Endocarditis due to vancomycin-resistant Enterococcus raffinosus successfully treated with linezolid: case report and review of literature

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ABSTRACT

Enterococcus raffinosus is scarcely found in clinical samples and even less frequently as etiologic agent of endocarditis. We are herein presenting one case of mitral prosthetic-valve endocarditis in a 77-y-o male due to a vancomycin-resistant Enterococcus raffinosus isolate, successfully treated with 6 weeks of linezolid, and a two-year follow up.

Key words: endocarditis, vancomycin resistance, Enterococcus raffinosus, linezolid

Vancomycin-resistant enterococci (VRE) were isolated for the first time in Argentina in 1996 (11). Afterwards, they increased in number, especially as colonizers. They mainly had the vanA genotype and belonged to the Enterococcus faecium species. However, a few isolates of VanB E. faecium, VanA and VanB Enterococcus faecalis, VanA Enterococcus avium, VanA Enterococcus gallinarum and VanA Enterococcus raffinosus have also been found in Argentina (6, 10). This latter species has scarcely been found in clinical samples and even less frequently as etiologic agent of endocarditis (8).

We are herein presenting a case of mitral prosthetic-valve endocarditis in a 77-y-o male due to a vancomycin-resistant isolate of E. raffinosus, successfully treated with 6 weeks of linezolid (LZD).

Case report. A 77-year-old man with bioprosthetic mitral valve replacement due to severe valve insufficiency and a recent history of cured viridans group streptococcal endocarditis, was admitted to hospital with a febrile episode. Five blood cultures were taken, all of which were positive for E. raffinosus, which was identified according to the scheme proposed by Teixeira et al. (13). Vancomycin resistance was rapidly recognized by a 6-mm zone in a disk diffusion test with a 30 µg disk of vancomycin. It was later confirmed by Etest (MIC = 1,024 µg/ml) and characterized as due to the vanA genotype by a specific PCR performed at our reference center. As expected for a VanA isolate, the MIC of teicoplanin was 32 µg/ml.

The prosthetic valve endocarditis diagnosis was confirmed by the appearance of a new murmur, the observation of a moderate to severe valve prolapse and light insufficiency of the mitral valve by transesophageal ultrasonography. Two peripheral periprosthetic jets, probably caused by periprosthetic leaks, were also observed.

Treatment began with intravenous LZD (600 mg every 12 hours) for four weeks followed by oral LZD (600 mg every 12 h) for two weeks. The isolate was susceptible to this drug (MIC = 2 µg/ml) by the macrobroth dilution method but was resistant to quinupristin-dalfopristin by the disk diffusion test. It was also resistant to penicillin (32 µg/ml), streptomycin (>1,024 µg/ml), gentamicin (>1,024 µg/ml), and rifampin (>32 µg/ml) by the Etest (AB-Biodisk, Solna, Sweden). During this treatment, the patient underwent another valve replacement. The infectious...
Table 1. Characteristics of patients with infective enterococcal endocarditis treated with linezolid.

<table>
<thead>
<tr>
<th>Patient N°, age/sex</th>
<th>Preexisting medical condition</th>
<th>Organism</th>
<th>Site of infection</th>
<th>Dose of linezolid</th>
<th>Duration of treatment (3)</th>
<th>Outcome</th>
<th>Previous antibiotic treatment (6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, 34 yr/F [3]</td>
<td>Hemodyalisis, Congenital cyanotic heart disease</td>
<td>VR <em>E. faecium</em></td>
<td>Native tricuspid and aortic valves</td>
<td>600 mg/12 h</td>
<td>3 d, i.v. 6 w, p.o.</td>
<td>Cure</td>
<td>Chloramphenicol and Q&amp;D</td>
</tr>
<tr>
<td>2, ND/ND [5]</td>
<td>None</td>
<td>VS <em>E. faecium</em></td>
<td>Pulmonic valve</td>
<td>600 mg/12 h</td>
<td>21 d ND (5)</td>
<td>Death during multiple therapy (probably therapy failure)</td>
<td>No</td>
</tr>
<tr>
<td>3, ND/ND [5]</td>
<td>Diabetes, hemodyalisis, recent abdominal aortic repair Prematurity, tracheostomy, atrial septal defect, indwelling central venous catheter</td>
<td>VR <em>Enterococcus</em> sp.</td>
<td>Not reported</td>
<td>600 mg/12 h</td>
<td>6 w ND</td>
<td>Cure</td>
<td>Alatrofloxacin and VAN</td>
</tr>
<tr>
<td>4, 78 yr/M [12]</td>
<td>Diabetes, coronary artery bypass, aortic valve replacement</td>
<td>VS <em>E. faecalis</em></td>
<td>Prosthetic aortic valve</td>
<td>600 mg/12 h</td>
<td>7 w ND</td>
<td>Cure</td>
<td>AMP + GEN</td>
</tr>
<tr>
<td>5, 4 mo/M [1]</td>
<td>Prematurity, tracheostomy, atrial septal defect, indwelling central venous catheter</td>
<td>VR <em>E. faecium</em></td>
<td>Native tricuspid valve</td>
<td>15 mg/kg every 8 h 15 mg/kg every 8 h</td>
<td>7 w, i.v. 2 w, p.o.</td>
<td>Cure</td>
<td>VAN</td>
</tr>
<tr>
<td>6, 64 yr/M [9]</td>
<td>Coronary artery disease, hypothyroidism, hypertension, chronic renal failure</td>
<td>VR <em>E. faecalis</em></td>
<td>Native pulmonic valve</td>
<td>600 mg/12 h</td>
<td>6 w, i.v.</td>
<td>Non-evaluable (1 w. after completion treatment, the patient died due to another cause)</td>
<td>VAN + GEN</td>
</tr>
<tr>
<td>7, 79 yr/F [15]</td>
<td>Prosthetic mitral valve</td>
<td>VR <em>E. faecalis</em></td>
<td>Prosthetic mitral valve</td>
<td>600 mg/12 h 600 mg/12 h</td>
<td>2 w, i.v + GEN 12 w, p.o.</td>
<td>Cure</td>
<td>VAN + GEN Q&amp;D + GEN DOX</td>
</tr>
<tr>
<td>8, 37 yr/F [14]</td>
<td>Hemodyalisis, four failed allografts. Bilateral subclavian subcutaneous hemodyalisis ports</td>
<td>VR <em>E. faecalis</em></td>
<td>Native aortic and mitral valves</td>
<td>600 mg/12 h</td>
<td>9 d, i.v.</td>
<td>Failure</td>
<td>No Cure with PEN + STR</td>
</tr>
<tr>
<td>9, 64 yr/M [2]</td>
<td>HIV, Hep C, cadaveric renal transplant, perinephric hematoma infected with VR <em>E. faecium</em></td>
<td>VR <em>E. faecium</em></td>
<td>Native mitral valve</td>
<td>600 mg/12 h</td>
<td>6 w, p.o.</td>
<td>Cure</td>
<td>Q&amp;D + AMS Q&amp;D + DOX</td>
</tr>
<tr>
<td>10, 40 yr/M [16]</td>
<td>Hemodyalisis, previous group B streptococcal endocarditis</td>
<td>VS <em>E. faecalis</em></td>
<td>Native tricuspid, aortic and mitral valves</td>
<td>600 mg/12 h</td>
<td>3 w, i.v.</td>
<td>Failure</td>
<td>AMP+GEN and LEV. Cure with AMP + STR and surgery</td>
</tr>
<tr>
<td>11, 77 yr/F [this study]</td>
<td>Bioprosthesis mitral valve replacement</td>
<td>VR <em>E. raffinosus</em></td>
<td>Prosthetic mitral valve</td>
<td>600 mg/12 h 600 mg/12 h</td>
<td>4 w, i.v. 2 w, p.o.</td>
<td>Cure</td>
<td>No</td>
</tr>
</tbody>
</table>

3ND: non determined.
process involved the valve annulus at the site of attachment with extension to adjacent structures. The valve was removed with extensive debridement and resection of the annular tissue. Replacement with a mechanical prosthetic valve was performed prior to reconstruction of the destroyed annulus. The patient had an uneventful recovery within a two-year follow-up. Cultures of the replaced valve tissue were negative.

Treatment of enterococcal endocarditis simultaneously resistant to vancomycin, penicillin and aminoglycosides is really a major challenge. Despite its already known bacteriostatic effect, LZD was chosen in this case for lack of better options. In fact, LZD also behaved as bacteriostatic agent in this isolate as shown in the corresponding time-killing curve (data not shown).

There has been limited experience in the use of LZD to treat infective endocarditis due to enterococci. Tsigrelis et al. described one case of endocarditis due to vancomycin-resistant (VR) E. faecalis in a 37-y-o female patient that had failed to respond to LZD therapy administered during nine days by intravenous route (case 8, Table 1). She had no predisposing heart condition but had undergone prolonged hemodyalisis, four failed allografts, multiple failed arteriovenous grafts and fistulas, and the placement of bilateral subclavian subcutaneous hemodialysis ports. Finally, she was successfully treated with placement of bilateral subclavian subcutaneous hemodialysis plus congenital heart disease in the first subgroup of 8 patients with VRE was not significantly different from the whole (cure = 75%, improvement = 12.5%, failure = 12.5%) (7).

In Table 1, in addition to the three previously commented cases, we included other seven enterococcal endocarditis episodes that were treated with LZD: four endocarditis due to VR E. faecalis, one of them susceptible to VAN (VS), one case due to an unidentified VR Enterococcus sp. and two cases due to VS E. faecalis.

Babcock et al. and Archuleta et al. reported the cure with LZD of two patients with endocarditis by VR E. faecium and severe preexisting medical conditions: hemodyalisis plus congenital heart disease in the first case, and HIV, hepatitis C plus renal transplantation in the second (2, 3).

Chien et al. partially described several patients infected with VRE. Among them, there was one patient who died due to VS E. faecium endocarditis after 21 days of therapy with LZD, and another case of endocarditis due to an unidentified VR Enterococcus sp. that was cured with a 7-week treatment with the same antibiotic (5).

Ang et al. reported the cure of a pediatric patient with a VR E. faecium endocarditis with 15 mg/kg/8 h LZD (1).

One of the two cases of VS E. faecalis endocarditis located in a prosthetic aortic valve and treated with LZD, was successfully cured with 7 weeks of antibiotic treatment. The other case, involving native tricuspid, aortic and mitral valves, failed after three weeks of intravenous therapy (12, 16).

The whole experience with these eleven patients (Table 1) is similar to that published by Birmingham et al. related to cases of VR E. faecium endocarditis recorded from compassionate treatments with LZD: 10 clinical cures, 2 clinical failures and one indeterminate case; 7 microbiological cures, and 4 microbiological failures (4).

Falagas et al. reviewed the efficacy of LZD in infective endocarditis due to multidrug-resistant gram-positive cocci and found approximately the same results: of 33 evaluable patients (25% of them with prosthetic valve), 21 (63.6%) were cured after LZD administration; in 66.7% of cases it was administered alone. Most cases were staphylococcal endocarditis, but the outcome of the subgroup of 8 patients with VRE was not significantly different from the whole (cure = 75%, improvement = 12.5%, failure = 12.5%) (7).

We described one case of mitral prosthetic-valve endocarditis in a 77-y-o male cured with 6 weeks of LZD. To the best of our knowledge, this is the first report of a case of prosthetic endocarditis due to a VR E. raffinosus isolate successfully treated with LZD, with a two-year follow-up. We will have to wait for other similar reports to define the best therapeutic scheme (dose, intervals, administration route and treatment duration).

Acknowledgements: We wish to acknowledge Biochemist Alejandra Corso from Servicio de Antimicrobianos, INEI-ANLIS “Dr. Carlos G. Malbrán”, Ciudad Autónoma de Buenos Aires, Argentina, for her contribution in the molecular characterization of the vanA genotype.

REFERENCES
4. Birmingham MC, Rayner CR, Meagher AK, Flavin SM, Batts DH, Shentag JJ. Linezolid for the treatment of multidrug-resistant,


