ERJ Express. Published on August 28, 2009 as doi: 10.1183/09031936.00104209

Newer fluoroquinolones for treating respiratory infection: do they mask tuberculosis?

Kwok Chiu Chang[*], Chi Chiu Leung[*], Wing Wai Yew[†], Tat Yan Lau[*], Wai Man Leung[*], Cheuk Ming Tam[*], Hin Chun Lam[*], Pui San Tse[*], Man Yee Wong[*], Shuk Nor Lee[*], Kit I Wat[*], Ying Hing Ma[*]

[*] Tuberculosis and Chest Service, Centre for Health Protection, Department of Health, Hong Kong SAR, China

[†] Tuberculosis and Chest Unit, Grantham Hospital, Hong Kong SAR, China

Corresponding author: Dr Kwok Chiu Chang, Wanchai Chest Clinic, 1st Floor, Wanchai Polyclinic, 99, Kennedy Road, Wanchai, Hong Kong.

[Tel: 852-25911147; Fax: 852-28346627; email: kc_chang@dh.gov.hk]

Financial support: Nil

Competing interest statement: All authors declare no conflict of interest.

Abstract (Word count=200)

Possible masking of tuberculosis in treatment of community-acquired respiratory infection by newer fluoroquinolones has not been examined in randomized controlled trials.

We undertook a randomized open-label controlled trial involving adults with community-acquired pneumonia or infective exacerbation of bronchiectasis encountered in government chest clinics in Hong Kong. 427 participants were assigned by random permutated blocks of 20 to receive either amoxicillin clavulanate (n=212) or moxifloxacin (n=215). Participants were followed for one year for active pulmonary tuberculosis.

Excluding three participants with positive baseline culture, 13 developed active pulmonary tuberculosis: 10 (4.8%) out of 210 given amoxicillin clavulanate, and three (1.4%) out of 214 given moxifloxacin. The difference was significant both by proportion and time-to-event analysis. Post-hoc analysis showed a significant decrease in the proportion with active pulmonary tuberculosis from 4.8% to 2.4% and 0% among participants given amoxicillin clavulanate (n=210), moxifloxacin for predominantly 5 days (n=127) and 10 days (n=87), respectively. The log rank test for trend also showed a significant difference between the three subgroups. Regression models reaffirmed the linear effect; the adjusted odds ratio (95% confidence interval) of active pulmonary tuberculosis after moxifloxacin exposure up to predominantly 10 days was 0.3 (0.1-0.9).

Newer fluoroquinolones appear to mask active pulmonary tuberculosis.

Key words: fluoroquinolones; tuberculosis

Introduction

With broad-spectrum anti-microbial coverage including beta-lactamase producing bacteria, penicillin-resistant *Streptococcus pneumoniae*, and pathogens causing atypical pneumonia, newer fluoroquinolones have demonstrated effectiveness in treatment of community-acquired respiratory infection [1-6]. The Infectious Diseases Society of America and the American Thoracic Society have recommended newer fluoroquinolones for treating community-acquired pneumonia in the presence of comorbidities or risk factors for drug-resistant *Streptococcus pneumoniae* infection [7]. Like older fluoroquinolones, which have demonstrated an important role in treatment of multidrug-resistant tuberculosis (TB) [8-11], newer fluoroquinolones have shown prominent anti-TB activity in the initial phase of TB treatment with potential for shortening treatment duration[12, 13].

Possible masking of active TB in the treatment of community-acquired pneumonia by fluoroquinolones has been suggested by retrospective analysis[14] but not been verified by randomized controlled trials in TB-endemic areas. Hong Kong is endemic for TB with annual notification rates around 80 per 100000 persons [15]. Patients with community acquired respiratory infections including pneumonia, infective exacerbation of bronchiectasis and active tuberculosis are commonly managed in government chest clinics. Thus we designed a clinical trial to test the null hypothesis that newer fluoroquinolones in the treatment of community-acquired respiratory infection would not mask active pulmonary TB.

Methods

Patients

We undertook a randomized open-label controlled trial involving patients with community-acquired pneumonia or infective exacerbation of bronchiectasis encountered in multiple government chest clinics in Hong Kong. Adult patients aged 18 years or older were eligible for enrollment if they had clinical signs and symptoms of community-acquired pneumonia or infective exacerbation of bronchiectasis with compatible findings on the chest radiograph. Symptoms and signs included one or more of the following: cough, sputum, haemoptysis, chest discomfort, shortness of breath, crackles, and fever. Patients without symptoms were also eligible in the presence of opacities compatible with consolidations on the chest radiograph. Exclusion criteria were: age below 18 years; confirmed or suspected pregnancy; positive baseline sputum acid-fast bacilli (AFB) smear or AFB culture, and either antibiotic was inappropriate for the clinical scenario such as a history of adverse events to amoxicillin clavulanate or moxifloxacin, significant renal impairment, or known congenital or acquired conditions associated with prolonged QT_c interval, symptomatic cardiac failure or arrhythmia.

Participants underwent baseline clinical assessment including evaluation by chest radiography, sputum microscopy and bacteriology including AFB culture. Chest radiographs and sputum AFB bacteriology were taken at six and 12 months after enrollment and whenever they were considered necessary by the attending physician according to the clinical progress. Further investigations, which included complete blood picture, liver and renal biochemistry, computerized tomography of thorax, and fibreoptic bronchoscopy, could be arranged by the attending physician according to the clinical condition and progress to aid diagnosis or evaluate severity.

Written informed consent was obtained from study participants before enrollment. Approval for conducting the study was obtained from the Ethics Committee of the Department of Health.

Procedures

A study coordinator allocated eligible patients by random permutated blocks of 20 in equal proportions to one of two arms: moxifloxacin 400 mg once daily for five days versus amoxicillin clavulanate 375 mg twice daily plus amoxicillin 750 mg twice daily for five days. Baseline dosing schedules were based on published literature about the efficacy of short-course antibiotic treatment of community-acquired pneumonia[16]. The attending physician was advised not to find out the identity of trial antibiotics unless it was indicated by the clinical condition such as severe adverse events. The attending physician could extend the duration of study antibiotics, repeat study antibiotics, or prescribe other antibiotics including fluoroquinolones subsequently according to the clinical progress.

Participants were followed for one year for active pulmonary TB, the primary endpoint. Active pulmonary TB was diagnosed when compatible clinical findings coexisted with one or more of the following conditions: isolation of *M. tuberculosis* complex in sputum or bronchial aspirate; compatible histopathological findings in lung tissue; and chest radiographic improvement after empirical TB treatment. The follow-up duration was defined as the time interval between enrollment and onset of TB treatment or, in the absence of TB, the last chest radiograph within one year. A grace period of one month after the study period was allowed to ascertain TB status within one year. The TB notification registry was used to help track down

all cases of active pulmonary TB.

Besides the primary endpoint, the following data were collected: demographics, smoking and drinking history, past health, presenting symptoms, initial chest radiographic findings, initial sputum bacteriology results including AFB culture, clinical and chest radiographic progress within the initial two weeks up to two months, total number of sputum specimens and chest radiographs taken, antibiotics prescribed throughout the study period including fluoroquinolones other than allocated moxifloxacin, and the final diagnosis.

Statistical analysis

Assuming a Cohen's h value of 0.3 [17] for the difference in proportions of active pulmonary TB within one year, a type I error of 5% by two-tailed analysis, and a statistical power of 80%, the sample size per arm would be 175. To allow for 20% loss to follow-up, we aimed at enrolling approximately 210 per arm. The primary endpoint was analyzed by modified intention to treat, which meant that all randomized participants would be analyzed except for those with positive baseline AFB smear or culture. Besides comparing the proportion of the primary endpoint in each treatment arm using statistical tests for categorical data, the Kaplan-Meier survival analysis was used to compare the time to the primary endpoint using the log rank test. The chi-squared test for trend, the log rank test for trend, and the likelihood ratio test statistic obtained from logistic risk models were used to examine whether there would be a dose-response relationship between the diagnosis of active pulmonary TB and moxifloxacin exposure. The chi-squared test (with or without Yates' correction) or the Fisher's exact test was used to analyze categorical data. Two-sample t tests or Mann Whitney U tests were used for examining continuous variables according to the data distribution pattern.

One-way ANOVA or Kruskal-Wallis H tests were used for comparing continuous variables involving more than two groups. Statistical significance was taken as $p \leq 0.05$. All analyses were done with SPSS version 10 (SPSS, Inc., Chicago, IL) and R version 2.9.0. This study was registered with hkclinicaltrials.com, number HKCTR-185.

Results

From September 2004 to March 2007, a total of 550 patients were assessed for study eligibility. Figure 1 shows the flow of study from assessment of eligibility to analysis. After excluding 123 patients, 427 patients were enrolled and randomly assigned to receive either amoxicillin clavulanate (n=212) or moxifloxacin (n=215). Enrolled and excluded subjects were comparable by age (p-value = 0.09 by two-sample t test) and by sex (p-value = 0.75 by chi-squared test).

Excluding three patients with positive baseline sputum culture, 424 participants were included in analysis by modified intention to treat. A total of 13 (3.1%) patients developed active pulmonary TB: 10 out of 210 [4.8%, 95% confidence interval (2.6%-8.5%)] given amoxicillin clavulanate, and three out of 214 [1.4%, 95% confidence interval (0.5%-4.0%)] given moxifloxacin. The difference was significant both by proportion (p-value = 0.045) and time-to-event analysis (p-value = 0.04). The prevalence of culture-proven pulmonary TB in the current cohort was 1.9%.

Tables 1 and 2 show the baseline characteristics and progress of participants. Patients assigned to receive moxifloxacin were largely comparable with those assigned to receive amoxicillin

clavulanate with p-values > 0.10 by statistical analysis except for previous TB treatment (p-value = 0.05) and chest pain (p-value = 0.04), neither of which were significantly associated with active pulmonary TB (p-values = 0.77 and 0.61, respectively).

Table 3 compares TB cases by the treatment arm. Patients with active pulmonary TB among the moxifloxacin arm were all given moxifloxacin for five days. None of the three TB cases in the moxifloxacin arm was confirmed bacteriologically whereas 8 out of the 10 TB cases given amoxicillin clavulanate were culture-proven; the difference was significant (p-value = 0.04).

A total of 379 (89.4%) and 360 (84.9%) patients were followed up for at least 91 days and 181 days, respectively. Loss to follow-up as estimated by expected person-days over a period of one year was approximately 16% overall, 18% for participants in the amoxicillin clavulanate arm, and 14% for the moxifloxacin arm. The annual incidence of active pulmonary TB per 100000 persons (95% confidence interval) was 3769 (2111-6262) overall, 6072 (3117-10773) for participants given amoxicillin clavulanate, and 1664 (461-4440) for participants given moxifloxacin. Using TB notification rates of Hong Kong in 2005 as the reference, the expected sex- and age-adjusted incidence rates of active pulmonary TB in the current cohort would be 240 (22-1108).

Two patients took fluoroquinolones before the diagnosis of culture-proven pulmonary TB. Both were allocated to amoxicillin clavulanate rather than moxifloxacin. One received ciprofloxacin 250 mg twice daily for two weeks and 500 mg twice daily for one week approximately 14 weeks and one week, respectively, before the sputum specimen that isolated *M. tuberculosis* was collected. The other received ciprofloxacin 250-500 mg twice daily for two weeks, and 500 mg twice daily for one week about 31 weeks and six weeks, respectively,

before the culture-positive sputum specimen was collected. Drug susceptibility testing showed bacillary susceptibility to ofloxacin in both.

Adverse events occurred in 11 patients allocated to moxifloxacin: hospitalization for pneumonia and acute exacerbation of chronic obstructive pulmonary disease (n=2), left pleural effusion (n=1), and acute respiratory distress syndrome that also occurred within two weeks after receiving standard TB treatment (n=1); dizziness (n=2); gastrointestinal upset (n=3); transient twitching of extremities plus slurring of speech (n=1); and bitter taste (n=1). Of these 11 patients, moxifloxacin was suspended in four: three for gastrointestinal upset and one for dizziness. Adverse events occurred in six patients allocated to amoxicillin clavulanate: hospitalization within one month after enrollment for pneumonia (n=1) and hypoglycemia (n=1); vague discomfort (n=2); diarrhea (n=1); and transient chills in extremities (n=1). Of these six patients, amoxicillin clavulanate was suspended in two patients for ill-defined symptoms (feeling hot and irritable) and generalized vague discomfort.

Post-hoc analysis of dose-response relationship

The significant negative association between active pulmonary TB and exposure to moxifloxacin prompted a closer examination for any dose-response relationship among three subgroups of participants with different moxifloxacin exposure. The proportion with active pulmonary TB decreased significantly from 4.8% among participants given amoxicillin clavulanate (n=210) to 2.4% and 0%, respectively, among those given moxifloxacin for 5-7 days (n=127) and 10-15 days within four weeks (n=87) (p-value = 0.03). The log rank test for trend also showed a significant difference between the three subgroups (p-value = 0.02).

Tables E1 and E2 in the online supplement compare baseline characteristics and progress of participants allocated to amoxicillin clavulanate (n=210), moxifloxacin for 5-7 days (n=127) and moxifloxacin for 10-15 days within four weeks (n=87). The three groups were largely comparable with p-values > 0.10 by statistical analysis except for the following factors: previous TB treatment (p-value = 0.04), history of bronchiectasis (p-value = 0.07), chest pain (p-value = 0.09), fever (p-value = 0.01), symptomatic response within the initial two months (p-value = 0.01), and chest radiographic progress within the initial two months (p-value = 0.05). None of these factors were significantly associated with active pulmonary TB except for the last two (p-values = 0.001 and < 0.001, respectively).

To further examine the dose-response relationship between moxifloxacin exposure and active pulmonary TB, we tested the null hypothesis that the exposure effect of moxifloxacin was linear by comparing a logistic risk model that assumed a linear effect and a more general model in which the exposure effect was assumed to be non-linear. Ten covariates were included in the model: allocated antibiotics (amoxicillin clavulanate, moxifloxacin for 5-7 days, and moxifloxacin for 10-15 days), fluoroquinolones other than allocated moxifloxacin, sex, age, history of drinking, past TB treatment, history of bronchiectasis, presence or absence of symptoms on presentation, and cavitation and extent of disease on initial chest radiographs. Significant collinearity was excluded. The null hypothesis could not be rejected (likelihood ratio test statistic = 1.40; p-value = 0.24). Findings reaffirmed a dose-response relationship between moxifloxacin exposure and diagnosis of active pulmonary TB. Table 4 shows a logistic risk model that assumes a linear effect for moxifloxacin exposure. The adjusted odds ratio (95% confidence interval) of active pulmonary TB after moxifloxacin exposure up to predominantly 10 days over four weeks was 0.3 (0.1-0.9), or 0.9 (0.3-3.0) after exposure for

one day. Logistic risk models have been used instead of Cox models because coefficients failed to converge during Cox regression analysis.

Discussion

The overall annual incidence rate of active pulmonary TB in the current cohort was approximately 16 times that the sex- and age-adjusted TB notification rates of Hong Kong in 2005. The observed prevalence (1.9%) of culture-proven active pulmonary TB in the current cohort was comparable with that observed in another local cohort hospitalized for community-acquired pneumonia [18]. Patients given amoxicillin clavulanate had significantly higher proportion of active pulmonary TB within one year than those given moxifloxacin (p-value = 0.045). Post-hoc analysis showed a significant decrease in the proportion with active pulmonary TB from 4.8% among participants given amoxicillin clavulanate to 2.4% and 0% among those given moxifloxacin for predominantly 5 days and predominantly 10 days within four weeks, respectively (p-value = 0.03 by the chi-squared test for trend). The linear effect was reaffirmed in regression models. A logistic risk model with a linear effect for moxifloxacin exposure showed that the adjusted odds ratio (95% confidence interval) of active pulmonary TB after moxifloxacin exposure up to predominantly 10 days over four weeks was 0.3 (0.1-0.9), or 0.9 (0.3-3.0) after exposure for one day.

With less error due to selection bias and confounding in comparison with retrospective studies, the current randomized controlled trial has put the risk of using fluoroquinolones for treating community-acquired respiratory infection into a better perspective. Dooley et al showed that initial empirical therapy with a fluoroquinolones was associated with a delay in TB treatment

(21 days versus 5 days) [14]. In a retrospective analysis involving 548 TB patients, Wang et al demonstrated exposure to fluoroquinolones delayed TB treatment and was associated with poor prognosis [19]. Our findings show that newer fluoroquinolones such as moxifloxacin appear to mask TB in proportion to the duration of exposure in TB-endemic areas.

Allowing use of non-study antibiotics and flexibility in the dosing duration of study antibiotics and frequency of chest radiographic examination and sputum AFB bacteriology probably rendered the current trial more like a real-life situation. Despite the lack of a double-blind placebo-controlled design, randomization was probably adequate as shown by Tables 1 and 2. It might be argued that in the absence of blinding, the attending physician might be prone to start empirical TB treatment in the moxifloxacin arm. If this were the case, more patients in the moxifloxacin arm would have received TB treatment. There were in fact more TB cases among patients allocated to receive amoxicillin clavulanate.

Although a dose-response relationship between moxifloxacin and masking of TB could be reaffirmed in the current study through regression models, the linear effect might have been better shown without regression analysis had the study design included two moxifloxacin arms with different treatment durations allocated by randomization. Symptomatic response and chest radiographic progress within the initial two months were deliberately excluded from regression analysis despite their significant association with both moxifloxacin exposure and active pulmonary TB; inclusion would have been inappropriate as moxifloxacin probably masks TB through improvement in symptom or chest radiography [20].

The small number of TB cases made it difficult for the current trial to address the association between newer fluoroquinolones and culture-negative pulmonary TB. Although a

retrospective study showed no significant association between fluoroquinolone exposure and an increased risk of culture-negative TB[21], further studies are warranted to examine whether prolonged or multiple courses of newer fluoroquinolones may reduce sputum culture yield of active pulmonary TB.

Another concern about treating community-acquired chest infection with fluoroquinolones is the emergence of fluoroquinolone-resistant TB. The small number of study participants with exposure to fluoroquinolones before a culture-positive sputum specimen was collected made it difficult for the current trial to address this issue. However, a number of studies have reported a low risk of fluoroquinolone-resistant TB among patients exposed to fluoroquinolones prior to the diagnosis of TB [22-24]. Huang et al found that resistance to fluoroquinolones was probably due to use of fluoroquinolones among patients with multidrug-resistant TB rather than the general community[25]. It has also been suggested that newer fluoroquinolones with better pharmacokinetic and pharmacodynamic properties help reduce the risk of developing drug resistance in *M. tuberculosis* [26]. Some preliminary evidence in that direction regarding high-dose moxifloxacin and levofloxacin were indeed obtained [27, 28]. However, the safety and tolerance of these higher dosages require further exploration [27]. Current data also favour shortening the duration of antibiotic treatment at an optimal dosage to reduce the risk of acquired resistance[24, 29]. In corroboration with recent findings of an association between fluoroquinolone-resistant TB and prolonged or multiple courses of fluoroquinolones[22, 30], the current study would caution against fluoroquinolone use in excess of five days or multiple courses in TB-endemic areas to reduce the risk of masking active TB alongside that of developing fluoroquinolone-resistant TB.

The impact of human immunodeficiency virus (HIV) infection on the findings of our clinical

trial could not be examined because the prevalence of HIV in Hong Kong was below 1%[15]. As the clinical and radiographic presentation of pulmonary TB in HIV-infected subjects become atypical with immunosuppression, whether findings of the current trial may also apply to areas that are endemic for both TB and HIV is uncertain.

In conclusion, newer fluoroquinolones such as moxifloxacin appear to mask active pulmonary TB in proportion to the duration of exposure in TB-endemic areas.

Acknowledgements

The authors would like to extend their gratitude to all nurses of the Tuberculosis & Chest Service for their invaluable help. Special thanks go to Ms Lucia Ku for coordinating the study, and Ms Ida Mak and Mr Bosco Wong for data entry.

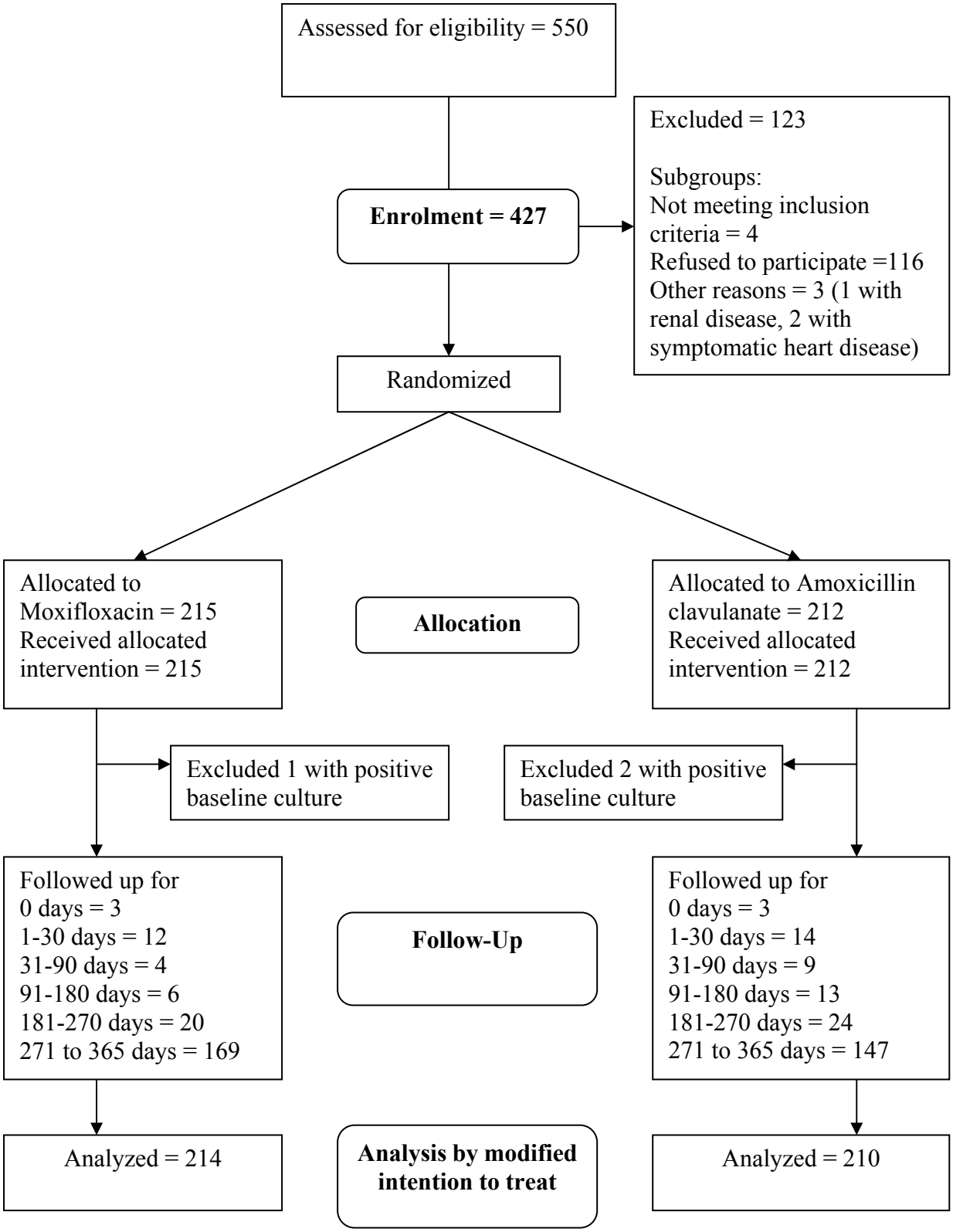

Fig 1 Flow chart from enrollment to analysis

Table 1 Baseline characteristics and treatment

Variables	Amoxicillin clavulanate (N=210)	Moxifloxacin (N=214)
Male	141 (67.1)	139 (65.0)
Mean age, years	64.6 (SD 13.7)	64.9 (SD 13.7)
Chinese	209 (99.5)	209 (97.7)
History of smoking	97 (46.2)	99 (46.3)
History of habitual drinking	15 (7.1)	12 (5.6)
Previous tuberculosis treatment	69 (32.9)	90 (42.1)
History of bronchiectasis	86 (41.0)	88 (41.1)
Diabetes mellitus	13 (6.2)	15 (7.0)
Symptomatic on presentation	198 (94.3)	194 (90.7)
Duration of symptoms		
< 2 week	118 (56.2)	120 (56.1)
2-4 weeks	10 (4.8)	20 (9.3)
1-2 months	38 (18.1)	35 (16.4)
> 2 months	31 (14.8)	27 (12.6)
Indefinite	13 (6.2)	12 (5.6)
Cough	182 (86.7)	179 (83.6)
Sputum	159 (75.7)	175 (81.8)
Haemoptysis	48 (22.9)	41 (19.2)
Shortness of breath	21 (10.0)	21 (9.8)

Chest Pain	21 (10.0)	10 (4.7)
Fever	21 (10.0)	26 (12.1)
Weight loss	9 (4.3)	14 (6.5)
Organisms isolated in sputum bacterial culture		
Commensals	142 (67.6)	135 (63.1)
Contaminants/ colonizers	8 (3.8)	18 (8.4)
Haemophilus influenzae	23 (11.0)	21 (9.8)
Streptococcus pneumoniae including one case with *Staphyloccus aureus*	7 (3.3)	5 (2.3)
Klebsiella pneumoniae	3 (1.4)	6 (2.8)
Pseudomonas aeruginosa	17 (8.1)	18 (8.4)
Others	10 (4.8)	11 (5.1)
Change on initial CXR*		
Lower zones only	110 (52.4)	126 (58.9)
Upper or mid zones	72 (34.3)	63 (29.4)
No change	16 (7.6)	14 (6.5)
Uncertain	12 (5.7)	11 (5.1)
Cavitations on initial CXR		
No	187 (89.0)	189 (88.3)
Yes	7 (3.3)	11 (5.1)
No change	16 (7.6)	14 (6.5)
Extent on initial CXR		
≤ equivalent of RUL	189 (90.0)	195 (91.1)
> equivalent of RUL	5 (2.4)	5 (2.3)

No change	16 (7.6)	14 (6.5)
Fluoroquinolones within 4 weeks before enrollment	1 (0.5)	1 (0.5)
Timing of first submission of sputum for AFB bacteriology		
0-1 day	133 (63.3)	147 (68.7)
>1 day	76 (36.2)	67 (31.3)
Not submitted	1 (0.5)	0 (0)
Duration of allocated antibiotics		
5-day	123 (58.6)	118 (55.1)
7-day	10 (4.8)	9 (4.2)
10-day	42 (20.0)	42 (19.6)
Two 5-days courses with two weeks	28 (13.3)	33 (15.4)
Others[†]	7 (3.3)	12 (5.6)

Note. Data are presented in number (%) unless stated otherwise. All comparisons show no significant difference (with p-values > 0.10) except for previous tuberculosis treatment (p-value = 0.05) and chest pain (p-value = 0.04). Results that were unavailable or not applicable were excluded from statistical analysis.

Abbreviations: CXR = chest radiograph; RUL = right upper lobe; SD = standard deviation.

[*] With reference to previous films or those in the initial two months. Uncertainty of change was due to absence of previous films and no change in the initial two months.

[†] Among patients allocated to receive amoxicillin clavulanate, five had two 5-day courses within 3-6 weeks, one had three 5-day courses within approximately two weeks, and one had four 5-day courses within three weeks. Among patients allocated to receive moxifloxacin, five had two 5-day courses within 3-4 weeks and seven had three 5-day courses within 2-4 weeks.

Table 2 Monitoring and progress

Variables	Amoxicillin clavulanate (N=210)	Moxifloxacin (N=214)
Duration of follow-up*		
Lost after enrollment	3 (1.4)	3 (1.4)
1-30 days	14 (6.7)	12 (5.6)
31-90 days	9 (4.3)	4 (1.9)
91-180 days	13 (6.2)	6 (2.8)
181-270 days	24 (11.4)	20 (9.3)
271-365 days	147 (70.0)	169 (79.0)
Mean duration between CXR, days	41.4 (SD 22.0)	42.4 (SD 20.6)
Mean duration between sputum specimens for AFB bacteriology, days	57.6 (SD 37.0)	57.8 (SD 37.5)
Further investigation by FOB or CT thorax		
No	176 (83.8)	187 (87.4)
FOB	7 (3.3)	8 (3.7)
CT thorax (including high resolution CT)	14 (6.7)	9 (4.2)
Both	13 (6.2)	10 (4.7)
Study antibiotics suspended		
No	207 (98.6)	210 (98.1)
Yes	2 (1.0)	4 (1.9)
Unavailable	1 (0.5)	0 (0)

Adverse events		
No	203 (96.7)	203 (94.9)
Yes	6 (2.9)	11 (5.1)
Unavailable	1 (0.5)	0 (0)
Symptomatic response within the initial two months		
Static or worse	21 (10.0)	23 (10.7)
Partial or complete improvement	182 (86.7)	188 (87.9)
Unavailable or not applicable	7 (3.3)	3 (1.4)
Progress on CXR within the initial two months		
Static or worse	52 (24.8)	41 (19.2)
Partial or complete improvement	152 (72.4)	167 (78.0)
Unavailable or not applicable	6 (2.9)	6 (2.8)
Given antibiotics after the initial two weeks	112 (53.3)	119 (55.6)
Given fluoroquinolones besides allocated moxifloxacin	23 (11.0)	27 (12.6)
Diagnoses		
Pneumonia	154 (73.3)	170 (79.4)
Infective exacerbation of bronchiectasis	17 (8.1)	17 (7.9)
Active pulmonary tuberculosis	10 (4.8)	3 (1.4)
MOTT lung disease	6 (2.9)	4 (1.9)
Fibrosis	7 (3.3)	4 (1.9)
Upper respiratory tract infection or bronchitis	5 (2.4)	6 (2.8)
Others[†]	8 (3.8)	6 (2.8)
Uncertain	3 (1.4)	4 (1.9)

Note. Data are presented as number (%) unless stated otherwise. All comparisons show no significant difference (with p-values > 0.10). Results that were unavailable or not applicable

were excluded from statistical analysis.

Abbreviations: AFB = acid-fast bacilli; CT = computerized tomography; CXR = chest radiograph; FOB = fibreoptic bronchoscopy; IQR = interquartile range; MOTT = mycobacteria other than tuberculosis; SD = standard deviation.

[*] Defined as the interval between enrollment and tuberculosis treatment within one year or, in the absence of tuberculosis treatment, the last chest radiograph within one year. A grace period of one month after the study period was allowed to ascertain tuberculosis status within one year.

[†] Others in the moxifloxacin arm included two cases of lung cancer, and one case each of sputum atypia, probably malignancy, Churg Strauss Syndrome, and idiopathic pulmonary fibrosis. Others in the amoxicillin clavulanate arm referred to eight cases of lung cancer.

Table 3 Comparing patients with active pulmonary tuberculosis in the two treatment arms

	Amoxicillin clavulanate (N=10)	Moxifloxacin (N=3)	p-value
Duration of allocated antibiotics > 5 days	4 (40)	0 (0)	> 0.2
Male	9 (90.0)	2 (66.7)	> 0.2
Median age (range), years	67.7 (33.5-84.4)	70.2 (24.6-71.6)	> 0.2
Symptomatic on presentation	7 (70.0)	2 (66.7)	> 0.2
Change on initial CXR in upper or mid zones*	8 (88.9)	3 (100)	> 0.2
Extent > the equivalent of right upper lobe	2 (20.0)	1 (33.3)	> 0.2
Cavities	2 (20)	0 (0)	> 0.2
Culture-proven TB	8 (80)	0 (0)	0.04
First sputum submitted within one day	2 (20.0)	2 (66.7)	> 0.2
Median time of collection of first positive culture (range), days	21 (5-282)	NA	NA
Median onset of TB treatment (range), days	23.5 (6-360)	12 (7-137)	> 0.2
Potential masking of TB through improvement in symptoms within the initial two months†	4 (44.4)	2 (66.7)	> 0.2
Potential masking of TB through improvement on CXR within the initial two months	2 (20.0)	1 (33.3)	> 0.2

Note. Data are presented in number (%) unless stated otherwise. Time is measured with reference to enrollment.

Abbreviations: CXR = chest radiograph; NA = not applicable; TB = tuberculosis

* Excluding one patient given amoxicillin clavulanate with unknown status

† Excluding one patient given amoxicillin clavulanate with no symptom at presentation

Table 4 A logistic risk model that assumes a linear effect for moxifloxacin exposure

Predictor variables	Odds ratio (95% CI)	p-value
Moxifloxacin exposure	0.3 (0.1-0.9)	0.03
Fluoroquinolones other than allocated moxifloxacin	2.6 (0.4-17.3)	0.33
Male	2.1 (0.4-11.7)	0.41
Age, years	0.97 (0.93-1.01)	0.16
History of drinking	2.8 (0.5-15.8)	0.24
Past tuberculosis treatment	0.6 (0.1-2.4)	0.43
History of bronchiectasis	0.4 (0.1-2.1)	0.30
Symptomatic on presentation	0.1 (0.0-0.5)	0.01
Cavitation on initial chest radiograph	4.0 (0.5-34.8)	0.22
Extent of disease > equivalent of right upper lobe on chest radiograph	29.5 (4.3-203.1)	<0.001

Note. History of smoking has been excluded owing to significant correlation with males.

Abbreviations: CI = confidence interval

References

1. Lode H, Garau J. Improving care for patients with respiratory tract infections. J Chemother 2002; 14 Suppl 2:22-28.
2. Tillotson GS. Role of gemifloxacin in community-acquired pneumonia. Expert Rev Anti Infect Ther 2008; 6:405-418.
3. Miravitlles M, Anzueto A. Moxifloxacin: a respiratory fluoroquinolone. Expert Opin Pharmacother 2008; 9:1755-1772.
4. Vardakas KZ, Siempos II, Grammatikos A, Athanassa Z, Korbila IP, Falagas ME. Respiratory fluoroquinolones for the treatment of community-acquired pneumonia: a meta-analysis of randomized controlled trials. CMAJ 2008; 179:1269-1277.
5. Petitpretz P, Arvis P, Marel M, Moita J, Urueta J. Oral moxifloxacin vs high-dosage amoxicillin in the treatment of mild-to-moderate, community-acquired, suspected pneumococcal pneumonia in adults. Chest 2001; 119:185-195.
6. Torres A, Muir JF, Corris P, Kubin R, Duprat-Lomon I, Sagnier PP, Hoffken G. Effectiveness of oral moxifloxacin in standard first-line therapy in community-acquired pneumonia. Eur Respir J 2003; 21:135-143.
7. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TMJ, Musher DM, Niederman MS, Torres A, Whitney CG, . Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007; 44 Suppl 2:S27-72.
8. Yew WW, Chan CK, Chau CH, Tam CM, Leung CC, Wong PC, Lee J. Outcomes of patients with multidrug-resistant pulmonary tuberculosis treated with ofloxacin/levofloxacin-containing regimens. Chest 2000; 117:744-751.

9. Yew WW, Chan CK, Leung CC, Chau CH, Tam CM, Wong PC, Lee J. 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.
10. Chan ED, Laurel V, Strand MJ, Chan JF, Huynh MN, Goble M, Iseman MD. Treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis. Am J Respir Crit Care Med 2004; 169:1103-1109.
11. Leimane V, Riekstina V, Holtz TH, Zarovska E, Skripconoka V, Thorpe LE, Laserson KF, Wells CD. Clinical outcome of individualised treatment of multidrug-resistant tuberculosis in Latvia: a retrospective cohort study. Lancet 2005; 365:318-326.
12. Rustomjee R, Lienhardt C, Kanyok T, Davies GR, Levin J, Mthiyane T, Reddy C, Sturm AW, Sirgel FA, Allen J, Coleman DJ, Fourie B, Mitchison DA. A Phase II study of the sterilising activities of ofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. Int J Tuberc Lung Dis 2008; 12:128-138.
13. Conde MB, Efron A, Loredo C, De Souza GRM, Graça NP, Cezar MC, Ram M, Chaudhary MA, Bishai WR, Kritski AL, Chaisson RE. Moxifloxacin versus ethambutol in the initial treatment of tuberculosis: a double-blind, randomised, controlled phase II trial. Lancet 2009; 373:1183-1189.
14. Dooley KE, Golub J, Goes FS, Merz WG, Sterling TR. Empiric treatment of community-acquired pneumonia with fluoroquinolones, and delays in the treatment of tuberculosis. Clin Infect Dis 2002; 34:1607-1612.
15. Tuberculosis & Chest Service of the Department of Health. Annual Report 2007. The Government of Hong Kong SAR.
16. Mandell LA, File TMJ. Short-course treatment of community-acquired pneumonia. Clin Infect Dis 2003; 37:761-763.

17. Cohen J. Statistical power analysis for the behavioral sciences (rev. ed.). New York: Academic Press; 1977.
18. Ko FWS, Lam RKY, Li TST, Fok JPC, Chan MCH, Ng TKC, Chan DPS, Hui DSC. Sputum bacteriology in patients hospitalized with acute exacerbations of chronic obstructive pulmonary disease and concomitant pneumonia in Hong Kong. Intern Med J 2005; 35:661-667.
19. Wang J, Hsueh P, Jan I, Lee L, Liaw Y, Yang P, Luh K. Empirical treatment with a fluoroquinolone delays the treatment for tuberculosis and is associated with a poor prognosis in endemic areas. Thorax 2006; 61:903-908.
20. Rothman, K. J. Epidemiology: an introduction. New York: Oxford University Press, Inc.; 2002.
21. Gaba PD, Haley C, Griffin MR, Mitchel E, Warkentin J, Holt E, Baggett P, Sterling TR. Increasing outpatient fluoroquinolone exposure before tuberculosis diagnosis and impact on culture-negative disease. Arch Intern Med 2007; 167:2317-2322.
22. Long R, Chong H, Hoeppner V, Shanmuganathan H, Kowalewska-Grochowska K, Shandro C, Manfreda J, Senthilselvan A, Elzainy A, Marrie T. Empirical treatment of community-acquired pneumonia and the development of fluoroquinolone-resistant tuberculosis. Clin Infect Dis 2009; 48:1354-1360.
23. Ginsburg AS, Grosset JH, Bishai WR. Fluoroquinolones, tuberculosis, and resistance. Lancet Infect Dis 2003; 3:432-442.
24. Ginsburg AS, Hooper N, Parrish N, Dooley KE, Dorman SE, Booth J, Diener-West M, Merz WG, Bishai WR, Sterling TR. Fluoroquinolone resistance in patients with newly diagnosed tuberculosis. Clin Infect Dis 2003; 37:1448-1452.

25. Huang T, Kunin CM, Shin-Jung Lee S, Chen Y, Tu H, Liu Y. Trends in fluoroquinolone resistance of Mycobacterium tuberculosis complex in a Taiwanese medical centre: 1995-2003. J Antimicrob Chemother 2005; 56:1058-1062.
26. Drlica K, Zhao X. Mutant selection window hypothesis updated. Clin Infect Dis 2007; 44:681-688.
27. Gumbo T, Louie A, Deziel MR, Parsons LM, Salfinger M, Drusano GL. Selection of a moxifloxacin dose that suppresses drug resistance in Mycobacterium tuberculosis, by use of an in vitro pharmacodynamic infection model and mathematical modeling. J Infect Dis 2004; 190:1642-1651.
28. Johnson JL, Hadad DJ, Boom WH, Daley CL, Peloquin CA, Eisenach KD, Jankus DD, Debanne SM, Charlebois ED, Maciel E, Palaci M, Dietze R. Early and extended early bactericidal activity of levofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. Int J Tuberc Lung Dis 2006; 10:605-612.
29. Low DE. Fluoroquinolones for treatment of community-acquired pneumonia and tuberculosis: putting the risk of resistance into perspective. Clin Infect Dis 2009; 48:1361-1363.
30. Devasia RA, Blackman A, Gebretsadik T, Griffin M, Shintani A, May C, Smith T, Hooper N, Maruri F, Warkentin J, Mitchel E, Sterling TR. Fluoroquinolone resistance in M. tuberculosis: the effect of duration and timing of fluoroquinolone exposure. Am J Respir Crit Care Med 2009. doi:10.1164/rccm.200901-0146OC.