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Meta-analysis on Effectiveness and Safety of Moxifloxacin in Treatment of Multidrug Resistant Tuberculosis in Adults

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Abstract

Background: Moxifloxacin, a fourth generation fluoroquinolone, which has good antibacterial activity against both Gram-positive cocci and Gram-negative bacteria. To date, there are no meta-analysis to evaluate the efficacy and safety of moxifloxacin for multidrug resistant tuberculosis (MDR-TB) treatment. This meta-analysis to explore the efficacy and safety of the moxifloxacin in treatment of MDR-TB in adults.

Methods: Databases of PubMed, Embase, Embase, Ovid, and Google Scholar databases were investigated for eligible literatures from their establishments to August, 2019. Included studies were selected according to precise eligibility criteria: MDR-TB confirmed by the clinical diagnostic criteria (at least 2 or more first-line drugs resistant to isoniazid and rifampicin). Study design was limited to retrospective studies, randomized controlled trials, or prospective cohort studies; the control group was treated with other drugs or no moxifloxacin. Statistical analysis was performed by RevMan 5.3 software.

Results: Eight studies with a total of 1447 patients were finally eligible for the final systematic review and meta-analysis. Moxifloxacin regimen was related to a significantly elevated treatment success rate compared with levofloxacin or conventional therapy regimen (OR=1.94; 95% CI=1.163.25, *P*=.01). No significant difference of sputum culture conversion rate (OR=1.15; 95% CI=0.821.60; *P*=0.43) was found between 2 groups. In addition, there was no significant difference in the increased risks of gastrointestinal trouble (OR=1.28; 95% CI=0.981.68; *P*=.05), hepatotoxicity (OR=0.91; 95% CI=0.641.30; *P*=.6), dermatologic abnormalities (OR=1.11; 95% CI=0.741.67; *P*=.62), and vision change (OR=1.47; 95% CI=0.742.89; *P*=.27) between the moxifloxacin-containing regimens and control group.

Conclusions: This meta-analysis revealed that the addition of moxifloxacin to the recommended regimen significantly improved the rate of treatment success in the treatment of MDR-TB, with no additional adverse moxifloxacin events.

Abbreviations: INH = isoniazid, MDR-TB = multidrug resistant tuberculosis, OR = odds ratio, RFP = rifampin, WHO = World Health Organization.

Keywords: adverse effects, moxifloxacin, multidrug resistant tuberculosis, treatment success rate

1. Introduction

Tuberculosis is an airborne infectious disease caused by *Mycobacterium* tuberculosis, which is one of the leading causes of infectious deaths attributed to a single micro-organism worldwide.[1,2] The World Health Organization (WHO) estimates that approximately 10.0 million people developed tuberculosis, and 1.6 million people of tuberculosis in 2017.[1,2] Therefore, tuberculosis remains a major global health threat and more efforts should be made to improve its treatment. At present, antituberculosis treatment depends on the combinations of bactericidal and sterilizing drugs to prevent the development of drug resistance.

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Drug-resistant *Mycobacterium* tuberculosis strains were first recognized soon after the introduction of streptomycin in 1944 and subsequently, drug resistance to other TB medications was proved.[3] The emergence of drug-resistant strains of *M tuberculosis* has complicated tuberculosis control and undermined the objectives of the WHOs End TB Strategy (95% reduction in deaths due to TB and a 90% reduction in TB incidence rate by the year 2035 compared to 2015). Multidrug-resistant tuberculosis (MDR-TB) is defined as *Mycobacterium* tuberculosis strains with in vitro resistance to the 2 most effective antituberculosis drugs, isoniazid (INH) and rifampin (RFP).[4] Treatment of MDR-TB remains difficult because of the high costs,[5,6] long-term treatment, and frequent adverse events.[7] In the case of these disorders, the success rate of treatment of MDR-TB is less than 70%.[4,8]

Fluoroquinolones were found to have good inhibitory effect on *Mycobacterium* tuberculosis,[9,10] which inhibit the superhelix of DNA and destroy the DNA replication of *Mycobacterium* tuberculosis through interfering with DNA gyrase.[11,12] Nowadays, many guidelines have recommend that later-generation fluoroquinolones should be utilized for MDR-TB patients, including moxifloxacin, levofloxacin, and gatifloxacin. Ciprofloxacin is no longer recommended because of its low efficacy compared with other fluoroquinolones.[1315]

Moxifloxacin has good pharmacokinetic profile (serum half-life of 1012h), few problematic drugdrug interactions, no need to adjust the dose of kidney and liver insufficiency, and a satisfactory safety profile in short-term use of up to 3 weeks in the treatment of community-acquired pneumonia, sinusitis, and intra-abdominal and complicated skin and soft tissue infections.[1618]

To date, there are no meta-analysis to evaluate the efficacy and safety of moxifloxacin for MDR-TB treatment. Hence, we systematically reviewed all articles that compared moxifloxacin to levofloxacin or other conventional therapy, and performed this meta-analysis of the available data to evaluate the effect of MDR-TB treatment with moxifloxacin.

2. Method

The manuscript has been prepared according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines for protocols.[19] Ethical approval was unnecessary in this study, because it was a meta-analysis of existing articles, and no individual patient data were handled.

2.1. Search strategy

A systematic search was conducted on Pubmed, Embase, Ovid, Google Scholar databases. The search terms were as follows: Moxifloxacin,'' tuberculosis,'' or pulmonary tuberculosis'' and their synonyms or similar words (from their inception to August, 2019). Searches were limited to English and were first screened by 2 independent reviewers. Furthermore, reference lists of all included researches and related comments were searched manually to find other possibly eligible articles.

2.2. Inclusion and exclusion criteria

For inclusion, articles were chosen on the basis of the following standards: MDR-TB confirmed by the clinical diagnostic criteria (at least 2 or more first-line drugs resistant to isoniazid and rifampicin). Study design was limited to retrospective studies, randomized controlled trials, or prospective cohort studies; the control group was treated with other drugs or no moxifloxacin.

Studies were excluded if: allergic to moxacin; combined with other diseases; they were performed in pediatric patients ($\leq$18 years old); pregnant and lactating women; abstracts, letters, case-control studies.

2.3. Assessment of methodological quality of included articles

All articles satisfied the inclusion criteria were estimated to evaluate the danger of bias for each outcome. The evaluation was conducted independently by 2 comments using the Cochrane Collaborations risk of bias tool as depictive in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions, version 5.1.0. 2011, http://handbook.cochrane.org/). If there is any disagreement in the evaluation study, we will discuss it. The results of the assessment measure the following areas: random sequence generation, allocation concealment, blinding, incomplete outcome data addressed, free of selective outcome reporting, and other possible sources of bias. The consequences of the meta-analysis were comprehended as the results of the study on the risk of bias.

2.4. Data extraction

Data collection and analysis were carried out in accordance with the standard Cochrane protocol.[20] Two authors independently reviewed and extracted the following data from every study: study design, study year, participants number, age, treatment success rates (The cured and completed treatment categories were defined as treatment success), sputum culture conversion rates, and adverse effects.

We attempted to find and exclude duplicate data from different studies. For multiple studies of repeated or overlapping data (by population, time, location, and results), we follow the PRISMA reporting guidelines when submitting manuscripts.

We attempted to identify and exclude duplicate data from research studies presented in separate publications. For cases in which we identified multiple studies with duplicated or overlapping data (by population, time, place, and outcome). We followed the PRISMA reporting guidelines in the presentation of our manuscript.

2.5. Statistical analysis

Meta-analysis was performed with the Cochrane Collaborations Review Manager Software (RevMan, version 5.1.). Odds ratio (OR) with 95% CI was performed to evaluate the treatment success rate, sputum negative conversion rate, and adverse effect rate. Heterogeneity was evaluated by I square test. Random effects model was used if heterogeneity was significant (I^2>50%). When heterogeneity was not detected or the heterogeneity was relatively small, fixed effects model was performed.

Funnel plots were used to evaluate the potential of publication bias. These charts showed the intervention effect of each research on the respective standard error. Symmetrical plots reveal no bias and any asymmetry of the plot would imply publication prejudice. Results were considered statistically significant at $P<.05$.

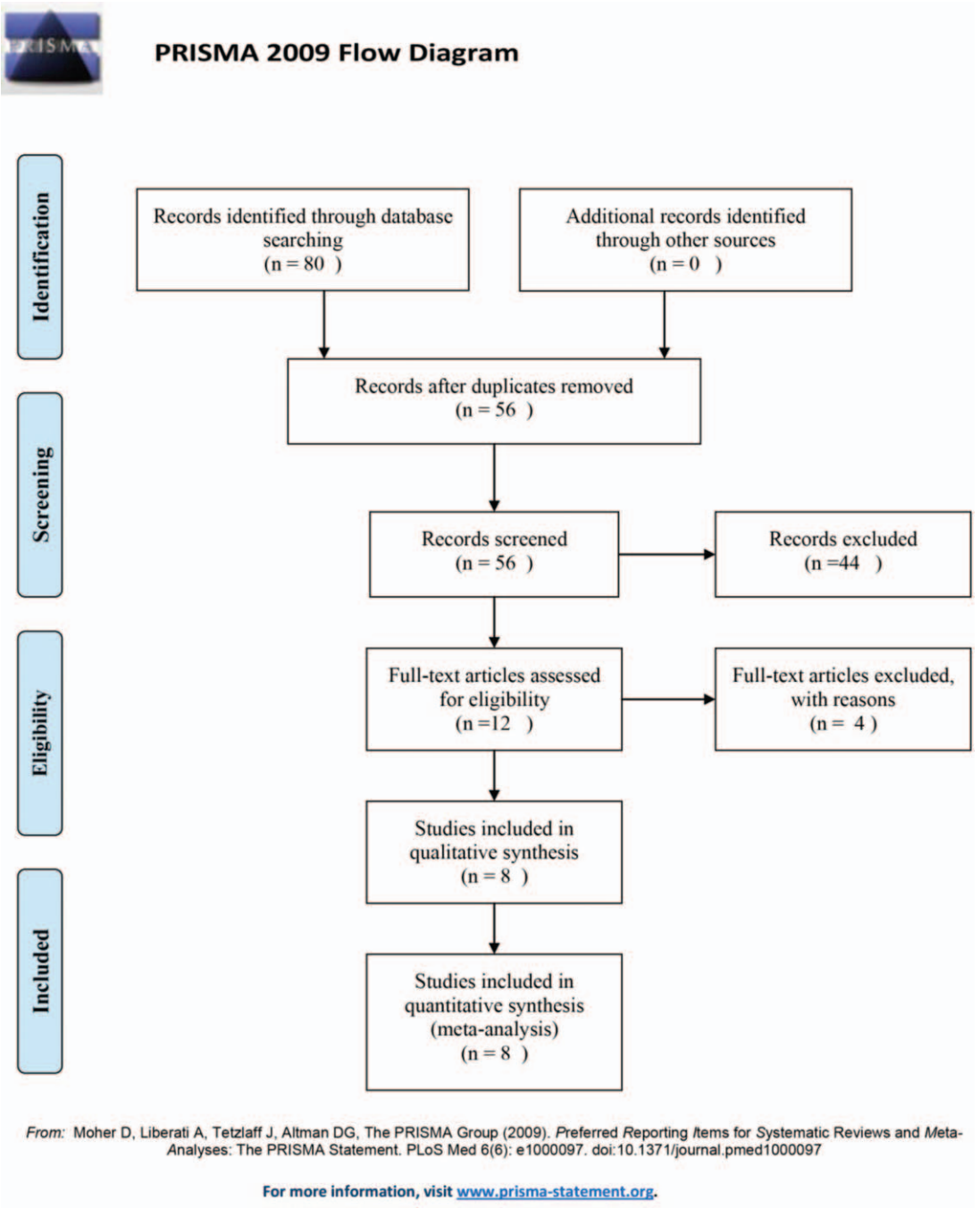

Figure 1. Flow chart showing results of the literature search and study inclusion.

3. Results

3.1. Literature selection and bias

In total 80 potentially related researches and abstracts were identified (Fig. 1). After removal of repeats (n=24) and filtration of abstracts (n=56), 12 full-text researches were evaluated for eligibility. Four studies were excluded for the following: nondrug resistant tuberculosis (n=2), drug-sensitive tuberculosis (n=2). Eight[2128] publications were ultimately eligible for final meta-analysis. No more citations were found from the reference review.

The detail of the risk-of-bias evaluation of included researches was summarized in Figure 2. All researches were evaluated as low risk according to appropriate randomization sequence. However, much relative information in the studies was not available, such as allocation concealment and blinding of participants and personnel, blinding of outcome assessment. Nevertheless, the overall methodological quality was generally fair, because random sequence generation and other possible sources of bias were evaluated.

Figure 2. Risk of bias assessment in randomized trials and single-arm studies. Green indicates low risk of bias, yellow indicates medium risk of bias, and red indicates high risk of bias.

3.2. Intervention characteristics

The included articles were performed between 2002 and 2016, involving 1447 patients of whom 680 underwent moxifloxacin containing regimens and 767 underwent levofloxacin or conventional therapy regimen. Among them, 5 reported treatment success rate; 2 reported sputum culture conversion rate and 5 reported adverse effect. The detail features of the meta-analysis studies are presented in Table 1.

3.3. Treatment success rate

The cured and completed treatment categories were defined as the success of treatment, and 8 studies reported the short-term mortality. The random-effects model was used to calculate the overall OR and 95% CI due to the detection of significant heterogeneity (I^2=50%). The overall OR was 1.94 (95% CI

Table 1

Main characteristics of the studies included in the meta-analysis.

Included studies	Study performed	Population	Studies design	Treatment	Sample size	Age, years	Sex (male/female)	Drug dose (cases)
Burman 2006	20032005	Africa and North America	Randomized trial	INH/RE/PZA/MOX vs. INH/RE/PZA/EMB	139:138	31 (24, 40)*	186:91	400 mg
Chien 2016	20062013	Taiwan	Retrospective nonrandomized study	MOX vs. CM/KAN	44:37	NA	38/6:29/6	400 mg
Dorman 2009	20062007	North America, Brazil, -South Africa, Spain, and Uganda	Double-blind, randomized controlled trial	RE/PZA/EMB/MOX vs. INH/RE/PZA/EMB	164:164	30 (25, 38)*	/	400 mg
Jiang 2013	20052010	China	Retrospective study	AMK/AMX/CLV/CM, /CLR/CFZ/INH /EMB/LZD/PAS/PA/PTO/PZA/RFB/RE/MOX vs. AMK/AMX/CLV/CM, /CLR/CFZ/INH /EMB/LZD/PAS/PA/PTO/PZA/RFB/RE/LVO	72:86	43.8±10.3:45.1±14.6	37/35:32/54	400 mg
Kang 2016	20102012	Korea	Prospective, multicenter, randomized, open-label trial	AMK/CYC/EMB/KAN/LZD/RFB/PAS/PZA/PTO/STE/MOX vs. AMK/CYC/EMB/KAN/LZD/RFB/PAS/PZA/PTO/STE/LVO	74:77	42(31,56):44 (2858)*	48/26:54/23	400 mg
Koh 2013	20102012	Korea	Prospective, multicenter, randomized, open-label trial	AMK/CYC/EMB/KAN/LZD/RFB/PAS/PZA/PTO/STE/MOX vs. AMK/CYC/EMB/KAN/LZD/RFB/PAS/PZA/PTO/STE/LVO	74:77	42 (31,56):44 (2858)*	50/27:54/24	400 mg
Lee 2011	20022005	Korea	Retrospective case-control study	AMI/AMX/CLV/CLR/CYC/EMB/PAS/PTO/PZA/RFB/TRI/MOX vs. AMI/AMX/CLV/CLR/CYC/EMB/PAS/PTO/PZA/RFB/TRI/LVO	48:123	42 (2853):42 (2851)*	27/21:48/75	400 mg
Yang 2017	20142016	China	Retrospective controlled study	AMK/DIP/EMB/RE/MOX vs. AMK/DIP/EMB/RE	65:65	50.2±4.7:51.1±3.9	37/28:42/23	400 mg

AMI=aminoglycosides, AMK=amikacin, AMX/CLV=amoxicillin/clavulanic acid, CFZ=clofazimine, CLR=clarithromycin, CM=capreomycin, CYC=cycloserine, DIP=dipasic, EMB=ethambutol, INH=isoniazid, KAN=Kanamycin, LVO=levofloxacin, LZD=linezolid, MOX=moxifloxacin, PA=pasiniazide, PAS=para-aminosalicylic acid, PTO=protionamide, PZA=pyrazinamide, RE=rifapentine, RFB=rifabutin, STE=streptomycin, SUL=sulfamethoxazole, TRI=trimethoprim.
* Median (IQR).

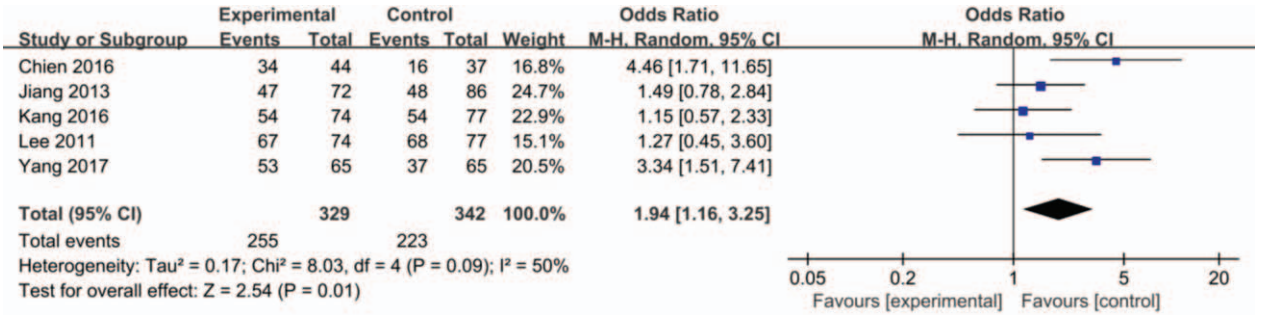

Figure 3. Forest plot of studies assessing treatment success rate after treatment for MDR-TB.

1.163.25, *P*=.01; Fig. 3), suggesting that when combining moxifloxacin containing regimens, the rate of treatment success was significantly enhanced than applying the levofloxacin or conventional therapy regimen.

3.4. Sputum culture conversion

The analysis of sputum culture conversion was accomplished at the endpoint of 2 or 3 months of treatment. Two studies were included. No significant difference of sputum culture conversion rate (OR=1.15; 95% CI=0.821.60; *P*=.43; Fig. 4) was found between the moxifloxacin-containing regimens and control group, with no heterogeneity among the studies (I^2=0%; heterogeneity *P*=.54).

3.5. Safety

There was no significant difference in the increased risks of gastrointestinal trouble (OR=1.28; 95% CI=0.981.68; *P*=.05; Fig. 5), hepatotoxicity (OR=0.91; 95% CI=0.641.30; *P*=.6), dermatologic abnormalities (OR=1.11; 95% CI=0.741.67; *P*=.62), and vision change (OR=1.47; 95% CI=0.742.89; *P*=.27) between the moxifloxacin regimen and levofloxacin or conventional therapy group.

Begg funnel diagram was used to evaluate the publication bias of articles. The shape of the funnel plot showed no evidence of significant asymmetry. The finding indicated that there was no publication biases may effect the consequences of meta-analysis (Fig. 6).

4. Discussion

Moxifloxacin, the fourth-generation fluoroquinolone, has good antibacterial activity against both gram-positive cocci and gram-negative bacteria, which has a broad spectrum of antibacterial activity, especially against respiratory pathogens.[29] The bactericidal activity of moxifloxacin is mediated by inhibiting DNA gyrase (topoisomer ase II) and topoisomerase IV, which are essential enzymes for bacterial DNA replication, transcription, repair, and recombination.[11] DNA gyrase is encoded by *gyrA* and *gyrB*, and topoisomerase IV is encoded by *parC* and *parE*.[12] Moxifloacin binds strongly to both DNA gyrase and poisomerase IV, thus reducing the occurrence of bacterial drug resistance.[30] Nowadays, more and more researches have been focused on the application of moxifloxacin in the treatment of TB. Many meta-analysis and review articles have evaluated the efficacy and safety of moxifloxacin in the treatment of nondrug resistant or the initial therapy of tuberculosis. Ruan et al[31] have summarized the clinical trials of moxifloxacin- or gatifloxacin-containing regimens and carried out a meta-analysis to assess the efficacy and safety of moxifloxacin or gatifloxacin in the treatment of drug-susceptible TB. The results showed that moxifloxacin or gatifloxacin might not be able to shorten treatment duration in the initial therapy for tuberculosis, despite their equivalent or even slightly better efficacy in early phase of treatment compared with the standard regimen. Furthermore, it is safe to include moxifloxacin or gatifloxacin in initial tuberculosis treatment. Xu et al[32] comprehensively investigated the efficacy and safety of moxifloxacin plus recommended regimens compared to recommended regimens alone for the treatment of TB. The meta-analysis suggests that the introduction of moxifloxacin into the recommended regimen for the treatment of nondrug resistant tuberculosis improves the clinical outcome by elevating the culture conversion rate and reducing the recurrence rate.

Current guidelines recommend that later-generation fluoroquinolones should be used for patients with MDR-TB.[1,15] Many clinical studies have explored the efficacy of moxifloxacin in the

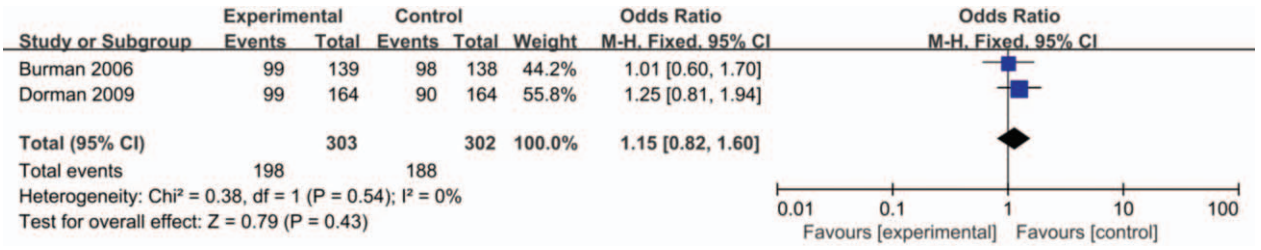

Figure 4. Forest plot of studies evaluating sputum culture conversion after 2 mo of treatment for MDR-TB.

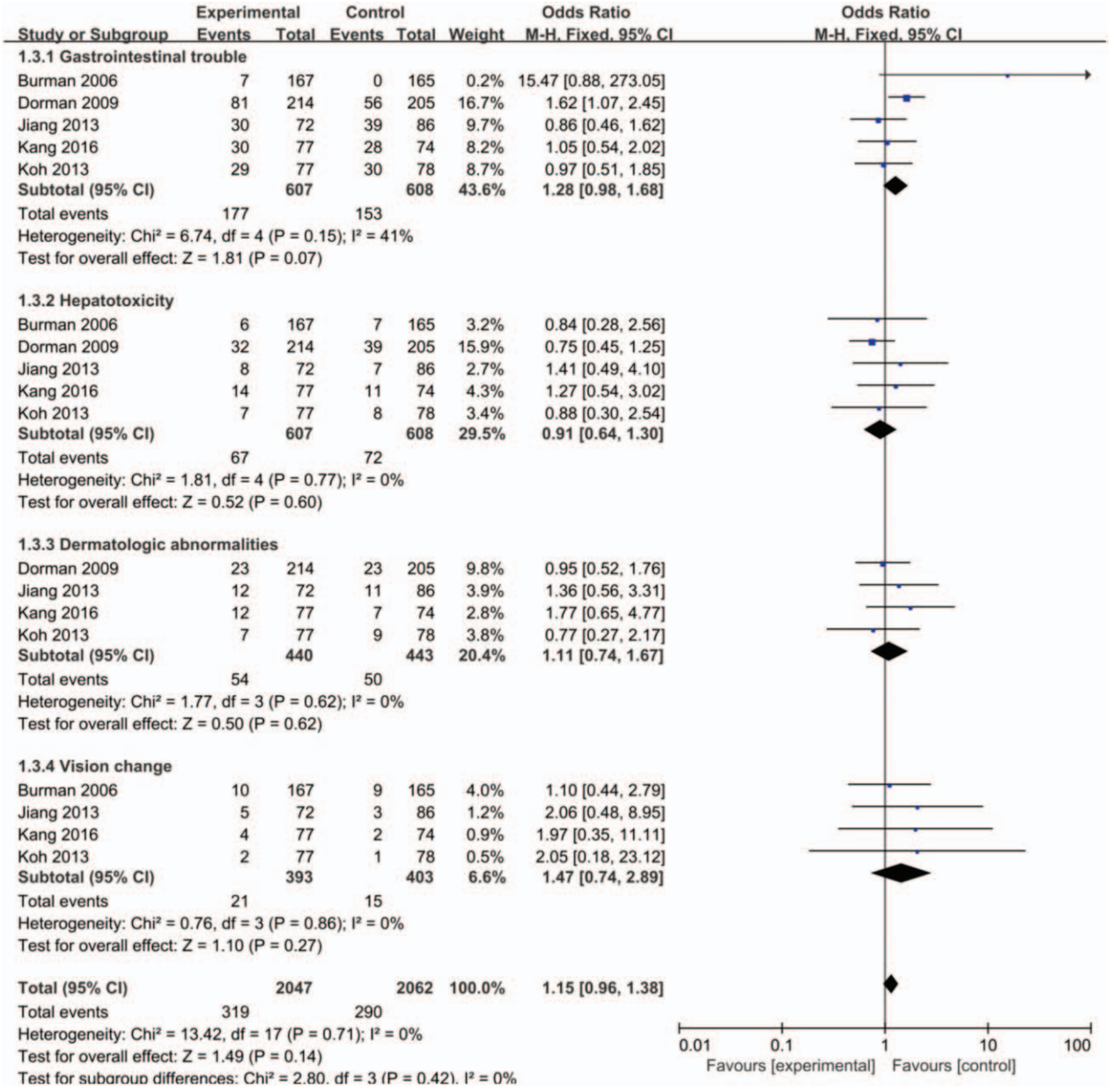

Figure 5. Forest plot of studies investigating adverse events during treatment.

treatment of multidrug resistant pulmonary tuberculosis. Chien et al[22] proved that a significant proportion of ofloxacin-resistant MDR-TB isolates were susceptible or had low-level resistance to moxifloxacin, indicating that patients with ofloxacin-resistant MDR-TB benefit from treatment with moxifloxacin. Jang et al[24] have demonstrated that, compared with levofloxacin, moxifloxacin did not show superior efficacy when incorporated into multidrug regimens used for the treatment of MDR-TB. To date, there is no meta-analysis to evaluate the efficacy and safety of moxifloxacin for MDR-TB treatment.

In this meta-analysis, 8 studies with a total of 1447 patients were finally eligible for the final systematic review and meta-analysis. Moxifloxacin regimen was related to a significantly elevated treatment success rate compared with levofloxacin or conventional therapy regimen (OR=1.94; 95% CI=1.163.25, *P*=.01). No significant difference of sputum culture conversion rates (OR=1.15; 95% CI=0.821.60; *P*=0.43) and AE were found between 2 groups.

Among patients with pulmonary tuberculosis, conversion of serial sputum cultures from positive to negative is a surrogate indicator of treatment response. Culture conversion after 8 weeks of treatment is a widely used indicator of treatment effectiveness tuberculosis.[33,34] The results show that the conversion rate of sputum culture in the 2 groups is similar, which may be due to the insufficient number of participants. It is well known that the recruitment and retention of participants in the MDR-TB trial is challenging.[35]

Adverse events did not differ between the 2 groups. The most common adverse events were related to the gastrointestinal system, hepatotoxicity, dermatologic abnormalities, and vision

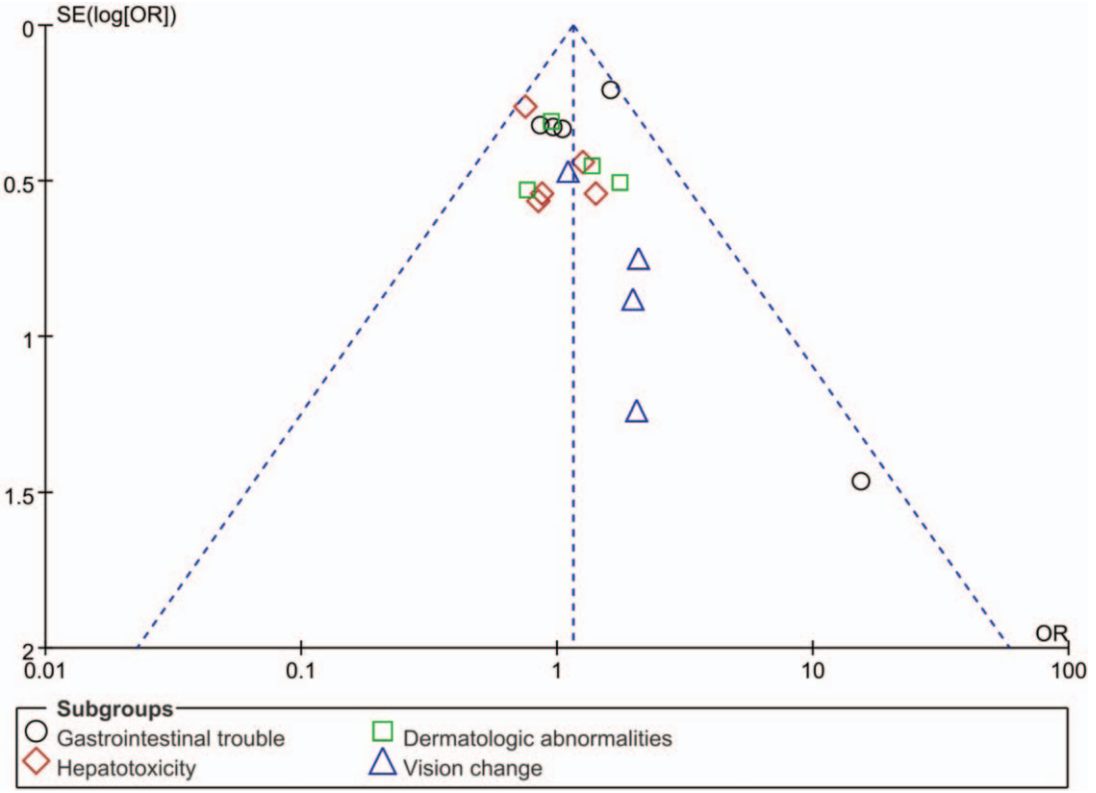

Figure 6. Funnel plot detailing publication bias of the literatures.

change. All adverse events of moxifloxacin have an acceptable safety profile that allows it to be used in studies of treatment of MDR-TB tuberculosis.

However, some potential limitations needed to be pointed out: our meta-analysis was restricted to publications in English language, those published in non-English-language journals or those reports did not included, which probably reduce the precision of combined estimates of treatment effects. The results of this meta-analysis were based on studies with relatively small sample sizes and, therefore, should be interpreted cautiously. More well-designed and large-scale randomized controlled clinical trials should be conducted for further analysis.

Pooled analysis demonstrated that the addition of moxifloxacin to the recommended regimen significantly increases the rate of treatment success in the treatment of MDR-TB, with no additional adverse events. Further research could increase confidence in the effect estimates and clarify the influence of potential confounders or effect modifiers.

Acknowledgments

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Author contributions

YG conceived and designed this review article. YL carried out the meta-analysis with the Cochrane Collaborations Review Manager Software (RevMan, version 5.1.). YG critically revised the article for important intellectual content. All authors have read and approved the final manuscript.

References

[1] World Health Organization. Global tuberculosis report, 2018. WHO/CDS/TB/2018.20. Geneva, Switzerland: WHO, 2018.
[2] Lange C, Aarnoutse RE, Alffenaar JWC, et al. Management of patients with multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2019; 23:64562.
[3] Wade MM, Zhang Y. Mechanisms of drug resistance in Mycobacterium tuberculosis. Front Biosci 2004;9:97594.
[4] Johnston JC, Shahidi NC, Sadatsafavi M, et al. Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. PLoS One 2009;4:e6914.
[5] Kang YA, Choi YJ, Cho YJ, et al. Cost of treatment for multidrug-resistant tuberculosis in South Korea. Respirology 2006;11:7938.
[6] White VL, Moore-Gillon J. Resource implications of patients with multidrug resistant tuberculosis. Thorax 2000;55:9623.
[7] Nathanson E, Gupta R, Huamani P, et al. Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. Int J Tuberc Lung Dis 2004;8:13824.
[8] Orenstein EW, Basu S, Shah NS, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. Lancet Infect Dis 2009;9:15361.
[9] Shandil RK, Jayaram R, Kaur P, et al. Moxifloxacin, ofloxacin, sparfloxacin, and ciprofloxacin against Mycobacterium tuberculosis: evaluation of in vitro and pharmacodynamic indices that best predict in vivo efficacy. Antimicrob Agents Chemother 2007;51:57682.
[10] Poissy J, Aubry A, Fernandez C, et al. Should moxifloxacin be used for the treatment of extensively drug-resistant tuberculosis? An answer from a murine model. Antimicrob Agents Chemother 2010;54:476571.
[11] Aubry A, Pan XS, Fisher LM, et al. Mycobacterium tuberculosis DNA gyrase: interaction with quinolones and correlation with antimycobacterial drug activity. Antimicrob Agents Chemother 2004;48:12818.

[12] Moadebi S, Harder CK, Fitzgerald MJ, et al. Fluoroquinolones for the treatment of pulmonary tuberculosis. Drugs 2007;67:207799.
[13] Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis: 2011 Update. Geneva: World Health Organization; 2011.
[14] Lange C, Abubakar I, Alffenaar JW, et al. Management of patients with multidrug-resistant/extensively drug-resistant tuberculosis in Europe: a TBNET consensus statement. Eur Respir J 2014;44:2363.
[15] South African National Tuberculosis Management Guidelines. Pretoria: National Department of Health; 2014.
[16] Peloquin CA, Hadad DJ, Molino LP, et al. Population pharmacokinetics of levofloxacin, gatifloxacin, and moxifloxacin in adults with pulmonary tuberculosis. Antimicrob Agents Chemother 2008;52:8527.
[17] Johnson JL, Hadad DJ, Boom WH, et al. Early and extended early bactericidal activity of levofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. Int J Tuberc Lung Dis 2006;10:60512.
[18] Gavin JR3rd, Kubin R, Choudhri S, et al. Moxifloxacin and glucose homeostasis: a pooled-analysis of the evidence from clinical and postmarketing studies. Drug Saf 2004;27:67186.
[19] McInnes MDF, Moher D, Thombs BD, et al. Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: the PRISMA-DTA Statement. JAMA 2018;319: 38896.
[20] Furlan AD, Pennick V, Bombardier C, et al. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. Spine (Phila Pa 1976) 2009;34:192941.
[21] Burman WJ, Goldberg S, Johnson JL, et al. Moxifloxacin versus ethambutol in the first 2 months of treatment for pulmonary tuberculosis. Am J Respir Crit Care Med 2006;174:3318.
[22] Chien JY, Chien ST, Chiu WY, et al. Moxifloxacin improves treatment outcomes in patients with ofloxacin-resistant multidrug-resistant tuberculosis. Antimicrob Agents Chemother 2016;60:470816.
[23] Dorman SE, Johnson JL, Goldberg S, et al. Substitution of moxifloxacin for isoniazid during intensive phase treatment of pulmonary tuberculosis. Am J Respir Crit Care Med 2009;180:27380.
[24] Jiang RH, Xu HB, Li L. Comparative roles of moxifloxacin and levofloxacin in the treatment of pulmonary multidrug-resistant tuberculosis: a retrospective study. Int J Antimicrobial Agents 2013;42:3641.
[25] Kang YA, Shim TS, Koh WJ, et al. Choice between levofloxacin and moxifloxacin and multidrug-resistant tuberculosis treatment outcomes. Ann Am Thorac Soc 2016;13:36470.
[26] Koh WJ, Lee SH, Kang YA, et al. Comparison of levofloxacin versus moxifloxacin for multidrug-resistant tuberculosis. Am J Respir Crit Care Med 2013;188:85864.
[27] Lee J, Lee CH, Kim DK, et al. Retrospective comparison of levofloxacin and moxifloxacin on multidrug-resistant tuberculosis treatment outcomes. Korean J Intern Med 2011;26:1539.
[28] Yang H, Zhao Y, Ma Y, et al. Effect of moxifloxacin on oxidative stress, paraoxonase-1 (PON1) activity and efficacy of treatment in patients with multiple drug-resistant tuberculosis. Trop J Pharmac Res 2017; 16:251520.
[29] Simoens S. Evidence for moxifloxacin in community-acquired pneumonia: the impact of pharmaco-economic considerations on guidelines. Curr Med Res Opin 2009;25:244757.
[30] Keating GM, Scott LJ. Moxifloxacin: a review of its use in the management of bacterial infections. Drugs 2004;64:234777.
[31] Ruan Q, Liu Q, Sun F, et al. Moxifloxacin and gatifloxacin for initial therapy of tuberculosis: a meta-analysis of randomized clinical trials. Emerg Microbes Infect 2016;5:e12.
[32] Xu P, Chen H, Xu J, et al. Moxifloxacin is an effective and safe candidate agent for tuberculosis treatment: a meta-analysis. Int J Infect Dis 2017;60:3541.
[33] Doherty TM, Wallis RS, Zumla A. Biomarkers of disease activity, cure, and relapse in tuberculosis. Clin Chest Med 2009;30:78396.
[34] Wallis RS. Sustainable tuberculosis drug development. Clin Infect Dis 2013;56:10613.
[35] Padayatchi N, Mac Kenzie WR, Hirsch-Moverman Y, et al. Lessons from a randomised clinical trial for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2012;16:15827.