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RESEARCH NOTE

Linezolid therapy for infective endocarditis

*P. Muñoz[1], M. Rodríguez-Creixéms[1], M. Moreno[2], M. Marín[1], V. Ramallo[3], E. Bouza[1] and the GAME Study Group**

Departments of [1]Clinical Microbiology-Infectious Diseases, [2]Cardiology and [3]Internal Medicine, Hospital General Universitario Gregorio Marañón, University of Madrid, Madrid, Spain

ABSTRACT

Linezolid is not yet recognised as a standard therapy for infective endocarditis. This report describes nine patients with endocarditis treated with linezolid and 33 similar cases from the medical literature. The majority of cases involved multiresistant strains, and the reasons for administering linezolid were refractory disease (60%), intolerance (28%), sequential therapy (12%) and a resistant pathogen (1%). Linezolid was administered for a mean of 37 days, with a successful outcome in 79% of cases. Reversible adverse effects were described in ten cases. The mean follow-up period was 8.5 months. Further data from randomised controlled clinical trials are needed to determine the efficacy and safety of linezolid for treating endocarditis.

Keywords Endocarditis, linezolid, methicillin-resistant *Staphylococcus aureus*, therapy, vancomycin-resistant enterococci

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Corresponding author and reprint requests: P. Muñoz, Hospital General Universitario Gregorio Marañón, Doctor Esquerdo 46, 28007 Madrid, Spain
E-mail: pmunoz@micro.hggm.es

*The GAME Study Group comprises: E. Bouza, M. Desco, M. A. García-Fernández, M. Marín, M. Martínez-Selles, M. Moreno, P. Muñoz, B. Pinilla, A. Pinto, V. Ramallo, M. Rodríguez-Creixéms, I. Tamallo and J.L. Vallejo.

Linezolid (LNZ) has excellent in-vitro activity against Gram-positive bacteria that cause endocarditis. However, linezolid is not yet recognised as a standard therapy for this condition because of concerns regarding its bacteriostatic activity and long-term toxicity. This report describes nine patients with endocarditis who were treated with linezolid and summarises another 33 cases reported previously in the literature.

LNZ was used to treat nine (8.5%) of 106 patients with endocarditis during a 13-month period because of refractory disease (n = 2) or intolerance to other drugs (n = 4), or for outpatient oral consolidation treatment (n = 3). The clinical features of these nine patients are summarised in Table 1. The mean age was 69 (range 57–82) years, and six were male. Underlying conditions included bone marrow and kidney transplantation (n = 2) and previous heart disease (n = 6). Aetiological agents were *Staphylococcus aureus* (n = 6), coagulase-negative staphylococci (n = 1), *Corynebacterium striatum* (n = 1) and *Streptococcus mutans* (n = 1). Eight cases involved the left side of the heart, with five cases occurring in prosthetic valves. Four patients required surgery. The median length of previous in-hospital therapy with other standard drugs was 22 (range 14–28) days, and the mean duration of LNZ therapy was 20 (range 14–28) days. All nine patients were cured, with no adverse effects or relapses.

At present, linezolid is not a standard therapy for endocarditis, although guidelines published recently by the American Heart Association consider it to be a reasonable alternative for cases of endocarditis caused by methicillin-resistant *S. aureus* (MRSA) or multiresistant enterococci. Experience with linezolid for the treatment of endocarditis is limited, and no comparative studies are available. Experimental models show discordant results, but 33 other cases of endocarditis treated with linezolid have been described previously in the literature [1–23]. The most important features of all 42 cases are summarised in Table 2. The mean age was 63 (range 1–82) years, and 63% of patients were male. All patients except one [11] had a severe underlying condition, with the most common being previous heart disease (62%) and renal insufficiency (26%).

Endocarditis was left-sided in 76% of cases and occurred on a prosthetic valve in 33% of cases.

Table 1. Features of nine patients with infectious endocarditis who were treated with linezolid (LNZ)

Case	Age/gender	Underlying condition	Valve	Prosthetic IE	Aetiology	Prior AMS /days	Indication for LNZ	Days on LNZ /route	Concomitant AMS	Post-LNZ therapy	Heart surgery	Clinical outcome	Adverse effects	Follow-up /months
1	73/F	Rheumatic heart disease; aortic and mitral VR	A	Yes	MRSA	V21	Breakthrough bacteraemia	21PO	No	No	Yes	Cure	No	17
2	76/F	Mitral insufficiency, oesophagitis	Mi	Yes	*Streptococcus mutans*	V 14	Penicillin allergy. Vancomycin intolerance	28PO	No	No	Yes	Cure	No	31
3	62/M	Aortic aneurism	A	Yes	MSSA	Cft21	Therapeutic failure and renal insufficiency	14PO	No	No	No	Cure	No	24
4	68/M	Aortic and mitral VR, stroke	A/Mi	Yes	CNS	V28	Outpatient therapy	14PO	No	No	Yes	Cure	No	18
5	81/M	Kidney TX pacemaker	A	No	MSSA	Clx R G21	Intolerance (renal insufficiency)	21PO	R	No	No	Cure	No	16
6	57/F	BMT	Atrial wall	No	*Corynebacterium striatium*	V Cft28	Intolerance (renal insufficiency)	28PO	No	No	No	Cure	Thrombo-cytopenia	13
7	74/M	COPD, prostate cancer	Mi	No	MRSA + *Enterococcus faecalis*	V + G28	Outpatient therapy	14PO	No	No	No	Cure	No	11
8	60/M	Hypertrophic stenosis, pacemaker	T	No	MSSA	Clx R28	Intolerance (renal insufficiency)	14PO	No	No	Yes	Cure	No	7
9	82/M	Kidney TX	A	No	MSSA	Clx28	Outpatient therapy	14PO	No	No	No	Cure	No	11

A, aortic; AMS, antimicrobial agents; BMT, bone marrow transplantation; Cft, ceftriaxone; Clx, cloxacillin; CNS, coagulase-negative staphylococci; COPD, chronic obstructive pulmonary disease; F, female; G, gentamicin; HLGR, high-level gentamicin-resistant; IE, infectious endocarditis; M, male; Mi, mitral; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S. aureus*; PO, oral; R, rifampicin; T, tricuspid; TX, transplantation; V, vancomycin; VR, valve replacement.

Table 2. Summary of 42 cases of infective endocarditis treated with linezolid

Male (%)	26/41 (63%)
Mean age/years (range)	63 (1–82)
Underlying conditions, *n* (%)	41 (98%)
Previous heart disease	26 (62%)
Renal insufficiency	11 (26%)
Cancer	8 (19%)
Diabetes mellitus	7 (17%)
Transplantation	4 (9.5%)
Endocarditis characteristics, *n* (%)	
Left-sided	32 (76%)
Prosthetic valve	14 (33%)
Multiple valve involvement	8 (9%)
Septic metastases[a]	6
Aetiology, *n* (%)[b]	
Staphylococcus	31 (74%)
Methicillin-resistant *S. aureus* (MRSA)	11
S. aureus with reduced susceptibility to vancomycin	11
Methicillin-susceptible *S. aureus*	4
Coagulase-negative *Staphylococcus*	5
Enterococcus spp.	10 (24%)
Vancomycin-resistant *Enterococcus*	7
High-level gentamicin-resistant *Enterococcus*	2
Others (*Streptococcus mitis* and *Corynebacterium striatum*)	2
Reasons for administering linezolid, *n* (%)	
Failure of previous treatment	25 (60%)
Intolerance	11 (28%),
Sequential therapy	5 (12%)
Initial treatment for multiresistant pathogen	1
Therapy of the endocarditis	
Mean duration of previous therapy	30 (4–90) days
Mean duration of linezolid administration	37 (7–156) days
Simultaneous drugs[c], *n*	11
Surgery, *n* (%)	12 (29%)
Adverse effects of linezolid therapy, *n* (%)	10 (24%)
Thrombocytopenia	9
Diarrhoea	1
Outcome	
Mean follow-up period	8.5 months
Cure, *n* (%)	33 (79%)
Non-related death, *n* (%)[d]	3
Related death, *n* (%)	6 (14%)

[a]Brain, aortic root, spleen, kidney, vertebra, epidural and psoas abscess.
[b]Two patients had endocarditis caused simultaneously by MRSA and *Enterococcus* spp.
[c]Aminoglycosides ($n = 5$), rifampicin ($n = 5$), fusidic acid ($n = 3$), and vancomycin ($n = 3$).
[d]Three patients were classified as clinical failures as they died during therapy, but without signs of endocarditis and with negative cultures.

Multiresistant bacteria predominated, including MRSA ($n = 11$), *S. aureus* with reduced vancomycin susceptibility ($n = 11$), vancomycin-resistant enterococci ($n = 7$), and high-level gentamicin-resistant *Enterococcus* spp. ($n = 2$). The most important reason for administering linezolid was previous failure of a more conventional antimicrobial regimen (60%). Thirty-eight patients had received previous therapy for a mean of 30 (range 4–90) days. Previous therapy was significantly longer in refractory patients (38 days vs. 21 days; p 0.03). Nevertheless, 22 refractory patients were persistently bacteraemic when linezolid therapy was commenced, and two patients experienced significant clinical deterioration (a CNS event and a constant fever with vegetation enlargement, respectively). Linezolid was administered for a mean of 37 days, but longer for refractory patients (46 vs. 24 days; p <0.01). The route of administration was specified for 32 patients, with 50% receiving oral therapy (Table 2). The outcome was significantly better in this group (a cure rate of 95% vs. 64%), probably because intravenous therapy was reserved for the most severely-ill patients.

Surgery was performed on 12 patients, and other drugs were given with linezolid to 11 patients. Adverse effects were uncommon, even with patients who received prolonged therapy [10,12], but nine patients had thrombocytopenia and one had minor diarrhoea. None of the patients experienced severe or permanent side-effects, and no relationship was found between toxicity and duration of linezolid therapy, or the presence of chronic renal failure, or previous use of vancomycin. However, the possibility of permanent neurological toxicity is a significant concern; thus, when therapy is for longer than 2 weeks, the possibility of reversible thrombocytopenia should be investigated on a weekly basis, especially for patients receiving haemodialysis. The use of linezolid for >28 days is not recommended.

The mean follow-up period was 8.5 months, and the outcome was considered to be successful for 33 (79%) patients. A favourable outcome was less common for patients with cancer (50% vs. 85%, p 0.02), but no difference in outcome was observed with respect to aetiology, the indication for linezolid, or prosthetic valve endocarditis. Three of the patients classified as clinical failures died while receiving therapy, but without signs of endocarditis and with negative cultures. Related death occurred with six (14%) patients, and was more common in patients with diabetes mellitus (43% vs. 9%; p 0.01) and cancer (37.5% vs. 9%, p 0.03), and those who received linezolid following previous treatment failure (20% vs. 6%; p 0.1).

The response was satisfactory for eight of 11 patients with MRSA (two of whom were also infected with *Enterococcus* spp.), and for seven of 11 patients with endocarditis caused by *S. aureus* with reduced susceptibility to vancomycin [7,12–14]. Endocarditis caused by vancomycin-resistant enterococci also showed a high response rate to linezolid, with four of five cases cured [3–6]. The patient who died had negative cultures 1 week after starting therapy [15]. This patient was receiving haemodialysis, which has been

associated previously with lower plasma levels of linezolid. It has been suggested that higher doses of linezolid may be necessary to achieve cure in some refractory cases. Moreover, an animal model of endocarditis in rabbits showed that the efficacy of linezolid was related to trough levels in plasma, and that high levels of linezolid are required to cure endocarditis. It is not clear which factors may be associated with unexpectedly low levels of linezolid, or whether a specific group of patients is especially predisposed to low levels.

A prospective, blind, comparative study would be necessary to clarify aspects such as the efficacy of linezolid for treatment of this condition and to exclude possible under-reporting of side-effects. The possibility of a reporting bias cannot be excluded, i.e., cases with a more favourable outcome have been reported. Finally, it can be argued that cure could be attributed to the use of previous or concomitant antibiotics prescribed to the patients. However, this seems unlikely, as most of the patients had refractory disease with persistent bacteraemia when linezolid therapy was commenced, despite prolonged previous standard treatment. Nevertheless, this possibility cannot be excluded in patients for whom linezolid was used as consolidation therapy, particularly as the duration of therapy for endocarditis is not clearly established. Longer follow-up periods may be needed to exclude a higher rate of relapse.

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