African Journal of Pharmacy and Pharmacology Vol. 6(1), pp. 57-65, 8 January, 2012
Available online at http://www.academicjournals.org/AJPP
DOI: 10.5897/AJPP11.762
ISSN 1996-0816 ©2012 Academic Journals

Full Length Research Paper

A meta analysis of the efficacy and safety of moxifloxacin in Chinese patients with multi-drug resistant pulmonary tuberculosisosis

Shaoxia Liu[1], Shanshan Chen [1], Xinwei Ren[2] and Guojun Zhang[1]*

[1]Department of Respiratory Medicine, First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, 450052, China.
[2]Department of Pharmacy, Second Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, 450014, China.

Accepted 13 December, 2011

This study was performed to evaluate the efficacy and safety of moxifloxacin in treating Chinese patients with multi-drug resistant pulmonary tuberculosisosis (MDR-TB). Medicinal databases and review articles were screened with pre-specified criteria for randomized controlled trials that reported the effects of and adverse reactions to moxifloxacin and other antituberculosisosis drugs in treating Chinese patients with MDR-TB. The quality of included studies was critically evaluated. A total of 948 articles were found and 12 articles finally included. Heterogeneity test: Sputum negative conversion analysis (Q statistic = 9.43, p = 0.58, I^2 = 0%), change of pulmonary tuberculosisosis cavity analysis (Q statistic = 2.93, p = 0.89, I^2 = 0%), focus absorption analysis (Q statistic = 20.13, p = 0.03, I^2 = 50%) and safety analysis (Q statistic = 10.98, p = 0.44, I^2 = 0%). The results of meta-analysis showed that compared with the control group, moxifloxacin was more effective in sputum negative conversion (OR = 3.34, 95% CI: 2.37 to 4.70) and focus absorption (OR = 2.53, 95% CI: 1.55 to 4.12). Moreover, moxifloxacin was safer than control group (OR = 0.73, 95% CI: 0.55 to 0.96). Funnel-plot displayed some unsymmetrical figures, indicating there were publication biases in each analysis. The evidence currently available shows that the moxifloxacin treatment on Chinese patients with MDR-TB is useful for the sputum negative conversion and focus absorption.

Key words: Moxifloxacin, pulmonary tuberculosisosis, systemic review, meta-analysis.

INTRODUCTION

In people with latent tuberculosis (TB), a group estimated to be one-third of the world's population, mycobacterium tuberculosis is presumed to lie in a nonreplicating (dormant) state in caseous lesions of the lungs, with little access to oxygen (Barry et al., 2009; Wayne and Hayes, 1996) or in extrapulmonary sites containing adipose tissue (Neyrolles et al., 2006). Since every year, there are mainly 500,000 reported cases of tuberculosis caused by strains of mycobacterium tuberculosis that are resistant to the key first-line drug isoniazid and rifampicin, agents that are active in multidrug-resistant tuberculosis are also needed (WHO, 2008). Additionally, the Chinese patients with MDR-TB were second in the world (WHO, 2006). The development of novel drug regimens for MDR-TB is an urgent global health priority (Young et al., 2006). Moxifloxacin is a fluoroquinolone that has potent *in-vitro* activity against MDR-TB (Ji et al., 1998; Gillespie and Billington, 1999). Earlier studies of moxifloxacin in murine models of tuberculosis showed that it had good bactericidal activity that was additive to isoniazi (Miyazaki et al., 1999; Lounis et al., 2001). Though there are several clinic studies (Burman et al., 2006; Conde et al., 2009; Dorman et al., 2009) about moxifloxacin in treatment of MDR-TB, the conclusions of which are not credible because of small sample size and lacks of systemic evaluation of methodologic quality.

In our present work, we make a systemic review about clinical random control trials (RCTs) focused on moxifloxacin in treatment of Chinese patients with MDR-TB in order to obtain the best evidence about the

*Corresponding author. E-mail: zhang450052@sina.com.

efficacy and safety of moxifloxacin in treating Chinese patients with MDR-TB.

METHODS

Search sources and strategy

The search strategy was made according to working handbook 4.2.7 from the Cochrane collaboration (Sackett et al., 2002). We systematically searched MEDLINE (1991 to September 2011), EMbase (1991 to September 2011), CBMdisc (1991 to September 2011) and CNKI (1994 to September 2011) for randomized trials examining the efficacy and safety of moxifloxacin on MDR-TB patients. In addition, we conducted a manual search of abstracts from selected conferences and we also searched by hand the bibliographies of all relevant trials. The following search criterion was used: (“pulmonary tuberculosisosis”, “pneumonophthisis” or "MDR-TB") and (“moxifloxacin", "avelox”, “moxifloxacinum”, “moxifloxacine” or “moxifloxacino”) and language was limited to English or Chinese.

Study selection

Two reviewers independently conducted the literature search and extraction of relevant articles. The title and abstract of potentially relevant studies were screened for appropriateness before retrieval of the full articles. The following selection criteria were used to identify published studies for inclusion in this meta-analysis: (a) study design-RCTs; (b) population- Chinese patients with MDR-TB (WHO-ISH Tuberculosisosis Guidelines Committee, 2003; Chinese guidebook on prevention and treatment of tuberculosisosis, 2002); (c) intervention: moxifloxacin versus other active antituberculosisosis agents such as levofloxacin and sparfloxacin; (d) outcome variable: sputum negative conversion rate, change of tuberculosis cavity rate, focus absorption rate and adverse reaction rate.

Data extraction

From each study, the following information was abstracted: author, year of publication, study design, characteristics of the population, simple size, treatment proposal, time of the therapy, sputum negative conversion rate, change of tuberculosis cavity rate, focus absorption rate and adverse reactions (ADRs) rate.

Assessment of study quality

Quality of the included studies was assessed based on a well-established, validated scale developed by Jadad et al. (1996). A Jadad score was calculated using the following 7 items: (i) Was the study described as a random trial? (ii) Was the randomization scheme described as appropriate? (iii) Was the study described as double-blind? (iv) Was the method of double blinding appropriate? (Were both the patient and the assessor appropriately blinded?) (v) Was there a description of dropouts and withdrawals? (vi) Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate; (vii) Deduct one point if the study was described as double blind but the method of blinding was inappropriate. The first five items were indications of good quality and each counted as one point towards an overall quality score. The final two items indicated poor quality and a point were subtracted for each if its criteria were met.

The range of possible scores was 0 to 5 (0 being weakest and 5 being strongest). Any study with a Jadad score < 3/5 was considered to be of poor quality and was excluded.

Statistical analysis

For dichotomous outcomes, we calculated a pooled odds ratio (OR) and 95% confidence interval (CI). The OR was defined as the odds of an outcome in those who received moxifloxacin compared with the odds in those who received other active agents. The ORs of different RCTs were combined by using the random effects model as previously described (Der and Laird, 1986), if true between-study heterogeneity exists or else using Mantel and Haenszel fixed-effects model instead (Mantel and Haenszel, 1959). Intertrial statistical heterogeneity was explored using the Cochran Q test with calculated I^2, indicating the percentage of the total variability in effect estimates among trials that are due to heterogeneity rather than to chance (Higgins et al., 2003). I^2 values of 50% or more indicate a substantial level of heterogeneity. We evaluated the presence of publication bias by means of visual inspection of the funnel plot (whether it was symmetrical or not). To exclude the possibility that any one study was exerting excessive influence on the results, we conducted a sensitivity analysis by excluding those studies with low quality and then rerunning the analysis to assess the change in ORs.

All *p* values were two-sided with statistical significance set at an α level of 0.05. We followed the “quality of reporting meta-analysis guidelines” for reporting and discussing these meta-analytical results (Moher et al., 1999). All the statistical analysis was carried out by the Cochrane collaboration’s RevMan 5.0 software.

RESULTS

Study characteristics

There were 948 articles relevant to the search term and 12 articles (Chen et al., 2009, 2011; Huang et al., 2011; Liang et al., 2011; Tang, 2008; Wang and Wang, 2009, Wang and Gao, 2010; Xiao et al., 2006; Zhang et al., 2007a, b; Zhao, 2007) involving 924 patients with MDR-TB (group moxifloxacin: 509 patients, group control: 415 patients) were included in this meta-analysis finally. Ages, sex ratio and initial blood pressure were similar in each group, respectively. The flow chart for the selection of RCTs to be included in our analysis is shown in Figure 1. The characteristics of the included trials were showed in Table 1.

Methodologic quality assessment

All the trials included in this meta-analysis mentioned the term ‘random’, but the detail method was illuminated in 1 article only. There were 12 trials mentioned, the term ‘double blind’, but only 9 articles explained the detail method. All the 12 trials described the data of the patients who withdrew during the treatment. According to the Jadad score, 9 articles and 3 articles were regarded as high quality literature and low quality literature, respectively (Table 1).

Heterogeneity test

We choose fixed-effect model to make meta-analysis because there were no significant heterogeneities among

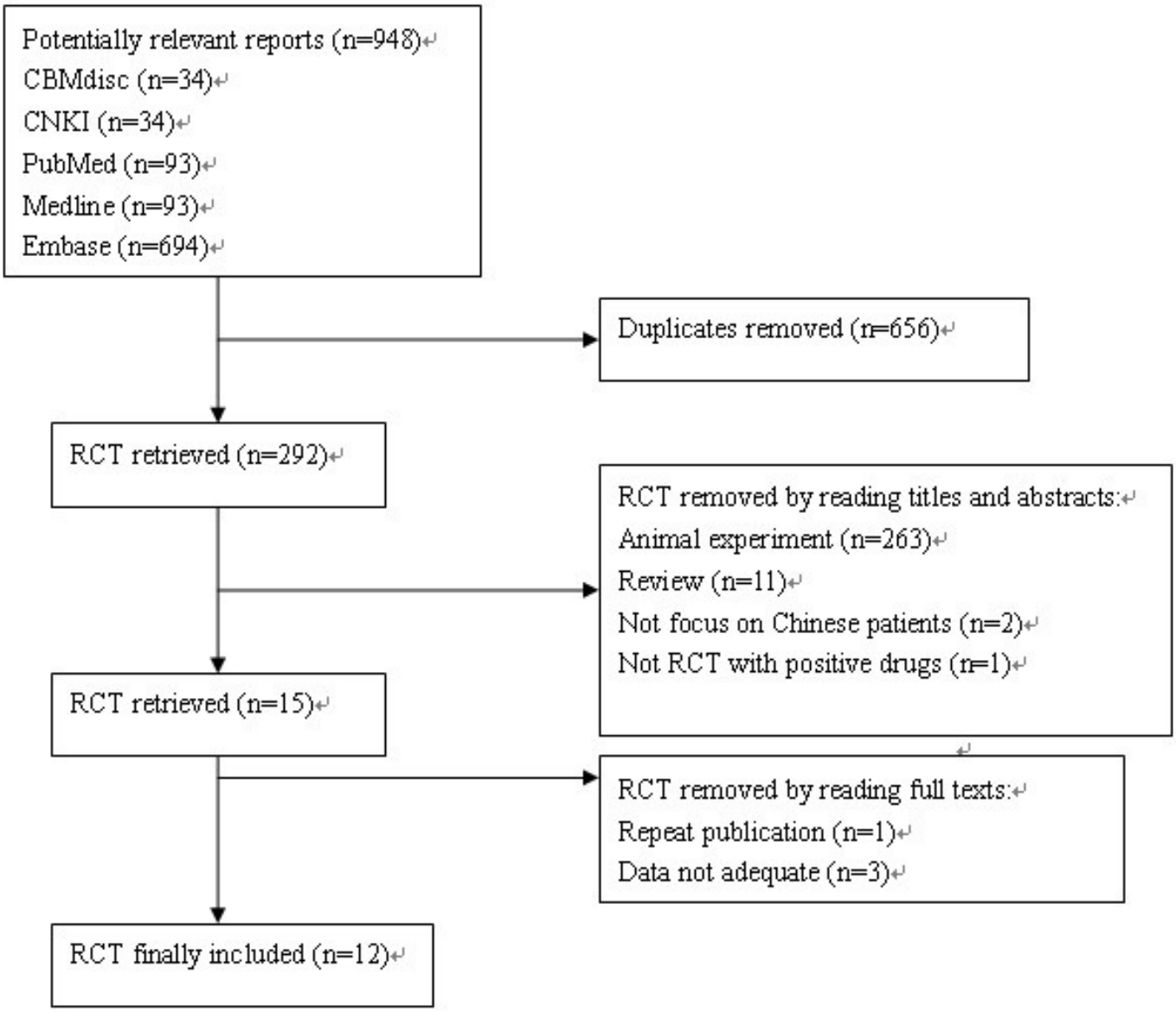

Figure 1. Chat for the search result and trials screen.

sputum negative conversion (Q statistic = 9.43, p = 0.58, I^2 = 0%), change of pulmonary tuberculosisosis cavity (Q statistic = 2.93, p = 0.89, I^2 = 0%) and safety analysis (Q statistic = 10. 89, p = 0.44, I^2 = 0%) in our primary analysis. Because of heterogeneity, random-effect model was used to make analysis for focus absorption (Q statistic = 20.13, p = 0.03, I^2 = 50%).

Meta-analysis of sputum negative conversion

Moxifloxacin and group control were recorded in all the 12 trials finally included. Active antituberculosis agents involved in this analysis were levofloxacin and sparfloxacin. The results of meta-analysis (OR = 3.34 95% CI: 2.37 to 4.70) confessed that moxifloxacin is more effective than control group in sputum negative conversion of Chinese patients with MDR-TB (Figure 2).

Meta-analysis of change of pulmonary tuberculosisosis cavity

Moxifloxacin and group control were recorded in all the 8 trials finally included. Active antituberculosis agents involved in this analysis were levofloxacin and sparfloxacin. The results of meta-analysis (OR = 1.38 95% CI: 0.99 to 1.90) confessed that there were no significant differences in changing cavity between

Table 1. Characterisics of the 12 randomized clinical studies included in this meta-analysis.

Author and Jaded score	Year	Duration (months)	Treatment Protocol (T/C)	Sample size (T/C)	Sputum negative conversion rate (%)	Change of tuberculosis cavity rate (%)	Focus absorption rate (%)	Adverse reaction rate (%)
Xiao et al. Score = 3	2006	21	T: M+CcrEPThZ C: V+CcrEPThZ	T: 35 C: 30	77.1 63.3	NA	NA	11.4 33.3
Zhang et al. Score = 3	2007	12	T: M+ADEL C: V+ADEL	T:62 C:64	93.5 86	61.3 53.1	80.6 76.6	38.7 53.1
Zhang et al. Score = 3	2007	12	T: M+DL C: V+DL	T: 31 C: 30	90.3 76.7	48.4 46.7	64.5 50	22.9 26.5
Zhang et al. Score = 3	2007	12	T: M+ADLE C: Sp+ADLE	T:36 C: 35	91.7 82.9	84.8 78.1	88.9 80	15.4 35.0
Zhao et al. Score = 2	2007	12	T: M+CDLTh C: V+CDLTh	T: 31 C: 31	87.1 74.2	NA	90.3 77.4	12.9 16.1
Tang et al. Score = 2	2008	12	T: M+DELTh C: V+DELTh	T: 62 C: 64	88.7 75	NA	91.9 75	16.1 18.8
Chen et al. Score = 2	2009	18	T: M+AmCDCcrPas C: V+AmCDCcrPas	T: 43 C: 42	95.3 71.4	97.7 85.7	97.7 85.7	32.6 31
Wang et al. Score = 3	2009	18	T: M+AEZL C: V+AEZL	T: 96 C: 96	93.8 91.7	56.3 51	82.2 85.4	23.9 28.1
Wang et al. Score = 3	2010	21	T: M+ADLThZ C: ADLThZ	T: 46 C: 47	87 59.6	NA	93.5 55.3	29.2 26.5
Chen et al. Score = 4	2011	12	T: M+DEThZ C: V+DEThZ	T:24 C: 27	91.6 74.1	66.6 55.6	83.3 66.7	23.7 22.8
Huang et al. Score = 3	2011	21	T: M+ALPZ C: V+ALPZ	T: 63 C: 63	92.1 57.1	80 71.1	79.4 46	4.5 4.5
Liang et al.	2011	18	T: M+ALPPasTh Z	T: 35	82.9	81.6	91.4	26.1

Table 1. Contd.

Score = 5	C: V+ ALPPasThZ	C: 30	60	79.2	80	22.2

(M: moxifloxacin; V: levofloxacin; Sp: capreomycin; A: amikacin; Am: amoxicillin and clavulanate potassium granules; C: capreomycin; Ccr: capreomycin: D: pasiniazide; E: ethambutol; L: rifapentini; P: pasiniazide; Pas: sodium aminosalicylat; Th: protionamide; Z: pyrazinamide).

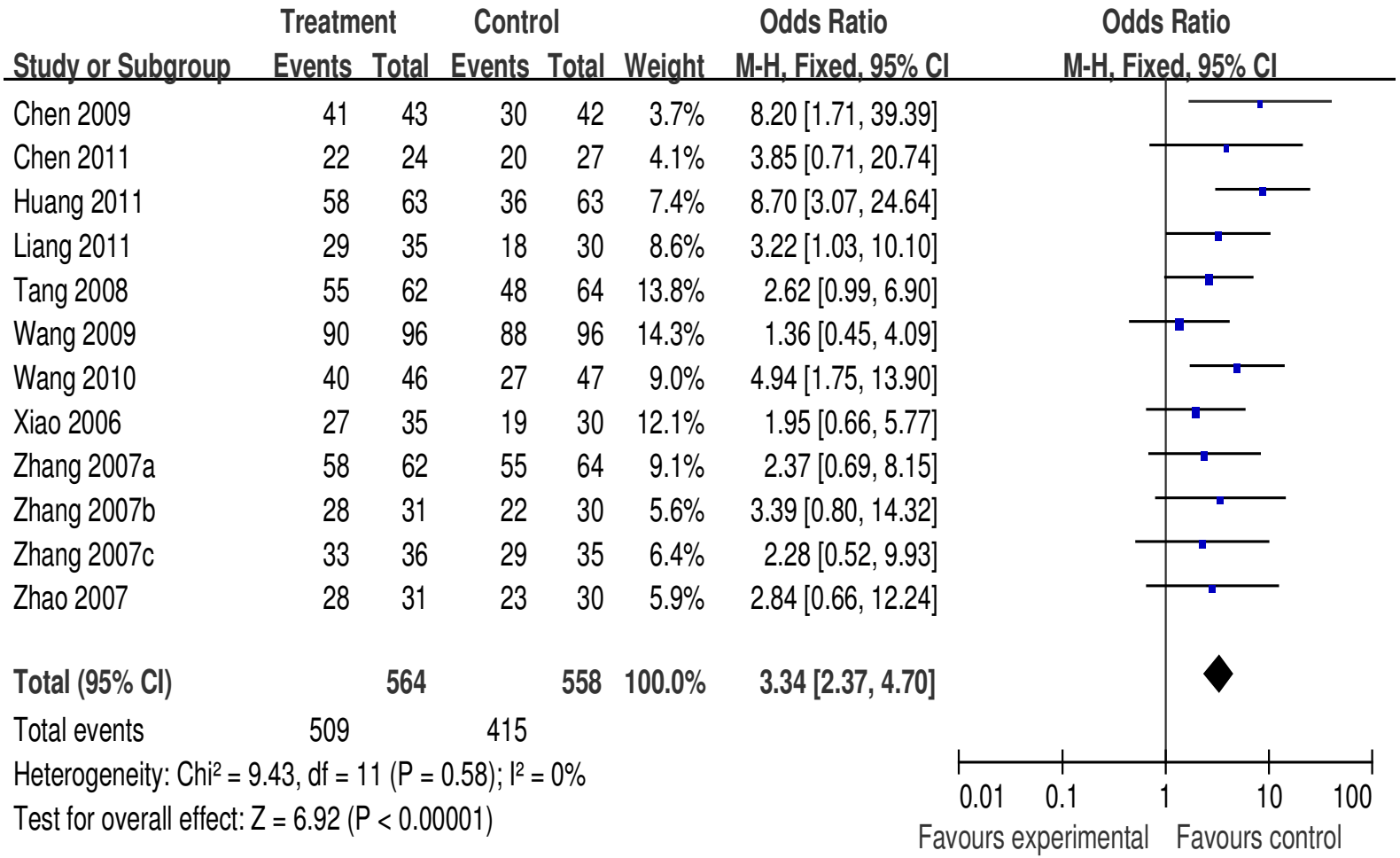

Figure 2. Sputum negative conversion between the treatment and control groups.

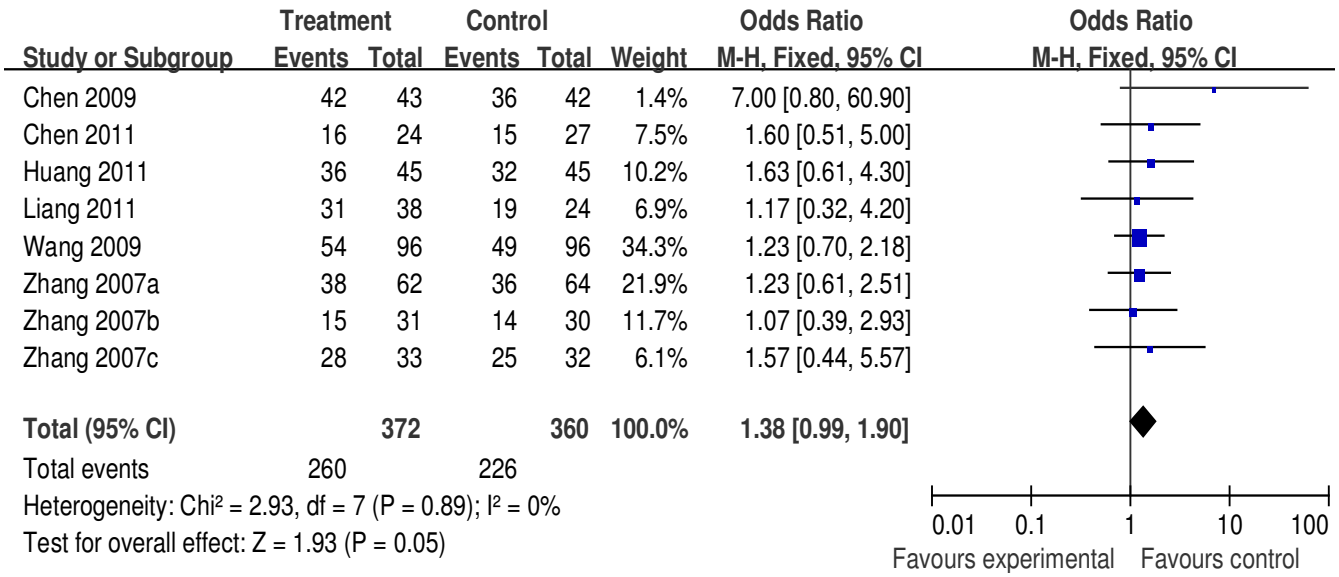

Figure 3. Change of tuberculosis cavity between the treatment and control groups.

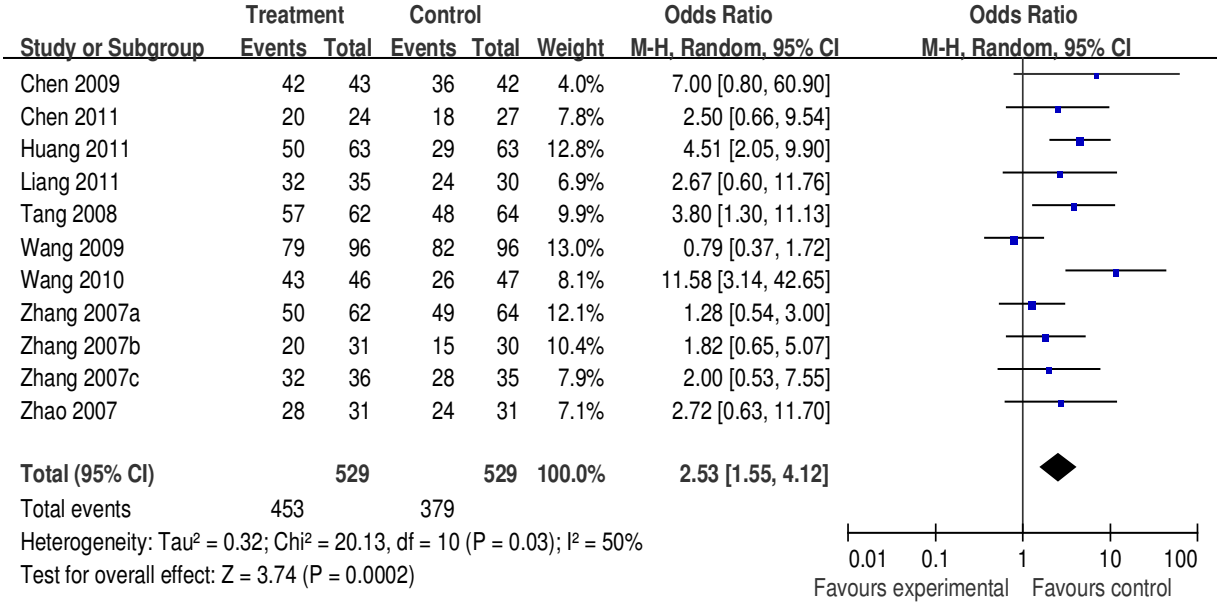

Figure 4. Focus absorption between the treatment and control groups.

Moxifloxacin and control group in treating Chinese patients with MDR-TB (Figure 3).

Meta-analysis of focus absorption

Moxifloxacin and control group were recorded in all the 11 trials finally included. Active antituberculosis agents involved in this analysis were levofloxacin and sparfloxacin

The results of meta-analysis (OR = 2.53, 95% CI: 1.55 to 4.12) confessed that moxifloxacin is more effective than control group in focus absorption in treating Chinese patients with MDR-TB (Figure 4).

Meta-analysis of safety

Adverse reaction rates of both moxifloxacin and control

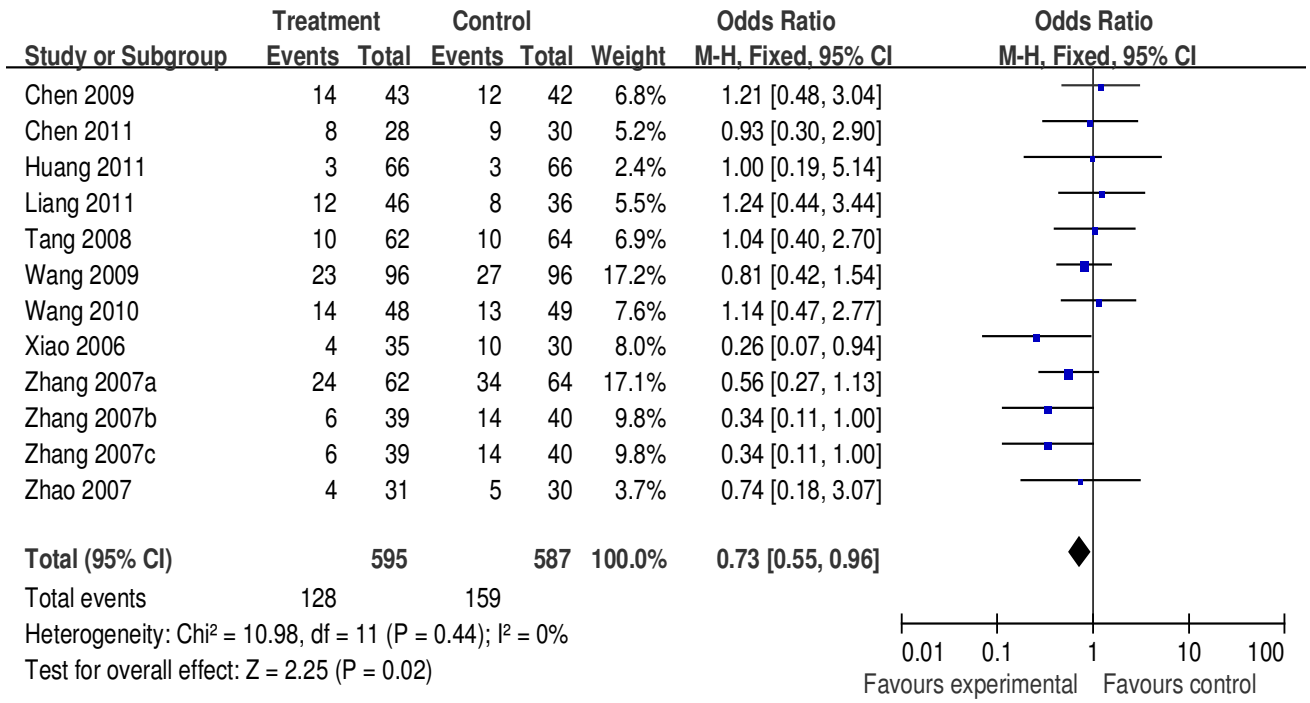

Figure 5. Adverse effect between the treatment and control groups.

group were recorded in all the 12 trials finally included. Main adverse reactions of moxifloxacin group were gastrointestinal symptoms and liver injuries. The results of meta-analysis (OR = 0.73 95% CI: 0.55 to 0.96) confessed that moxifloxacin is safer than control group in treating Chinese patients with MDR-TB (Figure 5).

Publication bias

An analysis of publication bias was conducted. The funnel plots to assess publication bias are shown in Figure 6. The shape of the funnel plots show some unasymmetries in all studies included in the meta-analysis. There exist some publication biases since the funnel plots were unsymmetrical based on a visual analysis (Figure 6). However, the publication biases might be relevant to some methodological insufficiencies: (1) Randomization method may not be rigorous because the specific program of randomization was inferred in only one literature. (2) Selection bias may exist for allocation concealment was not described in all of these articles included. (3) Selection bias, measuring bias and implementation bias may exist because 3 studies did not describe whether blind method was used or not.

DISCUSSION

A total of 12 literatures were finally included in this systemic review. All these articles including a sample size of 948 totally were RCTs. Jadad score in 9 out of the 12 articles were more than three points. All the trials included in this meta-analysis mentioned the term ‘random’, but the detail method was illuminated in 1 article only. Obviously, the included trials were lack of well-designed randomizations. A well-designed randomized controlled trial requires a thorough understanding of randomization so that better results could be achieved. Randomization includes three important steps, namely: sequence generation, allocation concealment and randomization implementation. Sequence generation is a method used to generate the random allocation sequence including details of any restriction. Allocation concealment is to implement the random allocation sequence. Randomization implementtation is to generate the allocation sequence. Well-men designed randomized controlled trials are required to evaluate moxifloxacin treatment versus routine treatment in Chinese population. It was suggested that we should be careful for randomization. Moxifloxacin, a novel fluoroquinolone that has potent *in-vitro* activity against MDR-TB. Compared with other fluoroquinolones, moxifloxacin has the characteristics of strong bactericidal activity that was additive to isoniazi.

The results of this systemic review showed that moxifloxacin were more effective than control group in sputum negative conversion and focus absorption in treating Chinese patients with MDR-TB. Thus, we can conclude that moxifloxacin has stronger effect compared with other active antituberculosisosis agents. The adverse

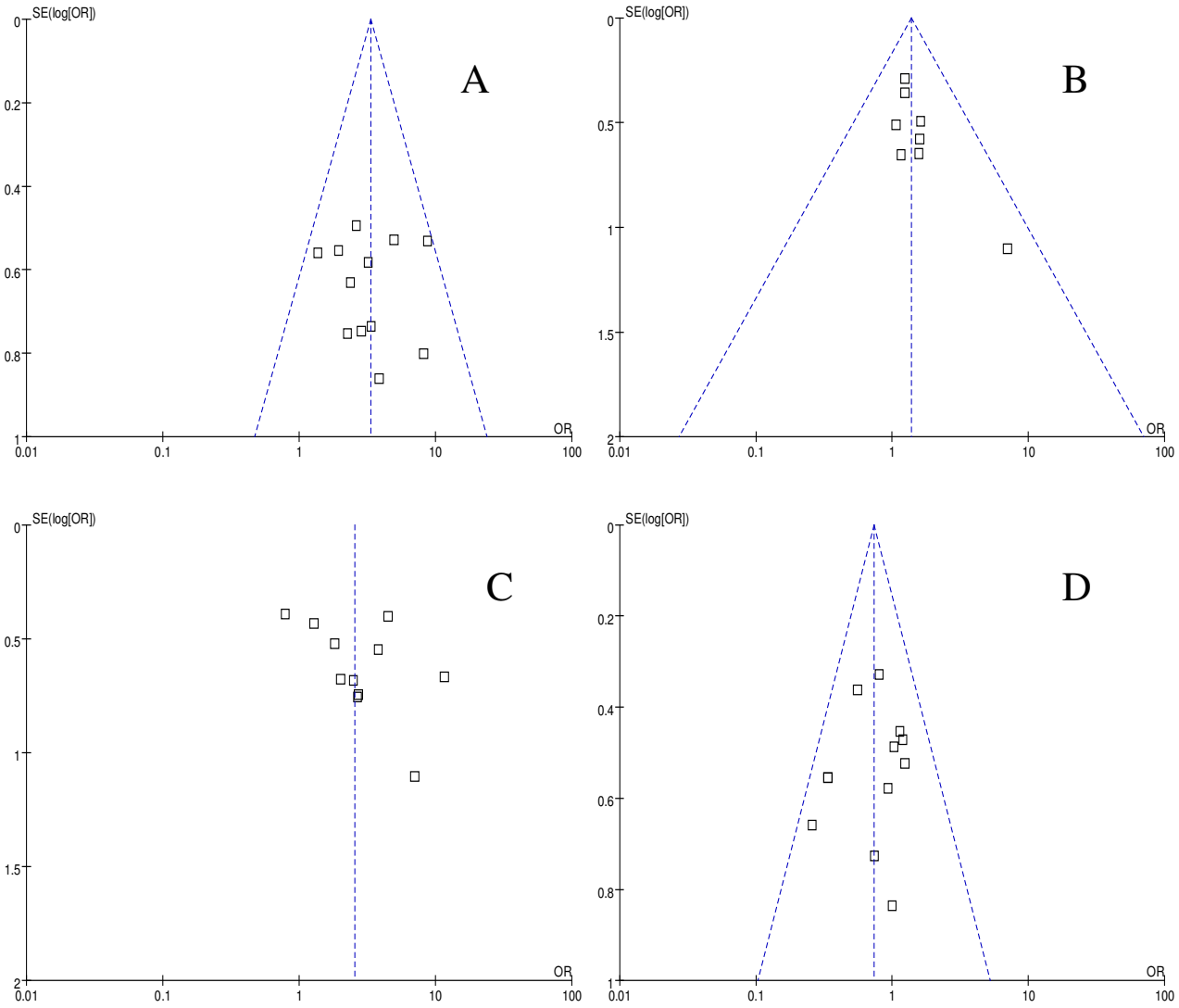

Figure 6. Funnel plot of sputum negative conversion tuberculosis cavity changes focus absorption and adverse effect.

reactions including gastrointestinal symptoms and liver injury mainly of moxifloxacin in treating MDR-TB referred in this study were less likely to happen. The results of this systemic review showed that moxifloxacin has less ADRs than control group in treating Chinese patients with MDR-TB. Therefore, we could conclude that moxifloxacin was safer compared with other active antituberculosisosis agents.

Conclusion

In summary, our systemic review initially demonstrated the therapeutic effects of moxifloxacin in Chinese patients with MDR-TB such as accelerating sputum negative conversion and improving focus absorption. However, all the clinical trials involved were of small samples without blind methods, their results may remain some uncertainties We urgently hope the high-quality, double-blinded, multi-centered RCTs will be carried out in future to further confirm its efficacy and safety.

ACKNOWLEDGEMENT

We appreciate Dr Xinwei Ren who rechecked the language of the paper.

REFERENCES

Barry CE, Boshoff HI, Dartois V, Dick T, Ehrt S, Flynn J, Schnappinger D, Wilkinson RJ, Young D (2009). The spectrum of latent tuberculosis: rethinking the biology and intervention strategies. Nat. Rev. Microbiol., 7: 845-855.

Burman WJ, Goldberg S, Johnson JL (2006). Moxifloxacin versus ethambutol in the first 2 months of treatment for pulmonary tuberculosis. Am. J. Respir. Crit. Care. Med., 174(3): 331-338.

Chen JL, Gu DL, Shi JW (2011). Observation of clinical curative effect on multi-drug resistant pulmonary tuberculosis in elderly patients. J. Clin. Pulm. Med., 16(7): 1046-1048 (In Chinese).
Chen Y, Zhang X, Zhang HM (2009). Comparison of moxifloxacin and levofloxacin in treating widely multi-drug resistant pulmonary tuberculosis. Clin. Med., 29(5): 49-50 (In Chinese).
Conde MB, Efron A, Loredo C (2009). Moxifloxacin versus ethambutol in the initial treatment of tuberculosis: a double-blind, randomized, controlled phase II trial. Lancet, 373(9670): 1183-1189.
Der Simonian R, Laird N (1986). Meta-analysis in clinical trials. Control Clin. Trials., 7: 177-188.
Dorman SE, Johnson JL, Goldberg S, Muzanye G, Padayatchi N, Bozeman L, Heilig CM, Bernardo J, Choudhri S, Grosset JH, Guy E, Guyadeen P, Leus MC, Maltas G, Menzies D, Nuermberger EL, Villarino M, Vernon A, Chaisson RE (2009). Substitution of moxifloxacin for isoniazid during intensive phase treatment of pulmonary tuberculosis. Am. J. Respir. Crit. Care. Med., 180(3): 273-280.
Huang YF, Dong JX, Li SL (2011). Efficacy of a combination of moxifloxacin in treatment of multi-drug resistant pulmonary tuberculosis. China Trop. Med., 11(4): 404-405 (In Chinese).
Gillespie SH, Billington O (1999). Activity of moxifloxacin against mycobacteria. J. Antimicrob. Chemother., 44: 393-395.
Higgins JP, Thompson SG, Deeks JJ. (2003). Measuring inconsistency in meta-analyses. BMJ, 327: 557-560.
Jadad AR, Moore RA, Carroll D Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ (1996). Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin. Trials., 17: 1-12.
Ji B, Lounis N, Maslo C, Truffot-Pernot C, Bonnafous P, Grosset J (1998). In *vitro* and in *vivo* activities of moxifloxacin and clinafloxacin against Mycobacterium tuberculosis. Antimicrob. Agents. Chemother. 42: 2066-2069.
Liang LL, Liu L, Ma Y (2011). Effects of anti-Tuberculosis containing with moxifloxacin or levofloxacin on multidrug resistant pulmonary tuberculosis. Chin. Gener. Pract., 14(5): 1451-1454 (In Chinese).
Lounis N, Bentoucha A, Truffot-Pernot C (2001). Effectiveness of once-weekly rifapentine and moxifloxacin regimens against Mycobacterium tuberculosis in mice. Antimicrob. Agents Chemother., 45: 3482-3486.
Mantel J, Haenszel W (1959). Statistical aspects of the analysis of data from retrospective studies of disease. J. Nat. Cancer Inst., 22: 719-748.
Moher D, Cook D, Eastwood S (1999). Improving the quality of reports of meta-analyses of randomised controlled trials: the QUORUM statement. Lancet, 354: 1896-1900.
Miyazaki E, Miyazaki M, Chen JM, Chaisson RE, Bishai WR (1999). Moxifloxacin (BAY12-8039), a new 8-methoxyquinolone, is active in a mouse model of tuberculosis. Antimicrob. Agents Chemother., 43: 85-89.
Neyrolles, Herna´ndez-Pando OR, Pietri-Rouxel F, Forne`s P, Tailleux L, Barrios Paya´n JA, Pivert E, Bordat Y, Aguilar D, Pre´vost MC, Petit C and Gicquel B (2006). Is adipose tissue a place for mycobacterium tuberculosis persistence?. PLoSOne, 1: e43.
Sackett DL, Clarke M, Oxman AD (2002). Cochrane Reviewers, Handbook 4.2, In Renew Manager. Versions 4.2.Oxford, England: The Cochrane Collaboration, pp. 13-36.
Tang J (2008). Observation of therapeutic effect of moxifloxacin on pulmonary tuberculosis. Chin. Med. Hera., 5(16): 72-73. (In Chinese).
Wang JF, Gao CR (2010). Treatment effect of regimen which contains the moxifloxacin on multi-drug resistant pulmonary tuberculosis. Chin. J. Clin. Pharm., 19(1): 33-35 (In Chinese).
Wang XX, Wang ZL (2009). The therapeutic effect of moxifloxacin in the retreatment of pulmonary tuberculosis. Chin. Mod. Med. 16(8): 58-60 (In Chinese).
Wayne LG, Hayes LG (1996). An in vitro model for sequential study of shiftdown of Mycobacterium tuberculosis through two stages of nonreplicating persistence. Infect. Immun., 64: 2062-2069.
WHO (2006). Global tuberculosis control: surveillance, planning, financing. Switzerland, Geneva, WHO.
WHO (2008). Global tuberculosis control 2008-surveillance, planning, financing. Geneva: World Health Organization, WHO/HTM/TB/2008.393.
Xiao P, Ma ZM, Fu HM, Deng ZX (2006). The role of moxiflocaxin in treatment of MDR pulmonary tuberculosis: a prospective randomized preliminary study. Chin. J. Pract. Med., 26(6)supp: 133-135 (In Chinese).
Young DB, Perkins MD, Duncan K, Barry CE (2006). Confronting the scientific obstacles to global control of tuberculosis. J. Clin. Invest., 18: 1255-1265.
Zhang XC, Li XX, Wang SP (2007a). The therapeutic effect of moxi floxacin and levofloxacin on multiple drug resistant pulmonary tuberculosis. Hebei Med. J., 29(6): 557-558. (In Chinese).
Zhang XC, Zhang XD, Wang SP (2007b).Therapeutic effects of moxifloxacin and sparfloxicin on multiple drug resistant pulmonary tuberculosis. Hebei Med. J., 29(8): 796-798 (In Chinese).
Zhao G (2007). The clinical study of moxifloxacin on multiple drug resistant pulmonary tuberculosis. Clin. Med., 27(11): 45-46. (In Chinese)