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Short Communication

Short- versus long-duration levofloxacin plus rifampicin for acute staphylococcal prosthetic joint infection managed with implant retention: a randomised clinical trial ☆

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ABSTRACT

Levofloxacin plus rifampicin (L+R) is the treatment of choice for acute staphylococcal prosthetic joint infection (PJI) managed with debridement and implant retention (DAIR). Long courses have been empirically recommended, but some studies have suggested that shorter treatments could be as effective. Our aim was to prove that a short treatment schedule was non-inferior to the standard long schedule. An open-label, multicentre, randomised clinical trial (RCT) was performed. Patients with an early post-surgical or haematogenous staphylococcal PJI, managed with DAIR and initiated on L+R were randomised to receive 8 weeks of treatment (short schedule) versus a long schedule (3 months or 6 months for hip or knee prostheses, respectively). The primary endpoint was cure rate. From 175 eligible patients, 63 were included (52% women; median age, 72 years): 33 patients (52%) received the long schedule and 30 (48%) received the short schedule. There were no differences between the two groups except for a higher rate of polymicrobial infection in the long-schedule group (27% vs. 7%; $P = 0.031$). Median follow-up was 540 days. In the intention-to-treat analysis, cure rates were 58% and 73% in patients receiving the long and short schedules, respectively (difference –15.7%, 95% CI –39.2% to 7.8%). Forty-four patients (70%) were evaluable per-protocol: cure rates were 95.0% and 91.7% for the long and short schedules, respectively (difference 3.3%, 95% CI –11.7% to 18.3%). This is the first RCT suggesting that 8 weeks of L+R could be non-inferior to longer standard treatments for acute staphylococcal PJI managed with DAIR.

1. Introduction

Infection is a dreaded complication of prosthetic joints. In some acute cases, debridement, antibiotics and implant retention (DAIR) may be attempted [1,2]. Staphylococci are the most frequent cause of acute prosthetic joint infection (PJI), with rifampicin having a key role in treatment [1–4]. Current guidelines recommend long courses in combination with a fluoroquinolone (e.g. levofloxacin) for a period between 3 months (hip prostheses) and 6 months (knee prostheses) [2,5].

However, these long treatments have been established empirically and present several drawbacks, such as toxic adverse effects [6] and the selection of resistant bacteria [7]. Also, in observational studies long treatments have failed to show better outcomes compared with shorter treatments [3,8,9].

We therefore aimed to prove that a short treatment schedule of levofloxacin plus rifampicin over 8 weeks was as effective as the longer standard treatment schedules.

2. Materials and methods

2.1. Setting

This was a prospective, open-label, comparative, randomised clinical trial (RCT) performed in 17 Spanish hospitals. Recruitment was from April 2009 to April 2013, with a follow-up scheduled for ≥1 year. The trial was recorded (EudraCT 2008-001863-31; ISRCTN registry no. ISRCTN35285839) and was approved by the local ethics committees of all participating hospitals.

2.2. Study design and population

Eligible patients met the following criteria: haematogenous or early post-surgical PJI (onset of symptoms within the first 30 days after placement of the prosthesis) caused by staphylococci [either *Staphylococcus aureus* or coagulase-negative staphylococci (CoNS)]; and PJI managed by DAIR, with a stable implant kept in place. Exclusion criteria are summarised in Fig. 1.

Following debridement, eligible patients who provided informed consent were assigned by simple randomisation to receive either a short schedule of treatment over 8 weeks (both hip and knee prostheses) or a standard long treatment of 3 months or 6 months (for hip or knee prostheses, respectively) [2,5]. Treatment consisted of the combination of rifampicin (600 mg once daily, after fasting) [10] and levofloxacin (750 mg once daily). The oral route was preferred as soon as the patient could tolerate it. In the case of polymicrobial infections, other antibiotics could also be used provided they had no antistaphylococcal activity (i.e. aztreonam, ceftazidime).

2.3. Follow-up and study endpoints

Baseline patient characteristics were defined according to Charlson [11]. Clinical, analytical and radiological assessments are summarised in Fig. 1.

The primary outcome was the cure rate, which was analysed as an intention-to-treat (ITT) analysis (all patients randomised) and a per-protocol (PP) analysis (patients randomised who did not abandon the study because of toxicity or other reasons) (see Fig. 1). Cure was considered when patients retained the prosthesis, clinical signs of infection were resolved, and there had been a progressive decrease in C-reactive protein (CRP) levels. Failure was defined as PJI-related death, or persistence/recurrence of signs of infection due to the original staphylococcus that caused the infection. The need for supplementary debridement was not considered a failure. Causes for exclusion from the PP analysis are summarised in Fig. 1 and Table 1. Patients excluded from the PP analysis were considered failures in the ITT analysis.

☆ The preliminary results of this study were presented at the 53rd Interscience Conference of Antimicrobial Agents and Chemotherapy (ICAAC), 10–13 September 2013, Denver, CO.

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