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Review

Prulifloxacin: a review focusing on its use beyond respiratory and urinary tract infections

Petros I. Rafailidis[a,b], Konstantinos A. Polyzos[a], Konstantinos Sgouros[a], Matthew E. Falagas[a,b,c,*]

[a] Alfa Institute of Biomedical Sciences (AIBS), 9 Neapoleos Street, 151 23 Marousi, Athens, Greece
[b] Department of Medicine, Henry Dunant Hospital, Athens, Greece
[c] Department of Medicine, Tufts University School of Medicine, Boston, MA, USA

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ABSTRACT

Prulifloxacin is a fluoroquinolone antibiotic that has been approved in several European countries for the treatment of lower urinary tract infections and exacerbations of chronic bronchitis. In this review, PubMed and Scopus databases were searched for potential uses of prulifloxacin beyond respiratory and urinary tract infections. Nine individual articles (eight randomised controlled trials and one cohort study) were regarded as eligible for inclusion in the review. Three of the studies were double-blinded, whilst six were open-label trials. Three studies referred to the treatment of patients with chronic bacterial prostatitis (CBP), one to prophylaxis of patients undergoing transrectal prostate biopsy, one to prophylaxis of women undergoing surgical abortion, two to patients with traveller's diarrhoea, one to diabetic patients with soft tissue infections or osteomyelitis, and one to improving tolerance of Bacillus Calmette–Guérin (BCG) instillations in patients with bladder cancer. Regarding CBP, prulifloxacin was non-inferior to its comparators, with a trend towards better microbiological outcomes at follow-up. Regarding traveller's diarrhoea, prulifloxacin resulted in better clinical and microbiological outcomes compared with placebo. Finally, prulifloxacin decreased the adverse events associated with BCG instillations in patients with bladder cancer, without affecting cancer recurrence rates. In summary, prulifloxacin appears to be a promising agent for the treatment of bacterial prostatitis and traveller's diarrhoea.

1. Introduction

Prulifloxacin, the lipophilic prodrug of ulifloxacin, is an oral fluoroquinolone agent with antimicrobial activity against Gram-negative and Gram-positive bacteria. Synthesised in Japan in 1987, it is now approved for use in several European countries, but not in the USA. Its indications include acute uncomplicated lower urinary tract infections (simple cystitis), complicated lower urinary tract infections and acute exacerbations of chronic bronchitis [1,2].

As with other fluoroquinolones, prulifloxacin displays a favourable pharmacokinetic and pharmacodynamic profile. Following absorption from the small intestine, prulifloxacin is immediately metabolised by serum esterases to the active metabolite ulifloxacin [3]. Ulifloxacin is characterised by a relatively high mean volume of distribution and therefore may display good penetration into peripheral target tissues. It has a long elimination half-life, thus allowing once-daily administration of prulifloxacin. Ulifloxacin is excreted mainly in the faeces, whilst a lower proportion is excreted in the urine [4,5]. This agent is mainly active against Gram-negative rods, including *Pseudomonas aeruginosa* but not *Acinetobacter*. With regard to Gram-positive bacteria, it shows some activity against *Streptococcus* spp., *Listeria monocytogenes*, meticillin-susceptible staphylococci and vancomycin-susceptible enterococci [6–13]. Finally, ulifloxacin is active against some anaerobes, including *Peptostreptococcus* spp. and *Prevotella bivia*, whereas its activity against *Bacteroides fragilis* and *Clostridium* spp. is weak [14,15].

Although the rationale for using prulifloxacin for the treatment of patients with urinary and respiratory tract infections is supported by adequate evidence [16–24], little emphasis has been given to the therapeutic potential of this antibiotic for the management of infections beyond its traditional use, including genital tract infections, gastrointestinal tract infections, bone and joint infections, and skin and soft-tissue infections. In this review, we sought to collect and evaluate the available published clinical evidence regarding the use of prulifloxacin beyond respiratory and urinary tract infections.

2. Data sources

The studies to be included in this systematic review were identified by searching PubMed and Scopus databases, both last accessed

* Corresponding author. Tel.: +30 694 61 10 000; fax: +30 210 68 39 605.
E-mail address: m.falagas@aibs.gr (M.E. Falagas).

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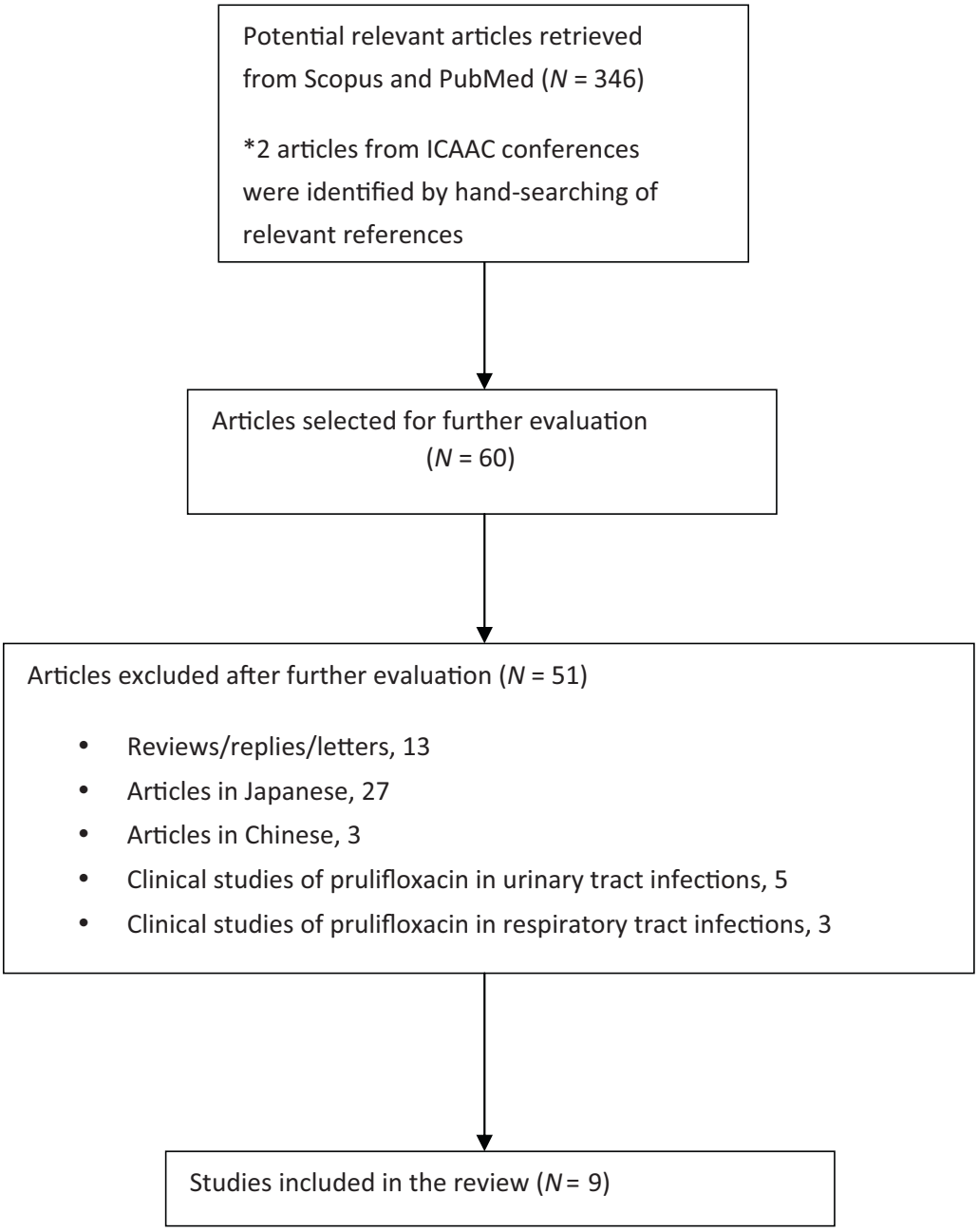

Fig. 1. Flow diagram of the selection process for included studies.

during September 2010. The search term applied to both of the databases was 'prulifloxacin'. References from relevant articles as well as conference papers were also hand-searched.

2.1. Study selection criteria

Two reviewers (KAP and KS) independently performed the literature search and assessed the retrieved studies for eligibility for inclusion. To be considered eligible for inclusion in the review, an article should have provided data regarding the clinical use of prulifloxacin beyond urinary and respiratory tract infections. Prostatitis was regarded as an infection of the genital tract and therefore studies referring to this condition were included in the review. Only articles written in English, German, French or Italian were included. No restriction on time of publication was set.

2.2. Data extraction

Data extracted from each of the evaluated articles consisted of study design, country and year to which each specific study referred, study population, characteristics of the treatment administered (type, dosage and duration) as well as outcomes of each study.

3. Synthesis of the available evidence

The selection process for included studies is depicted in Fig. 1. A total of nine individual articles [eight randomised controlled trials (RCTs) [25–32] and one non-comparative, prospective cohort study [33]] were regarded as eligible for inclusion in the review (Table 1). Three of these studies were double-blinded [25,30,31], whilst the rest were unblinded [26–29,32,33]. Regarding the included RCTs,

Table 1
Studies regarding the use of prulifloxacin beyond urinary and respiratory tract infections.

Reference	Study design	Country/year of publication	Study population	Compared arms	Primary outcomes[a]	Secondary outcomes[a]
Giannarini et al. [25]	SC, DB RCT	Italy, 2007	96 patients (age >18 years, median 42 years) with CBP	PRFX 600 mg qd (4 weeks) vs. levofloxacin 500 mg qd (4 weeks)	Microbiological eradication: overall, 32/44 (72.7%) vs. 32/45 (71.1%) *Escherichia coli*, 12/15 (80%) vs. 12/16 (75%) *Klebsiella pneumoniae*, 6/8 (75.0%) vs. 4/6 (66.7%) *Pseudomonas aeruginosa*, 1/2 (50%) vs. 2/4 (50%) *Proteus mirabilis*, 5/7 (71.4%) vs. 4/6 (66.7%)	NIH-CPSI reduction: 10.75 vs. 10.73 Recurrent infection: 5/32 (15.6%) vs. 11/32 (34.4%) AEs: 8/44 (18%) vs. 10/45 (22%) Withdrawal due to AEs: 2/48 (4%) vs. 1/48 (2%)
Cai et al. [26]	SC RCT	Italy, 2010	221 patients (age 18–45 years) with CBP due to *Chlamydia trachomatis*	PRFX 600 mg qd (2 weeks) vs. doxycycline 100 mg bid (3 weeks)	Clinical effectiveness: 90/109 (82.6%) vs. 81/102 (79.4%) NIH-CPSI reduction: 9.51 vs. 8.31 Microbiological eradication: 52/109 (47.7%) vs. 40/102 (39.2%) ($P<0.01$)	AEs: 3/109 (2.8%) vs. 2/102 (2.0%) Withdrawal due to AEs: 2/117 (1.7%) vs. 2/104 (1.9%)
Cai et al. [27]	SC RCT	Italy, 2009	143 patients (age 18–45 years, mean 32 years) with CBP	PRFX 600 mg qd + plant extracts [b] vs. PRFX 600 mg qd alone	Clinical effectiveness at 6 months: 96/106 (90.6%) vs. 8/37 (21.6%) ($P<0.01$) NIH-CPSI reduction: 18.3 vs. 10.2 ($P<0.01$) IPSS reduction: 12.7 vs. 6.25 ($P<0.01$) Clinical effectiveness at 1 month: 95/106 (89.6%) vs. 10/37 (27.0%) ($P<0.01$) NIH-CPSI reduction: 17.7 vs. 9.7 ($P<0.01$) IPSS reduction: 12 vs. 5.7 ($P<0.01$)	AEs: 3/106 (2.8%) vs. 1/37 (2.7%)
Mari [28]	SC RCT	Italy, 2007	432 males (age 44–82 years, mean 67 years) undergoing transrectal prostate biopsy	PRFX 600 mg qd: single dose (3 h before biopsy) vs. a 5-day course with the first dose 3 h before biopsy	Fever: 2/210 (0.95%) vs. 2/222 (0.90%) Local symptoms (haematuria, haemospermia, urine retention) without fever: 36/210 (17%) vs. 31/222 (14%)	N/A
Caruso et al. [29]	SC RCT	Italy, 2008	466 pregnant women (age 14–44 years, mean 26.7 years) undergoing surgical abortion	PRFX 600 mg qd: Group A (5 days after abortion), Group B (3 days after abortion), Group C (1 day before and 2 days after abortion)	PID: 16/153 (10.5%) vs. 11/155 (7.1%) vs. 4/158 (2.5%) Group C vs. A, $P<0.05$	N/A
Cavani [33]	Non-comparative, prospective, cohort study	Italy, 2007	60 patients (mean age 67 years): 30 with soft tissue infection and 30 with osteomyelitis	PRFX 600 mg qd ± teicoplanin or metronidazole. Mean duration of treatment, 18 days for soft tissue infection and 40 days for osteomyelitis [c]	Clinical effectiveness: soft tissue infection, 30/30 (100%); osteomyelitis, 26/30 (86.7%)	Safety: tendinitis or cardiovascular disease, N/R Withdrawal due to AEs, N/R Drug interactions, N/R
DuPont et al. [30]	MC, DB RCT	Mexico, Peru, 2008	282 patients (age ≥18 years, median 22 years) with traveller's diarrhoea	PRFX 600 mg qd (3 days) vs. placebo	TLUS (median): 24.2 h (mITT, ME), 20.6 h (ITT) vs. N/A [d]	Clinical success at TOC visit: ITT, 146/187 (78.1%) vs. 38/95 (40.0%); mITT, 99/126 (78.6%) vs. 25/61 (41.0%); ME, 86/110 (78.2%) vs. 23/55 (41.8%) ($P<0.01$)

Table 1 (*Continued*)

Reference	Study design	Country/year of publication	Study population	Compared arms	Primary outcomes[a]	Secondary outcomes[a]
					Patients with TLUS prior to TOC visit: ITT, 146/187 (78.1%) vs. 39/95 (41.1%); mITT, 99/126 (78.6%) vs. 26/61 (42.6%); ME, 86/110 (78.2%) vs. 23/55 (41.8%) ($P<0.01$)	Microbiological eradication: 80.9% vs. 52.7% ($P<0.01$) Relapse: ITT, 5/158 (3.2%) vs. 4/50 (8.0%); mITT, 3/106 (2.8%) vs. 3/35 (8.6%); ME, 3/93 (3.2%) vs. 2/31 (6.5%) AEs: 57/187 (30.5%) vs. 38/95 (40.0%) Withdrawal due to AEs: 2/187 (1.1%) vs. 1/95 (1.1%)
Steffen et al. [31]	MC DB RCT	India, Guatemala, Mexico, 2009	268 patients (age ≥18 years, mean 32 years) with traveller's diarrhoea	PRFX 600 mg qd (3 days) vs. placebo	TLUS (median): 33 h (ITT, mITT), 32 h (ME) vs. N/A [d] Patients with TLUS prior to TOC visit: mITT, 72/97 (74.2%) vs. 38/103 (36.9%) ($P<0.01$)	Microbiological eradication: mITT, 65/97 (67.0%) vs. 28/103 (27.2%); ME, 55/82 (67.1%) vs. 28/91 (30.8%) ($P<0.01$) AEs: N/S
Damiano et al. [32]	SC RCT	Italy, 2009	72 patients (age ≤85 years, mean 62 years) with non-muscle-invasive bladder cancer who underwent TUR	BCG instillations + PRFX 600 mg qd (3 days) after each instillation vs. BCG instillations alone	After 4th instillation, PRFX reduced the number of patients with moderate ($P=0.03$), severe ($P<0.01$) and overall AEs ($P=0.012$) Mild AEs: N/S Withdrawal or delay of instillation course due to AEs: 19% vs. 34% ($P=0.04$)	Cancer recurrence: at 3 months, 13.5% vs. 17%; at 6 months, 21.6% vs. 23%

SC, single centre; DB, double-blinded; RCT, randomised controlled trial; MC, multicentre; CBP, chronic bacterial prostatitis; TUR, transurethral resection; PRFX, prulifloxacin; qd, one daily; bid, every 12 h; BCG, Bacillus Calmette–Guérin; NIH-CPSI, National Institutes of Health–Chronic Prostatitis Symptom Index; IPSS, International Prostatic Symptom Score; PID, pelvic inflammatory disease; TLUS, time to last unformed stool; mITT, modified intention-to-treat population; ME, microbiologically evaluable population; ITT, intention-to-treat population; N/A, not applicable; TOC, test of cure; AEs, adverse events; N/S, not significant; N/R, not reported.

[a] *P*-values are shown only for statistically significant outcomes ($P<0.05$).

[b] *Serenoa repens* (160 mg), *Urtica dioica* (120 mg) (ProstaMEV®), quercetin (100 mg) and curcumin (200 mg) (FlogMEV®).

[c] This study was a non-comparative prospective cohort study, thus there were no compared arms.

[d] TLUS for the placebo group could not be estimated because >50% of the subjects were censored (TLUS > 120 h or clinical failures).

three referred to the treatment of patients with chronic bacterial prostatitis (CBP) [25–27], one to prophylaxis of patients undergoing transrectal prostate biopsy [28], one to prophylaxis of women undergoing surgical abortion [29], two to the treatment of traveller's diarrhoea [30,31] and one to the use of prulifloxacin for improving tolerance of Bacillus Calmette–Guérin (BCG) installations in patients with bladder cancer [32]. The cohort study involved diabetic patients with soft tissue infections or osteomyelitis [33].

3.1. Chronic bacterial prostatitis

A double-blinded RCT demonstrated the non-inferiority of prulifloxacin compared with levofloxacin in terms of efficacy and safety in the treatment of patients with CBP [25]. A total of 96 patients were randomised to either prulifloxacin 600 mg ($n=48$) or levofloxacin 500 mg ($n=48$) once daily for 4 weeks. Microbiological efficacy was assessed using the Meares–Stamey test 1 week after the end of therapy (first visit) and 6 months later in patients with confirmed eradication (second visit). Clinical efficacy was evaluated at the first visit using the National Institutes of Health–Chronic Prostatitis Symptom Index (NIH-CPSI), a relatively objective score that quantifies the symptoms of CBP. Causative pathogens included *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *P. aeruginosa* and *Enterococcus faecalis*. Prulifloxacin achieved microbiological eradication in 32 (72.7%) of 44 patients compared with 32 (71.1%) of 45 patients for levofloxacin (95% confidence interval for difference in microbiological eradication rates, −16.74 to 19.76; $P=0.8$). Amongst patients with confirmed eradication, 5 (15.6%) of 32 in the prulifloxacin group and 11 (34.4%) of 32 in the levofloxacin group demonstrated a positive Meares–Stamey test at the 6-month follow-up visit ($P=0.08$). Finally, prulifloxacin and levofloxacin were comparable with regard to clinical efficacy (reduction in NIH-CPSI score of 10.7 in both groups) and safety profile.

Another RCT demonstrated that a 2-week course of prulifloxacin was clinically equivalent and microbiologically superior to a 3-week course of doxycycline for CBP due to *Chlamydia trachomatis* [26]. A total of 221 patients were randomised to receive either prulifloxacin 600 mg once daily for 14 days ($n=117$) or doxycycline 100 mg twice daily for 21 days ($n=104$). At enrolment and 30

days after initiation of treatment, the clinical and microbiological statuses of subjects were assessed using the NIH-CPSI and a series of *Chlamydia* infection markers [microbiological cultures for uropathogenic bacteria and yeasts, DNA extraction and mucosal immunoglobulin A (IgA) analysis, seminal plasma interleukin (IL)-8 and serum IgA and IgG anti-*C. trachomatis* analysis], respectively. At the follow-up visit, clinical improvement (significant NIH-CPSI reduction) was observed in 90 (82.6%) of 109 patients in the prulifloxacin group and 81 (79.4%) of 102 patients in the doxycycline group ($P = 0.08$). However, prulifloxacin was found to be superior ($P < 0.001$) to doxycycline in terms of mucosal anti-*C. trachomatis* IgA and seminal plasma IL-8 reduction.

Furthermore, in a RCT evaluating the clinical efficacy of co-administration of prulifloxacin with several plant extracts (*Serenoa repens*, *Urtica dioica*, quercetin and curcumin) in the CBP setting, 143 patients were randomised to receive a 2-week regimen of either combination therapy ($n = 106$) or prulifloxacin alone ($n = 37$) [27]. Clinical efficacy was evaluated at two follow-up visits, 1 month and 6 months after initiation of treatment, using the NIH-CPSI and the International Prostatic Symptom Score (IPSS). One month after the initiation of treatment, 89.6% of patients treated with the combination regimen and 27.0% of those receiving antibiotic alone did not report any symptoms ($P < 0.01$). Significant differences were also found between groups in terms of NIH-CPSI and IPSS reduction. Similar results were found at the 6-month follow-up visit.

3.2. Prophylaxis in patients undergoing transrectal prostate biopsy

A RCT assessed the effectiveness of two prulifloxacin dosing regimens in patients undergoing transrectal prostate biopsy [28]. A total of 432 males were assigned to either a single 600 mg oral dose 3 h before the procedure ($n = 210$) or a 5-day course of prulifloxacin 600 mg once daily with the first dose given 3 h before the procedure ($n = 222$). The primary outcome was clinical effectiveness, defined as the absence of fever or other signs and symptoms of infection. The most frequent events were local symptoms (haematuria, haemospermia, urine retention) without occurrence of fever and were equally distributed amongst groups (17% vs. 14%). These symptoms resolved spontaneously within a few days. Rates of fever were similar between groups (0.95% vs. 0.90%).

3.3. Prophylaxis in women undergoing surgical abortion

An Italian RCT sought to evaluate the efficacy of different dosing regimens of prulifloxacin in the prevention of infection caused by surgical abortion [29]. In total, 466 women were randomised to three groups receiving prulifloxacin 600 mg once daily: Group A ($n = 153$) for 5 days after abortion; Group B ($n = 155$) for 3 days after abortion; and Group C ($n = 158$) 1 day before and 2 days after abortion. Abortions were performed in a range of gestational ages between 6 weeks and 11 weeks. Pelvic inflammatory disease rates were 10.5% in Group A, 7.1% in Group B and 2.5% in Group C. The regimen of Group C was more effective than that of Group A ($P < 0.05$), but not that of Group B. In summary, prulifloxacin administration 1 day before and for a few days after abortion surgery may be an effective way to prevent gynaecological infections.

3.4. Diabetic foot infections

A cohort study assessed the effectiveness and safety of prulifloxacin as outpatient therapy in the treatment of 60 patients with mild or moderate diabetic foot infection (30 cases of soft tissue infection and 30 cases of osteomyelitis) [33]. A mild or moderate infection was characterised by the presence of purulent material and signs of local inflammation with or without fever and leukocytosis. In soft tissue infections, prulifloxacin 600 mg once daily was administered for at least 15 days, whereas in the case of osteomyelitis the minimum duration of treatment was 40 days. Teicoplanin (200 mg intramuscular for at least 15 days) and metronidazole (7.5 mg/kg thrice daily for 10–15 days) were added, respectively, in the case of isolation of meticillin-resistant *Staphylococcus aureus* (MRSA) and anaerobic bacteria from the site of infection. The majority of infections were polymicrobial. Isolated bacteria included *S. aureus* (52%), coagulase-negative staphylococci (40%), *Enterococcus* spp. (35%), *P. mirabilis* (35%), *P. aeruginosa* (23%) and *Bacteroides* spp. (30%). Cure was achieved in all subjects (100%) with soft tissue infection and in 26 (86.7%) of 30 subjects with osteomyelitis. No cases of tendinitis or cardiovascular disease were observed.

3.5. Gastrointestinal infections

A double-blinded RCT presented at the 2008 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)/Infectious Diseases Society of America Annual Meeting sought to evaluate the potential role of prulifloxacin in the treatment of traveller's diarrhoea [30]. In total, 282 travellers were randomised to receive either prulifloxacin 600 mg ($n = 187$) or placebo ($n = 95$) once daily for 3 days. A test of cure (TOC) visit was carried out 1–3 days after the end of treatment, whilst a microbiological stool examination took place at baseline and 3–6 days after the end of treatment. Primary outcome was the duration of diarrhoea, defined as the time to last unformed stool (TLUS), whilst secondary outcomes were microbiological eradication and safety. Prulifloxacin was superior to placebo in terms of TLUS in the intention-to-treat (ITT), modified intention-to-treat (mITT) and microbiologically evaluable (ME) populations. Amongst patients treated with prulifloxacin, the median TLUS was 24.2 h in both the ME and mITT groups. The median TLUS in the placebo group was not determined because 52% of the subjects did not achieve wellness by the TOC visit. Microbiological eradication of causative pathogens, including *E. coli*, *Salmonella*, *Campylobacter* and *Shigella*, was observed in 80.9% and 52.7% of the subjects in the prulifloxacin and placebo groups, respectively ($P < 0.01$). Finally, prulifloxacin and placebo showed similar safety profiles.

A similar RCT (2009 ICAAC meeting) allocated 268 adult travellers with gastroenteritis to either prulifloxacin ($n = 133$) or placebo ($n = 135$) once daily for 3 days [31]. Prulifloxacin was superior to placebo in the ITT, mITT and ME populations regarding the resolution of diarrhoea ($P < 0.01$). Amongst prulifloxacin recipients, median TLUS after initiation of treatment was 33 h in the ITT and mITT groups and 32 h in the ME group. In the placebo group, a median TLUS could not be estimated. Isolated pathogens, including enterotoxigenic and enteroaggregative *E. coli*, *Shigella*, *Salmonella*, *Plesiomonas* and *Campylobacter* spp., were eradicated in 67.0% and 27.2% of patients given prulifloxacin and placebo, respectively ($P < 0.01$).

3.6. Prophylaxis against BCG-associated toxicity in the treatment of carcinoma of the bladder

An unblinded RCT demonstrated that prophylactic treatment with prulifloxacin improves tolerance to BCG instillations in patients with bladder cancer [32]. A total of 72 patients having undergone transurethral resection were randomised to a group treated with a 3-day course of prulifloxacin once daily after each weekly instillation ($n = 37$) or to a control group that received only BCG induction treatment ($n = 35$). Adverse events were self-reported after each instillation and were classified by the investigators as mild, moderate or severe according to a classification grid. Results showed that prulifloxacin significantly

decreased the proportion of subjects with moderate ($P = 0.03$), severe ($P = 0.008$) and overall ($P = 0.012$) adverse events after the fourth instillation. Adverse events related to BCG therapy made more patients stop or delay the course of instillations in the control group (34%) than in the prulifloxacin group (19%) ($P = 0.04$).

4. Discussion

This review shows that there may be a role for prulifloxacin in the treatment of infections beyond its current indications. Specifically, prulifloxacin is a promising therapeutic agent for the treatment of bacterial prostatitis and traveller's diarrhoea. In addition, prulifloxacin is associated with decreased toxicity due to BCG treatment for bladder cancer.

One of the most troublesome infections of the male genital tract is CBP [34]. Given that the prostate tissue is an anatomic department not easily penetrated, a favourable pharmacokinetic profile of an antibiotic is of great importance [35]. Ulifloxacin shows excellent penetration into prostate tissue, where its concentrations always exceed those in plasma. Mean prostate tissue/plasma concentration ratios following antibiotic administration ranged from 3.8 to 9.5 [36]. In addition, ulifloxacin is not only highly active against commonly involved Gram-negative pathogens (*E. coli*, *K. pneumoniae*, *P. mirabilis*) but also displays some activity against Gram-positive bacteria, including *Enterococcus* and *Staphylococcus* spp., which have recently been found to play an important role in CBP [37,38]. Another advantage of this antibiotic in the CBP setting is its immunomodulating effect. In vitro studies indicated that it can modulate the expression of pro-inflammatory cytokines, the role of which is well established in chronic prostatitis [39,40]. Ulifloxacin was also found to accumulate both in bacterial cells and polymorphonuclear neutrophils, where it acts on the morphology of microorganisms making them more prone to phagocytosis and enhances the phagocytic capacity of macrophages [41–43]. These are highly desirable properties in the treatment of persisting and recurrent infections such as CBP, since they create a hostile milieu for commonly involved bacteria [44]. Notably, Giannarini et al. [25] showed that prulifloxacin was microbiologically and clinically equivalent to levofloxacin, a reference drug for CBP [45]. This study also found a trend towards lower recurrence rates with prulifloxacin after 6 months.

The satisfactory accumulation of ulifloxacin in the gastrointestinal tract along with its potent activity against Gram-negative rods support its therapeutic potential in traveller's diarrhoea [6]. A large in vitro study comparing the activities of different antibiotics against a worldwide collection of gastroenteritis-producing pathogens indicated that ulifloxacin was highly active against *E. coli*, *Shigella*, *Salmonella*, *Yersinia*, *Aeromonas*, *Plesiomonas* and *Vibrio* spp. [minimum inhibitory concentrations for 90% of the organisms (MIC_{90}) $\leq$0.06 μg/mL]. Its spectrum of activity was similar to that of ciprofloxacin, but ulifloxacin was two- to four-fold more potent. Only rare strains of *E. coli* (3%), *Aeromonas* (2%) and *Campylobacter* spp. (14.7%) proved to be resistant [7]. These findings are in accordance with earlier data showing that the MICs of prulifloxacin against Enterobacteriaceae ranged from identical to four times lower compared with ciprofloxacin and from identical to eight times lower compared with levofloxacin and moxifloxacin [8,9].

Prulifloxacin has also been tested in the field of gynaecological infections as it penetrates rapidly into female genital organs. Mean tissue/plasma ratios for gynaecological tissues ranged from 1.5 to 3 [46]. Another potential advantage is that ulifloxacin has very little impact on lactobacilli, the dominating vaginal microflora that inhibits the growth of pathogenic and opportunistic microorganisms predisposing to genital tract infections [47]. A study assessing the in vitro activity of ulifloxacin against 60 anaerobic clinical isolates from patients with gynaecological and obstetric infections showed that ulifloxacin was potent against *Peptostreptococcus magnus* [MIC for 50% of the organisms (MIC_{50}) = 0.2 μg/mL] and *P. bivia* (MIC_{50} = 0.78 μg/mL) but not against *B. fragilis* (MIC_{50} = 3.13 μg/mL) [14]. Of note, the medication shows negligible activity against MRSA, which may cause serious gynaecological infections [48].

In diabetic foot infections, *S. aureus* is the most commonly involved pathogen, whilst anaerobes such as *B. fragilis* also play an important role [49]. In this context, moxifloxacin might be a more rational treatment option than prulifloxacin since it is active against both of these pathogens [50]. Nevertheless, one should not ignore the potent activity of prulifloxacin against *P. aeruginosa*, which is often involved in diabetic foot infections [8,10].

An in vitro study indicated that prulifloxacin, along with ciprofloxacin, were the most active fluoroquinolones against ciprofloxacin-susceptible strains of *P. aeruginosa* (MIC_{90} = 1 μg/mL) [8]. Another study found that prulifloxacin was generally more potent than other fluoroquinolones against 300 multiple-resistant (resistant to more than three primary antipseudomonal drugs) *P. aeruginosa* isolates. Rates of susceptibility were also higher for ulifloxacin (72%) than for ciprofloxacin (65%) and levofloxacin (61%). In this study, a time–kill experiment found that prulifloxacin was superior to ciprofloxacin and levofloxacin with regard to the extent and speed of killing. Furthermore, the investigators assessed these fluoroquinolones in terms of mutant preventing concentration [51–53], with prulifloxacin displaying the lowest values [10]. On the other hand, Montanari et al. [9] found that prulifloxacin and other fluoroquinolones were not active against community and nosocomial isolates of *P. aeruginosa*.

A theoretical advantage of prulifloxacin in patients with cardiovascular disease, such as diabetic patients, might be its safety profile in terms of QT interval prolongation, which constitutes a common adverse event of fluoroquinolone therapy [54]. Recent data point to a potentially decreased risk of cardiotoxicity associated with prulifloxacin in comparison with other quinolones [55–59]. Specifically, in a clinical trial involving healthy patients the maximum QTc prolongation during a 5-day course was 4 ms for prulifloxacin and 12 ms for moxifloxacin [55]. The effect of prulifloxacin fell into the 0–5 ms range, which is considered to be a range with no risk for torsades de pointes [59].

In conclusion, the addition of prulifloxacin to the therapeutic armamentarium has the potential to provide a useful alternative in the treatment of infections beyond the respiratory and urinary tracts. The advantages of single daily dosing, availability in oral form, satisfactory penetration to peripheral tissues along with potent antipseudomonal activity and minimal risk of cardiotoxicity are, at least theoretically, reasons for administration in the treatment of several types of infection. The available favourable clinical data regarding the use of prulifloxacin for genital tract infections and traveller's diarrhoea, as well as for improving tolerance of BCG instillations in patients with bladder cancer, need further corroboration by additional clinical studies.

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