CLINICAL EXPERIENCE WITH LINEZOLID IN THE TREATMENT OF RESISTANT GRAM-POSITIVE INFECTIONS

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This study presents our clinical experience with linezolid in 19 patients with serious resistant Gram-positive infections enrolled as part of the compassionate study. In this prospective, non-randomized, noncomparative study, 19 patients were enrolled as part of the National Compassionate Study Protocol conducted by Pharmacia-Upjohn. At the time of this writing, these patients had not been published in the literature. All of the patients had to have documented evidence of serious Gram-positive infections in normally sterile sites and should have been unable to tolerate available antimicrobial therapy or be unresponsive to available drugs. Clinical characteristics, laboratory values, and pharmacokinetic and pharmacodynamic parameters were obtained. Patients were followed both short-term and long-term after completion of therapy.

Nineteen patients were enrolled: 13 females and 6 males. The average age was 63 years. The average length of therapy with linezolid was 22 days. Methicillin-resistant *Staphylococcus aureus* (MRSA) was treated in eight patients, methicillin-resistant *Staphylococcus epidermidis* (MRSE) in two patients, vancomycin-resistant *Enterococcus faecium* (VREF) in eight patients, and coagulase-negative *Staphylococcus* in two patients. Co-infecting organisms include *Enterococcus* species colonization in six patients, *Pseudomonas* species in one patient, *Serratia marcenens* in one patient, and *Candida albicans* in one patient .

Sterile sites that were infected included bone and joint (wounds and septic joints) in six patients, gastrointestinal system (hepatobiliary, liver abscess, Crohn's) in five patients, genito-urinary (kidney and urine) in two patients, blood in five patients, respiratory in one patient, and aortic valve in 1 patient. Linezolid was given at 600 mg IV every 12 hours with a mean length of therapy of 22 days. Surgical drainage was used in combination with linezolid in 11 of the patients. Seventy nine percent of these patients achieved clinical and microbiologic cure, and none of the deaths reported in this series were related to the drug. Adverse events included skin rash in one patient, mild bone marrow suppression in two patients, and mild elevation in liver function tests in two patients. No life-threatening adverse events were noted.

It appears that linezolid, along with surgical intervention (when necessary), appears to be an effective treatment option for resistant Gram-positive infections. Long-term studies evaluating the possible resistance rates are necessary. (*J Natl Med Assoc.* 2001;93:386–391.)

Key words: Linezolid ♦ Gram-positive infection

A new class of antimicrobial agents, called oxazolidinone, was discovered in 1987.[1] This compound was found to be active in vitro and in vivo against antimicrobial-susceptible and antimicrobial-resistant staphylococci, streptococci, and enterococci.[2–5] Early therapeutic studies were performed, mainly in animal models, for infections caused by these particular Gram-positive organisms.[1,3–6]

However, there have been limited published studies attesting to the clinical efficacy of linezolid, with the exception one one study by Chien.[7] U.S. Food and Drug Administration (FDA) approval was given based on unpublished clinical trials involving more than 4000 patients, mostly on a compassionate use program.

Linezolid was chosen for clinical development on the basis of superior pharmacokinetic properties. This drug is bacteriostatic against staphylococci and enterococci. It has a unique mechanism of action in that it inhibits ribosomal protein synthesis by interfering with the initiation complex formation, thus causing bacterial cell death. Linezolid is also active against penicillin-resistant strains of *Streptococcus pneumoniae* and vancomycin-intermediate *Staphylococcus aureus*.[8,9] Linezolid was noted to be essentially inactive in vitro against Gram-negative microorganisms such as *Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa,* but has good in vitro activity against some anaerobic bacteria.[10] Linezolid action appears to be bacteriostatic and no concentration-dependent killing could be demonstrated for *Staphylococcus* or *Enterococcus.* The addition of amino glycosides did not enhance the activity against enterococcal strains.[11] Improved activity was noted against a variety of Gram-positive organisms, including strains with acquired multiple drug resistances.[3,12–15]

In addition, in vitro evolution of mutation does not develop readily.[3] In time, kill studies were performed using concentrations of 4 μg/mL, 8 μg/mL, and 16 μg/mL of linezolid; no bacteriocidal killing was observed.[16]

The antimicrobial activity of linezolid compared favorably with that of vancomycin against a methicillin-resistant *Staphylococcus epidermidis* (MRSE) infection. It also compared favorably with vancomycin in the treatment of experimental soft tissue infections caused by *Enterococcus faecalis* and *E. faecium.* Patel et al.[16] also noted in vitro activity against *E. gallinarium* and *E. casselflavus* when tested against linezolid.

Two studies with strains of methicillin-susceptible and methicillin-resistant *S. aureus* and *S. epidermidis* failed to recover linezolid-resistant mutants at concentrations that were twofold the MIC and above.[13,14] In addition, the drug appeared to be bacteriostatic by time-kill analysis studies. Adverse effects of this drug include bone marrow suppression, elevated liver function tests, skin rashes, nausea, diarrhea, and headaches.[17–19] Reversible thrombocytopenias have occurred, along with hepatic enzyme elevations and leukopenia.[7,8,18] Discoloration of the tongue occurred in one third of the patients associated with drinking green tea.[20] Overall, rates of adverse events were generally comparable to comparator antibiotics (e.g., vancomycin, penicillin, cephalosporins, and macrolides).[21]

In this study, we successfully treated patients with linezolid for a variety of infections, including bacteremia, bone and joint infections, soft tissue infections, kidney transplant infections, and endocarditis. The drug appears to be quite effective and safe, as seen in this group of patients.

MATERIALS AND METHODS

Patient Selection

Nineteen patients were enrolled in a Compassionate Use Study Program at two community hospitals in the El Paso area over a 1-year period. Case number 6a and 6b were the same patient and were included twice in the database as he presented on two different occasions with different site infections separated by a more than 1-year period (Table 1). The microbiology department evaluated all microbiologic samples, and all the patients enrolled were evaluated by the infectious disease consultation service. Patients enrolled in the study had to have evidence of actual site infection (culture from a normally sterile site if its source was blood, peritoneal space) with a resistant Gram-positive pathogen

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Table 1. Clinical Features and

Pt	Age	Sex	Underlying illness	Other ABT prior to linezolid	Culture site
1	80	M	Atrial fibrillation	V	rt. hip wound
2	71	F	DM, HTN, cholecystitis	M, T, MTDZ, C, CE, G	blood, bile
3	73	F	COPD, stroke, seizure	N, V	blood
4	39	F	DM, obesity	CZ, V	abd. wound
5	70	F	HTN, asthma, prophyria	CTZ, CLTH, V, LE, CFZ	trac.asp lung
6a	26	M	Wegener's disease, kidney transplant	T/S, C	Jp drain, abd. abcess
6b	26	M	Wegener's disease, kidney transplant	V, G	aortic valve
7	69	F	Obesity, DM	V	back wound
8	68	M	Swall dys, C.A., asp pneu, uti	U, P, V, CLND, G	trac.asp/blood
9	71	M	dis. Noca, Crohns disease	C, MTDZ, RO, U, G, V	peritoneal fluid
10	73	M	Pneumonia, CAD	CGGT	r/p fluid, abd. wound
11	72	F	CHF, Pulmo fibrosis, OBS, colitis	IMI, C, V, DXY, MTDZ	peritoneal fluid
12	76	F	Pneumonia	CLTH, CTZ	urine
13	69	F	DM, chronic renal failure	V, TO, CLEO	liver abcess/blood
14	37	F	Rheumatoid arthritis, uti, collagen	N, C	rt. hip wound
15	63	M	DM, stroke	V, CLF	rt. great toe
16	77	F	DM, HTN	V	rt. hip
17	77	F	Sepsis	V, LE, AMPH	urine
18	37	F	Lupus, renal failure	V, AMPH	cervical vertebrae
19	87	F	Multiple decubitis ulcers, RA, central line	V	blood

V, vancomycin; M, mefoxin; T, ticarcillin clauvunate; C, floxacin; CE, cefperazone; G, gentamycin; N, nafcillin; CZ, ciloxan GTTS; IMI, imipenem; DXY, doxycycline; CLEO, clindamycin; CLF, cefotaxine; AMPH, amphotericin; T/S, pulmonary disease; DM, diabetes mellitus; HTN, hypertension; C.A., cancer; asp pneu, aspiration pneumonia; uti, urinary organic brain syndrome; RA, rheumatoid arthritis; JP, Jackson-Pratt; rt., right; abd., abdominal; trac. asp, tracheal aspirate; *Enterococcus*; Coag(−)staph, coagulase-negative *Staphylococcus*.

(methicillin-resistant Staphylococcus aureus [MRSA], MRSE, vancomycin-resistant *Enterococcus* (VRE), multi-drug-resistant *S. pneumoniae*). Patients were enrolled based on their inability to tolerate available antibiotics such as severe drug reactions (e.g., to vancomycin), unresponsiveness to appropriate antibiotics such as persistence of bacteremia, progression of symptoms, surgical drainage, or by the severity of their illness. True bacteremia was defined as a positive blood culture obtained from two different sites 24 to 48 hours prior to enrollment in the study. All organisms were considered susceptible to linezolid by disk diffusion (>21 mm) as done by Pharmacia-Upjohn centers. Patients enrolled in the study also had to be approved and monitored by the Pharmacia-Upjohn monitor and had to be 18 years or older. Appropriate monitoring of liver function tests, complete blood counts, electrocardiograms, blood, site of infection cultures, and pharmacokinetic and pharmacodynamic parameters were obtained per protocol. Linezolid was given at 600 mg every 12 hours, intravenously or orally, based on the severity of the patient's illness. Gram-negative coverage was obtained by the use of aminoglycosides. Clinical cure was defined as no residual evidence of the original clinical symptoms. This was determined at two times, 7 to 10 days and 15 to 30 days after completion of therapy. Microbiologic cure was defined as clearance of the original infecting organism from the site at the end of treatment, as indicated by repeated negative cultures. The Pharmacia-Upjohn monitor reviewed patient information collected to ensure inclusion of appropriate data. Indeterminate was defined as when the patient died before completion of the study or before short-term or long-term follow-up. An appropriate informed consent was obtained from each patient as per the Hospital Institution Review Board Committee. Follow-up of all patients was done upon completion of antimicrobial treatment and post discharge.

Demographic Data

Organism	Clinical features	Co-organism	L.O.T	Outcome
MRSE	Wound dehis, red, drainage	none	58d	cure
VREF	s/p chole, JP drain	*Pseudomonas*	42d	cure
MRSA	weak, fever, mult.skin ulcers	*Serratia marcesens*	14d	cure
MRSE	Wound dehis, red, drainage	*E. Faecalis* (stool)	30d	cure
VREF	unres, infilt, pressors, DM	*C. parapsilosis*	14d	m-b failure
MRSA	low-grade temp, drainage	VRE (stool)	30d	cure
MRSA	fever	none	42d	failure
MRSA	serious drainage	none	14d	cure
VREF	unres, infilt, pressors	none	5d	failure
MRSA	rigid abd., drainage	none	14d	cure
VREF	persistant fever	none	14d	cure
VREF	rigidabd, drainage, P, tend, edema	none	7d	m-b failure
VREF	respiratory failure, pancytopenia	*E. faecalis* (stool)	14d	cure
VREF	fevers, WBCs, persis, jaundice	none	20d	cure
MRSA	hx of vanco allergy	VRE (stool)	28d	cure
MRSA	allergic rash to vanco day 8	*Enterococcus* (stool)	28d	cure
Coag(−) staph	allergic rash to vanco	*Enterococcus* (stool)	28d	cure
VREF	fevers, WBC, WBC in urine	none	12d	cure
Coag(−) staph	fever, pain in neck, failed 8 courses of vanc	none	12d	cure
MRSA	none	14d	cure	

cefzolin; CTZ, ceftriaxone; CLTH, azithromycin; U, ampicillin/sulbactam; P, piperacillin; CLND, clindamycin; CGTT, trimethoprim sulfa methaxole; LE, levofloxacin; CFZ, ceftazidine; MTDZ, metronidazole; COPD, chronic obstructive tract infection; dis Noca, disseminated nocardi; CAD, coronary artery disease; CHF, congestive heart failure; OBS, MRSA, methicillin-resistant *Staphylococcus aureus*; MRSE, methicillin-resistant uti, epidermidis; VREF, vancomycin-resistant

RESULTS

There were nineteen patients enrolled: thirteen females and six males (Table 1). The average age was 65 years (range 26 to 87 years). The average length of treatment with linezolid was 23 days (range 5 to 58 days). The average length of hospital stay was 38 days. The sites from where the pathogens were cultured included the bones and joints (six patients, 32%), gastrointestinal system (seven patients, 37%), genitourinary system (two patients, 11%), blood (five patients, 26%, two with MRSA and three with VRE), and aortic valve (one patient, 5%). Organisms isolated included MRSA (eight patients, 42%), MRSE (two patients, 11%), vancomycin-resistant *Enterococcus faecium* (VREF) (8 patients, 42%), and coagulase-negative *Staphylococcus* (two patients, 11%) (Table 2). Co-infecting organisms included *Enterococcus* species (six patients, 32%), *Pseudomonas* species (one patient, 5%), *Serratia marcescens* (one patient, 5%), and *Candida paropsilosis* (one patient, 5%). Evaluation of laboratory values included an average of white blood cells of 13,000 cells/mL, platelets of 282,000, hemoglobin of 9.9 mg/dL, alanine aminotransferase of 40, and aspartate aminotransferase of 41. Other antibiotics used in therapeutic regimens for these patients prior to the start of linezolid included vancomycin (12 patients), cephalosporin (eight patients), penicillin (five patients), aminoglycosides (six patients), quinolones (seven patients), amphotericin or fluconazole (seven patients), metronidazole (three patients), and trimethoprim-sulfamethoxazole (one patient). Seventy-nine percent (15 patients) of patients treated achieved microbiologic and clinical cure. Mortality rate was fifteen percent (three patients), although none of the deaths were related to the drug (Table 1). Only one (5%) patient developed a rash, two (11%) had mildly elevated liver function tests, and two (11%) patients had mild bone marrow suppression as indicated by new-onset anemia, leukopenia, and thrombocytopenia. No serious adverse events were noted.

CASE REPORTS

Case 1

This was a 71-year-old female with a history of diabetes mellitus who presented with fever and chills following the placement of a biliary stent for biliary tract obstruction. On examination, she appeared toxic but was hemodynamically stable. Vital signs showed a temperature of 103.2°F, pulse of 108 beats per minute, and blood pressure of 138/78 mm Hg. The physical exam was unremarkable except for tenderness in the right upper quadrant. Initial cultures from the Jackson Pratt biliary stent grew *Escherichia coli* sensitive to ticarcillin. Ticarcillin-clavulanate and metronidazole was administered. She continued to have a persistent fever with an elevated white blood cell count of 23,000 cells/mL; repeat blood cultures and biliary stent cultures were obtained. These cultures grew vancomycin-resistant *E. faecium* from both the blood cultures and the biliary stent fluid. She was started on linezolid (600 mg IV every 12 hours for 6 weeks), which was administered with complete resolution of the fever, leukocytosis, and bacteremia. Follow-up six months later did not reveal any evidence for relapse of the infection.

Case 2

This was an 87-year-old female with past history of dementia, severe debilitating rheumatoid arthritis, and exfoliative dermatitis who was admitted with fever and chills. On examination, she was noted to have a temperature of 102°F and blood pressure of 90/70 mm Hg. Significant physical findings included severe exfoliative dermatitis and cachexia. Three sets of blood cultures from the central line grew MRSA. The transthoracic echocardiogram was negative. Multiple superficial abrasions from her skin that were cultured also grew MRSA. Vancomycin was started, but the patient developed a generalized skin reaction to the drug and therefore was started on intravenous linezolid. She received 2 weeks of the drug with complete resolution of the fever, bacteremia, and leukocytosis. Follow-up after 6 weeks revealed no evidence of residual bacteremia or leukocytosis.

DISCUSSION

During the past decade, the emergence of resistance in Gram-positive cocci such as *Staphylococcus aureus, S. epidermides, Streptococcus pneumoniae, Enterococcus faecium,* and *E. faecalis* have created significant problems for the therapy of infections caused by these pathogens. A new class of antimicrobial agents, called oxazolidinones, has been recently developed, and linezolid is the first member of this new class. Oxazolidinones, including linezolid, have significant in vitro activity against many resistant Gram-positive pathogens.

Despite its bacteriostatic activity, linezolid appears to be able to cause significant bacterial cell death and/or bacterial inhibition. This drug appears to achieve significantly high MICs, enabling it to eradicate most Gram-positive infections. It does, however, have bacteriocidal activity against *Streptococcus,* making it a useful drug against infections caused by this organism.

We report our clinical experience in a community hospital setting with linezolid, the first member of this new class of antimicrobial agents. All patients mentioned in this study were part of the compassionate trial for this drug. The obvious limitation of this study is the fact that there is no control or comparative group and therefore one can not state definitively that the outcomes in these patients were due to linezolid. However, reasonable conclusions can certainly be drawn from this data. The clinical profiles of the patients treated included debilitated patients, immunosuppressed patients, patients with diabetes mellitus, patients on prednisone, and patients who had undergone multiple surgical procedures. All of these patients had undergone prolonged hospital stays or repeated hospitalizations, and had some form of intravascular access. All of these patients met strict definitions for actual site infections as outlined in the Materials and Method section. In fact, all of these patients had to be cleared by the Pharmacia-Upjohn monitor before enrollment into the study and therefore it is unlikely that any of these infections were colonizations. This is the largest study of resistant Gram-positive pathogens treated with linezolid in a community setting (Table 1). In fact, it is the only study that covers a wide variety of pathogens. The study published by Chien et al.[16] looked at the efficacy of linezolid with VRE infections alone and not other Gram-positive infections.

In this study, we report the first case of prosthetic valve endocarditis treated with linezolid (case 6b), and also report several other sterile site infections, such as biliary tree infection (case 2) and osteomyelitis (case 14). None of these patients had other drugs administered for Gram-positive coverage. All

Table 2. Coinfecting Organisms

Pathogens isolated	Percentages
1) Methicillin-resistant *Staphylococcus aureus*	42%
2) Methicillin-resistant *Staphylococcus epidermidis*	11%
3) Vancomycin-resistant *Enterococcus faecium*	42%
4) Coagulase-negative *Staphylocooccus aureus*	11%

antibiotics administered were given before the initiation of linezolid.

The adverse events in these patients included mild drug rash in one patient (5%), hypotension in one patient (5%), elevated liver function tests in two patients (11%), and bone marrow suppression in two patients (11%). Serious adverse events have included rashes, liver abnormalities, anemia, leukopenia, hypertension, hypotension, elevated amylase, serum sickness, and central nervous system toxic effects.[17]

The mortality rate in this study appeared to be low, especially when the treated infections varied in their severity and types of infecting organisms. Despite these limitations, it can be noted that none of these patients would have survived if it were not for the antimicrobial therapy and possibly other additional maneuvers such as removal of central lines and surgical debridement. Previous reports, published abstracts, and this study attest to the fact that linezolid appears to be a useful antimicrobial agent when used in the right setting along with appropriate surgical interventions (when needed). A randomized, double-blind, control study would be useful to definitively document its place in the treatment of Gram-positive infections.

REFERENCES

1. Antony SJ, Bitter KM, Moreland T, et al. Methicillin-resistant *Staphylococcus aureus* infection in a renal allograft recipient treated successfully with a novel new antimibcrobial agent (linezolid): new treatment options for infections due to resistant organisms. *Clin Infect Dis.* 1999;29:1341–1342.
2. Slee AM, Wuonola MA, McRipley RJ, et al. Oxazolidinones, a new class of synthetic antibacterial agents: in vitro and in vivo activities of DuP105 and DuP721. *Antimicrob Agents Chemother.* 1987;31:1791–1797.
3. Daly JS, Elipoulos GM, Reiszner E, et al. Activity and mechanism of action of DuP105 and DuP721: new oxazolidinone compounds. *J Antimicrob Chemother.* 1988;21:721–730.
4. Barry AL. In vitro evaluation of DuP105 and DuP721: two new oxazolidinone antimicrobial agents. *Antimicrob Agents Chemother.* 1988;32:150–152.
5. Neu HC, Novelli A, Saha G, et al. In vitro activities of two new oxazolidinone antimicrobial agents, DuP105 and DuP721. *Antimicrob Agents Chemother.* 1988;32:580–583.
6. Zajac I, Lam GW, Hoffman HE, et al. Pharmacokinetics of DuP721, a new synthetic oxazolidinone antibacterial. In: Program and abstracts of the 27th Interscience Conference of Antimicrobial Agents and Chemotherapy; 1987; New York, Abstract 247.
7. Jones RN, Johnson DM, Erwin ME. In vitro antimicrobial activities and spectra of U-100592 and U-100766, two novel fluorinated oxazolidinones. *Antimicrob Agents Chemother.* 1966;40:720–726.
8. Eliopoulos GM, Wennersten CB, Gold HS, et al. In vitro activities of new oxazolidinone antimicrobial agents against enterococci. *Antimicrob Agents Chemother.* 1996; 40:1745–1747.
9. Katz GW, Seo SM. In vitro activities of oxazolidinone compounds U-100592 and U-100766 against *Staphylococcus aureus* and *Staphylococcus epidermidis. Antimicrob Agents Chemother.* 1996;40:799–801.
10. Zurenko GE, Yagi BH, Schadaadt RD, et al. In vitro activities of U-100592 and U-100766, novel oxazolidinone antibacterial agents. *Antimicrob Agents Chemother.* 1996;40:839–845.
11. Bostic GD, Perri MB, Thal LA, et al. Comparative in vitro and bactericidal activity of oxazolidinone antibiotics against multidrug-resistant enterococci. *Diagan Microbiol Infect Dis.* 1998;30:109–112.
12. Patel R, Rouse MS, Piper KE, et al. In vitro activity of linezolid against vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus* and penicillin-resistant *Streptococcus pneumoniae. Diagan Microbial Infect Dis.* 1999;34:119–122.
13. Batts DH. Linezolid clinical development program: end of phase 2 results [Abstract no. XX]. In: Abstracts of the 2nd European Congress on Chemotherapy (Hamburg), 1998.
14. Stalker DJ, Wajszczuk CP, Batts DH. Linezolid saftey, tolerance in pharmacokinetics after intravenous dosing twice daily for 7.5 days [Abstract]. In: Proceedings of the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy, 28 September-1 October 1997, Toronto, Canada.
15. Stalker DJ, Wajszczuk CP, Batts DH. Linezolid safety, tolerance, and pharmacokinetics following oral drug dosing twice daily for 14.5 days. In: Program and abstracts of the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy (abstract A115). Washington, DC: American Society for Microbiology, 1997.
16. Chien JW, Kucia ML, Salata RA. Use of linezolid, an oxazolidinone, in the treatment of multidrug-resistant gram-positive bacterial infections. *Clin Infect Dis.* 2000; 30:146–151.
17. Birmingham MC, Zimmer GS, Hafkin B, et al. Outcomes with linezolid from an ongoing compassionate use trial of patients with significant, resistant, gram positive infections. Poster presentation at the International Conference on Antimicrobial Agents and Chemotherapy, San Francisco, September 1999.