A Pilot Study Evaluating Ceftriaxone and Penicillin G as Treatment Agents for Neurosyphilis in Human Immunodeficiency Virus–Infected Individuals

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To compare intravenous (iv) ceftriaxone and penicillin G as therapy for neurosyphilis, blood and CSF were collected before and 14–26 weeks after therapy from 30 subjects infected with human immunodeficiency virus (HIV)–1 who had (1) rapid plasma reagin (RPR) test titers >1 : 16, (2) reactive serum treponemal tests, and (3) either reactive CSF–Venereal Disease Research Laboratory (VDRL) tests or CSF abnormalities: (a) CSF WBC values ≥20/μL or (b) CSF protein values ≥50 mg/dL. At baseline, more ceftriaxone recipients had skin symptoms and signs (6 [43%] of 14 vs. 1 [6%] of 16; P = .03), and more penicillin recipients had a history of neurosyphilis (7 [44%] of 16 vs. 1 [7%] of 14; P = .04). There was no difference in the proportion of subjects in each group whose CSF measures improved. Significantly more ceftriaxone recipients had a decline in serum RPR titers (8 [80%] of 10 vs. 2 [13%] of 15; P = .003), even after controlling for baseline RPR titer, skin symptoms and signs, or prior neurosyphilis were controlled for. Differences in the 2 groups limit comparisons between them. However, iv ceftriaxone may be an alternative to penicillin for treatment of HIV-infected patients with neurosyphilis and concomitant early syphilis.

The diagnosis and treatment of neurosyphilis in persons infected with HIV type 1 are challenging. Neurosyphilis may be a more common complication of syphilis in those infected with HIV-1 [1, 2] and may be more difficult to diagnose because, similar to neurosyphilis, HIV infection itself may cause CSF pleocytosis or an elevated CSF protein concentration [3]. In addition, retrospective studies suggest that for 23%–60% of HIV-infected patients, currently recommended neurosyphilis therapy with penicillin G fails [4–6].

Ceftriaxone is a potential alternative to penicillin G for treatment of neurosyphilis. It is active against Treponema pallidum in animal models [7, 8], penetrates CSF well, and has a long half-life that enables it to be given once daily [9]. Successful treatment of patients who have asymptomatic or symptomatic neurosyphilis, with use of ceftriaxone (1 g im daily for 14 days), has been reported [10–12]. However, a retrospective study of im ceftriaxone for treatment of HIV-infected patients with neurosyphilis, latent syphilis, and presumed latent syphilis (many of whom were eventually found to have neurosyphilis) showed a 23% failure rate, based on serological criteria [13]. The goal of this study was to compare the responses of HIV-1–infected patients to neurosyphilis therapy with iv ceftriaxone and iv aqueous penicillin G.

Methods

Study population. HIV-1–infected patients with syphilis were eligible for enrollment in the study. Criteria for enrollment included (1) a serum rapid plasma reagin (RPR) test titer >1 : 16, confirmed with either a reactive serum microhemagglutination–T. pallidum (MHA-TP) test or a fluorescent treponemal antibody–absorbed (FTA-ABS) test, and (2) CSF abnormalities, including either (a) a reactive CSF–Venereal Disease Research Laboratory (VDRL) test, or (b) a CSF WBC count ≥20/μL or a CSF protein concentration ≥50 mg/dL. Subjects were excluded from the study if they had
been treated for syphilis within 1 year before enrollment, if they had received antibiotic therapy that would be active against *T. pallidum* within 45 days before enrollment, or if they had another documented CNS infection (other than with HIV-1) that could cause CSF abnormalities. Baseline CSF samples were collected within 7 days of initiation of therapy.

**Study protocol.** Subjects were enrolled from October 1991 through April 1994. They were randomized to receive 10 days of therapy with ceftriaxone (2.0 g iv once daily) or penicillin G (4 MU iv every 4 h). Lumbar punctures were repeated at week 14 and at weeks 26 and 52 for patients who had a reactive CSF-VDRL test, a CSF WBC count >5/μL, a CSF protein concentration >45 mg/dL, or a reactive serum RPR test at week 14. Peripheral blood CD4 lymphocyte counts were determined at baseline and at weeks 26 and 52. Serum RPR and CSF-VDRL samples from each patient were batched and run in parallel in a single assay.

**Serum and CSF measures.** Syphilis serologies included serum VDRL, RPR, MHA-TP or FTA-ABS, and CSF-VDRL tests and were performed according to established methods. CSF WBC counts and protein concentrations were determined according to standard laboratory methods at each site.

**Study design and statistical analysis.** Improvement in CSF measures and in serum RPR titers was defined categorically as (1) a 4-fold decline in initially reactive CSF-VDRL or serum RPR titer or a reversion to nonreactivity or (2) a 10% decline from an initial CSF WBC count ≥20/μL or in an initial CSF protein concentration ≥50 mg/dL. Differences in categorical variables were compared by Fisher’s exact test. The changes in CSF measures and in serum RPR titers as continuous variables were compared by the Mann-Whitney rank sum test. Associations between treatment response and clinical parameters were described by logistic regression for categorical variables and by linear regression for continuous variables. Although the sample size was small for the analyses of influence of initial RPR titer on treatment response, logistic regression analyses were used because the results of univariate analyses were consistent with the results from Fisher’s exact tests. All *P* values were two-tailed.

**Results**

**Baseline characteristics of all 36 subjects.** Thirty-six subjects were enrolled; 18 received ceftriaxone and 18 received penicillin. Most subjects were men (n = 33); 23 were black, 9 were white, and 4 were Hispanic. The median peripheral blood CD4 T cell count was 326/μL (range, 40–790/μL; n = 34), and the median age was 34 years (range, 24–59 years). There was no significant difference between the 2 treatment groups in race or ethnicity, baseline CD4 T cell counts, or ages.

A previous episode of syphilis or neurosyphilis was defined as an episode with a recorded date of onset that was >3 months before enrollment in the study. Fourteen subjects (78%) in each treatment group had a history of syphilis, with the median interval between prior diagnosis and enrollment of 45.5 months (range, 4–588 months). Eleven subjects had a history of neurosyphilis, with the median interval between prior diagnosis and enrollment of 20 months (range, 4–39 months). Prior neurosyphilis was more common in the penicillin-treated subjects (*P* = .06).

There was no difference between the treatment groups in the number of patients with neurological symptoms or signs, but more ceftriaxone recipients had skin symptoms or signs (8 [44%] of 18 vs. 2 [11%] of 18; *P* = .06). Baseline values for CSF-VDRL tests, CSF WBC counts, CSF protein concentrations, and serum RPR titers were similar in the 2 groups.

**Deviations from the protocol.** No baseline CSF abnormalities were noted in 1 subject in each treatment group. Two subjects in the ceftriaxone group had been treated with antibiotics active against *T. pallidum* <45 days before study enrollment. The subject in the penicillin group who did not have baseline CSF abnormalities and the 2 subjects in the ceftriaxone group who received antibiotics within 45 days before enrollment had follow-up data obtained and were included in the analysis to maintain an intent-to-treat approach. The patient without baseline CSF abnormalities in the ceftriaxone group did not have follow-up data obtained and thus could not be included in the follow-up analysis.

**Follow-up.** All but 3 ceftriaxone recipients received treatment for 10 days; 1 subject missed 1 dose of ceftriaxone and received 10 doses of ceftriaxone over 11 days, 1 was treated for 9 days, and 1 was treated for 11 days. Similarly, all but 3 penicillin recipients received therapy for 10 days; 1 subject experienced an anaphylactic reaction on the first day of treatment, was withdrawn from the study, and had no follow-up data obtained, and 2 subjects received treatment for 11 days.

We assessed improvement in CSF-VDRL test findings, CSF WBC counts, CSF protein concentrations, and serum RPR titers at follow-up in comparison with baseline values. For 2 subjects in each treatment group, serum from the baseline visit was not available for the batched assessment, and the results obtained at 2 weeks were used. The follow-up visit for this analysis was either the week-26 visit or the week-14 visit, if a week-26 visit was not made; as noted above, a lumbar puncture after the week-14 visit was not required for all subjects.

Baseline characteristics of the 30 subjects who were followed up are shown in table 1. Baseline serum RPR titers were higher in the ceftriaxone group, but this difference was not statistically significant. Significantly more penicillin recipients had a history of neurosyphilis; among these subjects, the median interval from prior diagnosis of neurosyphilis to enrollment was 20 months (range, 4–36 months). Significantly more subjects in the ceftriaxone group had skin symptoms and signs, but there were no other differences in symptoms and signs between the 2 groups (table 2).

Similar proportions of ceftriaxone recipients and penicillin recipients had improved CSF-VDRL titers (3 [43%] of 7 vs. 2 [29%] of 7), improved CSF WBC counts (5 [100%] of 5 vs. 4 [80%] of 5), or improved CSF protein concentrations (7 [58%] of 12 vs. 5 [56%] of 9). The proportions of subjects in 2 groups whose values normalized for CSF WBCs (2 [40%] of 5 vs. 4
[80%] of 5) or CSF protein concentrations (1 [8%] of 12 vs. 1 [11%] of 9) were also similar. Improvement in serum RPR titers was significantly more common among ceftriaxone recipients (8 of 10 [80%] vs. 2 of 15 [13%]; P = .003).

Because high serum RPR titers may decline more rapidly than low titers[14, 15], we reanalyzed the improvement in serum RPR titer in the 2 groups, controlling for initial titers; improvement in RPR titers remained significantly associated with treatment with ceftriaxone (P = .01). Improvement in serum RPR titers was also significantly associated with treatment with ceftriaxone after we controlled for skin symptoms and signs (P = .008) or controlled for both initial titer and skin symptoms and signs (P = .03).

All subjects whose follow-up data were available and who had a history of neurosyphilis were in the penicillin group; therefore, we were unable to include this variable in the logistic regression model. However, when we reanalyzed serum RPR response in the 19 subjects with no history of neurosyphilis, improvement remained significantly associated with ceftriaxone (P = .03). To date, the efficacy of these treatments and of iv or im ceftriaxone in HIV-1–infected patients with neurosyphilis has not been prospectively studied. In retrospective analyses, both im ceftriaxone and iv or im penicillin G are associated with high treatment-failure rates among HIV-1–infected patients [4–6, 13]. This randomized, open-label trial was designed to prospectively compare the effect of iv ceftriaxone versus iv penicillin in HIV-1–infected patients with neurosyphilis.

### Table 1. Baseline characteristics of the 30 HIV-1–infected subjects who received ceftriaxone or penicillin G for neurosyphilis and who were included in the follow-up analysis.

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>Ceftriaxone (n = 14)</th>
<th>Penicillin (n = 16)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 T cell count, cells/μL</td>
<td>289 (40–704)</td>
<td>378 (42–790)</td>
<td>&gt;.25</td>
</tr>
<tr>
<td>CSF WBC count &gt;20/μL</td>
<td>5/14 (36)</td>
<td>5/16 (31)</td>
<td>&gt;.25</td>
</tr>
<tr>
<td>CSF protein level &lt;50 mg/dL</td>
<td>12/14 (86)</td>
<td>11/16 (69)</td>
<td>&gt;.25</td>
</tr>
<tr>
<td>Reciprocal CSF-VDRL titer</td>
<td>7/10 (70)</td>
<td>7/13 (54)</td>
<td>&gt;.25</td>
</tr>
<tr>
<td>Reciprocal serum RPR titer</td>
<td>4 (1–64)</td>
<td>2 (1–8)</td>
<td>&gt;.25</td>
</tr>
<tr>
<td>Diagnosis of neurosyphilis before enrollment</td>
<td>1 (7)</td>
<td>7 (44)</td>
<td>.04</td>
</tr>
</tbody>
</table>

**NOTE.** Data are median (range), or no. of subjects positive/no. tested (%), or no. (%). RPR, rapid plasma reagin test; VDRL, Venereal Disease Research Laboratory test.  

**a** n = 15.  

**b** For those subjects with a reactive test.  

**Discussion**

High-dose iv aqueous penicillin or im procaine penicillin with oral probenecid is recommended for treatment of neurosyphilis [17]. This randomized, open-label trial was designed to prospectively compare the effect of iv ceftriaxone versus iv penicillin in HIV-1–infected patients with neurosyphilis.

### Table 2. Symptoms and signs in the 30 HIV-1–infected subjects who received ceftriaxone or penicillin G for neurosyphilis and were included in the follow-up analysis.

<table>
<thead>
<tr>
<th>Symptom or sign</th>
<th>Ceftriaxone (n = 14)</th>
<th>Penicillin (n = 16)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>10 (71)</td>
<td>10 (63)</td>
<td>&gt;.25</td>
</tr>
<tr>
<td>Skin</td>
<td>6 (43)</td>
<td>1 (6)</td>
<td>.03</td>
</tr>
<tr>
<td>CNS</td>
<td>3 (21)</td>
<td>2 (13)</td>
<td>&gt;.25</td>
</tr>
<tr>
<td>Peripheral nervous system</td>
<td>3 (21)</td>
<td>3 (19)</td>
<td>&gt;.25</td>
</tr>
<tr>
<td>Eye</td>
<td>2 (14)</td>
<td>3 (19)</td>
<td>&gt;.25</td>
</tr>
<tr>
<td>Meningeal</td>
<td>5 (36)</td>
<td>8 (50)</td>
<td>&gt;.25</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>0</td>
<td>1 (6)</td>
<td>&gt;.25</td>
</tr>
<tr>
<td>Argyll-Robertson pupils</td>
<td>1 (7)</td>
<td>0</td>
<td>&gt;.25</td>
</tr>
<tr>
<td>Ocular syphilis</td>
<td>3 (21)</td>
<td>1 (6)</td>
<td>&gt;.25</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>0</td>
<td>&gt;.25</td>
</tr>
</tbody>
</table>

**a** Lesions, rash, and/or dermatitis.  

**b** Personality change, ataxia, forgetfulness or memory loss, confusion, and/or difficulty in concentrating.  

**c** Tingling, extremity numbness or pain and/or previously diagnosed neuropathy.  

**d** Blurred vision, cloudiness, deteriorating vision, photophobia, and/or red eyes.  

**e** Headache, tinnitus, stiff neck, and/or fever (temperature >102°F).  

**f** Includes uveitis.
We based our definition of neurosyphilis on identifying the abnormalities of conventional CSF tests. We were not able to use identification of \textit{T. pallidum} DNA in CSF by PCR as a diagnostic tool or to use it to determine the efficacy of therapy because all pretherapy and posttherapy samples were negative. These results are consistent with those of a previous study that showed that PCR may have low utility for diagnosis of neurosyphilis in HIV-1-infected patients [18].

Unfortunately, only 30 subjects could be included in the follow-up analysis. Among these subjects, there were significant differences between the groups in baseline laboratory measures and in demographic features. Notably, subjects in the ceftriaxone group had higher baseline serum RPR titers, and more had skin symptoms and signs, suggesting that more subjects in this group had secondary syphilis and concomitant neurosyphilis. Because this is a setting in which disease may be confined to the meninges [19], it may be easier to cure than disease of longer duration that may involve meninges and brain parenchyma.

Although only 1 ceftriaxone-treated subject had a previous episode of neurosyphilis, nearly half of the penicillin-treated subjects had this history. These differences could influence response to therapy; serum RPR or VDRL titers decline more quickly after therapy in patients with earlier disease and in those with higher initial titers, and serum RPR and VDRL titers decline more slowly in patients who have had previous episodes of syphilis [14, 15]. Moreover, the penicillin group, which comprised a higher proportion of subjects with a history of neurosyphilis, may have inadvertently included patients for whom treatment had already failed.

We did not find a difference between the 2 treatment groups in terms of the proportions of subjects with improvements in CSF WBC, CSF protein concentration, or CSF-VDRL titers, but serum RPR titer improvements were significantly more common in subjects treated with ceftriaxone. This association remained significant after adjustment for baseline serum RPR titers, skin symptoms and signs, and prior neurosyphilis.

Our results may be interpreted in several ways. On the one hand, the CSF abnormalities seen in our patients may have been, at least in part, due to concomitant HIV-1 infection; these abnormalities would not be expected to improve after treatment with ceftriaxone or penicillin. Alternatively, the number of subjects included in the analysis of RPR titer improvement was greater than for any of the analyses of the 3 CSF abnormalities because not all subjects had each of the possible CSF abnormalities. Thus, our study had the greatest power to detect differences in serum RPR titers.

It is also possible that serum RPR titer is the first measure to improve after successful therapy and that improvement of CSF measures lags behind. Because the longest follow-up duration used in our analysis was 26 weeks, we may not have had sufficient time to observe differences in improvement in CSF measures. These latter interpretations might suggest that ceftriaxone was superior to penicillin in the treatment of our subjects. However, it is also possible that differences in the 2 treatment groups as outlined above may have been responsible for the observed differences in RPR titer improvement between the 2 groups. Although we were able to control for differences in baseline serum RPR titers, skin symptoms and signs, and prior neurosyphilis, we were unable to control for other suspected differences such as stage of syphilis.

Accordingly, the results of this study justify neither abandoning iv penicillin nor adopting iv ceftriaxone for the treatment of neurosyphilis in HIV-1-infected patients. They do suggest that iv ceftriaxone may be a reasonable alternative to penicillin for treatment of HIV-1-infected patients with neurosyphilis and concomitant early syphilis. Moreover, they show that the efficacy of high-dose iv penicillin, as assessed by response of CSF and serum measures, is not assured in patients with more advanced syphilis, particularly in those with prior neurosyphilis. Confirmation of these assertions awaits further study. In the meantime, clinicians must continue to follow CSF and serum measures carefully after treatment of neurosyphilis in HIV-1-infected patients.

### Participating Investigators and AIDS Clinical Trials Group (ACTG) Units

The participating investigators and ACTG units included Charles Raines and Vixen Rexroad, Johns Hopkins University; Maura Laverty and Jane Dowling, New York University; Sally Kruger, Harbor-University of California Los Angeles Medical Center; Irene Yangness and Barbara Longmire, University of North Carolina; Pam Donath, Northwestern University Medical School; Keith Chirgwin and Michael Augenbraun, State University School of Medicine; Scott Miner, University of California School of Medicine; Maura Laverty and Jane Dowling, New York University; Sally Kruger, Harbor-University of California Los Angeles Medical Center; Irene Yangness and Barbara Longmire, University of North Carolina; Pam Donath, Northwestern University Medical School; Keith Chirgwin and Michael Augenbraun, State University School of Medicine.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ceftriaxone (n = 14)</th>
<th>Penicillin (n = 16)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF WBCs, cells/µL</td>
<td>-64 (-140 to -35); n = 5</td>
<td>-55 (-100 to 0); n = 5</td>
<td>&gt;.25</td>
</tr>
<tr>
<td>CSF protein, mg/dL</td>
<td>-14 (-146 to 13); n = 13</td>
<td>-7 (-274 to 61); n = 9</td>
<td>&gt;.25</td>
</tr>
<tr>
<td>Reciprocal CSF-VDRL, log2</td>
<td>-1 (-1 to 1); n = 7</td>
<td>0 (-2 to 1); n = 7</td>
<td>&gt;.25</td>
</tr>
<tr>
<td>Reciprocal serum RPR titer, log2</td>
<td>-2 (-4 to 0); n = 10</td>
<td>-1 (-2 to 0); n = 15</td>
<td>.004</td>
</tr>
</tbody>
</table>

**NOTE**: Data are median (range). RPR, rapid plasma reagin test; VDRL, Venereal Disease Research Laboratory test.
University of New York (SUNY) at Brooklyn; Rob Roy MacGregor and Deb Dunbar, University of Pennsylvania; Richard Reichman and Jane Reid, University of Rochester; John Nienow and Dominick Reilly, University of Washington; Roy Steigbiegel and Ruth Tenzler, SUNY at Stony Brook; and Sheila Hussey and Anthony Japour, Harvard University and Boston Medical Center.

References


