Ampicillin Plus Ceftriaxone Regimen against Enterococcus faecalis Endocarditis

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Enterococcus faecalis infective endocarditis (EFIE) continues to represent a potentially fatal infectious disease characterized by elevated morbidity and mortality. Despite advances in antimicrobial therapy, changing demographics and the reduced availability of useful antibiotics combined with the dissemination of multi-drug resistant strains, the mortality rate remained unchanged in the last decades. Nowadays, optimizing the antibiotic regimen is still of paramount importance.

infective endocarditis | double beta-lactams therapy | ampicillin plus ceftriaxone | antibiotic resistance

1. Introduction

Despite major clinical advances in antimicrobial therapy, the prevalence and associated mortality of infective endocarditis (IE) have not markedly improved over the last several decades, especially those caused by fastidious germs such as Enterococci.

In particular, Enterococcus faecalis infective endocarditis (EFIE), accounting for the third frequent cause of both native and prosthetic valve IE in the community setting and the second cause of healthcare-associated infective endocarditis (HAIES), still poses major clinical and therapeutical issues [1][2]. Bacteremia and IE are common presentations of enterococcal disease, and the most frequent sources of bacteremia are the GI and genitourinary tracts among non-hospitalized patients, whereas urinary and intravascular catheters are the most common sources of nosocomial bacteremia, especially in those who have received antibiotics or with underlying conditions. Urinary tract infections and diagnostic/therapeutic instrumentation (such as urinary catheter, cystoscopy, prostatic biopsy and transurethral resection of the bladder or prostate) are potential causes of EFIE and the same risk factors are applied to the GI tract [3]. Moreover, E. faecalis is one of the main causative microorganisms of transcatheter aortic valve implantation-associated endocarditis (TAVIE), an emerging and poorly characterized infection marked by high mortality that is becoming prevalent with the increasing number of TAVI procedures performed in recent years [4]. Notably, E. faecalis seems to be the most frequent detected agent in TAVIEs diagnosed within two months after TAVI [5].

EFIE usually involves damaged heart valves and mitral and aortic valves are usually interested. Most patients with EFIE display a subacute course and the most common complication is heart failure occurring in about half of

patients, with a significant percentage requiring valve replacement [6].

With this purpose, experimental studies have been successfully performed in order to assess the synergism of the dual beta-lactam combination against clinical strains of E. faecalis , regardless of their susceptibility to aminoglycosides. Specifically, the basis for the synergistic activity of the double beta-lactam combination appears to be related to the differential and complementary saturation of E. faecalis penicillin-binding proteins (PBPs), thus generating the necessary bactericidal effect [7][8]. Thereafter, these experimental results were supported by clinical evidence, leading to an update of EFIE treatment guidelines [9][10].

2. An Unmet Need

Aminoglycoside-based regimens have been a cornerstone of antimicrobial therapy for EFIE and have been recommended as therapy of choice for decades. However, the effectiveness and safety of this therapeutic approach have been threatened by the increasing acknowledgement of aminoglycoside-resistant strains. Additionally, bearing in mind that the typical EFIE patient is older, often debilitated, with high rates of chronic renal failure and/or with enhanced risk of rapid renal impairment, the standard 4-to-6-week course of aminoglycoside therapy could result in serious, possibly life-threatening, nephrotoxic complications. It is against this background that, in recent years, a number of studies have been carried out in order to assess the validity of alternative therapeutic approaches, including a treatment regimen with different dosage and duration of aminoglycoside administration, with the main purpose of reducing the known toxicity. Moreover, not all clinical laboratories may have the capability for rapid determination of serum gentamicin concentrations available to assist in optimal dosing adjustments. These factors, as a whole, have prompted studies to evaluate the efficacy of non-aminoglycoside-containing regimens for the treatment of EFIE [11][12][13].

3. Preclinical Evidence for an Alternative Therapeutic Approach

In light of the few therapeutic alternatives, combinations of beta-lactams were tested in vitro and in vivo models of enterococcal experimental IE.

First, Mainardi and colleagues [14] reported in vitro synergy between amoxicillin and cefotaxime against clinical strains of E. faecalis , showing that the minimum inhibitory concentration (MIC) for amoxicillin decreased substantially in the presence of cefotaxime, and likewise, MIC of cefotaxime in the presence of amoxicillin. This effect was explained by the differential targeting of the PBPs by each beta-lactam compound, which, combined, cause a significant inactivation of PBPs 2, 3, 4 and 5, producing a marked impairment in E. faecalis cell wall synthesis [15]. This in vitro synergy was recently confirmed by Liao et al., demonstrating on time-kill curves a reduction in the number of colony-forming units (CFU) of E. faecalis after exposure to ampicillin and ceftriaxone when compared with those exposed only to ampicillin [16]. In addition, it was further corroborated in an in vitro pharmacodynamic study in which ampicillin-cephalosporin combinations showed an increased activity compared to

ampicillin alone against both strains of E. faecalis (ampicillin-susceptible gentamicin-susceptible strain (OG1X) and HLAR strain (HH22) over 24 h [17].

Similar synergistic findings were detected by Gavalda et al. [18] with the association of ampicillin and ceftriaxone against HLAR E. faecalis strains. These results have suggested that bactericidal ampicillin concentrations moved into the bactericidal ones by association with ceftriaxone, indeed extending the range of ampicillin's bactericidal effects and the period during which these concentrations are available. Along this line, the same authors have evaluated the usefulness of ceftriaxone combined with ampicillin, compared to ampicillin plus gentamicin, against E. faecalis with or without HLAR in rabbits with catheter-induced endocarditis, concluding that was effective as the treatment of choice [19]. Recently, in addition, according to a multiple antibiotic dosing scheme based on the half-lives of one of the tested antibiotics, the ampicillin and ceftriaxone combination exhibited synergistic interactions against E. faecalis in the Galleria melonella infection model [20].

Nevertheless, further studies are needed to achieve a more accurate estimation of pharmacodynamic parameters and the determination of the pharmacokinetic/pharmacodynamic (PK/PD) index, driving the efficacy of this combination, essential for a proper application in clinical practice.

4. A Critical Analysis of the Clinical Experience of This Therapeutic Alternative

These experimental results laid the groundwork for clinical studies aimed at establishing the true efficacy of this therapeutic approach in humans with EFIE.

The first one, conducted by Gavalda et al. [21] was an observational, multicenter, open-label clinical trial designed to evaluate the efficacy and the safety of treatment with ampicillin, 2 g every 4 h, plus ceftriaxone, 2 g every 12 h, as an antimicrobial option in patients with endocarditis caused by E. faecalis with or without HLAR. The clinical cure, defined as the resolution of the clinical findings of endocarditis with no evidence of active endocarditis at both the end of treatment and 3-month follow-up visit, achieved the rate of 67.4% (29 of 43 patients) among all patients. The treatment-related mortality rate of patients with HLAR EFIE was 28,6%, similar to rates reported in previous studies. With regard to adverse events, the double beta-lactam combination was well tolerated and only two patients had treatment-related side effects and no case of nephrotoxicity was recorded.

Notwithstanding the substantial limitations given by the small size of the sample, the lack of a random assignment and the delayed inclusion of patients with non-HLAR EFIE, the study provided significant results supporting the employment of double beta-lactam combination as an effective treatment for patients with HLAIR EFIE and, in addition, as a wise option for patients with high risk of nephrotoxicity, regardless of strain susceptibility.

With the aim of shedding light on this challenging issue, Pericas et al. [22] performed a monocenter retrospective analysis of a prospective cohort of EFIE patients treated from 1997 to 2011, with the objective to assess resistance patterns, epidemiology and clinical outcomes. Interestingly, through the collection and analysis of epidemiological

data, the authors detected an overwhelming increase in EFIE caused by HLAR strains over the course of the last years, along with an increase in the use of A+C therapy. Although the statistical power of results is limited by the small sample size, these data appear meaningful, indeed presenting a similar trend to the most recent reported relapse rates. Furthermore, similarly to Fernandez-Hidalgo and colleagues, the authors did not detect a significant difference in in-hospital mortality (27% vs. 23%), 1-year mortality (29% vs. 26%) and relapse rate (2 vs. 3) between patients respectively treated with A+G and those treated with A+C. Despite the survival and regression analyses showing no statistical difference in 1-year mortality between the two treatments, these parameters cannot be used to conclude that there are no clinical differences between groups because the study was not powered to detect this. Of note, patients who received A+G presented a higher incidence of renal failure during treatment, requiring a therapeutic switch to A+C and further influencing the results.

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