Clinical Management of MDR/XDR-TB

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EPIDEMIOLOGIC INFORMATATION OF MDR-TB

* Incidence varies according to reported sites
* High incidence is located in some geographic are a and not evenly distribution
* Data of sensitivity can not be directly compared because of different methodology
* No separation of previously treated and untreated cases
* High incidence is associated with poor compliance previous treatment history, HIV infection , contact with drug resistant case, inborn country

CLINICAL CLASSIFICATION OF DRUG RESISTANT TB

Epidemiology
- *Primary (initial)*
- *Secondary (acquired)*

Clinician
- *Drug resistance*
  - * *Monoresistance*
  - * *Polydrug or combined resistance*
- *Multidrug resistance*

WHO
- *Drug resistance among new cases*
- *Drug resistance among previously Treated cases*

Multidrug – Resistant Tuberculosis

Amenace That Threatens To Destabilize Tuberculosis Control

* *WHO and IUATLD*
  - *The median prevalence of MDR – TB: 1.1% in newly diagnosed patients*
  - *The median prevalence of MDR – TB: 7.0% in patients who have previously received anti-TB treatment*
* *MDR – TB : Threatening to destabilize global tuberculosis control*

Chest 2006; 130: 261 - 272

Emergence of Mycobacterium tuberculosis with Extensive Resistance to Second – Line Drugs Worldwide 2000 – 2004.

* *Increasing second line drug resistance from Green Light Committee*
* *CDC – WHO surveyed international network of TB laboratories.*
* *Population – based data – 4%, 19% and 15% of MDR – TB in U.S., Latvia, South, Korea were XDR - TB*

Extensively Drug Resistant Tuberculosis – United States,1993-2006

- During 1993-2006, 202,436 cultured confirmed cases of TB in U.S. and 190,312 had DST.
- 2,927(2%) were MDR, 1665(57%) had DST to fluoroquinolones and injectable drugs.
- 49(3%) were XDR. 32 cases were during 1993-1999 and 17 cases were during 2000-2006.
- HIV status was known in 29(59%) and of this 16(55%) were positive.
- Percentage of XDR-TB was increased in foreign-borne from 39% to76% during 1993-1999 to 2000-2006.

MMWR 2007:56;250-253

XDR–TB - a global threat

* *Between 2000 – 2004, of 17690 TB isolates in the world were MDR – TB 20% and XDR – TB 20% (Lancet 2006;368:964)*
* *Between 2003-2005, of 1284 TB isolates in Iran were MDR – TB 9.3% and XDR – TB 1% (CID 2006;316: 216)*

First Line Drugs

* Isoniazid
* Rifampicin
* Pyrazinamide
* Ethambutol
* Streptomycin

Second Line Drugs (6 classes)

* *Aminoglycosides : Kanamycin, Amikacin*
* *Fluoroquinolones : Levofloxacin, Moxifloxacin*
* *Polypeptides : Capreomycin*
* *Serine analog : Cycloserine*
* *Ethionamide*
* *Para-aminosalycylic acid*

Extensive MDR - tuberculosis

* *MDR – TB and*
* *Resist to at least 3 classes of second line drugs*

New Definition of XDR-TB (WHO/CDC October 2006)

- At least resistant to INH and RMP and
- Resistant to any one of fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin)
- Resistant ot one or more of the following injectable drugs : kanamycin, amikacin, capreomycin

Treatment Outcomes of XDR – TB and MDR – TB in Latvia (2000 – 2002) and U.S. (1993 – 2002)

	XDR No. (%)	MDR No. (%)
Latvia		
Total	115	1690
Cure / Completion	70 (61)	339 (69)
Death / Failure	30 (26)	83 (17)
Death	3 (3)	35 (7)
Failure	27 (23)	48 (10)

Treatment Outcomes of XDR – TB and MDR – TB in Latvia (2000 – 2002) and U.S. (1993 – 2002)

	XDR	*MDR*
	No. (%)	*No. (%)*
U.S.		
Total	*64*	*1513*
Completion	*20 (31)*	*828 (55)*
Death	*21 (33)*	*375 (25)*

Impact of XDR-TB

- No effective treatment
- Increasing morbidity and mortality (some report show survival time in days)
- Transmissible and spread disease in general population (especially in compromised host)
- Health care workers are risk to be infected

DRUG RESISTANCE SURVEILLANCE IN THAILAND. (PRIMARY RESISTANCE)

	1997 - 1998	2002
Number	1015	1505
Any resistance (%)	-	15.0
Mono resistance (%)		
INH	6.2	5.3
RMP	2.0	0.3
EMB	3.0	0.1
SM	5.6	4.8
MDR - TB	2.0	1.0

DRUG RESISTANCE SURVEILLANCE IN THAILAND. (SECONDARY RESISTANCE)

	1997 – 1998	2002
Number	-	170
Any resistance(%)	-	39.4
Mono resistance (%)	-	
INH	-	4.1
RMP	-	1.8
EMB	-	0.6
SM	-	5.3
MDR - TB (%)	-	20.6

PRIMARY DRUG RESISTANCE OF PYRAZINAMIDE

Study	year	No.	Resistance rate (%)
TB Division	1993	422	5.9
Central Chest Hospital	1995	141	7.8

Frequency of PZA Resistance in Previously Treated Tuberculosis (IJTLD July 2006)

- 127 M.tuberculosis strains of drug resistance and 47 sensitive strains were tested for PZA by BACTEC.
- 68 of 127 were resisted to PZA and 46 of 47 were sensitive to PZA
- PZA resistance related to MDR-TB

PRIMARY DRUG RESISTANCE OF FLUOROQUINOLONES IN THAILAND

	Resistance rate (%)	
	Ciprofloxacin	ofloxacin
Chierakul (1995)	7.0	-
Poonyasopan (1997)	8.3	-
Chuchottaworn (1998)	-	4.3

TREND OF DRUG RESISTANCE IN HIV SEROPOSITIVE PATIENTS (CENTRAL CHEST HOSPITAL)

YEAR	NO	% RESISTANCE				
		INH	RMP	SM	EMB	MDR
1989	47	23.4	10.4	29.8	6.4	6.4
1990	48	12.5	0.0	8.3	2.1	0.0
1991	80	2.5	8.8	13.8	0.0	0.0
1992	99	18.2	10.1	17.2	1.0	2.4
1993	132	14.4	10.6	13.6	0.8	4.5
1994	122	14.8	5.7	12.3	0.8	1.6
1995	189	9.5	7.4	10.1	2.6	3.7
1996	376	15.7	4.3	9.3	1.3	8.8
1997	336	26.2	26.5	17.0	2.1	5.7
2003	122	18.0	9.8	9.0	0.8	6.6

XDR-TB in Chest Disease Institute

Year	Number of Cases
1997	6
1998	6
1999	9
2000	4
2001	3
2002	5
2003	4
2004	5
2005	3
2006	8

What Is The Magnitude of MDR – TB in Thailand

- *From prevalence survey of drug resistance*
  400 – 800 cases / year if all new cases are untreated cases.
- *If 10% of new smear positive cases have history of treatment which have MDR of 20% and additional cases of 800 cases per year.*
- *If 10% of MDR-TB are XDR-TB, each year will XDR-TB of 40 -160 cases.*

WHAT DO WE NEED IN MDR-TB CARE

* *Correct diagnosis*
* *Good laboratory support*
* *Specialised and experienced institute*
* *DOT*
* *Availability and adequate drug*
* *Monitoring of treatment*

Risk Factors to Carry Drug Resistance TB

* *Previous history of treatment*
* *Failure*
* *Relapse*
* *HIV co-infection*
* *Addictions*
* *Contact with drug resistant patient*
* *Born in high prevalence country*

PRINCIPLE OF DRUG TREATMENT FOR MDR-TB

* Discriminating between "DR-TB" and "MDR-TB"
* Use " all drugs which are available and should be four or more "
* Aminoglycoside and Fluoroquinolone are two core drugs in regimen
* Duration of treatment at least 18 months or if smear turn to be negative after 6 months treatment, the treatment must be continued to 12 months after smear negative

Recommendations for MDR-TB Chemotherapy (1) ATS (2003)

* *Do not limit the regimen to 3 agents*
  - *Regimens employing 4 to 6 medications appear to be associated with better results.*

* *Total treatment duration:18-24 months (24 months when EMB or PZA resistant*

Recommendations for MDR-TB Chemotherapy (2) BTS (1998)

** Treatment should start with 5 or more drugs to which the organism is susceptible and cotinue until sputum culture conversion.*

** Drug treatment then has to be continued with at least 3 drugs for a minimum of nine further months and perhaps up to or beyond 24 months.*

Recommendations for MDR-TB Chemotherapy (3) WHO (2003)

** Regimen should consist of at least 4 drugs with either certain, or almost certain, effectiveness.*

** Treatment is for a minimum duration of 18 months becond conversion (extension to 24 months in "chronic cases" with extensive pulmonary damage).*

Two sensitive-drugs are clearly Not enough in MDR regime

Primary	Secondary	Failure of treatment (%)
INH	RFP	0.5
INH	SM	2
INH	EB	4
INH	PAS	12
INH	Ti	16
RFP	EB	18

After Hong YP/1999/Presented at RIT-Japan international course

In most cases three drugs are enough (?)

Only three 2nd-line drugs/before RFP era
From IJTALD.2006;10:829

Reporter	No. of patinets	Cured/completed treatment	%
Tousek	55	45	82
Zierski	32	31	97
Fischer	146	122	84
Kass	74	58	78
Pines	12	9	75
Somner	22	20	91
Kass	24	23	96

INH is probable useless in most cases of low grade INH resistance (2)

TH+CS/TH+PZA/TH+CS+PZA combined

with or without INH in INH resistant cases

Bull IUAT.1986,Vol.42/No.2:9-37

	Without INH	With INH
N	94	96
Unfavorable response at 52 w	9 (9)%	9 (9)%
Cx changed for toxicity	18 (19%)	23 (24%)

RESERVED DRUGS FOR TREATMENT

Ofloxacin	400-600	mg/day
Levofloxacin	400-600	mg/day
Streptomycin	15	mg/kg/day
Kanamycin	15	mg/kg/day
Amikacin	15	mg/kg/day
PAS	200	mg/kg/day
Pyrazinamide	1.0-1.5	gm/day
Ethambutol	0.8-1.2	gm/day
Ethionamide	500-750	mg/day
Cycloserine	500-750	my/day
Capreomycin	15	mg/kg/day

National MDR-TB Treatment Guideline 2005 (Thai)

* Category II is recommended in
  - Failure conventional regimen
  - Previous history of Treatment
  - Irregular treatment
  - Relapse
* Not recommended in known MDR-TB
* DOT is essential

National MDR-TB Treatment Guideline 2005 (Thai)

* Failure of Category I, likely to be MDR
* Recommended regimen
  - 2 Months : kanamycin (streptomycin), ofloxacin, PAS, ethambutol and pyrazinamide
  - 16 months : ofloxacin, ethambutol and pyrazinamide

National MDR-TB Treatment Guideline 2005 (Thai)

* Failure of Category II, likely to be MDR-TB plus EMB resistance
* Recommended regimen
  - 2 Months : kanamycin (streptomycin), Ofloxacin, PAS, pyrazinamide, ethionamide
  - 16 months : ofloxacin, PAS, pyrazinamide, ethionamide

EVALUATION OF TREATMENT

* Clinical signs and symptoms are not useful
* Sputum examination is the most reliable tool so smear must be done in every visit
* CxR is not useful, should be done every 6 months
* Laboratory monitoring must be done at base line and again when side effect is suspected, except with aminoglycoside treatment, renal function should be done every month

STUDY OF OFLOXACIN FOR MDR-TB TREATMENT IN THAILAND

SITES	:	SIRIRAJ HOSPITAL
	:	CENTRAL CHEST HOSPITAL
	:	TUBERCULOSIS DIVISION
DESIGN	:	PROSPECTIVE STUDY
PATIENT	:	PROVED MDR-TB , SMEAR POSITIVE
REGIMEN	:	Ofloxacin 600 mg / day
	:	Kanamycin 1 gm for 90 doses
	:	PAS 8-10 gm / day
	:	EMB 0.8-1.0 gm / day
	:	PZA 1.0-1.5 gm / day
DURATION	:	18 MONTHS OR 12 MONTHS AFTER CONVERSION

STUDY OF OFLOXACIN FOR MDR-TB TREATMENT IN THAILAND

* 22 PATIENTS WERE ENROLLED
* 25 % CONVERSION RATE AT 1 MONTH
* 75 % CONVERSION RATE AT 2 MONTH
* 78 % CONVERSION RATE AT END OF TREATMENT
* 99 % COMPLIANCE
* NO RELAPSE
* NO SERIOUS OR FATAL SIDE EFFECTS

Treatment of Multidrug-Resistant TB

Outcome of Pulmonary MDR-TB: A Six Year Follow-Up Study (1)

* Case ascertainment

  - 299 patients who were newly diagnosed with pulmonary MDR-TB from 1992 through 1996 enrolled
  - Their fate over the subsequent six years after commencing treatment detemined.

* Case management

  - Anti-tuberculosis drugs were self-administered with the support of public healthnurses who were responsible for supervising treatment during the whole treatment course

Eur Respir J 2006 July

Treatment of Multidrug-Resistant TB

Outcome of Pulmonary MDR-TB: A Six Year Follow-Up Study (2)

* Treatment Regimens

  - Individually-tailored treatment regimens were decided upon at a weekly staff conference after review of the case history and drug-susceptibility results

    * Streptomycin/kanamycin/enviomycin, 10-15mg/kg/day daily
    * Ofloxacin, 300-400 mg twice daily
    * Prothionamide, 250 mg 2 -3 times daily
    * Para-aminosalicylic acid, 150-200 mg/kb/day divided into 3-4 doses
    * Cycloserine, 250 mg 2-3 times daily

  - The duration of treatment, normally planned for 18 months.

Surgical Invention for MDR-TB

* *Consider in every MDR-TB patients*
* *Better outcome if adjunct to medication*
* *Criteria for surgery*
  - *Unilateral or single lesion that can be done in one operation*
  - *Still have 2 or more drugs which are sensitive*
  - *If it is possible smear should be negative at surgical time or 2-3 months after treatment*
* *Unfavorable outcome in patient with preoperative comorbidity, aspergillosis, operation time, transfusion and male*

(Ann Thorac Surg 2005;79:959-963)

NEW DRUGS FOR TUBERCULOSIS TREATMENT

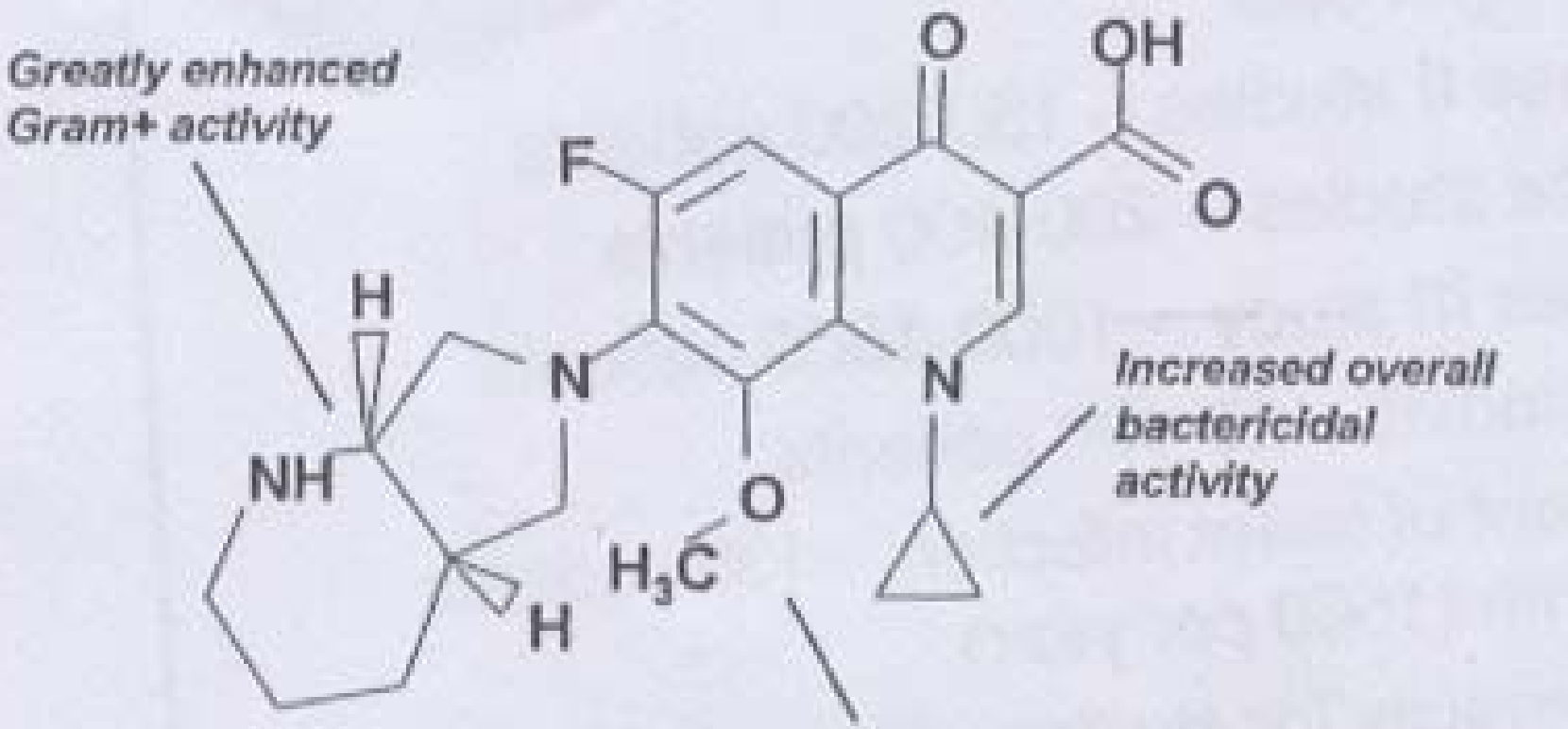
Fixed dose combination (FDC)- WHO formulation

- *Fuoroquinolones : ofloxacin, levofloxacin, gatifloxacin, moxifloxacin*
  - *MPC below Cmax*
  - *Sterilizing activity*
- *Oxazolidinones : linezolid*
- *Imidazole derivatives : PA 824*
- *Diarylquinoline : TMC 207*
- *Ketolides : telithromycin (no activities)*
- *Drug on latency stage : Glyoxylate shunt*

MOXIFLOXACIN

- *8 – methoxy fluoroquinolones*
- *Active against M. tuberculosis MIC 90 < 0.25 μg / ml (Cmax ~ 4 μg / ml)*
- *Moxifloxacin has antimycobacterial activity*
- *Moxifloxacin is a bactericial and sterilising activity against M.tb.*

Moxifloxacin (Avelox™)



Peterson U, *et al.* (1996). Presented at *36th ICAAC*, abstract F1

TBTC 27 STUDY

- Evaluate activity and safety of moxifloxacin
- Control 2HRZE compare to 2 HRZM and intermittent 38 times / week
- Two months conversion for moxifloxacin is 88% and 89% for ethambutol
- TBTC 27 study proves safety and activity of moxifloxacin

TBTC 28 STUDY

- *In animal model, substitute INH with moxifloxacin increase eradication fo M.tb.*
- *Study 28, design is substitutiion of INH with moxifloxacin for 6 months*
- *Outcoure of study will be used to determine next study 29 to short duration of treatment*

MEAN LOG_{10} COLONY-FORMING UNIT COUNTS* FROM LUNG HOMOGENATES

Treatment	Duration of Treatment (months) 0	2	3	4	5	6
A. Infected, untreated	7.80+0.21	7.63 ± 0.41	7.24 ± 0.41	8.06 ± 0.81	7.68 ± 0.51	7.34 ± 05.0
B. 2RHZ/4RH		3.36 ± 0.32	1.89 ± 0.40	0.39 ± 0.32	0	0
C. 2RHZM/4RHM		2.74 ± 0.48	1.26 ± 0.33	-0.29 ± 0.58	0	0
D. 2RHM/4RH		3.70 ± 0.25	2.11 ± 0.26	1.32 ± 0.37	-0.10 ± 0.57	-0.65 ± 0.32
E. 2RMZ/4RM		0.90 ± 0.58	-0.47 ± 0.43	0	0	0
F. 2MHZ/4MH		4.21 ± 0.25	3.67 ± 0.12	3.39 ± 0.18	2.63 ± 0.35	1.98 ± 0.22

MEAN LOG_{10} COLONY-FORMING UNIT COUNTS* FROM SPLEEN HOMOGENATES

	Duration of Treatment (months)					
Treatment	0	2	3	4	5	6
A. Infected, untreated	4.24+0.21	5.87 ± 0.18	6.14 ± 0.28	6.77 ± 0.93	6.37 ± 0.59	6.69 ± 0.67
B. 2RHZ/4RH		0.04 ± 0.70	-0.65 ± 0.32	0	0	0
C. 2RHZM/4RHM		0.40 ± 0.35	0	0	0	0
D. 2RHM/4RH		-0.23 ± 0.63	0	0	0	0
E. 2RMZ/4RM		0	0	0	0	0
F. 2MHZ/4MH		0.57 ± 0.39	0.23 ± 0.65	-0.26 ± 0.59	-0.65 ± 0.32	-0.62 ± 0.35

Diarylquinolines : D207910, TMC 207

- *Mode of action is anti ATP synthetase*
- *Active against M.tb both sensitive and resistant strain*
- *Active against non tuberculous mycobacteria*
- *Cmax of 2.2 μg / ml after 400 mg dose with long half life of 24 hrs*
- *Clinical phase IIb will be started soon*

MIC 99% of TMC 207

	No	MIC range (μg / ml)
H37Rv M. TB	1	0.030
M. TB, susceptible	6	0.030 – 0.120
M. TB, INH resistant	7	0.003 – 0.060
M. TB, RMP resistant	1	0.030
M. TB, MDR	2	0.030 – 0.030
M. TB, PZA resistant	1	0.030
M. TB, FQ resistant	2	0.060 – 0.120

MIC 99% of Nontuberculosis mycobacteria

	No	MIC range (μg / ml)
M. bovis	1	0.003
MAC	6	0.007 – 0.010
M. kansasii	7	0.003
M. marinum	1	0.003
M. fortuitum	2	0.007 – 0.010
M. abscessus	1	0.250
M. smegmatis	2	0.003 – 0.010
M. Ulcerans	1	0.500

DIARYLQUINOLINE : R207910 , TMC 207

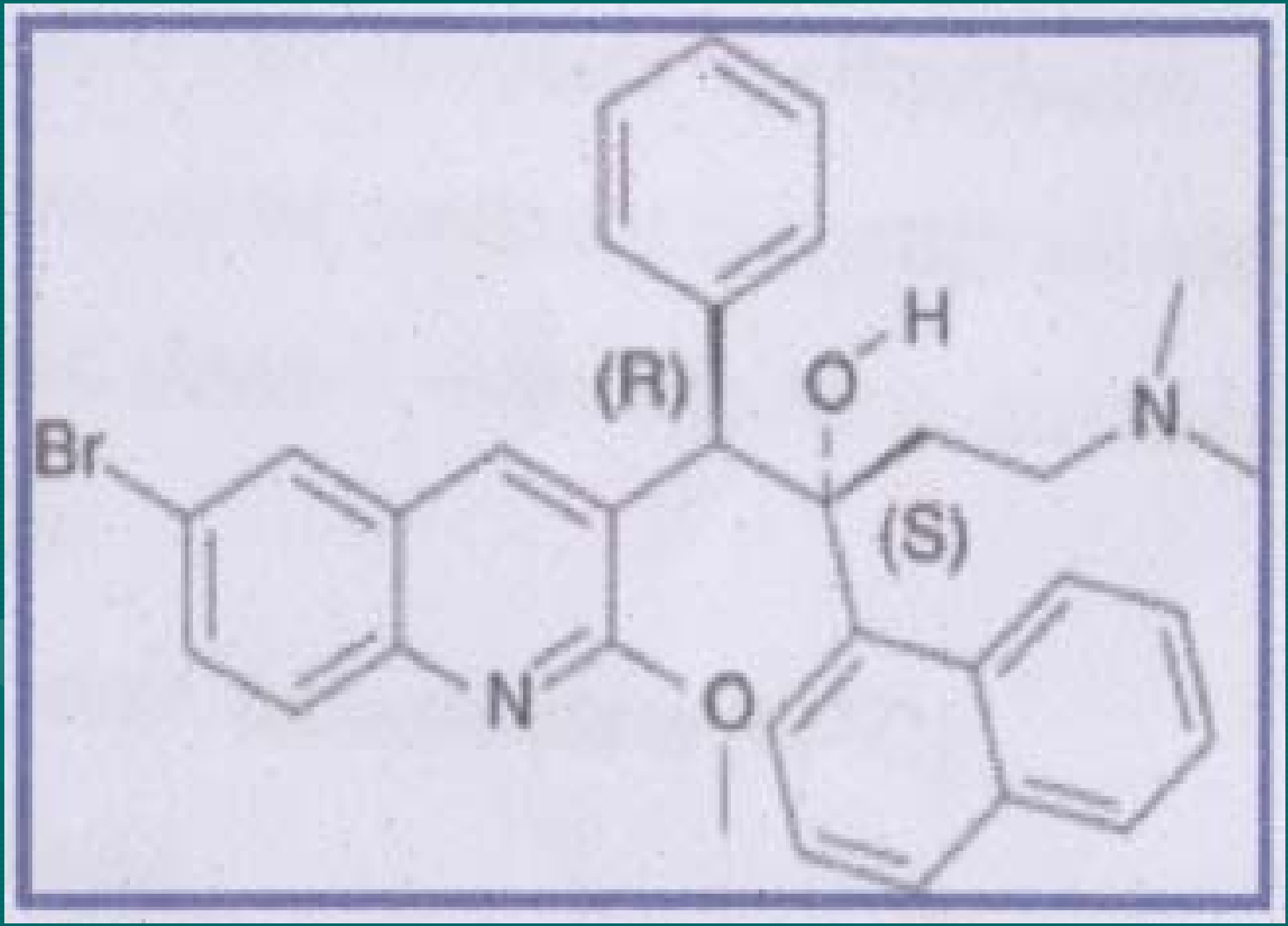


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TABLE 1. In vitro activities of linezolid against 117 clinical isolates of *M. tuberculosis*[a]

M. tuberculosis isolates (no. of isolates)	MIC (μg/ml)			
	Range	50%	90%	Geometric mean
Susceptible to first-line drugs (73)	0.25-1	0.5	0.5	0.524
Resistant to first-line drugs (44)	≤0.125-1	0.5	1	0.477
Resistant to one first-line drug (25)	≤0.125-1	0.5	1	0.529
Resistant to multiple first-line drugs (19)	0.25-1	0.5	0.5	0.417
All (117)	≤0.125-1	0.5	1	0.506

[a] The MIC of strain H37Rv (ATCC 27294) was 0.25 μg/ml.

Efficacy and Safty of linezolid in MDR-TB-a Report of Ten Cases

- *Ten MDR – B patients were treated with linezolid with other drugs*
- *Duration 6-40 (median 17) weeks and follow up 11 - 50 (median 24) weeks*
- *MIC < 4 mg/L for linezolid*
- *Nine were cured and 70% had serious ADR with withdrawal durg all*
- *Six with perihperal neuropathy and 5 with bone marrow suppression*

(J Infect 2006;52:92-6)

In Vitro Activities of Ketolides Telithromycin (HMR 3647) and HMR 3004 Compured to Those Clarithromycin Against Slowly Growing Mycobacteria at pH 6.8 and 7.4

- *MIC $\leq$20.0 mg/L for M. bovis BCG, M. ulcerans, M. avium M. paratuberculosis*
- *MIC $\geq$40.0 mg/L for M.tuberculosis, M.africanum, M. bovis, M. simiae*

(AAC 2000;44:2848-52)

Preclinical Testing of the nitroimidazopyran PA824 for Activity against M.TB in a Series of in vitro and in vivv Model

- *Derivative of metronidazole*
- *MIC against M. TB ≤1 mg/L*
- *Active against M. TB under condition of oxygen depletion*
- *In mouse infection model, PA824 is equivent to INH, RMP, gatifloxacin, moxifloxacin*

(AAC 2005;49:2294-301)

Conclusions (1)

** In any phase of MDR-TB chemotherapy, at least 3 sensitive drugs other than PZA should be combined to prevent further drug resistance.*

** In moderate cases, 3 sensitive drugs other than PZA are probably enough, even in initial phases of MDR-TB chemotherapy, for culture conversion and preventing further drug resistance.*

** In advanced cases, 4 or more sensitive drugs other than PZA may be necessary. But this is not yet concluded and controversial, and probably dependent partly on the indication of adjunctive surgery.*

Conclusions (2)

* *If sensitive, PZA should be used in initial 2 to 3 months. After that, when other sensitivedrugs can be used, PZA should be replaced by other sensitive drugs.*

•*Injectable drugs and fluoroquinolone should be used if possible.*

* *In case of INH low grade resistance, INH is probably not useful, and caution for TH cross resistance is necessary.*

WHO Global Task Force on XDR-TB

- Strengthen the quality of basic TB and HIV/AIDS control
- Scale up the programmatic management of MDR/XDR-TB
- Strengthen laboratory services
- Expand MDR/XDR-TB surveillance
- Deveopment and implement infection control
- Strengthen advocacy,communication and social mobilization
- Pursue resource mobilization at all levels
- Promote research and development


Thank you for your attention