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Comparison of serological responses to single-dose azithromycin (2 g) versus benzathine penicillin G in the treatment of early syphilis in HIV-infected patients in an area of low prevalence of macrolide-resistant *Treponema pallidum* infection

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Objectives: Effectiveness of single-dose azithromycin (2 g) in the treatment of early syphilis among HIV-infected patients has rarely been evaluated in the era of combination ART.

Methods: Consecutive HIV-infected patients with early syphilis, who received 2 g single-dose azithromycin or 2.4 MU benzathine penicillin G, between 2007 and 2014, were prospectively observed. Genotypic resistance to macrolides was determined in *Treponema pallidum* isolates identified from clinical specimens using PCR assays. Rapid plasma reagin (RPR) titres were determined at baseline and every 3 months after treatment. Primary outcome was a decline of RPR titre by ≥4-fold at 12 months after treatment.

Results: During the study period, 162 HIV-infected patients with early syphilis received benzathine penicillin G and 237 patients received azithromycin. At 12 months follow-up, the serological response rate for penicillin and azithromycin groups was 61.1% and 56.5% ($P=0.41$), respectively; respective response rate was 61.1% and 65.9% ($P=0.49$) if we only included patients infected with *T. pallidum* not harbouring macrolide resistance in the azithromycin group. In multivariate analysis, RPR titres ≥1:32 (OR 2.56; 95% CI 1.55–4.21) and prior syphilis (OR 0.54; 95% CI 0.35–0.81) were predictors of serological response. Most common adverse effects of azithromycin included diarrhoea (52.7%), nausea (22.4%), abdominal pain (18.6%), bloating (17.7%) and lassitude/somnolence (27.4%).

Conclusions: In the setting of a low prevalence of macrolide-resistant *T. pallidum*, 2 g single-dose azithromycin achieved a similar serological response to benzathine penicillin G in HIV-infected patients with early syphilis. Major adverse effects of azithromycin were gastrointestinal symptoms and lassitude/somnolence.

Introduction

The global incidence of syphilis has been increasing in developed as well as developing countries in recent years, particularly among MSM.[1–4] Other than behaviour modification, effective antibiotic treatment is a key component for the control of syphilis. According to current treatment guidelines in Canada, Europe and the USA, the standard treatment for early syphilis (primary, secondary and early latent syphilis) is single-dose (2.4 MU) benzathine penicillin G, although whether multiple doses of benzathine penicillin G are

needed for the management of early syphilis in HIV-infected patients remains controversial.[5–9] In the presence of penicillin allergy and benzathine penicillin G shortages that have occurred in several countries such as Japan and Taiwan,[10] ceftriaxone, doxycycline and azithromycin could be alternative agents for early syphilis, given the caveat that clinical studies assessing the effectiveness of these alternative treatments are limited.[6,7,11]

Azithromycin has been considered an alternative for treatment of early syphilis when *in vitro* and animal studies have demonstrated its effectiveness against *Treponema pallidum*.[12–14] Several clinical trials have demonstrated comparable clinical efficacy of single-dose azithromycin versus benzathine penicillin G, with the serological response rate ranging from 56% to 98%.[12,15,16] In HIV-negative patients, Hook and colleagues[17] have demonstrated the equivalent efficacy of 2 g single-dose azithromycin to single-dose benzathine penicillin G in a randomized controlled trial. As an alternative treatment option, azithromycin is more cost-effective, has a favourable adverse event profile[18,19] and causes much less frequent Jarisch–Herxheimer reaction when compared with benzathine penicillin G;[20] moreover, partner treatment, directly observed therapy and treatment of several other concurrent sexually transmitted diseases (STDs) can be conducted with the use of azithromycin.[7]

Despite the documented clinical efficacy of azithromycin, treatment failures among patients with primary and secondary syphilis have been noted since 2002.[19,21,22] Point mutations (A2058G and A2059G) of treponemal DNA have been shown associated with macrolide resistance and treatment failures.[22,23] The prevalence of macrolide resistance in *T. pallidum* is highly variable around the world; however, it reportedly ranges from 0% to 100% in different regions studied, and MSM have been identified as a risk group of infection with macrolide-resistant *T. pallidum* in the USA.[19,22,24–27] A significantly higher prevalence of *T. pallidum* harbouring A2058G mutation was detected in the isolates from MSM than from men who have sex with women (prevalence ratio 5.7; 95% CI, 2.9–10.8), particularly in the west region of the USA. In addition, higher prevalences of macrolide resistance in *T. pallidum* among MSM have also been reported in other studies.[19,25] Therefore, azithromycin, as an alternative agent for early syphilis, is not recommended for pregnant women and MSM according to the current Sexually Transmitted Diseases Treatment Guidelines of the CDC.[6,7]

In Taiwan, our multicentre surveillance study has demonstrated a low prevalence of macrolide resistance (0.7%) among the *T. pallidum* isolates in patients with syphilis who were predominantly HIV-infected MSM.[24,28] In this study, we aimed to compare the serological response of early syphilis to 2 g single-dose azithromycin versus single-dose benzathine penicillin G and to evaluate the tolerability of azithromycin among HIV-infected patients with access to combination ART (cART).

Methods

Study population and setting

This multicentre, prospective observational study was conducted between January 2007 and April 2014 at five hospitals designated for HIV care in northern (three hospitals), central (one) and southern (one) Taiwan where inpatient or outpatient HIV care, including cART and monitoring of CD4 cell counts and plasma HIV RNA load (PVL) are provided free-of-charge. According to the national guidelines for HIV care in Taiwan, non-treponemal serological tests for syphilis are recommended at least once yearly and on an as-needed basis as dictated by the clinical presentations and every 3–6 months over a period of 2 years for those who receive treatment for syphilis. The patients who receive stable cART are usually followed as outpatients every 3 months and monitoring of immunological and virological status is performed every 3–6 months. During the study period, the treatment regimens for syphilis were prescribed according to the STDs Treatment Guidelines of the CDC in 2006 and 2010.[7,29]

HIV-infected patients aged 20 years or over who presented with early syphilis and received single-dose benzathine penicillin G (2.4 MU) at the participating hospitals from January 2007 to April 2014 were included in this observational study. The methods were described previously.[8] From 2012 to 2013, there was a shortage of benzathine penicillin G in Taiwan and azithromycin or doxycycline became the treatment options instead of benzathine penicillin G.[11] Azithromycin was considered an alternative option to benzathine penicillin G because our previous surveillance study between 2009 and 2014 has shown that the prevalence of *T. pallidum* harbouring macrolide resistance mutations remained low (0.7%).[24,28] Patients receiving azithromycin who had completed follow-up for 12 months between 2012 and 2014 were included in this observational study using the same inclusion criteria with those who received benzathine penicillin G.[8]

Patients were excluded from analysis if antibiotics were concurrently given that were treatment options for syphilis such as ceftriaxone or doxycycline when early syphilis was diagnosed, or if those antibiotics were used for treatment of diseases other than syphilis during the 12 months of follow-up after azithromycin or benzathine penicillin G treatment was administered. Patients with rapid plasma reagin (RPR) titres $<$1:4 were not included because of concerns about increased risk of biological false-positive serology of syphilis (RPR titre of 1:1 or 1:2). Patients with symptomatic neurosyphilis or tertiary syphilis were also excluded. CSF examination was not routinely performed if there were no neurological symptoms. The study was approved by the Research Ethics Committees of the participating hospitals and patients gave written informed consent for detection of macrolide-resistant *T. pallidum* before receiving azithromycin (registration number, 201003110R).

Data collection

A standardized case record form was used to collect information on demographic characteristics, risk behaviour for HIV transmission, PVL and CD4 counts at baseline and during follow-up, cART, stage of syphilis, RPR titres before treatment and during the first 3 and 6 months of follow-up, and the first episode of recurrent syphilis and its stage. Azithromycin was taken under the direct observation of HIV case managers. To alleviate the gastrointestinal adverse effects, patients were advised to take a light meal before taking azithromycin. Cell phone calls were made to inquire about any adverse effects, including Jarisch–Herxheimer reactions, by case managers 24 and 48 h after azithromycin was administered using a standardized case record form.[20]

Laboratory investigations

Serological tests for syphilis were performed with the use of rapid RPR test (BD Macro-VueTMRPR Card tests, USA) and *Treponema pallidum* haemagglutination test (FTI-SERODIA-TPPA. Fujirebio Taiwan Inc., Taoyuan, Taiwan) at the participating hospitals. PVL and CD4 lymphocyte count were quantified by the Cobas Amplicor HIV-1 Monitor^{TM} Test, version 1.5 (Roche Diagnostics Corporation, Indianapolis, IN, USA) and FACSFlow (Becton Dickinson), respectively.

Treponemal DNA was extracted from clinical specimens using the Qiagen DNA minikit (Qiagen, Gmbh, Hildens, Germany) according to the manufacturer's protocol. The presence of *T. pallidum* was determined by amplification of the polymerase I gene (*polA*) as previously.[30] The detection of macrolide resistance mutations (A2058G or A2059G) in the 23S rRNA gene was performed using PCR–RFLP.[22]

Urine was collected to detect *Chlamydia trachomatis* and *Neisseria gonorrhoeae* concomitantly from patients with early syphilis who received

azithromycin. The detection of *C. trachomatis* and *N. gonorrhoeae* was performed with the use of a multiplex real-time PCR assay on an automated system (m2000; Abbott Molecular Diagnostics, Des Plaines, IL, USA).[31] Results were reported as positive or negative.

Definitions

Early syphilis that includes primary, secondary and early latent syphilis was defined according to STDs Treatment Guidelines of the CDC in 2010.[7] Patients were diagnosed as having primary syphilis if they had ulcers or chancres at the infection site; secondary syphilis if they developed skin rash, mucocutaneous lesions or lymphadenopathy in the presence of seroreactivity for *T. pallidum*; and early latent syphilis if seroconversion was documented within the past 12 months in the absence of clinical symptoms. Serological response was defined as a decline of an RPR titre by ≥4-fold from the baseline value at 12 months of azithromycin or benzathine penicillin G treatment.[17] Non-responders were those who received another course of treatment regardless of serological response during the follow-up; or those who failed to achieve a decline of RPR titres by ≥4-fold at 12 months following treatment. In addition, serofast was defined as either no change in RPR titres or ≤2-fold decrease or increase of RPR titres from baseline.[32]

Statistical analysis

All statistical analyses were performed using SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were compared using χ^2 or Fisher's exact test whereas non-categorical variables were compared using Student's *t*-test or Mann–Whitney *U*-test. All tests were two-tailed and $P<0.05$ was considered significant. Multiple logistic regression method was used to identify factors associated with serological response at 6 months of treatment. We included the variables with a $P<0.2$ in the univariate analysis or variables that were of biological significance such as antibiotic administered (benzathine penicillin G versus azithromycin) in the multivariate logistic regression models.

Results

During the study period, a total of 238 HIV-infected patients received 2 g single-dose azithromycin for treatment of early syphilis, among whom 85 patients had *T. pallidum* (identified with the use of PCR assays from clinical specimens) that did not harbour macrolide resistance mutations and 1 patient was excluded because of infection with *T. pallidum* harbouring macrolide resistance mutation (A2058G) (azithromycin group, $n=237$); and 162 HIV-infected patients with early syphilis received single-dose benzathine penicillin G (penicillin group) (Table 1). Table S1 (available as Supplementary data at *JAC* Online) shows the comparisons of baseline characteristics between 152 patients from whom *T. pallidum* was not identified in the clinical specimens collected and 85 patients infected with *T. pallidum* without harbouring macrolide resistance mutations. There were no differences in terms of age, risk for HIV transmission, RPR titres ≥1:32, CD4 count stratification, mean $\log_{10}$ PVL, PVL <400 copies/mL, concomitant chlamydial infection or receipt of cART. However, patients infected with *T. pallidum* without harbouring macrolide resistance mutations had a higher percentage of secondary syphilis, a lower percentage of early latent syphilis and prior syphilis, and a lower mean CD4 count than those who did not have *T. pallidum* identified.

All patients in the azithromycin group and penicillin group had follow-up RPR titres at 3, 6 and 12 months after treatment. The

Table 1. Clinical characteristics of patients receiving single-dose benzathine penicillin G (2.4 MU) or 2 g single-dose azithromycin for treatment of early syphilis

	Single-dose benzathine penicillin G ($n=162$)	2 g azithromycin ($n=237$)	*P* value
Age, mean (SD), years	32.0 (7.6)	33.1 (7.6)	0.26
Sexual preference, *n* (%)			
MSM	161 (99.4)	235 (99.2)	1.00
non-MSM	1 (0.6)	2 (0.8)	
Syphilis stage, *n* (%)			
primary	13 (8.0)	33 (13.9)	0.08
secondary	82 (50.6)	84 (35.4)	0.003
early latent	67 (41.4)	120 (50.6)	0.08
RPR titre, median (IQR)	64 (32–128)	64 (32–128)	0.72
RPR titre ≥1:32, *n* (%)	136 (84.0)	180 (75.9)	0.06
CD4 count, mean (SD), cells/mm^3	463 (240)	546 (237)	0.73
CD4 <200, *n* (%)	17 (10.5)	10 (4.2)	0.02
200 ≤ CD4 ≤ 350, *n* (%)	37 (22.8)	41 (17.3)	0.20
CD4 >350, *n* (%)	108 (66.1)	186 (78.5)	0.01
PVL, mean (SD), $\log_{10}$ copies/mL	2.98 (1.54)	2.22 (1.41)	<0.001
PVL <400 copies/mL, *n* (%)	89 (54.9)	174 (73.4)	<0.001
Prior history of syphilis, *n* (%)	57 (35.2)	161 (67.9)	<0.001
cART, *n* (%)	112 (69.1)	195 (82.3)	0.003

cART, combination ART; IQR, interquartile range; PVL, plasma HIV RNA load; RPR, rapid plasma reagin; SD, standard deviation.

clinical characteristics of patients in the azithromycin group and penicillin group are shown in Table 1. All except one patient in the penicillin group and two patients in azithromycin group were MSM. Compared with the patients in the penicillin group, patients in the azithromycin group had a lower percentage of secondary syphilis (35.4% versus 50.6%, $P=0.003$), CD4 count <200 cells/mm^3 (4.2% versus 10.5%, $P=0.02$), but had a higher percentage of CD4 count >350 cells/mm^3 (78.5% versus 66.1%, $P=0.01$), PVL <400 copies/mL (73.4% versus 54.9%, $P<0.001$), prior syphilis (67.9% versus 35.2%, $P<0.001$), taking cART (82.3% versus 69.1%, $P=0.003$) and lower mean $\log_{10}$ PVL (2.22 ± 1.41 versus 2.98 ± 1.54 copies/mL, $P<0.001$).

The serological response rates to single-dose benzathine penicillin G or azithromycin at 12 months are illustrated in Figure 1. Similar serological response rates were observed between the penicillin and azithromycin groups (61.1% versus 56.5%, $P=0.41$). If we only included those 85 patients confirmed to be infected with *T. pallidum* and not harbouring macrolide resistance mutations by PCR assays (Figure 1), we found that there were no statistically significant differences in the serological response rates between the penicillin group and azithromycin group at 12 months of follow-up (61.1% versus 65.9%, $P=0.49$).

In univariate analysis, factors associated with achieving serological response at 12 months in patients receiving benzathine penicillin G or azithromycin are shown in Table 2. More patients with higher RPR titres (RPR $\geq$1:32) achieved serological response than those with lower RPR titres (85.8% versus 69.9%, $P<0.001$), while patients with early latent syphilis (42.1% versus 53.6%, $P=0.03$) and a prior history of syphilis (48.1% versus 63.9%, $P=0.002$) were less likely to achieve serological response. In addition, there was no relationship between the stratifications of CD4 cell counts, $\log_{10}$ PVL, cART or treatment regimen administered for syphilis and serological response. In multivariate analysis using logistic regression (Table 2), patients with higher RPR titres (RPR $\geq$1:32) were more likely to achieve serological response with an adjusted odds ratio (AOR) of 2.56 (95% CI 1.55–4.21) while patients with a prior history of syphilis was less likely to achieve serological response (AOR 0.54; 95% CI 0.35–0.81). Patients receiving single-dose benzathine penicillin G appeared to have a similar serological response rate compared with those receiving 2 g single-dose azithromycin at 12 months of follow-up in multivariate analysis (AOR 0.94; 95% CI 0.59–1.47, $P=0.77$).

The tolerability of 2 g single-dose azithromycin was assessed among all 237 patients who took azithromycin under the direct observation of case managers (Table 3). The most common adverse effects included gastrointestinal discomfort such as diarrhoea (52.7%), loose stool passage (6.3%), abdominal pain (18.6%), nausea (22.4%) and abdominal bloating (17.7%). Other adverse effects such as vertigo, headache or dizziness were noted in a few patients but lassitude/somnolence was more commonly seen (27.4%). In addition, 14.8% of the patients receiving azithromycin with early syphilis experienced Jarisch–Herxheimer reactions.

There was no statistically significant difference between the patients with or without taking cART in terms of the frequency of adverse effects. Among the 195 patients who were taking cART, 52.8% ($n=103$) were taking PI-based regimens while the others were taking NNRTI-based regimens (Table S2). Patients who were taking PI-based regimens tended to have a higher percentage of

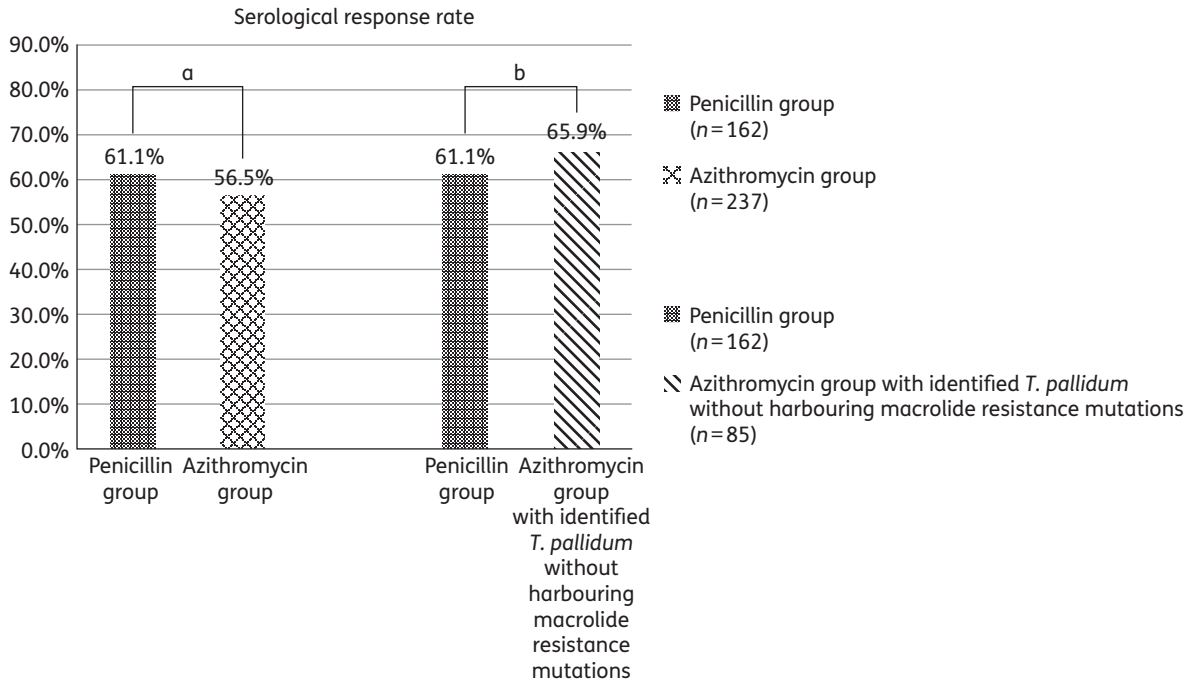

Figure 1. Serological response rates to single-dose benzathine penicillin G and 2 g single-dose azithromycin at 12 months of treatment. (a) All patients in the penicillin group and all 237 patients in azithromycin group (risk difference: −4.6%, 95% CI: −14.4 to 5.2, $P=0.41$). (b) All patients in the penicillin group and 85 patients with identified *T. pallidum* without harbouring macrolide resistance mutations in the azithromycin group (risk difference: 4.8%, 95% CI: −7.8 to 17.3, $P=0.49$).

Table 2. Factors associated with serological response to single-dose benzathine penicillin G or 2 g single-dose azithromycin at 12 months of follow-up in univariate and multivariate analysis

	Univariate analysis			Multivariate analysis		
	Responders ($n=233$)	Non-responders ($n=166$)	*P* value	AOR	95% CI	*P* value
Age, mean (SD), years	32.7 (8.1)	32.7 (6.9)	0.35	1.03	0.99–1.05	0.11
Risk, *n* (%)						
MSM	232 (99.6)	164 (98.8)	0.57	—	—	—
non-MSM	1 (0.4)	2 (1.2)		—	—	—
Syphilis stage, *n* (%)						
primary	29 (12.4)	17 (10.2)	0.53	1	—	—
secondary	106 (45.5)	60 (36.1)	0.07	1.38	0.70–2.74	0.35
early latent	98 (42.1)	89 (53.6)	0.03	1.16	0.72–1.88	0.55
RPR titre, median (IQR)	1:64 (32–128)	1:64 (16–128)	0.001			
RPR titre ≥1:32, *n* (%)	200 (85.8)	116 (69.9)	<0.001	2.56	1.55–4.21	<0.001
CD4 count, mean (SD), cells/mm^3	500 (220)	529 (267)	0.11			
CD4 < 200, *n* (%)	18 (7.7)	9 (5.4)	0.42	1	—	—
200 ≤ CD4 ≤ 350, *n* (%)	39 (16.7)	39 (23.5)	0.10	1.12	0.49–2.76	0.72
CD4 > 350, *n* (%)	176 (75.5)	118 (71.1)	0.36	0.63	0.37–1.06	0.08
PVL, mean (SD), $\log_{10}$ copies/mL	2.59 (1.54)	2.44 (1.46)	0.08			
PVL <400 copies/mL, *n* (%)	150 (64.4)	113 (68.8)	0.46	1.26	0.59–2.70	0.55
Prior history of syphilis, *n* (%)	112 (48.1)	106 (63.9)	0.002	0.54	0.35–0.81	0.003
cART, *n* (%)	178 (76.4)	129 (77.7)	0.81	1.30	0.58–2.93	0.52
Single-dose benzathine penicillin G, *n* (%)	99 (42.5)	63 (40.0)	0.41	0.94	0.59–1.47	0.77

BPG, benzathine penicillin G; cART, combination ART; IQR, interquartile range; PVL, plasma HIV RNA load; RPR, rapid plasma reagin; SD, standard deviation.

Table 3. Adverse effects in patients taking or not taking cART who received azithromycin for treatment of early syphilis

Symptom, *n* (%)	All patients ($n=237$)	Patients with cART ($n=195$)	Patients without cART ($n=42$)	*P* value
Diarrhoea	125 (52.7)	103 (52.8)	22 (52.4)	>0.99
Loose stool	15 (6.3)	12 (6.2)	3 (7.1)	0.73
Abdominal pain	44 (18.6)	36 (18.5)	8 (19.0)	>0.99
Nausea	53 (22.4)	42 (21.5)	11 (26.2)	0.54
Vomiting	3 (1.3)	3 (1.5)	0 (0)	>0.99
Abdominal bloating	42 (17.7)	34 (17.4)	8 (19.0)	0.82
Dizziness	41 (17.3)	33 (16.9)	8 (19.0)	0.82
Headache	9 (3.8)	8 (4.1)	1 (2.4)	>0.99
Vertigo	7 (3.0)	5 (2.6)	2 (4.8)	0.61
Lassitude/somnolence	65 (27.4)	53 (27.2)	12 (28.6)	0.85
Palpitation	0 (0)	0 (0)	0 (0)	—
Jarisch–Herxheimer reaction	35 (14.8)	28 (14.4)	7 (16.7)	0.64

cART, combination ART.

diarrhoea than those who were taking non-PI-based regimens (56.3% versus 48.9%, $P=0.36$), and patients taking non-PI-based regimens had a significantly higher frequency of lassitude/somnolence (34.8% versus 20.4%, $P=0.02$).

Discussion

In this multicentre, prospective observational study of HIV-infected patients who were predominantly MSM, we demonstrate that patients receiving 2 g single dose azithromycin achieved similar serological response rates to those receiving single-dose benzathine penicillin G for early syphilis, regardless of detection of *T. pallidum* without macrolide resistance mutations by PCR assays in the clinical specimens. A high RPR titre (RPR ≥1:32) was an independent predictor of achieving serological response (AOR, 2.56; 95% CI, 1.55–4.21), while a prior history of syphilis was associated with poor serological response after treatment (AOR, 0.54; 95% CI, 0.35–0.81).

Whether azithromycin can be used as an effective alternative to benzathine penicillin G depends on the prevalence of *T. pallidum* with macrolide resistance mutations in areas studied. During 2007–09, a surveillance study to detect 23S rRNA A2058G point mutation in *T. pallidum* strains was conducted across the USA, and the prevalence of macrolide-resistant *T. pallidum* differed from the West region to the Midwest and South regions.[33] In Taiwan, our surveillance study revealed that the prevalence of macrolide resistance of *T. pallidum* remained low.[24,28] While the study population in our study consisted mostly of MSM and HIV-infected patients, our surveillance study suggests that azithromycin could be an alternative option to benzathine penicillin G in the treatment of early syphilis among HIV-infected MSM in Taiwan.

Since 2002, several clinical trials have shown the clinical efficacy of azithromycin for early syphilis (Table S3).[12,15–17] However, the participants enrolled in those studies comprised a higher percentage of female patients (38%–68%) and a lower percentage of subjects with HIV infection (0%–52.1%); moreover, HIV-infected patients had limited access to cART in these reported studies. Therefore, the study results cannot inform the clinical decision in the treatment of early syphilis using azithromycin in HIV-infected MSM when shortage of benzathine penicillin G occurs. While our study demonstrated similar serological response rates between patients in the azithromycin and penicillin groups at 12 months of treatment, the response rates to benzathine penicillin G (61.1%) and azithromycin (56.5% for overall cases and 65.9% for cases of macrolide-susceptible *T. pallidum* infection) are lower compared with those reported in the randomized clinical trial comparing 2 g single-dose azithromycin and benzathine penicillin G in an HIV-negative population.[17] Because the PCR assays used in this study may not be of sufficient sensitivity in the detection of *T. pallidum*, those patients without *T. pallidum* being detected could be cases of macrolide-resistant *T. pallidum* infection. Other causes for non-response encountered in both treatment groups are shown in Table S4. Cases of reinfection indicated by the appearance of new chancres or ≥4-fold increases of RPR titres after initial achievement of serological response increased at 12 months follow-up (56.3%). Similar to our previous report,[8] the lower response rates for the two treatment groups were likely because of higher rates of reinfections with syphilis in HIV-infected MSM.[34,35]

Treatment with azithromycin for early syphilis has several benefits. First, as an alternative oral agent, azithromycin could be administered under supervision in the setting of outpatient clinics. Second, azithromycin is also an effective treatment agent for non-gonococcal urethritis and gonococcal infection, though it is not recommended as routine use for the latter because of concerns about evolving resistance.[7,36] In Taiwan, previous studies have shown *in vitro* activity of azithromycin for *N. gonorrhoeae*.[37,38] Among the 85 patients in our study, 1 had concomitant gonococcal urethritis and 7 chlamydial urethritis who were successfully treated with azithromycin (Table S1). Third, treatment with azithromycin was recently shown to be associated with a significantly lower risk of Jarisch–Herxheimer reactions than that with benzathine penicillin G (14.1% versus 56.3%) and a delayed onset of Jarisch–Herxheimer reactions (8 h versus 4 h).[20]

In our study, gastrointestinal symptoms and lassitude/somnolence were the main adverse effects encountered in patients receiving azithromycin, which appears to be more frequent than those reported in previous clinical trials, in which gastrointestinal symptoms and lassitude/somnolence occurred in 10%–24.4% and 6.7% of the subjects, respectively.[12,17] We postulate that concurrent use of cART and phone calls to actively obtain information on adverse effects might play a role. However, the higher percentage of diarrhoea distributed nearly equally among patients with or without concurrent cART in our study (52.8% versus 52.4%, $P > 0.99$). Limited by the sample size, we were not able to find a statistically significant difference in terms of frequency of diarrhoea between patients who were taking PI-based regimens and those taking non-PI-based regimens in a further analysis of patients taking cART and azithromycin. The association between non-PI-based regimens and a higher frequency of lassitude/somnolence may be attributed to the fact that NNRTI such as efavirenz causes more CNS symptoms than PIs.[39]

There are several limitations in our study and interpretation of our results should be cautious. First, our study is not a randomized controlled trial and the two groups of patients had significant differences in several baseline characteristics for which we were not able to avoid confounding in the analyses. Second, the two groups of patients were included in different periods because of the shortage of benzathine penicillin G in Taiwan; most patients who received azithromycin were enrolled mainly in 2012–13 while most of the patients in the penicillin group was enrolled between 2007 and 2012, although the follow-up schedules for RPR titres were the same for the two treatment groups. Third, our cohort study comprised convenience samples of consecutive patients seeking syphilis treatment and was not powered to demonstrate non-inferiority of azithromycin to benzathine penicillin G. Assuming the lower boundary of the two-sided 95% CI (one-sided $\alpha = 0.025$) for the difference of the serological response rate between the two groups set at -0.1 (i.e. the non-inferiority margin was set to 10%) with serological response rate of 75% for penicillin group, at least 232 patients will be needed for each group to confirm the non-inferiority of azithromycin to benzathine penicillin G with a power of 80%.[8] Lastly, our study was conducted in an area of low prevalence of *T. pallidum* with macrolide resistance and the results may not be generalized to areas of higher prevalence of *T. pallidum* with macrolide resistance.

In conclusion, our study suggests that, in the settings of a low prevalence of macrolide-resistant *T. pallidum*, azithromycin had a similar serological response rate to that of benzathine penicillin G in HIV-infected MSM. The major adverse effects of azithromycin are gastrointestinal symptoms and lassitude/somnolence in those individuals concurrently taking cART.

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Transparency declarations

None to declare.

Supplementary data

Tables S1 to S4 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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