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ORIGINAL PAPER

Efficacy of teicoplanin monotherapy following initial standard therapy in *Enterococcus faecalis* infective endocarditis: a retrospective cohort study

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Abstract

Purpose Teicoplanin is often used in *Enterococcus faecalis* infective endocarditis as a relay in case of penicillin side effects, or in outpatients. We assessed the efficacy of teicoplanin used as continuation therapy after initial standard treatment of *E. faecalis* endocarditis.

Methods All adult patients consecutively diagnosed between 1997 and 2016 for *E. faecalis* endocarditis were retrospectively reviewed. Patients who received standard therapy (ST) were compared to those switched to teicoplanin to complete the treatment (teicoplanin therapy, TT).

Results Seventy-one patients were enrolled: 34 in the ST group and 37 in the TT group. Amoxicillin was replaced by teicoplanin after a median duration of 18 days (IQ_{25-75} 12–21). Teicoplanin (5.8 ± 2.3 mg/kg) was administered for a median duration of 29 days (IQ_{25-75} 25–34). Gentamicin therapy was similar. Overall duration of antimicrobial therapy was 42 days (IQ_{25-75} 35–43) in the ST group, and 46 days (IQ_{25-75} 43–49) in the TT group ($p = 0.001$). Global and endocarditis-related mortality rates were 22/34 (65%) and 13/34 (38%) in the ST group, and 14/37 (38%) and 3/37 (8%) in the TT group ($p \leq 0.05$). Relapses occurred in 2/26 patients who survived the treatment phase in the ST group (8%) and in 3/37 in the TT group (8%, $p = 0.68$). All relapses in the TT group occurred in patients presenting prosthetic valve endocarditis. Finally, 20 patients were cured in the ST group (59%), and 33 patients in the TT group (89%, $p = 0.003$).

Conclusions In *E. faecalis* endocarditis, the switch to teicoplanin in selected patients following an initial phase of standard treatment represents an alternative, particularly for outpatient therapy. Caution should be exercised in cases of prosthetic valve endocarditis.

Keywords *Enterococcus faecalis* · Infective endocarditis · Teicoplanin · Amoxicillin

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Introduction

Enterococcus faecalis is the third cause of infective endocarditis (IE) after Staphylococci and Streptococci [1]. The 2015 European and US Guidelines for the treatment of *E. faecalis* IE recommend 4–6 weeks of intravenous ampicillin or amoxicillin combined with 2–6 weeks of gentamicin or 6 weeks of ampicillin or amoxicillin with high-dose ceftriaxone [2, 3]. Vancomycin administered concomitantly with gentamicin is an alternative for enterococcal IE in β-Lactam-intolerant patients, or in patients with penicillin-resistant *E. faecalis*. Teicoplanin is a lipoglycopeptide with a close spectrum to vancomycin in terms of Gram-positive organisms but with a safer clinical profile [4]. Preclinical studies [5–9] and uncontrolled clinical studies [10–15] have highlighted the potential beneficial effects of teicoplanin in the management of Gram-positive bacterial EI, including enterococcal IE. Based on these data, teicoplanin was used in clinical practice in our institution after initial standard treatment as continuation therapy to treat enterococcal IE in patients allergic to amoxicillin, developing side effects related to amoxicillin, to avoid the use of a central venous catheter in patients with poor venous access, or to allow outpatient parenteral antimicrobial therapy (OPAT), taking advantage of the long half-life of teicoplanin. Our aim was to retrospectively assess the efficacy of this approach, focusing on IE relapses in particular.

Methods

Patients and data collection

The study population comprised the cohort of all adult patients consecutively diagnosed between 1997 and 2016 with infective endocarditis due to *E. faecalis* at Toulouse University Hospital (South of France; 2800 beds). Patients were selected from the Programme de Médicalisation des Systèmes d'Information, a national database which records administrative and medical information on discharge for every hospital stay in France [16], if they had a discharge diagnosis code for endocarditis (I33.0 ICD-10) and a positive blood culture for *E. faecalis* during the study period. Patients with definite ampicillin-susceptible *Enterococcus faecalis* IE according to Duke's modified criteria were enrolled (2 major criteria, or 1 major criterion and 3 minor criteria, or 5 minor criteria) [2]. Exclusion criteria were: infected intra-cardiac pacemaker/defibrillator or extra-cardiac device; no initial dual therapy; treatment by vancomycin or daptomycin; < 14 days of teicoplanin; lack of data; and follow-up < 1 month. Enterococcal infections with high-level resistance to aminoglycosides (HLAR) not treated by high-dose ceftriaxone were also excluded.

We extracted data for each patient, including age, gender, comorbid conditions, previous heart disease, prosthetic valve, IE-related data (sites of entry, symptom duration, infected valve(s), and vegetation size), IE-related complications at diagnosis (perivalvular abscess, cardiac failures, secondary infectious foci (clinically symptomatic or radiologically diagnosed), and treatment (duration, surgery indication according to ESC guidelines [2]). Teicoplanin therapeutic drug monitoring (TDM) was performed using Fluorescence Polarisation Immunoassay (FPIA) or Liquid Chromatography (LC) depending on the calendar period. Trough concentrations higher than 15 mg/L using the LC method or 30 mg/L via the FPIA method were deemed efficient [17].

Efficacy

Patients who received conventional therapy with amoxicillin initially combined with gentamicin or for 6 weeks with ceftriaxone (Standard therapy, ST) were compared to those in whom amoxicillin was replaced by teicoplanin to complete the treatment period (teicoplanin therapy, TT). Judgement criteria comprised global mortality, IE-related mortality and occurrence of *E. faecalis* bloodstream infection during the follow-up period. When samples were available, *E. faecalis* strains at IE diagnosis and subsequent *E. faecalis* bloodstream infections were compared by pulsed-field gel electrophoresis [18].

Data were systematically collected until 30 June 2017 by consulting the medical records and contacting referral physicians.

Statistical analysis

Statistical analysis was performed with SAS software (version 9, SAS Institute, Cary, NC). The tests were two-sided with a p value of < 0.05 which was deemed statistically significant.

Continuous data are presented as the mean ± standard deviation or median and interquartile range (IQR), depending on the statistical distribution.

The assumption of normality was evaluated using the Shapiro–Wilk test. The comparisons between treatment groups were carried out using (1) Chi-squared or Fisher exact tests for categorical variables and (2) the Student t test or Mann–Whitney test when the assumptions of the t test were not met (normality verified by the Shapiro–Wilk test and homoscedasticity by the Fisher–Snedecor test) for quantitative parameters.

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The approval of the Institutional Ethics Committee was obtained to carry out this study [CNIL (French Data Protection Act) 2151593v0].

Results

Enrolment and baseline patient characteristics

Between January 1997 and December 2016, 135 adult patients were diagnosed with a definite *E. faecalis* IE. Of these, 18 patients with pacemaker, defibrillator or extra-cardiac infected devices, 7 patients who had not received initial gentamicin or ceftriaxone therapy, 14 patients who were given vancomycin or daptomycin, 3 patients who received teicoplanin for less than 14 days and 22 patients with a lack of data were excluded. We finally included 71 patients for analysis, 34 in the ST group and 37 in the TT group. The characteristics of the population at diagnosis are shown in Table 1. Compared to the ST group, the TT group presented fewer cases of healthcare-related IE [1/37 (3%) versus 7/34 (21%), $p=0.02$] and perivalvular abscesses [3/37 (8%) versus 9/34 (26%), $p=0.04$]. The frequency of extra-cardiac infectious foci [6/34 (18%) in the ST group versus 10/37 (27%) in the TT group, $p=0.24$] and heart failure [8/34 (24%) in the ST group versus 5/37 (14%) in the TT group, $p=0.21$] did not differ.

Treatment

In the ST group, amoxicillin was administered for a median duration of 42 days (IQ_{25-75} 34–43). In the TT group, amoxicillin was replaced by teicoplanin after a median period of 18 days (IQ_{25-75} 12–21) ($p=0.0001$). The reason for the change to teicoplanin was highlighted in only 23 out of 37 patients, and was related to amoxicillin-related side effects in 7/23 (30%) or OPAT in 15/23 (70%). Both groups received similar initial gentamicin therapy (3 mg/kg once a day, 20 days, IQ_{25-75} 13–27 for the ST group, and 16 days IQ_{25-75} 14–18 for the TT group, $p=0.19$). Only

Table 1 Characteristics of the study population, of the infective endocarditis, and outcome

	Standard therapy (ST) ($n=34$)	Teicoplanin therapy (TT) ($n=37$)	*p*
Age (mean, SD)	67 (15)	67 (21)	0.41
Male sex (%)	28 (82)	24 (65)	0.10
Age-adjusted Charlson score (mean, SD)	4.2 (2.3)	3.9 (2.9)	0.59
Diabetes (%)	7 (20)	4 (10)	0.26
Chronic kidney disease (%)	9 (26)	5 (14)	0.17
Cancer (%)	5 (15)	5 (14)	0.99
Immunodeficiency (%)	8 (24)	7 (17)	0.44
Neuro-cognitive disorders (%)	3 (9)	5 (14)	0.71
History of IE (%)	2 (6)	6 (16)	0.26
Duration of symptoms > 90 days (%)	2 (6)	2 (5)	0.99
Previously known valvulopathy (%)	15 (44)	26 (70)	0.03
Prosthetic valve IE (%)	12 (35)	16 (43)	0.49
Native valve IE (%)	22 (65)	21 (57)	0.49
Aortic IE (%)	18 (53)	16 (43)	0.41
Mitral IE (%)	9 (26)	18 (49)	0.05
Aortic and mitral IE (%)	7 (21)	2 (5)	0.08
Vegetation (%)	15 (44)	20 (54)	0.40
Vegetation size (mm, median, IQ 25–75)	12 (10–18)	12.8 (8.5–15)	0.11
Follow-up (days, median IQ 25–75)	468 (23–1284)	783 (126–1227)	0.27
Global mortality (%)	22 (65)	14 (38)	0.02
IE-related mortality (%)	13 (38)	3 (8)	0.05
Relapses in patients who survived treatment phase (%)	2/26 (8)	3/37 (8)	0.68

7/71 patients (9.8%) received gentamicin for 6 weeks, six in the ST group and one in the TT group. Three patients received ceftriaxone because of HLAR *E. faecalis* strain, one in the ST group for 43 days, and two in the TT group for 15 and 18 days. Teicoplanin was administered throughout the study period after a loading dose regimen of 3–5 injections twice a day followed by a single daily intravenous injection of 5.8 ± 2.3 mg/kg for a median period of 29 days (IQ_{25-75} 25–34). The antibiotic treatment was administered for a shorter period overall in the ST group (42 days, IQ_{25-75} 35–43) compared to the TT group (46 days, IQ_{25-75} 43–49, $p = 0.001$). Data on teicoplanin TDM were available for 30 out of the 37 patients (81%), with 4 (IQ_{25-75} 2–6) TDM per patient. Effective concentrations in more than half of the samples were recorded in 27 out of 30 patients (90%). Cardiac surgery was indicated [23/34 (68%) in the ST group versus 18/37 (49%) in the TT group, $p = 0.11$] and performed when indicated to the same extent [17/23 (74%) in the ST group versus 11/18 (61%) in the TT group, $p = 0.38$]. The mean duration of the hospital stay was 31 ± 6 days in the ST group compared to 24 ± 1 days in the TT group ($p = 0.19$).

Efficacy

Global and IE-related mortality were higher in the ST group than in the TT group [22/34 (65%) versus 14/37 (38%), $p = 0.02$, and 13/34 (38%) versus 3/37 (8%), $p = 0.05$, respectively]. Mortality curves are presented in Fig. 1. With a mean delay of 102 days (range 4–309 days) after the end of antibiotic treatment, a positive blood culture with *E. faecalis* was documented in 5 patients who survived the treatment phase, 2 out of 26 in the ST group (8%) and 3 out of 37 in the TT group (8%, $p = 0.68$) (Table 2). In all cases, the *E. faecalis* strain displayed similar antimicrobial susceptibility compared to the previously identified *E. faecalis* strain. Pulsed-field gel electrophoresis demonstrated the similarity between both *E. faecalis* strains in the only patient with available samples. Four of the five relapses occurred in patients with prosthetic valve EI, including two in which cardiac surgery was indicated but refuted due to advanced age and comorbid conditions. Focusing on the teicoplanin group, among the 37 patients who survived the treatment phase, the 3 relapses occurred in the 16 patients with prosthetic valve EI, while none were documented in the 21 patients with native valve EI, accounting for 2 out of the 3 IE-related deaths in this group. It should be noted that, in these three patients, *E. faecalis* strains displayed MIC for teicoplanin < 0.5 mg/L and TDM revealed optimal concentrations. Finally, considering patients who did not die from *E. faecalis* IE or experience relapses, 20 patients were cured in the ST group (59%), and 33 patients in the TT group (89%, $p = 0.003$). No difference was found between groups regarding side effects, including allergic reactions, renal and cochleo-vestibular toxicity.

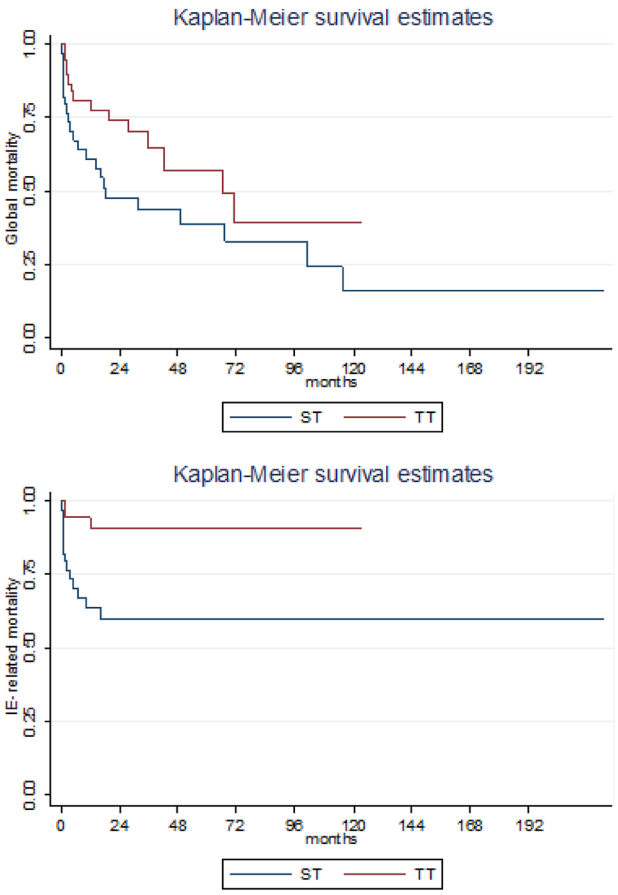

Fig. 1 Kaplan–Meier survival estimates of global and infective endocarditis-related mortality in standard therapy (ST) and teicoplanin therapy (TT) groups

Discussion

This paper focuses on a patient cohort with definite *E. faecalis* IE who switched to teicoplanin following an initial 2-week phase of amoxicillin combined with gentamicin or high-dose ceftriaxone. We report on a favourable outcome without IE-related deaths or relapse in 33 out of 37 patients. Three relapses were observed in patients with prosthetic valve IE.

It is widely accepted that enterococci are inhibited but not killed by penicillin or vancomycin monotherapy. The synergistic action of penicillin or vancomycin in combination with aminoglycosides is required to kill susceptible strains of enterococci [3]. The interest in teicoplanin for the treatment of enterococcal IE was mentioned some time ago with most of the data generated in the 1990s. Teicoplanin proved to be as effective as amoxicillin in animal models of enterococcal IE with a bacterial reduction in vegetation and freedom from relapse in > 90% of animals, both parameters being increased by adjunct gentamicin therapy [6]. Teicoplanin was shown to be more effective than vancomycin against

Table 2 Main characteristics of patients who presented a new *E. faecalis* bloodstream infection on completion of therapy

Group	Native or prosthetic valve	Surgical indication	Treatment (days)	Reason for teicoplanin switch	Delay between the end of treatment and new positive *E. faecalis* blood cultures (days)
ST	Native	No	Amoxicillin (28) Gentamicin (8)	–	8
ST	Prosthetic	Yes, refuted	Amoxicillin (42) Gentamicin (23)	–	128
TT	Prosthetic	No	Amoxicillin (12) Gentamicin (12) Teicoplanin (31)	Venous access	62
TT	Prosthetic	No	Amoxicillin (24) Gentamicin (15) Teicoplanin (22)	OPAT	309
TT	Prosthetic	Yes, refuted	Amoxicillin (1) Gentamicin (15) Teicoplanin (39)	Allergy to amoxicillin	4

enterococci in vitro and in animal models of enterococcal IE [6, 7, 9]. The few published cases of enterococcal IE (< 40 cases) suggest that teicoplanin may be effective, although doses of teicoplanin varied from 3 to 15 mg/kg with or without a loading dose regimen [10–15]. Although it is difficult to draw conclusions from the 33 published cases with available detailed outcomes, failure was recorded in 4 patients not receiving dual therapy with gentamicin or receiving low-dose teicoplanin [10, 12, 13]. Teicoplanin was shown by autoradiography to poorly penetrate vegetation and to concentrate only on the periphery [19]. This diffusion gradient could explain the difficulty in sterilising vegetation, particularly on prosthetic valves, and the failures reported in the literature in patients with low teicoplanin plasma concentrations. These considerations highlight the fact that initial combination therapy and high local concentrations are required to promote the eradication of bacteria [12]. In our study, the switch to teicoplanin was made after more than 2 weeks of initial combination therapy comprising amoxicillin and gentamicin or ceftriaxone, when IE is likely to be controlled and requires potentially straightforward continuation therapy. Teicoplanin has a long terminal elimination half-life warranting an appropriate loading dose regimen to reach steady state. Using Monte Carlo simulations to evaluate the ability of several dosage regimens, it was shown that a loading dose regimen with 5×800 mg doses is necessary to achieve a target attainment probability $\geq 90\%$ at day 3 [20], in accordance with EMA recommendations regarding the use of teicoplanin in bone and joint infections and IE (12 mg/kg every 12 h for 3–5 doses followed by a maintenance dose of 12 mg/kg daily) [17]. In our study in which patients received a mean teicoplanin loading and maintenance dose of 5.8 ± 2.3 mg/kg, the latency needed to reach steady state was probably less crucial because patients were already taking effective antibiotic therapy. Nevertheless, this relatively low dosage regimen allowed teicoplanin trough concentrations to be reached in most patients. In this setting, the switch to teicoplanin was associated with a high cure rate except for prosthetic valve IE which is a particularly demanding context with a potential restriction on the use of teicoplanin.

OPAT was the main reason for switching to teicoplanin. The latter is particularly interesting for OPAT and has already been used successfully [14, 15]. Although OPAT with a discontinuous regimen of amoxicillin and high-dose ceftriaxone (4 g once daily) offers an alternative [21], this strategy may require a long-term central catheter prone to catheter-related infections [22]. The pharmacokinetic profile of teicoplanin allows a once daily administration strategy following a loading dose period, as previously discussed [17]. Intramuscular or subcutaneous administration of teicoplanin after an initial intravenous loading dose represents an alternative to the intravenous route [20], and is already used in staphylococcal bone and joint infection [23]. Selected patients performing well after 2 weeks of amoxicillin-gentamicin or amoxicillin-ceftriaxone therapy in a hospital environment and ready for home discharge could be candidates for completing an OPAT using teicoplanin either intravenously, intramuscularly or by the subcutaneous route, provided that optimal therapeutic targets have already been achieved and are regularly monitored. In this respect, it was recently shown that oral antibiotic treatment, mainly comprising a combination of amoxicillin and moxifloxacin or linezolid, was not inferior to continued intravenous antibiotic treatment in patients with left sided *E. faecalis* IE who were in a stable condition [24].

One strength of our study is that our cohort is representative of a prospective cohort study evidencing that *E. faecalis* IE occurs mostly in elderly male patients with comorbid conditions [25]. Both the IE with a difficult to treat microbe, particularly on prosthetic valves, and the debilitating conditions of these patients led to the severe prognosis within our study of an IE-related mortality rate of 23%, which is consistent with the 28.9% 1-year mortality rate identified in the literature [25]. Our study nevertheless has limitations, primarily because of its retrospective nature and relatively small sample size. Although the main patient characteristics were similar in both groups, patients who were switched to teicoplanin in the TT group suffered from less severe IE than those who received amoxicillin throughout treatment in the ST group, the latter having higher frequencies of healthcare-related IE and perivalvular abscesses, together with a trend for a more frequent indication of cardiac surgery. This may account for the worse outcome observed in this group. Amoxicillin was, therefore, probably continued in the more severe patients, with a switch to teicoplanin for less severe patients. Among the many factors that can influence the outcome of IE, the small number of patients precluded multivariate analysis which would highlight the impact of teicoplanin on the outcome of IE. Teicoplanin TDM was not available for seven patients, although all of them were cured. Finally, except for one patient, we could not rule out that the relapses were due to recurrent infections.

In conclusion, the switch to teicoplanin after an initial 2-week phase of amoxicillin combined with gentamicin or ceftriaxone appears to be effective in selected patients with less severe *E. faecalis* IE. Caution should, however, be exercised to date in prosthetic valve IE and with reference to the optimal dosage regimen required to achieve effective teicoplanin trough concentrations. To this end, teicoplanin, particularly by the subcutaneous route, may represent an alternative approach for OPAT in those patients. Further controlled studies comparing standard therapy to a switch to teicoplanin or oral antibiotic treatment in *E. faecalis* IE are required.

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Author contributions TDN and MF analysed data and wrote the manuscript; AS performed the statistical analysis; DD and MG analysed microbiological data; DM analysed therapeutic drug monitoring; and BM, PD and GMB supervised the project. All the authors contributed to the final version of the manuscript.

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Compliance with ethical standards

Conflict of interest All the authors confirm that they have no conflict of interest to declare.

Ethical approval All the authors confirm that this study was performed in accordance with the Ethical Standards of the Institutional and National Research Committee and with the 1964 Helsinki Declaration and its later amendments. The approval of the Institutional Ethics Committee was obtained to carry out this study [CNIL (French Data Protection Act) 2151593v0].

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