Treatment of Tularemia with Fluoroquinolones: Two Cases and Review

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Streptomycin, gentamicin, and tetracycline are currently considered the antimicrobials of choice for the treatment of tularemia. Preliminary data suggest that quinolones may be effective alternative agents; however, clinical experience is limited, and their role in treating severe disease is uncertain. We recently treated two acutely ill immunocompromised patients who had presumed “atypical” pneumonia with levofloxacin. Both patients had an excellent clinical response and were diagnosed with tularemia only when blood cultures subsequently yielded Francisella tularensis. Neither patient relapsed during 12 months of follow-up. Including our two cases, a total of 10 cases of tularemia treated with quinolones have been reported. In all 10 cases, a favorable clinical response was documented, and no relapses occurred. We conclude that the quinolones appear promising for the treatment of even severe tularemia, and they should be considered efficacious alternative agents for patients who do not require parenteral therapy or are intolerant of more standard treatment regimens.

Tularemia is an uncommonly diagnosed infection in the United States. Current treatment recommendations for tularemia include aminoglycosides (streptomycin or gentamicin) and tetracyclines [1, 2]. Cases of tularemia also have been treated with other agents including chloramphenicol, imipenem, and quinolones [1, 2]. The quinolones, in particular, are a potentially attractive treatment option because they are generally well tolerated, achieve adequate blood levels after oral administration, and have excellent intracellular penetration. In addition, although in vitro susceptibility testing for Francisella tularensis is not well standardized, MICs for many clinical isolates can be achieved with orally administered quinolone regimens [3, 4]. The quinolones also appeared to be equivalent to doxycycline in an animal model of tularemia [5]. Besides, several cases documenting the successful treatment of tularemia with quinolones have been reported [2–4, 6].

We describe two immunocompromised patients (one receiving chronic immunosuppressive therapy after liver transplantation and one with advanced HIV infection) who both developed bacteremic typhoidal tularemia and were treated successfully with levofloxacin. In addition, we review the English-language literature on the treatment of tularemia with quinolones.

Literature Review

A MEDLINE search of the English-language literature (1966–1998) for cases of tularemia treated with a quinolone was done. In addition, references of these articles were reviewed for additional potential cases.

Case Reports

Case 1. A 50-year-old man was admitted to the hospital for evaluation of fever, chills, and myalgias of 2 days’ duration. He had received an orthotopic liver transplant 3 years earlier because of hepatitis C and alcohol-related cirrhosis. Immunosuppressive medications at admission included 10 mg of prednisone and 75 mg of azathioprine daily. Other medical conditions included insulin-dependent diabetes mellitus, end-stage renal disease (for which he was being treated with hemodialysis), and hypertension. He denied recent travel, animal exposure, tick bite, or ill contacts.

He appeared ill and had an oral temperature of 39.5°C, blood pressure of 180/100 mm/Hg, and heart rate of 120. Physical examination revealed no new abnormalities, and specifically, no lymphadenopathy, skin lesions, hepatosplenomegaly, or pharyngeal lesions were present. Results of routine hematologic and serum chemistry tests were unchanged from baseline values. A chest radiograph obtained at admission was unremarkable. Blood and urine specimens for culture were obtained, intravenous fluids were administered, and the patient was observed during a period without antibiotic therapy; an initial diagnosis of viral syndrome was made.

Over the next 72 hours, he continued to have high-grade fevers, and a repeated chest radiograph showed a new right middle lobe infiltrate. On hospital day 3, fiberoptic bronchoscopy with bronchoalveolar lavage was done, and therapy with intravenous levofloxacin (500 mg daily) was begun for presumed bacterial pneumonia. Within 48 hours of initiating levofloxacin treatment, he became afebrile and felt better. Stains and cultures of bronchoalveolar lavage fluid specimens for bacterial, viral, fungal, mycobacterial, and parasitic pathogens remained negative. The levofloxacin...
dosage was changed to 500 mg orally q.d. on hospital day 5, and he was discharged on hospital day 7 to complete a 14-day course of oral levofloxacin therapy for presumed community-acquired pneumonia.

Two days after discharge, tiny gram-negative coccobacilli that were subsequently identified as F. tularensis (biovar palearctica) by the Washington State Public Health Laboratories, Seattle (and later confirmed by the Division of Vector-Borne Diseases, Centers for Disease Control and Prevention, Fort Collins, CO), were growing on two sets of cultures of blood obtained at admission. The patient was contacted, and he was feeling well. The course of levofloxacin treatment was extended to 21 days. At a 12-month follow-up, the patient was doing well and was without evidence of relapse.

Case 2. A 33-year-old man with C3 AIDS and a CD4 cell count of 220/µL presented to a different hospital with the acute onset of fever, dry cough, headache, and myalgias. His history was remarkable for a remote episode of cryptosporidiosis, chronic active hepatitis C virus infection, and chronic alcohol abuse. Two weeks before admission, he had had extensive contact with numerous pets, including a dog, cat, rabbit, and hedgehog. He did not recall specifically having been bitten and denied tick exposure. His outpatient medications included zidovudine, lamivudine, nelfinavir, and finasteride.

He appeared acutely ill and had an oral temperature of 40.1°C, blood pressure of 138/76 mm/Hg, and heart rate of 100. Physical examination revealed mild pharyngeal erythema, mild generalized lymphadenopathy (unchanged from baseline), and decreased breath sounds at the right lung base. No hepatosplenomegaly or rash was noted. No significant changes in results of routine blood chemistry analyses or complete blood cell counts from baseline values were noted. A chest radiograph showed ill-defined bibasilar abnormalities. Blood (including that for mycobacterial cultures), urine, and sputum specimens for cultures were obtained, and therapy with intravenous levofloxacin (500 mg q.d.) was begun for presumed community-acquired pneumonia. He became afebrile, and his condition clinically improved within 48 hours; he was discharged on hospital day 7 to complete a 14-day course of oral levofloxacin therapy for presumed community-acquired pneumonia.

Approximately 3 weeks after discharge, small gram-negative rods that were subsequently confirmed to be F. tularensis (biovar palearctica) by the Centers for Disease Control and Prevention (Fort Collins, CO) were growing on mycobacterial cultures of blood obtained at admission. The patient was doing well, and no additional therapy for tularemia was given. He did not relapse during 12 months of follow-up.

Discussion

There are several interesting features about the two cases of tularemia presented here. Both of the patients were immunocompromised: one was receiving chronic immunosuppressive therapy following liver transplantation and one had advanced HIV infection. Both patients presented with a nonspecific febrile illness consistent with the typhoidal form of tularemia that was diagnosed only when cultures of blood obtained at initial evaluation subsequently yielded F. tularensis. Both patients had a rapid clinical response to treatment with levofloxacin. We are aware of only two other reported cases of tularemia in immunocompromised patients: a child with advanced HIV infection [7] and a child with chronic granulomatous disease [8]. In addition, even though isolation of Francisella from blood is extremely uncommon [9, 10], F. tularensis was isolated from blood specimens from three of these four immunocompromised patients. Although lymphohematogenous dissemination is thought to be common in patients with symptomatic tularemia, the underlying immunodeficiencies in these patients may have increased the probability of a positive blood culture.

Biochemical characterization separates the species of F. tularensis into three distinct biovars: tularensis, palearctica, and novicida [11]. F. tularensis biovar tularensis is the most prevalent biovar in North America and is considered more virulent than the other biovars [11]. All isolates from the three immunocompromised patients for whom a bacteriologic diagnosis of tularemia was established (our two cases and [7]) were definitively identified as the less virulent biovar palearctica. The underlying immunodeficiencies in these patients may have allowed the expression of disseminated disease with this less virulent biotype.

Review of the English-language literature (from 1966 to 1998) revealed a total of 10 cases (including the cases reported herein) of tularemia treated with a quinolone (table 1). The clinical manifestations of tularemia in these 10 patients included ulceroglandular tularemia (4 patients), oculoglandular tularemia (1), as well as the more severe pneumatic (3) and typhoidal (2) forms of the disease. A quinolone was used as primary therapy in eight cases and as secondary therapy (after relapse) in two. Regardless of whether a quinolone was used as primary or secondary therapy, clinical cure was documented in 100% of cases, with none of the 10 patients having relapses (duration of follow-up ranged from 2 to 12 months). By comparison, relapse rates associated with gentamicin and tetracycline have been estimated to be 6% and 12%, respectively [1]. Given the small number of cases of tularemia treated with quinolones, however, additional experience will be necessary to confirm this apparently low relapse rate.

Since no standardized method for determining antimicrobial susceptibilities of Francisella is currently available, no formal susceptibility testing was done on our patients’ isolates. Using an agar dilution method, however, Scheel et al. [4] found that ciprofloxacin MICs for all of 20 F. tularensis isolates tested could be readily achieved with oral adminis-
On the basis of the good oral bioavailability of the quinolones, oral regimens could potentially be used to treat tularemia. In our review, eight of 10 patients received a quinolone that was administered orally, and all were clinically cured (table 1). Both of the new patients described herein received 48 hours of parenteral therapy followed by a course of oral therapy. The time to defervescence in our two immunocompromised patients was similar to that previously reported for otherwise healthy patients with tularemia [3]. It should be noted, however, that quinolones are relatively contraindicated for pediatric patients and patients younger than 18 years of age, thereby limiting the utility of quinolones for treating tularemia in these patients.

Although clinical experience is limited, the results of in vitro susceptibility testing, experience with animal models, and excellent response of even severe bacteremic typhoidal tularemia in our two immunocompromised patients was similar to that previously reported for otherwise healthy patients with tularemia [3]. It should be noted, however, that quinolones are relatively contraindicated for pediatric patients and patients younger than 18 years of age, thereby limiting the utility of quinolones for treating tularemia in these patients.

Acknowledgments

The authors thank Dr. Martin Schriefer (Division of Vector-Borne Diseases, Centers for Disease Control and Prevention, Fort Collins, CO) and Mike McDowell (Washington State Public Health Laboratories, Seattle) for assisting with the identification of the blood isolates.

Table 1. Clinical characteristics of patients with tularemia who were treated with a quinolone.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (y)/sex</th>
<th>Form of disease</th>
<th>Method of diagnosis</th>
<th>Antimicrobial therapy (dosage)</th>
<th>Relapse</th>
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<tr>
<td>[2]</td>
<td>44/F</td>
<td>Ulceroglandular</td>
<td>Serology</td>
<td>Gm Cpf (750 mg b.i.d. for 28 d)</td>
<td>Yes; No</td>
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<tr>
<td>[3]</td>
<td>59/M</td>
<td>Pneumonic</td>
<td>Serology</td>
<td>Cpf (750 mg b.i.d. for 10 d)</td>
<td>No</td>
</tr>
<tr>
<td>[3]</td>
<td>53/M</td>
<td>Pneumonic</td>
<td>Serology</td>
<td>Cpf (750 mg b.i.d. for 10 d)</td>
<td>No</td>
</tr>
<tr>
<td>[3]</td>
<td>68/M</td>
<td>Pneumonic</td>
<td>Serology</td>
<td>Cpf (750 mg b.i.d. for 10 d)</td>
<td>No</td>
</tr>
<tr>
<td>[3]</td>
<td>41/F</td>
<td>Ulceroglandular</td>
<td>Serology</td>
<td>Nfx (400 mg b.i.d. for 10 d)</td>
<td>No</td>
</tr>
<tr>
<td>[4]</td>
<td>37/F</td>
<td>Ulceroglandular</td>
<td>Serology</td>
<td>Dox, Amox Cpf (750 mg b.i.d. for 14 d)</td>
<td>Yes; No</td>
</tr>
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<td>[6]</td>
<td>58/F</td>
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<td>Serology</td>
<td>Cpf (500 mg b.i.d. for 10 d)</td>
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<tr>
<td>[PR]</td>
<td>50/M</td>
<td>Typhoidal</td>
<td>Blood culture</td>
<td>Lvx (500 mg q.d. for 21 d)</td>
<td>No</td>
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<tr>
<td>[PR]</td>
<td>33/M</td>
<td>Typhoidal</td>
<td>Blood culture</td>
<td>Lvx (500 mg q.d. for 13 d)</td>
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</table>

NOTE. Amox = amoxicillin; Cpf = ciprofloxacin; Dox = doxycycline; Gm = gentamicin; Lvx = levofloxacin; Nfx = norfloxacin; PR = present report.

References