The Effects of Ciprofloxacin on Chest Radiographic Regression in Patients with Drug Intolerance or Resistant Tuberculosis

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Background: The aim of this study was to identify the clinical efficacy of ciprofloxacin as a second-line anti-tuberculosis agent in pulmonary tuberculosis patients with drug intolerance or resistance.

Methods: There were 20 patients with drug related adverse effects or drug resistance enrolled in the ciprofloxacin treatment group (CG). There were also 32 patients enrolled in the non-ciprofloxacin treatment group (NCG) that maintained conventional drug regimens or the addition of other drugs like streptomycin. The radiographic presentation was evaluated using score grading. The speed and outcome of regression in the chest radiographic presentations were also evaluated.

Results: Data showed the CG had significantly more rapid regression than the NCG in drug-resistant patients ($p<0.01$). For the adversely effected patients in the CG, the mean scores of pre- and post-treatment were 3.1 ± 0.2 and 2.2 ± 0.3 ($p<0.001$), respectively. For the adversely effected patients in the NCG, the mean score of pre-treatment was 3.7 ± 0.4 and post-treatment mean score was 3.0 ± 0.4 ($p<0.05$). For the drug-resistant patients in the CG, the mean scores of pre- and post-treatment were 4.3 ± 0.4 and 3.4 ± 0.5 ($p<0.05$), respectively. For the drug-resistant patients in the NCG, the mean score of pre-treatment was 3.7 ± 0.3 and post-treatment mean score was 3.2 ± 0.3 (no significant difference). Obviously, the CG had the same effects compared with the NCG in adverse-effect group. On the other hand, the CG had the tendency of more rapid radiographic regression and better radiographic outcomes than the NCG in drug-resistant patients.

Conclusions: Ciprofloxacin provides a better option for second-line drug treatment for pulmonary tuberculosis when patients cannot use conventional anti-tuberculosis agents.

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Key words: ciprofloxacin, pulmonary tuberculosis, drug intolerance, drug resistance.

Tuberculosis remains a problem of enormous dimensions worldwide. There were estimated 7.96 million new cases and 1.87 million deaths in 1997.[1,2] Tuberculosis also accounted for approximately 7% of all deaths, and nearly 20% of deaths of persons between 15 to 59 years of age.[3] Pulmonary

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tuberculosis makes up the majority of human tuberculous disease. In 1999, tuberculosis was reported as the 12th leading cause of death in Taiwan. With a prevalence of 61.32/100000 people, and a mortality rate of 6.88/100000 people, it still is a major problem in Taiwan. Recently, the WHO reported that the spread of drug resistant tuberculosis in Asia could seriously hamper the global effects to control tuberculosis.[4]

In treating pulmonary tuberculosis, isoniazid (H), rifampicin (R), ethambutol (E), pyrazinamide (P), and streptomycin (S) are currently effective in most patients. Isoniazid and rifampicin are the two dominant drugs and should prolong the therapeutic period before discarding them.[5] Drug related adverse effects and drug resistance are two major reasons for the above situation. Therefore, using new regimens to replace or add to conventional medication is advised.

Ciprofloxacin (C), a kind of fluoquinolones, is an anti-microbial agent with highly effective penetration and concentration in macrophages.[6] Ciprofloxacin was used as an anti-tuberculosis drug in adult patients who could not tolerate the standard regimens or had to be treated using alternative combinations due to resistance problems.[7] Other second-line drugs, like ethionamide or cycloserine are associated with an increased risk of side effects. Nevertheless, in some reports, ciprofloxacin did not have the superior effects of the conventional medications in the tuberculous management.[8-10] Thus, although incorporation of fluoquinolones in second-line regimens for the treatment of multi-drug resistant tuberculosis (MDR-TB) has been recommended by many authorities, including the World Health Organization (WHO), there is still a dearth of evidence on the role of fluoquinolones in the management of pulmonary tuberculosis.[5,11]

During the treatment of tuberculosis, monthly checks of symptoms and signs and acid fast bacilli smear and culture of sputum specimens should be obtained. Inadequate collection of sputum and smear-culture incompatibility shows the difficulties of following up the patients. One researcher reported that patients with persistent presence of acid-fast bacilli but negative culture got more radiographic improvement than those with positive culture.[12] Interpretation of radiographic data on admission could improve the adequacy of respiratory isolation greater than interpretation of historic or clinical data.[13] Generally, in spite the lack of sputum examination after complete treatment, improvement in the chest X-ray and/or signs and symptoms of tuberculosis allows the clinician to classify the individual as a negative or positive clinical case of tuberculosis.[14] To our knowledge, there are no data on which to assess the appropriateness of ciprofloxacin on disease regression using chest X-ray results.

This retrospective study was conducted to determine whether ciprofloxacin was properly used as the second line anti-tuberculosis agent. Meanwhile, the speed and outcomes of regression in the chest radiographic presentation were also evaluated compared with patients who did not use ciprofloxacin.

METHODS

Patient population and demographic data

The present study is a retrospective study that was conducted to analyze 1236 patients who were diagnosed and treated as pulmonary tuberculosis in our Thoracic Medicine inpatient or outpatient departments in the Lin-Kou Medical Center of Chang Gung Memorial Hospital, from January 1998 through October 2001. Mycobacterium tuberculosis infection was identified by smear and culture from productive sputum or bronchial washing specimen via bronchoscopy.

Fifty-two patients who had been regularly followed up at our hospital and completed the treatment course were included. Chest radiography was performed every 3 months during treatment period and 3 months after the completion of treatment. Totally, 23 patients had adverse effects after anti-TB drugs, and 29 patients had drug resistance.

Adverse effects (AE) included drug-related hepatotoxicity (transaminase level exceeded 150 IU, three times the upper limit of normal and the presence of symptoms and signs, like nausea, vomiting, fatigue, jaundice and tea color urine) that related to isoniazid and/or rifampicin and dermatological allergies presented by macules or papules that mainly related to rifampicin. Drug resistance (DR) was defined as culture of mycobacterium tuberculosis showing resistance to at least isoniazid or rifampicin. Underlying medical diseases (UMD) included diabetes mellitus, liver cirrhosis, end stage renal disease under regular hemodialysis, pneumoconiosis, and

pulmonary malignancy. The treatment period for ciprofloxacin treatment was defined as the beginning of ciprofloxacin use to the end of treatment.

Twenty patients who had drug related adverse effects or drug resistance were enrolled in the ciprofloxacin treatment group (CG), and received ciprofloxacin (15-20 mg/kg per day, equal to 500 mg twice a day) to add or replace the conventional medications. Thirty-two patients were also enrolled in the non-ciprofloxacin treatment group (NCG). They had the same baseline factors of adverse effects or resistance but continuously took conventional medications. Conventional medications included 5 mg/kg of isoniazid, 10 mg/kg of rifampicin, 20 mg/kg of ethambutol, 25 mg/kg of pyrazinamide every day, and/or 1 g of streptomycin intramuscularly injected two or three times every week.

If drug-induced hepatitis was suggested or obscured, then isoniazid, rifampicin and pyrazinamide use were discontinued and if a rash occurred then all anti-tuberculous were discontinued. Once the adverse effects improved, drugs were reintroduced one by one. When the responsible drug was not known, the timing and order of the rechallenge were at the discretion of the treating physicians.

As for the medication use in these two populations, the CG (20 patients) had 13 patients using ciprofloxacin to replace original drugs that caused adverse effects. Among the other seven patients with drug resistance, five patients added ciprofloxacin to their original drug regimens including isoniazid and rifampicin and two patients used ciprofloxacin to replace isoniazid and rifampicin that was associated with resistance. For the NCG (32 patients), 7 of 10 patients with adverse effect continued the original drug regimens including isoniazid and rifampicin and 2 patients took isoniazid, ethambutol, pyrazinamide to avoid rifampicin and another one patient used ethambutol and streptomycin to replace isoniazid and rifampicin that caused side effects. Among the other 22 patients with drug resistance, all of them continued to use their original medications and streptomycin was added for 3 patients.

Grading of disease extent on chest radiography

Posteroanterior chest radiographs were taken from all patients at the time of their initial diagnosis, every 3 months throughout the treatment period and at least 3 months after cessation of the treatment. A grading of the extent of disease (ranging from 0 to 6, 0= no involvement; 1 = trivial; 2= slight; 3 = limited; 4 = moderate; 5 = extensive; 6 = gross) proposed by the WHO (1960) was adapted to assess the severity of the disease.[15]

Regression on chest radiography

The study population was allocated to one of three groups according to the resolution of pulmonary lesions: (1) the rapid regression group (RR) showed more than 50% improvement in the extent of disease on chest radiography within 3 months of commencing treatment, and either complete resolution within 9 months of treatment or residual fibrotic lesions which were unchanged for at least 3 months after cessation of the treatment; (2) the intermediate regression group (IR) showed 50% improvement in the extent of disease on chest radiography after 3-6 months of treatment, and either complete resolution within 9 months of treatment or residual fibrotic lesions which were unchanged for at least 3 months after cessation of the treatment; and (3) the slow regression group (SR) showed less than 50% improvement in the extent of disease on chest radiography after 6 months of treatment, and either persistent active pulmonary lesions or incomplete resolution within 9 months after cessation of the treatment.[16]

To avoid observer bias, two thoracic physicians who were not aware of the laboratory results or clinical presentations initially assessed the radiographs independently, and they arrived at the same grading for 48 of 52 patients. Two patients were assessed IR by one observer and RR by the other; one patient was assessed RR by one observer and IR by the other; one patient was assessed IR by one observer and SR by the other. After discussion, consensus agreement was reached for the grouping for these four patients. Assessment throughout the study was also performed blind.

Statistical analysis

The parametric variables of the demographic data, including age and treatment period were evaluated using two-tailed unpaired Student's *t* test with Welch's correction. Data are represented as mean$\pm$ SD. Chi-square test was applied to the non-parametric variables, including sex and underlying medical disease. The regression of chest radiography was

also analyzed using the chi-square method. The outcomes of chest radiography in the CG and NCG used to compare the resolution before and after treatment was evaluated using the two-tailed paired Student's *t* test, and data was showed as mean±standard error. Meanwhile, we also controlled for age, gender, underlying medical disease, drug resistance, adverse effect factor and treatment period with logistic regression analysis to exclude any potential confounding effects on patient's radiographic regression. A *p* value of less than 0.05 was considered significant.

RESULTS

Of the 52 patients, 20 patients were enrolled in the CG and 32 patients belonged to the NCG. There were 13 and 10 patients with adverse effects to drugs in the CG and NCG, respectively. Drug resistance was found in 7 patients in the CG and 22 patients in the NCG. Table 1 shows the demographic characteristics among these patients. Most of the factors including age, sex, UMD, treatment period showed no significant differences between these two groups. The effects of the parameters, including age, sex, UMD, DR, AE, treatment period and ciprofloxacin use on the radiographic regression were analyzed using the logistic regression method. We found that only ciprofloxacin use had significant effects on the speed of radiographic regression and the other factors had independent effects with no confounding (Table 2). To further study the intervention effects of ciprofloxacin use on the speed of radiographic regression, we found that the CG had a significantly more rapid regression than the NCG did in drug-resistant patients ($p<0.01$, Fig. 1).

Table 1. Demographic Characteristics of the CG and NCG Patients

	CG	NCG	*p*
Number	20	32	
AE/DR	13/7	10/22	
Age (AE/DR)	64.2±4.2/57.3±6.9	65.1±3.6/55.2±3.8	0.88/0.80
Gender (AE/DR)	M11F2/M4F3	M9F1/M12F10	0.70/0.90
UMD (AE/DR)	2/3	7/3	0.39/0.09
TP (AE/DR)	9.7±1.0/11.8±1.9	10.4±0.7/12.3±1.1	0.56/0.75

Age and TP represented as mean±SEM

Abbreviations: M: male; F: female; CG: ciprofloxacin group; NCG: non-ciprofloxacin group; AE: adverse effect defined as in the text; DR: drug resistance to at least H (Isoniazid) or R (Rifampicin); UMD: underlying medical disease defined as in the text; TP (months): treatment period.

Table 2. Logistic Regression Analysis to Evaluate Factors Affecting the Speed of Chest Radiogaphic Regression With or Without Confoundedness (Hosmer and Lemeshow test)

Case number: 52				Forward stepwise: remove CIPRO factor			
Dependent variable				Dependent variable			
SR IR: 30				SR IR: 23			
RR: 22				RR: 9			
Variables	Score	df	*p*	Variables	Score	df	*p*
Age	1.57	1	0.21	Age	2.72	1	0.10
Gender	0.02	1	0.89	Gender	0.19	1	0.67
UMD	1.05	1	0.31	UMD	1.67	1	0.20
AD	0.32	1	0.57	AD	1.71	1	0.19
DR	0.51	1	0.47	DR	0.03	1	0.87
CIPRO	6.86	1	0.01	TP	0.08	1	0.78
TP	0.42	1	0.52				
overall	15.12	7	0.03	overall	9.41	6	0.15

Abbreviations: SR, IR, RR: slow regression group, intermediate regression group, rapid regression group, defined in the text; df: degree of freedom; CIPRO: ciprofloxacin use or not; UMD: underlying medical disease define as in the text; DR: drug resistance to at least H (Isoniazid) or R (Rifampicin); TP (month): treatment period.

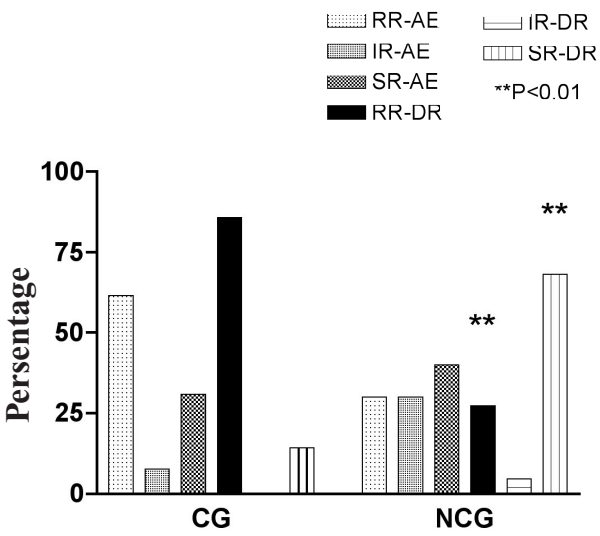

Fig. 1 Percentage of degree of regression on chest radiography between the CG and NCG, $^{**}p<0.01$, RR and SR of the CG compared with the NCG in drug-resistant patients.

The outcomes of the radiographic presentations were also evaluated using score grading. There were no significant differences of the baseline scores of chest radiography between the CG and NCG in either adverse-effect or drug-resistant patients. We performed further investigation of radiographic scores on chest radiography before and after complete treatment whether ciprofloxacin was used or not (Table 3). In the CG associated with adverse effects, the mean scores of pre- and post-treatment were 3.1 ± 0.2 and 2.2 ± 0.3, respectively ($p<0.001$). In the NCG with adverse effects, the mean score of pre-treatment was 3.7 ± 0.4 and post-treatment mean score was 3.0 ± 0.4 ($p<0.05$). In the CG associated with drug resistance, the mean scores of pre- and post-treatment were 4.3 ± 0.4 and 3.4 ± 0.5, respectively ($p<0.05$). In the NCG with drug resistance, the mean score of pre-treatment was 3.7 ± 0.3 and post-treatment mean score was 3.2 ± 0.3 (no significance). Obviously, the CG had the same effects compared with the NCG in adverse effects. On the other hand, the CG had the tendency of more rapid radiographic regression and better radiographic outcomes than the NCG after the completion of treatment in the drug-resistant patients (Table 3).

Forty-six patients had negative sputum cultures for tuberculosis or had no sputum during the period of treatment, and the other 6 patients displayed persistently positive cultures. Treatment failure was defined as relapse after treatment or persistently positive sputum culture. Three patients in the CG (2 in AE and 1 in DR) and eight patients in the NCG (1 in AE and 7 in DR) presented with either relapse post-treatment or treatment failure denoted by persistent culture positive after 6 months of treatment or worsening chest X-rays. No significant adverse effects were associated with ciprofloxacin use.

Table 3. Radiographic Scores before and after Complete Treatment with (CG) or without Ciprofloxacin (NCG) Use in Adverse-effect (AE) and Drug-resistant (DR) Groups

	Number	Pre-treatment	Post-treatment	*p*
AE				
CG	13	3.1 ± 0.2	2.2 ± 0.3	<0.001
NCG	10	3.7 ± 0.4	3.0 ± 0.4	<0.05
DR				
CG	7	4.3 ± 0.4	3.4 ± 0.5	<0.05
NCG	22	3.7 ± 0.3	3.2 ± 0.3	NS

Abbreviations: NS: no significance

DISCUSSION

Standard anti-tuberculosis treatment with conventional regimens is still the mainstream therapeutic treatment. Unfortunately, if drug related adverse effects or drug resistance occurs, various second-line drugs make it difficult to choose which one is the optimal. In this study, ciprofloxacin was used and produced rapid radiographic regression and lesser extent of disease on chest X-ray after the completion treatment in the drug-resistant patients compared with those who did not use ciprofloxacin. In the drug-intolerant patients, ciprofloxacin had the tendency to lessen the extent of the disease on chest X-ray, although it did not have statistical significance.

Although the inactive tuberculosis lesions are not infectious, residual lesions that alter the expression of pulmonary function are usually fibrotic. Ciprofloxacin decreased this sequel when getting more radiographic resolution in patients with either related adverse effects or drug resistance. Ciprofloxacin also appears to be tolerated as well as or better than other second-line anti-tuberculosis medications and was safe to use long term.[17]

In vitro and animal investigations have demon-

strated the anti-mycobacterial activity of some fluoroquinolones, including ciprofloxacin, but information regarding their clinical usefulness in mycobacterial infections is sparse.[18] Kahana et al. treated TB patients with combinations of ciprofloxacin and one or two other anti-tuberculosis agents and found 14 of their 15 patients had susceptibility of the infecting mycobacteria to ciprofloxacin. Our results showed that ciprofloxacin improved the outcomes and chest -X-ray regression in patients with drug intolerant or resistant tuberculosis without adverse effects, suggesting that ciprofloxacin is a promising antimycobacterial agent for the treatment of adult patients who can not tolerate standard regimens or must be treated using alternative combinations due to resistance problems. Although chest radiography showed improvement, we could not provide clinical information to show the same results. It needs further study to confirm.

The early bactericidal and sterilizing activities of ciprofloxacin were evaluated in the treatment of adult patients using smears positive for pulmonary tuberculosis. Kennedy et al. demonstrated that ciprofloxacin alone had useful early bactericidal activity that resulted in a mean daily fall of 0.20 log10cfu/ml/day during 7 days compared with 0.25 log10cfu/ml/day for isoniazid.[19] Some researchers also reported that the early bactericidal activity of ciprofloxacin in high dosage was much higher in patients receiving isoniazid.[20] Clinically, it is still conflicting to determine the early effectiveness of ciprofloxacin by examining the sputum because of inadequate sputum collection or smear-culture incompatibility. However, in spite of the lack of sputum examination after the completion of treatment, improvement on the chest X-ray of tuberculosis allows the clinician to classify the individual as a culture negative or clinical case of tuberculosis.[14] Our data showed that ciprofloxacin had significant effects on the speed of radiographic regression, suggesting, ciprofloxacin has an early clinical efficiency in the treatment of patients with drug resistant tuberculosis.

Kahana et al.[18] reported that adverse reactions to ciprofloxacin were few and included nausea, crystalluria, and febrile reaction. Berning et al.[17] also demonstrated that ciprofloxacin was generally well tolerated and the adverse effects led to a ciprofloxacin dosage changes only in 2 patients (3%) and discontinuation of ciprofloxacin in 5 patients (7%). Our patients all tolerated the treatment regiment without adverse effects, suggesting ciprofloxacin appears to be tolerated as well as or better than other "second-line" anti-mycobacterial drugs.

The fluoroquinolones are promising new anti-tuberculosis agents. However, Kennedy et al.[19] reported the sterilizing activity of ciprofloxacin did not appear to be equal to that of the combination of pyrazinamide and ethambutol, especially in HIV-infected patients, suggesting the clinical routine of ciprofloxacin treatment was controversial. Although incorporation of fluoquinolones for the treatment of drug resistant tuberculosis has been recommended, there is still a dearth of evidence on the indications and timing when fluoquinolones should be used in the management of pulmonary tuberculosis. Yew et al.[21] treated 25 patients who had extensive pulmonary tuberculosis and hepatitis induced by anti-tuberculosis drugs with ciprofloxacin together with other relatively non-hepatotoxic drugs, either during the interim phase awaiting recovery of liver function in some, or as definitive therapy as required by the compromised hepatic status of others. All of their patients improved using the ciprofloxacin-containing regimens. Our data also showed that all patients with intolerance to first-line anti-TB medications had good responses to ciprofloxacin containing regimens, suggesting intolerant tuberculosis is also an indication for the use of fluoquinolones.

In conclusion, we suggest the use of ciprofloxacin as a better option of second-line drug to treat pulmonary tuberculosis when patients cannot use conventional anti-tuberculosis agents.

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Ciprofloxacin影響藥物耐受不良或抗藥性結核病患的胸部病兆

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背 景： 此研究是爲了探討當肺結核病患對於傳統抗結核藥物耐受不良或抗藥菌種出現時，ciprofloxacin作爲第二線藥物的臨床療效。

方 法： 20位有藥物耐受不良或抗藥菌種的肺結核病患歸入ciprofloxacin治療組，使用ciprofloxacin來合併或取代傳統抗結核藥物。另外有32位病患在相同情況下，仍維持原先傳統抗結核藥物，則歸入非ciprofloxacin治療組。胸部攝影以評分系統作分級。胸部病兆消散速度在兩群病患中亦同時作比較。

結 果： 資料顯示在具抗藥性結核病患ciprofloxacin治療組比非ciprofloxacin治療組胸部病兆消散較快 ($p<0.01$)。在ciprofloxacin治療組的藥物耐受不良病患，治療前和治療後的胸部攝影評分爲3.1±0.2以及2.2±0.3 ($p<0.001$)。而對於非ciprofloxacin治療組的藥物耐受不良病患，治療前的胸部攝影評分爲3.7±0.4，治療後爲3.0±0.4 ($p<0.05$)。在ciprofloxacin治療組的具抗藥性結核病患，治療前和治療後的胸部攝影評分爲4.3±0.4以及3.4±0.5 ($p<0.05$)。而對於非ciprofloxacin治療組的藥物耐受不良病患，治療前的胸部攝影評分爲3.7±0.3，治療後爲3.2±0.3 (無統計學之差異)。很顯然地在藥物耐受不良病患中，ciprofloxacin使用在兩組病患的胸部病兆改善具相同臨床療效。除此之外在具抗藥性結核病患中，ciprofloxacin治療組比非ciprofloxacin治療組在治療過程中有較快胸部病兆消散以及治療後有較好的胸部病兆改善。

結 論： 對於肺結核病患無法使用傳統第一線抗結核藥物，如藥物耐受不良或具抗藥性結核時，在此我們提供一個第二線藥物的良好選擇ciprofloxacin，來治療這類病患。

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關鍵字：ciprofloxacin，肺結核，藥物耐受不良，抗藥性。

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