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Good Clinical Outcomes but High Rates of Adverse Reactions during Linezolid Therapy for Serious Infections: a Proposed Protocol for Monitoring Therapy in Complex Patients

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We assessed the toxicity and clinical outcomes associated with linezolid therapy (mean duration, 29 ± 28 days; range, 8 to 185 days) in 44 patients with serious gram-positive infections. Although a clinical cure was achieved in 73% of the cases, 28/44 (64%) had adverse reactions (thrombocytopenia, *n* = 13; anemia, *n* = 7; gastrointestinal, *n* = 12; peripheral neuropathy, *n* = 1; serotonin syndrome, *n* = 1), such that a systematic monitoring protocol was developed.

The emergence of serious infections due to multiresistant gram-positive pathogens, including heterogeneous vancomycin-intermediate *Staphylococcus aureus* (hVISA), has necessitated the increasing use of linezolid (4). Linezolid has documented efficacy in a range of conditions requiring generally short-course therapy (15–18). Although a number of postmarketing studies have assessed the adverse reactions (ARs) associated with linezolid (4, 15–17), few have evaluated complex patients with multiple comorbidities who often require prolonged therapy. To better assess the efficacy and toxicity of linezolid in this patient group, we undertook a retrospective review of consecutive patients treated with linezolid at our institution.

We retrospectively assessed the medical records of all patients treated intravenously (i.v.) or orally with linezolid for >7 days during the 40 months from December 2000 to April 2004 at the Austin Hospital, a 480-bed university teaching hospital. The patient information collected included age, sex, presence of diabetes or immunosuppressive conditions, need for hemodialysis and/or intensive care unit admission during hospitalization, prior antibiotic therapy, clinical and bacteriological indication for linezolid therapy, ARs, and clinical outcomes. The clinical definitions used were as follows: cure, absence of clinical or laboratory evidence of infection or causative pathogen after completion of antimicrobial therapy and at follow-up; failure/relapse, recovery of the index pathogen from sterile-site specimens or clinical deterioration resulting in retreatment or death attributable to infection during follow-up; indeterminate, death of the patient from causes other than infection or treatment-related toxicity during the follow-up period.

Only events fulfilling the definition of "definite" or "probable" ARs (12) to linezolid were recorded. Hematological definitions used were as follows: mild, moderate, and severe anemia, defined as hemoglobin levels of 100 to 130 g/liter, 80 to 99 g/liter, and <80 g/liter, respectively; mild, moderate, and severe thrombocytopenia, defined as platelet counts of 100×10^9 to 150×10^9/liter, 50×10^9 to 99×10^9/liter, and $<50 \times 10^9$/liter, respectively; leucopenia, total leukocyte count of $<4.0 \times 10^9$/liter (neutropenia, $<2.0 \times 10^9$/liter). If anemia or thrombocytopenia existed at the baseline, an AR was recorded only if the lowest hemoglobin or platelet count was <80% of the baseline value. The contribution of all concomitant medications known to cause blood dyscrasias was assessed in each case.

Forty-four patients received 48 courses of linezolid (all 600 mg/12 h) during the study period (seven patients had been previously included in a linezolid efficacy study [8]), of which 26 were oral only, 8 were i.v. only, and 14 were a combination of i.v. and oral therapy. All patients received linezolid therapy alone, except one patient who was given linezolid in combination with rifampin and fusidic acid. The mean patient age was 61 ± 18 years (standard deviation [SD]; median, 66 years; range, 22 to 86 years). Thirty-nine patients had received vancomycin prior to the commencement of linezolid. Four of these patients had endocarditis (methicillin-resistant *S. aureus*, *n* = 2; hVISA, *n* = 1; methicillin-resistant *Staphylococcus epidermidis*, *n* = 1) and were subsequently changed to linezolid, completing their treatment course with a mean of 29 days (range, 16 to 39 days) of linezolid therapy. Details regarding pathogens, clinical features, and ARs are shown in Table 1. Underlying comorbidities were present in 23 (53%) of the patients.

The mean linezolid treatment duration was 29 ± 28 (SD) days (median, 21 days; range, 8 to 185 days), and the mean duration of posttherapy follow-up was 13.5 ± 9.4 months (median, 12.8 months; range, 0.5 to 37 months). ARs to linezolid occurred in 28/44 (64%) patients (one AR, *n* = 19; two ARs, *n* = 5; three ARs, *n* = 2; four ARs, *n* = 2). Seven patients (16%) had severe ARs requiring drug discontinuation, which included thrombocytopenia (*n* = 3), pancytopenia (*n* = 2), angioedema (*n* = 1), and rash (*n* = 1), with a mean time to onset of ARs of 20 ± 10 (SD) days (range, 11 to 39 days).

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TABLE 1. Clinical features, outcomes, and adverse reactions associated with prolonged linezolid therapy

Parameter	Total	No. of patients with treatment duration (days) of:			No. of patients cured		
		7–14	15–28	>28	Medical treatment alone	Medical and surgical treatment	Total
No. (%) of patients	44	12 (27)	16 (36)	16 (36)	17 (39)	15 (34)	32 (73)
Clinical indications							
Osteomyelitis/septic arthritis	22	5	7	10	5	11	16
Skin and soft tissue infection	5	2	1	2	3		3
Deep abscess	4	1	3		2	1	3
Bacterial endocarditis	4		1	3	2	2	4
Prosthetic graft	4	2	2		2	1	3
Other[a]	5	2	2	1	3		3
Pathogens							
MRSA[j]	16	6	5	5	6	7	13
hVISA/VISA	18	2	7	9	5	6	11
VRE[n]	2		1	1	2		2
Other[b]	8	4	3	1	4	2	6
Adverse reactions							
Required drug cessation	7	2	4	1			
GIT[k]/hepatic[c]							
Nausea/vomiting	10		4	6			
Taste disturbance	1			1			
Diarrhea	2			2			
Increased ALT[l]	3	1		2			
Thrombocytopenia[m]							
Mild	8		3	5			
Moderate	3		2	1			
Severe[d]	2		1	1[e]			
Anemia[f]							
Mild	1			1			
Moderate[g]	2	1		1			
Severe[g]	4		2	2			
Pancytopenia (including leukopenia)[h]	2	1	1				
Other[i]	4	1	2	1			

[a] Central venous cannula sepsis ($n = 2$) and persistent bacteremia of unknown source ($n = 3$).
[b] Methicillin-susceptible *S. aureus* ($n = 1$), *S. haemolyticus* ($n = 1$), methicillin-resistant *S. epidermidis* ($n = 3$), and coagulase-negative staphylococci ($n = 3$).
[c] Twelve patients experienced 16 ARs.
[d] Both patients had preexisting mild or moderate thrombocytopenia. Platelet counts decreased by >50% from the baseline.
[e] One patient required a platelet transfusion 40 days after commencing linezolid.
[f] Six patients required red cell transfusion after a mean of 29 ± 9.1 (SD) days (range, 19 to 39 days; median, 26.5 days).
[g] All patients had preexisting mild anemia.
[h] Leukocyte counts in these two patients were 2.8×10^9/liter (neutrophils, 1.6×10^9/liter) and 1.7×10^9/liter (neutrophils, 1.0×10^9/liter).
[i] See text for details.
[j] MRSA, methicillin-resistant *S. aureus*.
[k] GIT, gastrointestinal tract.
[l] ALT, alanine transaminase.
[m] For definitions of levels of thrombocytopenia and anemia, see the text.
[n] VRE, vancomycin-resistant enterococci.

Table 2 describes the correlation between ARs and patients' underlying comorbidities and disease severity.

Thrombocytopenia and nausea and/or vomiting were the two most frequent ARs. Among patients who developed thrombocytopenia, 62% received heparin concurrently, but this was not considered to be responsible for the AR since platelet counts recovered with cessation of linezolid alone in all cases. Other notable ARs included peripheral neuropathy (after 185 days of treatment) and severe serotonin syndrome in a patient concomitantly receiving a pethidine (meperidine) infusion. While the serotonin syndrome responded rapidly to pethidine and linezolid withdrawal, the neuropathy finally improved after 6 months and required prolonged gabapentin therapy. One cirrhotic patient developed lactic acidosis after 20 days on linezolid. A lactate level of 10 mmol/liter was preceded by severe nausea and vomiting and resolved promptly after withdrawal of linezolid.

Age was not associated with the presence or absence of any specific AR (mean ± SD, 62.9 ± 18.1 years versus 58.4 ± 17.2

TABLE 2. Presence of ARs and underlying comorbidities

Comorbidity or disease severity (no. of patients)[a]	No. of patients with following key AR[a] among 44 study patients:		
	Thrombocytopenia (n = 13)	Anemia (n = 7)	Nausea (n = 10)
Required ICU care (11)	2[b]	2[c]	1
Diabetes (11)	7	2	4
Hemodialysis (12)	6	1	2
Immunosuppression or malignancy (6)	1	1	1

[a] Some patients had more than one comorbidity and AR. ICU, intensive care unit.
[b] One patient was in the ICU at the time of the AR.
[c] No patients were in the ICU at the time of the AR.

years, respectively; $P = 0.43$) nor with the most common AR, i.e., hematological abnormalities (mean ± SD, 63.7 ± 16.5 years versus 59.6 ± 18.6 years, respectively; $P = 0.45$).

This is the largest case series of seriously ill patients with multiple comorbidities used to evaluate clinical outcomes and toxicity associated with often prolonged linezolid therapy (13, 15). Despite its retrospective nature, our study found good clinical outcomes (73% overall cure rate) with serious infections (endocarditis, prosthetic graft, and joint) and gram-positive pathogens (methicillin-resistant *S. aureus*, hVISA, vancomycin-resistant enterococci) but identified high rates of ARs, especially gastrointestinal and hematological toxicity (Table 1).

Gastrointestinal ARs occurred in 12/44 (27%) patients, with the majority of these due to nausea (n = 10, 23%)—a rate higher than that observed in previously reported phase 3 trials and the compassionate-use program (4, 16). Notably, all of our patients experiencing nausea were receiving oral linezolid.

Our observed rate of thrombocytopenia (30%) was higher than that in the phase 3 trials (16) but similar to that reported in two previous case series assessing thrombocytopenia (2, 14). Consistent with prior reports (4), thrombocytopenia appeared to be duration dependent, occurring more frequently in those treated for greater than 14 days (0/13 versus 13/13, $P < 0.001$, Fisher's exact test). Of note, given that renal excretion is the main route of linezolid clearance (5), 6 of the 12 patients receiving hemodialysis developed thrombocytopenia versus 7/32 nonhemodialysis patients ($P = 0.07$, chi-square test) (Table 2), suggesting that drug or metabolite accumulation may play a role in this AR, despite the fact that linezolid is known to be removed by conventional intermittent hemodialysis (6). Unfortunately, no serum drug or metabolite levels were collected from our patients to assess this issue more closely, but it is the subject of currently ongoing research by our group. Contrary to the suggestion by others (13, 16), we found that although heparin was frequently coadministered to many of our patients, it did not appear to be the cause of thrombocytopenia in any, since platelet counts always improved with cessation of linezolid alone. We also found linezolid-associated anemia to be relatively common (16%), especially in patients treated for longer than 3 weeks. Four of seven patients had a hemoglobin level of <75% of the baseline level, consistent with prior definitions (16), and three had hemoglobin levels of 75 to 80% of the baseline values. Our relatively high rates of blood dyscrasias were in contrast to reports from two recent comparative trials of linezolid and vancomycin (13, 15). However, in the study by Nasraway et al. (13), only 72 of 356 patients received linezolid for longer than 14 days and none received more than 21 days of therapy. Meanwhile, Rao et al. (15) assessed only a limited number of relatively well orthopedic patients (n = 20). In comparison, we observed 32 patients treated for >14 days and many (16/44) who received linezolid for prolonged durations (>28 days). Interestingly, in these seriously ill patients there was no apparent correlation between intensive care unit admission and development of blood dyscrasias.

Notably, we identified four serious, rare, linezolid-related ARs (peripheral neuropathy, angioedema, serotonin syndrome, and lactic acidosis). Linezolid-associated lactic acidosis has been previously rarely reported (1, 3, 9), while our case of peripheral neuropathy is unusual since the patient gradually recovered sensory function after many months of supportive therapy (11). Despite the known theoretical risk, we report the first case of serotonin syndrome associated with concurrent linezolid and pethidine therapy (3, 7, 10).

Given the encouraging outcomes obtained with linezolid therapy but frequent difficulties with tolerability in clinical practice, we have developed a management protocol for toxicity surveillance including (i) a review of concurrent medications with cessation of selective serotonin reuptake inhibitors (2-week washout preferable), monoamine oxidase inhibitors, tramadol, and pethidine prior to commencement of linezolid; (ii) twice-weekly hematological (hemoglobin, leukocytes, and platelets) and liver function assessments during therapy; (iii) assessment of serum lactate when nausea and/or reduced serum bicarbonate occurs; and (iv) routine ophthalmologic and neurological assessment for patients expected to receive greater than 28 days of linezolid therapy, as recommended by Lee et al. (11).

Linezolid appears to be a clinically effective agent for seriously ill complex patients with severe infections, but its potential associated ARs require systematic monitoring during therapy.

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