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Fosfomycin-trometamol (FT) or fluoroquinolone (FQ) as single-dose prophylaxis for transrectal ultrasound-guided prostate biopsy (TRUS-PB): A prospective cohort study

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ABSTRACT

Objectives: The increasing incidence of fluoroquinolones (FQ) resistance may lower its efficacy in preventing UTI following transrectal ultrasound-guided prostate biopsy (TRUS-PB). We assessed the efficacy and safety of FQ and fosfomycin-trometamol (FT) in patients undergoing TRUS-PB.
Methods: A prospective observational study was conducted between April 2017 and June 2019 and enrolled men undergoing TRUS-PB and receiving a single-dose of FQ (FQ-arm) or FT (FT-arm) for UTI prophylaxis per physician's choice. The primary efficacy endpoint was self-reported TRUS-PB UTI. We assessed baseline factors associated with UTI with logistic regression.
Results: A total of 222 men were enrolled, 141/222 (64%) received FQ, and 81/222 (36%) FT. The median age was 67.6 years [IQR, 61.4–72.1] and the Charlson score was 3 [IQR, 3–5]. The overall incidence of self-reported TRUS-PB UTI was 12% (24/197, (95%CI, 8%–17%)): 15% (17/116, (95% CI, 10%–17%)) in FQ-arm, versus 9% (7/81, 95% CI (5%–13%)) in FT-arm (RR = 0.55 (95% CI, 0.22–1.40), p-value = 0.209). No baseline characteristic was significantly associated with TRUS-PB UTI. Safety was similar between the arms: the rate of the reported adverse event was 31% (36/116, (95% CI, 25%–37%) in the FQ-arm versus 36% (28/81, (95% CI, 28%–41%)) in the FT-arm (RR = 1.17 (95% CI, 0.64–2.15), p = 0.602).
Conclusions: TRUS-PB UTI prophylaxis with FT and FQ has similar efficacy and safety. A randomized comparison of these two antibiotics is warranted.

Introduction

Transrectal ultrasound-guided prostate biopsy (TRUS-PB) is essential for the diagnosis of prostate cancer. The morbidity associated with TRUS-PB is approximately 25%, and post TRUS-PB bacteriuria is the second leading cause of morbidity (Djavan et al., 2001; Aus et al., 1996). Antibiotic prophylaxis significantly reduces the occurrence of infectious complications and relies on fluoroquinolone (FQ) (Liss et al., 2017). Over the last decade, the global rate of infectious complications increased despite antimicrobial prophylaxis (Halpern et al., 2017; Aly et al., 2015; Carignan et al., 2012; Loeb et al., 2011). A direct relationship with an increase in antimicrobial resistance has been suggested (Halpern et al., 2017;

Abbreviation: ANSM, Agence Nationale de Sécurité du Médicament et des produits de santé; AUA, American Urological Association; FQ, Fluoroquinolones; FT, Fosfomycin-trometamol; CI 95%, 95% confidence interval; IDSA, Infectious Disease Society of America; IQR, interquartile range; MRI, Magnetic resonance imaging; RR, Relative risk; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; TRUS-PB, Transrectal ultrasound-guided prostate biopsy; UTI, Urinary tract infection.

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Aly et al., 2015; Carignan et al., 2012; Loeb et al., 2011). Indeed, selective pressure due to antibiotic overuse, and particularly FQ use, is a well-known risk factor for the development of antibiotic resistance (de Lastours and Fantin, 2015; Liss et al., 2015). In post TRUS-PB UTI, the leading pathogen is *Escherichia coli (E. coli)* (Liss et al., 2017; Liss et al., 2015). In *E. coli*, the resistance rate to FQ (FQR) has been reported to be as high as 25%, and the expression of extended spectrum beta-lactamase (ESBL) keeps rising. Bacterial resistance to FQ is associated with a lower efficacy of antimicrobial prophylaxis and an increase in the rate of urinary tract infection (UTI) occurring after TRUS-PB (Liss et al., 2017; European Centre for Disease Prevention and Control, 2019). FQ are also associated with various side effects (confusion, tendinopathy, liver toxicity, and arterial aneurysms), which increase with age (Perletti et al., 2013; Stahlmann and Lode, 2013). These data emphasize the potential benefit of considering alternative antibiotics such as fosfomycin-trometamol (FT) for empirical antimicrobial prophylaxis of TRUS-PB (Liss et al., 2017; Liss et al., 2015).

FT can be administered orally or intravenously and is effective in complicated UTI (Falagas et al., 2016; Kaye et al., 2019). A single oral dose of 3-g is rapidly distributed in tissues and achieves acceptable intraprostatic concentrations in the uninflamed prostate (Gardiner et al., 2014; Rhodes et al., 2015). FT is bactericidal and active against a wide range of pathogens responsible for UTI, including *E. coli, Citrobacter spp., Enterobacter spp.,* and *Klebsiella spp.* (Gardiner et al., 2014). In *E. coli*, resistance rate to FT remains very low in France, at 0.6% (Anon, 2017). In contrast to FQ, the severity of adverse events (diarrhea in less than 5%) and the impact on fecal flora is limited (Knothe et al., 1991). These properties have prompted the investigation of FT as an alternative antimicrobial prophylaxis in patients undergoing prostate biopsies (Senol et al., 2010; Fahmy et al., 2016; Lista et al., 2014; Sen et al., 2015; Van Besien et al., 2019).

From 2014 to 2019, the results of 4 open-label randomized trials (RCTs) comparing FT to FQ (ciprofloxacin) have been published (Fahmy et al., 2016; Lista et al., 2014; Sen et al., 2015; Van Besien et al., 2019). In addition, a meta-analysis conducted by Noreikaite et al., including these RCTs, showed that the rate of UTIs was significantly lower in patients receiving FT (M-H = 0.20, fixed, 95% CI (from 0.13 to 0.30), $p < 0.001$) (Noreikaite et al., 2018). Urine cultures from patients given FT also showed significantly lower resistance rates (M-H = 0.27, fixed, 95% CI (from 0.15 to 0.50), $p < 0.001$) (Noreikaite et al., 2018). The adverse effect profile was similar (M-H = 1.13, fixed, 95% CI (from 0.51 to 2.50), p = 0.330) (Noreikaite et al., 2018). However, these studies had several limitations. None of the RCTs was double-blind, and significant variations were observed regarding antimicrobial administration in terms of timing (from 1 h to 24 h prior biopsy for FT and ciprofloxacin) and duration (1 or 2 doses of FT and 1–10 doses of ciprofloxacin). Sample size was limited, biopsy technique and follow-up were heterogeneous across trials. Above all, the definition of UTI as a primary endpoint was not in agreement with FDA requirements (symptomatic or asymptomatic, febrile or not) (Food and Drug Administration, 2018). These data were therefore not sufficient to change guidelines or modify the urologists' prescription behavior (Johnson et al., 2015; Ouzzane et al., 2011). There is need of a sufficiently powered double-blind randomized trial to establish the non-inferiority and potentially the superiority of FT as an alternative to FQ either as a targeted or empirical antimicrobial prophylaxis (Fahmy et al., 2016; Lista et al., 2014; Sen et al., 2015; Van Besien et al., 2019). In 2017, urologists in our center started to prescribe FT instead of FQ. Pending the results of such a randomized trial, we believed that it is important to report real-life data as an external validation of the general concept of FT as an alternative to FQ in TRUS-PB.

The objectives of the present study were to estimate the real-life efficacy and safety of FT compared to FQ as an antibiotic prophylaxis for TRUS-PB.

Materials and methods

Study design and settings

Timelines

Early 2017, urologists in our university-affiliated hospital decided to switch patients from FQ to FT for antibiotic prophylaxis before TRUS-PB. Reasons for this switch were multifactorial: previous use of FQ for TRUS-PB, post TRUS-PB UTI resistant to FQ, the high risk of carriage of ESBL-producing strain or FQ-resistant strain, and willingness to try alternative prophylaxis.

This observational monocentric prospective cohort study was conducted between April 2017 and June 2019. It enrolled men undergoing TRUS-PB for suspicion of prostate cancer. According to the physician's choice, patients were receiving either FQ (ciprofloxacin, levofloxacin or ofloxacin) or FT as antibiotic prophylaxis for TRUS-PB.

Study visits

Three visits were performed: one before the biopsies, one at the time of biopsies, and one after the biopsies. The study visits were part of routine care.

The first visit (baseline) consisted of the assessment of patient' eligibility to the study, information, and enrollment (written informed consent) in the cohort. Patients were not enrolled if they had: fever on the day of TRUS-PB ($\geq$38.0 °C) and/or had known allergy or intolerance to FQ and/or FT, and/or positive urine culture requiring antibiotic therapy in the week before TRUS-PB. Antibiotic prophylaxis was prescribed according to the physician's choice. The reasons driving the prescription of FQ or FT were not collected. Recommendations for single-dose drug administration were given to the physicians. The dose recommended for FT was 3 g. For FQ, we recommended a single dose of ciprofloxacin (500 mg), or levofloxacin (500 mg), or ofloxacin (400 mg). Patients were instructed to take an oral single dose of the prescribed antibiotic, after fasting, 2 h prior to the biopsies.

The second visit (for biopsies) was planned 2–4 weeks after the baseline visit. The TRUS-PB was performed according to the French and European guidelines (Mottet et al., 2017). In brief, patients were placed in the lithotomy position. The periprostatic block was obtained with the injection of 20 mL of bupivacaine 1% without adrenaline in the Denonvillier fascia (ultrasound-guided). At least 6 systematic cores were taken from each lobe using a 18 Gauge biopsy needle. Two additional cores were taken from each target identified by multiparametric MRI. The following information was collected by the physician who performed the biopsies: patients' age, history of prostate biopsy and antibiotic intake, Charlson' score, hospitalization and travelling history, type, dose and timing of antibiotic prophylaxis, and details of TRUS-PB procedure. Additionally, all patients were planned to undergo a first rectal swab (rectal swab #1, ESwab^{TM}, Copan) performed before the biopsy. A self-questionnaire to assess the occurrence of symptoms of UTI (efficacy) and safety was provided to the patients. They were instructed to report any clinical signs of post TRUS-PB UTI (efficacy) and/or adverse event (safety), using a predefined list of clinical signs and adverse events items, detailed in Table S3. Patients were informed to consult their general practitioner or at the hospital emergency room in case of signs of UTI. Management of post TRUS-PB UTI, including urine culture and initiation of antibiotic therapy, was left to the physician's choice.

The third visit (Day 30 visit) was scheduled 30 days after the biopsy procedure. The pathology report of prostate biopsies was

disclosed to the patients. The self-questionnaire for the assessment of UTI and safety were collected. A second rectal swab (rectal swab #2, ESwab™, Copan) for rectal carriage of antibiotic resistant strains was also self-performed by the patient. When patients were not showing up for the third visit or when the self-questionnaire was missing, a phone call to the patient, to screen for death and missing information, was conducted by a dedicated research assistant trained on the study protocol.

Study endpoints

The primary efficacy endpoint was the occurrence of post TRUS-PB UTI as defined by the occurrence of self-reported clinical signs of UTI after TRUS-PB, based on the presence of at least one of the following signs or symptoms: pelvic pain and/or pain/burning when urinating and/or frequent urination and/or urgency and/or leaking and/or acute urinary retention and/or hematuria associated or not with fever ≥38 °C or chills. Secondary efficacy endpoints were the occurrence of microbiologically documented post-TRUS-PB UTI based on urine analysis according to US Food and Drug Administration (FDA) definition (Food and Drug Administration, 2018), self-reported antibiotic intake, and hospitalization (all causes and related to post TRUS-PB UTI). Safety endpoints were the occurrence of post TRUS-PB self-reported adverse events among a list of items, including digestive, neurological, cutaneous, musculoskeletal, and urinary symptoms.

Antibiotic resistance testing in rectal swabs

Rectal swabs collected at the second (before antibiotic prophylaxis) and third visits (after antibiotic prophylaxis) were stored at −80 °C. The analysis of microbiological samples, to screen for rectal carriage of antibiotic resistance strains in *E. coli*, including FQ-resistance, FT-resistance, and ESBL production, was performed at the end of the study. Therefore, the results of rectal swabs analysis were not used to manage the patients. The results of the second rectal swab are not reported here. They are part of a substudy that aims to estimate the emergence of antibiotic resistance, and the results will be presented elsewhere. Resistances to FQ and FT were detected by using selective chromogenic agar UriSelect™4 (BIO-RAD) supplemented with 1 mg/L ciprofloxacin for FQ or with 128 mg/L fosfomycin and 25 mg/L of glucose-6-phosphate for FT. ESBL was detected using CHROMID® BLSE agar (BioMérieux), and phenotypic ESBL confirmations were determined by the disk diffusion method. Minimal inhibitory concentrations (MICs) were tested by Etest® (BioMérieux). Results were interpreted according to EUCAST standards.

Compliance with research ethics standards

The study protocol was approved by the "Comité de Protection des Personnes" (CPP) of Paris area–number 10 (CPP-IDF 10) under the number "2017-A00550-53." An information of the French drug agency –"Agence Nationale de Sécurité du Médicament et des produits de santé" (ANSM) was also performed under the same number.

Statistical analysis

Patients' characteristics, prevalence, and incidence of primary and secondary efficacy endpoints are described using descriptive statistics, including frequency and percentages, median, and the interquartile range [IQR]. We investigated baseline factors associated with the occurrence of post-TRUS-PB UTI and secondary endpoints (including safety) using logistic regression. Associations are reported as relative risks (RR) with 95% confidence intervals (95% CI). All tests were two-tailed, and p-values lower than 0.05 were considered as statistically significant. Statistical analyses were performed with the R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

This observational study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Vandenbroucke et al., 2007).

Results

A total of 222 men undergoing TRUS-PB were enrolled in the study, as shown in Figure 1.

Patients' characteristics

The median age was 67.6 years [IQR 61.4–72.1] and median Charlson score was 3 [IQR 3–5]. Of the 222 men enrolled, 100 (45%) patients had previously undergone prostate biopsy, 123 (55%) patients had traveled abroad within the last 12 months, and 69 (31%) patients had received antibiotics within the last 6 months. Eight (4%) patients reported having a UTI in the past 3 months, Table 1. A single dose of FQ prophylaxis (FQ-arm) was given to 141 (64%) patients, and a single dose of 3 g of FT prophylaxis (FT-arm) was given to 81 (36%) patients. In FQ-arm, a single dose of FQ prophylaxis was 500 mg ciprofloxacin in 128/141 (91%) patients, 500 mg levofloxacin in 6/141 (4%), and 400 mg ofloxacin in 7/141 (5%) patients. Overall, the median time between antimicrobial prophylaxis and TRUS-PB was 2.3 h [IQR, 2.0−2.8].

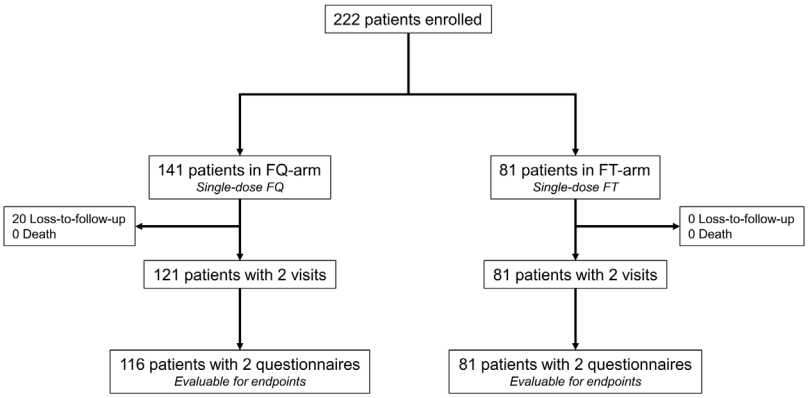

Figure 1. Flow-chart of study enrollment and follow-up.
The first visit includes the collection of consent to participate in the study, prostate biopsy, collection of clinical characteristics, and received antibiotic prophylaxis
The second visit includes systematic collection of the occurrence of post TRUS-PB study endpoints: UTI, antibiotic intake, and adverse event (including hospitalization and death). When patients were not presenting at the third visit or the self-questionnaire was missing, a systematic phone call to the patient was performed by a dedicated research assistant trained to the study protocol to screen for death and missing information.

Table 1
Patient baseline characteristics.

Patient' characteristics	FQ-arm *n = 141*	FT-arm *n = 81*	Total *n = 222*
Age, Med [IQR]	67.4 years [61.2–72.1]	67.8 years [62.8–72.1]	67.6 years [61.4–72.1]
Charlson' score, Med [IQR]	4 [3–5]	3 [2–4]	3 [3–5]
History of prostate biopsy	61/141 (43%)	39/81 (48%)	100/222 (45%)
Traveled abroad in prior 12 months	75/141 (53%)	48/81 (59%)	123/222 (55%)
Hospitalization in prior 12 months	14/89 (16%)	15/80 (19%)	29/169 (17%)
Antibiotic intake in prior 6 months	44/141 (31%)	25/80 (31%)	69/222 (31%)
Urinary tract Infection in prior 3 months	5/141 (4%)	3/81 (4%)	8/222 (4%)
Time between antibiotic intake and TRUS-PB[a], Med [IQR]	2.5 h [2.1–2.9]	2.1 h [2.0–2.5]	2.3 h [2.0–2.8]
Prostate volume, Med [IQR]	44 g [35–60]	50 g [40–65]	45 g [35–62]
TRUS-PB: number of prostate biopsies, Med [IQR]	13 [12–14]	13 [12–14]	13 [12–14]
TRUS-PB: diagnosis of prostate cancer	95/141 (67%)	19/81 (23%)	114/222 (51%)
Time between TRUS-PB (visit # 1) and visit #2	28 days [22–36]	31 days [26–36]	29 days [22–36]

[a] TRUS-PB: Transrectal ultrasound-guided biopsy of the prostate.

Most of the men enrolled (202/220, 91%) had two follow-up visits with the urologist (visit #1 for biopsy and visit #2 at Day 30): 121/141 (86%) in the FQ-arm and 81/81 (100%) in the FT-arm. A total of 197 (89%) patients answered two questionnaires and were assessed for primary and secondary endpoints: 116/141 (82%) in the FQ-arm and 81/81 (100%) in the FT-arm. One hundred and eighty-five patients had a rectal swab during visit #1, of which 42 (23%) were carrying an FQ-resistant strain: 25/127 (20%) in the FQ-arm and 17/58 (29%) in the FT-arm. No FT resistance was observed. No death was observed in any of the study arms.

Incidence of post-TRUS-PB UTI and secondary endpoints

The median duration between the two follow-up visits was 29 days [IQR, 22–36]. Among patients evaluable for the primary and secondary endpoints, the cumulated follow-up time was 6861 days (228.7 months): 3790 days (126.3 months) in the FQ-arm and 3071 days (102.4 months) in the FT-arm. The overall incidence of self-reported post TRUS-PB UTI was 12% (95%CI, 8%–17%). In the FQ-arm, the incidence was 15% (95% CI, 10%–17%), while in the FT-arm, the incidence was 9% (95% CI, 5%–13%), corresponding to a relative-risk of 0.55 (95% CI, 0.22–1.40), p-value = 0.209, Table 2. When considering urine analysis according to FDA guidelines, the overall incidence of clinically and microbiologically defined UTI was 4% (n = 7/197; 95% CI, 1%–6%): 5% (n = 6/116; 95% CI, 2%–8%) in FQ-arm versus 1% (n = 1/81; 95% CI, 0%–3%) in the FT-arm. The median time from TRUS-PB to self-reported UTI was 5 days [IQR, 2.5–6.5]. None of the patients' baseline characteristics were significantly associated with the occurrence of post TRUS-PB UTI after adjustment on the study arm, Table 3. Among the 116 men receiving FQ, 107 (92%) were screened for rectal carriage of FQ resistance, of whom 18/107 (17%) patients were positive. In these patients, the rectal carriage of FQ-resistant strain was not associated with an increase in post TRUS-PB UTI (p = 0.280). Details of post-TRUS-PB UTI clinical symptoms are reported in Table S1. Out of 24 patients with post TRUS-PB UTI, 12 had a urine culture, which was positive in 7 (6 in the FQ-arm, 1 in the FT-arm). Microorganisms identified were as follows: *E. coli* in 3, *K. oxytoca* in 3, and *K. pneumoniae* in 1 patient. Details of susceptibility to FQ, FT, and ESBL production according to study arm are reported in Table S2.

Antibiotic intake, hospitalization (all causes and due to UTI), and adverse events occurring after TRUS-PB are detailed in Table 2. Though hospitalization rate was numerically higher in the FQ-arm (13/116 (11%) versus 3/81 (4%), p-value = 0.071), no statistically significant difference was observed for any of the secondary endpoints, Table 2. Details of adverse events are reported in Table S3.

Discussion

The overall incidence of self-reported (12%) and microbiologically documented (4%) post TRUS-PB UTI appears high (from 2- to 12-fold increase) as compared to the rate reported in France and in the literature (1%–7%) and highlights the issues in the definition used (Djavan et al., 2001; Carignan et al., 2012; Food and Drug Administration, 2018; Nam et al., 2013; Campeggi et al., 2014; Shoag et al., 2019; Anastasiadis et al., 2015). In our study, the rate of post TRUS-PB UTI was not significantly different between the FT and FQ arms, across the definition used for UTI. Similarly, the rate of antibiotic intake and hospitalization after TRUS-PB was not different from the FT-arm than that of the FQ-arm. The safety profile (adverse event) of FT was similar to FQ. Our study provides reassuring real-life data regarding the efficacy and safety of FT as compared to FQ and underlines the need for the implementation of a large double-blind randomized trial.

In patients receiving FQ, we were not able to demonstrate an association between prior rectal carriage of FQ resistance and an increased in post TRUS-PB UTI (Liss et al., 2015; Van Besien et al.,

Table 2
Prevalence and incidence of primary and secondary clinical endpoints.

Clinical endpoints[b]	FQ-arm n= *116*	FT-arm *n= 81*	Total *n= 197*	RR[a]	95%CI	p-value
Post-TRUS-PB UTI	17/116 (15%) (95%CI, 10–17%)	7/81 (9%) (95%CI, 5–13%)	24/197 (12%) (95%CI, 8–17%)	0.55	(0.22–1.40)	0.209
Post-TRUS-PB microbiologically documented UTI	6/116 (5%) (95%CI, 2–8%)	1/81 (1%) (95%CI, 0–3%)	7/197 (4%) (95%CI, 1–6%)	–		
Post-TRUS-PB antibiotic intake	14/116 (12%) (95%CI, 8–17%)	7/81 (9%) (95%CI, 5–13%)	21/197 (11%) (95%CI, 6–15%)	0.70	(0.27–1.82)	0.462
Post-TRUS-PB hospitalization (all causes)	13/116 (11%) (95%CI, 7–16%)	3/81 (4%) (95%CI, 1–6%)	16/197 (8%) (95%CI, 4–12%)	0.30	(0.08–1.11)	0.071
Post-TRUS-PB hospitalization (due to UTI)	9/116 (8%) (95%CI, 4–11%)	1/81 (1%) (95%CI, 0–3%)	10/197 (5%) (95%CI, 2–8%)	0.15	(0.02–1.20)	0.073
Post-TRUS-PB adverse events	36/116 (31%) (95%CI, 25–37%)	28/81 (36%) (95%CI, 28–41%)	64/197 (32%) (95%CI, 26–39%)	1.17	(0.64–2.15)	0.602

95% CI: 95% Confidence Interval.
100 person-month: incidence rate per hundred persons per month.
[a] RR: Relative Risk. For the computation of each RR, the reference class is the FQ-arm. For Post-TRUS-PB microbiologically documented UTI, the number of events did not allow to compute the relative risk of FT-arm as compared to FQ-arm.
[b] As reported by the patients on self-questionnaire.

Table 3
Factors associated with post-TRUS-PB UTI occurrence – univariable and multivariable analysis.

Patient' characteristics	Post TRUS-PB UTI *evaluable in 197 patients*		Raw association			Adjusted on study arm *FQ-arm as the reference class*		
	Absencen= 173	*Presencen= 24*	RR[†]	IC95%	p-value	aRR[a]	IC95%	p-value
Fosfomycin-trometamol (FT) arm vs. Fluoroquinolone (FQ) arm	74 / 173 (43%)	7 / 24 (29%)	0.55	(0.22–1.40)	0.209	–	–	–
Age, Med [IQR]	67.9 [62.3–72.2]	65.0 [58.9–71.8]	0.95	(0.90–1.01)	0.100	0.96	(0.90–1.01)	0.115
Charlson' score, Med [IQR]	3 [2–5]	4 [3–5]	1.03	(0.77–1.38)	0.828	0.97	(0.71–1.32)	0.856
History of prostate biopsy	82 / 173 (47%)	8 / 24 (33%)	0.55	(0.23–1.36)	0.199	0.56	(0.23–1.39)	0.215
Traveled abroad within 12 previous months	95 / 173 (55%)	16 / 24 (67%)	1.64	(0.67–4.04)	0.280	1.70	(0.69–4.20)	0.252
Hospitalization within 12 previous months	24 / 133 (18%)	1 / 15 (7%)	0.32	(0.04–2.59)	0.288	0.33	(0.04–2.64)	0.297
Antibiotic intake within 6 previous months	51 / 172 (30%)	10 / 24 (42%)	1.69	(0.71–4.07)	0.237	1.70	(0.71–4.11)	0.234
Urinary tract infection within 3 previous months	6 / 173 (3%)	1 / 24 (4%)	1.21	(0.14–10.51)	0.863	1.22	(0.14–10.75)	0.855
prostate volume, Med [IQR]	50 g [36–64]	44 g [35–65]	1.00	(0.97–1.02)	0.703	1.00	(0.97–1.02)	0.834
Number of tissue samples per prostate biopsy session, Med [IQR]	13 [12–14]	12 [12–14]	1.01	(0.73–1.39)	0.947	1.02	(0.74–1.41)	0.905
Diagnosis of prostate cancer on biopsy	85 / 173 (49%)	14 / 24 (58%)	1.45	(0.61–3.44)	0.400	1.16	(0.45–3.03)	0.759

95% CI: 95% Confidence Interval.
[a] (a)RR: (adjusted) relative risk. For the computation of each RR, the reference class is the FQ-arm. For Post-TRUS-PB microbiologically documented UTI, the number of events did not allow to compute the relative risk of the FT-arm as compared to the FQ-arm. aRR were systematically adjusted on treatment arm.

2019). Furthermore, none of the patients receiving FT developed post TRUS-PB UTI due to FT-resistant strain, despite a high rate of *in vitro* mutations in the literature (10^{-7} to 10^{-6} cells among Gram-negatives) (Shoag et al., 2019). On the other hand, in patients with UTI treated with FT, a low likelihood of mutation was described (<1%) (Nilsson et al., 2003). It was suggested to be related to a high fitness cost, but remains unclear (Nilsson et al., 2003; Couce et al., 2012; Pourbaix et al., 2017). A genome-wide study showed that in *E. coli*, only the overexpression of *murA* can produce significant resistance to FT (Couce et al., 2012). This was achieved at low fitness cost, lower than that imposed by other mutations conferring FT resistance (Couce et al., 2012). But, in a murine model of ascending UTI due to *E. coli*, resistance to FT was associated with a decrease in virulence, due to fitness cost (Pourbaix et al., 2017). Therefore the paradox remains and is likely to be due to sampling and sample size issue. In this regard, clinical data, including ours, are reassuring (Fahmy et al., 2016; Lista et al., 2014; Sen et al., 2015; Van Besien et al., 2019; Noreikaite et al., 2018).

The potential benefit of culture-guided antimicrobial prophylaxis has not been demonstrated yet, and larger studies are required (Liss et al., 2017; Liss et al., 2015; Van Besien et al., 2019). Empirical use of FT could be as effective as culture-guided antimicrobial prophylaxis and is easier to implement as a new strategy to prevent post TRUS-PB UTI. As highlighted by the Infectious Disease Society of America (IDSA) in a recent survey, single-dose FQ was the dominating regimen used for prophylaxis and FT was never considered (Johnson et al., 2015). The rate of culture-guided antimicrobial prophylaxis was below 10% (Johnson et al., 2015). In France, the use of FT as an alternative to FQ is not yet recommended either by the urology or the infectious diseases societies or the French drug agency (ANSM) (Ouzzane et al., 2011).

Our study had limitations. As this is a nonrandomized monocentric cohort study, enrolling nonconsecutive patients who are receiving FQ or FT according to the physician's choice, selection biases are likely to exist, leading to different rates of FQ resistance between study arms at baseline. However, men enrolled in our study were screened for prostate cancer as part of a standard of care, and the other baseline characteristics of participants were similar across study arms. Because of the relatively small sample size and number of events, the statistical power to manage confounding factors and to identify factors associated with post TRUS-PB UTI and other secondary endpoints were limited. The definition of UTI used in our study relied on self-reported clinical symptoms because urine analysis was not mandatory after TRUS-PB and might have led to a bias in the measurement of UTI occurrence (Food and Drug Administration, 2018; Naber et al., 2001). But, when considering a combined criterion, including physical signs of UTI and urine analysis (according to the FDA recommendations), the incidence of post TRUS-PB UTI remained high, at 4% (Food and Drug Administration, 2018). The incidence observed in our study can be linked to a high frequency of known risk factors of post TRUS-PB UTI at baseline: history of prior prostate biopsy (45%), antibiotic use before TRUS-PB (32%), and exposure to ESBL-E through traveling abroad (55%) (Walker et al., 2016).

This cohort study suggests that the efficacy and safety of FT are comparable to those of FQ in the prevention of post-TRUS-PB UTI. The implementation of a large multicentric double-blind non-inferiority trial is urgently needed.

Summary

Fluoroquinolone (FQ) resistance is increasing among *Enterobacteriaceae*. Fosfomycin-trometamol (FT) is therefore a potential alternative to FQ for UTI prophylaxis following prostate biopsy. In all, 141 men received FQ and 81 FT in a prospective observational study. Efficacy of FT was similar to that of FQ for the prevention of post TRUS-PB UTI (RR = 0.55 (95% CI, 0.22–1.40), p-value = 0.209). The safety profile of FT was similar to that of FQ. A randomized comparison of the two antibiotics is warranted.

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Conflict of interest

None to declare.

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Appendix A. Supplementary data

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