursue without the availability of well characterised biobanks containing biospecimens from patients who have had adequate follow-up to establish long-term treatment outcome. We review progress in tuberculosis biomarker development and efforts being made to harness resources to meet future challenges.

(Wallis RS, et al. Lancet Infect Dis 2013;13:362)

	Associated outcome	Proposed level of certainty*
Month 2 culture status	Required duration of treatment[4] Relapse[5]	III III
Mycobacterium tuberculosis DNA (GeneXpert MTB/RIF assay)	Treatment effect[6] Extent of disease at start of treatment[7,8]	I I
M tuberculosis RNA	Treatment effect[9–11]	I
Liquid culture time to positive in automated liquid culture	Treatment failure[12] Treatment effect[13–16] Relapse[17]	I I I
Early bactericidal activity, 7–14 days	Inability to distinguish curative *vs* non-curative treatment[18] Inability to distinguish 6 *vs* 18 month regimens[19] Inability to detect curative effect of linezolid[20]	No role† No role† No role†
Serial colony counts, 1–2 months	Treatment effect Correlation with month 2 status[21,22]	I I
PET/CT imaging	Treatment effect[23]	I
Sputum Ag85	Treatment failure and relapse[16–18]	II
Antiphospholipid antibody	Treatment effect[24]	I
Urine lipoarabinomannan	Treatment effect[25]	I
Urine tuberculosis DNA	Treatment effect[26]	I
Antialanine dehydrogenase antibody	Treatment failure[27]	II
Volatile organic compounds	Active tuberculosis[28–30]	I
Interferon γ release assay (ELISPOT or whole blood)	Latent infection treatment (no effect)[31,32] Latent infection effect[33] Treatment failure[34] Subsequent active tuberculosis[35–37]	No role† I I III
Whole blood bactericidal activity	Treatment effect[38,39] Correlation with month 2 status[40]	II II
Neopterin	Treatment effect[41] Relapse[42]	II II
Soluble intercellular adhesion molecule-1	Treatment effect[43]	I
Soluble interleukin-2R	Treatment effect[44]	I
Soluble tumour necrosis factor receptor, granzyme B	Extent of disease at start of treatment[45]	I
Sputum interferon γ	Treatment effect[46]	I
C-reactive protein	Treatment effect, death[47–49]	I
Soluble urokinase plasminogen activator receptor	Death[50] Correlation with month 2 status[51]	II II

(Continues on next page)

	Associated outcome	Proposed level of certainty†
(Continued from prevous page)		
Natural killer T cells	Extent of disease at start of treatment[28]	I
Mycobacterial growth inhibition assays	Vaccine effect[52,53] Revaccination (no effect)[54] Correlation with other markers[52,53,55–59]	II II II
Interleukin 18	Subsequent active tuberculosis[60]	II
Natural killer and CD4 T cells	Subsequent active tuberculosis[60]	II
Bcl2	Subsequent active tuberculosis[60]	II
Whole blood interferon γ release assay	Subsequent active tuberculosis[35,61] Diagnosis of subclinical tuberculosis[36]	II II
Transcriptomics	Diagnosis of active tuberculosis *vs* latent infection[62,63] Treatment effect[62,87]	I I
Proteomics	Diagnosis of active tuberculosis *vs* other chronic inflammatory diseases[65]	I I
Metabolomics	Diagnosis of active tuberculosis *vs* latent disease[66]	I
microRNA	Diagnosis of active tuberculosis *vs* latent disease[67]	I

ELISPOT=enzyme-linked immunosorbent spot assay. *Data do not support a role as biomarker. †III=high certainty, capturing differences in clinical outcomes across treatment groups in prospective randomised trials; II=intermediate certainty, predicting differences in outcomes in patients in non-interventional studies; and I=low certainty, biological plausibility without association with clinical outcome.

Table: **Candidate biomarkers in tuberculosis**

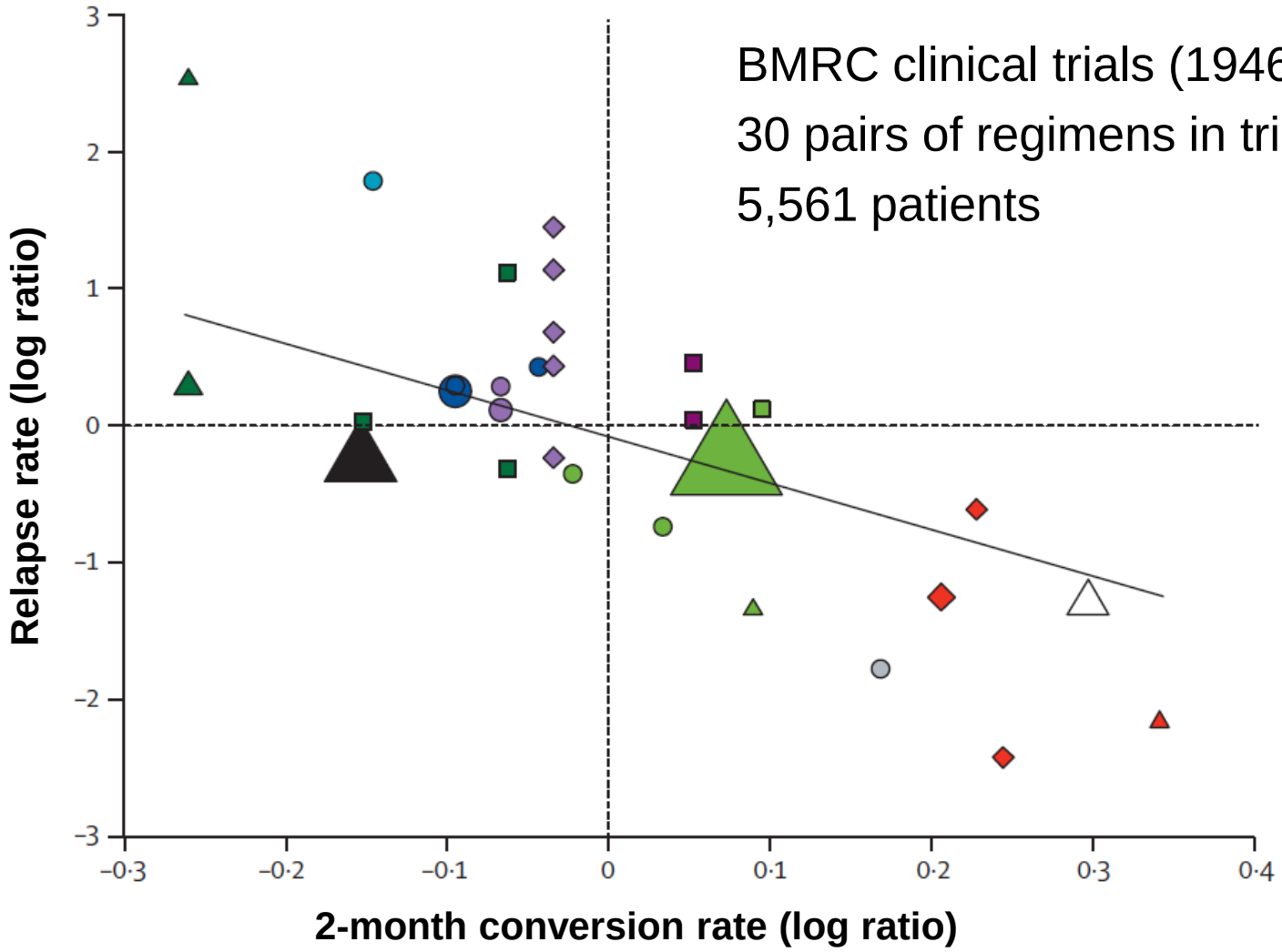
(Wallis RS, et al.
Lancet Infect Dis 2013;13:362)

Candidate Biomarkers in TB

	Associated outcome	Proposed level of certainty*
Month 2 culture status	Required duration of treatment[4]	III
	Relapse[5]	III
Mycobacterium tuberculosis DNA (GeneXpert MTB/RIF assay)	Treatment effect[6]	I
	Extent of disease at start of treatment[7,8]	I
M tuberculosis RNA	Treatment effect[9–11]	I
Liquid culture time to positive in automated liquid culture	Treatment failure[12]	I
	Treatment effect[13–16]	I
	Relapse[17]	I
Early bactericidal activity, 7–14 days	Inability to distinguish curative *vs* non-curative treatment[18]	No role†
	Inability to distinguish 6 *vs* 18 month regimens[19]	No role†
	Inability to detect curative effect of linezolid[20]	No role†
Serial colony counts, 1–2 months	Treatment effect	I
	Correlation with month 2 status[21,22]	I
PET/CT imaging	Treatment effect[23]	I

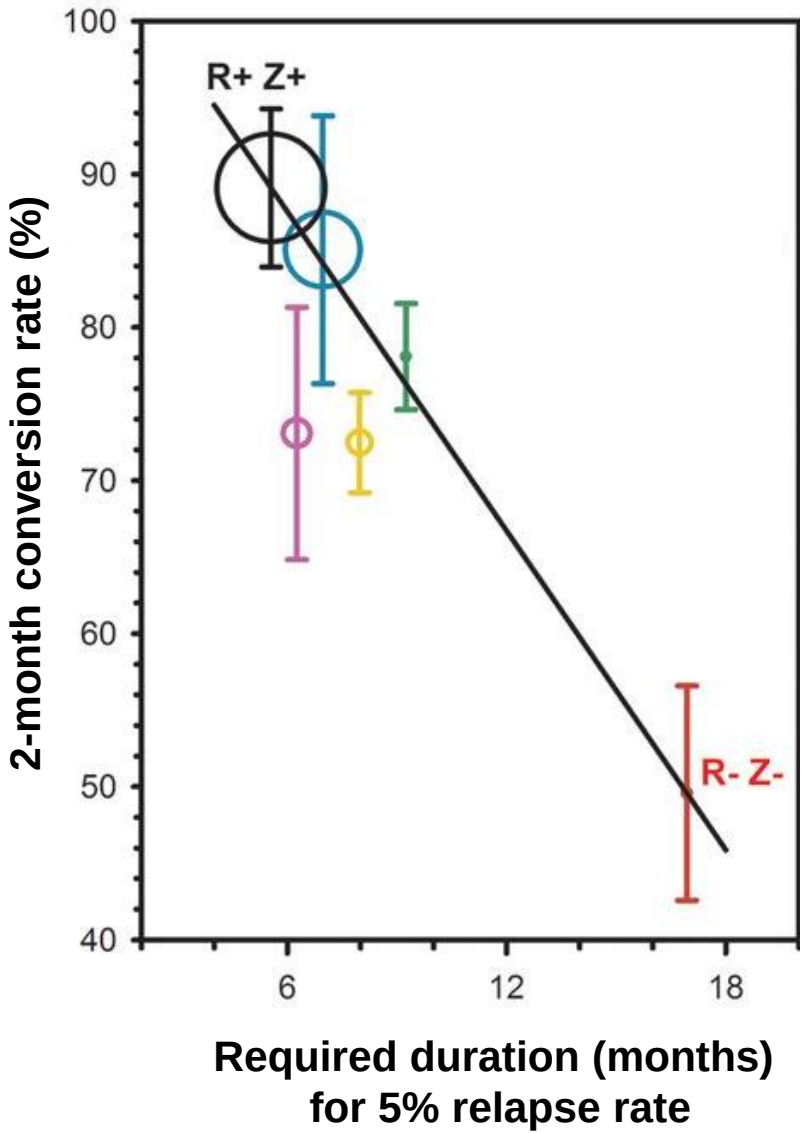
(Wallis RS, et al. Lancet Infect Dis 2013;13:362)

2개월 배양음전과 재발과의 관련성



(Wallis RS. Lancet Infect Dis 2010;10:68)

2개월 배양음전과 치료기간과의 관련성



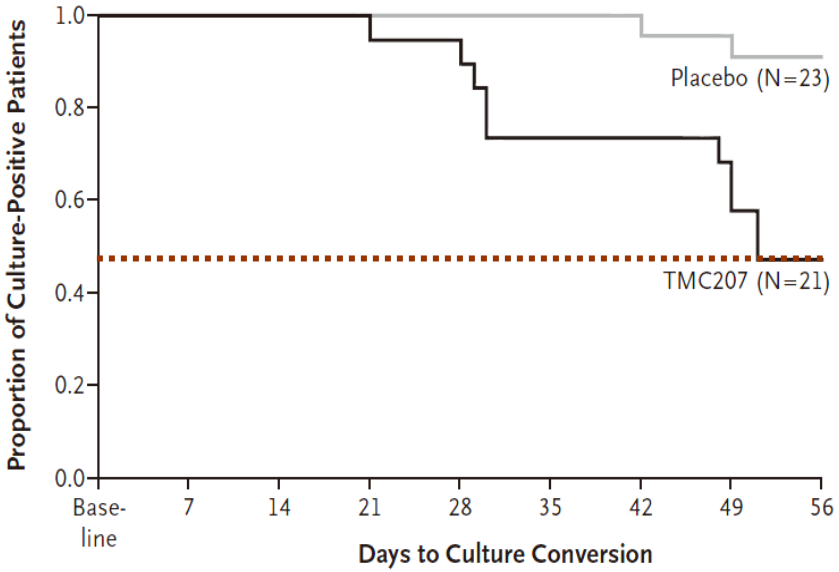
Meta-analysis

arms: 90

subjects: 11,286

(Wallis RS.
Clin Infect Dis 2013;56:106)

Bedaquiline (TMC 207), NEJM 2009



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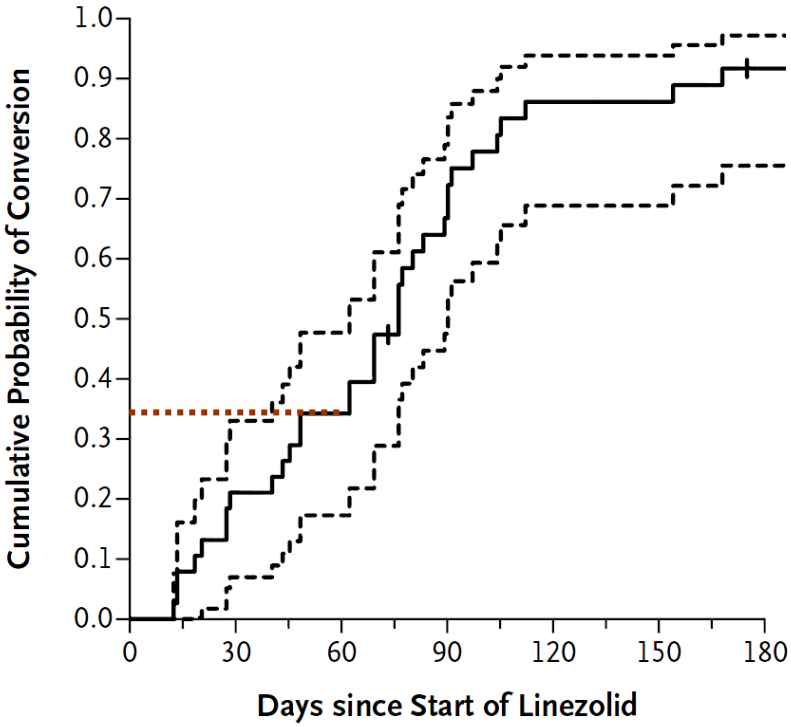

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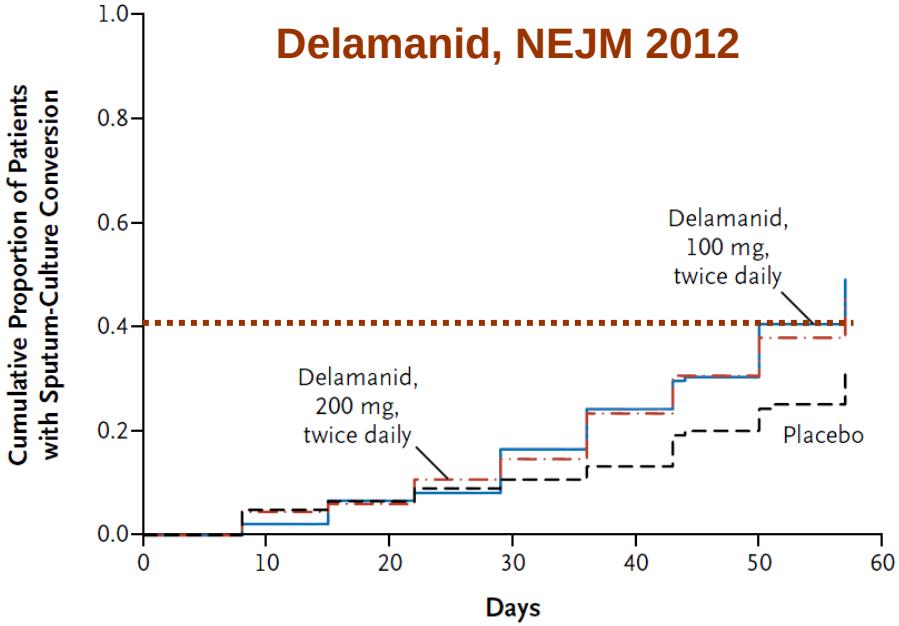

14-day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial

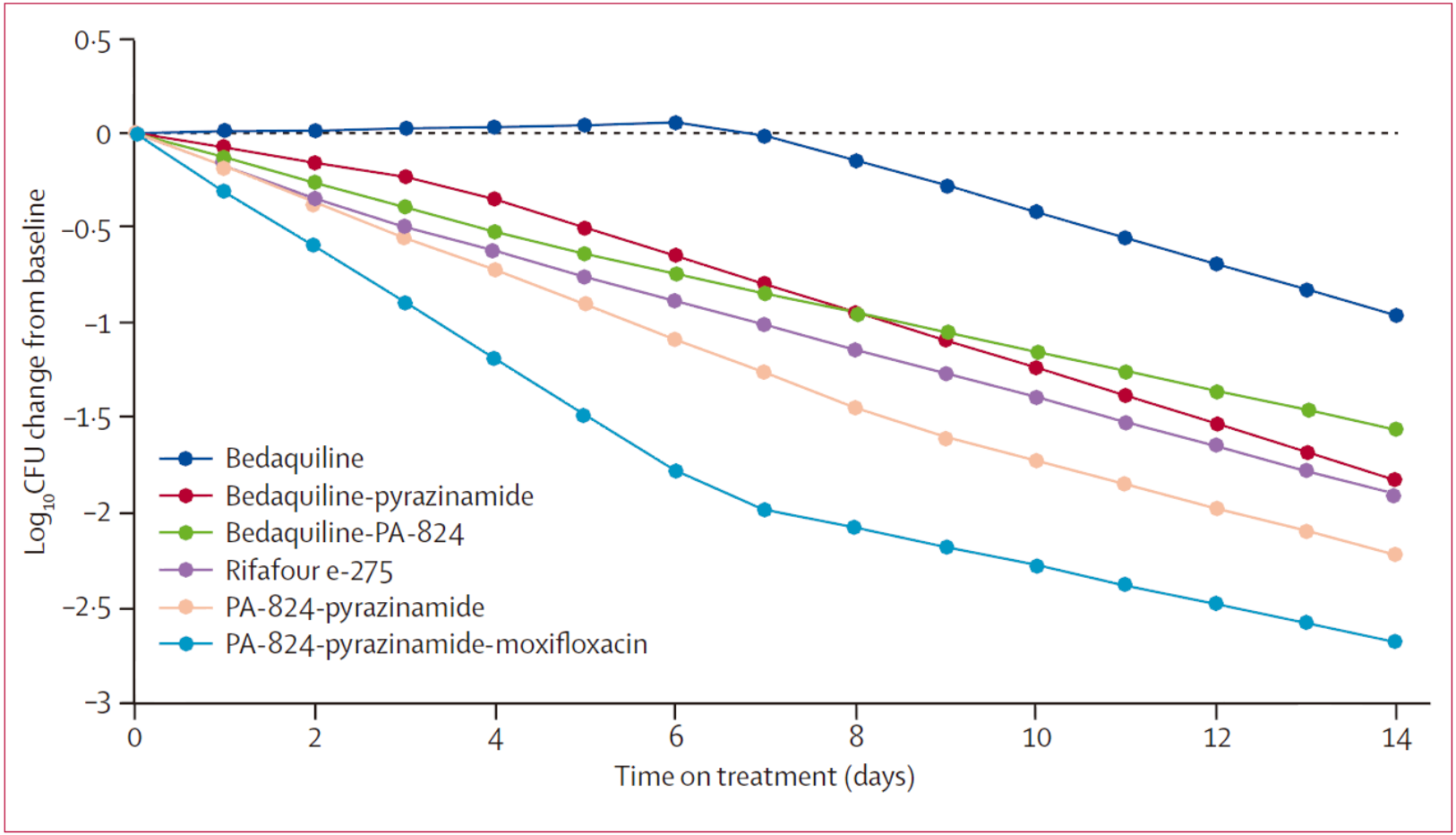

Figure 2: **Bilinear regression showing the fall in mean log_{10}CFU from baseline**
CFU=colony forming unit.

(Diacon AH, et al. Lancet 2012;380:986)

Candidate Biomarkers in TB

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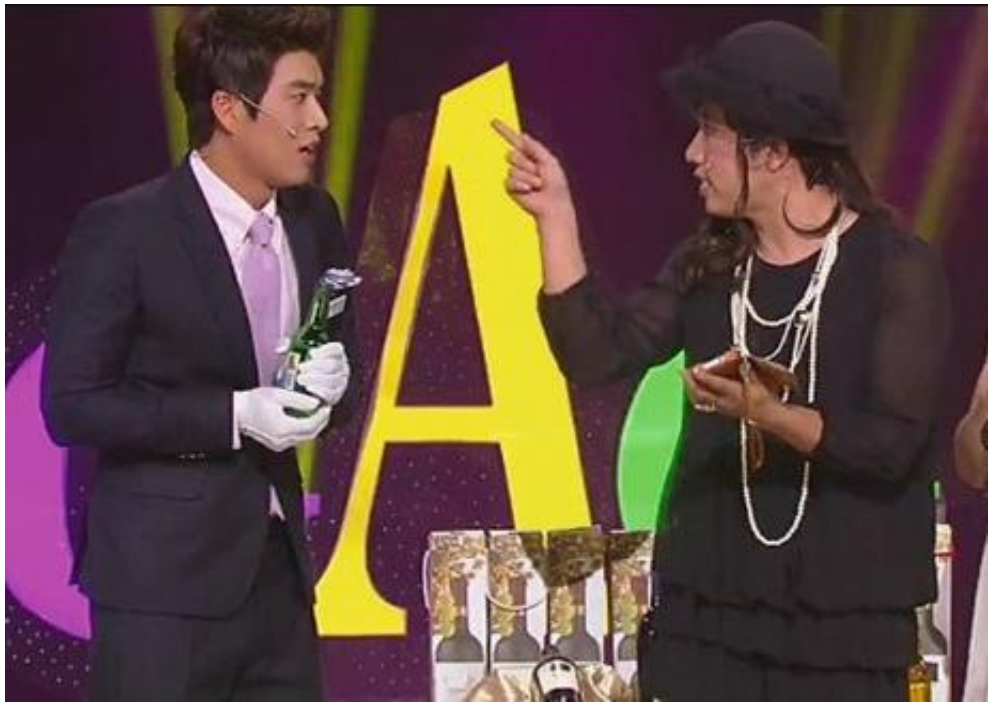
(Wallis RS, et al. Lancet Infect Dis 2013;13:362)

MDR-TB 단기치료(6-9개월) 가능한가?



기간이 짧아.
짧아도 너~~무 짧아.