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Outcome of pulmonary multidrug-resistant tuberculosis: a 6-yr follow-up study

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ABSTRACT: A retrospective study was performed to determine factors associated with the outcome of pulmonary multidrug-resistant tuberculosis (MDR-TB) in Taipei, Taiwan.

All patients newly diagnosed with pulmonary MDR-TB in a referral centre from 1992–1996 were enrolled and their outcome over the subsequent 6 yrs was determined.

A total of 299 patients were identified, comprising 215 (71.9%) males and 84 (28.1%) females with a mean age of 47.3 yrs. The patients received a mean of 3.7 effective drugs. Out of the 299 patients, 153 (51.2%) were cured, 31 (10.4%) failed, 28 (9.4%) died and 87 (29.1%) defaulted. Of the 125 patients receiving second-line drugs with ofloxacin, 74 (59.2%) were cured. Those who received ofloxacin had a lower risk of relapse than those receiving only first-line drugs (hazard ratio (HR) 0.16, 95% confidence interval (CI) 0.03–0.81) and a lower risk of TB-related death than those receiving second-line drugs but not ofloxacin (adjusted HR 0.50, 95% CI 0.31–0.82).

In conclusion, multidrug-resistant tuberculosis patients who received ofloxacin were more likely to be cured, and were less likely to die, fail or relapse. The utility of new-generation fluoroquinolones, such as moxifloxacin, in the treatment of multidrug-resistant tuberculosis needs to be evaluated. Default from treatment is a major challenge in the treatment of multidrug-resistant tuberculosis.

KEYWORDS: Death, follow-up, multidrug resistant, relapse, tuberculosis

Multidrug-resistant tuberculosis (MDR-TB), which is defined as a disease with isolates resistant to at least isoniazid and rifampin, compromises response to anti-TB treatment [1–3]. MDR-TB is prevalent in a number of countries [4].

Recommended treatment of MDR-TB includes the use of second-line anti-TB drugs [5]. To date, there have been no randomised controlled trials to evaluate the treatment of MDR-TB. Treatment regimens are determined individually for each patient, taking into account the results of susceptibility testing [6–12], or are standardised regimens [13–15] depending on the local situation.

The management of MDR-TB in Taipei, northern Taiwan, has been highly specialised in a referral centre, the Chronic Disease Control Bureau (CDCB), which was the headquarters of a TB control system functioning for >40 yrs (until 2002), with a network of public health nurses distributed in all townships and villages, responsible for TB services [16]. The majority of MDR-TB patients identified in general hospitals were referred to the CDCB for further management. Treatment of MDR-TB has increasingly included the use of ofloxacin in the second-line treatment regimen [17]. To understand the long-term outcome of MDR-TB, a consecutive series of MDR-TB cases were reviewed and followed up over time, with specific attention paid to the results of the use of ofloxacin for treatment. The results of this follow-up study are reported here.

METHODS

Case ascertainment

Patients with MDR-TB were identified from the Mycobacteriology Laboratory of the CDCB (Taipei, Taiwan). Patients who were newly diagnosed with pulmonary MDR-TB from 1992–1996 were enrolled in this study in 2000, and their outcome over the subsequent 6 yrs after commencing treatment determined. All drug-susceptibility testing was performed in the CDCB [18]. Medical records were reviewed and information was collected on age, sex, history of TB treatment, drug susceptibility, HIV status, medications used for treatment, adverse reactions occurring during treatment for which medications had to be stopped, and outcome of treatment.

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SUPPORT STATEMENT
C-Y. Chiang and D.A. Enarson proposed the original idea and designed the study. C-Y. Chiang, M-C. Yu, K-J. Bai, R-M Huang, C-J. Hsu, J. Suo, and T-P. Lin collected information and followed up patients. C-Y. Chiang and D.A. Enarson analysed and interpreted the data. All authors were involved in drafting the manuscript and gave final approval of the manuscript

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Treatment regimens

First-line drugs included isoniazid, rifampin, streptomycin, ethambutol and pyrazinamide. All others were defined as second-line drugs.

Individually tailored treatment regimens were decided upon at a weekly staff conference after review of the case history and drug-susceptibility results. Some patients continued the treatment of first-line drugs without changing to second-line drugs if they: 1) demonstrated good response to first-line anti-TB drugs; 2) refused to take, or were thought unlikely to adhere to, treatment with second-line drugs; 3) could not tolerate second-line drugs; or 4) died before they could be established on second-line drugs. For purposes of analysis the patients were assigned to one of three treatment groups: 1) those who never received second-line drugs for up to 1 month; 2) those who received second-line drugs for $\geqslant$1 month and who never received ofloxacin; and 3) those who received second-line drugs for $\geqslant$1 month and who received ofloxacin.

Anti-TB drugs were self-administered with the support of public health nurses who were responsible for supervising treatment during the whole treatment course.

The second-line drugs used, and the dosages at which they were prescribed, were as follows: prothionamide 250 mg 2–3 times daily; para-aminosalicylic acid (PAS) 150–200 mg·kg^{-1}·day^{-1} divided into 3–4 doses; cycloserine 250 mg 2–3 times daily; ofloxacin 300–400 mg *b.i.d*; kanamycin/enviomycin 10–15 mg·kg^{-1}·day^{-1} daily. The duration of treatment, normally planned for 18 months, was usually determined at the once-weekly staff conference after review of the patient's response to treatment.

Follow-up and outcome analysis

For the purposes of this study, the definitions of treatment outcome were as follows. 1) Cure: culture negative and documented to remain culture negative $\geqslant$1 month later, and never documented to become positive again up to 18 months after commencing treatment. 2) Failure: remained positive or became positive again $\geqslant$12 months after commencing the course of treatment. 3) Death: died of any cause during treatment. 4) Default: interrupted treatment for $\geqslant$2 months before the planned completion of treatment. 4) Transfer: transfer to other healthcare facilities and the result not known.

Patients considered eligible for relapse were those cured at 18 months following the commencement of treatment. Patients were judged to have relapsed if they presented again as bacteriologically positive.

Outcomes were determined by chart review, telephone contact, home visit and review of the national TB register. The cohort began with the date of effective treatment, which was defined as either the date of commencing second-line drugs, or, in those who received only first-line drugs, the date of collection of sputum that demonstrated isolates of MDR strains. The national TB register provided a comprehensive database for follow-up [16]. MDR-TB cases were periodically matched with the national TB register to identify relapse. The fate of all cases in the series was determined up to 6 yrs' follow-up by January 2004 from dates of effective treatment.

Statistical analysis

Categorical variables were analysed by Fisher's exact test with a p-value <0.05 considered statistically significant. To assess the risk of relapse, patients who were cured were followed up until relapse or last contact. Cases with post-treatment follow-up of $\geqslant$54 months were censored at 54 months. Kaplan–Meier survival estimates and log-rank test were used to evaluate factors associated with relapse. To assess the risk of death of MDR-TB patients, all patients were followed up from the time of effective treatment until death or last contact. Cases with follow-up of $\geqslant$72 months were censored at 72 months. Kaplan–Meier survival estimates and log-rank test were used to evaluate factors associated with both TB-related death and overall death. For TB-related death analysis, patients who died after documented cure and did not have evidence of relapse were censored. All significant variables were entered into a multivariate Cox proportional-hazards model and a final fitted model for both overall death and TB-related death was determined by backward elimination using the likelihood ratio test. The final model was checked by diagnostics including link test, graphical methods and residual analysis. The study was approved by the ethics review committee of the CDCB.

RESULTS

In total, 299 patients who were newly diagnosed with pulmonary MDR-TB from 1992–1996 were identified, comprising 215 (71.9%) males and 84 (28.1%) females with a mean (range) age of 47.3 (16–83) yrs. Of these, 26 (8.7%) were aged $<$25 yrs, 107 (35.8%) aged 25–44 yrs, 126 (42.1%) aged 45–64 yrs and 40 (13.4%) aged $\geqslant$65 yrs. None of the 39 patients tested for the HIV antibody were seropositive. The patients had previously received a mean (range) of 3.6 anti-TB drugs and were infected with organisms that were resistant to a mean of 3 (2–6) drugs.

The patients received a mean (range) of 3.7 (0–7) effective drugs to which isolates were susceptible *in vitro*. Out of the 299 patients, 61 (20.4%) were treated with first-line drugs alone (group 1), 113 (37.8%) with at least one second-line drug but not ofloxacin (group 2), and 125 (41.8%) with second-line drugs including ofloxacin (group 3). Neither sex ($p=0.92$) nor age ($p=0.84$) was associated with the use of second-line drugs or the use of ofloxacin. Ofloxacin was used increasingly during 1992–1996 (Chi-squared test for trend, $p<0.001$). Those who received ofloxacin were more likely to be smear positive ($p<0.001$) and to have isolates resistant to a larger number of drugs tested ($p<0.05$). Of the 238 patients receiving at least one second-line drug, 138 (53.8%) began second-line drug treatment within 4 months of sputum collection. Out of the 299 patients, 11 (3.7%) had resection surgery, 225 (75.3%) had been admitted to hospital for a mean of 1.4 months (median 1 month, range 0–11 months).

Outcome of treatment

The outcome of treatment of all 299 patients was determined; thus no patient was classified as ''transfer''. In total, 153 (51.2%) patients were cured, 31 (10.4%) failed, 28 (9.4%) died, and 87 (29.1%) defaulted. Treatment outcome was significantly different among the three treatment groups ($p=0.001$). Of the 61 patients in group 1, 35 (57.4%) were cured, 7 (11.5%) died,

and 19 (31.2%) defaulted. Of the 113 in group 2, 44 (38.9%) were cured, 19 (16.8%) failed, 16 (14.2%) died, and 34 (30.1%) defaulted. Of the 125 patients in group 3, 74 (59.2%) were cured, 12 (9.6%) failed, 5 (4%) died, and 34 (27.2%) defaulted. Among those MDR-TB patients who received at least one second-line anti-TB drug, males were significantly more likely to default ($p=0.02$); patients aged 45–64 yrs were significantly more likely to fail or die ($p=0.02$); and patients who received ofloxacin were significantly more likely to be cured ($p=0.002$), and were less likely to die or fail, as compared with other patients.

Among the 153 patients who were cured, full information was available to evaluate the entire bacteriological course of 139 (90.8%). Among these 139 patients, 115 (82.7%) and 126 (90.6%) had sputum culture conversion within 3 and 6 months, respectively. Among the 31 patients who were treatment failures, full information was available to evaluate the entire bacteriological course of 29 patients, of which 26 (90.0%) remained persistently positive up to 12 months.

Relapse

The 153 patients who were cured comprised a total of 7,606 eligible person-months of follow-up after treatment completion, calculated from the point of cure to the point of relapse, death or 54 months' follow-up. The actual follow-up consisted of 5,927 person-months (78% of the eligible follow-up). Of these patients, 10 (6.5%) relapsed: five (14.3%) out of the 35 in group 1, three (6.8%) of the 44 in group 2, and two (2.7%) of the 74 in group 3. The risk of relapse was 4.2 per 1,000 person-months for group 1, 1.7 per 1,000 person-months for group 2, and 0.7 per 1,000 person-months for group 3. Among all variables, only treatment group was associated with relapse. The risk of relapse was not significantly different either between group 1 and group 2 (hazard ratio (HR) 0.41, 95% confidence interval (CI) 0.10–1.70), or between groups 2 and 3 (HR 0.39, 95% CI 0.06–2.31). Patients in group 3 were significantly less likely to relapse than those in group 1 (HR 0.16, 95% CI 0.03–0.81). Kaplan–Meier estimates for relapse-free by treatment group of the 153 cured patients are shown in figure 1.

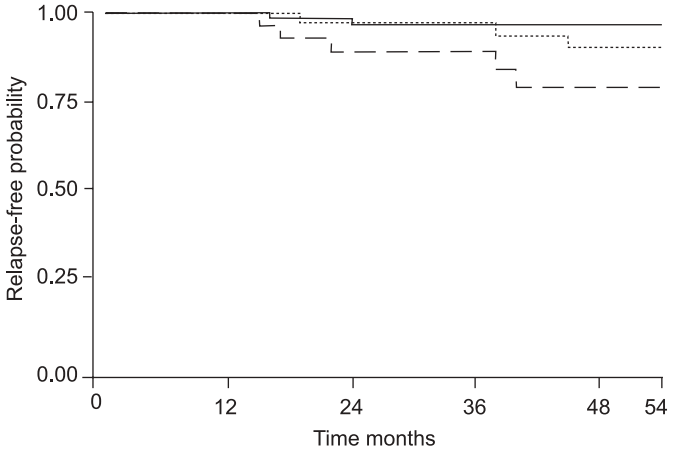

FIGURE 1. Kaplan–Meier estimates for relapse-free by treatment group of 153 cured pulmonary multidrug-resistant tuberculosis patients. – – –: treatment group 1; ····: treatment group 2; ——: treatment group 3.

Death

In total, 85 (28.4%) patients who died over the 6-yr follow-up experienced a TB-related death (table 1). Variables associated with TB-related deaths in univariate analysis were treatment group, age group, primary MDR-TB, and number of effective drugs used. Multivariate Cox proportion-regression analysis revealed statistically significant HRs for the variables treatment group, age group and those receiving less than two effective drugs. In the analysis, treatment group 2 was significantly different from the other two groups. The comparison of group 1 *versus* group 2 as baseline gave an adjusted HR 0.43 (95% CI 0.20–0.90). The comparison of group 3 *versus* group 2 as baseline gave an adjusted HR 0.50 (95% CI 0.31–0.82). Comparing the $\geqslant$45 with the $<$45 yr age group resulted in an adjusted HR 2.16 (95% CI 1.33–3.52). Receiving more than two effective drugs, compared with those receiving at least two effective drugs, gave an adjusted HR 2.27 (95% CI 1.05–4.91). The risk of TB-related death was not significantly different between groups 1 and 3 (adjusted HR 0.86, 95% CI 0.36–1.96). The risk of TB-related death was 6.4, 8.8 and 4.2 per 1,000 person-months for groups 1, 2 and 3, respectively. TB-related Kaplan–Meier survival estimates by treatment group, adjusted for age group and number of effective drugs used, are shown in figure 2.

Over the 6 yrs of follow-up starting with the commencement of treatment, 99 (33.1%) of the 299 patients died of any cause (table 1). Multivariate Cox proportion-regression analysis revealed that only age $\geqslant$45 yrs remained significantly associated with death from any cause after adjusting for sex, treatment group, receiving at least two effective drugs and primary MDR-TB (adjusted HR 2.04, 95% CI 1.28–3.24).

Adverse reactions

Among the 238 patients who received second-line drugs, 51 (21.4%) patients had adverse reactions that required medications to be stopped. Among the 209 patients who received PAS, 19 (9.1%) discontinued due to nausea/vomiting (n=13), hepatitis (n=3) or skin reaction (n=3); among the 218 patients who received prothionamide, 23 (10.6%) discontinued due to nausea/vomiting (n=14), hepatitis (n=4), skin reaction (n=3) or vertigo/dizziness (n=2); and among the 51 patients who received cycloserine, five (9.8%) discontinued due to convulsion (n=1), suicide ideation (n=1) or mental problems (n=3). Three patients died of liver complications. One patient with liver cirrhosis developed liver decompensation when receiving prothionamide, PAS, ofloxacin and streptomycin simultaneously, while the second patient developed hepatitis receiving prothionamide, PAS, ofloxacin and HERZS (isoniazid, ethambutol, rifampicin, pyrazinamide and streptomycin), and the third developed hepatitis with prothionamide, PAS and HRZ. Prothionamide or PAS were the most likely factor responsible for the fatality events. Ofloxacin has fewer side-effects than other second-line anti-TB drugs.

DISCUSSION

The present study revealed that, among MDR-TB patients who received second-line drugs, those who received ofloxacin were significantly more likely to be cured, and were less likely to die

TABLE 1 Univariate analyses of factors associated with 6-yr tuberculosis (TB)-related death and overall death of pulmonary multidrug-resistant TB (MDR-TB) patients

	Patients n	Death		p-value#	
		TB-related	Overall	TB-related	Overall
Total	299	85 (28.4)	99 (33.1)		
Treatment group				0.009	0.004
1	61	15 (25.0)	19 (31.2)		
2	133	44 (38.9)	50 (44.3)		
3	125	26 (20.8)	30 (24.0)		
Sex				0.09	0.03
Female	84	18 (21.4)	20 (23.8)		
Male	215	67 (31.2)	79 (36.7)		
Age group yrs				<0.001	<0.001
⩽44	133	23 (17.3)	26 (19.6)		
⩾45	166	62 (37.4)	73 (44.0)		
Type of MDR-TB				0.02	0.02
Primary	32	3 (9.4)	4 (12.5)		
Acquired	267	82 (30.7)	95 (35.6)		
Smear				0.09	0.08
Positive	233	74 (31.8)	86 (36.9)		
Negative	31	4 (12.9)	6 (19.4)		
Not done	35	7 (20.0)	7 (20.0)		
Number of drugs isolates were resistant to				0.24	0.43
2	93	20 (21.5)	25 (26.9)		
3	107	30 (28.0)	36 (33.6)		
⩾4	99	35 (35.4)	38 (38.4)		
Number of drugs unused before				0.50	0.31
0–2	92	27 (29.4)	33 (35.9)		
⩾3	207	59 (28.0)	66 (31.9)		
Number of effective drugs used				0.02	0.04
0–1	33	14 (42.4)	15 (44.5)		
2–6	266	71 (26.7)	84 (31.6)		

Data are expressed as n or n (%). #: p-value calculated with Kaplan–Meier analysis with long-rank test.

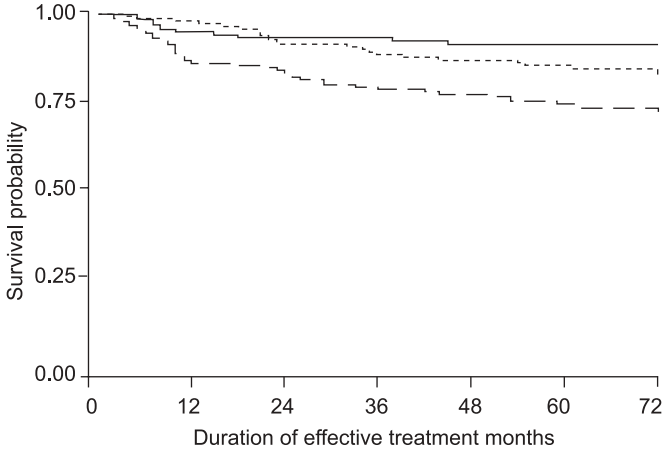

FIGURE 2. Tuberculosis-related Kaplan–Meier survival estimates by treatment group of 299 pulmonary multidrug-resistant tuberculosis patients, adjusted for age group and number of effective drugs used. – – –: treatment group 2; ····: treatment group 3; ——: treatment group 1.

or fail, as compared with patients who received second-line drugs but not ofloxacin. MDR-TB patients successfully treated with second-line drugs with ofloxacin have a low relapse rate, comparable with fully susceptible TB patients. However, the proportion of patients cured by treatment of MDR-TB remains low, mainly due to a high proportion of patients that defaulted from treatment.

In the present study, patients who received only first-line drugs were more likely to be cured than those who received second-line drugs without ofloxacin. The difference in outcome between those who received only first-line drugs and those who received second-line drugs without ofloxacin was entirely due to the higher proportion of patients who failed in the latter group. This almost certainly illustrates that the first group was a highly selected group as compared with the others and the results cannot be generalised to other settings. Furthermore, the current relapse study revealed that patients who received first-line drugs were significantly more likely to relapse than those who received second-line drugs with ofloxacin. The poor results reported here associated with the continuation of first-line drugs in MDR-TB patients, for

whatever reason, argue strongly for the use of second-line drugs for all patients known to have MDR-TB.

Ofloxacin is important in the treatment of MDR-TB, consistent with findings of studies from Denver, CO, USA [6], Turkey [8], and Hong Kong [9]. The lower frequency of adverse reactions to ofloxacin is important [6, 8, 9, 19, 20]. Furthermore, the low relapse rate is a crucial finding. A higher relapse rate has been reported when a low-dose ofloxacin and a shorter duration of treatment (300 $mg \cdot day^{-1}$ for 12 months with a relapse rate of 20.5% [19] and 400 $mg \cdot day^{-1}$ for 9 months with a relapse of 11% [21]) was applied. Thus, dosage and treatment duration are important. Moreover, the role of fluoroquinolone in the treatment of MDR-TB was further highlighted in the present study. Those who received ofloxacin had a lower risk of TB-related death than those who received second-line drugs but not ofloxacin, which is consistent with findings of the study from Denver [6].

Clearly, fluoroquinolones have considerable promise in the treatment of MDR-TB, especially the new generation fluoroquinolones. The potency of *in vitro* activity against *Mycobacterium tuberculosis* of several new-generation fluoroquinolones is much greater than ofloxacin [22–24]. The most potent are moxifloxacin and gatifloxacin, followed by sparfloxacin and levofloxacin [22, 23]. A retrospective study from Hong Kong [20] revealed that levofloxacin was more efficacious than ofloxacin when incorporated into multidrug regimens used for the treatment of MDR-TB and should be the drug of choice in the treatment of MDR-TB. Moxifloxacin is probably even more promising in the treatment of TB [25–29]. The *in vitro* early bactericidal activity of moxifloxacin has been shown to be better than that of ofloxacin [25]. Using a murine model, NUERMBERGER *et al.* [26] showed that the combination of moxifloxacin, rifampin and pyrazinamide reduced the time to culture conversion. They also showed that it reduces the treatment duration to cure TB [27] when compared with the standard regimen of isoniazid, rifampin and pyrazinamide. Furthermore, VEZIRIS *et al.* [28] have shown that the combination of moxifloxacin, thionamide, pyrazinamide and amikacin is much more powerful than the combination of ofloxacin or ciprofloxacin with the other three drugs. Moxifloxacin is well tolerated in long-term administration [29] and its role as a first-line anti-TB agent in humans has been under investigation. A recent study comparing moxifloxacin *versus* ethambutol in the first 2 months of treatment for pulmonary TB reveals that adding moxifloxacin to isoniazid, rifampicin and pyrazinamide did not affect 2-month sputum culture status, but did show increased activity at earlier time points, as compared with ethambutol, isoniazid, rifampicin and pyrazinamide [30]. Clearly, fluoroquinolones are playing, and will continue to play, an important role in the treatment of MDR-TB. Thus, it is prudent to avoid indiscriminate use of fluoroquinolones in the treatment of respiratory infections before excluding TB because there is cross-resistance within the fluoroquinolone class [22], and incidental monotherapy of fluoroquinolone in TB can easily lead to fluoroquinolone resistance [31].

Although fluoroquinolones bear considerable promise in the treatment of MDR-TB, adherence to treatment is critical. Even when second-line drugs are employed, the proportion of patients cured by treatment of MDR-TB remains low, as noted in the present study and confirmed by most of the previous reports in which the full cohort was reported: Korea 48.2% [11] and 44.1% [12]; France 33% [13]; Peru 48% [15]; and Latvia 66% [32]. The exception is a case series from Turkey (77%) [8], where the definitions used for treatment were different from those used in all the other papers in which a full cohort was reported so it is difficult to compare the results. The unsatisfactory outcome was mainly explained by those patients who defaulted. The frequency was similar in this study to results reported from Korea (39% [11] and 28.9% [13]), France (19.6%) [12], Latvia (13%) [32] and Peru (11%) [15]. The high defaulter rate might be partially explained by the frequency of adverse reactions to the second-line drugs used, a high number of tablets to be taken per day and a long duration of treatment. To improve outcome of MDR-TB, particular attention must be directed to develop a strategy to address this issue.

Resection surgery has been shown to be associated with a favourable outcome [6, 33, 34]. This could not be analysed in the present study because only a limited number of patients received surgery. The use of second-line drugs should be monitored closely. The deaths from hepatic complications and the substantial proportion of patients who discontinued drugs due to adverse reactions is a matter of concern.

In summary, multidrug-resistant tuberculosis patients successfully treated with second-line drugs with ofloxacin have a low relapse rate, comparable with patients infected with fully susceptible tuberculosis. The utility of new generation fluoroquinolones, such as moxifloxacin, in the treatment of multidrug-resistant tuberculosis needs to be evaluated. However, defaulting from treatment is a major challenge in the treatment of multidrug-resistant tuberculosis. Strategies to reduce defaulters are crucial in the treatment of multidrug-resistant tuberculosis.

REFERENCES

1 Schaaf HS, Botha P, Gie RP, *et al.* The 5-year outcome of multidrug resistant tuberculosis patients in the Cape Province of South Africa. *Trop Med Intern Health* 1996; 1: 718–722.

2 Goble M, Iseman MD, Madsen LA, Waite D, Ackerson L, Horsburgh CR Jr. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. *N Engl J Med* 1993; 328: 527–532.

3 Espinal MA, Kim SJ, Suarez PG, *et al.* Standard short-course chemotherapy for drug-resistant tuberculosis. Treatment outcomes in 6 countries. *JAMA* 2000; 283: 2537–2545.

4 Espinal MA, Laszlo A, Simonsen L, *et al.* Global trends in resistance to antituberculosis drugs. *N Engl J Med* 2001; 344: 1294–1303.

5 Crofton J, Chaulet P, Maher D, *et al.* Guidelines for the management of drug-resistant tuberculosis. Geneva, World Health Organization, 1996; pp.1–40.

6 Chan ED, Laurel V, Strand MJ, *et al.* Treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis. *Am J Respir Crit Care Med* 2004; 169: 1103–1109.

7 Park SK, Kim CT, Song SD. Outcome of chemotherapy in 107 patients with pulmonary tuberculosis resistant to isoniazid and rifampicin. *Int J Tuberc Lung Dis* 1998; 2: 877–884.

8 Tahaoglu K, Törün T, Sevim T, *et al.* The treatment of multidrug-resistant tuberculosis in Turkey. *N Engl J Med* 2001; 345: 170–174.

9 Yew WW, Chan CK, Chau CH, *et al.* Outcomes of patients with multidrug-resistant pulmonary tuberculosis treated with ofloxacin/levofloxacin-containing regimens. *Chest* 2000; 117: 744–751.

10 Mitnick C, Bayona J, Palacios E, *et al.* Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru. *N Engl J Med* 2003; 348: 119–128.

11 Kim HJ, Hong YP, Kim SJ, Lew WJ, Lee EG. Ambulatory treatment of multidrug-resistant pulmonary tuberculosis patients at a chest clinic. *Int J Tuberc Lung Dis* 2001; 5: 1129–1136.

12 Flament-Saillour M, Robert J, Jarlier V, Grosset J. Outcome of multi-drug-resistant tuberculosis in France. A nationwide case-control study. *Am J Respir Crit Care Med* 1999; 160: 587–593.

13 Park SK, Lee WC, Lee DH, Mitnick CD, Han L, Seung KJ. Self-administered, standardized regimens for multidrug-resistant tuberculosis in South Korea. *Int J Tuberc Lung Dis* 2004; 8: 361–368.

14 Van Deun A, Hamid Salim MA, Kumar Das AP, Bastian I, Portaels F. Results of a standardised regimen for multidrug-resistant tuberculosis in Bangladesh. *Int J Tuberc Lung Dis* 2004; 8: 560–567.

15 Suárez PG, Floyd K, Portocarrero J, *et al.* Feasibility and cost-effectiveness of standardised second-line drug treatment for chronic tuberculosis patients: a national cohort study in Peru. *Lancet* 2002; 359: 1980–1989.

16 Chiang C-Y, Enarson DA, Yang S-L, Suo J, Lin T-P. The impact of national health insurance on the notification of tuberculosis in Taiwan. *Int J Tuberc Lung Dis* 2002; 6: 974–979.

17 Suo J, Yu M-C, Lee C-N, Chiang C-Y, Lin T-P. Treatment of multidrug-resistant tuberculosis in Taiwan. *Chemotherapy* 1996; 42: Suppl. 3, 20–23.

18 Chiang C-Y, Hsu C-J, Huang R-M, Lin T-P, Luh K-T. Antituberculosis drug resistance among retreatment tuberculosis patients in a referral center in Taipei. *J Formos Med Assoc* 2004; 103: 411–415.

19 Maranetra KN. Quinolones and multidrug-resistant tuberculosis. *Chemotherapy* 1999; 45: Suppl. 2, 12–18.

20 Yew WW, Chan CK, Leung CC, *et al.* Comparative roles of levofloxacin and ofloxacin in the treatment of multidrug-resistant tuberculosis: preliminary results of a retrospective study from Hong Kong. Chest 2003; 124; 1476–1481.

21 Mangunnegoro H, Hudoyo A. Efficacy of low-dose ofloxacin in the treatment of multidrug-resistant tuberculosis in Indonesia. *Chemotherapy* 1999; 45: Suppl. 2, 19–25.

22 Ginsburg AS, Grosset JH, Bishai WR. Fluoroquinolones, tuberculosis, and resistance. *Lancet Infect Dis* 2003; 3: 432–442.

23 Sulochana S, Rahman F, Paramasivan CN. *In vitro* activity of fluoroquinolones against *Mycobacterium tuberculosis*. *J Chemother* 2005; 17: 169–173.

24 Rodríguez JC, Cebrián L, López M, Ruiz M, Jiménez I, Royo G. Mutant prevention concentration: comparison of fluoroquinolones and linezolid with *Mycobacterium tuberculosis*. *J Antimicrob Chemother* 2004; 53: 441–444.

25 Gosling RD, Uiso LO, Sam NE, *et al.* The bactericidal activity of moxifloxacin in patients with pulmonary tuberculosis. *Am J Respir Crit Care Med* 2003; 168: 1342–1345.

26 Nuermberger EL, Yoshimatsu T, Tyagi S, *et al.* Moxifloxacin-containing regimen greatly reduces time to culture conversion in murine tuberculosis. *Am J Respir Crit Care Med* 2004; 169: 421–426.

27 Nuermberger EL, Yoshimatsu T, Tyagi S, *et al.* Moxifloxacin-containing regimens of reduced duration produce a stable cure in murine tuberculosis. *Am J Respir Crit Care Med* 2004; 170: 1131–1134.

28 Veziris N, Truffot-Pernot C, Aubry A, Jarlier V, Lounis N. Fluoroquinolone-containing third-line regimen against *Mycobacterium tuberculosis in vivo*. *Antimicrob Agents Chemother* 2003; 47: 3117–3122.

29 Valerio G, Bracciale P, Manisco V, Quitadamo M, Legari G, Bellanova S. Long-term tolerance and effectiveness of moxifloxacin therapy for tuberculosis: preliminary results. *J Chemother* 2003; 15: 66–70.

30 Burman WJ, Goldberg S, Johnson JL, *et al.* Moxifloxacin *versus* ethambutol in the first two months of treatment for pulmonary tuberculosis. *Am J Respir Crit Care Med* 2006; 174: 331–338.

31 Grimaldo ER, Tupasi TE, Rivera AB, *et al.* Increased resistance to ciprofloxacin and ofloxacin in multidrug-resistant *Mycobacterium tuberculosis* isolates from patients seen at a tertiary hospital in the Philippines. *Int J Tuberc Lung Dis* 2001; 5: 546–550.

32 Leimane V, Riekstina V, Holtz TH, *et al.* Clinical outcome of individualised treatment of multidrug-resistant tuberculosis in Latvia: a retrospective cohort study. *Lancet* 2005; 365: 318–326.

33 Chiang C-Y, Yu M-C, Bai K-J, Lin T-P, Lee Y-C. Pulmonary resection in the treatment of patients with pulmonary multidrug-resistant tuberculosis in Taiwan. *Int J Tuberc Lung Dis* 2001; 5: 272–277.

34 Park SK, Lee CM, Heu JP, Song SD. A retrospective study for the outcome of pulmonary resection in 49 patients with multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2002; 6: 143–149.