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Moxifloxacin plus rifampin as an alternative for levofloxacin plus rifampin in the treatment of a prosthetic joint infection with *Staphylococcus aureus*

Marjan Wouthuyzen-Bakker [a,*], Eduard Tornero [b], Laura Morata [c], Prashant V. Nannan Panday [d], Paul C. Jutte [e], Guillem Bori [f], Greetje A. Kampinga [g], Alex Soriano [c]

[a] Department of Internal Medicine / Infectious Diseases, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands
[b] Department of Orthopaedic Surgery, Sant Joan de Déu, Barcelona, Spain
[c] Service of Infectious Diseases, Hospital Clínic, University of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
[d] Department of Clinical Pharmacy, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands
[e] Department of Orthopaedic Surgery, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands
[f] Department of Orthopaedic Surgery and Traumatology, Hospital Clinic, University of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
[g] Department of Medical Microbiology and Infection Prevention, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands

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ABSTRACT

Objectives: The combination of a fluoroquinolone with rifampin is one of the cornerstones in the treatment of prosthetic joint infections (PJI) caused by staphylococci. Moxifloxacin is highly active against methicillin–susceptible *Staphylococcus aureus* (MSSA) and, therefore, is an attractive agent to use. However, several studies reported a lowering in serum moxifloxacin levels when combined with rifampin. The clinical relevance remains unclear. We determined the outcome of patients with early acute PJI caused by MSSA treated with either moxifloxacin/rifampin or levofloxacin/rifampin.
Methods: Medical files of patients treated with moxifloxacin/rifampin (University Medical Centre Groningen) or levofloxacin/rifampin (Hospital Clinic Barcelona) were retrospectively reviewed (2005–2015). Treatment failure was defined as the need for revision surgery and/or suppressive therapy, death by infection or a relapse of infection during follow-up.
Results: Differences in baseline characteristics between the two cohorts were observed, but prognostic parameters for failure, as defined by the KLIC-score (Kidney failure, Liver cirrhosis, Index surgery, C–reactive protein and Cemented prosthesis), were similar in the two groups (2.9 [1.5 SD] for the moxifloxacin group vs. 2.2 [1.2 SD] for the levofloxacin group [$P = 0.16$]). With a mean follow-up of 50 months (36 SD) in the moxifloxacin group, and 67 months (50 SD) in the levofloxacin group ($P = 0.36$), treatment was successful in 89% vs. 87.5%, respectively ($P = 0.89$). None of the failures in the moxifloxacin group were due to rifampin– or moxifloxacin–resistant *S. aureus* strains.
Conclusion: Our data indicate that moxifloxacin combined with rifampin is as clinically effective as levofloxacin/rifampin for early acute PJI caused by MSSA.

1. Introduction

The combination of a fluoroquinolone with rifampin is one of the cornerstones in the treatment of prosthetic joint infections (PJI) caused by staphylococci. In 1998, Zimmerli et al. demonstrated a success rate of 100% using ciprofloxacin plus rifampin in combination with debridement and retention of the implant (DAIR) in patients with acute infection [1]. The success rate was only 67% in patients who were treated with ciprofloxacin monotherapy. In addition, several studies have shown that rifampin combinations with agents other than fluoroquinolones are less successful [2,3]. These important findings have led to an international recommendation to use ciprofloxacin or levofloxacin in combination with rifampin as a first–line oral therapy in staphylococci infections [4].

Moxifloxacin is a newer fluoroquinolone with a high oral bioavailability and bone penetration [5–7]. Compared with levofloxacin and ciprofloxacin, moxifloxacin exhibits a lower MIC for methicillin–susceptible *Staphylococcus aureus* (MSSA). In addition, moxifloxacin has a lower potential than other quinolones to

* Corresponding author. University Medical Centre Groningen, Groningen, The Netherlands.
E-mail address: m.wouthuyzen-bakker@umcg.nl (M. Wouthuyzen-Bakker).

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induce bacterial resistance because of its high intrinsic activity against intracellular targets, and no dose adjustments are necessary for patients with renal insufficiency [8,9]. Therefore, moxifloxacin is an attractive antimicrobial agent in the treatment of PJI. However, some studies on tuberculosis have shown that rifampin lowers moxifloxacin serum levels by 30%, whereas levofloxacin and rifampin was associated with no lowering of levofloxacin serum levels in patients with pyogenic spondylodiscitis [10–12]. In addition, moxifloxacin alone shows high intra-variability in serum levels and bone concentrations [11–13]. The clinical relevance of these findings remains unclear. San Juan et al. demonstrated a cure rate of 71% in patients with orthopaedic implant-related staphylococcal infections with moxifloxacin monotherapy and retention of the implant [14]. So far, there are no data reporting the outcome of patients with PJI treated with moxifloxacin/rifampin combination therapy.

Therefore, we retrospectively compared two cohorts of patients with early acute PJI caused by MSSA who were treated with rifampin combined with either moxifloxacin or levofloxacin. The objective of our study was to compare the clinical outcome of both cohorts.

2. Patients and methods

2.1. Data collection

We retrospectively analysed the medical files of patients who were treated with moxifloxacin and rifampin (at the University Medical Centre Groningen [UMCG], The Netherlands) and levofloxacin and rifampin (at the Hospital Clinic of Barcelona, Spain) in the period 2005–2015. The use of these two different antibiotic regimens is the standard first–line oral antimicrobial therapy in the respective University Hospitals. Patients with early acute PJI (i.e. < 3 months post-operatively and symptoms < 3 weeks) of knee or hip, caused by MSSA and treated with DAIR, were included in the analysis. A PJI was diagnosed according to the diagnostic criteria described by the Musculoskeletal Infection Society (MSIS) [15]. Several baseline characteristics were collected, including the parameters that are prognostic for treatment failure according to the KLIC score (i.e. Kidney failure, Liver cirrhosis, Index surgery, C-Reactive Protein [CRP], and Cemented prosthesis) [16].

2.2. Surgical approach

For a debridement, pre-existing incisions of the arthroplasty were used. A DAIR consisted of extensive excision of necrotic/infected tissue, lavage of 6–9 L of saline, exchange of mobile components and mechanical cleaning with brushes of the exposed surfaces of the fixed components. When mobile components were not exchanged according to the judgment of the orthopaedic surgeon (i.e. fixed components and/or clinical suspicion of superficial wound infection), this was recorded. At the UMCG, in general, gentamicin bead chains and/or gentamicin-impregnated collagen sponges were inserted at the time of the DAIR. According to protocol, the gentamicin bead chains were removed 2 weeks after insertion and an extra lavage of the joint was performed. When there were still active signs of infections as judged by the orthopaedic surgeon (i.e. persistent wound leakage, persistent rise of inflammatory parameters and/or purulent wound discharge during surgery), a second debridement was performed during this surgery.

2.3. Antimicrobial treatment

After DAIR, patients were treated empirically with broad-spectrum antibiotics and were switched to intravenous cloxacillin or flucloxacillin 12 g/24h for 7–14 days after culture results became available. The intravenous induction period was followed by an oral antibiotic regimen, using levofloxacin 500 mg QD combined with rifampin 600 mg QD (Hospital Clínic) or moxifloxacin 400 mg QD combined with rifampin 450 mg BID (UMCG). Rifampin was generally added after debridement as soon as the antibiogram was available. For all cases, *S. aureus* was considered susceptible to moxifloxacin or levofloxacin if they were found susceptible to ciprofloxacin according to EUCAST breakpoints, as determined by disk diffusion, Vitek 2 or Etest. Before the start of moxifloxacin, an electrocardiogram was performed to rule out a prolonged QT-interval and was repeated 1 week later whilst on treatment. In case of polymicrobial infections, an extra antimicrobial agent with specific activity against the other microorganism(s) was added when necessary. The total duration of antimicrobial therapy was generally approximately 90 days.

2.4. Clinical outcome

Failure of treatment was defined as the need for revision surgery and/or suppressive antimicrobial therapy because of persistent infection during antimicrobial treatment, death–related infection, a reinfection or relapse of infection with *S. aureus* during follow-up. Follow-up cultures were reviewed to evaluate the development of rifampin–resistant *S. aureus* strains.

2.5. Follow-up

After discharge, patients were followed at the outpatient clinic at monthly intervals during the period of antimicrobial treatment. After discontinuation of antibiotic treatment, patients were followed every 3–6 months during the first year after DAIR and annually afterwards. The end point of follow-up was defined as the last visit of the patient at the outpatient clinic of the orthopaedic or rheumatology department or as the time point of failure.

2.6. Statistical analysis

Within this retrospective cohort study, comparison between groups for continuous variables was analysed using an independent student t-test or Mann-Whitney U test if the data were not equally distributed. Levene's test was used to test for equality between variances. Continuous variables were depicted as mean and standard deviation (SD) or median and interquartile range (IQR). For categorical variables, a Chi-square test was used. A Fisher exact-test was performed when appropriate. A Kaplan-Meier survival curve was used to depict treatment success for both groups from the time of debridement. A log-rank test was applied to compare treatment success. *P*-values < 0.05 were considered statistically significant. Statistical analysis was performed using SPSS, version 20.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Patient characteristics

A total of 58 patients were included in the analysis. Table 1 shows the patient characteristics of the moxifloxacin (n = 18) vs. the levofloxacin (n = 40) group. Patients were followed with mean duration of 50 months (34 SD) in the moxifloxacin group and 67 months (50 SD) in the levofloxacin group ($P = 0.29$). Comorbidity and ASA classification were similar in the two groups. The degree of inflammation before debridement, as a surrogate parameter for the severity of infection, was the same for the moxifloxacin and levofloxacin groups (median CRP 5.8 [2.4–8.7 IQR] and 3.8 [1.7–8.0 IQR] mg/dL respectively, $P = 0.61$). The moxifloxacin group contained more hips (72%) compared with the levofloxacin group

Table 1
Patient characteristics. Characteristics of patients with early acute PJI caused by methicillin–susceptible *S. aureus*.

	Moxifloxacin plus rifampin (n = 18)	Levofloxacin plus rifampin (n = 40)	*P*-value
Baseline characteristics			
Sex			
- male	7 (39)	23 (58)	0.26
- female	11 (61)	17 (42)	0.26
Age, years	66.7 (13.7)	69.8 (9.6)	0.31
Body Mass Index (kg/m^2)	31.2 (4.6)	31.4 (4.2)	0.89
Comorbidity			
- **diabetes mellitus**	1 (6)	5 (13)	0.65
- **chronic renal insufficiency**	1 (6)	1 (3)	0.53
- **liver cirrhosis**	0 (0)	1 (2)	1.00
- **cardiovascular disease**	2 (11)	3 (8)	0.64
- **chronic obstructive pulmonary disease**	0 (0)	2 (5)	1.00
- **rheumatoid arthritis**	3 (17)	2 (5)	0.17
- **malignancy**	0 (0)	2 (5)	0.3
ASA classification[b]			
- **ASA I-II**	14 (78)	25 (63)	0.96
- **ASA III-IV**	4 (22)	15 (37)	0.96
Medication			
- **immunosuppressive drugs**	3 (17)	1 (3)	0.08
- **acenocoumarol**	2 (11)	1 (3)	0.22
Polymicrobial infection	7 (39)	5 (13)	0.03[a]
C-Reactive Protein before DAIR[c] (mg/dL)	5.8 (2.4–8.7)	3.8 (1.7–8.0)	0.61
Prosthesis			
Joint			
- **hip**	13 (72)	11 (28)	0.003[a]
- **knee**	5 (28)	29 (73)	0.003[a]
Indication prosthesis			
- **osteoarthritis**	13 (72)	34 (85)	0.29
- **hip fracture**	2 (11)	4 (10)	1.00
- **rheumatoid arthritis**	3 (17)	2 (5)	0.17
Cemented prosthesis	16 (89)	29 (73)	0.30
Revision prosthesis	3 (17)	3 (8)	0.36
Surgical approach			
No. of DAIRS[c]	1.5 (0.5)	1.0 (0.2)	< 0.001[a]
Exchange of mobile components	11 (61)	29 (73)	0.36
Use of gentamicin beads and/or sheets	16 (89)	0 (0)	< 0.001[a]
Antimicrobial treatment			
No. days intravenous antimicrobial treatment	14 (14–22)	8 (4–12)	< 0.001[a]
No. days oral antimicrobial treatment	76 (74–76)	71 (45–100)	0.76
Total no. days of antimicrobial treatment	90 (90–95)	85 (51–107)	0.25
KLIC score[d]	2.9 (1.5)	2.2 (1.2)	0.16
Months of follow-up	49.7 (35.9)	67 (50.1)	0.29

[a] *P*-values < 0.05 were considered statistically significant.
[b] American Society of Anesthesiologists.
[c] Debridement Antibiotics and Implant Retention.
[d] KLIC score: score for predicting treatment failure in patients with early acute PJI and treated with DAIR (**K**idney failure, **L**iver cirrhosis, **I**ndex surgery, **C**-Reactive Protein, and Cemented prosthesis). Nominal variables are depicted as: n (%), continuous variables are depicted as: mean (SD) or median (interquartile range) when not normally distributed.

(28%) ($P = 0.001$), and consisted of more polymicrobial infections (39% vs. 13%, respectively; $P = 0.03$).

3.2. Surgical approach

As described in the patient and method section, the surgical approach differed between the two groups. Most patients in the moxifloxacin group (89%) received gentamicin–impregnated beads (n = 12) and/or sponges (n = 4). During the surgical procedure to remove the gentamicin beads and perform a lavage, 9 of 12 patients underwent a second debridement based on the pre- and/or intra-operative decision of the orthopaedic surgeon. The percentage of patients with a second debridement in the levofloxacin group was only 2.5% (n = 1) ($P < 0.001$). In 8 of 9 patients who underwent an extra debridement in the moxifloxacin group, *S. aureus* was not isolated anymore in the intraoperative cultures.

3.3. Antimicrobial treatment

The median number of days of intravenous antimicrobial treatment was higher in the moxifloxacin group (14 days [14–22 IQR]) than in the levofloxacin group (8 days [4–12 IQR]) ($P < 0.001$), but the total number of days on antimicrobial treatment was the same (90 days [90–95 IQR] versus 85 days [51–107 IQR], respectively [$P = 0.25$]). In the moxifloxacin group, 2/18 patients received an additional oral antimicrobial agent during the whole treatment period because of a polymicrobial infection that also had *S. aureus* activity (linezolid and clindamycin). In the levofloxacin group, this was the case in 2/40 patients (linezolid and cotrimoxazole).

3.4. Prognostic risk score for failure

Because of the above-mentioned differences in the groups, we also calculated the KLIC score, which is a prognostic risk score for treatment failure in early acute PJI, as described in the patient and method section. The KLIC score was the same in the moxifloxacin and levofloxacin groups (mean score 2.9 [1.5 SD] versus 2.2 [1.2 SD], respectively [$P = 0.16$]), which corresponds to a chance of treatment failure of 4.5–19.4% [16].

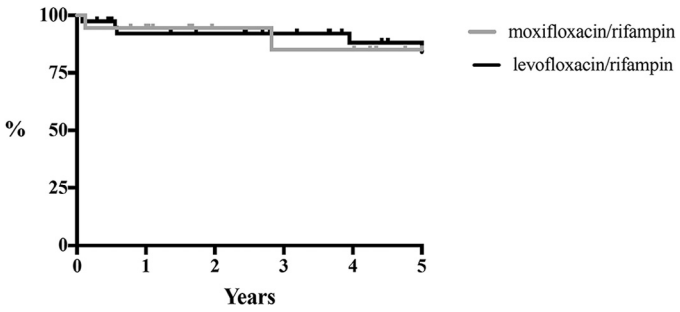

Fig. 1. Clinical outcome. Treatment success (%) of moxifloxacin/rifampin (n = 18) vs. levofloxacin/rifampin (n = 40) in patients with early acute PJI caused by methicillin–susceptible *S. aureus* and retention of the implant.

3.5. Clinical outcome

Treatment was successful in 16/19 patients (89%) in the moxifloxacin group vs. 35/40 patients (87.5%) in the levofloxacin group ($P = 0.89$). Fig. 1 shows the cumulative survival within 5 years after debridement in both groups (log-rank test, $P = 0.99$). Almost half the patients failed despite receiving antimicrobial therapy. In the moxifloxacin group, 1 of 2 patients (50%) failed during treatment, which required an extraction of the prosthesis, and 2 of 5 (40%) patients failed during treatment in the levofloxacin group ($P = 1.0$); 1 patient died due to an infection, and 1 patient was put on suppressive therapy because of clinical failure. In both cohorts, 1 patient had a relapse of infection with *S. aureus* during follow-up. In 14 of 18 patients in the moxifloxacin group, no follow-up cultures with *S. aureus* were available. There were no rifampin- or moxifloxacin–resistant *S. aureus* strains detected in the 4 patients with follow-up cultures during and after treatment (including the 2 patients with treatment failure). In the levofloxacin group, follow-up cultures with *S. aureus* were available for only 2 of 40 patients, and neither of them had levofloxacin–resistant strains. Because of the relatively small numbers of patients in the moxifloxacin group and the high success rate (2/18), we considered it not feasible to perform a multiple regression analysis on the parameters that were different between the two groups.

4. Discussion

As previous studies have shown that rifampin significantly reduces moxifloxacin serum levels, the aim of our study was to evaluate the outcome of patients with early acute PJI caused by MSSA and treated with the moxifloxacin/rifampin combination. Our results show a success rate of 89%, which is comparable to the 87.5% success rate we observed in patients treated with levofloxacin and rifampin. None of the failures in the moxifloxacin group were due to rifampin–resistant *S. aureus* strains. Our data indicate that moxifloxacin could be an effective alternative for levofloxacin in the treatment of PJI with retention of the implant.

To the best of our knowledge this is the first study to evaluate the efficacy of moxifloxacin combined with rifampin in the treatment of PJI. Several studies demonstrate a worrisome interaction of rifampin with several antimicrobials; e.g. rifampin has been shown to decrease the serum levels of cotrimoxazol, clindamycin, linezolid and fusidic acid [17–21]. Therefore, these combinations should be used with caution in the treatment of implant infections. Tornero et al. demonstrated in Gram-positive PJI that when these so–called 'rifampin–dependent antibiotics' are used in the treatment of acute infections, only 72% of the infections are successfully treated, compared with 92% when 'rifampin–independent antibiotics' are used [20]. Despite the clear interaction that has also been demonstrated with moxifloxacin, we observed no negative effect on clinical outcome. The moxifloxacin $AUC_{0–24h}$ has been observed to decrease approximately 30% when combined with rifampin (from 48 to 33 mg x h/L) [11–13]. The pharmacodynamic target associated with bactericidal activity against *S. aureus* is an $AUC_{0\text{-}24h}/MIC \geq 80$ [22]. Taking into account a 40% protein binding ($fAUC_{0\text{-}24h}$ of 20) and a MIC_{90} of 0.12 mg/L, the ratio is 166, which would be enough even for bone infections considering a bone penetration of around 50% [5–7].

Our study should be viewed in the light of some limitations. For example, we included a relatively small number of patients in the moxifloxacin group. In addition, we observed several differences between the moxifloxacin and levofloxacin groups. Although the moxifloxacin group had a very high success rate, the observed differences make direct comparison between the antibiotic regimens complex. The most relevant difference between the groups was the surgical approach, with the use of gentamicin beads and/or sponges in the moxifloxacin group. Because of this, most patients in this group underwent a second lavage, and half the patients an extra debridement. The use of gentamicin–impregnated material remains controversial [23]. Extra surgery with additional disruption of the soft tissue might also have a negative effect by disturbing wound healing and exposing the patient to a new infection. Kuiper et al. analysed whether the use of gentamicin beads and sponges was associated with treatment success in patients with early PJI, but a logistic regression analysis did not show any association [24]. Therefore, it is not likely that this difference in surgical approach had a major impact on the treatment outcome. The moxifloxacin group had a higher rate of hip PJI and a longer duration of intravenous antimicrobial treatment, but several studies have shown that the affected joint and a shorter duration of intravenous therapy are not risk factors for failure [2,22,25]. Indeed, the KLIC score, a prognostic risk score for treatment failure in early PJI, was the same in both groups. In addition, because the number of polymicrobial infections was higher in the moxifloxacin group, and this has been associated with a higher failure rate, the treatment success of moxifloxacin is unlikely to be overestimated in the studied patients [2,25].

In conclusion, the excellent activity of moxifloxacin against staphylococci, its high genetic barrier for resistance and its easy usage in patients with renal insufficiency, makes moxifloxacin an attractive agent to use in clinical practice. Our data indicate that moxifloxacin and rifampin combination therapy can be used as an alternative for levofloxacin and rifampin in the treatment of early acute PJI caused by MSSA. As this was a retrospective study design, with observed baseline differences between the cohorts and a relatively small sample size, the non-inferiority of moxifloxacin to levofloxacin should ideally be studied in a randomized controlled trial to ultimately prove its efficacy.

Declarations

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