Fosfomycin versus ciprofloxacin for febrile neutropenia prophylaxis in high-risk haematological patients (FOVOCIP): a phase 3, open-label, multicentre, randomised, non-inferiority trial

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Summary

Background Prophylaxis with fluoroquinolones in high-risk neutropenic patients is currently under scrutiny. The FOVOCIP study aimed to evaluate the efficacy and safety of fosfomycin compared to ciprofloxacin in this population.

Methods This was a multicentre, randomised, phase-3, non-inferiority, open-label trial performed in 11 centres in Spain. Adults diagnosed with acute leukaemia or recipients of a Haematopoietic Stem Cell Transplant were randomised to receive oral fosfomycin or oral ciprofloxacin as prophylaxis. The primary endpoint was rate of

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For the Spanish translation of the Summary, see the Supplementary Materials section.

febrile neutropenia. Intention-To-Treat (ITT) and Per-Protocol (PP) analyses were done for the primary endpoint, with a non-inferiority margin of −5%.

Findings A total of 174 patients were screened and 166 randomized (83 per arm, 50% female). In the ITT population, febrile neutropenia occurred in 74.7% (62 of 83 patients) and 73.49% (61 of 83 patients) in the fosfomycin and ciprofloxacin group, respectively. The corresponding success rates (patients without febrile neutropenia) were 25.3% in the fosfomycin group and 26.51% int the ciprofloxacin group, risk difference −1.2%, (95% confidence interval [CI]: −14.5 to 12.12, lower boundary of the 90% CI −12.3). In the PP population, febrile neutropenia occurred in 82.19% (60 of 73 patients) and 76.25% (61 of 80 patients) in the fosfomycin and ciprofloxacin group respectively. The corresponding success rates were 17.81% in the fosfomycin group and 23.75% in the ciprofloxacin group, risk difference −5.94%, (95% CI: −18.75 to 6.86, lower boundary of the 90% CI −16.7). Gram negative bacteria were responsible for 90% and 10% of the bacteraemias in the fosfomycin and ciprofloxacin group, respectively. Two patients (3%) in the experimental group became colonized by multidrug resistant Gram-negative bacteria, compared with nine patients (11%) in the control group (P = 0.04). There were no differences in other safety endpoints.

Interpretation Fosfomycin did not demonstrate non-inferiority to ciprofloxacin in the prevention of febrile neutropenia in high-risk haematological patients. The higher incidence of Gram-negative bacteraemia also discourages its use. This trial is registered with ClinicalTrials.gov (NCT05311254) and EUDRACT (2021-000354-25) and is complete.

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Keywords: Clinical trial; Prophylaxis; Febrile neutropenia

Introduction

More than a decade ago, antibacterial prophylaxis with fluoroquinolones was recommended for neutropenic patients with an expected duration length of neutropenia longer than 7 days.[1] However, this practice has been questioned in recent years due to the increase incidence of multidrug resistant Gram-negative bacteria (MDRGNB). The current resistance rate to fluoroquinolones is around 50% in haematopoietic stem cell units in Europe and Asia,[2–6] Appendix 1, pp 3–4, and is associated with prolonged or repeated exposure to antibiotics of this group. This resistance has led to the loss of efficacy of antibiotics and clonal expansion of resistant strains in patients with baseline colonization by Extended Spectrum Beta-Lactamase (ESBL)-producing *Enterobacterales*.[7] Moreover, a meta-analysis and recent reports have not confirmed that using fluoroquinolones reduces mortality in these patients.[8,9] However, discontinuing their use has led to an increase in BGN bacteraemia and an excess of serious complications, including ICU admissions.[10] In an effort to preserve the protective benefits conferred by prophylaxis while adapting clinical practice to the evolving reality, experts recommend assessing the baseline fluoroquinolone resistance rate and restricting their use to settings where the baseline resistance rate does not exceed 20%[11] or where they do not exist at all.[12]

The toxicity of fluoroquinolones represents an additional problem. The neurological and musculoskeletal toxicity, exacerbated by the addition of corticosteroids, occurs more frequently in vulnerable populations such as haematological patients. Other particularly relevant adverse effect in these patients is prolongation of the QT interval, enhanced by the addition of drugs routinely used in these patients, such as posaconazole, midostaurin or ondansetron, among others. This poor safety profile has prompted regulatory agencies to recommend restricting the use of these drugs.

In view of the evidence, the focus should not be limited exclusively to the debate for or against fluoroquinolones, but should instead shift toward the search for alternative antibiotics. Among the drugs already investigated, third-generation cephalosporins have been associated with an incidence of febrile neutropenia of 85% and breakthrough infections caused by Gram-negative bacteria.[13] The efficacy of cotrimoxazole is constrained by its myelotoxicity and lack of activity against *Pseudomonas aeruginosa*.[14] Non absorbable antibiotics were discarded due to limited efficacy and tolerability.[15]

Fosfomycin is a bactericidal antibiotic with a broad-spectrum potential activity against both Gram-positive and Gram-negative bacteria, including strains of ESBL and/or carbapenemase-producing *Enterobacterale* and multidrug resistant *P. aeruginosa*, which makes its use attractive even in endemic settings. It has as a good safety profile and has no effect on cardiac conduction.[16]

Research in context

Evidence before this study

Fluoroquinolone prophylaxis is recommended to prevent bacterial infections in haematologic patients with prolonged neutropenia. However, this practice has been questioned in recent years due to the increase incidence of multidrug-resistant Gram-negative bacteria, and the adverse events associated with this family of antibiotics. In this context, the identification of alternative antibiotics is a priority. We conducted a search in PubMed for clinical trials comparing fluoroquinolones with other agents for preventing infections in patients with prolonged neutropenia. The search focused on the period starting in 2005, when the European Conference on Infections in Leukaemia (ECIL) warned about the use fluroquinolones, through the February 2021. The search was limited to literature in English. We used the terms "febrile neutropenia AND antibacterial prophylaxis". We found 289 results. We identified four single-centre, retrospective before-after studies comparing fluroquinolones with piperacillin-tazobactam (n = 1), cotrimoxazole/colistin (n = 1), a third-generation cephalosporin (n = 1), or a combination of meropenem, piperacillin-tazobactam, and ceftriaxone (n = 1). Two single arm, retrospective studies reported the clinical experience with cefpodoxime (n = 1) and fosfomycin (n = 1) in haematological patients. No randomised clinical trial was found.

Added value of this study

The FOVOCIP study is the first prospective, randomised trial assessing oral fosfomycin for infection prevention in haematologic patients, and the first since 2005 comparing any antibiotic with fluoroquinolones According to the predefined criterion, fosfomycin did not demonstrate non-inferiority compared to ciprofloxacin. The colonisation rate by multidrug-resistant Gram-negative bacteria under fosfomycin was significantly lower than with ciprofloxacin. However, ninety percent of bacteraemias that occurred under fosfomycin prophylaxis were caused by Gram-negative bacteria.

Implications of all the available evidence

Although FOVOCIP did not include bioavailability targets, the low efficacy in prophylactic efficacy observed in this trial, together with evidence from previous studies in non-neutropenic patients showing limited bioavailability, suggests that calcium fosfomycin formulation is inadequate. Future research should therefore focus on assessing the bioavailability of alternative oral formulations of fosfomycin in neutropenic patient populations. Finding alternative antibacterial agents to fluoroquinolones for preventing of infections in neutropenic patients remains challenging.

There is limited clinical research on the oral formulation of this drug in onco-haematological patients, with only one retrospective study conducted in 42 patients, forty percent of whom were diagnosed with acute leukaemia.[17] The rate of febrile neutropenia was 55%, which compares favourably to the 65% rate reported in a randomised trial of levofloxacin versus placebo.[18] None of the Gram-negative bacteria recovered in the former study were resistant to fluoroquinolones. This study points out the potential of oral fosfomycin in the prevention of infections in patients with high-risk neutropenia, particularly in settings with a high prevalence of resistance to fluoroquinolones. Indeed, the broad spectrum of activity of fosfomycin, together with the low resistance rate and good safety profile, makes it possible to hypothesize that it could be an alternative to fluoroquinolones even in settings with a high prevalence of multi-resistant bacteria. The possibility of having more than one family of prophylactic antibiotics with proven efficacy would also make it possible to reduce the resistance associated with continued exposure to the same antibiotic, and to select one treatment or another based on bacterial ecology and local resistance.

In this context, this study aims to investigate the efficacy of an alternative drug to fluoroquinolones, fosfomycin, for the prevention of febrile neutropenia in high-risk neutropenic patients.

Methods

Study design

The FOVOCIP study was an investigator-driven, multicentre, randomised, controlled, phase 3, non-inferiority trial comparing the efficacy and safety of oral ciprofloxacin with oral fosfomycin to prevent febrile neutropenia in patients with acute leukaemia who were treated with intensive chemotherapy and/or recipients of a Haematopoietic Stem Cell Transplant (HSCT). The study was designed as a non-inferiority trial without a placebo control arm because, despite the growing scrutiny, fluoroquinolones have not been definitively proven inferior to placebo in randomized clinical trials. Furthermore, the latest guidelines still recommend considering the use of antibacterial prophylaxis for high-risk patients undergoing their first chemotherapy cycle, if the aim is to prevent fever and infection.[12,19] For all of the above reasons, we concluded that it would not have been ethically justifiable to conduct a study with a control arm lacking an active drug.

The study was carried out in eleven public academic hospitals in Spain belonging to the public National Health System. Investigators from Hospital Universitario Central de Asturias (Oviedo, Spain) led the study. All participating centres regularly treat patients diagnosed with acute leukaemia and perform HSCT.

The overall design and trial protocol can be found in Appendix 5 (pp 13–53). Details of the principal investigator and the number of patients included in each centre are provided in the Appendix, p54.

After the start of the initial version of FOVOCIP clinical trial protocol (version 2.1, July 19, 2021), two relevant amendments were approved, none of which changed the initial design. Amendment one (May 11, 2022) allowed the intravenous administration of prophylactic drugs in case of oral intolerance, and to collect rectal exudates instead of faecal samples if the patients were unable to collect the stool sample prior to receiving the first dose of empirical antibacterial therapy. Amendment two (December 29, 2022) allowed to include three additional centres.

This is a non-commercial study where the sponsor is a non-profit foundation, (FINBA, Fundación para la Investigación e Innovación Biosanitaria en el Principado de Asturias). The Instituto de Investigación Marqués de Valdecilla (IDIVAL) was responsible for study management and central statistical data monitoring and analysis. The Trial Management Team was responsible for day-to-day operational running of the trial. The Clinical Trials Agency and SCReN (Spanish Clinical Research Network) were responsible for obtaining authorization from the local ethics committee and notifying to the Spanish Agency of Medicines and Medical Devices of the start-up of the study.

Participants

Adult patients of 18 years of age or older who and met one of the following criteria were recruited: a) diagnosis of acute leukaemia who were to receive a first course of intensive chemotherapy; b) recipients of a first allogeneic HSCT with myeloablative conditioning; c) Patients eligible to receive a first allogeneic HSCT with reduced-intensity conditioning or an autologous HSCT with at least one of the following risk factors: performance status (Eastern Cooperative Oncology Group score) ≥2; expected grade 3–4 mucositis; age ≥65 years; Haematopoietic Comorbidity Transplant Index ≥3; serum albumin <35 g/L; active or refractory neoplasia at the time of stem cell transplantation; total dose of etoposide ≥500 mg/m^2; total dose of cytarabine ≥1 g/m^2. Patients suffering from fever of infectious origin, any documented infection or treated with broad-spectrum antimicrobial therapy within 4 weeks of the first study treatment were excluded.

Selection of patients was performed in two different settings depending on the therapeutic procedure. In subjects with a suspected diagnosis of acute leukaemia where the diagnosis of the neoplasm was made as an inpatient, the selection took place once the diagnosis had been confirmed and prior to the start of intensive chemotherapy. In HSCT recipients, selection took place on an outpatient basis during the pre-transplant evaluation. All patients provided written informed consent.

Randomisation and masking

Following verification of the informed consent and the inclusion and exclusion criteria by the principal investigator in each centre, the Clinical Trials Agency belonging to the SCReN network randomly assigned the case to the control or experimental group in 1:1 ratio, stratified by recruiting site and baseline condition (acute leukaemia or HSCT). Randomization within each stratum was performed using a computer-generated randomisation programme using the block technique with fixed-size blocks. The process of randomization was centralized, so the investigator did not know the treatment to which the candidate was to be assigned until the randomisation was concluded. Treatment allocation was not masked from patients and clinicians.

Procedures

Once participants gave consent, the following study procedures were performed: medical history and concomitant medication, ECOG performance status, complete physical examination, vital signs, haematology, biochemistry, coagulation, electrocardiogram, and screening for MDRGNB gut colonization by microbiological culture of rectal exudates. This screening was repeated weekly during the neutropenic period until study completion. Patient microbiome evolution was studied by metataxonomic sequencing of faecal samples collected from each study subject at the selection visit and at the end of the study. See Appendix 3 (pp 7,8) for details of the microbiological methods.

Patients assigned to the control arm received oral ciprofloxacin 500 mg twice a day; those assigned to the experimental arm received oral fosfomycin calcium 500 mg three times a day. The dose of oral fosfomycin was selected based on the Summary of Product Characteristics of the drug. In both cases, prophylaxis was initiated within 24 h after the initiation of chemotherapy.

Study visits were planned in days 1, 8, 15, 22 and 29 and the same study procedures as in the selection visit were repeated. Prophylactic treatment was stopped when any of the following events took place: febrile neutropenia requiring antibacterial treatment; Absolute Neutrophil Count (ANC) ≥ 0.5 × 10^9/L or in case absolute neutrophil count does not reach this count, for a maximum of 60 days; subject withdrawal consent for the study; death. A follow up visit was planned fifteen days after the end of study.

Adverse events were recorded in the patient's medical records and in the electronic case report forms. The severity of adverse events were classified based on the patient's symptoms according to the version of the Common Toxicity Criteria for Adverse Events (version 5034) of the National Cancer Institute. Serious adverse events were defined as any adverse event that is potentially life threatening, requires hospitalisation or

prolongs existing hospitalisation. The investigator assessed the relationship between the adverse event and the treatment assigned to the patient.

Outcomes

The primary outcome of the study was febrile neutropenia. Fever was defined as a single oral temperature of 38.3 °C or a temperature of 38 °C sustained over a 1-h period.[20] If the patient was receiving any medication with a high probability of inducing fever or had been previously transfused, at least a positive culture or an infected site was required to be ascribed to infection. When febrile neutropenia occurred and infection was suspected, prophylactic antibiotics were stopped, and antimicrobial therapy was administered according to standard and local guidelines.

Secondary endpoints were both efficacy and safety endpoints. Efficacy endpoints included rate and type of documented infections according to Han's criteria[21] and survival. In case death did not occur within the study period, subjects were censored at the date of last study assessment. Safety end points included adverse events related to prophylactic drugs, rate of patients colonized by MDRGNB and changes in gut microbiome produced under both prophylactic strategies during the study period.

Sample size calculation

The null hypothesis is that prophylactic fosfomycin is inferior to ciprofloxacin in the prevention of febrile neutropenia in high-risk neutropenic patients. The data contributing used for the sample size calculations come from randomized clinical trials showing that the rate of febrile neutropenia in this population under prophylactic fluoroquinolones ranges from 65% to 73% in centres with a rate of resistance of no more than 27%.[8] Considering that the actual rate of resistance to fluoroquinolones in haematological wards in Spain and other regions is around 50%,[2,4–6] (Appendix 1, pp 3,4), we anticipated a success rate of 17% in the control arm, which is consistent with recent reports.[22–24] Previous literature showed a febrile neutropenia incidence of 55% with fosfomycin,[17] which conversely, translates into a 45% success rate. In this trial, we set a conservative success rate estimation of 30% with fosfomycin. The non-inferiority margin was stablished at –5% for this study. Thus, the alternative hypothesis in which the sample size was calculated is H_1: $\Pi_f - \Pi_c \leq -0.05$ where Π_f and Π_c are the probabilities of not occurring febrile neutropenia in the fosfomycin and ciprofloxacin arms, respectively. That is, fosfomycin is better than ciprofloxacin or only worse by no more than 5%. The decision to set the non-inferiority margin at 5% was closely related to the assumption of a 17% success rate in the ciprofloxacin group. A 5% reduction in efficacy would imply a success rate of 12% in preventing febrile neutropenia. According to the existing literature, this is essentially equivalent to providing no prophylaxis at all, especially in the context of acute leukemia (AL) or allogeneic stem cell transplant (allo-SCT).[9,10,18] With a one-sided alpha level of 0.05 and an 80% power, a sample of 136 patients, with two equal groups of 68 was calculated to be required (Sealed Envelope Ltd. 2012. Power calculator for binary outcome non-inferiority trial. [Online] Available from: https://www.sealedenvelope.com/power/binary-noninferior). To allow for a 15% drop out, we intended to recruit 156 patients.

Once the trial was initiated, no changes were made to the primary endpoint or the non-inferiority margin.

Statistical analysis

For qualitative and quantitative variables, relative and absolute frequencies with exact 95% CIs and the median and interquartile range were used, respectively. The analysis of the primary endpoint was performed in the Intention-to-Treat (ITT) and in the Per-Protocol (PP) population. The ITT population was defined as all patients who were enrolled and randomized. The PP population consisted of all patients who did not have major protocol deviations, as determined by the principal investigator and had received prophylactic drugs for at least of 24 h. The rate of febrile neutropenia and documented infections were compared between the two arms with a Chi-square test. The difference in the proportion and the associated 95% CIs are provided.

Safety analysis was performed in all patients who received at least one dose of fosfomycin or ciprofloxacin. Proportion of patients with gut colonization by MDRGNB at the end of the study was compared between the two groups. The microbiome evolution analysis was studied by metataxonomic analysis by using the bioinformatic pipeline of Qiime2 and the *phyloseq* package for R. After rarefaction to an even depth, alpha diversity indexes were compared using a two-way ANOVA, including sampling time (beginning and end of study) and study groups as factors. Relative abundance at the phylum and genus level were calculated and used for beta diversity and evaluated using Bray–Curtis distances and Unifrac values. Principal coordinates analysis (PCoAs) was computed to identify all sources of variation, followed by Permutational Multivariate Analysis of Variance (PERMANOVA). Differences in abundance of microbial taxa at phylum and genus levels between groups were assessed using Wilcoxon and ANCOMBC2 tests. P-values were adjusted for multiple comparisons using the Benjamini-Hochberg procedure with a false discovery rate of 5%. An adjusted P-value <0.05 was considered significant. A more detailed description of microbiological methods can be found in Appendix 3 (pp 7,8).

This trial is registered with ClinicalTrials.gov, number NCT05311254 and EUDRACT 2021-000354-25.

Ethics Approval

The study was approved by the Ethics Committee at Hospital Universitario Central de Asturias (REF: 2022:088), the Spanish Agency of Medicines and Health Products and the Institutional Review Board at each participating site. Written informed consent was obtained from patients.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation or, writing of the report.

Results

Between March 14, 2022, and May 29, 2024, 174 patients were screened and 166 randomized across 11 centres. An interim analysis was performed for the primary outcome measure after the inclusion of 70 patients and the Data and Safety Monitoring Board recommended continuing recruitment to achieve the full sample size. Eighty-three (50%) patients were randomly assigned to receive oral fosfomycin and 83 (50%) to receive ciprofloxacin (ITT population).

Thirteen protocol deviations were identified. Seven patients received non-indicated empirical antibiotics due to drug-induced fever without being neutropenic, two patients had been previously treated with intensive chemotherapy, two patients had received broad spectrum antibiotics in the previous month, one patient never received any study drug, and another patient received non-intensive chemotherapy with venetoclax and azacitidine. These thirteen patients were excluded from the analysis in the PP population (Fig. 1).

Patient demographics and clinical characteristics by study group are summarised in Table 1. In the ITT population, median age was 58 (51–66) years in the experimental group and 59 (50–65) in the control group. Forty-seven (57%) female patients were assigned to the experimental group and 36 (43%) to the ciprofloxacin group. Acute leukaemia of myeloid lineage was the predominant diagnosis in both the experimental and control arms with 39 of 43 patients (91%) and 34 of 41 patients (83%) patients, respectively. Autologous and

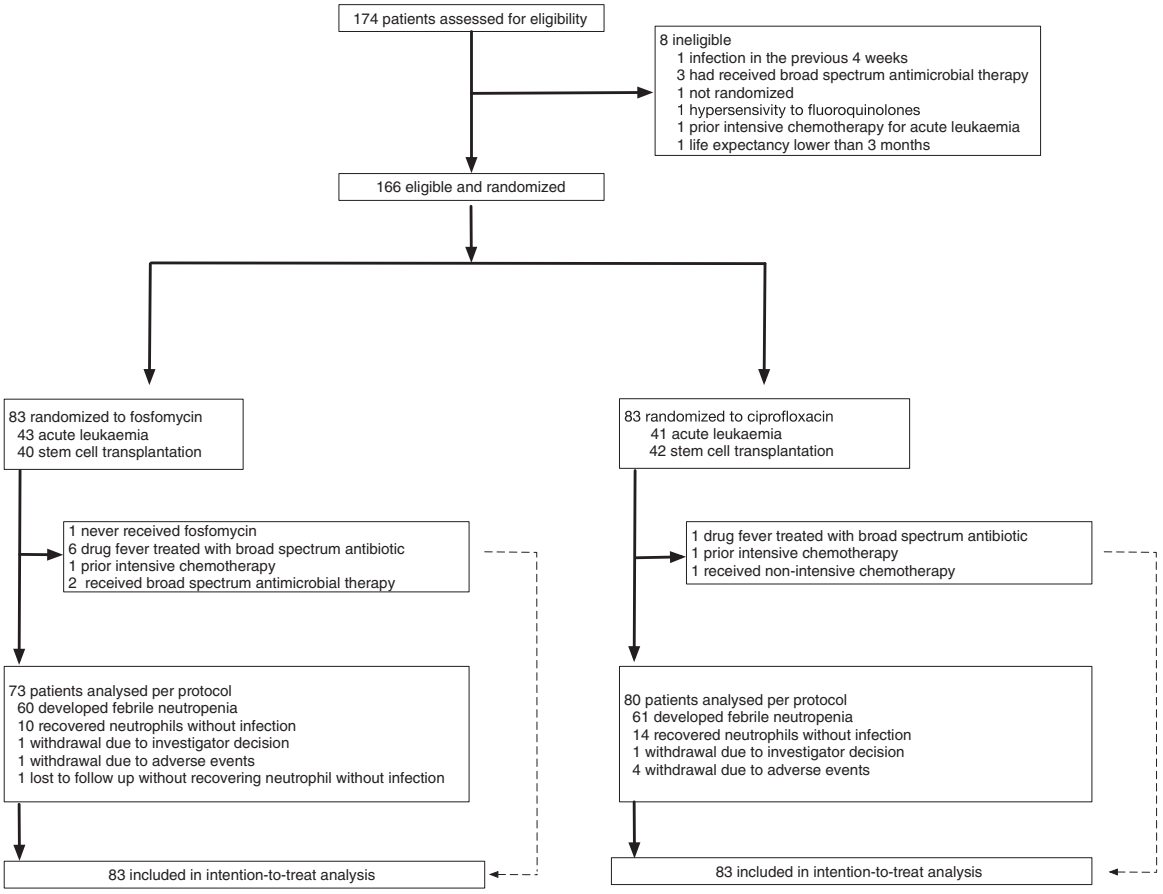


Fig. 1: Trial profile.

	Intention-to-Treat		Per-Protocol	
	Fosfomycin N = 83	Ciprofloxacin N = 83	Fosfomycin N = 73	Ciprofloxacin N = 80
Age, median (interquartile range), yr	58 (51–66)	59 (50–65)	59 (52–67)	57 (50–65)
Sex n° (%)				
Male	36 (43)	47 (57)	31 (41)	45 (59)
Female	47 (57)	36 (43)	43 (55)	35 (45)
Acute leukaemia n° (%)	43 (52)	41 (49)	39 (53)	39 (82)
AML	39 (91)	34 (83)	35 (90)	32 (82)
ALL	4 (9)	7 (7)	4 (10)	7 (18)
Stem cell Transplantation n° (%)	40 (48)	42 (51)	34 (47)	41 (51)
Autologous	36 (90)	35 (83)	31 (91)	35 (85)
Allogeneic	4 (10)	7 (17)	3 (9)	6 (15)
Duration of neutropenia median (interquartile range), days				
$<0.5 \times 10^9$/L	10 (7–24)	11 (6–24)	10 (7–24)	11 (6–23)
$<0.1 \times 10^9$/L	8 (5–17)	8 (5–16)	8 (5–17)	8 (5–16)
Baseline colonization by MDRGNB n° (%)	11 (13)	7 (8)	9 (12)	6 (7)

Yr: year; n°: number; AML: acute myeloid leukaemia; ALL: acute lymphoid leukaemia; MDRGNB: multidrug-resistant Gram-negative bacteria.

Table 1: **Baseline characteristics of the Intention-to-Treat and Per-Protocol populations.**

allogeneic stem cell transplants were performed in 36 of 40 patients (90%) and 4 of 40 (10%) patients in the experimental group and 35 (83%) and 7 (17%) of 42 patients in the control group. Median duration of neutropenia below 0.5×10^9/L was 10 (7–24) and 11 (6–24) days in the experimental and control arm, respectively. Eleven of 83 patients (13%) in the experimental group were colonized at baseline by MDRGNB (ESBL-producing Enterobacterales in 10 patients, and both carbapenemase- and ESBL-producing Enterobacterales in one patient), compared to 7 of 83 patients (8%) colonized by ESBL-producing Enterobacterales in the control group (P = 0.9).

In the primary analysis of the ITT population, febrile neutropenia occurred in 74.7% (62 of 83 patients) and 73.49% (61 of 83 patients) in the fosfomycin and ciprofloxacin group, respectively. The corresponding success rates (patients without febrile neutropenia) were 25.3% (21 of 83 patients) in the fosfomycin group and 26.51% (22 of 83 patients) int the ciprofloxacin group, difference –1.2%, (95% confidence interval [CI]: –14.5 to 12.12, lower boundary of the 90% CI –12.3). In the PP population, febrile neutropenia occurred in 82.19% (60 of 73 patients) and 76.25% (61 of 80 patients) in the fosfomycin and ciprofloxacin group respectively. The corresponding success rates were 17.81% (13 of 73) in the fosfomycin group and 23.75% (19 of 80) in the ciprofloxacin group, difference –5.94%, (95% CI: –18.75 to 6.86, lower boundary of the 90% CI –16.7). Therefore, the criterion for noninferiority was not met in either the ITT or the PP populations. These results are summarized in Table 2.

The characteristics of infections were analysed in the PP population and are shown in Table 3. The most frequent presentation of febrile neutropenia was fever of unknown origin, which accounted for 35 of 60 (58%) febrile episodes in the experimental group and 35 of 61 (57%) of the episodes in the control group. Two patients developed septic shock under fosfomycin prophylaxis.

	Fosfomycin	Ciprofloxacin	Difference (95% CI)
Intention-to-Treat analysis			
Number of patients	83	83	
Number of febrile neutropenia n° (%)	62 (74.7)	61 (73.49)	
Rate of success n° (%) [95% CI]	21 (25.30) [15.95–34.6]	22 (26.51) [17.01–36]	–1.21 [–14.5 to 12.12]
Per-Protocol analysis			
Number of patients	73	80	
Number of febrile neutropenia n° (%)	60 (82.19)	61 (76.25)	
Rate of success n° (%) [95% CI]	13 (17.81) [9–26.6]	19 (23.75) [14.4–33.1]	–5.94 [–18.75 to 6.86]

In the Intention-to-Treat population the non-inferiority analysis for the risk difference showed a 90% CI of –12.3 to 9.9%. In the Per-Protocol population the non-inferiority analysis for the risk difference showed a 90% CI of –16.7 to 4.88%.

Table 2: **Efficacy analysis.**

	Fosfomycin	Ciprofloxacin
Patients developing febrile neutropenia	60	61
Fever of unknown origin n (%)	35 (58)	35 (57)
Bacteraemia n (%)	11 (18)	10 (16)
Non-bacteraemia n (%)		
Microbiologically documented		
Urinary tract infections	3 (5)	3 (5)
Viral enteritis	3 (5)	
Covid19	–	1 (2)
Clinically documented		
Odontogenic/oral mucositis	1 (2)	3 (5)
Intestinal mucositis	7 (12)	9 (15)

Three urinary tract infections caused by *E. cloacae* complex were detected in the fosfomycin group. Three urinary tract infections due to *E. coli* (2) and *P. aeruginosa* (1) were detected in the ciprofloxacin group. Two ESBL- and carbapenemase-producing Enterobacterales isolates were detected in each of these groups. A single patient developed oral abscess due to ESBL-producing *E. coli*.

Table 3: **Type of first infection during prophylaxis in the Per-Protocol population.**

One of them in the context of bacteriemia due to *Klebsiella variicola*. No microorganism was recovered in the second patient. Twenty patients developed bacteraemia, ten under fosfomycin prophylaxis and 10 under ciprofloxacin. Gram-positive bacteria accounted for the majority of bacteraemias in the ciprofloxacin group (9 of 10 bacteraemia) whereas Gram-negative bacteria predominated in the fosfomycin group (9 of 10 bacteraemias) (Table 4 and Appendix 4, Table 2, p12). One of the nine patients colonized at baseline by ESBL-producing *Escherichia coli* in the experimental group developed bacteraemia by the same strain. No patient

	Fosfomycin N = 10	Ciprofloxacin N = 10
Escherichia coli	3	1
Pseudomonas aeruginosa	1	0
Enterobacter cloacae complex	2	0
Klebsiella spp.	1	0
Other Gram - *Capnocytophaga sputigena* *Leclercia adecarboxylata*	2	0
Haemophilus influenzae	0	0
Streptococcus pneumoniae	1	0
Enterococcus faecium	0	1
Streptococcus viridans group	0	2
Streptococcus agalactiae	0	1
Coagulase-negative staphylococci	0	4
Fusobacterium nucleatum	0	1
Total	10	10

Three Gram-negative bacteria in fosfomycin and none in ciprofloxacin arm exhibit multidrug resistant phenotype.

Table 4: **Causes of bacteraemia in the Per-Protocol population.**

colonized in the control group developed bacteraemia due to the MDRGNB isolates. Fosfomycin susceptibility of the recovered isolates was available for four patients, half of whom were resistant. In Appendix 4, Table S1 shows the description of patients with bacteraemia together with the gut colonization status and fosfomycin susceptibility.

During the study period, 2 of 83 patients (3%) in the experimental group became colonized, compared to 9 of 83 patients (11%) in the control group (P = 0.04 for the difference in proportions). In the experimental group, colonization was limited to ESBL-producing Enterobacterales in both patients. In the control group, six patients were colonized with ESBL-producing Enterobacterales, and three patients were colonized with both ESBL- and carbapenemase-producing Enterobacterales. These colonised patients exhibited a 100% fluoroquinolone resistance rate.

Microbiome profiling

The microbiome status was analysed using 208 faecal samples obtained from 127 patients. The analysis was stratified by treatment and time point. Alpha diversity, measured with the Shannon index, decreased significantly between the beginning and the end of prophylaxis in both groups, with no differences between groups (P <0.0001 and 0.9 in within and between group factors in ANOVA test, respectively, Fig. 2a). Similar results were observed using other indexes (Appendix 4, Fig. S1, p9). A significant association was found between greater loss of alpha diversity as measured with the Shannon index (but not with Chao1, Observed features or Fisher indexes) and the development of Gram-negative bacteraemias, t-test P = 0.03, P = 0.94, P = 0.94 and P = 0.98, respectively).

Beta diversity PCoA at the genus level, stratified by treatment group at the end of prophylaxis, did not show separation between groups (Fig. 2b). PERMANOVA test revealed that 2.2% of the variation in microbiota composition was explained by treatment group. The same results were obtained when Unifrac values were calculated (R^2= 0.02).

In the differential abundance analysis at the genus level, only *Lacticaseibacillus* was significantly increased after fosfomycin prophylaxis (adjusted P = 0.043). At the phylum level, *Verrucomicrobiota* was significantly increased in the ciprofloxacin group (adjusted P <.00001 (Appendix 4, Table S2, p12). Dynamics of the microbial community at the phylum level is shown in Appendix 4, Fig. S2, p10.

Safety

During the trial, 479 events were registered in the safety population: 230 in the experimental group and 249 in the control group. The most common adverse events in the experimental (n = 82 patients) versus the control (n = 83 patients) group were mucositis (35 [43%] versus

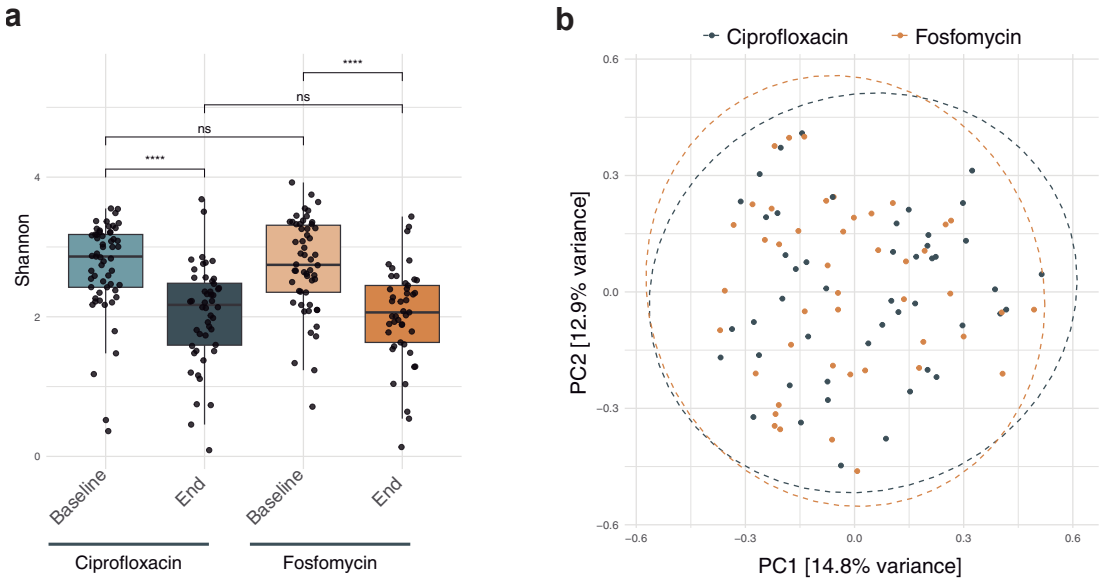


Fig. 2: a) Box plots of Shannon alpha diversity indexes at the beginning (57 patients in the ciprofloxacin group, 54 in the fosfomycin group) and end of prophylactic treatment (48 patients in the ciprofloxacin group, 45 in the fosfomycin group). b) Bray Curtis based PCoA plot of taxonomic features at the end of prophylaxis grouped by treatment group (48 patients in the ciprofloxacin group, 45 in the fosfomycin group). Patients did no segregated differently, R^2= 0.022.

33 [41]%), nausea (19 [23%] versus 21 [25%]), diarrhoea (18 [22%] versus 16 [19%]) and exanthema and skin toxicity (16 [19%] versus 24 [29]%). Nine adverse events were reported as serious (SAE). Three occurred in the experimental group: one mucositis, one septic shock without microbiological documentation and one sepsis occurring twelve days after the end of prophylactic treatment; The other six SAE occurred in the control arm: one *E. coli* bacteraemia, one leukaemic progression, one multiorgan failure, one mucositis, one myoclonus and one seizure. Grade 3–4 QTc interval prolongation was recorded in 1 patient in the ciprofloxacin group. Three additional patients in the fosfomycin group experienced grade 1–2 QTc prolongation. These events were detected at the end of treatment in all cases and resolved following withdrawal of the medication. All of these patients were taking at least one other medication that could potentially prolong the QT interval (azoles in three patients and ondansetron in two patients). These events were detected at the end of treatment in all cases and resolved following withdrawal of the medication. There were two deaths in the control group, one due to tumour lysis syndrome leading to multiorgan failure and one due to leukaemia progression. No deaths were recorded in the experimental group. A detailed description of adverse events is shown in Table 5.

The investigator prematurely discontinued prophylactic treatment in two patients (one in each treatment arm) due to the detection of contamination in the apheresis product requiring antibacterial treatment, and the development of hyperleukocytosis associated with G-CSF administration, respectively.

Adverse events leading to treatment discontinuation were found in one and four patients in the control and experimental arm, respectively. These events were seizures (n = 1), myoclonus (n = 1), mucositis (n = 1), central catheter infection in the next day of the beginning of prophylaxis (n = 1) and gastroenteritis due to rotavirus (n = 1). Absolute neutrophil counts in these last two events were 5×10^9/L and 1.75×10^9/L, respectively.

Discussion

Identification of new antibiotics effective against multiresistant bacteria is a research priority,[25] especially in high-risk populations such as neutropenic patients. In the particular case of fluoroquinolones this need becomes even more important, given their toxicity and the increasing rate of resistance to this family. Here, we report the results of the FOVOCIP trial, comparing oral fosfomycin to oral ciprofloxacin for the prevention of febrile neutropenia in haematological patients with high-risk neutropenia. Fosfomycin did not meet the prespecified criteria for non-inferiority in either the Intention-to-Treat, or the Per-Protocol population. The evidence that oral fosfomycin is not a valid alternative to fluoroquinolones allows to be focused on other antibacterial agents.

	Grade 1-2		Grade 3		Grade 4		Grade 5	
	Fosfomycin (n = 82)	Ciprofloxacin (n = 83)	Fosfomycin (n = 82)	Ciprofloxacin (n = 83)	Fosfomycin (n = 82)	Ciprofloxacin (n = 83)	Fosfomycin (n = 82)	Ciprofloxacin (n = 83)
Mucositis	33 (40)	31 (37)	1 (1)	1 (1)	1 (1)	1 (1)	0	0
Nausea	18 (22)	21 (25)	1 (1)	0	0	0	0	0
Diarrhoea	17 (21)	16 (19)	1 (1)	0	0	0	0	0
Vomiting	7 (8)	9 (11)	1 (1)	0	0	0	0	0
Constipation	8 (10)	12 (14)	1 (1)	1 (1)	0	0	0	0
Exanthema/skin toxicity	15 (18)	24 (29)	1 (1)	0	0	0	0	0
Abdominal pain	5 (6)	3 (4)	1 (1)	0	0	0	0	0
Seizures	0	0	0	0	0	1 (1)	0	0
Myoclonus	0	0	0	0	0	1 (1)	0	0
Acute abdomen	0	0	0	1 (1)	0	0	0	0
Acute leukaemia progression	0	0	0	0	0	0	0	1 (1)
Multiorgan failure due to tumour lysis syndrome	0	0	0	0	0	0	0	1 (1)
Allergic transfusion reaction	0	0	0	1 (1)	0	0	0	0
Atrial fibrillation	0	1 (1)	1 (1)	0	0	0	0	0
Prolongation of QT interval	3 (4)	0	0	1 (1)	0	0	0	0
Headache	6 (7)	7 (8)	0	1 (1)	0	0	0	0
Insomnia	3 (4)	1 (1)	1 (1)	0	0	0	0	0
Lumbago	2 (2)	1 (1)	1 (1)	0	0	0	0	0
Subarachnoid haemorrhagic	0	0	0	0	1 (1)	0	0	0
Subdural haematoma	0	0	0	0	1 (1)	0	0	0

Data are number of patients (%). Grade 1-2 adverse events are reported if they occurred in ≥10% patients if no grade 3–5 event was observed for each adverse event. All the grade 3–5 events are shown.

Table 5: **Non-infectious adverse events during the study until the follow-up period (safety population).**

Despite the broad-spectrum activity of fosfomycin against Gram positive and Gram-negative bacteria, several reasons may explain the lower-than-expected activity of the drug, in particular. The first one is related to pharmacokinetics. Several studies have highlighted the limited oral bioavailability and marked interindividual variability associated with the calcium salt formulation of fosfomycin, which was used in our study.[26] Secondly, it has been reported that the *FosA* gene, which contributes to fosfomycin resistance, is widely distributed among some Gram-negative bacteria, including *K. pneumoniae*, *K. oxytoca*, *Enterobacter cloacae* and *P. aeruginosa*, among others. Moreover, chromosomally located *FosA* gene may be transferred to *E. coli*, which lacks *FosA*.[27] The objective of the present study was not to analyse the expression of the Fos gene or other resistance mechanisms. However, ninety percent of the bacteraemias that occurred in the fosfomycin group were caused by Gram-negative bacteria, four of which showed resistance to the drug. This suggests that resistance to fosfomycin is a clinically relevant phenomenon that limits the drug's applicability. Thirdly, although there is evidence of the efficacy of fosfomycin as monotherapy,[28] we cannot exclude that monotherapy may have been suboptimal in the present study. It is known that fosfomycin acts synergistically when combined with broad-spectrum antibiotics, and that such combinations may reduce the emergence of resistance.[16] Since the available clinical evidence has been obtained in the context of infection treatment rather than prophylaxis and most of the antibiotics with which fosfomycin exhibits synergistic activity are administered intravenously, we opted to administered it as monotherapy in these stable patients.

The experience gathered in this study highlights the methodological challenges inherent in designing and conducting a study capable of establishing the non-inferiority of fosfomycin compared to ciprofloxacin. In particular, the observed efficacy results in both groups were not as expected, which reduced the statistical power of the study to evaluate the primary point, as well as mortality and bacteraemia. The absence of historical placebo-controlled trials to define the efficacy of the active control constituted a source of uncertainty during the design of the trial. Nevertheless, we considered that this limitation did not compromise the validity of the study, as prior experience with the drug in comparable patient populations was available. The observed success rate of 25% and 18% in the ITT and PP populations indicate that our initial projections were overly optimistic. On the other hand, the efficacy of ciprofloxacin was higher than expected. The definition of the expected success rate in the ciprofloxacin group was also a matter of debate during the design of the study. Given the possibility that the effect size of the drug reported in previous studies could be overestimated owing to

current resistance rates, we assumed a 50% reduction in the expected efficacy of the control arm. If we had assumed a success rate similar to that reported a decade ago, many researchers would likely have considered the approach overly optimistic. The 25% success rate observed in the present study suggests an attenuation of efficacy, which nevertheless, does not entirely compromise the therapeutic value of the drug. The observation that only one of the bacteraemic episodes occurring in the ciprofloxacin group was attributable to Gram negative bacteria and, that none of the nine colonized patients by MDRGNB strains in the ciprofloxacin arm developed bacteraemia secondary to colonizing strains provides additional support for this interpretation. Finally, despite the strict definition of febrile neutropenia, we acknowledge the possibility of bias arising from differences among clinicians in setting the threshold for initiating antibiotic treatment.

Toxicity did not represent a concern in either group. Gastrointestinal adverse events were frequent, as it would be expected in patients undergoing intensive chemotherapy. In this regard, the incidence of grade 1–2 gastrointestinal adverse events was similar between the two groups. Of note, six patients in the experimental group experienced grade 3–4 gastrointestinal toxicity as compared to one patient in the control group. Regarding the microbiological safety, although the loss of diversity in the microbiota was also similar between the experimental and control groups, the ability to selecting multi-resistant Gram-negative bacteria was greater in the ciprofloxacin results, in line with previous reports.[29] In contrast, as previously mentioned, more patients in the fosfomycin group developed Gram negative bacteraemias. These seemingly contradictory results highlight the need to further explore the complex relationships between microbiota, colonisation and infection in neutropenic patients.

The study also has several strengths that should be highlighted: first, the strict inclusion criteria ensured that patients were representative of a population at high risk of infection; second, the participation of 11 hospitals distributed throughout Spain guarantees the representativeness of the Spanish population; third, it prospectively assess the complex interactions between prophylaxis, colonization and bloodstream infections, addressing an existing knowledge gap on this topic[30]; finally, the FOVOCIP study is the first prospective, randomised trial assessing fosfomycin for infection prevention in haematological patients, and the first since 2005 comparing any antibiotic with fluoroquinolones.

In conclusion, this regimen of oral calcium fosfomycin failed to demonstrate non-inferiority and appears less effective than ciprofloxacin, with a particularly high rate of Gram-negative bacteraemia. Given the low numbers of patients, the microbiological benefit of fosfomycin in decreasing MDRGNB colonisation must be consider of uncertain clinical significance.

Based on the actual rates of success observed in the FOVOCIP study, a future non-inferiority trial would require the inclusion of several thousand patients. Although we believe that such study is feasible, we think that the results of FOVOCIP suggest that research should be directed towards the search for alternative drugs.

Contributors

TB and JFD were responsible for formulating the overall research questions and the methodological design of the study and were responsible for obtaining public block from the Instituto de Salud Carlos III and Agencia SEKUENS. AFM, TB and JFD interpreted the results and wrote the draft of the manuscript. TB was the clinical coordinator investigator and JFD the microbiological coordinator. PLU, AJGH, BBP, SC, LSB, MLC, MPZ, MTO, KH, JL, MLA, RRV, PM and MA were responsible for inclusion and follow-up of patients. PL prepared the samples for metataxonomic analysis. AMFV, EGB, MI, MMP, JC, LL, CS, GRC, GM, RB performed the microbiological analysis and interpreted the results. TB, JFD and MdT performed and interpreted the metataxonomic analysis. All authors read and approved the final manuscript.

Data sharing statement

Due to ethical restrictions, data and study material could be shared under reasonable proposals by contacting the corresponding author.

The raw sequencing data have been deposited in SRA with the following accession number: PRJNA1439972.

Declaration of interests

MLC reports lecture fees from AMGEN and SOBI. RRV reports lectures fees from Daiichi Sankyo, Jazz Pharma, Servier, Astellas and Pfizer. PM reports grants from AbbVie, Astellas, BMS/Celgene, Daiichi Sankyo, Janssen, Karyopharm, Novartis, Pfizer, Teva; consulting fees from Astellas, Agios, Tolero Pharmaceutical, Glycomimetics, Forma Therapeutics, BMS/Celgene, Daiichi Sankyo; lecture fees from AbbVie, Astellas, BMS/Celgene, Daiichi Sankyo, Incyte, Janssen, Novartis, Pfizer, Sanofi, Servier, Teva and support for participation on advisory board from AbbVie, Astellas, BMS/Celgene, Daiichi Sankyo, Incyte, Janssen, Karyopharm, Novartis, Pfizer, Sanofi, Servier, Syndax, Teva. MTO reports lecture fees from Jazz Pharmaceuticals, AbbVie, Gilead-Kite, Johnson&Johnson, BeOne; support fo attending meetings from AbbVie and BeOne; support for participation on advisory board from Johnson&Johnson, BeOne. JL reports lectures fees from AbbVie, Amgen, Astellas, Celgene, GlaxoSmithKline; support for attending meetings from Servier, Sanofi. TB reports grants from AbbVie; consulting fees from AbbVie, Jazz Pharmaceuticals and Astellas; lectures fees from Otsuka; support for attending meetings from AbbVie and Otsuka. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2026.101698.

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