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Full Length Research Paper

Efficacy and safety profile of moxifloxacin in treatment of urogenital system infections: A meta-analysis of randomized controlled trials

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This meta-analysis was performed to evaluate the efficacy and safety profile of moxifloxacin in treatment of urogenital system infections. PubMed, EMBASE, Science Direct, ClinicalTrials.gov, Cochrane Central Register of Controlled Trials, CBM (Chinese Biomedical Literature Database), CNKI (Chinese National Knowledge Infrastructure), Wan Fang Data and VIP INFORMATION were searched from January 1999 to May 2011 to comprehensively collect randomized controlled trials (RCTs) that compared moxifloxacin with conventional antibiotics therapy in patients with urogenital system infections. Clinical cure rates, clinical effective rates, pathogens eradication rates and incidence of adverse drug reactions were pooled using meta-analysis performed by Review Manager 5.1 software. Relative risk (RR) and 95% confidence interval (95%CI) were calculated in a random-effects model or in a fixed-effects model. Twenty-two trials including a total of 3940 patients were included for meta-analysis. The results of meta analysis showed that clinical cure rates, clinical effective rates and pathogens eradication rates of moxifloxacin were higher than conventional therapy [RR = 1.08, 95%CI (1.02, 1.14), P = 0.008; RR = 1.09, 95%CI (1.04, 1.14), P = 0.0005; RR = 1.04, 95%CI (0.99, 1.09), P = 0.08]; the incidences of adverse drug reactions between moxifloxacin and control group were not statistically significant [RR = 0.88, 95%CI (0.72, 1.06), P = 0.17]. In three large studies of pelvic inflammatory disease (PID) patients, no statistically significant difference was found between moxifloxacin monotherapy group and control group about clinical cure rates, microbiological success rates and the incidences of adverse drug reactions [RR = 0.98, 95%CI (0.95, 1.02), P = 0.33; RR = 1.06, 95%CI (0.96, 1.16), P = 0.25; RR = 0.85, 95%CI (0.68, 1.05), P = 0.13]. Moxifloxacin can be suggested as the regimen of choice for treatment of urogenital system infections.

Key words: Meta-analysis, moxifloxacin, efficacy, urogenital system infections, pelvic inflammatory disease.

INTRODUCTION

Urogenital system infections are among the most frequently seen and encountered infectious diseases of humans in the world. They are one of the leading causes of acute diseases and chronic health impairment (Skerk et al., 2010; Hannan et al., 1993). Urinary tract infections mainly include pyelonephritis, cystitis, urethritis, while genital system infections cover pelvic inflammation disease (PID), vaginitis, and cervicitis in women and prostatitis in men. Anatomically, the urinary and genital systems are close, and susceptible to cross-infection. Sexually transmitted infections are important public health problem, numerous complications leaving permanent consequences on the human health as well as large expenses that health-care system and individuals have to pay for their detection, prevention and treatment (Skerk et al., 2010; Minichiello et al., 2011). Urinary tract infections

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are the most common bacterial infections in humans and the most common reason for justified antibiotic prescriptions (Foxman ., 2002).

Urogenital system infections are mostly caused by Escherichia coli, Enterococcus, Staphylococcus, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Proteus mirabilis* (Bebear et al., 2008). For the past few years, some atypical pathogens, such as *Mycoplasma* and *Chlamydia*, are accounting for more and more infections (Wagenlehner and Naber, 2006). Fluoroquinolones which are among the alternatives for empirical antibiotic treatment of some urogenital system infections have become widely accepted for treatment of urogenital system infections because of their favorable pharmacokinetic and pharmacodynamic properties (Pathania and Sharma., 2010; Wagenlehner and Naber., 2006; Naber, 2001). Clinical practice has proved that fluoroquinolones are a good choice for urogenital system infections (Wagenlehner and Naber, 2006). However, the most important drawback in the treatment of urogenital system infections is that bacterial resistance quickly appears. A four-year prospective study reported that there is high intrinsic resistance to the quinolones among strains of *Pseudomonas aeruginosa* (43.4%), *E. coli* (26.3%) and *Proteus* spp. (17.1%), and rising rates of resistance were observed in *P. aeruginosa* (14.6% increase), *Staphylococcus aureus* (9.8%), and *E. coli* (9.7%) after four years (Omigie et al., 2009).

Moxifloxacin, a new fluoroquinolone antibiotic that acts by inhibiting bacterial topoisomerases II and IV, not only possesses increased activity against typical, atypical and anaerobic bacteria, but also has enhanced potential to minimize the emergence of bacterial resistance (Bebear et al., 2008; Lode and Schmidt., 2008a; Boswell et al., 2002; Brueggemann et al., 1997). There is no known cross-resistance between moxifloxacin and other kinds of antimicrobials, such as beta-lactams, macrolides, aminoglycosides and tetracyclines (Keating and Scott, 2004). Moxifloxacin achieves good tissue penetration and high concentrations in clinically relevant tissues and fluids (Lode and Schmidt, 2008b). Based on the safety profile and the pharmacokinetic behavior of moxifloxacin, a dosage regimen of 400 mg given once daily, are effective and well tolerated for the treatment of various infections (Stass et al., 2001). Moxifloxacin, taken as respiratory fluoroquinolone, is mainly used for the treatment of acute bacterial exacerbation of chronic bronchitis, community-acquired pneumonia (Miravitlles, 2005), acute bacterial sinusitis (Lode et al., 2008b), complicated skin and skin-structure infections (Muijsers and Jarvis , 2010) and complicated intra-abdominal infections (Cheadle et al., 2010). Because of the desirable pharmacokinetic and concentration in tissues and fluids, we want to find out whether moxifloxacin can be considered as an alternative for the treatment of urogenital infections. Although Naber et al. (Bebear et al., 2008) discovered that the urinary excretion of moxifloxacin (20%) was lower than ciprofloxacin (43%), ofloxacin (81%) and levofloxacin (84%) and the indications of moxifloxacin are not included urogential infections (Foxman et al., 2011), in some countries, such as China, France, Russia, and England, moxifloxacin is used for treatment of urogenital system infections (Zheng, 2010; Su et al., 2010; Judin et al., 2010; Meng and Ding, 2009; Tang et al., 2009; Wang and Pei, 2009a, b; Jin et al., 2009; Wang et al., 2009; Zhang et al., 2009; Heystek and Ross, 2009; Li, 2008; Per et al., 2009; Zhang et al., 2007; Sun, 2007; Ross et al., 2006; Luo et al., 2006; Luo et al., 2006; Gao et al., 2005; Tian et al., 2005; Zhang et al., 2004; Cai et al., 2003).

Research findings from those clinical studies of the efficacy and safety profile of moxifloxacin in treatment of urogenital system infections have been inconsistent. Therefore, aiming to compare the efficacy and safety profile of moxifloxacin monotherapy with conventional antibiotic treatment for treatment of urogenital infections, we conduct a meta-analysis of randomized controlled trials (RCTs).

MATERIALS AND METHODS

Data sources

Studies were identified by extensively searching the PubMed, EMBASE, Science Direct, ClinicalTrials.gov, Cochrane Central Register of Controlled Trials, CBM (Chinese Biomedical Literature Database), CNKI (Chinese National Knowledge Infrastructure), Wan Fang Data and VIP INFORMATION were searched from January 1999 to May 2011. The search terms were moxifloxacin, Avelox, urinary tract infections, urogenital infections, pelvic inflammatory disease and nongonococcal urethritis. The language of the literatures was not restricted to English. In addition, references of the relevant articles were reviewed in order to identify additional studies not detected by the initial search.

Study selection

Two reviewers (Yanping Mu and Xun Deng) independently searched literatures and examined relevant randomized controlled trials (RCTs). Any disagreement about study selection or data extraction was resolved by consensus with the third reviewer (Yong Wang, MD). For meta-analysis, all studies had to meet the following inclusion criteria: (1) A study described as RCT; (2) patients with urogenital infections had no statistically significant differences in baseline characteristics; (3) comparison of the efficacy and safety of moxifloxacin and other conventional antibiotics; (4) The outcome measures were clinical treatment success (defined as “clinical cure” and “clinical effective”. “Clinical cure” was the normalization of acute signs, symptoms related to infection and laboratory test results with no requirement for further antibiotic therapy, and “clinical effective” was the aggregation of cure and improvement), microbiological treatment success (defined as the eradication of baseline pathogens) and adverse drug reactions.

Non-randomized studies were excluded, as well as case reports, reviews with insufficient details to meet the inclusion criteria, abstracts in the proceedings of scientific conferences, experimental trials and trials focusing on pharmacokinetics or pharmacodynamics, and children and pregnant female.

Data extraction

Two of the authors independently extracted data from the trials that

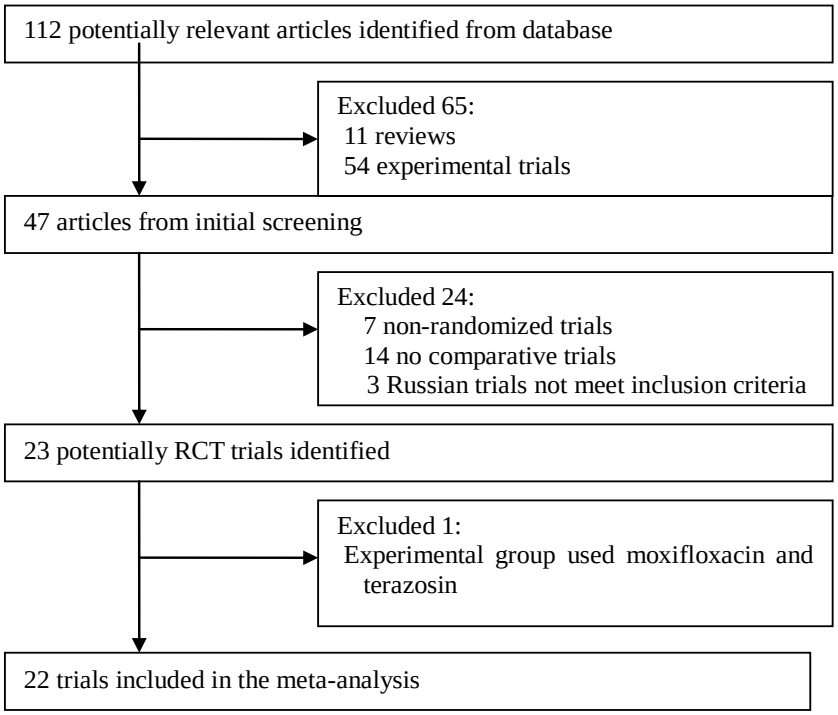

Figure 1. Flow diagram of the process for selecting articles for a meta-analysis of moxifloxacin compared with conventional medical treatment in the treatment of urogenital infections.

met the inclusion criteria using. Authors would be contacted for missing data when necessary. For each trial, the following data were extracted: disease; number of patients in each group; mean age and sex distribution of each group; drug regimen, including doses and treatment duration; clinical cure rates; clinical effective rates; pathogens eradication rates and the incidences of adverse drug reaction.

Assessment of study quality

Quality assessment of the RCTs included in the meta-analysis was independently performed by the same reviewers according to Cochrane Handbook 5.0.1 and Juni et al. (Juni et al., 2001; Jadad et al., 1996), which assesses the descriptions of randomization procedures, allocation concealment, double blinding and dropouts\withdrawals of the included trials. Each author rated the quality of the trials using Jadad grade (maximum grade=A; minimum grade = C; grade ≥ B = good quality).

Statistical analysis

Data were analyzed using Review Manager 5.1. Included articles were pooled and weighed (Juni et al., 2009). Relative risk (RR) and 95% confidence interval (95%CI) were calculated in a random-effects model or in a fixed-effects model. Heterogeneity was assessed by calculating a χ^2 test and the quantity of heterogeneity was measured with I^2 statistic. If heterogeneity (P<0.1 or I^2>50%) was found among the trials, random-effects model would be chosen, otherwise fixed-effects model chosen. If heterogeneity was evident (I^2>70%), the inferior quality study should be eliminated to analyze.

RESULTS

Study selection process

The flow diagram (Figure 1) shows the process of selecting articles for meta-analysis of moxifloxacin compared with conventional therapy for urogenital infections. Twenty-two (Zheng, 2010; Su et al., 2010; Judin et al., 2010; Meng et al., 2009; Tang et al., 2009; Wang and Pei, 2009a; Wang and Pei, 2009b; Jin et al., 2009; Wang et al., 2009; Zhang et al., 2009; Heystek and Ross, 2009; Li, 2008; Per et al., 2009; Zhang et al., 2007; Sun, 2007; Ross et al., 2006; Luo et al., 2006; Luo et al., 2006; Gao et al., 2005; Tian et al., 2005; Zhang et al., 2004; Cai et al., 2003) were finally selected from the 112 articles.

Study characteristics

The main characteristics of twenty-two included RCTs are presented in Table 1. Twenty-two RCTs involving 3940 patients were ultimately confirmed that met the criteria for inclusion in the meta-analysis. Among the patients included in the trials, the mean age was 36.87 years, and 82.61% (3255/3940) of the patients were women. All of the trials enrolled patients with urogential system infections, nine of which were researched patients with

Table 1. Study characteristics of included RCTs.

Study	Country	Type of disease	Treatment	No. of patients (male/female)	Mean age, y	Drug regimen	Clinical cure rate	Clinical effective rate	Pathogen eradication rate	Incidence of ADR
Zheng HZ[23] 2010	China	UTI	MFX	32 (20/12)	40.8 ± 4.1	400 mg, po, qd × 10d	75.0 (24/32)	90.6 (29/32)	87.5	9.4 (3/32)
			LVFX	31 (19/12)	39.8 ± 3.7	200 mg, po, bid × 10d	64.5 (20/31)	87.1 (27/31)	74.2	6.6 (2/31)
Su XD[24] 2010	China	NGU	MFX	60 (60/0)	32	400 mg, po, qd × 14d	40.0 (24/60)	90.0 (54/60)	-	6.7 (4/60)
			AZI	60 (60/0)	34	500 mg, po,qd × 14d	33.3 (20/60)	71.7 (43/60)	-	10.0 (6/60)
Judlin [25] 2010	France	PID	MFX	228 (0/228)	35.2 ± 8.4	400 mg, po, qd × 14d	78.4 (152/194)	-	90.0 (27/30)	56.6 (129/228)
			LVFX/MTZ	232 (0/232)	35.4 ± 8.7	500 mg LVFX,po,qd + 500 mg MTZ, po, bid × 14d	81.6 (155/190)	-	84.6 (22/26)	56.9 (132/232)
Meng W[26] 2009	China	Acute PID	MFX	25 (0/25)		400 mg po, qd ×14d	92.0 (23/25)	100.0 (25/25)	-	16.0 (4/25)
			CTRX/AZI	25 (0/25)	19~61	CTRX250 mg, im, qd + AZI500 mg,po,qd ×14d	80.0 (20/25)	96.0 (24/25)	-	32.0 (8/25)
Tang JD[27] 2009	China	UTI	MFX	50 (8/42)		400 mg, iv, qd × 3d or 14d	86.0 (43/50)	92.0 (46/50)	91.5 (43/47)	6.0 (3/50)
			OFLX	50 (7/43)	43.1 ± 25.6	200 mg, iv, bid × 3d or 14d	84.0 (42/50)	90.0 (45/50)	91.3 (42/46)	6.0 (3/50)
Wang G[28] 2009(a)	China	NGU	MFX	80 (0/80)	18 ~ 58	400 mg, po, qd ×14d	56.3 (45/80)	91.3 (73/80)	90.0 (72/80)	10.0 (8/80)
			AZI	80 (0/80)		500 mg, po, qd × 14d	55.0 (44/80)	91.3 (73/80)	91.3 (73/80)	6.3 (5/80)
			MINO	80 (0/80)		100 mg, po, bid × 14d	57.5 (46/80)	93.8 (75/80)	92.5 (74/80)	11.3 (9/80)
Wang G[29] 2009(b)	China	UTI	MFX	150 (0/150)		400 mg, po, qd × 7d	60.0 (90/150)	96.0 (144/150)	89.9 (169/188)	8.0 (12/150)
			GAT	149 (0/149)	31 ± 0.5	400 mg, po, qd × 7 d	56.4 (84/149)	95.3 (142/149)	87.1 (162/186)	8.7 (13/149)

Table 1 cont

Jin X[30] 2009	China	UTI	MFX	121	-	400 mg, po,qd × 10d	93.4 (113/121)	95.1 (115/121)	95.7 (116/121)	9.1 (11/121)
			SPFX	121		300 mg ,po,qd × 10d	92.6 (112/121)	95.9 (116/121)	96.7 (117/121)	9.1 (11/121)
Wang X[31] 2009	China	NGU	MFX	60 (0/60)	-	400 mg, po, qd × 12d	63.3 (38/60)	81.7 (49/60)	-	5.0 (3/60)
			CLA	60 (0/60)		500 mg, po, qd × 12d	48.3 (29/60)	65.0 (39/60)	-	0 (0/60)
Zhang YH[32] 2009	China	UTI	MFX	40 (23/17)	39 ± 8	400 mg, iv, qd × 7d	87.5 (35/40)	95.0 (38/40)	77.5 (31/40)	5.0 (2/40)
			GAT	40 (24/16)	37 ± 9	400 mg, iv, qd × 7d	85.0 (34/40)	92.5 (37/40)	76.9(30/39)	7.5 (3/40)
Heystek[33] 2009	England	PID	MFX	232 (0/232)	29.1 ± 7.2	400mg,po, qd ×14d	96.5 (224/232)	-	93.5 (43/46)	44.0 (151/343)
			DOX/MTZ/CPFX	202 (0/202)	28.5 ± 7.0	DOX 100 mg, bid × 14d + MTZ400 mg, tid × 14d + CPFX500 mg	98.0 (198/202)	-	89.7 (35/39)	49.7 (162/326)
Li SQ[34] 2008	China	UTI	MFX	90		400 mg, po, qd × 10d	94.4 (85/90)	97.8 (88/90)	96.7 (87/90)	7.8 (7/90)
			LVFX	86		200mg,po,bid × 10d	86.0 (74/86)	91.9 (79/86)	94.2 (81/86)	9.3 (8/86)
Pei YH[35] 2008	China	Female RTI	MFX	62 (0/62)	30.5	400mg,po,qd ×14d	66.1 (41/62)	91.9 (57/62)	89.5 (51/57)	8.1 (5/62)
			CPFX	50 (0/50)		200 mg, po, bid × 14d	40.0 (20/50)	62.0 (31/50)	72.7 (32/44)	-
Zhang GH[36] 2007	China	Urogential infections	MFX	38 (26/12)	45 ± 13	400 mg, po, qd × 7d	60.5 (23/38)	86.8 (33/38)	91.3 (42/46)	2.6 (1/38)
			GAT	38 (25/13)	45 ± 12	200 mg, ivgtt, bid × 7d	63.2 (24/38)	89.5 (34/38)	92.0 (46/50)	5.3 (2/38)

Table 1. contd.

Sun GQ[37] 007	China	NGU	MFX	45 (26/19)	28.3 ± 11	400 mg, po, qd × 12 ~ 14d	75.0 (33/44)	93.2 (41/44)	91.8 (45/49)	18.2 (8/44)
			AZI	41 (26/15)	27.36 ± 12	500 mg, po, qd × 12~14d	29.3 (12/41)	75.6 (31/41)	75.6 (31/41)	14.6 (6/41)
Ross[38] 2006	England	PID	MFX	384 (0/384)	30.1 ± 8.4	400 mg, po, qd × 14d	90.2(248/275)	-	87.5 (49/85)	22.5 (85/378)
			OFLX/MTZ	365 (0/365)	30.5 ± 8.5	OFLX400 mg + MTZ500mg,po,bid ×14d	90.7(262/289)	-	82.1 (46/56)	30.9(112/363)
Luo XM[39] 2006	China	UTI and RTI	MFX	56 (0/56)	27.6 ± 3.1	400mg,po,qd×12d	78.6 (44/56)	91.1(51/56)	-	12.5 (7/56)
			DOX	56 (0/56)	27.5 ± 2.0	1 pill, po, bid × 14d	51.8 (29/56)	76.8(43/56)	-	73.2 (41/56)
Luo JL[40] 2006	China	Urogential infections	MFX	52	18 ~ 60	400 mg, po, qd × 14d	65.4 (34/52)	92.3 (48/51)	93.3 (56/60)	9.6 (5/52)
			GAT	50		200 mg, po, bid × 14d	64.0 (32/50)	90.0 (45/50)	88.5 (54/61)	10.0 (5/50)
			CPFX	48		200 mg, po, bid × 14d	41.7 (20/48)	64.6 (31/48)	57.9 (33/57)	10.4 (5/48)
Gao HY[41] 2005	China	UTI	MFX	22	42.6 ± 10	Morning 400 mg + one placebo, evening two placebo, po × 7-14d	52.6 (10/19)	84.2 (16/19)	100.0 (14/14)	65.0 (13/20)
			LVFX	22 (1/43)	43.5 ± 17.7	200 mg, po, bid × 7-14d	47.1 (8/17)	82.4 (14/17)	72.7 (8/11)	40.9 (9/22)
Tian YP[42] 2005	China	Urogential infections	MFX	29 (41/17)	19 ~ 45	400 mg, po, qd × 7d	79.3 (23/29)	93.1 (27/29)	89.7 (26/29)	55.2 (16/29)
			THI	29		500 mg, po, tid × 7d	58.6 (17/29)	65.5 (19/29)	58.6 (17/29)	62.2 (18/29)
Zhang WF[43] 2004	China	Urogential mycoplasma infection	MFX	43		400 mg, po, qd × 14d	74.4 (32/43)	95.3 (41/43)	90.7 (39/43)	9.3 (4/43)
			SPFX	43 (33/96)	29.6	200 mg, po, qd × 14d	65.1 (28/43)	90.7 (39/43)	88.4 (38/43)	11.6 (5/43)
			LVFX	43		200 mg, po, bid × 14d	53.5 (23/43)	69.8 (30/43)	67.4 (29/43)	16.3 (7/43)
			MFX	20 (1/19)	42 ± 13	Morning 400 mg + one placebo, evening two placebo, po × 7 - 14d	90.0 (8/20)	95.0 (19/20)	94.7 (18/19)	27.2 (6/22)
			LVFX	20 (1/19)	42 ± 14	200 mg, po, bid × 7 - 14d	85.0 (17/20)	90.0 (18/20)	100.0 (19/19)	27.2 (6/22)

MFX: Moxifloxacin; LVFX: levofloxacin; AZI: azithromycin; OFLX: ofloxacin; MTZ: metronidazole; SPFX: sparfloxacin; GAT: gatifloxacin; CTRX: ceftriaxone sodium; CLA: clarithromycin; CPFX: ciprofloxacin; TRZ: terazosin; CAZ: ceftazidime; DOX: doxycycline; MINO: Minocycline; THI: thiamphenicol; UTI: urinary tract infections; NGU: non gonococcal urethritis; PID: pelvic inflammation disease; RTI: reproductive tract infection.

urinary tract infections (UTI), four pelvic inflammation disease (PID), five non-gonococcal urethritis (NGU), four urogenital infections and one reproductive tract infection (RTI).

Patients in the moxifloxacin group received moxifloxacin at dosage of 400 mg once a day (orally or intravenously), while the control group received the recommended dose of other antibiotics (according to different countries), such as levofloxacin, azithromycin, ofloxacin, metronidazole, sparfloxacin, gatifloxacin (sparfloxacin and gatifloxacin have been

Table 2. Quality assessment of included RCTs.

Study ID	Randomization	Allocation concealment	Double blinding	Dropouts\withdraws	Jadad Grade
Zheng HZ 2010	Yes	Unclear	Unclear	No	B
Su XD 2010	Yes	Unclear	Unclear	No	B
Judlin 2010	Adequate	Yes	Yes	Yes	A
Meng W 2009	Yes	Unclear	Unclear	No	B
Dang JD 2009	Yes	Unclear	Unclear	No	B
Wang G 2009(a)	Yes	Unclear	Unclear	No	B
Wang G 2009(b)	Yes	Unclear	Unclear	No	B
Jin X 2009	Yes	Unclear	Unclear	No	B
Wang X 2009	Yes	Unclear	Unclear	No	B
Zhang YH 2009	Yes	Unclear	Unclear	No	B
Heystek 2009	Yes	Unclear	Yes	Yes	B
Li SQ 2008	Yes	Unclear	Unclear	No	B
Pei YH 2008	Yes	Unclear	Unclear	No	B
Zhang GH 2007	Yes	Unclear	Unclear	No	B
Sun GQ 2007	Yes	Unclear	Unclear	Yes	B
Ross 2006	Yes	Unclear	Yes	Yes	B
Luo XM 2006	Yes	Unclear	Unclear	No	B
Luo JL 2006	Yes	Unclear	Unclear	No	B
Gao HY 2005	Adequate	Unclear	Yes	Yes	B
Tian YP 2005	Yes	Unclear	Unclear	No	B
Zhang WF 2004	Yes	Unclear	Unclear	No	B
Cai SF 2003	Adequate	Unclear	Yes	No	B

withdrawn from the American market, respectively, in 2005 due to QT prolongation and in 2006 due to dysglycemia). All patients included in the meta-analysis received antimicrobial treatment for a period of no less than seven days and a maximum of fourteen days.

The quality assessment of included RCTs is presented in Table 2. There studies clarified adequate randomization procedures, one reported allocation concealment, five used double blinding and five reported numbers of dropouts\withdrawals. One were eventually assessed to be good in terms of methodology with a Jadad score A (Juni et al., 2001), the other twenty-one were B.

Comparisons of effectiveness

Clinical success

All the twenty-two studies provided specific data for analysis of clinical cure. Clinical cure rate in the moxifloxacin group [1513 (77.7%) of 1947 patients] was higher than control group [1370 (72.91%) of 1879 patients], whilst statistically significant difference was found [RR = 1.08, 95%CI (1.02, 1.14), P = 0.008] (Figure 2).

19 studies (Zheng, 2010; Su et al., 2010; Meng et al., 2009; Tang et al., 2009; Wang et al., 2009a; Wang et al., 2009b; Jin et al., 2009; Wang et al., 2009; Zhang et al., 2009; Li, 2008; Per et al., 2009; Zhang et al., 2007; Sun, 2007; Luo et al., 2006; Luo et al., 2006; Gao et al., 2005; Tian et al., 2005; Zhang et al., 2004; Cai et al., 2003) provided relevant data for analysis of clinical effectiveness which consisted of clinical cure and improvement. Clinical effective rate in the moxifloxacin group [1156 (92.9%) of 1244 patients] was higher than the control group [1035 (85.0%) of 1217 patients], while statistically significant difference was found [RR = 1.09, 95%CI (1.04, 1.14), P = 0.0005] (Figure 3).

Microbiological treatment success

17 (Judin et al., 2010; Tang et al., 2009; Wang et al., 2009a; Wang et al., 2009b; Jin et al., 2009; Zhang et al., 2009; Heystek and Ross., 2009; Li, 2008; Per et al., 2009; Zhang et al., 2007; Sun, 2007; Ross et al., 2006; Luo JL et al., 2006; Gao et al., 2005; Tian et al., 2005; Zhang et al., 2004; Cai et al., 2003) of the 22 RCTs provided microbiological eradication data. 1088 (90.8%) of the 1198 patients in the moxifloxacin group and 1001 (86.5%) of the 1157 patients in the control group achieved eradication of the baseline pathogens. The overall pathogens eradication rate in the moxifloxacin group (90.8%, 1088/1198) was higher than control group (86.52%, 1001/1157), while statistically significant

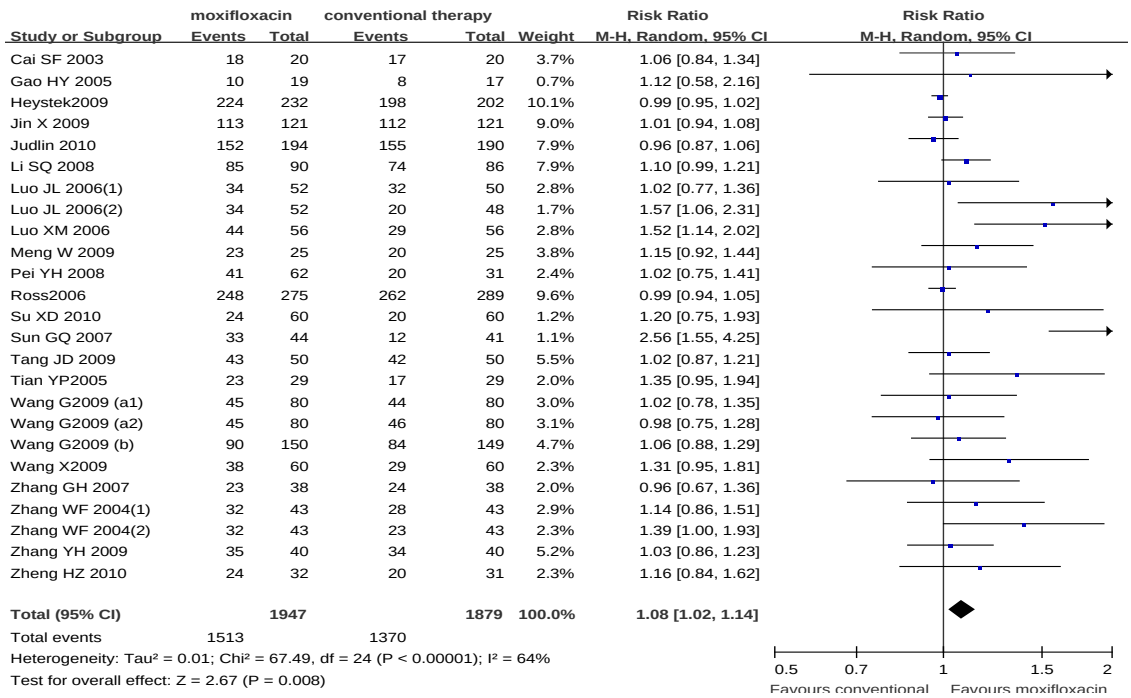

Figure 2. Meta-analysis of cure rates of moxifloxacin and conventional therapy.

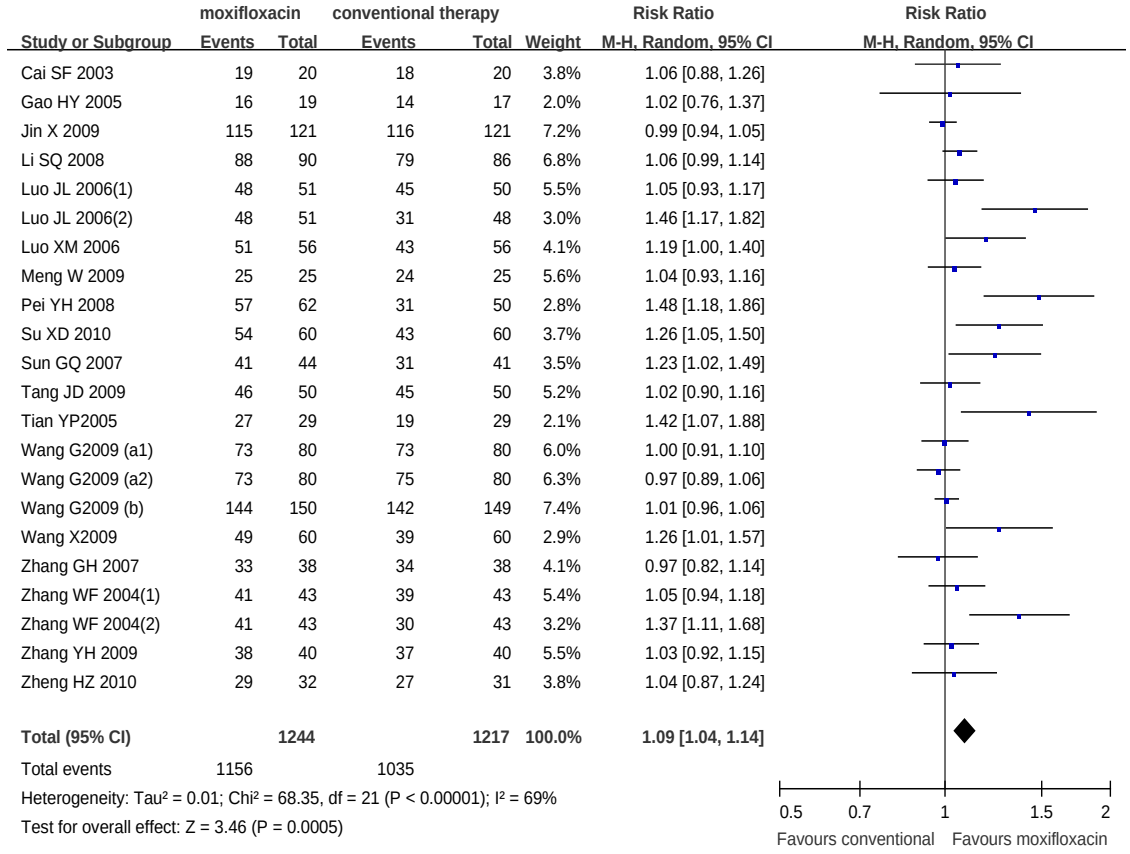

Figure 3. Meta-analysis of clinical effective rates of moxifloxacin and conventional therapy.

difference was found [RR = 1.04, 95% (0.99, 1.09), P=0.08] (Figure 4).

Comparisons of safety

All of the twenty-two RCTs provided adverse drug reaction data. In the total evaluable population, the incidence of adverse drug reaction between moxifloxacin group [509 (23.8%) of the 2136 patients] and control group [580 (27.9%) of the 2077 patients] had no statistically significant difference [RR = 0.88, 95%CI (0.72, 1.06), P = 0.17] (Figure 5).

Comparisons of PID patients

Judin (Judin et al., 2010), Heystek (Heystek et al., 2009) and Ross (Ross et al., 2006) altogether researched 1643 pelvic inflammatory disease (PID) patients. As the their studies recommended moxifloxacin as first-line therapy for pelvic inflammatory disease, we exclusively performed a meta-analysis for them. For the primary measure of efficacy [clinical cure rate at test-of-cure (TOC)], moxifloxacin was non-inferior to comparator (moxifloxacin: 624/701, 89.0%; comparator: 615/681, 90.3%) with no statistically significant difference between moxifloxacin and control group [RR = 0.98, 95%CI (0.95, 1.02), P = 0.33] (Figure 6). Microbiological success rates were 90.2% (119/132) for moxifloxacin and 85.1% (103/121) for comparator, whilst no statistically significant difference was found [RR = 1.06, 95%CI (0.96, 1.16), P = 0.25] (Figure 7). No statistically significant difference was found [RR = 0.85, 95%CI (0.68, 1.05), P = 0.13] (Figure 8) between moxifloxacin [38.5% (315/949)] versus the comparator [45.9% (406/884)] about adverse drug reaction rates.

DISCUSSION

We conducted this meta-analysis to compare the efficacy and safety of moxifloxacin monotherapy with conventional antimicrobial therapy for urogenital system infections. The overall RR of clinical rate, clinical effective rate and pathogens eradication rate of moxifloxacin were higher than control group. The results of meta-analysis indicated that efficacy of moxifloxacin was superior to conventional antibiotics therapy with statistically significant difference [Clinical cure rate: RR = 1.08, 95%CI (1.02, 1.14), P = 0.008; clinical effective rate: RR = 1.09, 95%CI (1.04, 1.14), P = 0.0005; pathogens eradication rate: RR = 1.04, 95% (0.99, 1.09), P = 0.08]. The safety profile analysis regarding the incidence of adverse drug reactions had no significant difference between moxifloxacin and control group [RR = 0.88, 95%CI (0.72, 1.06), P = 0.17]. Moreover, the efficacy and safety profile for PID patients (Judin, 2010; Heystek, 2009; Ross, 2006) were separately analyzed. These three large randomized controlled trials supported the efficacy of moxifloxacin for the treatment of uncomplicated PID. Clinical cure rates observed in the MONALISA (Judin et al., 2010) study were 78.4% for moxifloxacin versus 81.6% for levofloxacin plus metronidazole. Heysteck (2009) reported a clinical cure rate of 81.5% in women treated with moxifloxacin versus 83.2% in those treated with the doxycycline plus metronidazole plus one dose of ciprofloxacin. In the MAIDEN (Ross et al., 2006) study, clinical cure rate was achieved in 90.2% for moxifloxacin versus 90.7% for ofloxacin plus metronidazole. Meta-analysis indicated that the difference of efficacy between moxifloxacin monotherapy group and combination therapy group was not statistically significant (Clinical cure rates: RR = 0.98, 95%CI (0.95, 1.02), P = 0.33). In addition, no statistically significant differences were found in pathogens eradication rates (RR = 1.06, 95%CI (0.96, 1.16), P = 0.25) and the incidences of adverse drug reactions (RR = 0.85, 95%CI (0.68, 1.05), p = 0.13). Moxifloxacin monotherapy, 400 mg once daily for 14 days, is an effective and well-tolerated treatment for women with PID. Therefore, moxifloxacin can be recommended as the first-line therapy for uncomplicated PID.

In all the included studies, moxifloxacin had the advantage of using single dose per day and did not need combination because of broad coverage to pathogens. Monotherapy is always associated with greater compliance than combination therapy (Haggerty and Ness, 2007), especially for outpatients. The administration of moxifloxacin was intravenous or oral and its medication time was free from diet (Instruction of Moxifloxacin Hydrochloride Tablets). Moxifloxacin can be accessible to inpatients and outpatients with greater compliance. The most common adverse events reported in the included studies were gastrointestinal disturbances and central nervous system reactions, such as nausea, diarrhea, vomiting, dizzy and headache. Serious adverse events were not reported in the enrolled articles. Balfour et al. (1999) demonstrated that in contrast to some other fluoroquinolones, moxifloxacin appears to have a low propensity for causing phototoxic and central nervous system (CNS) excitatory effects, and the most common adverse events are gastrointestinal disturbances.

This meta-analysis is not without limitations. Certain limitations affecting the results of this meta-analysis should be taken into account. Firstly, our findings may be affected by the quality of trials included in the meta-analysis. Only five of the included trials were double blinding, and only three clarified adequate randomization procedures. A sensitivity analysis was performed including only trials that were double-blinded, the comparisons of pathogens eradication rates and incidence of adverse drug reaction were consistent with the primary results. The primary clinical effective rate of moxifloxacin was superiority to conventional antibiotics

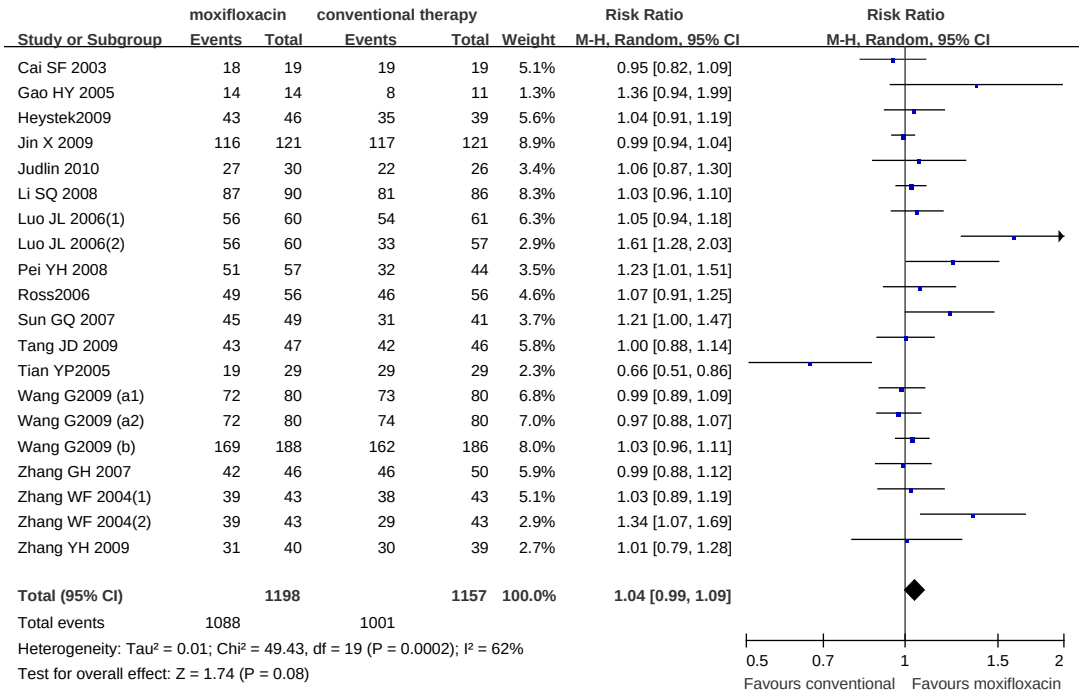

Figure 4. Meta-analysis of pathogens eradication rates of moxifloxacin and conventional therapy.

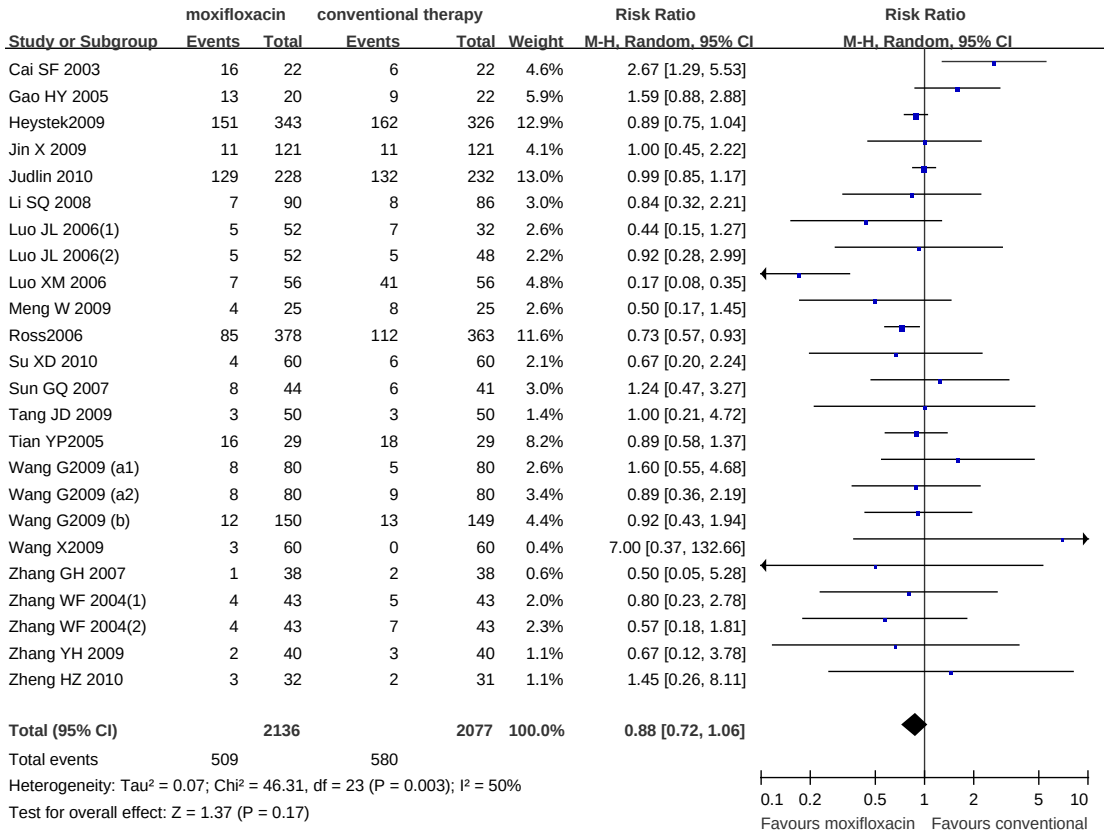

Figure 5. Meta-analysis of the incidences of adverse drug reactions of moxifloxacin and conventional therapy.

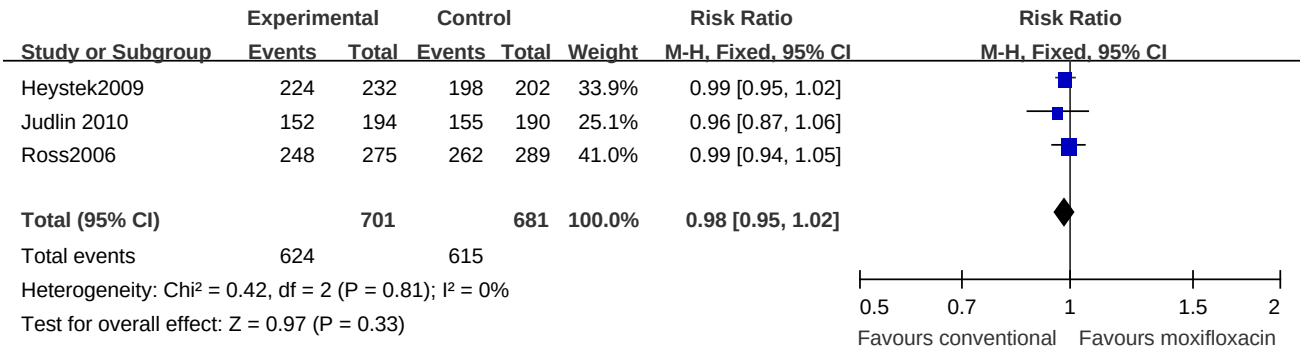

Figure 6. Meta-analysis of clinical cure rates of moxifloxacin and conventional therapy in the three PID studies.

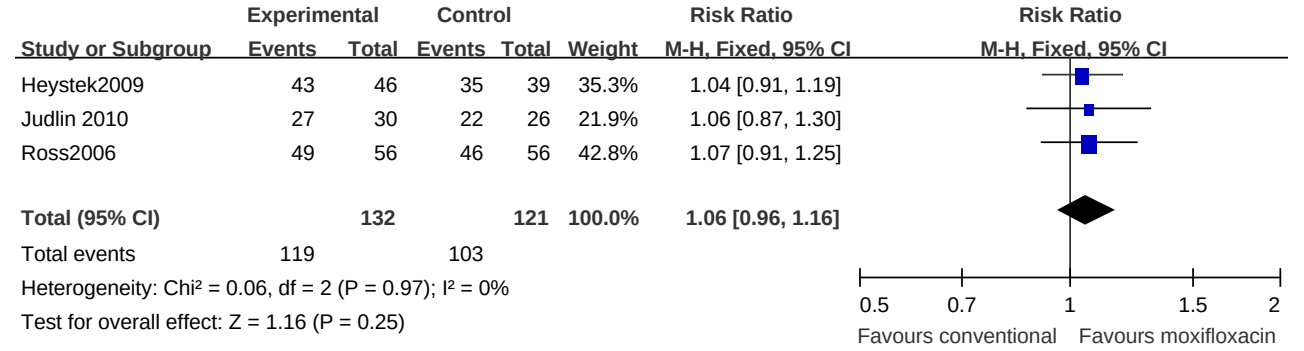

Figure 7. Meta-analysis of microbiological success rates of moxifloxacin and conventional therapy in the three PID studies.

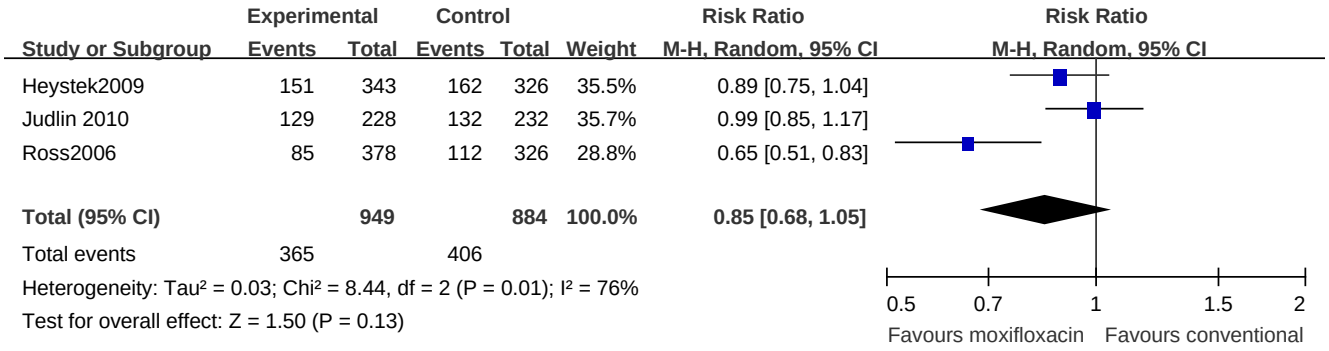

Figure 8. Meta-analysis of the incidence of adverse reaction of moxifloxacin and conventional therapy in the three PID studies.

therapy with statistically significant difference, but not finding statistically significant difference at sensitivity analysis. Secondly, heterogeneity was found among the included trials, we cannot make symmetrical funnel plots. Publication bias can lead to overestimation in meta-analysis. The funnel plot is frequently used to detect publication bias which can lead to overestimation in meta-analysis (Souza et al., 2007). However, heterogeneity does not preclude pooling of the results because individual patients are directly compared only with other patients within the same trial, and not across trials (Lau et al., 1998; Thompson, 1994) Although some limitations exist in this meta-analysis, we believe that moxifloxacin can be considered using for the treatment of urogenital infections for the following reasons. First, the results of this meta-analysis revealed that the clinical cure

rate and clinical effective rate achieved with moxifloxacin tended to be higher than obtained in the groups that received conventional antibiotic treatment and the incidence of adverse drug reactions of moxifloxacin was not significantly different from the control group. Second, the compliance of patients is influenced by the complexity of the dosage regimen. The simple usage of moxifloxacin (400 mg, once a day, PO/IV) offer benefits compared with regimens that require combination therapy or multiple dosing. Moreover, it does not need to adjust the dosage of moxifloxacin for elderly patients and those patients with renal or mild hepatic impairment (Ball et al., 2004). Third, in a review article, Bambeke et al. (Van and Tulkens, 2009) concluded that moxifloxacin did not reveal significantly higher incidences of drug-related adverse effects than for comparators. It was coincident with result of this meta-analysis. Certainly, further high quality RCTs are required.

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