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Suppressive antibiotic therapy with oral doxycycline for *Staphylococcus aureus* prosthetic joint infection: a retrospective study of 39 patients

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ABSTRACT

The aim of this study was to describe the use of oral doxycycline as suppressive antibiotic therapy (SAT) in patients with *Staphylococcus aureus* periprosthetic (hip or knee) joint infections. The medical charts of all patients with surgical revisions for *S. aureus* hip or knee prosthetic joint infections (PJIs) who were given doxycycline-based SAT because of a high risk of failure of various origins were reviewed. Data regarding tolerability and effectiveness of doxycycline-based SAT were analysed. A total of 39 patients (mean age 66.1 ± 16.3 years) received doxycycline-base SAT in the period from January 2006 to January 2014. PJIs involved the hip in 23 patients (59.0%) and the knee in 16 (41.0%), and were qualified as early in 15 patients (38.5%). Methicillin-resistant *S. aureus* (MRSA) accounted for 22% of the total number of bacterial strains identified. All patients included in the study had surgery, which consisted of debridement and implant retention in 32 (82.1%). Adverse events likely attributable to SAT were reported in six patients (15.4%), leading to discontinuation of SAT in three (7.7%). A total of 29 patients (74.4%) remained event-free and 10 (25.6%) failed, including 8 (20.5%) relapses and 2 (5.1%) superinfections. Overall, 8 of the 10 failure cases were related to a doxycycline-susceptible pathogen. These results suggest that oral doxycycline used as SAT in patients treated for *S. aureus* hip or knee PJIs has an acceptable tolerability and effectiveness and appears to be a reasonable option in this setting.

1. Introduction

Prosthetic joint infections (PJIs) require both surgical intervention and antibiotic therapy conducted in light of the most recent guidelines for the management of these potentially life-threatening infections [1,2]. Suppressive antibiotic therapy (SAT) differs from curative antibiotic therapy in that it aims to increase the likelihood of retaining a functional prosthesis in patients with a lower probability of remission due to suboptimal surgery and/or curative antibiotic therapy and/or poor general health status. So far, there has been no consensus on the definition and use of SAT or the optimal choice and duration of antibiotic. Doxycycline appears to be an attractive candidate for SAT owing to its high oral bioavailability (close to 100% [3]), high bone concentrations [4], long half-life [5], acceptable tolerance including as prolonged therapy even in elderly patients [6,7] and low cost (not exceeding €1–5/day). Doxycycline is active against most Gram-positive cocci, including methicillin-resistant staphylococci [8]. Data on the use of oral tetracyclines as SAT in patients with PJIs are scarce, although the Infectious Diseases Society of America (IDSA) recommends tetracyclines (minocycline and doxycycline) as the preferred antibiotics for SAT in PJIs due to methicillin-resistant *Staphylococcus aureus* (MRSA) [2].

The objectives of the present study were to describe the tolerance and effectiveness of oral doxycycline used as SAT for *S. aureus* hip or knee PJIs in patients treated with surgical revision but considered to be at higher risk of failure given their suboptimal antibiotic therapy, suboptimal surgical management and/or poor general condition.

2. Materials and methods

2.1. Study design and population

This retrospective study was performed at the French National Reference Centre for Complex Osteoarticular Infections in the North West region of France (Gustave Dron Hospital, Tourcoing, France;

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and Roger Salengro Hospital, Lille, France). Medical charts of all adult patients with PJI (hip and knee) who received oral doxycycline-based SAT from January 2006 to January 2014 were reviewed. All patients included in the study had surgical management including debridement, antibiotics and implant retention (DAIR), resection arthroplasty, or one- to two-step implant exchange. Therapeutic strategies were decided for each patient during multidisciplinary meetings of orthopaedic surgeons, infectious diseases consultants, microbiologists and anaesthesiologists. In each case, the patient was aware of the different therapeutic options and took part in the final decision.

2.2. Definitions

PJI was defined according to the IDSA criteria for PJI [2]. PJI was classified as early (i.e. infection within 3 months of arthroplasty), delayed (i.e. 3–12 months after arthroplasty) or late (i.e. >12 months after arthroplasty) [2]. Remission was defined as the absence of signs of infection assessed ≥24 months after the end of the curative treatment and then at the last contact with the patient. Failure was defined as any other outcome, including death except when it was not in relation to the PJI. Relapse was defined as the occurrence of PJI at the initial site caused by the same bacterial species (based on the antibiotic susceptibility profile) with or without acquisition of resistance to doxycycline, and superinfection was defined as a new infection at the initial site caused by an organism distinct from the initial strain.

2.3. Microbiology

The antibiotic susceptibility profile of all pathogens identified from perioperative samples was assessed by the agar diffusion technique using the procedure and interpretation criteria proposed by the Comité de l'Antibiogramme de la Société Française de Microbiologie annual guides from 2006–2014 (http://www.sfm-microbiologie.org).

2.4. Surgical management and curative antibiotic therapy

DAIR was used in patients with a well-fixed prosthesis, no sinus tract and for whom the infection had been diagnosed within 4 weeks after implantation or the delay from the onset of the infectious symptoms and re-intervention was <3 weeks [1,2]; DAIR was also indicated in patients with poor overall condition for whom no alternative surgery would have been acceptable despite a time from implantation to revision and/or a duration of the infection prior revision exceeding the current recommended deadlines. In all DAIR cases, the mobile parts (polyethylene) of the prosthesis were changed. In the other cases, the indications for one- or two-stage exchange followed the current recommendations [1,2]. In cases of re-implantation of a new prosthesis, the duration of antibiotic therapy depended on the results of intraoperative sample cultures (i.e. 2 weeks in the case of negative culture results if antibiotic therapy had been stopped ≥2 weeks prior to the intervention, and 6–12 weeks in the case of positive culture results). New implants were mostly uncemented. Resection arthroplasty was performed in patients for whom joint replacement would not have produced any functional benefit. All surgical procedures were performed without antibiotic prophylaxis. A combination of antimicrobial agents administered intravenously was begun intraoperatively immediately after samples were taken. The combination consisted of a broad spectrum β-lactam agent (e.g. cefotaxime, cefepime, piperacillin/tazobactam, aztreonam or imipenem) and a second antimicrobial agent active against methicillin-resistant staphylococci (vancomycin or daptomycin). Empirical post-operative antibiotic therapy was continued until the results of intraoperative sample cultures were available and was then modified in accordance with the culture results (curative antibiotic therapy). Antibiotics were selected based on the patient's characteristics and were administered following the recommendations of Zimmerli et al [9]. Following discharge from the hospital, patients were followed-up both by the referring surgeon and the infectious diseases consultant 1 month after discharge and at the end of antibiotic treatment. The total duration of curative antimicrobial therapy was 6 weeks to 6 months according to the pathogen and prosthesis involved, followed by SAT. Patients were candidates for SAT if they (i) had been operated suboptimally (e.g. removal of the infected implants not feasible, incomplete or performed outside recommended deadlines), (ii) had received non-optimal curative antibiotic therapy (e.g. impossibility to use rifampicin-containing combinations), (iii) underwent complex orthopaedic surgery exposing to limb-threatening conditions in case of relapse or (iv) had profound immunosuppression (e.g. chemotherapy for cancer) or poor overall condition (e.g. severe cardiac, liver renal, neurological diseases) exposing to a higher risk of failure.

2.5. Suppressive antibiotic therapy (SAT)

SAT was initiated in patients who were considered in remission at the end of the curative treatment but were considered at higher risk of failure (see above). Specific information was provided to the patients regarding the rational of this unconventional treatment and the expected benefit on their outcome as well as the potential adverse events related to prolonged use of oral doxycycline therapy. Particular attention was paid to potential skin and digestive toxicity as well as drug–drug interactions. Doxycycline-based SAT was considered only in patents without known contraindications, especially allergy and ongoing gastroduodenal diseases, which were eliminated by fibroscopic assessment if indicated. Until the results of the study reported by Byren et al were published [10], the majority of patients were proposed a 2-year duration of doxycycline-based SAT. From the beginning of 2010, we took into account the recommendations of Byren et al and asked patients to continue SAT (i.e. continued SAT) as long as they had the infected prosthesis.

2.6. Follow-up

Patients were followed-up by their referring surgeon once annually for a minimum of 2 years. All patients receiving SAT were seen in consultation by the infectious diseases consultant twice a year, where the efficacy and tolerability of SAT were assessed. Patients were systematically asked to note the number of missing doses during the period between two consultations. Missing data on patient outcome after the end of antibiotic treatment were obtained by telephone contact with the patient himself/herself or his/her General Practitioner, or when applicable by reviewing medical records in cases of re-admission.

2.7. Statistical analysis

An intention-to-treat analysis was performed in the present study (i.e. all patients treated with doxycycline-based SAT including those who received <6 months of SAT) in order to avoid any underestimation of failures. Fisher's exact test or Pearson's χ^2 test were used for categorical data, whereas Student's *t*-test was used for continuous data.

2.8. Ethical consideration

All patient data collected were anonymised and were recorded on a standardised form preventing any personal identification according to procedures defined by the French information protection