Successful Treatment of Disseminated *Mycobacterium chelonae* Infection with Linezolid

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We describe a 57-year-old man with steroid-dependent myasthenia gravis and progressive ulcerating leg nodules due to clarithromycin-resistant *Mycobacterium chelonae.* The patient was successfully treated with linezolid.

Linezolid is an oxazolidinone available as an oral or iv antibiotic that has activity against most species of gram-positive bacteria [1], including the clinically significant rapidly growing mycobacteria [2]. Wallace et al. [2] recently reported that 94% of 50 isolates of *Mycobacterium chelonae* were inhibited by linezolid at MICs of ⩽16 μg/mL, with a modal MIC of 8 μg/mL. This included strains that are resistant to clarithromycin. The authors noted that linezolid was a possible choice as a companion treatment drug for infection with these isolates. We report the first case of the use of linezolid for treatment of *M. chelonae* in an isolate that was resistant to clarithromycin.

The patient was a 57-year-old man with a 30-year history of corticosteroid-dependent myasthenia gravis and a 1-year history of worsening right–lower leg ulcerating nodules. He could recall no antecedent trauma. Amoxicillin-clavulanate and ciprofloxacin had been administered for weeks without improvement. Examination of a biopsy specimen of a nodule revealed necrotizing granulomatous inflammation with microabscesses. Culture yielded *M. chelonae* with an MIC of clarithromycin of ⩽0.25 μg/mL. Clarithromycin (500 mg b.i.d.) was administered, and during the initial 2–3 months, the nodules regressed. Cultures of wound specimens were positive 4 months into therapy, however, and susceptibility testing revealed resistance to clarithromycin (MIC, >8 μg/mL). By 6 months into therapy, the nodules were worsening, and imipenem and azithromycin were administered. As the nodules continued to worsen, tobramycin was added to the treatment regimen. Twelve months into therapy, antimicrobial agents were discontinued and the patient was referred for a second opinion and consideration of amputation.

On examination, the patient was cachectic, wheelchair bound, and extremely weak. There were innumerable violaceus, ulcerating nodular lesions that extended circumferentially from the right distal thigh downward to the dorsum of the foot. The nodules were limited to the right lower extremity. Peripheral pulses were intact. MRI with gadolinium enhancement revealed extensive inflammation and subcutaneous abscesses, but there was no fascial invasion or bony involvement.

He underwent extensive surgical debridement of the right lower extremity, a nearly degloving-type procedure from the knee down. The saphenous vein had to be excised at the level of the femoral canal because of invasion and intraluminal "cheesy" material. He underwent split-thickness skin grafting. Clarithromycin and tobramycin were administered postoperatively, but they were discontinued within 2 weeks because of both gastrointestinal (GI) and vestibular toxicity/intolerance. All operative sites healed, and after 6 weeks of treatment with clarithromycin and tobramycin, he was transferred to an extended care facility. During the course of the hospitalization, pyridostigmine bromide was administered for his myasthenia gravis, and steroids were tapered and discontinued.

By 2 months after the patient's discharge, innumerable nodules had recurred over the calf and tibia, and amputation was entertained. The isolate was submitted to the Mycobacteria/Nocardia Laboratory at the University of Texas Health Center (Tyler), and it was identified as *M. chelonae* using PCR restriction analysis [3]. By means of broth microdilution susceptibility testing [4, 5], the isolate was determined to be resistant to clarithromycin (MIC, 64 μg/mL), ciprofloxacin (MIC, 4 μg/mL), doxycycline (MIC, >128 μg/mL), and sulfamethoxazole (MIC, >64 μg/mL). The isolate had an MIC of linezolid of 4 μg/mL, and it was susceptible to amikacin (MIC, 16 μg/mL) and tobramycin (MIC, 2 μg/mL).

Under a compassionate-use protocol of Pharmacia & Upjohn, iv linezolid (600 mg b.i.d.) was administered for 90 days, with complete resolution of all nodular lesions. (Linezolid was given intravenously rather than orally because of complex GI problems that included peptic ulcer disease). At follow-up 5 months and 12 months after the cessation of linezolid treat-

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ment, all the prior lesions were healed and there was no sign of relapse.

M. chelonae causes a variety of chronic soft-tissue and bone infections, but most commonly, it produces a disseminated cutaneous infection with multiple painful draining nodular skin lesions, as in this case [6, 7]. Previous corticosteroid use has been noted as the major risk factor [6].

Drug treatment of *M. chelonae* has been problematic because of the paucity of effective oral antimicrobial agents [6]. Until the advent of linezolid, clarithromycin, azithromycin, and related macrolides were the only drug group (class) available to use as oral drugs with activity against all untreated isolates of *M. chelonae.* Fewer than 25% of isolates are susceptible to such drugs as doxycycline, minocycline, sulfonamides, and ciprofloxacin [5, 6]. Clarithromycin is considered the drug of choice for treatment of *M. chelonae* disease [8]; however, previous studies and treatment failures have emphasized the risk of developing mutational resistance when using clarithromycin as monotherapy for disseminated cutaneous disease [9, 10]. This case illustrates the excellent potential for linezolid in the treatment of *M. chelonae* infection. The toxicity of long-term use (i.e., 3–6 months) of linezolid is unknown, however, and in 2001, reversible myelosuppression was added to the warning section of the prescribing information. This will require monitoring with complete blood counts with any long-term therapy. Linezolid is also relatively expensive when compared with other oral agents, including clarithromycin. With this in mind, we suggest the initial combination of linezolid and clarithromycin for disseminated cutaneous disease due to *M. chelonae* for the first 4–8 weeks, as tolerated, followed by continuation of clarithromycin alone to complete 6 months of therapy [8]. Additional information about the clinical efficacy and potential toxicities of long-term therapy of *M. chelonae* with linezolid is needed.

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