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Moxifloxacin-rifampicin combination for the treatment of non-staphylococcal Gram-positive orthopedic implant-related infections

Association moxifloxacin et rifampicine dans le traitement des infections ostéoarticulaires sur matériel à bactéries à Gram positif hors staphylocoque

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Mots clés : infection ostéoarticulaire ; moxifloxacine; rifampicine

ABSTRACT

Objective. We aimed to describe the effectiveness and safety of the moxifloxacin-rifampicin combination in non-staphylococcal Gram-positive orthopedic implant-related infections.

Methods. Patients treated with the moxifloxacin-rifampicin combination for an implant-related infection from November 2014 to November 2016 were retrospectively identified from the database of the referral centers for bone and joint infections in Western France.

Results. Twenty-three cases of infection due to *Streptococcus* spp. (n=12), *Cutibacterium acnes* (n=6), and *Enterococcus faecalis* (n=5) were included. Ten patients with hip prosthesis were included. Infection was polymicrobial in 11 cases. According to the MIC, moxifloxacin was 1.5 to 11.7 times as active as levofloxacin against non-staphylococcal Gram-positive bacteria. We reported an 81.8% success rate, and no severe adverse effect.

Conclusion. The moxifloxacin-rifampicin combination is a valuable alternative for the treatment of non-staphylococcal Gram-positive implant-related infections because of the good activity of moxifloxacin against these bacteria and the potential activity on the biofilm.

RESUME

Objectif. Décrire l'efficacité et la tolérance de l'association moxifloxacine et rifampicine dans le traitement des infections ostéoarticulaires sur matériel à Gram positif hors staphylocoque.

Méthodes. Les cas traités entre novembre 2014 et novembre 2016 ont été rétrospectivement identifiés dans la base de données des Centres de Référence pour les Infections Ostéoarticulaires Complexes du Grand Ouest.

Résultats. Vingt-trois cas d'infections à *Streptococcus* spp. (n=12), *Cutibacterium acnes* (n=6) et *Enterococcus faecalis* (n=5) ont été inclus. L'infection était polymicrobienne dans 11 cas. Les concentrations minimales inhibitrices de la moxifloxacine étaient 1,5 à 11,7 fois inférieures à celles de la lévofloxacine. Le taux de succès était de 81,8 %. Aucun effet indésirable grave n'a été observé.

Conclusion. L'association moxifloxacine-rifampicine est une alternative intéressante pour le traitement des infections sur matériel à Gram positif hors staphylocoque, du fait d'une bonne activité de la moxifloxacine contre ces bactéries et d'une potentielle activité sur le biofilm.

INTRODUCTION

The recommended treatment for orthopedic implant-related infections caused by non-staphylococcal Gram-positive bacteria (NSGPB), mainly *Streptococcus* spp., *Enterococcus* spp., and *Cutibacterium acnes*, is intravenous penicillin G or amoxicillin [1,2]. However, the duration of intravenous treatment and best oral regimen remain controversial.

Rifampicin usually has a good in vitro activity against NSGPB [3-5] and, among fluoroquinolones, moxifloxacin usually has the lowest minimum inhibitory concentration (MIC) [6].

We aimed to describe the safety and effectiveness of the rifampicin-moxifloxacin oral combination in non-staphylococcal Gram-positive orthopedic implant-related infections.

METHODS

We performed a retrospective study and identified cases from the database of the six reference centers for bone and joint infections in Western France (Tours, Rennes, Angers, Brest, Nantes, Poitier), which can be solicited for advice or for clinical management. The charts of all patients who received the moxifloxacin-rifampicin combination between November 2014 and November 2016 were reviewed. Patients were included if signs of infection related to the orthopedic implant were present (fever, redness, sinus tract, or implant loosening) and if *Streptococcus* spp. or *Enterococcus* spp. were isolated from at least two joint aspirates and/or intraoperative samples. Three or more positive intraoperative samples were required for *C. acnes*. Infection was classified as polymicrobial when several bacteria were isolated from the intraoperative samples (at least two samples for coagulase-negative staphylococci). Infections were classified as follows: *i*) early postoperative infection, when the infection was

diagnosed within the first 30 days following surgery, *ii*) late chronic infection, when the infection was diagnosed more than 30 days after surgery with gradual, indolent onset of symptoms, *iii*) acute hematogenous infection, when the infection was diagnosed with acute onset in a previously well-functioning prosthesis. MICs were measured using the E-test method (E-TEST® bioMérieux).

The follow-up period was calculated from the start of treatment with rifampicin and moxifloxacin. Failure was defined as death related to the infection, additional surgery to control the infection, or when signs of infection remained or reappeared during follow-up. Success was assessed only for patients with a 12-month follow-up period minimum. This study obtained review and approval from Rennes University Hospital Ethics Review Board.

RESULTS

Twenty-three cases were included (Table I), all from the center of reference of Rennes (20 cases managed in Rennes hospital, and three cases managed in Saint-Malo hospital). The median age was 61 years (range, 29-92), the median weight was 76 kg (range, 58-114), and the sex ratio was 1.5. Underlying conditions included moderate renal and cardiac dysfunction (patients 1 and 9), alcohol abuse (patient 16), osteosarcoma (patients 18 and 22), and rheumatoid arthritis treated with anti-TNF therapy (patient 17). The most frequent orthopedic implants were hip prosthesis (n=10, 43.4%) and plates for long bone osteosynthesis (n=5, 21.8%). Infections were classified as late chronic infections (n=12, 52.1%), early postoperative infections (n=7, 30.4%), or acute hematogenous infections (n=4, 17.4%). Streptococci were isolated in 12 cases (52.0%), *C. acnes* in six cases (26.0%), and *Enterococcus faecalis* in five cases (21.7%). The infection was polymicrobial in 11 cases (47.8%), most frequently with *Staphylococcus aureus* (n=7). Initial surgical management was debridement and implant

retention for all early postoperative infections (except for patient 15) and acute hematogenous infections. Implant exchange (n=8) or removal (n=4) was performed for all late chronic infections. Twenty patients received empirical post-operative antibiotic treatment (in patients 4, 5, and 8, no infection was suspected prior to surgery; treatment was started when the microbiological results were available), including a beta-lactam (n=14), vancomycin (n=3), or vancomycin plus a beta-lactam (n=3). Culture-guided intravenous treatment was amoxicillin alone for monomicrobial infections (n=11), cefazolin for co-infections with streptococci and *S. aureus* (n=4), or beta-lactam/beta-lactamase inhibitor (n=7). The median duration of total intravenous treatment was 14 days (range, 0-42) before oral switch to the moxifloxacin-rifampicin combination. Median dosage of rifampicin was 11 mg/kg/day (range, 8-13), mostly once a day. Only one patient, weighing 114 kg, received moxifloxacin 400 mg twice a day because peak serum concentration was considered low (1.7 mg/l) with 400 mg once a day. No other antibiotic was associated, even in cases of polymicrobial infections. MICs for both moxifloxacin and levofloxacin were available for 20 patients. Compared with levofloxacin, moxifloxacin was 2.6 to 11.7 times more active against *Streptococcus* spp. (range of MICs, 0.064-0.25 mg/l), 1.5 to 8 times more active against *C. acnes* (range, 0.047-0.125 mg/l), and 2 to 5.3 times more active against *E. faecalis* (range, 0.094-0.5 mg/l). Total duration of antimicrobial treatment was six to 16 weeks. This regimen was followed by indefinite chronic oral antimicrobial suppression with penicillin for patients 7 and 22.

In patient 21 only, moxifloxacin was discontinued after 15 days because of dizziness and arthromyalgia. Gastrointestinal tract disorder was the most frequent adverse effect reported (n=3). Spontaneously resolving liver function abnormalities (isolated elevated hepatic enzymes, grade two) were reported in three patients. One patient (patient 9) died of hemorrhagic shock complicating treatment with heparin. After a median follow-up of 20.5

months (range, 13-44) the global success rate was 81.8% (18/22). Among the four failures, only patient 4 experienced relapse. Patients 12 and 21 presented with re-infections with *S. epidermidis* and patient 23 experienced clinical failure, not microbiologically confirmed.

DISCUSSION

We reported our experience with the oral combination of moxifloxacin and rifampicin in the treatment of non-staphylococcal Gram-positive orthopedic implant-related infections, which highlights high success rate (81.8%) despite factors usually associated with poor outcome: *i*) polymicrobial infection in 47.8% of cases, *ii*) isolation of *Enterococcus* spp. in 18.8% of cases, *iii*) and implant retention in 40.9% of cases [1,7]. We only deplored one relapse, for which surgical procedure and timing of antibiotic initiation were not optimal. Recent studies on prosthetic joint infections involving NSGPB reported a “not-so-good” success rate despite prolonged intravenous therapy: 58% in a large multicenter study of *Streptococcus* spp. infections when implant was retained [8] and 56% in *Enterococcus* spp. infections [7]. However, in a series of *C. acnes* infections treated with a rifampicin combination therapy in two-thirds of cases, success rate was close to 90% [9]. The good success rate reported in the present article might be explained by the effectiveness of the moxifloxacin-rifampicin combination on the biofilm usually associated with foreign-body infection. Indeed, rifampicin alone or in combination with a fluoroquinolone has been shown to be effective *in vitro* against *E. faecalis* and *C. acnes* biofilms [4,5]. Moreover, two recent observational studies advocated the use of rifampicin in streptococcal periprosthetic joint infections, particularly in cases of implant retention [8,10]. The favorable blood/bone ratio [11] and the high bioavailability of moxifloxacin and rifampicin also allow a short initial intravenous treatment; median duration was 14 days in our series. The combination of moxifloxacin and rifampicin has already been

used in staphylococcal prosthetic joint infection and the success rate was not different than that reported with the levofloxacin-rifampicin combination in a recent retrospective study [12]. In our series, the seven cases of co-infection with *S. aureus* were associated with favorable outcomes.

Our data confirms the in vitro superiority of moxifloxacin against NSGPB, which was 1.5 to 11.7 as active as levofloxacin according to MICs. There were no other cases than those included in our study, with both levofloxacin and moxifloxacin MICs available, over the study period in our two centers. However, activity of moxifloxacin against *Enterococcus* spp. is unpredictable, particularly against *E. faecium* [6]; it seems preferable to determine MIC before choosing this drug. Pharmacokinetic interaction between rifampicin and moxifloxacin is expected to be weak because moxifloxacin is entirely metabolized during the phase II of glucuronidation and sulfation whereas rifampicin is particularly known as an inducer of phase I isoenzymes of cytochrome P450. However, reduction of moxifloxacin plasma concentration has been reported in patients treated with rifampicin and isoniazid for tuberculosis [13]. The clinical relevance of this interaction is still debated [12,14] and extrapolation to non-tuberculosis patients has to be confirmed.

The European Medicines Agency raised concerns about the potential hepatotoxicity of moxifloxacin and recommended in 2008 a restriction of its use. However, a recent case control study was unable to show a greater risk for moxifloxacin compared with levofloxacin or amoxicillin [15]. Only mild and transient elevations in aminotransferase levels were reported in our study. Fluoroquinolones, and particularly moxifloxacin, have been associated with prolongation of the QT interval by inhibition of the cardiac potassium channel, but few studies have explored the clinical impact. In a nationwide cohort study in Taiwan the use of moxifloxacin was associated with a higher risk of ventricular arrhythmia or cardio-vascular

death compared with amoxicillin-clavulanic acid. However, the association persisted after treatment discontinuation, suggesting that other factors than the treatment itself might be involved. Moreover, the absolute risk of cardiovascular death associated with the use of moxifloxacin was very low and not significantly higher compared with levofloxacin [16]. No cardiac event was reported in our series, but an electrocardiogram should be performed before initiating moxifloxacin to look for QT interval prolongation.

Conclusion

Our results suggest that the moxifloxacin-rifampicin combination is a valuable alternative for the treatment of non-staphylococcal Gram-positive implant-related infections because of the good activity of moxifloxacin against these bacteria and the potential activity of this combination therapy on the biofilm.

Disclosure of interests

The authors declare no conflict of interests.

Acknowledgment

FF and CA conceived and designed the study. FF, AJG, TG, MCV, and MD contributed to the acquisition of data. FF analyzed the data. FF, EP, and MCV wrote the final report.

All authors reviewed and approved the final version of the article.

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REFERENCES

1. Osmon DR, Berbari EF, Berendt AR, Daniel Lew, Zimmerli W, Steckelberg JM, et al. Diagnosis and Management of Prosthetic Joint Infection: Clinical Practice Guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2013;1:e1-25.
2. Stahl JP, Guery B, Bru JP, Gauzit R, Lina B, Piroth L, et al. Clinical practice recommendations. Osteoarticular infections on materials (prosthesis, implant, osteosynthesis). *Med Mal Infect* 2009;39:815-63.
3. Khasseba J, Hellmark B, Davidsson S, Unemo M, Nilsson-Augustinsson A, Söderquist B. Antibiotic Susceptibility of *Propionibacterium Acnes* Isolated from Orthopaedic Implant-Associated Infections. *Anaerobe* 2015;32:57-62.
4. Furustrand T, Ulfarsson U, Corvec S, Betrisey B, Zimmerli W, Trampuz A. Role of Rifampin against *Propionibacterium Acnes* Biofilm in Vitro and in an Experimental Foreign-Body Infection Model. *Antimicrob Agents Chemother* 2012;56:1885-91.
5. Holmberg A, Mörgelin M, Rasmussen M. Effectiveness of Ciprofloxacin or Linezolid in Combination with Rifampicin against *Enterococcus Faecalis* in Biofilms. *J Antimicrob Chemother* 2012;67:433-39.
6. Hoogkamp-Korstanje JA, Roelofs-Willemsse J. Comparative in Vitro Activity of Moxifloxacin against Gram-Positive Clinical Isolates. *J Antimicrob Chemother* 2000;45:31-39.
7. Tornero E, Senneville E, Euba G, Petersdorf S, Rodriguez-Pardo D, Lakatos B, et al. Characteristics of Prosthetic Joint Infections Due to *Enterococcus* Sp. and Predictors of Failure: A Multi-National Study. *Clin Microbiol Infect* 2014;20:1219-24.
8. Lora-Tamayo J, Senneville E, Ribera A, Bernard L, Dupon M, Zeller V, et al. The Not-So-Good Prognosis of Streptococcal Periprosthetic Joint Infection Managed by Implant Retention: The Results of a Large Multicenter Study. *Clin Infect Dis* 2017;64:1742-52.

9. Jacobs AM, Van Hooff ML, Meis JF, Vos F, Goosen JH. Treatment of prosthetic joint infections due to *Propionibacterium*. Similar results in 60 patients treated with and without rifampicin. *Acta Orthop* 2016;87:60-6.
10. Fiaux E, Titecat M, Robineau O, Lora-Tamayo J, El Samad Y, Etienne M, et al. Outcome of patients with streptococcal prosthetic joint infections with special reference to rifampicin combinations. *BMC infectious diseases* 2016;16 :568.
11. Landersdorfer CB, Kinzig M, Hennig FF, et al. Penetration of Moxifloxacin into Bone Evaluated by Monte Carlo Simulation. *Antimicrob Agents Chemother* 2009; 53:2074-81.
12. Wouthuyzen-Bakker M, Tornero E, Morata L, Nannan Panday PV, Jutte PC, Bori G, et al. Moxifloxacin plus Rifampin as an Alternative for Levofloxacin plus Rifampin in the Treatment of a Prosthetic Joint Infection with *Staphylococcus Aureus*. *Int J Antimicrob Agents* 2018;51:38-42.
13. Nijland HM, Ruslami R, Suroto AJ, Burger DM, Alisjahbana B, van Crevel R, et al. Rifampicin Reduces Plasma Concentrations of Moxifloxacin in Patients with Tuberculosis. *Clin Infect Dis* 2007;8:1001-7.
14. Manika K, Chatzika K, Papaioannou M, et al. Rifampicin-Moxifloxacin Interaction in Tuberculosis Treatment: A Real-Life Study. *Int J Tuberc Lung Dis* 2015; 19:1383-87.
15. Kaye JA, Castellsague J, Bui CL, et al. Risk of Acute Liver Injury Associated with the Use of Moxifloxacin and Other Oral Antimicrobials: A Retrospective, Population-Based Cohort Study. *Pharmacotherapy* 2014; 34:336-49.
16. Chou HW, Wang JL, Chang CH, Lai CL, Lai MSL, Chan KA. Risks of Cardiac Arrhythmia and Mortality among Patients Using New-Generation Macrolides, Fluoroquinolones, and β -Lactam/ β -Lactamase Inhibitors: A Taiwanese Nationwide Study. *Clin Infect Dis* 2015; 60:566-77.

Tableau I. Infections ostéoarticulaires sur matériel à Gram positif hors staphylocoque traitées par l'association moxifloxacine et rifampicine

Table I. Non-staphylococcal Gram-positive implant-related infections treated with the moxifloxacin-rifampicin combination (23 patients)

Nb	Implant	Classification of infection ^a	Non- staphylococcal bacteria ^d	Co-infection ^d	Surgical management	Intravenous treatment (days)	Total treatment (weeks)	Follow- up (months)	Out- come
1	Hip prosthesis	Early postop.	<i>E. faecalis</i>	<i>S. aureus</i>	Debridement	18	10	13	Success
2	Spinal arthrodesis	Early postop.	<i>S. agalactiae</i>	<i>S. aureus</i>	Debridement	17	12	37	Success
3	Hip prosthesis	Late chronic	<i>S. dysgalactiae</i>	<i>S. aureus</i>	2-stage exchange	12	12	42	Success
4	Hip prosthesis	Late chronic	<i>C. acnes</i>	-	1-stage exchange ^b	14	12	26	Failure
5	Osteosynthesis	Late chronic	<i>C. acnes</i>	-	1-stage exchange	0	12	21	Success
6	Spinal arthrodesis	Early postop.	<i>S. anginosus</i>	<i>P. vulgaris</i> <i>Prevotella</i> spp.	Debridement	21	12	44	Success

7	Knee prosthesis	Acute	<i>S. pyogenes</i>	-	Debridement	21	12	20	Success
8	Hip prosthesis	Late chronic	<i>C. acnes</i>	-	1-stage exchange ^b	42	12	27	Success
9	Hip prosthesis	Early postop.	<i>E. faecalis</i>	<i>S. aureus</i>	Debridement	19	1.2	0.5	Death
				<i>P. vulgaris</i>					
10	Hip prosthesis	Late chronic	<i>S. pneumoniae</i>	-	2-stage exchange	14	10	21	Success
11	Hip prosthesis	Acute	<i>S. gordonii</i>	-	Debridement	14	12	23.5	Success
12	Osteosynthesis	Late chronic	<i>C. acnes</i>	-	Removal	18	12	3.5	Failure
13	Ankle arthrodesis	Late chronic	<i>E. faecalis</i>	<i>E. cloacae</i>	Removal	12	6	20	Success
				<i>A. prevotii</i>					
14	Spinal arthrodesis	Late chronic	<i>C. acnes</i>	-	Removal	19	12	24	Success
15	Osteosynthesis	Early postop.	<i>E. faecalis</i>	<i>S. aureus</i>	Removal	12	8	21	Success
				<i>E. cloacae</i>					
16	Osteosynthesis	Early postop.	<i>S. constellatus</i>	<i>Prevotella</i> spp.	Debridement	21	6	20	Success
17	Hip prosthesis	Late chronic	<i>S. dysgalactiae</i>	<i>S. aureus</i>	2-stage exchange	9	6	15	Success

18	Hip prosthesis	Early postop.	<i>C. acnes</i>	-	Debridement	21	15	20	Success
19	Hip prosthesis	Late chronic	<i>S. agalactiae</i>	-	1-stage exchange	9	12	20	Success
20	Osteosynthesis	Late chronic	<i>S. dysgalactiae</i>	<i>S. aureus</i>	Removal	9	6	17	Success
21	PIP ^c prosthesis	Late chronic	<i>E. faecalis</i>	<i>S. schleiferi</i>	2-stage exchange	7	8	2.5	Failure
22	Knee prosthesis	Acute	<i>S. dysgalactiae</i>	-	Debridement	38	16	15.5	Success
23	Knee prosthesis	Acute	<i>S. dysgalactiae</i>	-	Debridement	11	1	0.75	Failure

^a Early postoperative (“early postop.”), late chronic or acute hematogenous (“acute”) ^bPartial exchange (femoral implant only) for patients 4 and 8 ^cProximal interphalangeal joint

^d*Enterococcus faecalis, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus, Streptococcus pyogenes, Streptococcus constellatus, Streptococcus gordonii, Streptococcus pneumoniae, Cutibacterium acnes, Enterococcus faecalis, Staphylococcus aureus, Staphylococcus schleiferi, Proteus vulgaris, Enterobacter cloacae, Anaerococcus prevotii*