The Optimal Dose of Penicillin When Treating Syphilis in HIV-Infected Persons: Enough, Already?

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Despite unambiguous and prescriptive recommendations in national guidelines [1], clinicians are still unsure of the optimal antibiotic regimen to treat human immunodeficiency virus (HIV)-infected persons with early syphilis. The recommendation to use a single 2.4-million-unit (MU) dose of long-acting benzathine penicillin G (BPG) to treat all persons with early syphilis has been viewed with suspicion, given case reports of early neurological complications of syphilis occurring in HIV-infected patients presenting after receiving this (and other) regimens [2].

In this issue of Clinical Infectious Diseases, Ganesan et al attempt to answer an important question: Are multiple doses of 2.4 MU BPG better than a single dose when treating HIV-infected persons with early syphilis? This question came about as a result of several observations.

Biologically, Treponema pallidum disseminates into the central nervous system (CNS) early after infection. Lukehart et al found that 3 of 3 HIV-infected patients with early syphilis and no neurological symptoms who were documented to have *T. pallidum* in their cerebrospinal fluid (CSF) and were treated with a single dose of 2.4 MU of BPG failed to clear the organism from their CSF [3]; the only HIV-infected patient who cleared *T. pallidum* from the CSF received >1 dose of BPG. In contrast, all HIV-uninfected persons cleared *T. pallidum* from the CSF whether they were treated with a single dose of 2.4 MU BPG or multiple doses. The numbers were small, but this study suggested that a single dose of BPG may be insufficient to eradicate *T. pallidum* from the CNS in HIV-infected persons.

Clinically, ≥2 doses of BPG were used to treat symptomatic neurosyphilis in the pre-HIV antibiotic era, with good clinical responses [4]. Indeed, 3 doses of 2.4 MU BPG was a recommended alternate regimen for the treatment of neurosyphilis until 1982 [5]. Its use was abandoned in the early 1980s after studies demonstrated a lack of consistent treponemicidal penicillin concentrations in the CSF of persons treated with this regimen [6]. Whether CSF treponemicidal concentrations of penicillin are necessary to cure neurosyphilis is not known; the decades of successful clinical experience with this regimen might argue against it. Nonetheless, the use of BPG for the treatment of neurosyphilis fell out of favor.

Given these biological and clinical observations, there was great interest in using enhanced antibiotic regimens to treat early syphilis in the HIV era. A randomized controlled trial (RCT) consisting of oral amoxicillin and probenecid in addition to single-dose BPG therapy for early syphilis was conducted in the 1990s, but the study was underpowered to address that question in HIV-infected individuals, as only a small number of immunocompromised persons were recruited and completed follow-up [7]. Moreover, the enhanced therapy used in that study had never been a standard regimen used to treat neurosyphilis. Consequently, the question of whether enhanced BPG therapy would improve outcomes remained unanswered.

Ganesan et al performed a retrospective analysis of 478 cases (provided by 350 subjects) of early syphilis in HIV-infected patients followed in the US Military HIV Natural History study from 1986 to 2013. These patients were treated with 1 dose of 2.4 MU BPG (29%), ≥2 doses of 2.4 MU BPG (53%), or other regimens including non-penicillin-based regimens (18%). Early syphilis cases were identified if there was a documented seroconversion from a negative to a positive nontreponemal test in the preceding...
365 days. Response to treatment was assessed at 13 months and was defined as a ≥4-fold decline in nontreponemal antibody titers following therapy. Among those whose pretreatment titer was 1:4 or lower, response to treatment was defined by seroreversion (ie, a switch from a reactive to a nonreactive test). Multivariate Cox proportional hazards models were utilized to examine factors associated with treatment response. The authors found that there was no statistically significant difference in serologic response to treatment in HIV-infected patients receiving a single dose of BPG compared with those receiving ≥2 doses of BPG. Overall, about 97% of cases had responded to therapy by 24 months. The authors also found that higher pretreatment nontreponemal antibody titers and CD4 counts were associated with a faster response to therapy.

These findings are certainly encouraging as they provide additional support for the current Centers for Disease Control and Prevention recommendations to use a single dose of 2.4 MU of BPG to treat all patients with early syphilis. The study, however, has some significant limitations. It was a retrospective study, and therefore subject to selection bias. This is critical, as selection of treatment regimen was not random; “sicker” patients may have gotten additional doses of BPG, which may have masked the benefits of enhanced therapy. Additionally, patients generally had robust CD4 counts (median, 494 cells/µL), viral loads were low (median, 1.9 log_{10} copies/mL), and the majority (69%) were on antiretroviral therapy at the time of syphilis diagnosis. This is important because many studies have suggested that more advanced immunosuppression may be associated with worse syphilis serological and clinical outcomes [8–10]. The authors also had to deal with missing data and the challenge of distinguishing between syphilis treatment failures and reinfections. These limit this study’s ability to put this important question to rest once and for all. Unpublished data from a large prospective multicenter Taiwanese study comparing 1 vs 3 doses of BPG found no statistically significant differences in serological responses at 6 and 12 months between the 2 groups in the per-protocol analysis and no difference between the groups in ever achieving a serological response (a carry-forward analysis suggested improved serological outcomes favoring the 3-dose group with an 8% difference in serologic responses between both groups) [11]. That study was also subject to selection biases given the lack of randomization.

So what more do we need to settle this question? Do we need an RCT that compares outcomes of 1 vs 3 doses of BPG in HIV-infected persons? Ideally, yes, but conducting any such trial would present some significant challenges. The study would need to recruit enough HIV-infected subjects, preferably some with advanced immunosuppression, to demonstrate clinically significant difference in outcomes in that population. Any study that also recruits HIV-uninfected persons would need to ensure an adequate sample of HIV-infected subjects to address the question in the immunosuppressed population. Follow-up would have to be conducted for at least 1 year given the slower nontreponemal serological responses in those who are HIV-infected. The study would need adequate behavioral data from all subjects to correctly distinguish treatment failures from reinfections. These are significant challenges, but the bigger issue is the choice of an outcome measure. Studies to date, including this one by Ganesan et al and the prospective Taiwanese study, have used the 4-fold serological decline of nontreponemal antibody titers as the outcome measure, with the assumption that 4-fold nontreponemal titer declines are a biomarker for improved clinical outcomes. However, as recently demonstrated, factors other than disease activity may significantly influence nontreponemal titers in HIV-infected persons [12]. Consequently, the clinical implications of demonstrating a difference in serological responses between groups are not clear.

The goal of using enhanced therapy is to try and prevent syphilis disease progression. In the setting of HIV coinfection, this mainly refers to early neurosyphilis—meningeal or meningovascular involvement that usually occurs within the first year after infection [13,14]. The use of early neurosyphilis as the primary outcome would be ideal because it is the most clinically meaningful, but the rarity of this condition makes it difficult to power a study for that outcome. Indeed, of the information available to us, neither the Ganesan et al study nor the study from Taiwan reported any clinical cases of early neurosyphilis among its subjects who failed serologically, (or data were not available). Thus, will an RCT of 1 vs 3 doses of BPG whose primary outcome is a 4-fold serological decline in nontreponemal antibodies provide meaningful information beyond that provided by the Ganesan et al and Taiwanese studies, or are the latter studies sufficient? In our opinion, until diagnostics that better reflect syphilis disease activity become available, these questions will continue to linger and no feasible study, irrespective of its design, will be enough.

Notes

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