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BALOFLOXACIN (Q-35), NEW FLUOROQUINOLONE AS AN ANTI-INFECTIVE: A SYSTEMATIC REVIEW

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ABSTRACT

Very limited clinical studies are available for Balofloxacin (Q-35), a new fluoroquinolone showing clinical effectiveness. Thus, a systematic review was carried out to assess the safety, efficacy and tolerability as an anti-infective agent using scientific databases (PubMed and Cochrane Library). Databases were screened using term "Balofloxacin" for available studies. The search strategy was developed according to Biondi-Zoccai with English language restriction and was set to Oct 2011. All randomized trials, comparative studies, controlled clinical trials and in-vitro/in-vivo studies showing efficacy on human clinical isolates were taken into account. Upon extensive search we found 36 and 12 studies in PubMed and Cochrane Library respectively. 7 studies including 4 free full text and 3 abstracts from PubMed database while 4 clinical trial abstracts from Cochrane Library were included for systematic review. A single randomized controlled trial (RCT) was found through Cochrane Library showing comparison between balofloxacin 100 mg with levofloxacin 200 mg twice daily for 7 to 10 days. As far as its clinical effectiveness is concerned for urinary and respiratory tract infections, it is found to be equivalent to ofloxacin but the evidence in terms of RCTs is rarely available in scientific databases. Thus, we conclude that more RCTs are required to be conducted to proof its superiority in terms of efficacy and safety.

Key Words: Fluoroquinolone, Anti-infective agent, PubMed, Cochrane Library, Randomized Controlled Trial

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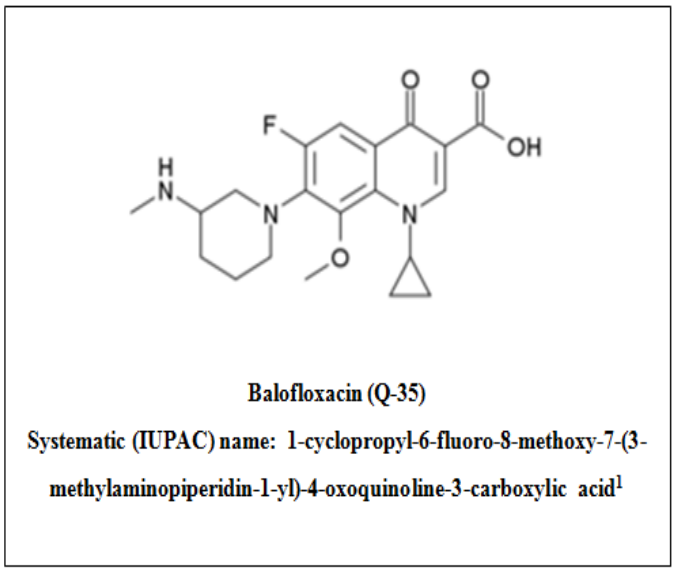
INTRODUCTION

Balofloxacin (Q-35), an orally active fluoroquinolone antibiotic of molecular mass 389.42 g/mol with chemical formula $C_{20}H_{24}FN_3O_4$[1] has been developed for the treatment of urinary tract infection (UTI).[2] (Figure 1)



Balofloxacin (Q-35)

Systematic (IUPAC) name: 1-cyclopropyl-6-fluoro-8-methoxy-7-(3-methylaminopiperidin-1-yl)-4-oxoquinoline-3-carboxylic acid[1]

Figure 1: Structure of Balofloxacin (Q-35)

Pharmacokinetic data revealed that Balofloxacin is well-absorbed after oral doses.[3] It has time to peak concentration of 1 hour.[3, 4] In healthy subjects, mean peak plasma levels of 2.2 µg/mL were achieved 1 hour after single doses of 200 mg.

Optimal doses for oral route have not been clearly established while analysis of data from pharmacokinetic studies suggests[3] that twice daily dosing may be required in many patients. In RTI, UTI (uncomplicated or complicated) and obstetric or gynecological infections oral doses of 100 to 400 mg once or twice daily have been administered. Duration of therapy was 3 to 14 days in RTI/UTI and 3 to 9 days in obstetric/gynecological infections. [5, 6, 7]

As pharmacokinetic data revealed that most of an oral dose is excreted unchanged in the urine[3], dose reduction may be required in patients with renal impairment. Delayed and reduced urinary recovery and a prolonged half-life of balofloxacin have been reported in elderly subjects (66 to 79 years of age), total/renal clearance was also reduced and renal clearance correlated significantly with creatinine clearance (CLcr). The absorption of the drug was also delayed in the elderly, most likely related to reduce gastrointestinal motility.[3] Dose adjustments for balofloxacin in elderly patients should be based on renal function. However, specific guidelines are unavailable.

Balofloxacin was approved by the Korean FDA in December 2001 for UTI. In March 2002, phase II trials were underway for RTI.[2] Limited data are available on this drug molecule and the product monograph for this molecule is unavailable online. Moreover, this product is not licensed by USFDA, so unavailable in US market. On search in database there were no indication, labeling and other instructions found that are provided by FDA. Balofloxacin is available in India under various brand names and is prescribed for the treatment of uncomplicated UTI such as cystitis and urethritis.[8]

This review was undertaken through a systematic search strategy focused on the randomized controlled clinical trial data available as well general in-vitro and in-vivo studies to assess the safety, efficacy and tolerability of Balofloxacin as an anti-infective agent in the group of fluroquinolones. This systematic review was carried out from scientific databases to understand its existence and importance as an anti-infective agent.

MATERIALS AND METHODS

Search Strategy:

Pertinent studies were searched in PubMed (updated October 2011) by one of the investigator using the term “Balofloxacin” by initiating limits to only randomized controlled trials, controlled clinical trials, comparative study, clinical trial (Phase I-IV), practice guidelines in humans for full text and abstracts ("balofloxacin"[Supplementary Concept] OR "balofloxacin"[All Fields]) AND ("loattrfull text"[sb] AND "loattrfree full text"[sb] AND "humans"[MeSH Terms] AND (Clinical Trial[ptyp] OR Randomized Controlled Trial[ptyp] OR Clinical Trial, Phase I[ptyp] OR Clinical Trial, Phase II[ptyp] OR Clinical Trial, Phase III[ptyp] OR Clinical Trial, Phase IV[ptyp] OR Comparative Study[ptyp]) AND English[lang] AND medline[sb]).

The search strategy was developed according to Biondi-Zoccai.[9] The language restriction was enforced to English and the search strategy was set to an end on month of October, 2011. Even the search was carried out using term “Balofloxacin” without approaching any limits in the PubMed site ("balofloxacin"[Supplementary Concept] OR "balofloxacin"[All Fields]).

The Cochrane Controlled Trial Register (Cochrane Library) without language restriction was searched using term “Balofloxacin” and advanced search was carried out through the entire Cochrane library with a date range from 1990 to 2011.

Inclusion criteria:

All randomized trials, comparative studies, controlled clinical trials with free full text article that evaluated balofloxacin as an anti-infective agent in various infections were potentially eligible.

Trials were included if all participants were adults of either gender and the drug was used against infections. Studies or trials were even eligible if balofloxacin was compared with placebo, other fluoroquinolones or anti-infective. Studies of in-vitro and in-vivo category which predicted its efficacy as an anti-infective on human clinical isolates were also included for review.

The primary outcome measure was the proportion of its antibacterial activity, clinical significance in terms of total cure effective rates, bacterial clearance rate. Safety was assessed through evidence of various adverse drug events. The secondary outcome measure was detection of MIC_{90}, bactericidal activity against various bacterial strains, mutation through gene or enzyme inhibition.

Data extraction and analysis: All titles and abstracts were screened independently by authors (BKP and AP) and irrelevant studies were discarded. The full texts of the remaining studies were assessed to determine if the inclusion criteria was met. Data were extracted onto standard pre-prepared forms.

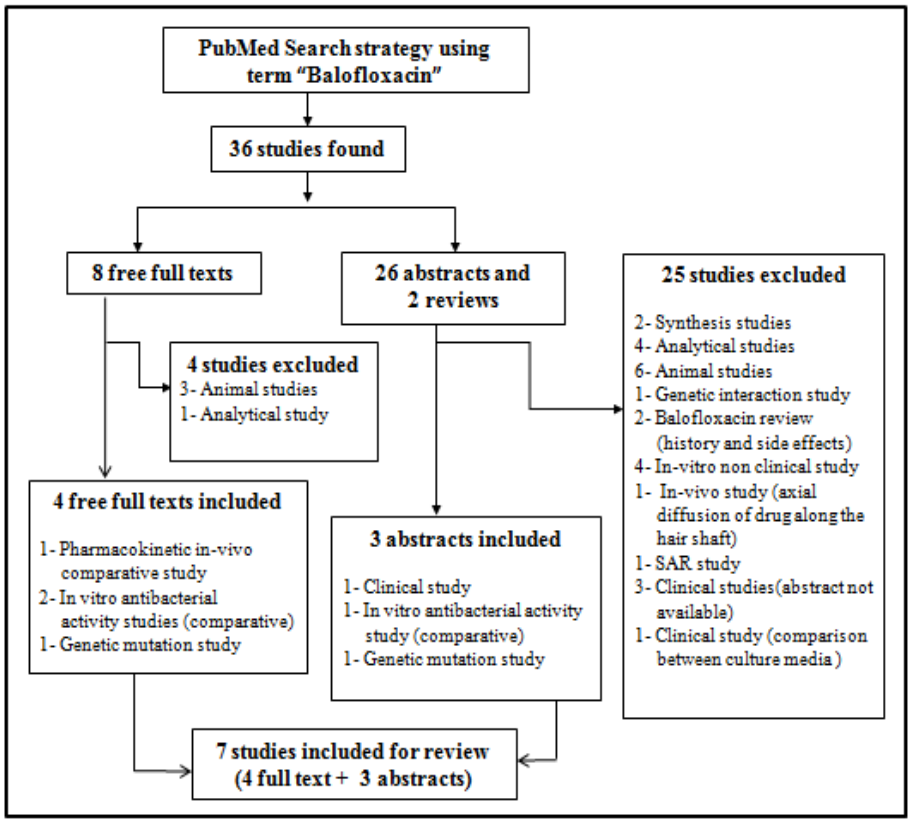


Figure 2a:PubMed search strategy

RESULTS AND DISCUSSION

PubMed

Literature search:

The results obtained from search strategy using PubMed for term "Balofloxacin" is depicted in Figure 2a.

Upon extensive search we found 36 studies of which 8 were free full texts and only abstract was found for 28 studies. Amongst searched studies, 4 studies available as free full text[3, 10-12] and 6 studies as abstract[13-18] were reviewed analyzed. Out of the 6 abstracts, 3 clinical studies[16-18] were eligible according to the title but not included, as full text/abstract was unavailable in the database. The requested information to allow inclusion of these trials could not be obtained from the authors. 7 studies were therefore included in this review.

Study characteristics:

When limits were applied

A single clinical pharmacokinetic comparative study between balofloxacin and grepafloxacin using 10 elderly study subjects was found (Table 1).

When limits were removed

A clinical in vivo study involving 89 subjects were assessed for safety, efficacy and usefulness of balofloxacin (Table 2.1). There were 3 in-vitro comparative antibacterial activity studies showing comparison between balofloxacin and other fluoroquinolones (Table 2.2). Finally, 2 studies were of genetic mutation showing effect of mutation on balofloxacin (Table 2.3).

The pharmacokinetics and tolerability of Balofloxacin compared to grepafloxacin by HPLC technique where the venous and urine samples were collected to assess the drug concentration within various time intervals. The result showed that the absorption of both fluoroquinolones was slightly delayed and the plasma excretion of balofloxacin was prolonged because it was principally excreted through renal route. This study did not describe any adverse event of balofloxacin in elderly patients which lead to conclusion by Kozawa O et al that it was well tolerated and do not require any dose alteration for healthy elderly people. As the volunteers were exclusively females in this study, this might have a limitation in terms of pharmacokinetics properties related to gender.[3]

Table 1: Characteristics of the clinical study using Balofloxacin when limit was applied to PubMed search strategy

Author, Year, Country	Type of study	No. of subjects (n)	Group 1	Group 2	Assessment criteria	Study outcome
Kozawa O et al, 1996, Japan[7]	Pharmacokinetic In-vivo Comparative study	n=10	Balofloxacin 200mg OD	Grepafloxacin 200mg OD for 7 days	Blood biochemistry, hematology tests and urinalysis. Concentrations were quantitated by reversed-phase HPLC, Cmax and Tmax	Absorption of Grepafloxacin was delayed and the C-max and AUC were increased in the elderly by 31% and 48%, respectively, over those in younger adults on the basis of dose normalized to body weight

HPLC: High-Performance Liquid Chromatography, **AUC:** Area Under Curve

Table 2.1: Characteristics of the clinical study using Balofloxacin when limit was removed from PubMed search strategy

Author , year, country	Type of study	No. of subjects enrolled	Group 1	Group 2	Assessment criteria	Study outcome
Obana M et al, 1995, Kanagawa[13]	Clinical study	n= 89	Balofloxacin 200 mg BID for 3 days to patients with cholera, 7 days to patients with Salmonella enteritis and 5 days to patients with other conditions of infectious enteritis including shigellosis	None	Fecal drug concentration and intestinal microbial flora	Drug was effective for Shigella spp. in 41 (100%), Salmonella spp. in 12 (85.7%) and enteropathogenic/ enterotoxigenic Escherichia coli in 8 cases (100%). The drug found to be effective in 2 patients with acute infectious enteritis

Table 2.2: Characteristics of the In-vivo/In-vitro studies using Balofloxacin when limit was removed from PubMed search strategy

Author , year, country	Type of study	No. of strains/ isolates (n)	Group 1	Group 2	Assessment criteria	Study outcome
Fukuyama M et al, 1995[14]	In vitro antibacterial activity study (Comparative)	(43 strains of Vibrio cholerae, 1 strain of Campylobacter spp., 4 strains of Aeromonas spp., 3 strains of Plesiomonas shigelloides, 1 strain of Vibrio mimicus and 1 strain of Vibrio cholera	Balofloxacin	Norfloxacin, Ofloxacin and Ciplofloxacin	MIC90 of Balofloxacin was assessed	MIC90 of Balofloxacin against 43 strains of Shigella spp., 13 strains of Salmonella spp. and 9 strains of E. coli were 0.39, 0.39, 0.2 µg/ml, respectively. All strains of Aeromonas spp. and P. Shigelloides were inhibited by the conc. under 0.39 and 0.05 µg /ml
Ito T,1995, Japan[10]	In vitro antibacterial activity study (Comparative)	18 strains of MRSA and 3 strains of Staphylococcus epidermidis	Balofloxacin (Q-35) and its analogues (drug initially dissolved in 0.1 N NaOH, diluted with water, and neutralized with 0.1 N HCl)	Sparfloxacin, Tosufloxacin, and Ofloxacin	MICs were determined by the two fold agar dilution Method, Detection of gyrA mutation in S. aureus, Bactericidal activity	Q-35 produced bactericidal activity against sparfloxacin-resistant staphylococci, whereas ofloxacin, tosufloxacin, and sparfloxacin did not show bactericidal activities until after 3 h of exposure to quinolones
Ito T et al, 1992, Japan[11]	In vitro antibacterial activity study (Comparative)	Isolates collected from various laboratories and hospitals	Balofloxacin (Q-35) (drug initially dissolved in 0.1 N NaOH, diluted with water, and neutralized with 0.1 N HCl	Ofloxacin, Ciprofloxacin, Tosufloxacin, lomefloxacin and Sparfloxacin	Determination of MICs, Bactericidal activity, Inhibition of DNA gyrase	Activity of Q-35 was 4-16 fold greater than those of ofloxacin, ciprofloxacin and lomefloxacin but equal to those of tosufloxacin and sparfloxacin in case of S.Aureus, MRSA, Staphylococcus epidermidis, S.Pneumoniae and S. Pyogenes

HPLC-ESI-MS: High Performance Liquid Chromatography-Electrospray Ionisation-Mass Spectrometry, **MIC:** Minimum Inhibitory Concentration,

HPLC: High-Performance Liquid Chromatography, **MRSA:** Methicillin-Resistant Staphylococcus Aureus, **DNA:** Deoxyribonucleic Acid

Table 2.3: Characteristics of the Genetic mutation study using Balofloxacin when limit was removed from PubMed search strategy

Author, Year, Country	Type of study	No. of strains/ isolates (n)	Assessment criteria	Study outcome
Betanzos-Cabrera G et al, 2009, Mexico[15]	Genetic muatation	*S. epidermidis* strains were isolated from patients with conjunctivitis (n = 23), endophthalmitis (n = 14) and corneal ulcers (n = 7)	MICs were determined by broth and agar dilution method for moxifloxacin, gatifloxacin, balofloxacin, rufloxacin and pazufloxacin. Mutations were identified by sequencing the gyrA and parC genes, and their expression was determined by reverse transcriptase PCR	13.6% (6/44) of the strains were quinolone resistant showed mutations at Ser84Phe for the gyrA gene, and Ser80Phe for the parC gene. *S. epidermidis* strains isolated from three ocular pathologies were gatifloxacin and moxifloxacin resistant due to mutations on the gyrA and parC genes.
Takahashi H et al, 1998, Japan[12]	Genetic muatation	110 clinical isolates of *S. aureus* collected out of 292 isolates so as to include isolates with various degrees of susceptibility and resistance to ofloxacin	MICs of each agent were determined by broth microdilution method. Mutations in genes encoding the subunits of DNA gyrase and DNA topoisomerase IV was examined and detected by PCR and restriction fragment length polymorphism analysis	GyrA and grlA mutations thus appear to impart high levels of fluoroquinolone resistance in many *S. aureus* clinical isolates

MIC: Minimum Inhibitory Concentration, **DNA:** Deoxyribonucleic Acid, **PCR:** Polymerase Chain Reaction

Table 3: Characteristics of clinical trials using advanced search for Balofloxacin in Cochrane Library

Author , year, country	Type of study	No. of subjects (n)	Group 1	Group 2	Allocation concealment/ Blinding	Assessment criteria	Study outcome
Zhang DY et al, 2008[19]	RCT	n=210 (3 withdrawals)	104 cases in balofloxacin group (twice daily for 7 to 10 days at the dose of 100mg)	103 cases in levofloxacin group (twice daily for 7 to 10 days at the dose of 200mg)	randomized, double-blinded study	in FAS & PPS analysis the total cure rates and effective rate, bacterial clearance rates, adverse reactions	Balofloxacin tablet is as effective and safe as levofloxacin tablet in the treatment of minor and moderate urinary tract infection.
Kumazawa J et al, 1996[20]	CCT (dose finding study)	n=119 (22 withdrawals)	balofloxacin 200 mg/day balofloxacin 200 mg/day	balofloxacin 400 mg/day ofloxacin 600 mg/day	Randomization not mentioned double blinded study Non blinded study	Clinical efficacy rate, bacteriological eradication rate, general safety rate, adverse events, usefulness	the optimal dosage of balofloxacin in the treatment of complicated urinary tract infections is 400 mg/day administered in two divided doses
Nakashima M et al, 1995[21]	CCT- Clinical phase I study (single oral administration)	Not defined	200 mg balofloxacin	400 mg balofloxacin	Randomization and Blinding not mentioned	safety and pharmacodynamics	Balofloxacin can be clinically administered in patients with infectious diseases, because it is safe and shows excellent pharmacodynamics
Nakashima M et al, 1995[22]	CCT – Clinical phase I study (Repeated oral administration)	n=12	Balofloxacin 200 mg every 12 hours	Balofloxacin 300 mg every 12 hours	Randomization and Blinding not mentioned	safety, pharmacodynamics, and influence on intestinal bacterial flora	Extremely slight elevation of GPT was observed, levels of blood concentration were in good accordance with the simulation curve, and showed no phenomena suggestive of accumulation

RCT: Randomized Controlled Trial, **CCT:** Controlled Clinical Trial**, FAS:** Full Analysis Set**, PPS:** Per Protocol Set, **GPT:** Glutamic-Pyruvic Transaminase

Ito T *et al* carried out an in-vitro study to predict the antibacterial activity of Q-35 against clinical isolates of *Staphylococcus aureus, methicillin-resistant staphylococcus aureus (MRSA), Staphylococcus epidermidis*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes* and were simultaneously compared with other fluoroquinolones like ofloxacin, ciprofloxacin, tosufloxacin, lomefloxacin, and sparfloxacin. The activity of Q-35 was predicted to be 4 to 16 fold greater than other fluoroquinolones but had equal effect to those of tosufloxacin and sparfloxacin against these organisms but, for 82 ciprofloxacin-resistant staphylococci (MIC_{90} = 100 ug/ml), Q-35 was the most active of the new quinolones tested (MIC_{90} = 6.25 µg/ml). This study predicts various minimum inhibitory concentrations against the different bacterial strains and concluded result by suggesting that Q-35 should be further studied for its in-vitro activity. [11]

Another in-vitro antibacterial comparative study was carried out by same author on the bactericidal effects of balofloxacin, sparfloxacin, tosufloxacin, and ofloxacin on 18 strains of *MRSA* and 3 strains of *Staphylococcus epidermidis* by a viable count method. Bacterial strains used were recent clinical isolates collected from various hospitals in Japan and all *S.aureus* strains were resistant to methicillin agar dilution, in-vitro. Q-35 produced the greatest bactericidal response after 1 hr of exposure compared with the other quinolones tested. After a 4-hr exposure, Q-35 decreased the viable counts from $1.7x10^7$ CFU/ml to approximately 10^4 CFU/ml at drug concentrations that were greater than the MIC. Tosufloxacin and sparfloxacin produced no bactericidal effect until after 2 hr of exposure to quinolone at all of the concentrations tested. After 4 or 6 hr, tosufloxacin and sparfloxacin exhibited weak bactericidal activity at values greater than the MIC. Q-35 exhibited bactericidal activity against resistant strains of *S.aureus* ATJ-26 (sparfloxacin resistant), ATJ-27 (resistant) at values greater than the MIC. The study though confirms about balofloxacin effectiveness against *S.aureus* resistant strains to sparfloxacin through in-vitro study but do not focus on its exact mechanism of bacterial killing. They proposed that the introduction of a methoxy group into the 8 position of quinolones contributed to these activities. [10]

One study was carried out by Takahashi H et al to predict the distribution of fluoroquinolone resistance-associated point mutations in genes encoding the subunits of DNA gyrase and DNA topoisomerase IV using 110 clinical isolates of *Staphylococcus aureus*. Point mutations were detected by polymerase chain reaction (PCR) and restriction fragment length polymorphism analysis and mutations were further characterized by sequencing of PCR products. 70% of isolates showed mutations at Ser84 of GyrA whereas, 77 of 110 isolates were identified as GrlA

Ser80 mutants. The findings of the study confirmed that GyrA and GrlA are both important determinants of quinolone resistance in *S.aureus*. This study has limitations to few patterns of mutations. The study predicts that balofloxacin can be resistant to *S.aureus* isolates through these particular mutations. The study showed balofloxacin comparison with other fluoroquinolones for genetic mutation. In general the study specifies even organisms can develop resistance to balofloxacin like other fluoroquinolones by genetic mutations. [12]

Other 3 studies were available as abstract[13-15] of which 1 was clinical study, [13] 1 in-vitro study [14] and 1 is a genetic mutation study.[15]

Obana M et al conducted a clinical study to investigate efficacy, safety and usefulness of balofloxacin for patients with acute infectious enteritis and the carriers mainly shigellosis. The dosing of balofloxacin includes 200 mg twice daily dose for 3 days to patients with cholera, 7 days to patients with Salmonella enteritis and 5 days to patients with other conditions of infectious enteritis including shigellosis. The efficacy was analyzed in 89 of the 135 patients who received the administration (43 patients with shigellosis, 14 with Salmonella enteritis, 8 with enteropathogenic/ enterotoxigenic Escherichia coli enteritis, 3 with cholera, 7 with enteritis with other pathogenic bacteria, 6 with polymicrobial infectious enteritis and 8 with acute enteritis that was pathogen-negative). Patients bearing symptoms and who thus could be analyzed for drug efficacy, the drug was markedly effective or effective 50/52 (96.2%). Bacteriologically, the drug was effective for Shigella spp. in 41 (100%) of 41, Salmonella spp. in 12 (85.7%) of 14, and enteropathogenic/enterotoxigenic *Escherichia coli* in 8 of 8 cases. The results suggest that balofloxacin is highly useful for infectious enteritis such as that caused by shigellosis.[13]

Similar to that of Obana M et al, Fukuyama M et al assessed antibacterial activity of balofloxacin against isolates from patients with bacterial enteritis in-vitro. Balofloxacin was compared with norfloxacin, ofloxacin and ciprofloxacin. Bacterial strains used in this experiment were freshly isolated from patients with infectious enteritis just before balofloxacin therapy. The isolates were 43 strains of *Vibrio cholerae*, 1 strain of Campylobacter spp., 4 strains of Aeromonas spp., 3 strains of *Plesiomonas shigelloides*, 1 strain of *Vibrio mimicus*. MIC_{90} of balofloxacin against 43 strains of Shigella spp., 13 strains of Salmonella spp. and 9 strains of *E. coli* were 0.39, 0.39, 0.2 µg/ml, respectively. All strains of Aeromonas spp. and *P. Shigelloides* were inhibited by the concentrations under 0.39 and 0.05 µg/ml.[14]

Resistance of quinolones due to mutations in the gyrA and parC genes were assessed using *Staphylococcus epidermidis* strains isolated from patients with endophthalmitis, corneal ulcers

and conjunctivitis in one study. *S. epidermidis* strains were isolated from patients with conjunctivitis (n=23), endophthalmitis (n=14) and corneal ulcers (n=7). MICs were determined by broth and agar dilution methods for moxifloxacin, gatifloxacin, balofloxacin, rufloxacin and pazufloxacin. Mutations were identified by sequencing the gyrA and parC genes, and their expression was determined by reverse transcriptase polymerase chain reaction. Study results found that 13.6% (6/44) of the strains were quinolone resistant. In endophthalmitis, 21.4% were gatifloxacin, moxifloxacin and balofloxacin resistant. In corneal ulcers, 14.2, 14.2 and 28.5% were gatifloxacin, moxifloxacin and balofloxacin resistant, respectively, and in conjunctivitis only 4.3% were gatifloxacin resistant. The 6 strains with quinolone resistance showed mutations at Ser84Phe for the gyrA gene, and Ser80Phe for the parC gene. Gatifloxacin did not change the expression levels of gyrA and parC genes.[15]

Cochrane Library

Literature search:

The result obtained from Cochrane Library for advanced search using term "Balofloxacin" (1990-2011) is depicted in Figure 2b.

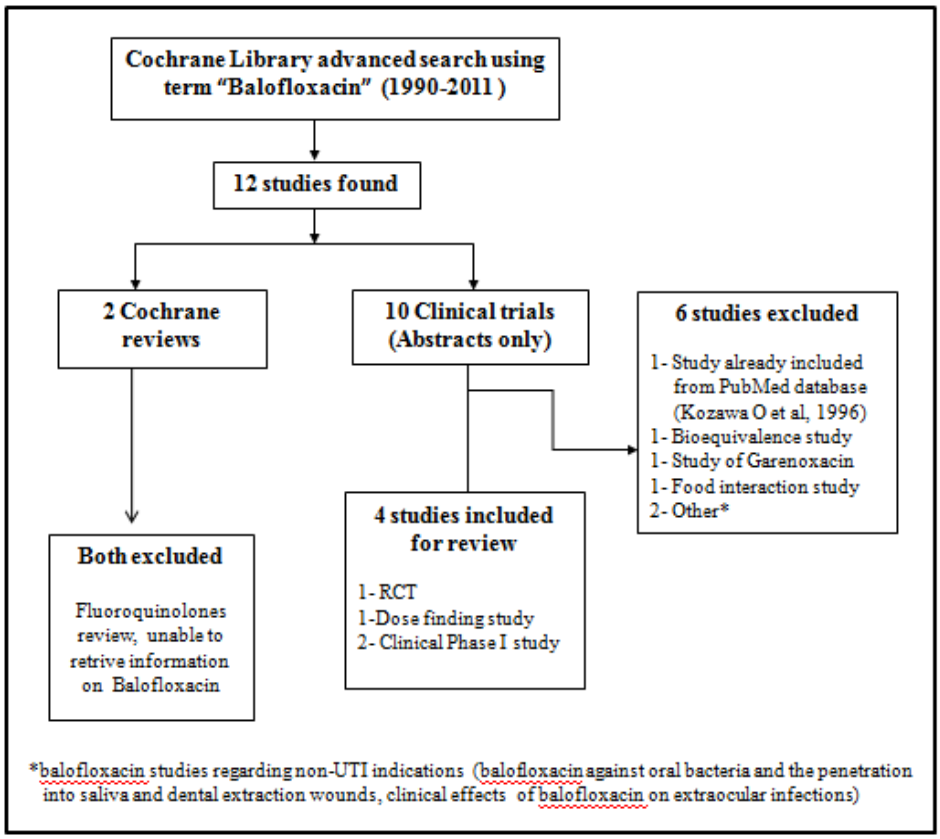


Figure 2b: Cochrane Library search strategy

Of the 12 titles and abstracts screened, 2 were Cochrane review abstracts and 10 were clinical trial abstracts among which 1 randomized controlled trial (RCT)[19], 1 Dose finding study[20] and 2 Clinical Phase I studies[21,22] were included for review. Both Cochrane reviews were excluded as both were regarding wide ranging review on fluoroquinolones with no information for balofloxacin. Among 10 clinical trials, 6 were excluded which includes 1 bioequivalence study, 1 study of garenoxacin, 1 food interaction study and 2 other studies regarding non-UTI indications of balofloxacin and a clinical trial by Kozawa O et al was also excluded as it is already included through PubMed database.

Study characteristics:

The characteristics of the 4 clinical trials are shown in Table 3. A total of 341 patients were assessed. However study population was not defined in a study conducted by Nakashima M et al.[21] 2 comparative studies showed comparison between balofloxacin 200 mg in group 1 for both studies while 300mg in one study[22] and 400 mg in another study[21] in group 2 respectively. A randomized clinical trial was carried out taking 210 subjects and comparing balofloxacin 100 mg with levofloxacin 200 mg twice daily for 7 to 10 days.[19] A dose finding study with 119 subjects was carried out to find out the optimal dose for complicated UTI comparing balofloxacin 200 mg/day with balofloxacin 400 mg/day and ofloxacin 600 mg/day.[20]

Zhang DY et al conducted a randomized, double blind, placebo-controlled study of balofloxacin versus levofloxacin in the treatment of UTI. Both groups were administered tablets twice daily for 7 to 10 days at the dose of 100 mg for balofloxacin and 200mg for levofloxacin. The clinical efficacy was analyzed by full analysis set (FAS) and the per-protocol set (PPS) analysis for 100 cases in balofloxacin group and 103 cases in levofloxacin group. At the end of treatment, in FAS analysis the total cure rates and effective rates were 69.23% and 95.19% in balofloxacin group, 67.96% and 97.09% in levofloxacin group; in PPS analysis the total cure rates and effective rates were 70% and 97% in balofloxacin group, 67.96% and 97.09% in levofloxacin group. The bacterial clearance rates were 93.18% and 90.70% respectively. Main adverse reactions were leucopenia, gastrointestinal symptoms, elevated conjugated bilirubin and abnormal urine. The authors concluded that balofloxacin tablet is as effective and safe as levofloxacin tablet in the treatment of minor and moderate UTI.[19]

A dose finding study of balofloxacin for its oral use in the treatment of complicated UTIs was carried out by Kumazawa JA et al. The study compared a balofloxacin 200 mg/day group (L group) with a balofloxacin 400 mg day group (H group) as a double blind study, and with an

ofloxacin 600 mg/day group (C group) as a non blind study, in regard to clinical efficacy, safety and usefulness. Of a total of 119 cases, clinical efficacy was evaluated in 30 cases in the L group, 33 cases in the H group and 34 cases in the C group. The overall clinical efficacy rate was 76.7% in the L group, 78.8% in the H group and 85.3% in the C group. With regard to polymicrobial infection, the overall clinical efficacy rate was 66.7% in the L group, 71.4% in the H group and 70.0% in the C group. The overall bacteriological eradication rate was 86.4% in the L group, 86.3% in the H group and 87.5% in the C group. The number of strains appearing after treatment was 5 (in 4 patients, 13.3%) in the L group, 3 (in 2 patients, 6.1%) in the H group and 8 (in 6 patients, 17.6%) in the C group. Adverse events were observed in 1 case in the L group (2.8%), in 6 in the H group (14.3%) and in 2 in the C group (4.9%). The general safety rate was 97.0% in the L group, 91.9% in the H group and 100% in the C group. The usefulness was 78.6% in the L group, 76.8% in the H group and 81.8% in the C group. Based on the results of this study and open clinical studies, it was concluded that the optimal dosage of balofloxacin in the treatment of complicated UTIs is 400 mg/day administered in two divided doses.[20]

Nakashima M et al investigated safety and pharmacodynamics of balofloxacin for single oral administration to healthy male volunteers. A preliminary test was performed on two patients at each dose of 10 mg, 20 mg and 50 mg during fasting by single administration. Subsequently, oral administration was initiated at 100 mg and then gradually increased to 200 and 100 mg as the test. The drug was administered at a dose of 200 mg twice before and after breakfast to the same subject by the cross-over method in which a one-week drug-cessation period was included for the purpose of investigating the influence of meals. One patient in the group to which 200 mg was administered post-prandially, had mild and transient dull headache, and one in the group to which 400 mg was administered had symptoms resembling dizziness. The study suggests that balofloxacin can be clinically administered in patients with infectious diseases, because it is safe and shows excellent pharmacodynamics.[21]

Same author conducted clinical phase I study of balofloxacin for repeated oral administration to healthy male volunteers at a dose of 200 or 300 mg every 12 hours for assessment of its safety, pharmacodynamics and influence on intestinal bacterial flora. Slight physical disorder of the abdominal region appeared in two subjects each in every administration group (each consisting of six subjects). Subjective symptoms began to appear 3-4 days after administration but they subsided with defecation on the day after administration or the following day. One subject in the 200 mg group had mild, transient constipation.[22]

CONCLUSION

Balofloxacin showed bactericidal activity against various strains as claimed in in-vitro / in-vivo studies and is also susceptible to mutation at gyrA gene level. As far as its clinical effectiveness is concerned for UTI and RTI it is found to be equivalent to ofloxacin but the evidence in terms of RCTs is rarely available in scientific databases. Thus, we conclude that more RCTs are required to prove its superiority in terms of efficacy and safety compared to other fluoroquinolones.

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