

# CASE REPORT

## Oral Doxycycline for Treatment of Neurosyphilis in Two Patients Infected with Human Immunodeficiency Virus

S. Lena Kang-Birken, Pharm.D., FCCP, Uldine Castel, M.D., and John G. Prichard, M.D.

The frequency of syphilis has been increasing during the past 5 years primarily among men who have sex with men, many of whom are infected with the human immunodeficiency virus (HIV). Data on treatment options other than intravenous or intramuscular penicillin for syphilis are very limited. We describe two HIV-infected patients with asymptomatic neurosyphilis who were successfully treated with oral doxycycline. The first patient was a 45-year-old Hispanic man with well-suppressed HIV RNA who had a positive Venereal Disease Research Laboratory (VDRL) titer of 1:128. His cerebral spinal fluid (CSF) revealed a positive VDRL titer of 1:16, and an elevated white blood cell count of 96 cells/mm<sup>3</sup> and protein level of 89 mg/dl. He received high-dose doxycycline 200 mg twice/day for 28 days. Two months later, his CSF VDRL titer, white blood cell count, and protein level decreased to 1:4, 5 cells/mm<sup>3</sup>, and 60 mg/dl, respectively. The second patient was a 37-year-old Caucasian man with complications from acquired immunodeficiency disease. A routine VDRL titer was found to be 1:64. Although the CSF VDRL was nonreactive, both his white blood cell count and protein level were elevated at 29 cells/mm<sup>3</sup> and 46 mg/dl, respectively. High-dose doxycycline 200 mg twice/day was prescribed for 28 days. Three months later, the patient's VDRL titer decreased to 1:2; his CSF white blood cell count decreased significantly to 1 cell/mm<sup>3</sup>, and his protein level was within normal limits. Clinicians should be aware that an extended course of high-dose, oral doxycycline may be an effective and safe alternative regimen to intravenous or intramuscular penicillin, without requiring hospitalization or home health care, for the treatment of neurosyphilis in HIV-infected patients. Prospective trials are needed to assess the long-term efficacy oral doxycycline for neurosyphilis.

**Key Words:** neurosyphilis, doxycycline, HIV, human immunodeficiency virus.

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In 2004, the incidence of syphilis increased to 2.7 cases/100,000 persons from 2.1 cases/100,000 persons in 2001.<sup>1</sup> The Centers for Disease Control and Prevention (CDC) estimated that approximately 64% of all syphilis cases in 2004 were in men who have sex with men.<sup>1–3</sup> This

From the Immunology Clinic, Ventura County Public Health, Ventura, California (all authors); and the Department of Pharmacy Practice, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, California (Dr. Kang-Birken).

For reprints, visit <http://www.atypon-link.com/PPI/loi/phco>. For questions or comments, contact S. Lena Kang-Birken, Pharm.D., FCCP, Department of Pharmacy Services, Cottage Health System, P.O. Box 689, Santa Barbara, CA 93103; e-mail: [lbirken@pacific.edu](mailto:lbirken@pacific.edu).

increase in incidence has been attributed to increased rates of human immunodeficiency virus (HIV) coinfection, high-risk sexual behavior, and use of drugs such as methamphetamines.<sup>3</sup>

Infection with HIV type 1 (HIV-1) alters the natural history and treatment outcome of *Treponema pallidum* infection (syphilis).<sup>4</sup> In HIV-infected persons, primary syphilis may present with multiple or atypical lesions that rapidly ulcerate, rather than a single painless nodule at the site of contact. Progression to secondary syphilis generally occurs 2–8 weeks after primary inoculation, reflecting ongoing replication and dissemination of *T. pallidum* in

the absence of an effective host immune response. The most common manifestations are macular or pustular skin lesions on the palms and soles, generalized lymphadenopathy, and constitutional symptoms including fever, malaise, anorexia, arthralgias, and headache. Such symptoms may persist from a few days to several weeks before resolving or evolving to latent or later stages. Late syphilis generally manifests as neurosyphilis and cardiovascular disease. Neurosyphilis occurs earlier among persons with HIV-1 infection; however, most patients remain free of symptoms. The CDC recently estimated the risk of symptomatic, early neurosyphilis as 1.5% among HIV-positive men who contract syphilis from other men.<sup>5</sup>

The standard treatment regimen for HIV-1-infected patients with neurosyphilis is intravenous aqueous crystalline penicillin G 18–24 million units/day, administered as 3–4 million units every 4 hours or by continuous infusion for 10–14 days.<sup>6</sup> An alternative regimen is procaine penicillin 2.4 million units once/day by intramuscular injection plus oral probenecid 500 mg 4 times/day for 10–14 days. In cases of penicillin allergy, limited data suggest that intravenous ceftriaxone 2 g/day for 10–14 days may be effective.<sup>7</sup> Although these treatment regimens have remained effective, there are disadvantages. Intravenous or intramuscular therapy requires hospitalization or home health care, which may not be feasible or desirable for some patients. Probenecid is often poorly tolerated, and the frequent dosing schedule may result in poor compliance. Thus, additional antibiotic regimens are needed that are both efficacious and can be delivered in a more convenient manner.

Although the CDC recommends oral doxycycline as alternative therapy for only primary and secondary syphilis,<sup>6</sup> the United Kingdom National Guideline recommends doxycycline as an alternative agent to treat neurosyphilis.<sup>8</sup> We describe two HIV-1-infected patients whose asymptomatic neurosyphilis responded well to oral doxycycline therapy.

## Case Reports

### Patient No. 1

A 45-year-old Hispanic man was referred to the immunology clinic for routine care of his HIV infection. He was diagnosed with HIV-1 infection 1 year earlier and was being treated with efavirenz 600 mg/day, tenofovir disoproxil

fumarate 300 mg/day, and emtricitabine 200 mg/day. He had not experienced any HIV-related opportunistic infections or malignancies. His other medical history was significant only for hepatitis B and depression. His risk factor for HIV-1 acquisition was sex with men.

At the clinic visit, the patient's CD4<sup>+</sup> T-cell count was 425 cells/mm<sup>3</sup> and HIV RNA was less than 48 copies/ml. His complete blood cell count and chemistry panel results were within normal limits, with the exception of a mildly elevated serum creatinine concentration of 1.2 mg/dl (normal range 0.6–1.2 mg/dl; estimated creatinine clearance 68 ml/min [normal > 50 ml/min]). Other routine laboratory tests revealed a reactive rapid plasma reagin (RPR). He also had a positive Venereal Disease Research Laboratory (VDRL) titer of 1:128, and the fluorescent treponemal antibody absorption (FTA-ABS) assay was reactive. The patient reported no complaints; he denied rash, joint pain, headache, or visual changes.

A lumbar puncture was performed, and the cerebral spinal fluid (CSF) examination showed an elevated protein level of 89 mg/dl (normal range 15–45 mg/dl) and white blood cell count of 96 cells/mm<sup>3</sup> (normal range 0–2 cells/mm<sup>3</sup>). The CSF VDRL titer was positive at 1:16.

Hospitalization and intravenous aqueous penicillin G for 10–14 days was recommended. However, the patient was reluctant to be hospitalized due to his fear of losing his part-time employment, the financial burden it would incur, and the possibility of deportation. Thus, with no other reasonable options, to provide affordable treatment as an outpatient, high-dose oral doxycycline 200 mg twice/day was prescribed for 28 days. The patient had weekly follow-up visits at the clinic. He initially reported mild gastric distress after the morning dose and was advised to take the morning dose after breakfast. He reported no other complaints and successfully completed the therapy.

One month later, the patient's repeat VDRL titer decreased to 1:64. A second lumbar puncture, performed 2 months after completion of therapy, showed a decreased CSF VDRL titer of 1:4. Both protein level and white blood cell count decreased significantly to 60 mg/dl and 5 cells/mm<sup>3</sup>, respectively. The patient remained asymptomatic.

### Patient No. 2

A 37-year-old Caucasian man was referred to

the immunology clinic after being hospitalized with *Pneumocystis jiroveci* pneumonia. He was found to be HIV positive with a CD4<sup>+</sup> T-cell count of 79 cells/mm<sup>3</sup> and an HIV RNA of greater than 750,000 copies/ml. He was treated with lopinavir 200 mg–ritonavir 50 mg twice/day and tenofovir disoproxil fumarate 300 mg–emtricitabine 200 mg once/day. He was also diagnosed with esophageal candidiasis and Kaposi's sarcoma. One month later, he developed cytomegalovirus colitis, anemia, and hypogonadism.

At the initial clinic visit, syphilis screening with VDRL was nonreactive. However, 9 months later, the patient's VDRL titer was positive at 1:64. The patient was asymptomatic. Analysis of his CSF revealed a slightly elevated white blood cell count (3 cells/mm<sup>3</sup>) and a protein level within normal limits (43 mg/dl); his CSF VDRL was nonreactive. His CD4<sup>+</sup> T-cell count was 267 cells/mm<sup>3</sup>, and his HIV viral load was nondetectable at less than 400 copies/ml. The patient was diagnosed with secondary syphilis (< 1 yr from conversion). As the patient did not have any evidence of neurosyphilis, he was treated with intramuscular benzathine penicillin 2.4 million units/week for 3 weeks, which was successful. His VDRL titer decreased by 4-fold to 1:16 at 2 months and to 1:1 at 5 months after treatment.

Exactly 1 year after the diagnosis of secondary syphilis, the patient's VDRL titer was positive again at 1:64, and his FTA-ABS assay was reactive. Although the CSF VDRL continued to be non-reactive, both his white blood cell count and protein level were elevated at 29 cells/mm<sup>3</sup> and 46 mg/dl, respectively, suggesting probable neurosyphilis.<sup>9</sup> The patient had no complaints, and denied rash, joint pain, headache, or any problems with visual acuity. He continued to receive the same antiretroviral therapy, having achieved viral suppression (HIV RNA < 400 copies/ml).

The patient refused hospitalization for intravenous penicillin therapy due to fear of losing his job, and the outpatient parenteral treatment was not an option, as the patient could not afford the copayment for home health care. Oral doxycycline 200 mg twice/day was prescribed for 28 days. The patient initially complained of some dizziness and abdominal pain, but they resolved spontaneously over the next few weeks. He also experienced mild photosensitivity but completed the course without any further complications.

Three months after the completion of therapy, the patient's VDRL titer was 1:2. His CSF VDRL

was still nonreactive, and his white blood cell count and protein level were within normal limits (1 cell/mm<sup>3</sup> and 43 mg/dl, respectively). Subsequent syphilis screening tests continued to be nonreactive 2 years later.

## Discussion

Asymptomatic neurosyphilis occurs in 8–40% of untreated HIV-1–infected patients.<sup>10, 11</sup> The diagnosis of asymptomatic neurosyphilis is made in patients who have no clinical manifestations but have one or more CSF abnormalities such as pleocytosis, an elevated protein level, a decreased glucose concentration, or a positive VDRL response. The diagnosis, however, can often be challenging in individuals with a mild level of CSF pleocytosis in the absence of reactive VDRL.<sup>9, 11</sup> Some investigators have recommended the following diagnostic criteria: lack of neurologic signs and symptoms, reactive syphilis serologic test result, and the presence of one or more abnormal findings during examination of CSF specimens (white blood cell count > 10 cells/mm<sup>3</sup> and/or protein > 50 mg/dl, without an alternative diagnosis; and/or a reactive CSF VDRL test result).<sup>10</sup>

Recommendations for the management of HIV-1–infected patients with syphilis are similar to the management of HIV-uninfected persons with syphilis. However, the treatment options have not been sufficiently evaluated in HIV-1–infected patients. The standard treatment regimen for neurosyphilis is intravenous aqueous crystalline penicillin G for 10–14 days.<sup>3</sup> An alternative regimen is intramuscular procaine penicillin once/day with oral probenecid 4 times/day for 10–14 days. In our two patients, we did not use either treatment regimen for several reasons. First, neither patient was willing to come to the clinic for daily intramuscular injections for up to 2 weeks. Second, compliance with 4-times/day dosing of probenecid could not be guaranteed for 2 weeks with the patients' inconsistent work schedules, which could jeopardize adherence to HIV therapy due to the increased pill burden and frequency of administration. Finally, potential drug interactions can occur between probenecid and some of the antiretroviral drugs such as tenofovir disoproxil fumarate and emtricitabine, which are both renally eliminated. Probenecid may compete for renal tubular secretion, thereby potentially increasing the concentrations of tenofovir disoproxil fumarate and emtricitabine. However, due to a lack of clinical data, we could not confidently manage the potential drug interactions.

The tetracycline group of antibiotics exhibit treponemicidal activity. The minimum inhibitory concentration and the minimum bactericidal concentrations of tetracycline using an in vitro tissue culture system were 0.2 mg/L and 0.5 mg/L, respectively.<sup>12</sup> Doxycycline, a long-acting derivative of tetracycline, demonstrates similar treponemicidal activity, but its longer half-life allows for less frequent dosing, and it is better tolerated.<sup>13</sup> Animal data demonstrated high CSF levels of doxycycline, which were 5 times the concentration of tetracycline in the brain due to its lipophilic property.<sup>14</sup> Based on these data, researchers investigated doxycycline concentrations in the CSF of five patients.<sup>15</sup> A high dose of oral doxycycline 200 mg twice/day was evaluated in patients with latent syphilis or neurosyphilis. The patients were instructed to take the drug with meals for 21 days. The mean doxycycline serum level was 5.8 µg/ml, and the mean CSF level was 1.3 µg/ml, which exceeded the typical minimum inhibitory concentration for *T. pallidum*. Penetration into CSF varied from 11–56%, with a mean of 26%. The patients remained compliant with the twice-daily dosing regimen and reported excellent tolerance. This small study demonstrated a potential advantage of high-dose doxycycline in the treatment of neurosyphilis. However, the investigators did not report whether the patients displayed any symptoms associated with neurosyphilis or their HIV status. The recommendation by the United Kingdom National Guidelines<sup>8</sup> on doxycycline as an alternative regimen for neurosyphilis was based on this study's findings.

The CDC treatment guideline considers a 4-fold decrease in nontreponemal titers (e.g., from 1:64 to 1:16) by 6–12 months of follow-up as an appropriate response regardless of the drug selection.<sup>6</sup> A slower serologic improvement has been described in HIV-infected patients after completion of treatment.<sup>16</sup> Our two patients completed the 28-day treatment with high-dose oral doxycycline without any complications. Both patients' CSF VDRL titers decreased by 4-fold as early as 2 months after completion of therapy, meeting the CDC's criteria for appropriate response. In addition, both patients tolerated the therapy well with minimal adverse effects.

## Conclusion

Our two HIV-1-infected patients with asymptomatic neurosyphilis were successfully treated

with oral doxycycline. Shortly after the completion of therapy, the patients' nontreponemal titers met the appropriate response criteria of a 4-fold decrease. Both patients tolerated the treatment well with minimal adverse effects. Clinicians should be aware that an extended course of high-dose, oral doxycycline may be an effective and safe alternative regimen to intravenous or intramuscular penicillin, without requiring hospitalization or home health care, for the treatment of neuro-syphilis in HIV-infected patients. Prospective trials are needed to assess the long-term efficacy of oral doxycycline for neurosyphilis.

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