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Comparison of Doxycycline and Benzathine Penicillin G for the Treatment of Early Syphilis

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ABSTRACT Doxycycline is the preferred recommended second-line treatment for the treatment of early syphilis. Recent reports showed a declining efficacy trend of doxycycline in treatment of early syphilis. The aim of our study was to assess the serological response to the treatment for early syphilis with doxycycline compared with benzathine penicillin G and evaluate whether doxycycline is still an effective agent for the treatment of early syphilis. A record-based retrospective study was conducted. Patients were diagnosed with early syphilis in an sexually transmitted disease (STD) clinic from January 1, 2008 to December 31, 2014. They were treated with a single dose of benzathine penicillin G 2.4MU or oral doxycycline 100 mg twice daily for 14 days. Pearson's chi-squared test was used for data analysis. 601 cases were included in the final study sample: 105 (17.5%) patients received a 14-day course of doxycycline (doxycycline group), and 496 (82.5%) patients received single-dose benzathine penicillin G (BPG group). The serological responses at 6 months and 12 months after treatment were compared. No statistically significant differences were found between the two groups at 6 months (69.52% vs. 75.00%, P=0.245), and at 12 months (92.38% vs. 96.17%, P=0.115). Doxycycline is still an effective agent for the treatment of early syphilis.

KEY WORDS: syphilis, doxycycline, penicillin, treatment

INTRODUCTION

Syphilis is a complex systemic illness caused by the spirochete *Treponema pallidum* which is transmitted both sexually and from mother to child (1). The incidence rate of syphilis has risen rapidly in China since 1978 (2,3), and it is one of the most common STDs in economically developed regions (4). The total reported incidence of syphilis in China increased from 8.71 cases/100,000 people in 2005 to 32.04 cases/100,000 people in 2011, showing a yearly increase of 25.5% (5).

According to the treatment guidelines for sexually transmitted diseases (STDs) by the Centers for Disease

Control and Prevention (CDC) (2015) (6), benzathine penicillin G (BPG) is the preferred treatment agent for syphilis, and one dose of BPG (2.4 million units (MU)) administered intramuscularly is recommended for early syphilis (primary, secondary, and early latent syphilis). The major advantages of BPG treatment are its safety, effectiveness, and the favorable adherence to single dose schedule for early syphilis (7). Doxycycline and cephalosporins are recommended as alternate agents in non-pregnant patients if they are allergic to penicillin or unable to tolerate treatment with BPG. Although more recent studies indicate a lower rate (<2.5%) of cross-reactivity between cephalosporins and penicillin, the risk for penicillin cross-reactivity between most second-generation (cefoxitin) and all third generation cephalosporins (cefixime and ceftriaxone) is negligible (6). Until now, there had been no related data to evaluate the efficacy of doxycycline in treatment of early syphilis in Shandong, China. We thus conducted a record-based retrospective study to compare the serological response rates of patients with early syphilis treated with BPG and doxycycline and to evaluate whether doxycycline is an effective agent for the treatment of early syphilis.

METHODS

Study setting

We conducted a record-based retrospective study. Participants were aged from 16 to 70 with early syphilis (in the primary, secondary, or early latent stages) diagnosed at a STD clinic between January 1, 2008 and December 31, 2014. This study was approved by the Human Medical and Ethics Committee of the specialized institute.

Data collection

Diagnoses of primary, secondary, and early latent syphilis were made by trained clinicians at the sexually transmitted disease clinics on the basis of current US CDC criteria. Patient information about demographic characteristics, sexual history, symptoms, laboratory test results, diagnosis, and therapy were recorded in detail by clinicians.

Table 1. Baseline characteristics of patients in the benzathine penicillin G (BPG) treatment group and the doxycycline treatment group

	BPG (n=496)		Doxycycline (n=105)		P value
	n	%	n	%	
Age (years)					
Median (IQR)	30 (24-40)		31 (25-41)		
10-19	39	7.9	4	3.8	0.382
20-29	204	41.1	40	38.1	
30-39	125	25.2	31	29.5	
40+	128	25.8	30	28.6	
Sex					0.078
Male	244	49.2	42	40.0	
Female	252	50.8	63	60.0	
Ethnicity					0.751
Han	480	96.8	98	93.3	
Minority	16	3.2	2	6.7	
Stage of syphilis					0.711
Primary	99	20.0	19	18.1	
Secondary	252	50.8	58	55.2	
Early latent	145	29.2	28	26.7	
RPR titer					0.313
≤1:4	50	10.1	10	9.5	
1:8	40	8.1	12	11.4	
1:16	165	33.2	25	23.8	
1:32	106	21.4	28	26.7	
≥1:64	135	27.2	30	28.6	
Co-infection with other STDs					0.154
Yes	90	18.1	13	12.4	
No	406	81.9	92	87.6	

Table 2. Serological response and non-response rates in BPG and doxycycline group.

	BPG		Doxycycline	
	n	%	n	%
Titers drop 4-fold	236	47.58	39	37.14
Titers drop 8-fold	106	21.37	28	26.67
Titers drop 16-fold or greater				
Serofast	135	27.21	30	28.57
	69	13.91	15	14.28
Serological non-responders	19	3.83	8	7.62

Patients with a positive rapid plasma regain (RPR) test and *Treponema pallidum* particle assay (TPPA) test were candidates to be assessed. All patients in this study were treated with doxycycline 100 mg orally twice daily for 14 days or single-dose BPG 2.4 MU. Only patients who were allergic to penicillin or who refused intramuscular BPG were treated with doxycycline.

Definitions

Serological response was defined as a decline of RPR titer by 4-fold or greater from the baseline value at 6 or 12 months of doxycycline or BPG treatment if initial RPR titer was 1:8 or higher. If RPR titer was 1:4, 1:2, or 1:1 at baseline for primary syphilis or secondary syphilis, successful treatment was considered to be when the lesions disappeared and RPR turned to be negative after treatment. If follow-up was inadequate to determine the serological outcome of treatment, the patients would then be excluded. Patients with primary syphilis whose serological test results were nonreactive at the time of treatment were excluded, because this study focused on serological responses. All the subjects were HIV-negative and without other bacterial infections and received timely follow-up, because most HIV-positive patients were referred to the HIV Control and Prevention Center in Jinan.

Data analysis

Pearson's chi-squared test or Fisher's exact test were used to compare the categorical variables. Results were considered statistically significant at $P<0.05$ (2-tailed). Data were analyzed using SPSS (Version 17.0).

We compared the time to serological response between the patients receiving doxycycline and patients receiving BPG. Time to serological response was defined as the earliest date after therapy when a 4-fold drop in rapid plasma regain titer was documented. Figures were generated to estimate the serological response rates at 6 months and 12 months after treatment (Figure 1) and the yearly changes of total efficacy rates during the study period (Figure 2).

RESULTS

Of the 747 primary syphilis cases reported during the study period, 601 cases were included in the final study sample. Overall, the median age of participants was 33 years old and 286 (47.6%) were men. Of these 286 male patients, 8 patients identified themselves as man who had had sex with man (MSM); 118 patients (19.6%) had primary syphilis, 310 (51.6%) had secondary syphilis, and 173 (28.8%) had early latent syphilis. There was a similar distribution of patient characteristics in each treatment group (Table 1). During the study period, 105 (17.5%) patients received a 14-day course of doxycycline, and 496 (82.5%) patients received single-dose BPG. All patients in both groups were followed-up for at least 12 months.

We compared the serological response at 6 months and 12 months after treatment. Table 2 presents the serological response and non-response rates in detail. There was no statistically significant difference between the doxycycline group and the penicillin group at 6 months (69.52% vs. 75.00%, $P=0.245$), and at 12 months (92.38% vs. 96.17%, $P=0.115$) (Figure 1). The estimated median efficacy time was 106 days (mean=127.4; range 30-296) in the doxycycline group and 132 days (mean=146.8; range 28-395) in the BPG group. The yearly efficacy trends of doxycycline and BPG are shown in Figure 2. In total, there was no difference in the yearly efficacy of doxycycline ($P=0.274$).

DISCUSSION

Doxycycline is a recommended alternative in the treatment of patients with syphilis who are allergic to or intolerant of BPG. Non-treponemal titers are the most widely used criterion in evaluating the response to syphilis treatment (8-12). In recent years, clinical observations (13,14) have shown a declining efficacy of doxycycline in treatment of early syphilis.

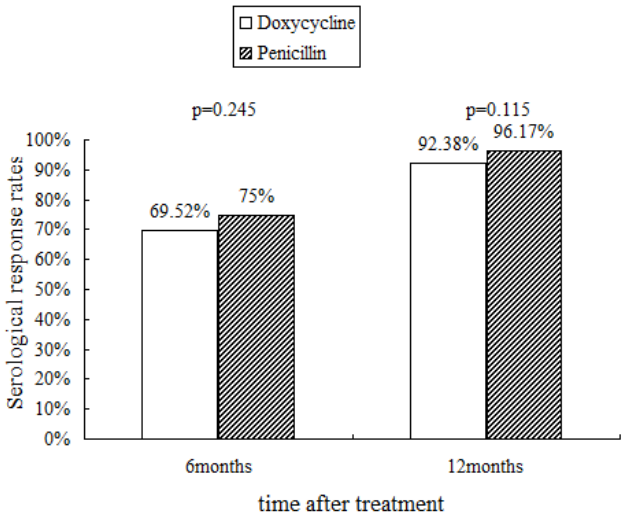

Figure 1.

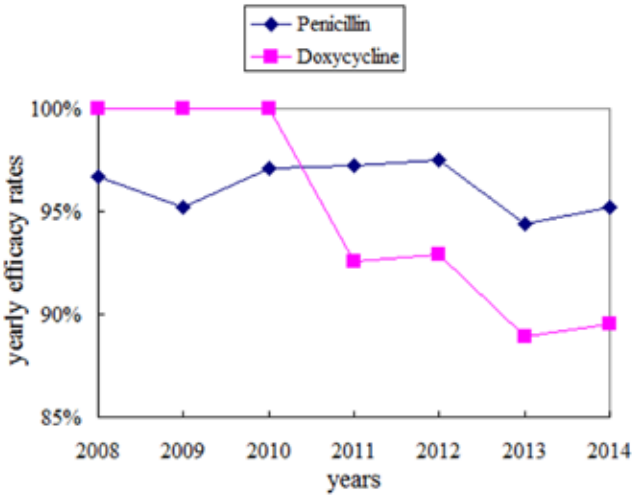

Figure 2.

A multi-center observational study from Taiwan (13) showed a lower efficacy rate both in the penicillin and doxycycline group in the treatment of early syphilis in HIV-infected patients. Li J *et al.* (14) also demonstrated a declining trend of doxycycline efficacy in the treatment of early syphilis in Beijing, China. Of the 641 early syphilis cases in the study, 606 (94.5%) received penicillin and 35 (5.5%) received doxycycline/tetracycline. The efficacy rate in the doxycycline/tetracycline group was 82.9% (29/35). Our results were consistent with these recent studies and demonstrate that doxycycline still appears to be an effective agent for the treatment of early syphilis.

Time to Serological Treatment Success

In a Baltimore study (15), successful treatment for primary, secondary, and early latent syphilis (defined as a minimum 4-fold decrease in baseline rapid plasma reagin test titer by 9-13 months) was reported within 106 days for doxycycline, compared with 137 days for penicillin. In the study by Wong *et al.* (16), the estimated median times were 43 days for doxycycline and 72 days for BPG. Our results, along with the results of these two studies, indicate that doxycycline had the same serological response time as BPG.

CONCLUSION AND LIMITATIONS

Notably, the comparison of the serological response rate at 6 months and 12 months after treatment is one of the strengths of this study. However, there are still some limitations that need to be given full consideration. Firstly, because this was a retrospective study and treatment was not randomly allocated, confounding factors such as age, sex, and combination with other STDs need to be considered. However, baseline characteristics of the two treatment arms were comparable on the demographic and clinical characteristics examined. Secondly, treatment adherence is another key question. There is no exact record on treatment adherence to ensure that full-dose treatment with a 14-day course of oral doxycycline was followed by all patients, and patients who followed the physician's advice were more likely to return for follow-up serological testing. Additionally, other factors, such as re-infection, serofast state, or even resistance to doxycycline might result in the lower efficacy of doxycycline in our study. Thirdly, our surveillance data had excluded HIV-infected patients, which may influence the serological response rate compared with patients with simple syphilis. In fact, there were 5 primary syphilis cases with HIV-infection that were excluded from the study and treated at a dedicated HIV clinic. Fourthly, the record was based on a questionnaire survey in the STD clinic. We presume the reason for the low rate of MSM in Shandong has something to do with the traditional culture. Most patients are ashamed or refuse to admit homosexual behavior in China.

In conclusion, the results of our study demonstrate that doxycycline still appears to be an effective agent for the treatment of early syphilis.

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