Jarisch-Herxheimer Reaction after Penicillin Therapy among Patients with Syphilis in the Era of the HIV Infection Epidemic: Incidence and Risk Factors

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The incidence of and risk factors for Jarisch-Herxheimer (JH) reaction were investigated prospectively among 240 human immunodeficiency virus (HIV)–infected and 115 HIV-uninfected patients with syphilis who received penicillin treatment. The overall rate of JH reaction was 31.5% (34.6% in HIV-infected patients and 25.2% in HIV-uninfected patients). In multivariate analysis, risk factors for JH reaction included high rapid plasma reagin (RPR) titers (per $\log_2$ RPR increase, risk ratio [RR], 1.19; 95% confidence interval [CI], 1.04–1.37), early syphilis (RR, 8.59; 95% CI, 4.75–15.56), and prior penicillin treatment (RR, 0.39; 95% CI, 0.20–0.78).

Caused by *Treponema pallidum*, syphilis remains a global problem, and it is estimated that >12 million people are infected every year [1]. After the introduction of modern antimicrobial therapy, the incidence of syphilis decreased for 5 decades. The incidence of syphilis had periods of increase in the mid-1980s and 1990s and has been rising again since 2000, especially the incidence of primary and secondary syphilis [2]. The re-emergence of primary and secondary syphilis is an important issue in the era of the human immunodeficiency virus (HIV) infection epidemic, because primary syphilis may enhance both the transmission and the acquisition of HIV [3, 4].

In accordance with current treatment guidelines [5], patients with early syphilis are recommended to receive a single dose of benzathine penicillin G; those with late latent syphilis or unknown duration are treated with 3 weekly doses of benzathine penicillin G. Following penicillin treatment of syphilis and other spirochetal diseases, a substantial proportion of patients may develop Jarisch-Herxheimer (JH) reaction, a syndrome composed of some of the following features: abrupt onset of fever, chills, myalgias, tachycardia, vasodilatation with flushing, exacerbated skin rash, or mild hypotension [6–8]. The reaction was described originally by Jarisch in 1895 and several years later by Herxheimer and Krause [9]. The overall rate of JH reaction for syphilis is estimated to be 10%–25% and may be as high as 50%–75% among patients with primary and secondary syphilis after receipt of penicillin before the HIV infection epidemic [10–12]. In this study, we aimed to investigate the incidence of and risk factors for JH reaction among HIV-infected and HIV-uninfected patients with syphilis after receipt of penicillin therapy.

Methods. From 1 January 2007 through 31 December 2009, patients who were diagnosed with syphilis and received penicillin were enrolled in this prospective observational study in 4 designated hospitals for HIV infection care, located in northern (2 hospitals), central (1), and southern (1) Taiwan. Patients with syphilis were enrolled from the HIV case management program and from voluntary counseling and testing for HIV infection; both programs were implemented by Taiwan Centers for Disease Control as public health responses to control HIV infection and sexually transmitted diseases. The study was approved by the institutional review board of each hospital, and participants gave written informed consent.

The diagnosis of syphilis was made on the basis of a titer of rapid plasma reagin (RPR) $\geq$1:2 (RPR Card test; Becton-Dickinson) and confirmed by *T. pallidum* particle agglutination (SERODIA-TPPA; Fujirebio) assays on the basis of a titer of $\geq$1:320. Patients with syphilis who previously were not known to be HIV-infected were tested for anti-HIV antibody by enzyme immunoassay, followed by confirmation by Western Blot assays.

Treatment guidelines for sexually transmitted diseases were followed to determine the stage and treatment of syphilis [5]. For HIV-infected patients with early syphilis, the decision to administer 1 dose or 3 doses of benzathine penicillin was made

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Table 1. Clinical Characteristics of 355 Patients with Syphilis

Characteristics	HIV-infected (n = 240)	HIV-uninfected (n = 115)	P
Age, mean ± SD, y	34.6 ± 8.6	39.7 ± 21.6	<.001
Male sex	239 (99.6)	97 (84.3)	<.001
Sexual orientation			
MSM	218 (90.8)	84 (73.0)	<.001
Heterosexual	22 (9.2)	31 (27.0)	
Prior history of syphilis treatment	82 (34.2)	13 (11.3)	<.001
Stage of syphilis			
Early[a]	119 (49.6)	41 (35.7)	.017
Late latent	121 (50.4)	74 (64.3)	
Median RPR titer (IQR)	1:64 (16–128)	1:16 (8–64)	<.001
⩾1:32	171 (71.3)	56 (48.7)	<.001
JH reaction	83 (34.6)	29 (25.2)	.088
Type of reaction			
Fever	49 (59.0)	11 (38.0)	
Skin rash	5 (6.0)	9 (31.0)	
Fever plus skin rash	29 (35.0)	9 (31.0)	
Other associated symptoms			NA
Chills	17 (20.5)	3 (10.3)	
Gastrointestinal upset	1 (1.2)	1 (3.4)	
Myalgias	4 (4.8)	3 (10.3)	
Headache	3 (3.6)	2 (6.9)	
Dizziness	7 (8.4)	2 (6.9)	
Facial flushing	7 (8.4)	1 (3.4)	
Onset of JH reaction following penicillin treatment, hours (IQR)	4 (2–5)	4 (2–5)	.95
CD4 count, mean ± SD, cells/μL	409 ± 256.6	NA	NA
<200	45 (18.8)		
200–350	66 (27.5)		
>350	129 (53.7)		
Plasma HIV RNA load, mean ± SD, $\log_{10}$ copies/mL	3.6 ± 1.5		
<400 copies/mL	97 (40.4)	NA	NA
Receipt of HAART	156 (65.0)	NA	NA

NOTE. Data are no. (%) of patients, unless other indicated. HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; IQR, interquartile range; JH reaction, Jarisch-Herxheimer reaction; NA, not applicable; RPR, rapid plasma reagin; SD, standard deviation.

[a] Early syphilis includes primary, secondary, and early latent syphilis.

at the discretion of treating physicians. A case record form was used to record demographic and clinical characteristics and treatment. A telephone call was made by case managers to the patients within 24 hours of penicillin therapy to inquire about the reaction after treatment with the use of a standardized form.

Early syphilis included primary, secondary, and early latent syphilis. JH reaction was defined as presence of fever (temperature, >38.0°C) and/or acute exacerbation of maculopapular skin rashes within 24 hours of receipt of penicillin therapy for syphilis.

All statistical analyses were performed with SPSS, version 17.0 (SPSS). Categorical variables were compared by Fisher exact test or χ^2 test. Noncategorical variables were compared by Mann-Whitney U test. Factors with $P < .2$ were included for multivariate analysis using logistic regression. All comparisons were 2-tailed, and $P < .05$ was considered to be significant.

Results. During the study period, 355 patients with 381 episodes of syphilis were enrolled, including 240 HIV-infected patients and 115 HIV-uninfected patients. Twenty-six HIV-infected patients (10.8%) developed recurrent syphilis within 1 year of penicillin therapy, which was diagnosed by clinical history, a 4-fold rise of RPR titers after initial decrease, and/or development of new genital ulcers. The demographic and clinical characteristics of the patients with syphilis are shown in Table 1. Compared with HIV-uninfected patients with syphilis, HIV-infected patients were younger, were more likely to be

Table 2. Univariate Analysis of Factors Associated with Jarisch-Herxheimer Reaction

Variable	JH reaction (n = 112)	No JH reaction (n = 243)	P
Age, mean ± SD, y	31.5 ± 9.4	38.5 ± 15.6	<.001
Early syphilis	92 (82.1)	68 (28.0)	<.001
RPR titer ⩾1:32	92 (82.1)	135 (55.6)	<.001
Prior history of syphilis treatment	17 (15.1)	78 (32.1)	<.001
CD4 cell count ⩽200 cells/μL	11/83 (13.1)	34/157 (19.2)	.12
Plasma viral load <400 copies/mL	31/83 (37.3)	66/157 (42.0)	.49
Receipt of HAART			
Any duration	49/83 (59.0)	107/157 (68.2)	.09
<1 month	15/83 (18.1)	31/157 (19.7)	.23
<6 months	23/83 (27.7)	41/157 (26.1)	.22

NOTE. Data are no. (%) or proportion (%) of patients, unless otherwise indicated. HAART, highly active antiretroviral therapy; RPR, rapid plasma reagin; SD, standard deviation.

homosexual males, had higher RPR titers, were more likely to present with early syphilis, and were more likely to have been diagnosed previously with syphilis. Among HIV-infected patients, more than half (53.7%) had CD4 counts >350 cells/μL, and 65.0% of them were receiving highly active antiretroviral therapy (HAART) when syphilis was diagnosed.

The overall incidence of JH reaction was 31.5% (95% confidence interval [CI], 27.0%–36.0%). HIV-infected patients had a higher incidence of JH reaction than HIV-uninfected patients (34.6% vs 25.2%; $P = .088$); however, the difference did not reach statistical significance. Of 26 patients with recurrent syphilis, 6 (23.1%) had JH reaction after penicillin therapy for the first episode, but none developed JH reaction when they received penicillin for the second episode. Of 20 patients who received 3 doses of penicillin and developed JH reaction after the first dose, none developed JH reaction after the second or third dose.

The spectrum of JH reaction, other than fever, rashes, or fever with exacerbation of skin rashes, is shown in Table 1. The median time to development of JH reaction was 4 hours (interquartile range, 2–5 hours) for the 2 groups. Fever resolved spontaneously or with antipyretics within 2 to 3 hours, whereas skin rashes subsided with antihistamine within the next 24 hours on most occasions.

Compared with patients without JH reaction, patients with JH reaction were younger (31.5 vs 38.5 years; $P < .001$), more likely to present with early syphilis (82.1% vs 28.0%; $P < .001$) and to have a RPR titer ⩾1:32 (82.1% vs 55.6%; $P < .001$), and less likely to have a prior penicillin treatment (15.1% vs 32.1%; $P < .001$) (Table 2). Among HIV-infected patients, we found no associations between JH reaction and CD4 cell count, plasma HIV RNA load, or receipt of HAART (data not shown).

In multivariate logistic regression, $\log_2$ increase in RPR titer and early syphilis were independently associated with an increased risk for JH reaction, with a risk ratio of 1.19 (95% CI, 1.04–1.37; $P = .012$) for per-$\log_2$ RPR increase and 8.59 (95% CI, 4.75–15.56; $P < .001$) for early syphilis, compared with late latent syphilis. Prior penicillin treatment for syphilis was associated with a reduced risk for JH reaction, with a risk ratio of 0.39 (95% CI, 0.20–0.78; $P = .007$).

Discussion. Release of lipoproteins, cytokines, and immune complex shortly after treatment for syphilis or other spirochetes has been proposed as the cause of JH reaction in immunocompetent patients [13]. In this study, we found that 58.0% of HIV-infected patients with primary and secondary syphilis developed JH reaction, a rate similar to that reported in the literature before the HIV infection epidemic (50%–75%) [10–12]; in addition, for each 2-fold increase of RPR titer, the risk of JH reaction increased by 19%, suggesting that a higher load of spirochetes in the early stages of syphilis increases the risk of JH reaction when patients receive bactericidal agents.

Hypersensitivity reaction has also been proposed to contribute to JH reaction, because the reaction develops with the same severity among patients at different stages of syphilis, even though late latent syphilis has been considered to contain fewer treponemal spirochetes than early syphilis [14]. Our finding that prior penicillin therapy for syphilis reduces the risk for JH reaction by 61% suggests that desensitization may occur after the previous course of treatment.

In this study, our findings argue against the possibility of penicillin allergy, because most episodes of JH reaction developed 4 hours after treatment, previous penicillin treatment for syphilis reduced the risk for JH reaction, and furthermore, patients who developed JH reaction following the first dose of penicillin did not have recurrent symptoms after the second or third dose during the same course of treatment.

Most often, JH reaction is harmless and self limited; however, the patients may be frightened by the reaction without coun-

seling before treatment and, on rare occasions, the reaction might be severe enough to result in failure to continue treatment [10]. The implications of our findings are that patients to be treated with penicillin for syphilis should be well informed of the manifestations, timing of onset, and risk of JH reaction following treatment, to alleviate their fears about the treatment of syphilis.

There are several limitations of our study. First, the definitions for JH reaction are nonspecific, and there are no readily available surrogate markers to detect JH reaction. Diagnosis is made clinically on the basis of the presentations and timing following penicillin therapy for syphilis. Second, symptoms of JH reaction were obtained by telephone call within 24 hours, and only the symptoms that were most notable to the patients were reported. In addition, laboratory tests were not performed and whether there were any delayed manifestations is unknown, and therefore the spectrum of JH reaction may have been underrecognized. Third, the sample size of our study remains small, which limits our subgroup analyses in attempts to identify other factors for JH reaction in HIV-infected patients, such as increases of CD4 cell count after HAART.

In conclusion, early syphilis and high RPR titers are associated with an increased risk for JH reaction, whereas prior penicillin therapy is associated with a low risk for JH reaction, in patients with syphilis who receive penicillin in accordance with the guidelines.

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