New antituberculous agents for drug-resistant TB

Symposium Belgian Society of Infectiology and Clinical Microbiology
November 2009
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Definitions

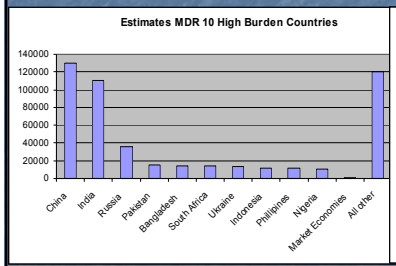
- MDR-TB multidrug resistance to, at least, isoniazid and rifampicin. Primary or acquired.
- XDR-TB is MDR-TB plus resistance to a fluoroquinolone and, at least, one second-line injectable agent (amikacin, kanamycin, capreomycin)

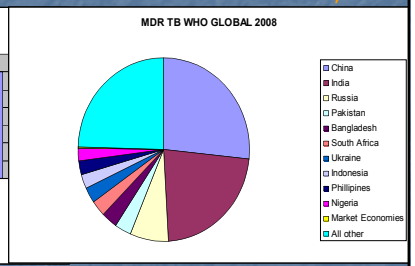
Due to: poorly managed TB care and patient non-adherence.

incorrect prescribing, poor quality of drugs, erratic supply, inadequate laboratory infrastructure, human resources constraints and limited access to health services

WHO MDR-TB Estimates 2008

Total Global Estimate = 511,000





Market economies include n=159 from USA

Global Plan to Stop TB : 1.6Mi MDR patients to be treated by 2015

MDR-TB drugs per WHO guidelines

RANK	ANTIBIOTICS	ANTIMYCOBACTERIAL ACTIVITY
1	**AMINOGLYCOSIDES**	Bactericidal on replicating organisms
a	Streptomycin	
b	Kanamycin	
c	Amikacin	
d	Capreomycine	
2	**ETHIONAMIDE**	Bactericidal
3	**PYRAZINAMIDE**	Bactericidal at acidic pH
4	**OFLOXACIN**	Low bactericidal
5	**ETHAMBUTOL**	Bacteriostatic
6	**CYCLOSERINE**	Bacteriostatic
7	**P.A.S.**	Bacteriostatic

Treatment outcomes in MDR-TB

8506 pts/33 studies	Success	Failure	Default	Death
Individualized	64	6	12	11
standardized	54	18	12	11

Criteria leading to enhanced success, if combined 69% success rate
- Treatment duration of at least 18 months
- Use of DOT strategy throughout

Criteria with no effect on treatment outcome
- Number of resistant drugs in the regimen
- Number of drugs
- % receiving fluoroquinolones
- HIV prevalence

E. Orenstein et al. Lancet Inf Dis, March 2009

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Overview new MDR-TB drugs

- Fluoroquinolones: moxi- and gatifloxacin
- Oxazolidinone: Linezolid, PNU-100840
- Nitro-imidazoles: PA-824 and OPC-67683
- Diamines or Ethambutol derivatives: SQ109
- Diarylquinolines: TMC207

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Fluoroquinolones

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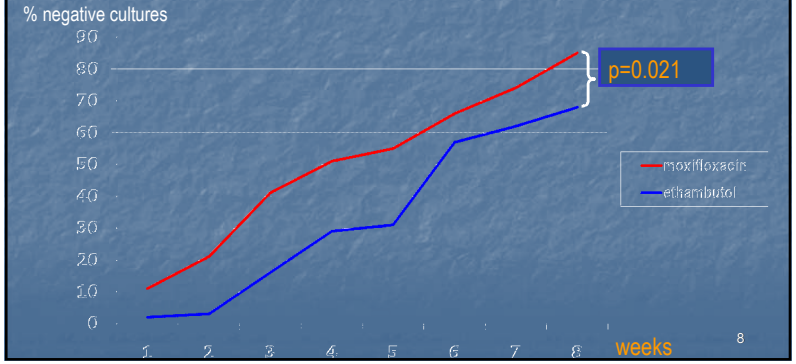
Moxifloxacin vs. Ethambutol

Chaisson ICAAC 2007

HRZ+**ethambutol or moxifloxacin**

170 patients, 146 analyzed



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Moxifloxacin, gatifloxacin vs. EMB (OFLOTUB Study)

Table 6 Patients with negative sputum cultures at 8 weeks

	7H11 plates		MGIT tubes	
	Total patients	Negative culture *n* (%)	Total patients	Negative culture *n* (%)
Control	50	32 (64)	47	17 (36)
GFX	52	40 (77)*	48	21 (44)
MXF	44	36 (82)†	40	16 (40)
OFX	53	28 (52)	48	15 (31)
Total	199	136 (68)	183	69 (38)

* GFX vs. control, $P = 0.155$.
† MXF vs. control, $P = 0.058$.
MGIT = mycobacteria growth indicator tube; GFX = gatifloxacin; MXF = moxifloxacin; OFX = ofloxacin.

Rustomjee et al. 2008. IJTLD.

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Moxifloxacin vs. INH

Dorman, ICAAC 2007

- RZE + **isoniazid or moxifloxacin**
- 433 patients, 344 (79%) analyzed
- 252 (73%) excavation+, 36 (11%) VIH+

Moxifloxacin : 60% (103/171) culture negative at 2 months
Isoniazid : 55% (93/173) cultures negative at 2 months

p=0,37

→**poor results due to improved culture techniques**

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Moxi- , Gatifloxacin

- MIC: 0.03 – 0.5 µg/ml
- Mainly being investigated for DS-TB and treatment shortening potential (time to conversion analysis)
- M substitutes H or E, G substitutes E in phase II/III trials
- Cross-class resistance issues
- Concerns M has QT prolongation effect and G has dysglycemia effects

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Oxazolidinones

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Linezolid

- MIC = 0.5 µg/ml (Alcala, AAC 2003)
- Mechanism of action : inhibition of the synthesis of proteins by blocking the initiation complex
- Pharmacokinetics (Gee, AAC 2001) at 600 mg x 2/day
  - Cmax = 18 µg/ml
  - Half-life = 5 hours
  - Time dependant activity ? (40%>MIC)
  - Absorption interaction with H and Z

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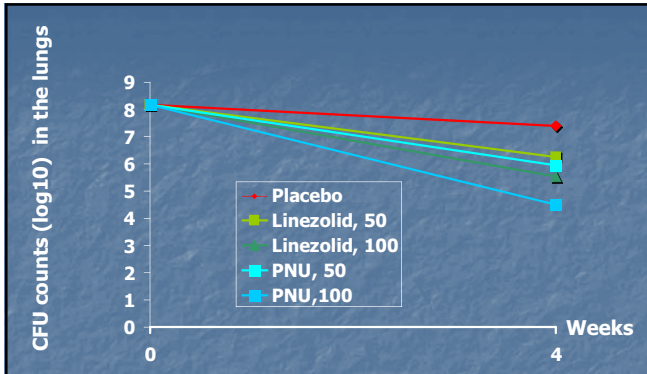

Activity of Oxazolidinones in the mouse model.

Cynamon et al. 1999. AAC.

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PNU-100480

- Currently in Phase I trials
- In murine model both bactericidal and sterilizing activity, resulting in treatment shortening potential
- R+PNU is equally effective as R+H+PNU in continuation phase
- No cross-resistance with existing TB-drugs

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Relapse assessment Linezolid vs PNU-100480

	Proportion (%) of mice with relapse after treatment		
Treatment group	3 mths	4 mths	6 mths
2RHZ + 4RH	n.d.	18 of 20 (90)	0 of 20 (0)
2RHZU + 2RHU	9 of 20 (45)	1 of 20 (5)	n.d.
2RHZU + 2RU	7 of 20 (35)	1 of 20 (5)	n.d.
2RHZU + 2RH	17 of 20 (85)	7 of 20 (35)	n.d.
2RHZL + 2RHL	n.d.	20 of 20 (100)	n.d.
2RHZL + 2RH	n.d.	20 of 20 (100)	n.d.

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Conclusions

- Linezolid displays a limited (bacteriostatic) activity in vitro, in the mouse model and in patients.
- PNU-100480 has sterilizing activity in the murine model and may be capable of shortening treatment duration for DS as well as MDR-TB

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Nitro-imidazoles

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PA-824 and OPC-67683

MIC vs. *M. tuberculosis* H37Rv	(μg/ml)
Isoniazid	0.05
PA-824	0.015-0.25
OPC-67683	0.006-0.024
Rifampicin	0.25

- Metronidazole derivatives
- Active on DS-TB and MDR-TB strains.
- Inhibition of cell wall lipids and protein synthesis
- No cross resistance with standard TB-drugs
- Cross resistance with PA-824

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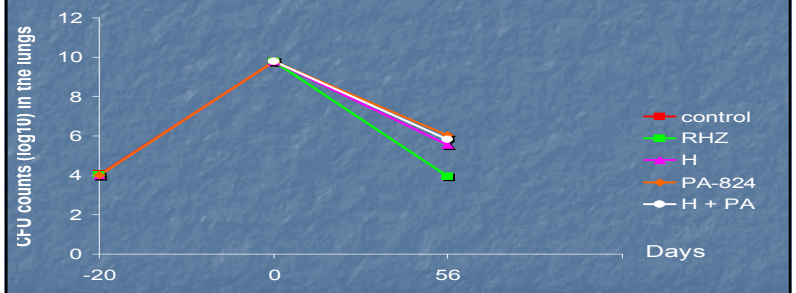
Activity of PA-824 alone against M. tuberculosis in mice



Tyagi et al. 2005. AAC.

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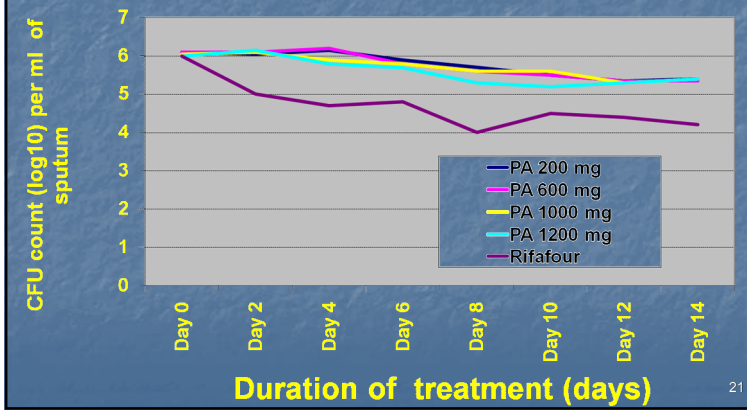
Early Bactericidal Activity of PA-824 in patients with pulmonary tuberculosis



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Conclusions

- PA-824 :
  - MIC: 0.015 – 0.25 µg/ml
  - No cross resistance with anti-TB drugs but cross resistance with OPC-67683.
  - When used at 100 mg/kg in mice, similar activity than that of INH .
  - Can not shorten DS-TB treatment in the mouse model.
  - In patients, limited EBA. Phase II started.

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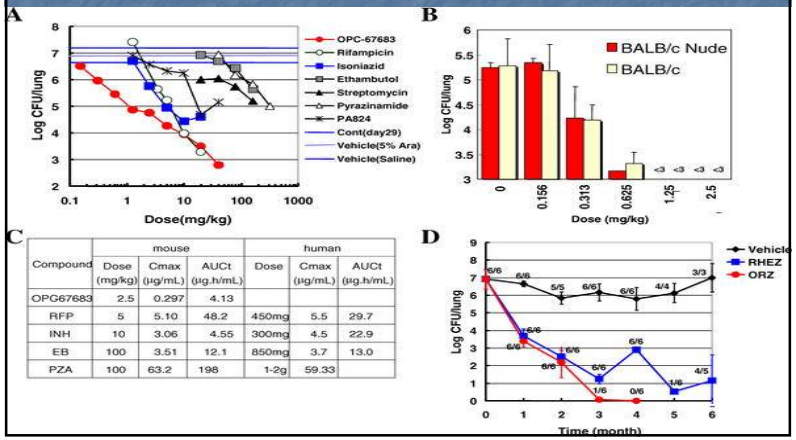
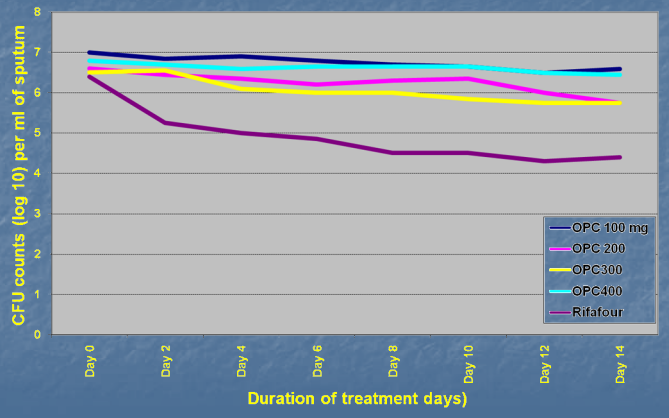
Activity of OPC-67683 against *M. tuberculosis* in the mouse model.



Compound	mouse			human		
	Dose (mg/kg)	Cmax (µg/mL)	AUCt (µg.h/mL)	Dose	Cmax (µg/mL)	AUCt (µg.h/mL)
OPG67683	2.5	0.297	4.13			
RFP	5	5.10	48.2	450mg	5.5	29.7
INH	10	3.06	4.55	300mg	4.5	22.9
EB	100	3.51	12.1	850mg	3.7	13.0
PZA	100	63.2	198	1-2g	59.33	

Early Bactericidal Activity of OPC-67683 in patients with pulmonary tuberculosis



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Conclusions

- OPC-67683 :
  - MIC 0.006 – 0.024 µg/ml
  - No cross resistance with anti-TB drugs but cross resistance with PA-824.
  - Much more active than PA-824 in the mouse model.
  - Potential to shorten treatment duration
  - In patients, limited EBA. Phase II ongoing

Ethambutol derivatives

Activity of SQ109 against *M. tuberculosis* in the mouse model

Nikonenko et al. 2007. AAC.

TABLE 1. CFU in lungs of mice treated for 4 weeks with a three-drug regimen[a]

Treatment duration and group (dose in mg/kg)	Log CFU/lung ± SD
Time 0	
Untreated control	6.11 ± 0.04
2 wks	
Untreated control	6.16 ± 0.02
INH (24) + RIF (20) + EMB (100)	4.64 ± 0.23[b]
INH (25) + RIF (20) + SQ109 (10)	4.46 ± 0.12[b]
3 wks	
Untreated control	6.34 ± 0.34
INH (24) + RIF (20) + EMB (100)	4.38 ± 0.05[c]
INH (25) + RIF (20) + SQ109 (10)	3.80 ± 0.10[c]
4 wks	
Untreated control	6.42 ± 0.76
INH (25)	4.61 ± 0.15
INH (25) + RIF (20)	4.27 ± 0.15
INH (25) + RIF (20) + EMB (100)	3.86 ± 0.14[d]
INH (25) + RIF (20) + SQ109 (10)	3.26 ± 0.12[d]

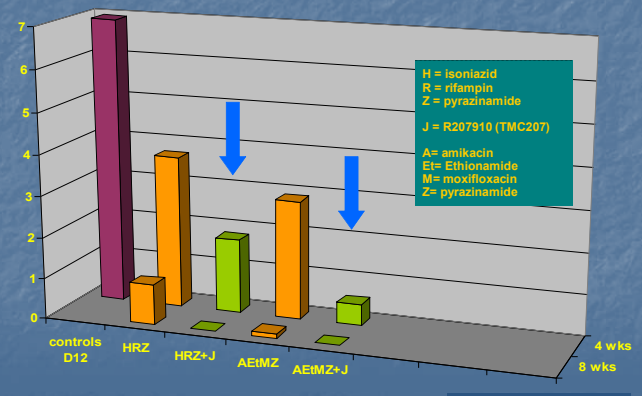
[a] Therapy with drug combinations was initiated 3 weeks after *M. tuberculosis* H37Rv infection.
[b] Statistically significant difference (0.18), $P = 0.0011$.
[c] Statistically significant difference (0.58), $P = 0.001$.
[d] Statistically significant difference (0.60), $P = 0.008$.

Conclusions

- MIC: 0.16-0.64µg/ml DS and MDR-TB
- Inhibition cell wall synthesis
- No cross resistance with ethambutol or any first line TB drug (H, R, Z)
- In the mouse model, the addition of SQ109 to RHZ is more effective than RHZ.
- Phase I multidose safety study started in 2009

Diarylquinolines

J accelerates bacterial killing when added to SOC for MDR TB



Lounis et al. 2006. AAC.

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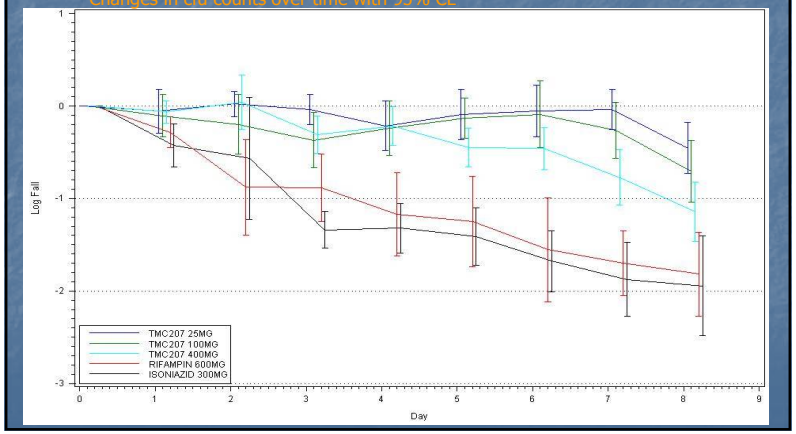
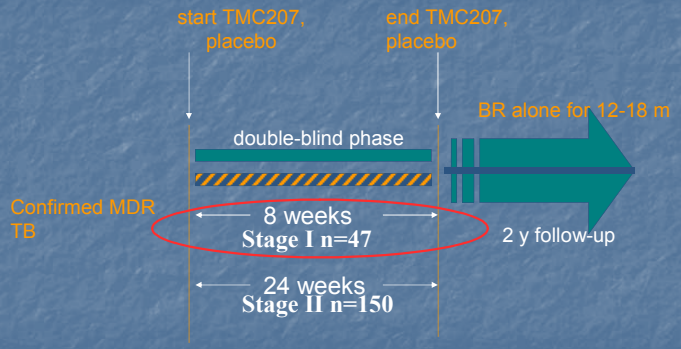
EBA with TMC207

Changes in cfu counts over time with 95% CL



Activity of TMC207 in MDR-TB patients



BR regimen: kanamycin, FQ, ethionamide, PZA, cycloserine

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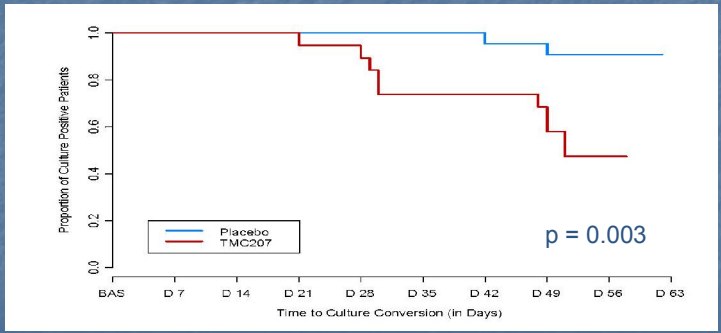
Time to culture conversion (MGIT) on ITT population (n=44)



(a) p-value from Cox proportional model adjusting for strata

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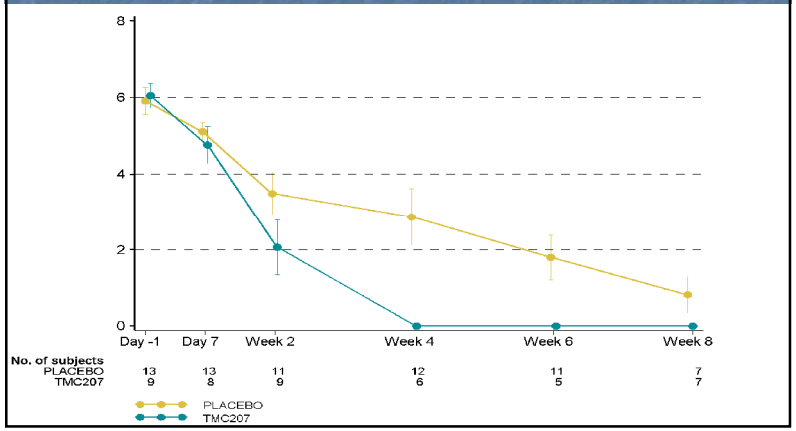
Mean (± SD) log_{10} CFU count (SSCC)



Conclusions

- MIC: 0.03µg/ml
- No cross-resistance with existing TB drugs
- Potential for treatment shortening
- Sterilizing activity in mouse model
- In patients : EBA limited activity, good activity in phase II

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BACK-UP SLIDES

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EBA of linezolid

Dietze et al. 2008. AJRCCM.

TABLE 2. EARLY BACTERICIDAL ACTIVITY: DAYS 0 TO 2

Drug	n	Mean EBA (log_{10} cfu/ml/d)	SD	95% CI
INH, 300 mg once daily	10	0.67	0.35	0.42 to 0.91
Linezolid, 600 mg twice daily	9*	0.26	0.42	−0.06 to 0.59
Linezolid, 600 mg once daily	10	0.18†	0.27	−0.01 to 0.37

Definition of abbreviations: cfu = colony-forming units; 95% CI = 95% confidence interval; EBA = early bactericidal activity; INH = isoniazid; SD = standard deviation.

* One patient in the linezolid 600 mg twice-daily arm withdrew after randomization before receiving any doses of study drug.

† $P < 0.01$ compared with INH.

EBA of linezolid

Dietze et al. 2008. AJRCCM. AJRCCM.

TABLE 3. EXTENDED EARLY BACTERICIDAL ACTIVITY: DAYS 2 TO 7

Drug	n	Mean Extended EBA (log_{10} cfu/ml/d)	SD (95% CI)	Mean Slope of cfu between Days 2 and 7; b2–7* (log_{10} cfu/ml/d)	SD (95% CI)
INH, 300 mg once daily	8†	0.16	0.11 (0.06 to 0.25)	0.13	0.16 (0.02 to 0.24)
Linezolid, 600 mg twice daily	9‡	0.04	0.11 (−0.04 to 0.13)	0.06	0.08 (−0.01 to 0.12)
Linezolid, 600 mg once daily	10	0.09	0.17 (−0.03 to 0.20)	0.06	0.16 (−0.04 to 0.17)

Definition of abbreviations: cfu = colony-forming units; 95% CI = 95% confidence interval; EBA = early bactericidal activity; INH = isoniazid.

* The rate of fall in sputum colony-forming units between Days 2 and 7 (b2–7) was estimated as the slope of the linear regression obtained from fitting the six sputum values from Day 2 to Day 7 (24).

† One patient in the INH arm discontinued study drug after 5 days because of minor, self-limited hemoptysis that precluded collection of sputum suitable for the colony-forming unit assay. Quantitative cultures for Days 3 and 7 for another patient in the INH arm were contaminated and colony-forming unit data are not available for this patient for calculation of extended EBA.

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

Linezolid : in patients

- **Clinical use of linezolid (Fortun, JAC 2005)**
  - 5 patients treatead with linezolid + thiacetazone, clofazimine or amoxicilline/clavulanate.
  - All the isolates were sensitive in vitro (MIC ≤0.5 mg/L).
  - **Negativation of the sputum culture s after 6 weeks of treatment .**
  - 3 cures (duration of treatment : 5-24 months).
  - 1 lost to follow –up after 5 months of treatment.
  - 1 patient under treatment after 11 months.
  - 4 patients with anemia that need transfusions
  - 2 peripherial neuropathies
  - 1 pancreatitis

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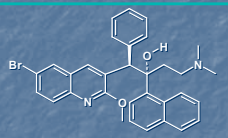
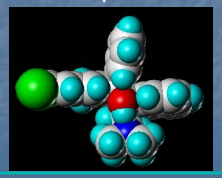
In vitro activity of TMC207

Non-mycobacteria: MIC ≥4 µg/ml

- *St. aureus*
- *Str. Pyogenes*
- *E. faecalis*
- *E. faecium*
- *S. typhimurium*
- *E. coli*
- *P. aeruginosa*
- *H. influenzae*
- *H. pylori*
- *M. pneumoniae*



R207910
TMC207
Compound J



Mycobacteria: MIC ≤0.060 µg/ml

- *M. tuberculosis*
- *MDR M. tuberculosis*
- *M. bovis*
- *M. avium*
- *M. kansasii*
- *M. fortuitum*
- *M. marinum*
- *M. smegmatis*

Andries et al. 2005, Science

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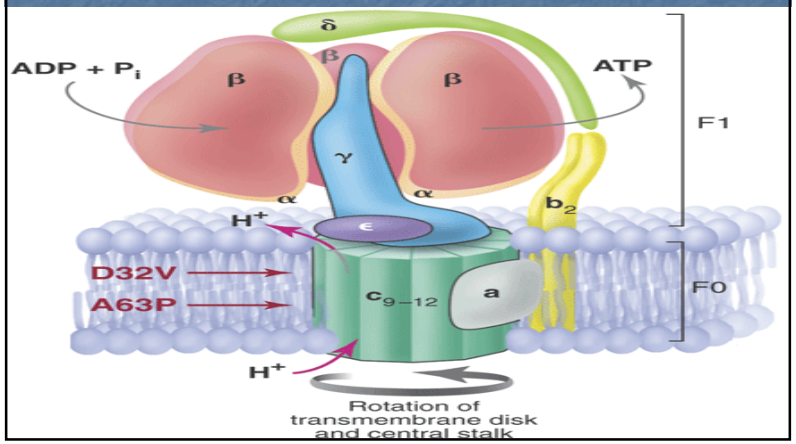
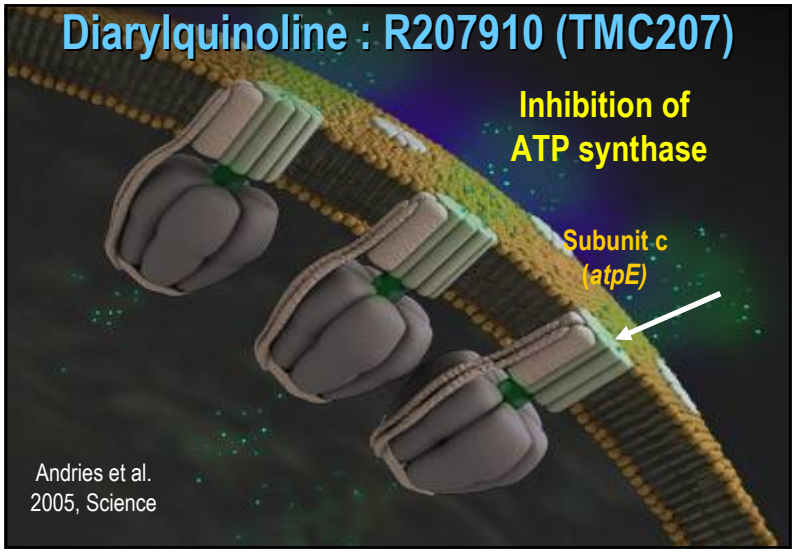
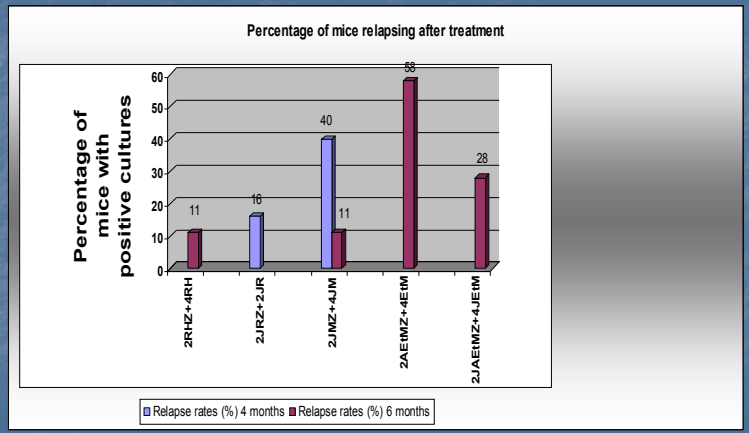
ATP Synthase (cible du R207910)



Diarylquinoline : R207910 (TMC207)

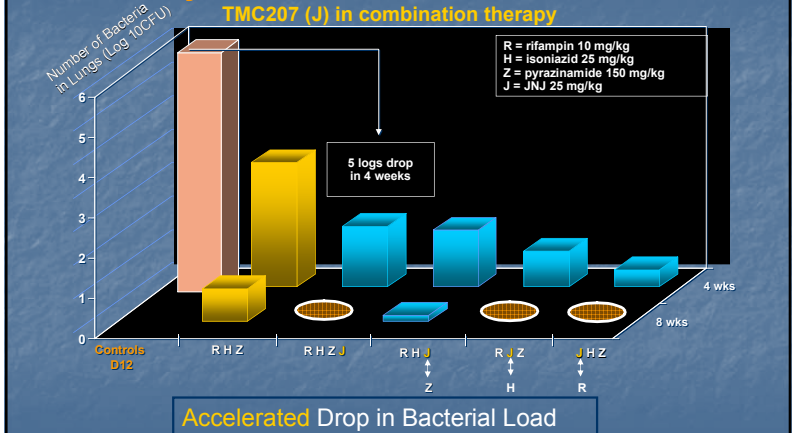


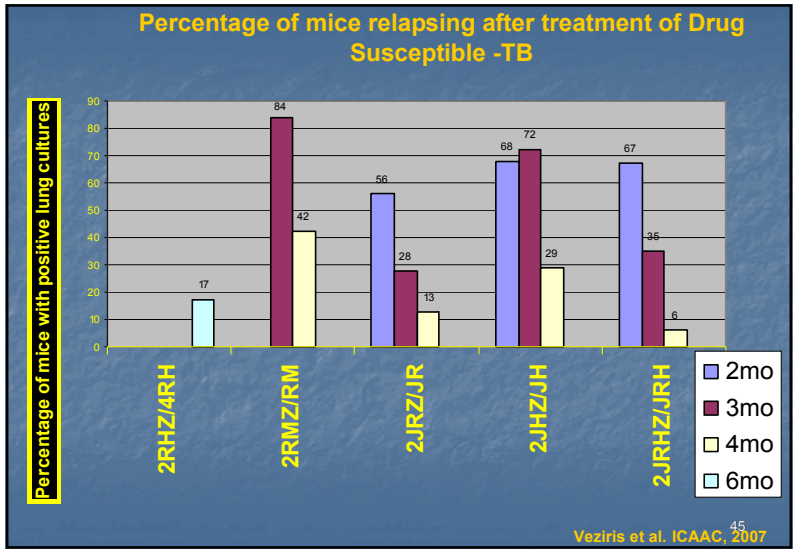
Percentage of mice relapsing after treatment of MDR-TB

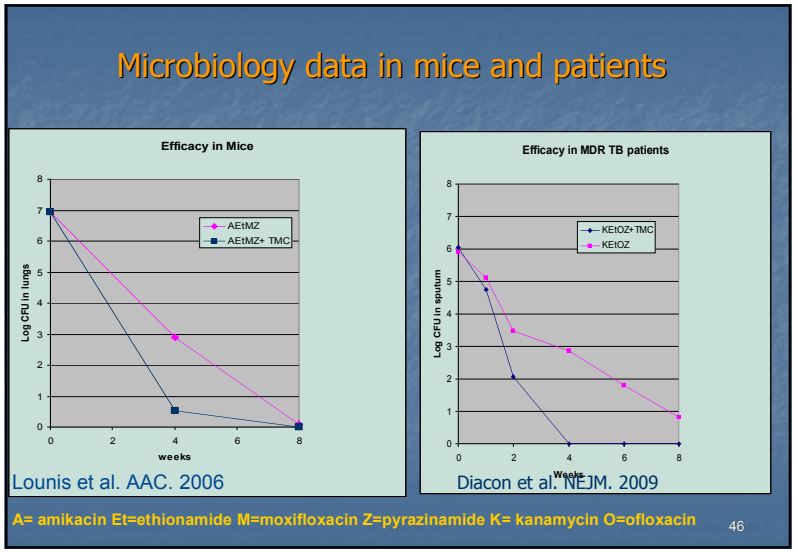


Ibrahim et al. 2008, ICAAC

Activity of TMC207 in the mouse model




Percentage of mice relapsing after treatment of Drug Susceptible -TB
Percentage of mice with positive lung cultures
90
80
70
60
50
40
30
20
10
0
84
42
17
56
28
13
68
72
29
67
35
6
2RHZ/4RH
2RMZ/RM
2JRZ/JR
2JHZ/JH
2JRHZ/JRH
2mo
3mo
4mo
6mo
Veziris et al. ICAAC, 2007
45


Microbiology data in mice and patients
Efficacy in Mice
Log CFU in lungs
weeks
AEtMZ
AEtMZ+ TMC
Lounis et al. AAC. 2006
Efficacy in MDR TB patients
Log CFU in sputum
Weeks
KEtOZ+TMC
KEtOZ
Diacon et al. NEJM. 2009
A= amikacin Et=ethionamide M=moxifloxacin Z=pyrazinamide K= kanamycin O=ofloxacin
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