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Treatment of *Candida glabrata* native valve endocarditis with rezafungin: a case report

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Introduction

An uncommon complication of fungal infection is endocarditis, burdened by higher mortality rates (from 40% to 60% according to different studies) than bacterial endocarditis. *Candida* spp. accounts for approximately 50% of all fungal endocarditis and its incidence is expected to increase due to advances in the care of patients with underlying malignancy and rheumatologic diseases, within the intensive care units and the increasing use of intravascular or intracardiac device.[1–3] The distribution of *Candida* species as the aetiology of endocarditis differs from the distribution of candidaemia alone.[1] *C. glabrata* globally constitutes the second leading cause of invasive candidiasis (IC) and its reduced frequency in endocarditis may reflect the lack of several pathogenic attributes.[4] However, this species has a remarkable propensity to acquire and then express resistance mutations in the presence of selective pressure.[5] The treatment of candida endocarditis typically involves a combined approach of antifungal therapy (AFT) and surgery.[6–8] The recommended initial AFT regimens are lipid amphotericin B, with or without flucytosine, or a high-dose echinocandin. The proposed duration of AFT is at least 6 weeks and a step-down therapy to an azole in infections caused by azole-susceptible isolates may be considered assuming the patient is clinically stable and has cleared candidaemia.[6–8] Following completion of initial therapy, long-term suppressive AFT is prudent in the setting of prosthetic valve endocarditis or if surgery is not performed.[1,8] Rezafungin is the first molecule of the new generation of long-acting echinocandins. It has several advantages over the already approved echinocandins as it has better stability, pharmacokinetic/phamacodynamic (PK/PD) parameters (half-life > 130 h, minimal interpatient variability and enhanced tissue penetration) and improved safety profile, which would allow higher dose regimes and thus prevent (or reduce) the selection of resistant strains.[9] STRIVE and ReSTORE trials lead to rezafungin FDA's approval for the treatment of candidaemia and IC in adult patients who have limited or no alternative treatment options.[10] However, rezafungin has yet to be tested extensively in those forms of IC requiring > 4 weeks of antifungal treatment. In these scenarios the favourable PK/PD characteristics of rezafungin might prove advantageous.

We present the first case of candida endocarditis managed with suppressive weekly rezafungin infusions.

Case description

A 70-year-old woman was admitted on 27 July 2023 to an emergency room in Trento for a 1 day course of disorientation and urinary incontinence. Remote medical history included type 2 diabetes, arterial hypertension and polymyalgia rheumatica treated with low-dose glucocorticoids (methylprednisolone 4 mg/day). Peripheral vein blood cultures were collected on pyrexia and proved positive for *C. glabrata* with a MIC of 8 mg/L, thus being susceptible to increased exposure dose of fluconazole, according to the revised EUCAST clinical breakpoints.[11] High-dose intravenous (IV) anidulafungin (200 mg/day) was started and transthoracic echocardiogram demonstrated 3 mm vegetations on the native aortic valve, which were subsequently confirmed by transoesophageal echocardiogram. Cardiac surgery was repeatedly deemed unfeasible due to the patient's overall poor fitness. Fundus oculi examination as well as follow-up blood cultures were negative. The patient continued double dosage anidulafungin infusions, according to guidelines,[7,8] for approximately 6 weeks, during which time informed consent and institutional review board approval was obtained through expanded access to begin administration of rezafungin for compassionate use. During hospitalization the patient developed *Enterococcus faecalis* catheter-related bloodstream infection, successfully treated with catheter removal and a 7-day course of antibiotic treatment. Transoesophageal echocardiogram was repeated on 18 September, demonstrating resolution of aortic vegetations. The patient was then discharged and suppressive antifungal treatment with IV rezafungin was started on 22 September with a loading dose of 400 mg, followed by maintenance dosing of 200 mg weekly. During suppressive therapy, we observed a gradual reduction in C-reactive protein and β-D-Glucan (BDG) values, the latter until negativity. Unfortunately, the patient at the seventh infusion presented with a 5 day course of fever and neurological deterioration and was diagnosed with *Klebsiella pneumoniae* CTX-M+ urosepsis. We began IV ertapenem, sending the patient back to the long-term care facility to which she had been admitted a few days earlier. Antibiotic therapy was then discontinued (8 days total) due to sepsis resolution. Four days later, the patient again developed fever and deteriorating general condition; long-term care facility physicians decided to initiate palliative treatment. The patient died on 14 November.

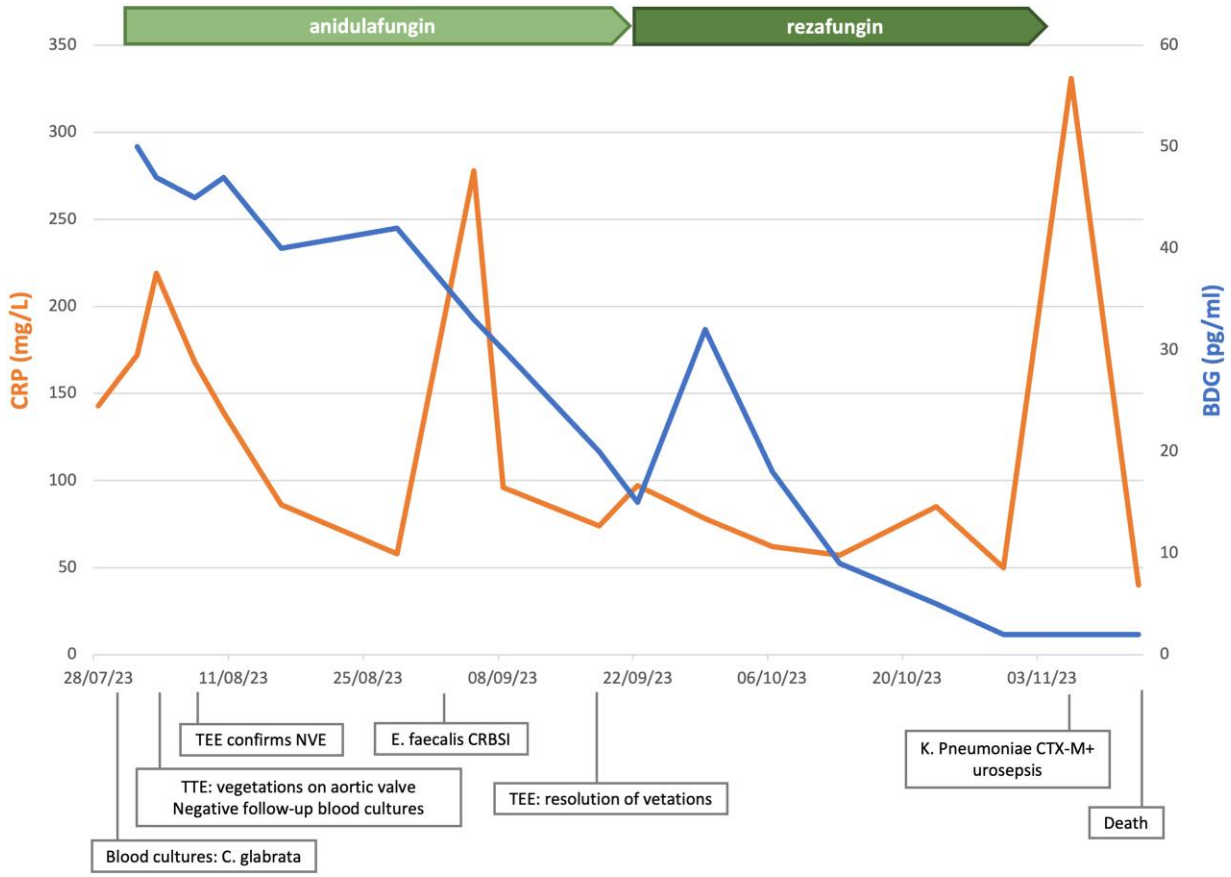

Figure 1. Clinical course and therapeutic management. Abbreviations: BDG, β-D-Glucan; CRBSI, catheter-related bloodstream infection; CRP, C-reactive protein; NVE, native valve endocarditis; TOE, transoesophageal echocardiogram; TTE, transthoracic echocardiogram.

Figure 1 shows the clinical course and therapeutic management of the patient.

Discussion

Most of the clinical experience regarding suppressive AFT in candida endocarditis has been with azole antifungals, particularly fluconazole. However, a recent European multicentre study demonstrated reduced sensitivity to fluconazole in 88% of *C. glabrata* isolates, with an increasing trend of resistant isolates.[4] In addition, it is well-known that azoles exhibit drug interactions that may limit their use, especially in frail elderly patients undergoing polypharmacotherapy. In our case, considering the MIC of the isolate, the QT prolongation demonstrated during hospitalization as well as the ongoing therapy with a selective serotonin receptor inhibitor, also to promote compliance, we opted to use rezafungin as suppressive therapy. BDG has a great negative predictive value concerning IC, but its prognostic role is still to be defined due to lack of data, although a decline in BDG levels in IC has been correlated with successful treatment outcomes.[12] In our case there was a transient rise of BDG values at the switch from anidulafungin to rezafungin. This may have been a random event, as it was not related to any clinical change in the patient (no fever or haemodynamic worsening). STRIVE and ReSTORE trials confirmed rezafungin non-inferiority compared to caspofungin for all-cause mortality, with a potential early treatment benefit, possibly reflecting rezafungin's front-loaded dosing regimen.[10] PK/PD evaluations have shown that first-generation echinocandins, when used at standard dosage, contrary to rezafungin, are unlikely to provide sufficient therapeutic exposures to treat highly resistant isolate.[13] Less frequent dosing of rezafungin might also reduce the duration of hospitalization as well as the requirement for central catheter placement and the resulting risk of catheter-related adverse outcomes.

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Transparency declarations

The authors do not have any associations that might pose a conflict of interest.

Author contributions

G.M. drafted the original draft and edited the article; all co-authors critically revised the manuscript. All authors read and approved the final manuscript. G.M. is the guarantor of the paper.

Data availability

All data needed to evaluate the conclusions in this article are included in the paper. Additional data related to this paper may be requested from the authors. Written informed consent was given by the patient of the reported case.

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