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

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ABSTRACT: Possible masking of tuberculosis (TB) in treatment of community-acquired respiratory infection by newer fluoroquinolones has not been examined in randomised controlled trials.

We undertook a randomised, 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 1 yr for active pulmonary TB.

Excluding three participants with positive baseline culture, 13 developed active pulmonary TB: 10 (4.8%) out of 210 were given amoxicillin clavulanate, and three (1.4%) out of 214 were given moxifloxacin. The difference was significant by both proportion and time-to-event analysis. *Post hoc* analysis showed a significant decrease in the proportion with active pulmonary TB 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 TB after moxifloxacin exposure up to predominantly 10 days was 0.3 (0.1–0.9).

Newer fluoroquinolones appear to mask active pulmonary TB.

KEYWORDS: Fluoroquinolones, tuberculosis

With broad-spectrum antimicrobial coverage including β-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 (CAP) in the presence of comorbidities or risk factors for drug-resistant *S. 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 CAP by fluoroquinolones has been suggested by retrospective analysis [14], but not been verified by randomised controlled trials in TB-endemic areas. Hong Kong is endemic for TB with annual notification rates at ~80 per 100,000 persons [15]. Patients with community-acquired respiratory infections including pneumonia, infective exacerbation of bronchiectasis and active TB 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 randomised, open-label controlled trial involving patients with CAP or infective exacerbation of bronchiectasis encountered in multiple government chest clinics in Hong Kong. Adult patients aged ⩾18 yrs were

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eligible for enrolment if they had clinical signs and symptoms of CAP 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 <18 yrs; confirmed or suspected pregnancy; positive baseline sputum acid-fast bacilli (AFB) smear or AFB culture, and when either amoxicillin clavulanate or moxifloxacin 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 QTc 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 6 and 12 months after enrolment 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, computerised 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 enrolment. Approval for conducting the study was obtained from the Ethics Committee of the Dept of Health of Hong Kong Special Administrative Region.

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 5 days *versus* amoxicillin clavulanate 375 mg twice daily plus amoxicillin 750 mg twice daily for 5 days. Baseline dosing schedules were based on published literature about the efficacy of short-course antibiotic treatment of CAP [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 1 yr for active pulmonary TB, the primary end-point. Active pulmonary TB was diagnosed when compatible clinical findings coexisted with one or more of the following conditions: isolation of *Mycobacterium 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 enrolment and onset of TB treatment or, in the absence of TB, the last chest radiograph within 1 yr. A grace period of 1 month after the study period was allowed to ascertain TB status within 1 yr. The TB notification registry was used to help track down all cases of active pulmonary TB.

Besides the primary end-point, 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 2 weeks up to 2 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 1 yr, a type I error of 5% by two-tailed analysis, and a statistical power of 80%, the sample size per arm would be 175 patients. To allow for 20% loss to follow-up, we aimed at enrolling ~210 patients per arm. The primary end-point was analysed by modified intention to treat, which meant that all randomised participants would be analysed except for those with positive baseline AFB smear or culture. Besides comparing the proportion of the primary end-point in each treatment arm using statistical tests for categorical data, the Kaplan–Meier survival analysis was used to compare the time to the primary end-point 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 analyse 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 $p \leqslant 0.05$. All analyses were done with SPSS version 10 (SPSS, Inc., Chicago, IL, USA) and R version 2.9.0. This study was registered with www.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=0.09 by two-sample t-test) and by sex (p=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 (CI) 2.6–8.5%)) were given amoxicillin clavulanate, and three out of 214 (1.4% (95% CI 0.5–4.0%)) were given moxifloxacin. The difference was significant both by proportion (p=0.045) and time-to-event analysis (p=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

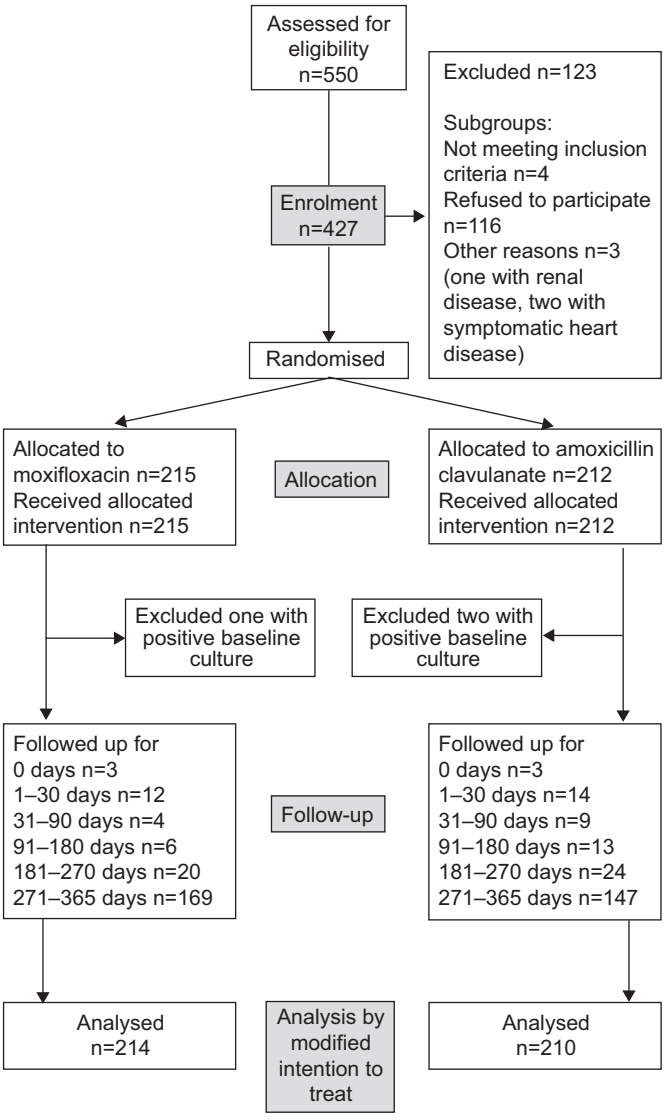

FIGURE 1. Flow chart from enrolment to analysis.

clavulanate with p-values >0.10 by statistical analysis except for previous TB treatment (p=0.05) and chest pain (p=0.04), neither of which were significantly associated with active pulmonary TB (p=0.77 and p=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 5 days. None of the three TB cases in the moxifloxacin arm was confirmed bacteriologically, whereas eight out of the 10 TB cases given amoxicillin clavulanate were culture-proven; the difference was significant (p=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 1 yr was ~16% overall, 18% for participants in the amoxicillin clavulanate arm, and 14% for the moxifloxacin arm. The annual incidence of active pulmonary TB per 100,000 persons (95% CI) was 3,769 (2,111–6,262) overall, 6,072 (3,117–10,773) for participants given amoxicillin clavulanate, and 1,664 (461–4,440) 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 (22–1,108).

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 2 weeks and 500 mg twice daily for 1 week, ~14 weeks and 1 week, respectively, before the sputum specimen that isolated *M. tuberculosis* was collected. The other received ciprofloxacin 250–500 mg twice daily for 2 weeks, and 500 mg twice daily for 1 week, ~31 weeks and 6 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 as follows: hospitalisation 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 2 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 a 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: hospitalisation within 1 month after enrolment for pneumonia (n=1) and hypoglycaemia (n=1); vague discomfort (n=2); diarrhoea (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 generalised 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 4 weeks (n=87; p=0.03). The log rank test for trend also showed a significant difference between the three subgroups (p=0.02).

Online supplementary tables E1 and E2 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 4 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=0.04), history of bronchiectasis (p=0.07), chest pain (p=0.09), fever (p=0.01), symptomatic response within the initial 2 months (p=0.01), and chest radiographic progress within the initial 2 months (p=0.05). None of these factors were significantly associated with active pulmonary TB except for the last two (p=0.001 and p<0.001, respectively).

TABLE 1 Baseline characteristics and treatment

Variables	Amoxicillin clavulanate	Moxifloxacin
Subjects n	210	214
Male	141 (67.1)	139 (65.0)
Age yrs	64.6±13.7	64.9±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 TB 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 weeks	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/colonisers	8 (3.8)	18 (8.4)
Haemophilus influenzae	23 (11.0)	21 (9.8)
Streptococcus pneumoniae including one case with *Staphylococcus 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 enrolment	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 days	123 (58.6)	118 (55.1)
7 days	10 (4.8)	9 (4.2)
10 days	42 (20.0)	42 (19.6)
Two 5-day courses with 2 weeks	28 (13.3)	33 (15.4)
Others¶	7 (3.3)	12 (5.6)

Data are presented as n (%) or mean±SD, unless otherwise indicated. All comparisons show no significant difference (with $p>0.10$) except for previous tuberculosis (TB) treatment ($p=0.05$) and chest pain ($p=0.04$). Results that were unavailable or not applicable were excluded from statistical analysis. CXR: chest radiograph; RUL: right upper lobe; AFB: acid-fast bacilli. #: with reference to previous films or those in the initial 2 months. Uncertainty of change was due to absence of previous films and no change in the initial 2 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 ~2 weeks, and one had four 5-day courses within 3 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.

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; $p=0.24$). 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% CI) of active pulmonary TB after moxifloxacin exposure up to predominantly 10 days over 4 weeks was 0.3 (0.1–0.9), or 0.9 (0.3–3.0) after exposure for 1 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 ~16 times that of 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 hospitalised for CAP [18]. Patients given amoxicillin clavulanate had a significantly higher proportion of active pulmonary TB within 1 yr than those who were given moxifloxacin ($p=0.045$). *Post hoc* analysis showed a significant decrease in the proportion with active pulmonary TB from 4.8%

TABLE 2 Monitoring and progress

Variables	Amoxicillin clavulanate	Moxifloxacin
Subjects n	210	214
Duration of follow-up#		
Lost after enrolment	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)
Duration between CXR days	41.4±22.0	42.4±20.6
Duration between sputum specimens for AFB bacteriology days	57.6±37.0	57.8±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 2 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 2 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 2 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 TB	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)

Data are presented as n (%) or mean±SD, unless otherwise indicated. All comparisons show no significant difference (with $p>0.10$). Results that were unavailable or not applicable were excluded from statistical analysis. CXR: chest radiograph; AFB: acid-fast bacilli; FOB: fibreoptic bronchoscopy; CT: computerised tomography; TB: tuberculosis; MOTT: mycobacteria other than TB. #: defined as the interval between enrolment and TB treatment within 1 yr or, in the absence of TB treatment, the last CXR within 1 yr. A grace period of 1 month after the study period was allowed to ascertain TB status within 1 yr. ¶: 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.

among participants given amoxicillin clavulanate to 2.4% and 0% among those given moxifloxacin for predominantly 5 days and predominantly 10 days within 4 weeks, respectively ($p=0.03$ by 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% CI) of active pulmonary TB after moxifloxacin exposure up to predominantly 10 days over 4 weeks was 0.3 (0.1–0.9), or 0.9 (0.3–3.0) after exposure for 1 day.

TABLE 3 Comparing patients with active pulmonary tuberculosis (TB) in the two treatment arms

	Amoxicillin clavulanate	Moxifloxacin	p-value
Subjects n	10	3	
Duration of allocated antibiotics >5 days	4 (40)	0 (0)	>0.2
Male	9 (90.0)	2 (66.7)	>0.2
Age yrs	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 greater than the equivalent of the RUL	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 1 day	2 (20.0)	2 (66.7)	>0.2
Time of collection of first positive culture days	21 (5–282)	NA	NA
Onset of TB treatment days	23.5 (6–360)	12 (7–137)	>0.2
Potential masking of TB through improvement in symptoms within the initial 2 months[¶]	4 (44.4)	2 (66.7)	>0.2
Potential masking of TB through improvement on CXR within the initial 2 months	2 (20.0)	1 (33.3)	>0.2

Data are presented as n (%) or median (range), unless otherwise indicated. Time is measured with reference to enrolment. CXR: chest radiograph; RUL: right upper lobe; NA: not applicable. [#]: excluding one patient given amoxicillin clavulanate with unknown status. [¶]: excluding one patient given amoxicillin clavulanate with no symptoms at presentation.

With less error due to selection bias and confounding in comparison with retrospective studies, the current randomised controlled trial has put the risk of using fluoroquinolones for treating community-acquired respiratory infection into a better perspective. DOOLEY *et al.* [14] showed that initial empirical therapy with fluoroquinolones was associated with a delay in TB treatment (21 days *versus* 5 days). In a retrospective analysis involving 548 TB patients, WANG *et al.* [19] demonstrated that exposure to fluoroquinolones delayed TB treatment and was associated with poor prognosis. Our findings show that newer fluoroquinolones, such as moxifloxacin, appear to mask TB in proportion to the duration of exposure in TB-endemic areas.

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

Predictor variables	OR (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 yrs	0.97 (0.93–1.01)	0.16
History of drinking	2.8 (0.5–15.8)	0.24
Past TB 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 greater than equivalent of right upper lobe on chest radiograph	29.5 (4.3–203.1)	<0.001

History of smoking has been excluded owing to significant correlation with males. TB: tuberculosis.

Allowing use of nonstudy 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, randomisation 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 randomisation. Symptomatic response and chest radiographic progress within the initial 2 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 symptoms 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.* [25] found that resistance to fluoroquinolones was probably due to use of fluoroquinolones among patients with multidrug-resistant TB rather than the general community. 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 5 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 HIV infection on the findings of our clinical trial could not be examined because the prevalence of HIV in Hong Kong was <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.

CLINICAL TRIALS

This study was registered with www.hkclinicaltrials.com (number HKCTR-185).

STATEMENT OF INTEREST

None declared.

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