Outcomes of MDR/XDR-TB Patients Treated with Linezolid: Experience in Thailand

Chaiyos Roongruangpitayakul MD*,
Charoen Chuchottaworn MD*

** Department of Respiratory Medicine, Central Chest Institute of Thailand, Nonthaburi, Thailand*

Background: *Multi-drug-resistant/extensively drug-resistant tuberculosis (MDR/XDR-TB) becomes an increasing problem in management. Linezolid has been off-label used in treatment of MDR/XDR-TB with major adverse effects.*
Objective: *To study outcomes of MDR/XDR-TB patients treated with linezolid in Central Chest Institute of Thailand.*
Material and Method: *MDR/XDR-TB patients treated with linezolid from 2009-2012 were retrospective analyzed.*
Results: *Seventeen from 24 cases had finished treatment. Linezolid, capreomycin, cycloserine, clofazimine, moxifloxacin, ethambutol, kanamycin, ethionamide, and PAS were used in 24, 21, 8, 7, 5, 5, 2, 2, and 2 cases respectively. Long-term injection of capreomycin was used in 14/17cases for an average of 14.7 months. Three point three drugs were used as an average. Average conversion time of smear and culture were 53.5 and 52.1 days respectively. Treatment time averaged 19.1 months. Fifteen of 24 cases were cured, seven were still ongoing treatment, all had sputum culture conversion, and two cases failed. There was no relapse in 13 cases after a follow-up that averaged 10.6 months. Linezolid was stopped in five cases from peripheral or optic neuropathy. Capreomycin was stopped in four cases from vestibulotoxic and nephrotoxic.*
Conclusion: *Linezolid has good efficacy in treatment of MDR/XDR-TB with major adverse effect and should be used with caution. If capreomycin is susceptible or likely active, long-term injection should be considered when likely active drugs are not enough to strengthen the regimen.*

Keywords: *Capreomycin, Drug-resistant, Linezolid, Treatment, Tuberculosis*

J Med Assoc Thai 2013; 96 (10): 1273-82
Full text. e-Journal: *http://jmat.mat.or.th*

There were 8.7 million new cases of tuberculosis (TB) in 2011[1]. Furthermore, 1.4 million people died from TB in that year[1]. Worldwide, 3.7% of new cases and 20% of previously treated cases are estimated to have multi-drug-resistant tuberculosis (MDR-TB). Additionally, extensively drug-resistant tuberculosis (XDR-TB) has been reported in 84 countries. The average proportion of XDR-TB is 9% of MDR-TB[1]. Treatment success of MDR-TB is 48%, and 33% among XDR-TB patients[1]. MDR-TB is defined as *Mycobacterium tuberculosis* resisting to isoniazid and rifampicin. Pre-XDR-TB is defined as *M. tuberculosis* resisting to isoniazid, rifampicin, any one of fluoroquinolones, or one injectable agent but not both. XDR-TB is defined as *M. tuberculosis* resisting to isoniazid, rifampicin, any one of fluoroquinolones, and at least one injectable agent (capreomycin, kanamycin, amikacin)[2,3]. There are five groups of drug that can be used in drug resistant tuberculosis from WHO recommendation in 2008[2]. Injectable agents and fluoroquinolones are the important part of the regimen[4-6]. In XDR-TB, drugs that can be used in the regimen are even in smaller quantity, lack potency, and are more toxic. Group 5 drugs, agents of unclear efficacy (clofazimine, linezolid, amoxicillin-clavulanate, thiacetazone, clarithromycin, and carbapenems) are unavoidably used[4].

Linezolid is an oxazolidinone that is used for treatment of gram-positive bacterial infections[4]. In vitro linezolid has high antibacterial activity against *M. tuberculosis* and has been off-label used in treatment of MDR/XDR-TB in many case report, case series (from China, Korea, India, USA, and Europe), systematic review, and meta-analysis[7-19]. The dosage and duration of linezolid is still unknown, but 600 mg/day dosage had the same efficacy as more than 600 mg/day dosage but fewer incidence of serious side effect[7]. Treatment success was averaged 81.8%. The most common adverse effects were neuropathy 47.1%, anemia 38.1%, and thrombocytopenia 11.8%. During treatment, linezolid was stopped because of major adverse events 68.4% (54 from 79 cases)[7]. Fluoroquinolone resistance, capreomycin resistance,

Correspondence to:
Roongruangpitayakul C, Department of Respiratory Medicine, Central Chest Institute of Thailand, Nonthaburi 11000, Thailand.
Phone: 0-2591-3442, Fax: 0-2591-9970
E-mail: chaiyos40@hotmail.com

and extensive in vitro drug resistance are the important risk factors for poor outcomes in drug-resistant tuberculosis (DR-TB)[20].

Material and Method

Between 2009 and 2012, MDR/XDR-TB patients treated with linezolid at Central Chest Institute of Thailand (CCIT), which is a referral hospital for complicated DR-TB, were analyzed retrospectively. All cases were treated as outpatient and would be admitted if complication, serious adverse effect occurred, or close monitoring was needed. Sputum smear AFB by fluorescein microscopy, culture with Lowenstein Jensen medium (LJ medium), drug susceptibility test (DST) by proportional method to isoniazid, rifampicin, ethambutol, streptomycin, kanamycin, and ofloxacin was done in all cases at first visit and every two to four weeks. Furthermore, DST from supranational reference lab (SRL) was included in three cases. Individualized treatment regimen was used based on previous drugs used, drug adverse effect, and DST results. Linezolid and one injectable agent that was susceptible or likely susceptible were included in all cases. Linezolid was started at 600 mg/day and would be decreased to 300 mg/day or stopped if major adverse effect occurred. Capreomycin (15 mg/kg/day) was used in 21 cases and was injected intramuscular daily for three to six months or culture conversion then adjusted to thrice a week and twice a week later until the treatment was finished. Newer generation fluoroquinolones that DST showed susceptible or likely susceptible (not previously used) was included. Group 1 drug that was still susceptible as well as group 4 and group 5 drugs that had less potency and were likely susceptible but not previously used, were included. Therefore, the patients were receiving at least four drugs in the regimen. Treatment continued at least 18 months and until negative sputum culture for more than one year or until serious adverse effect occurred and no other medications could be substituted for the remaining regimen. Directly-observed treatment, short-course (DOTS) was implemented in all cases. All cases were followed-up every one to two weeks during first three to six months, and every three to four weeks after that. Complete blood count (CBC) and renal function were tested every visit to detect early, any serious adverse effect. All cases were followed-up after complete treatment for more than one year, except two cases that were transferred out after complete treatment. Outcomes are defined as cure, complete treatment, default, death, or failure by WHO criteria[2]. Pregnancy, renal impairment, patient who cannot tolerate long-term medication by injection, and frequent follow-up was excluded. This study was approved by the ethic committee of the hospital.

Results

Seventeen of 24 cases had finished treatment and outcomes were analyzed. Demographic characteristics of patients with MDR/XDR-TB and treatment data are shown in Table 1. From 24 cases, seven cases were XDR-TB, 11 cases were Pre-XDR-TB, four cases were MDR-TB, and two cases were DR-TB according to DST. All cases had been treated with first and second-line drugs and failed (positive sputum smear and culture more than one year after treatment even though DST showed susceptible to drugs used and DOTS was implemented). All had pulmonary TB and positive sputum smear and culture to *M. tuberculosis*. Twenty-two cases had cavity on CXR (91.7%). There were three cases of pleural involvement, one case of pericardial involvement, and one case of associated meningitis. Anti-HIV was done in 12 cases and all were negative. Two cases had surgery after negative sputum smear. There were 16 male and 8 female with age ranged from 23 to 63 years old (mean 41.2). All had been previously treated for 12 to 142 months (average 53.7). The average numbers of all anti-tuberculosis drugs previously used were 10 (range 6-15) isoniazid, rifampicin, ethambutol, and pyrazinamide (PZA) had been used in all cases. Streptomycin, kanamycin, amikacin, ofloxacin, levofloxacin, and moxifloxacin had been used in 18, 19, four, 22, six, and six cases respectively. Five cases had comorbid disease (diabetes mellitus, hypertension). Drug-resistance of isoniazid, rifampicin, ethambutol, streptomicin, kanamycin, capreomycin, ofloxacin, ethionamide, cycloserine, and p-aminosalicylic acid (PAS) were 91.7 (22/24), 100 (24/24), 41.7 (10/24), 79.2 (19/24), 33.3 (8/23), 20 (1/5), 78.3 (18/23), 62.5 (5/8), 33.3 (2/6), and 28.6 (2/7)% (Fig. 1). The mean number of drugs initially used for MDR/XDR-TB treatment were 3.3 (range 2-6), and at the end of the treatment were 2.2 (range 2-3). Linezolid, capreomycin, cycloserine, clofazimine, moxifloxacin, ethambutol, kanamycin, ethionamide, and PAS were used in 24, 21, eight, seven, five, five, two, two, and two cases respectively. Long-term injection of capreomycin was used in 14/17 cases average 14.7 months. Average time that the patient used linezolid, capreomycin, kanamycin,

Table 1. Demographic characteristics of patients with MDR/XDR-TB and treatment data

Patient	Sex/ age	Time culture conversion (days)	Drugs previously used in addition to HRZE and clinically failure	DST resistant	Current drugs in addition to LZD	Initial (reduce) dose LZD (mg/d)	Total duration LZD/IA/FLQ (total weeks)	Total duration treatment (mo.)	Number drugs used initial (final)	Outcomes	Time follow-up (mo.)
1	M/52	63	AMK,OFX,ETO,CS,PAS	S,H,R,OFX	CM	600	78/78/- (78)	19.5	2 (2)	Cure	10
2	M/41	42	S,OFX,ETO,PAS,CLR	H,R,E	K,MFX,CS	600 (300)	22/28/78 (81)	20.5	4 (2)	Cure	NA
3[a]	F/29	35	S,K,OFX,MFX,ETO, CS,PAS	S,H,R,OFX	CM	600	74/74/- (74)	18.5	2 (2)	Cure	22
4	M/57	21	S,K,OFX,ETO,CS,PAS	S,H,R,E,OFX	CM	600 (300)	60/62/- (62)	15.5	2 (2)	Cure	27
5	F/31	56	K,OFX,MFX,ETO,CS, PAS,S	S,H,R,K,OFX	CM,E	600 (300)	77/78/- (78)	19.5	3 (2)	Cure	13
6	M/36	14	S,K,OFX,LFX,ETO, PAS,AMK	S,H,R,E,K,OFX	CM	600	65/65/- (65)	16.3	2 (2)	Cure	20
7	M/38	35	S,K,OFX,PAS	S,H,R,E,OFX	CM,MFX,ETO,CS	600	71/1/69 (86)	21.5	5 (3)	Cure	NA
8	M/59	35	S,K,OFX,ETO,CS,PAS	S,H,R,K,OFX	CM	600	76/76/- (76)	19.0	2 (2)	Cure	3
9	M/50	28	S,K,MFX,ETO,CS,PAS	S,H,R,OFX	CM	600 (300)	76/77/- (77)	19.3	2 (2)	Cure	10
10	F/34	49	K,OFX,LFX,MFX,ETO,CS, PAS	S,H,R,K,OFX,ETO, PAS,CM	CM,E	600	22/43/- (44)	11.0	3 (2)	Failure	6
11	F/31	94	OFX,PAS	H,R	CM,ETO,CS	600	80/24/- (80)	20.0	4 (2)	Cure	10
12	M/50	75	S,K,LFX,ETO,CS,PAS	H,R,OFX	CM,MFX,E	600 (300)	60/80/21 (80)	20.0	4 (2)	Cure	8
13	M/38	84	S,K,OFX,ETO,CS,PAS	S,H,R,E,OFX,ETO	CM	600 (300)	81/82/- (82)	20.5	2 (2)	Cure	4.5
14	M/23	NA	S,K,OFX,ETO,CS,TMC207[b]	S,H,R,E,K,OFX	CFZ,CS	600	75/-/- (75)	18.8	3 (2)	Cure	4
15	M/51	112	S,K,OFX,ETO,CS,PAS	R	CM,MFX	600 (300)	33/48/70 (77)	19.3	3 (2)	Cure	3
16	M/25	77	K,OFX,ETO,PAS	H,R,E,OFX	CM,CS	600 (300)	76/28/- (77)	19.3	3 (2)	Failure	NA
17[a]	F/23[c]	35	S,OFX,LFX,ETO,CS,PAS	S,H,R,OFX	K,MFX,E,CS,PAS	600	72/11/46 (77)	19.3	6 (3)	Cure	3
18	F/45	105	S,K,OFX,ETO,CS,PAS	S,H,R	CM,E	600			3	On Rx	
19	M/57	NA	S,AMK,OFX,LFX, MFX,ETO,CS,PAS	S,H,R,Z,E,K,AMK, OFX,MFX,ETO	CM,CFZ,CS,PAS	600			5	On Rx	

[a] Surgery, lobectomy

[b] Salvage regimen after 24 weeks TMC207 and other second-line drug (SLD), sputum smear and culture negative at start of treatment with LZD and no other active drug can be used in continuation phase

[c] Pregnancy and abortion in week 11, 16 respectively kanamycin, LZD, MFX was withheld 5 weeks and restart after abortion

MDR/XDR-TB = multi-drug-resistant/extensively drug-resistant tuberculosis; DST = drug susceptibility; S = streptomycin; H = isoniazid; R = rifampicin; E = ethambutol; Z = PZA; K = kanamycin; AMK = amikacin; CM = capreomycin; OFX = ofloxacin, LFX = levofloxacin; MFX = moxifloxacin; ETO = ethionamide; CS = cycloserine; PAS = p-aminosalicylic acid; LZD = linezolid; CFZ = clofazimine; AMX/CLV = amoxicillin/clavulanate; CLR = clarithromycin; IA = injecting agents (kanamycin, amikacin, capreomycin); FLQ = new generation fluoroquinolones; On Rx = on treatment, mo. = month; NA = not available

Table 1. (cont.)

Patient	Sex/ age	Time culture conversion (days)	Drugs previously used in addition to HRZE and clinically failure	DST resistant	Current drugs in addition to LZD	Initial (reduce) dose LZD (mg/d)	Total duration LZD/IA/FLQ (total weeks)	Total duration treatment (mo.)	Number drugs used initial (final)	Outcomes	Time follow-up (mo.)
20	M/32	98	S,K,OFX,ETO,CS,PAS	S,H,R,OFX	CM,CFZ,CLR, AMX/CLV	600			5	On Rx	
21	M/39	NA	S,K,AMK,OFX,LFX,ETO, CS,PAS,AMX/CLV,CLR	S,H,R,E,K,OFX,ETO, CS	CM,CFZ	600			3	On Rx	
22	F/63	56	K,OFX,ETO,PAS	S,H,R,OFX,PAS,LFX	CM,CFZ,CS	600			4	On Rx	
23	M/54	77	S,K,OFX,ETO,CS,PAS,CLR	S,H,R,E	CM,CFZ	600			3	On Rx	
24	F/30	NA	S,K,OFX,MFX,ETO,CS,PAS	S,R,K,ETO,CS	CM,CFZ	600			3	On Rx	

[a] Surgery, lobectomy

[b] Salvage regimen after 24 weeks TMC207 and other second-line drug (SLD), sputum smear and culture negative at start of treatment with LZD and no other active drug can be used in continuation phase

[c] Pregnancy and abortion in week 11, 16 respectively kanamycin, LZD, MFX was withheld 5 weeks and restart after abortion

MDR/XDR-TB = multi-drug-resistant/extensively drug-resistant tuberculosis; DST = drug susceptibility; S = streptomycin; H = isoniazid; R = rifampicin; E = ethambutol; Z = PZA; K = kanamycin; AMK = amikacin; CM = capreomycin; OFX = ofloxacin, LFX = levofloxacin; MFX = moxifloxacin; ETO = ethionamide; CS = cycloserine; PAS = p-aminosalicylic acid; LZD = linezolid; CFZ = clofazimine; AMX/CLV = amoxicillin/clavulanate; CLR = clarithromycin; IA = injecting agents (kanamycin, amikacin, capreomycin); FLQ = new generation fluoroquinolones; On Rx = on treatment, mo. = month; NA = not available

INH = isoniazid; RMP = rifampicin; EMB = ethambutol; STM = streptomycin; Km = kanamycin; Cm = capreomycin; OFX = ofloxacin; ETO = ethionamide; Cs = cycloserine; PAS = p-aminosalicylic acid

Fig. 1 Drug susceptibility test.

and moxifloxacin and the total treatment time was 64.7, 58.3, 19.5, 56.8, and 74.6 weeks. Two cases had surgery (lobectomy) at 28 and 42 weeks after treatment. Both cases were sputum smear negative before the operation. Prolonged air leak complication occurred in one case.

Table 2 shows that 15 of 17 cases were cured (88.2%) and 2 failed (11.8%). Additionally, seven cases were still ongoing treatment and all had sputum culture conversion. The average duration of treatment was 19.1 months (range 15.5-21.5 months). No relapse in the 13 cases that had an average followed-up of 10.6 months. Average conversion time of sputum smear and culture were 53.5 and 52.1 days respectively (Fig. 2). In two failure cases, Case 10 had sputum culture positive at 23 weeks again after turned to negative at seven weeks, DST later showed capreomycin resistance, and linezolid was stopped from peripheral neuropathy adverse effect at 23 weeks. Case 16 had sputum smear positive at 74 weeks again after turned to negative at three weeks. The patient had interrupted the medication for two weeks, for three episodes during flood crisis in Thailand in 2011 because the road was cut-off and capreomycin was stopped at seven months from nephrotoxic.

Linezolid had major adverse effect in 10/24 (41.7%) included three peripheral neuropathy, two optic neuropathy, three bone marrow suppression, and two transient visual impair. Linezolid dosage was adjusted from 600 to 300 mg/day in 8/24 (33.3%) from major adverse effect (Table 3). However, linezolid was permanently stopped from major adverse effect in five cases (29.4%). Time for linezolid usage before withdrawal was 22, 23, 33, 60, and 65 weeks.

All peripheral neuropathy was irreversible after stopping the medication and vitamin B supplement. All optic neuropathy were reversible. Marrow suppression was reversible after decreased the dosage from 600 to 300 mg/day. One case of anemia needed blood transfusion. Two cases of linezolid had transient visual impaired that reversed to normal after stopping the medication and restarted at 300 mg/day after optic neuropathy had been excluded.

Capreomycin was stopped in four of 21 cases (19.1%) from vertigo (vestibulotoxic) in one case and increase serum creatinine more than 2 mg % in three cases. Time for capreomycin usage before withdrawal was 1, 5, 10, and 34 weeks. Serum creatinine returned to normal after stopping medication and vertigo resolved. One case had transient slight-hearing loss after capreomycin injection for a few minutes and returned to normal when the dosage was decreased. Hearing loss did not occur again. Ethambutol was

Table 2. Treatment outcomes in 17 cases

	XDR-TB	Pre-XDR-TB	MDR-TB	All
Cure	4 (80.0%)	8 (88.9%)	3 (100%)	15 (88.2%)
Failure	1 (20.0%)	1 (11.1%)	-	2 (11.8%)
All	5	9	3	17

* All cases had failed to first and second-line drugs even though DST show susceptible, positive culture and smear more than 12 months of treatment with directly-observed treatment, short-course (DOTS) was implemented

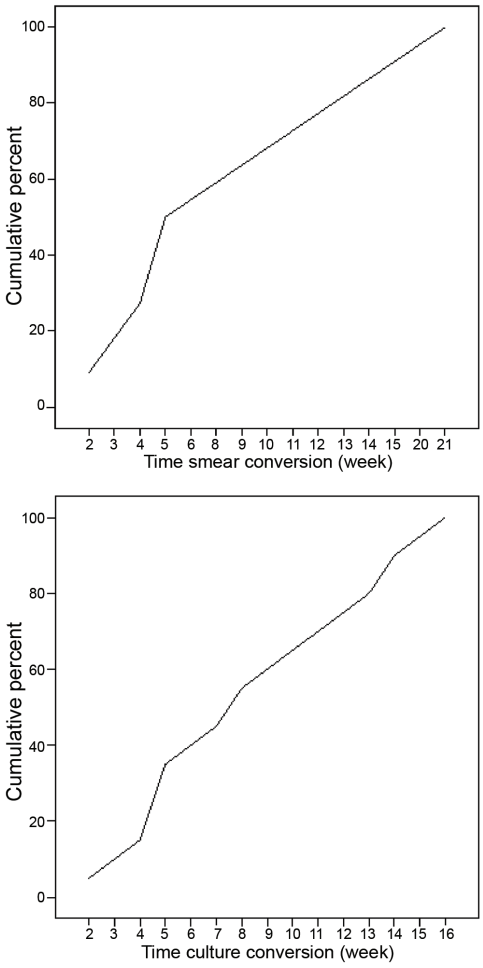

Fig. 2 Time smear and culture conversion in cumulative frequency.

Table 3. Adverse effects

Adverse effects	Linezolid (n = 24)	Capreomycin (n = 21)	Moxifloxacin (n = 5)
Peripheral neuropathy	3 (S)		
Optic neuropathy	2 (S,R)		
Transient visual impairment[a]	2 (T,R)		
Anemia	2 (T,R)		
Thromocytopenia	1 (T,R)		
Eosinophilia	1 (C,R)		
Vertigo		1 (S,R)	
Increase creatinine >2 mg %		3 (S,R)	
Transient hearing loss		1 (T,R)	
Arthralgia			1 (S,R)

[a] Not include case which co-administration with ethambutol, and ethambutol was stopped
S = stop drug; T = temporary stop and restart with lower dosage; C = continue drug, and reduce dosage; R = reverse of adverse effect

stopped in three cases from optic neuropathy at 5, 20, and 25 weeks; all were reversible. Cycloserine was stopped in two cases from diplopia and depression. Moxifloxacin was stopped in one case from arthralgia.

Case 14, linezolid was added as salvage regimen after the patient had finished 24 weeks of Bedaquiline (TMC207) and sputum smear negative in another trial, and DST later showed resistance to the remaining drugs. Injectable agent and fluoroquinolones were not added, but clofazimine and cycloserine were added to linezolid. Case 17, the patient had pregnancy during week 11, linezolid, moxifloxacin, kanamycin were stopped for 5 weeks (but ethambutol, cycloserine, PAS were continued) and restarted again after abortion. Case 15, DST showed rifampicin resistance and the patient had major adverse effects to many drugs and clinically failed to the other first, second-line drugs. Case 24 whose DST showed rifampicin, streptomycin, kanamycin resistance was clinically failed to the other first, second-line drugs.

Discussion

Nearly all first and second-line drugs had been used in all cases of the present study and failed. DST also showed resistance to isoniazid, rifampicin, streptomycin, kanamycin, ofloxacin, and ethionamide, which had a good correlation to drug used history, except ethambutol that had 41.7% resistance. Most cases were Pre-XDR-TB according to DST, but they failed all first-line drugs, kanamycin, ofloxacin, ethionamide, cycloserine, and PAS, which clinically they failed to treatment the same as XDR-TB. Injectable agents and fluoroquinolones are the important component of the regimen for MDR-TB treatment, but in XDR-TB, these two drugs are resistant, the remaining drugs that were still susceptible from second-line drugs DST are used but their efficacy is uncertain because some of them are bacteriostatic, and the reliability of second-line drugs DST is still questionable, not reproducible, and lack of correlation between second-line DST results and clinical response[21,22]. They had been previously used in many cases in the present study and failed. Capreomycin was only available at CCIT in Thailand, so all 24 cases had certainly never been expose to this drug, although there could be cross resistance between capreomycin, kanamycin, and amikacin, but it was believed to be a likely active drug. Chan et al[23] reported that MDR-TB strains resistant to fluoroquinolones and streptomycin but susceptible to second-line injection drug had a better prognosis than XDR-TB (% long-term success rate 75% compare with 20% in XDR-TB). Migliori et al[24] reported that capreomycin-resistance yielded a higher proportion of failure and death than capreomycin-susceptible (60.9% vs. 28.1%) while resistance to either kanamycin or amikacin alone was not an important indicator of poor prognosis. For these reasons, capreomycin was chosen in the main component of the present study regimen. Linezolid had been used in treatment of MDR and XDR-TB in many case reports, meta-analysis, and systemic reviews[4-19], with good outcomes. However, it had many major adverse effects including bone marrow suppression and peripheral and optic neuropathy, and was stopped early. A dose of 600 mg/day of linezolid had less toxicity, especially a bone marrow suppression of than 1,200 mg/day without compromising their efficacy.

Linezolid and capreomycin were the main component that was used in nearly all cases of the present study. Seven cases used only these two drugs and an additional three cases used linezolid, capreomycin, and ethambutol. However, ethambutol was stopped at 20 to 25 weeks for optic neuropathy. Eight of 10 cases were cured, one was still ongoing treatment, and one was a failure case, which DST later showed capreomycin resistance, and linezolid was stopped because of peripheral neuropathy adverse effect in that cases (case 10). Fluoroquinolones had also cross resistance in their group, but levofloxacin and moxifloxacin has been used despite ofloxacin resistance. There are findings that levofloxacin is effective against ofloxacin-resistant strains. This suggests that cross-resistance between fluoroquinolones is not always complete[6]. Levofloxacin or moxifloxacin would be added in the regimen if it was not previously used even though the patient had ofloxacin-resistance. Even though the number of drugs used in the present study was less than four as WHO recommended because there were no likely active drugs that could be added and some had adverse reaction to the susceptible drug, but the outcomes was good. More drugs of uncertain efficacy would increase adverse effect in some case and would decrease patient compliance. Ethambutol had been used and failed in previous treatment in four cases but DST showed drug-susceptible, so its efficacy was questioned. From four cases that ethambutol and linezolid had been used together, three cases needed to stop medication temporary from optic neuropathy, and linezolid was restarted again without recurrent of optic neuropathy in all three cases. Ethambutol, which was used at the

lowest dose (15 mg/kg/day), was presumed to be the cause of this adverse effects. This is the important result. When ethambutol and linezolid are used together, this will have more optic neuropathy side effect than when they are used separately. No serious adverse effects from long-term injection of capreomycin occurred with close monitoring of renal function. All adverse effects were reversible after the medication was stopped. Peripheral neuropathy and optic neuropathy were the main adverse effects why linezolid was stopped early. Marrow suppression was resolved after reducing linezolid dosage to 300 mg/day.

From the present study, linezolid, capreomycin (not previously used and likely active or DST showed susceptible), and new generation fluoroquinolones should be used as the important component in the treatment of XDR-TB, Pre-XDR-TB, and some cases of MDR-TB. The remaining drugs that are likely active or DST showed susceptibility should be added to have at least four drugs. When linezolid was stopped early because of major adverse effect, the other drugs that are likely active must be added to the remaining regimen. Mitnick et al[25] used an average of 5.3 drugs including cycloserine, injectable drug, and fluoroquinolone in treatment of MDR-TB and XDR-TB, with long-term injection lasting an average of 15.4 months (11.4-19.7). They had good outcomes (success 65.6, 60.4% respectively). Linezolid was not used in their study.

Table 4 compared results of the present study with the other 12 studies. The present study had good outcomes comparable to the study of Schecter[12]. The linezolid dose and duration were not much different. The present study used long-term capreomycin injection, but less proportion of case that used new generation fluoroquinolones (because it was unlikely active, and most cases previously failed to new generation fluoroquinolones).

The present study has several limitations from its retrospective design, selection bias, non-randomization, and small number of patients. However, the study implies that there is still a chance of cure in these complicated drug-resistant TB patients that are difficult to treat with a smaller number of available drugs until new drugs and better strategy to stop drug-resistant TB are developed.

In conclusion low dose 600 mg/day of linezolid can achieve good outcomes (88% cure) in treatment of MDR/XDR-TB with major adverse effect (41.7%). However, linezolid was stopped in five cases (29.4%). Linezolid should be carefully used in

Table 4. Comparison of studies that use linezolid in treatment of MDR/XDR-TB patients

Author year	Country	Number MDR (XDR) case	LZD dose mg/d (number of case)	LZD duration (mo.)	% LZD permanent stop	% FLQ use	% IA use	Total duration (mo.)	Number drugs used	Major adverse effect	Outcomes	
Park[8] 2003-2004	Korea	8 (5)	1,200 adj. to 600 (6) 600 (2)	10.7	3/8 (37.5%)	4/8 (50.0%)	7/8 (87.5%)	NA	5.0	2/8 (25.0%)	COT 1 Conv. 8 Die 2	(100%)
Anger[9] 2000-2006	USA	16 (10)	1,200 (11) 400-800 (5)	16.0	6/16 (37.5%)	12/16 (75.0%)	10/16 (62.5%)	≥18.0 COT	5.0	6/16 (37.5%)	COT 11/16 Die 3 Relapse 1 Stop[a] 1	(69.0%)
Udwadia[10] 2000-2007	India	18 (7)	600 (18)	20.6	NA	NA	NA	20.6	NA	11/18 (61.0%)	Cure 11/18 Fail 4 Default 3	(61.1%)

FLQ = new generation fluoroquinolone; IA = injecting agent (kanamycin, amikacin, capreomycin); LZD = linezolid; COT = complete of treatment; Conv. = sputum conversion; S/E = side effect; adj. = adjust; TIW = thrice a week; NA = not available; mo. = month

[a] Stop from intolerance to antituberculosis and HIV medicine

[b] 14/17 use thioridazine in the regimen

[c] 17 from 51 cases of Koh 2007-2009 share the same data of Koh 2007-2008

References (8-19)

Table 4. (cont.)

Author year	Country	Number MDR (XDR) case	LZD dose mg/d (number of case)	LZD duration (mo.)	% LZD permanent stop	% FLQ use	% IA use	Total duration (mo.)	Number drugs used	Major adverse effect	Outcomes	
Migliori[11] 2001-2007	Belarus, Germany, Italy, Switzerland	85 (10)	1,200 (57) 600 (28)	8.0	19/85 (22.4%)	NA	NA	NA	NA	27/85 (31.8%)	Cure 23 COT 13 Success 36/45 Die 9/45	(80.0%)
Schecter[12] 2003-2007	USA	30 (3)	600 (28) 450 (1) 600 TIW (1)	18.9	3/30 (10.0%)	27/30 (90.0%)	29/30 (96.7%)	23.6	5.0	9/30 (30.0%)	Cure 22/25 Fail 1 Default 2	(88.0%)
Abbate[b][13] 2002-2008	Argentina	- (17)	NA	NA	0/17	14/17 (82.4%)	0/17	NA	4.2	9/17 (52.9%) All S/E	Cure 11 Conv. 4 Success 15 Default 2	(64.7%) (88.2%)
Koh[c][14] 2007-2008	Korea	24 (12)	600 (7) 300 (17)	12.8	2/24 (8.3%)	21/24 (87.5%)	19/24 (79.2%)	NA	6.0	2/24 (8.3%)	Conv. 22/24	(91.7%)
Koh[c][15] 2007-2009	Korea	51 (26)	300 (51)	14.8	14/51 (27.5%)	NA	NA	NA	5.0	14/51 (27.5%)	Favorable 40/51 Cure 33, COT 1, Conv. 6 Fail 10 Die 1	(78.0%)
Villar[16] 2004-2009	Portugal	16 (12)	1,200 (15) 600 (1)	15.8	NA	14/16 (87.5%)	9/16 (56.3%)	NA	5.0	1/16 (6.3%)	Cure 8, Conv. 4 Success 12/16 Die 1 Default 1	(75.0%)
Xu[17] 2007-2010	China	18 (15)	1,200 (15) 900 (3) adj. to 600 (13) 900 (4) 300 (1)	6.0	1/18 (5.6%)	15/18 (83.3%)	7/18 (38.9%)	NA	7.0	17/18 (94.4%) All S/E	Cure 9/15 Fail 2 Default 1 Relapse 3	(60.0%)
Tangg[18] 2009-2010	China	- (14)	1,200x2 mo. 600 mg later	6.5	2/14 (14.3%)	14/14 (100%)	2/14 (14.3%)	24.0	7.2	3/14 (21.4%)	Conv. 14/14	(100%)
Singla[19] 2006-2011	India	29 (16)	1,200 (11) 600 (18)	24.0	3/29 (10.3%)	29/29 (100%)	29/29 (100%)	24.0	6.0	5/29 (17.2%)	Favorable 21/29 Cure 9, Conv. 12 Fail 2, Die 3 Default 3 Treat 12	(72.4%)
Roongruangpitayakul 2009-2012	Thailand	24 (7)	600 (24) adj. to 300 (8)	16.0	5/17 (29.4%)	5/24 (20.8%)	23/24 (95.8%)	19.1	3.3	10/24 (41.7%)	Cure 15/17 Conv. 7 Fail 2	(88.2%)

FLQ = new generation fluoroquinolone; IA = injecting agent (kanamycin, amikacin, capreomycin); LZD = linezolid; COT = complete of treatment; Conv. = sputum conversion; S/E = side effect; adj. = adjust; TIW = thrice a week; NA = not available; mo. = month

[a] Stop from intolerance to antituberculosis and HIV medicine

[b] 14/17 use thioridazine in the regimen

[c] 17 from 51 cases of Koh 2007-2009 share the same data of Koh 2007-2008

References (8-19)

specialized clinic that has experience in management of complicated drug-resistant tuberculosis. If capreomycin is susceptible or likely active, long-term injection should be considered when likely active drugs in the regimen are not enough to strengthen the regimen.

Potential conflicts of interest

None.

References

1. World Health Organization. Global tuberculosis report 2012 [Internet]. 2012 [cited 2012 Dec 1]. Available from: www.who.int/tb/publications/global_report/en/
2. Guideline for the programmatic management of drug-resistant tuberculosis [Internet]. 2008 [cited 2012 Dec 1]. Available from: www.who.int/tb/challenges/mdr/en/
3. Banerjee R, Allen J, Westenhouse J, Oh P, Elms W, Desmond E, et al. Extensively drug-resistant tuberculosis in california, 1993-2006. Clin Infect Dis 2008; 47: 450-7.
4. Dooley KE, Obuku EA, Durakovic N, Belitsky V, Mitnick C, Nuermberger EL. World Health Organization group 5 drugs for the treatment of drug-resistant tuberculosis: unclear efficacy or untapped potential? J Infect Dis 2013; 207: 1352-8.
5. Chang KC, Yew WW. Management of difficult multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis: update 2012. Respirology 2013; 18: 8-21.
6. Caminero JA, Sotgiu G, Zumla A, Migliori GB. Best drug treatment for multidrug-resistant and extensively drug-resistant tuberculosis. Lancet Infect Dis 2010; 10: 621-9.
7. Sotgiu G, Centis R, D'Ambrosio L, Alffenaar JW, Anger HA, Caminero JA, et al. Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. Eur Respir J 2012; 40: 1430-42.
8. Park IN, Hong SB, Oh YM, Kim MN, Lim CM, Lee SD, et al. Efficacy and tolerability of daily-half dose linezolid in patients with intractable multidrug-resistant tuberculosis. J Antimicrob Chemother 2006; 58: 701-4.
9. Anger HA, Dworkin F, Sharma S, Munsiff SS, Nilsen DM, Ahuja SD. Linezolid use for treatment of multidrug-resistant and extensively drug-resistant tuberculosis, New York City, 2000-06. J Antimicrob Chemother 2010; 65: 775-83.
10. Udwadia ZF, Sen T, Moharil G. Assessment of linezolid efficacy and safety in MDR- and XDR-TB: an Indian perspective. Eur Respir J 2010; 35: 936-8.
11. Migliori GB, Eker B, Richardson MD, Sotgiu G, Zellweger JP, Skrahina A, et al. A retrospective TBNET assessment of linezolid safety, tolerability and efficacy in multidrug-resistant tuberculosis. Eur Respir J 2009; 34: 387-93.
12. Schecter GF, Scott C, True L, Raftery A, Flood J, Mase S. Linezolid in the treatment of multidrug-resistant tuberculosis. Clin Infect Dis 2010; 50: 49-55.
13. Abbate E, Vescovo M, Natiello M, Cufre M, Garcia A, Gonzalez MP, et al. Successful alternative treatment of extensively drug-resistant tuberculosis in Argentina with a combination of linezolid, moxifloxacin and thioridazine. J Antimicrob Chemother 2012; 67: 473-7.
14. Koh WJ, Kwon OJ, Gwak H, Chung JW, Cho SN, Kim WS, et al. Daily 300 mg dose of linezolid for the treatment of intractable multidrug-resistant and extensively drug-resistant tuberculosis. J Antimicrob Chemother 2009; 64: 388-91.
15. Koh WJ, Kang YR, Jeon K, Kwon OJ, Lyu J, Kim WS, et al. Daily 300 mg dose of linezolid for multidrug-resistant and extensively drug-resistant tuberculosis: updated analysis of 51 patients. J Antimicrob Chemother 2012; 67: 1503-7.
16. Villar M, Sotgiu G, D'Ambrosio L, Raymundo E, Fernandes L, Barbedo J, et al. Linezolid safety, tolerability and efficacy to treat multidrug- and extensively drug-resistant tuberculosis. Eur Respir J 2011; 38: 730-3.
17. Xu HB, Jiang RH, Li L, Xiao HP. Linezolid in the treatment of MDR-TB: a retrospective clinical study. Int J Tuberc Lung Dis 2012; 16: 358-63.
18. Tangg SJ, Zhang Q, Zheng LH, Sun H, Gu J, Hao XH, et al. Efficacy and safety of linezolid in the treatment of extensively drug-resistant tuberculosis. Jpn J Infect Dis 2011; 64: 509-12.
19. Singla R, Caminero JA, Jaiswal A, Singla N, Gupta S, Bali RK, et al. Linezolid: an effective, safe and cheap drug for patients failing multidrug-resistant tuberculosis treatment in India. Eur Respir J 2012; 39: 956-62.
20. Yew WW, Lange C, Leung CC. Treatment of tuberculosis: update 2010. Eur Respir J 2011; 37: 441-62.

21. Kim SJ, Espinal MA, Abe C, Bai GH, Boulahbal F, Fattorin L, et al. Is second-line anti-tuberculosis drug susceptibility testing reliable? Int J Tuberc Lung Dis 2004; 8: 1157-8.
22. Kim SJ. Drug-susceptibility testing in tuberculosis: methods and reliability of results. Eur Respir J 2005; 25: 564-9.
23. Chan ED, Strand MJ, Iseman MD. Multidrug-resistant tuberculosis (TB) resistant to fluoroquinolones and streptomycin but susceptible to second-line injection therapy has a better prognosis than extensively drug-resistant TB. Clin Infect Dis 2009; 48: e50-2.
24. Migliori GB, Lange C, Centis R, Sotgiu G, Mutterlein R, Hoffmann H, et al. Resistance to second-line injectables and treatment outcomes in multidrug-resistant and extensively drug-resistant tuberculosis cases. Eur Respir J 2008; 31: 1155-9.
25. Mitnick CD, Shin SS, Seung KJ, Rich ML, Atwood SS, Furin JJ, et al. Comprehensive treatment of extensively drug-resistant tuberculosis. N Engl J Med 2008; 359: 563-74.

การศึกษาผลการรักษาวัณโรคดื้อยาหลายขนาน (MDR/XDR-TB) ด้วยยาไลนีโซลิดในคนไทย

ไชยยศ รุ่งเรืองพิทยากุล, เจริญ ชูโชติถาวร

วัตถุประสงค์: *วัณโรคดื้อยาหลายขนานกำลังเป็นปัญหาในการรักษามากขึ้น ยาไลนีโซลิดมีประสิทธิภาพที่ดีในการรักษาผู้ป่วยวัณโรคชนิดดื้อยาหลายขนาน (MDR/XDR-TB) แต่มีฤทธิ์ข้างเคียงที่มีอันตราย*

วัสดุและวิธีการ: *รายงานผู้ป่วยวัณโรคชนิดดื้อยาหลายขนานที่ได้รับการรักษาด้วยยาไลนีโซลิดระหว่าง พ.ศ. 2552-2555 ที่สถาบันโรคทรวงอก 24 ราย ได้รับการทบทวน 17 ราย ได้รับการรักษาครบ*

ผลการศึกษา: *มีการใช้ยาไลนีโซลิด, แคปปรีโอมัยซิน, ไซโคลเซอร์รีน, คลอฟลาซิมีน, ม็อกซิฟล็อกซาซิน, อีแทมบูทอล, กานามัยซิน, เอธิโอนามัย, พีเอเอส, ในผู้ป่วยจำนวน 24, 21, 8, 7, 5, 5, 2, 2, 2 ราย ตามลำดับ 14 ใน 17 ราย ได้รับการฉีดคาปรีโอมัยซินนานเฉลี่ย 14.7 เดือน จำนวนยาที่ใช้ในการรักษาเฉลี่ย 3.3. ค่าเฉลี่ยเวลาที่เสมหะย้อมสีทนกรดไม่พบเชื้อวัณโรค 53.5 วัน ค่าเฉลี่ยเวลาที่เสมหะเพาะไม่พบเชื้อวัณโรค 52.1 วัน ระยะเวลาในการรักษาทั้งหมดเฉลี่ย 19.1 เดือน ผลการรักษาในผู้ป่วย 24 ราย 15 ราย หายขาด, 2 ราย ล้มเหลว, 7 ราย ยังรับการรักษา และทุกรายเสมหะย้อมสีทนกรดไม่พบเชื้อวัณโรคหลังการรักษา ไม่มีการกำเริบซ้ำในผู้ป่วย 13 ราย ที่ติดตามไปเป็นเวลาเฉลี่ย 10.6 เดือน ผู้ป่วย 5 ราย ต้องหยุดยาไลนีโซลิดเนื่องจากอาการข้างเคียงที่อันตราย peripheral neuropathy และ optic neuropathy ผู้ป่วย 4 ราย ต้องหยุดยาแคปปรีโอมัยซินเนื่องจากอาการข้างเคียงที่อันตราย vestibulotoxic และ nephrotoxic*

สรุป: *ยาไลนีโซลิดมีประสิทธิภาพที่ดีในการรักษาผู้ป่วยวัณโรคชนิดดื้อยาหลายขนานแต่มีฤทธิ์ข้างเคียงที่มีอันตราย และควรใช้ด้วยความระมัดระวังอย่างใกล้ชิดถ้ามีหลักฐานว่ายาแคปปรีโอมัยซินยังไม่มีการดื้อยา ควรใช้ยาแคปปรีโอมัยซินฉีดระยะยาวร่วมในการรักษาเมื่อไม่มียาที่มีประสิทธิภาพพอเพียงในสูตรยาที่ใช้อยู่ เพื่อทำให้ผลการรักษาดีขึ้น*
