Original research

Clinical efficacy and tolerability of 1.5 g/day oral amoxicillin therapy without probenecid for the treatment of syphilis

Kazuhiko Ikeuchi, Kazuaki Fukushima, Masaru Tanaka, Keishiro Yajima, Akifumi Imamura

ABSTRACT

Objectives Intramuscular benzathine penicillin G is not available in certain countries. In a previous report, 3 g/day amoxicillin with probenecid was shown to be effective in treating syphilis in patients with HIV; however, 7.3% of patients changed their therapy owing to adverse events. The objective of this study was to assess the clinical efficacy and tolerability of 1.5 g/day amoxicillin without probenecid for the treatment of syphilis.

Methods The routine clinical records of patients diagnosed with syphilis and treated with 1.5 g/day amoxicillin at a tertiary care hospital between 2006 and 2018 were retrospectively analysed. Syphilis was diagnosed if serum rapid plasma reagin (RPR) titres were ≥8 RU and the Treponema pallidum latex-agglutination test was positive. Serological cure was defined as a ≥fourfold decrease in the RPR titre within 12 months in symptomatic early syphilis and within 24 months in latent syphilis.

Results Overall, 138 patients (112 with HIV) were analysed. The percentages of primary, secondary, early latent, late latent and syphilis of unknown duration were 8.0%, 50.0%, 25.4%, 5.8% and 10.9%, respectively. The median treatment duration was 4.5 weeks (IQR 4–8 weeks), which was not related to the stage of syphilis. Two patients (1.5%) changed treatment due to skin rash. The rate of serological cure was 94.9% (131/138; 95% CI 89.8% to 97.9%) in patients with HIV and 100% (26/26; 95% CI 86.8% to 100%) in patients without HIV. Treatment duration was not related to the treatment efficacy.

Conclusion The regimen of 1.5 g/day amoxicillin without probenecid is highly effective with a low switch rate in patients with and without HIV.

INTRODUCTION

Syphilis is an STI disease caused by the spirochaete Treponema pallidum. WHO estimated that there were 6.3 million new cases of syphilis in adolescents and adults aged 15–49 years worldwide.1 In the USA, the incidence of syphilis is increasing in men who have sex with men (MSM) and in women and men who have sex with women.2 In the MSM population with syphilis, the rate of coinfection with HIV was relatively high (41.6%).3 Furthermore, a high frequency of asymptomatic neurosyphilis was reported in patients with HIV.4

Although intramuscular benzathine penicillin G is the standard therapy for non-neurosyphilis,3 it is unavailable in some countries, including Japan. In a previous retrospective cohort, 3 g/day amoxicillin with probenecid, which increased the blood concentration of amoxicillin by inhibiting the renal tubular excretion, showed a 95.5% efficacy rate for syphilis in patients with HIV.6 Pharmacokinetically, however, serum treponemicidal level of amoxicillin can be achieved by the standard dose (1.5 g/day) without probenecid.7 8 Plus, taking a high dose of antibiotics could induce increased adverse events. Although Japanese STD guideline has recommended 1.5 g/day of amoxicillin from 2002,9 evidence is lacking. Here, we conducted a retrospective cohort study of oral amoxicillin 1.5 g/day without probenecid in patients with and without HIV.

METHODS

Study design

The routine clinical records of patients diagnosed with syphilis and treated with amoxicillin between 2006 and 2018 at the Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital were retrospectively reviewed. An episode of syphilis was defined as an elevation in the rapid plasma reagin (RPR) titre (≥8 RU) and a positive Treponema pallidum latex-agglutination test (TPLA) result (Sekisui Medical, MEDIACE RPR and TPLA). The exclusion criteria were as follows: (1) treated with a dose of amoxicillin other than 1.5 g/day, (2) treated with probenecid, (3) symptomatic syphilis with an RPR titre <8.0 RU, (4) antimicrobial treatment initiated by a previous physician, (5) RPR titre at treatment initiation (within 28 days) was unavailable and (6) RPR titre was not followed up for 12 months in symptomatic early syphilis and 24 months in latent syphilis. Patients who started treatment by a previous physician were excluded because RPR titre was not followed up for 12 months.
and latent syphilis of unknown duration were classified as late syphilis. Early latent syphilis was defined as asymptomatic syphilis acquired within 12 months.

The primary outcome was serological cure. According to the Centers for Disease Control and Prevention’s (CDC) STD guidelines, serological cure was defined as a ≥fourfold decrease in the RPR titre within 12 months in symptomatic early syphilis and 24 months in latent syphilis. Patients who failed to achieve a ≥fourfold decrease in the RPR titre during the defined period or required additional treatment were defined as treatment failure. Reinfection was defined as a ≥fourfold increase in the RPR titre, after the previous episode of syphilis had previously met the serological cure criteria. Secondary outcomes included (1) the proportion of a change in antibiotics (ie, tolerability) and (2) time to a twofold and fourfold decrease in the RPR titre.

Data collection
The following variables were collected from routine clinical records: age, sex, previous history of syphilis, stage of syphilis, baseline RPR titre, baseline TPLA titre, HIV infection, CD4 counts, HIV viral load, duration of amoxicillin treatment and adverse events. RPR titre and clinical symptoms were also followed by medical record until serological cure. Even in patients who did not meet the serological cure criteria, the RPR titre and neurological symptoms were retrieved from the medical records for as long as possible.

Statistical analysis
Data analysis was performed using EZR V.1.41 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is based on R. The proportion of patients with serological cure and an exact 95% CI was calculated using the binomial distribution. We did not estimate the risk factor of treatment failures as the number of treatment failures was too small (n=7). Baseline characteristics were compared between patients with and without HIV using the Mann-Whitney U test for continuous variables and Fisher’s exact test for categorical variables. Statistical significance was defined as a two-sided p value <0.05.

RESULTS
During the study period, 218 patients with syphilis received oral amoxicillin and 80 patients were excluded (figure 1). Seventeen patients were treated by different doses of amoxicillin monotherapy (7.5 g, n=4; 1.0 g, n=1; 2.25 g, n=12) and four patients received 3 g/day amoxicillin and probenecid, but baseline characteristics were similar to other patients (data not shown). RPR titre was not followed until defined periods (ie, 12 months in early syphilis and 24 months in latent syphilis) in 30 patients: 10 patients who did not come to hospital for follow-up RPR tests (HIV, n=1; non-HIV, n=9), 7 patients who changed hospitals (HIV, n=6; non-HIV, n=1) and 13 patients in whom adequate RPR tests were not performed by their physicians (HIV, n=10; non-HIV, n=3).

A total of 138 patients, including 112 patients with HIV and 26 patients without HIV, were analysed. Median follow-up period was 3 months (IQR 2–5.25 months; range 1–53 months). Compared with the group of patients without HIV, those with HIV had more men (100% vs 53.8%, p<0.001), a higher median age (44 vs 34 years, p<0.05), a history of syphilis treatment (50.1% vs 0%, p<0.001), a higher median RPR titre (129.8 vs 77.8 RU, p<0.05) and a higher median TPLA titre (8234 vs 3435 TU, p<0.05). In patients with HIV, the median CD4 count was 481/μL (IQR 351.3–575.3/μL), and the percentage of patients with HIV viral load <50 copies/mL was 80.4% (90/112).

The rate of serological cure was 94.9% (131/138; 95% CI 89.8% to 97.9%) overall, 93.8% (105/112; 95% CI 87.5% to 97.5%) in patients with HIV, 100% (26/26; 95% CI 86.8% to 100%) in patients without HIV, 94.8% (109/115; 95% CI 89.0% to 98.1%) in early syphilis and 95.7% (22/23; 95% CI 78.1% to 99.9%) in late syphilis. The median treatment duration was 4.5 weeks (IQR 4–8 weeks; range 4–14 weeks), which was not related to the stage of syphilis or treatment efficacy (online supplemental table 1). All seven patients with treatment failures had HIV; however, their CD4 counts and HIV viral loads were not significantly different from those of patients with HIV with serological cure. In the treatment failure group, lumbar puncture tests were not performed; however, no patient developed neurological symptoms, ocular symptoms or dementia from the start of treatment to the last visit (median 66 months; range 24–102 months). Among them, five patients achieved a fourfold decline in RPR titre after 25–55 months without additional treatment (table 2). Patient 4 developed a rash and elevation in the RPR titre in the 12th month, most likely due to reinfection rather than treatment failure. This patient received another course of treatment with 1.5 g/day amoxicillin for 4 weeks and achieved a fourfold decrease in the RPR titre after 6 months. Patient 2 showed a 66% decrease in the RPR titre after 16 months and changed hospitals.

The median time to a fourfold decrease in the RPR titre was 3 months (range 1–14 months) in patients with serological cure. Among the 138 patients, 57.2% (79/138) achieved a fourfold decrease within 3 months, 82.6% (114/138) within 6 months and 93.5% (129/138) within 12 months (figure 2). The percentage of twofold decrease in RPR titre was 77.5% (107/138) within 3 months, 94.9% (131/138) within 6 months and 98.6% (136/138) within 12 months. Of note, all 107 patients who achieved a twofold decline in the RPR titre within 3 months met the criteria of serological cure later, during the follow-up period.

Two female patients without HIV and without any history of syphilis changed amoxicillin to tetracycline (one minocycline and the other doxycycline) because of a skin rash (2/138, 1.5%; 95% CI 0.2% to 5.2%). After changing the antibiotics, both recovered successfully. One male patient with HIV reported skin pruritus; however, he completed 8 weeks of amoxicillin therapy. No other adverse events, such as diarrhea or liver enzyme elevation, were reported in the medical records.

Figure 1 Study flow chart. RPR, rapid plasma reagin.

218 patients were diagnosed with syphilis and received oral amoxicillin therapy during the study period

Exclusions
- Treated with amoxicillin other than 1.5 g/day dose, n=21
- Four patients received probenecid
- Symptomatic syphilis - RPR 8.0 RU, n=4
- Treatment initiation by previous doctor, n=13
- RPR titre on treatment initiation is unavailable, n=12
- RPR titre was not followed until 12 months in symptomatic early syphilis and 24 months in latent syphilis, n=30

138 patient were treated with 1.5 g/day of amoxicillin
112 patients living with HIV
26 patients living without HIV

Figure 1 Study flow chart. RPR, rapid plasma reagin.
rate of treatment switching due to adverse events. In a previous report, 286 patients were treated with 3 g/day of amoxicillin with probenecid, and 273 patients (95.5%) achieved a ≥fourfold decrease in the RPR titre within 24 months regardless of stage. Nevertheless, 28 patients (9.8%) experienced adverse events, including skin rash, fever and diarrhoea. Among them, 21 patients (7.3%) switched to doxycycline and 7 patients discontinued treatment after a median of 10 days, while only 2 patients without HIV changed the treatment in our study, and none of the patients with HIV changed their treatment.

Pharmacokinetically, 1.5 g/day oral amoxicillin can achieve sufficient serum treponemicidal levels. To estimate the treponemicidal level of the antibiotics, the T. pallidum immobilisation assay has been used because of difficulties in culturing in vitro. The antibiotic level to inhibit 50% of T. pallidum mobilisation is reported as 0.003 µg/mL of penicillin and 0.070 µg/mL of amoxicillin. WHO determined the treponemicidal level of penicillin as 0.018 µg/mL (0.03 IU/mL) with safety margins based on these results. Following this, the estimated treponemicidal level of amoxicillin was extrapolated to be 0.42 µg/mL. Even a single dose of 0.5 g oral amoxicillin can achieve a treponemicidal level for 6–8 hours, therefore, we believe that 1.5 g/day amoxicillin is effective for syphilis. Recently, a culture system of T. pallidum in vitro has been developed, which is expected to provide a more accurate estimate of the minimum inhibitory concentration of antibiotics.

### Table 1  Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n=138)</th>
<th>Patients with HIV (n=112)</th>
<th>Patients without HIV (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>43 (34–49)</td>
<td>44 (36–50)</td>
<td>34 (27–43)</td>
</tr>
<tr>
<td>Male sex</td>
<td>126 (91.3%)</td>
<td>112 (100%)</td>
<td>14 (53.8%)</td>
</tr>
<tr>
<td>CD4 counts (µL)*</td>
<td>–</td>
<td>481 (351.3–575.3)</td>
<td>–</td>
</tr>
<tr>
<td>HIV-RNA &lt;50 copies/mL</td>
<td>–</td>
<td>90 (80.4%)</td>
<td>–</td>
</tr>
<tr>
<td>History of syphilis</td>
<td>57 (41.3%)</td>
<td>57 (50.1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Stage of syphilis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11 (8.0%)</td>
<td>6 (5.4%)</td>
<td>5 (19.2%)</td>
</tr>
<tr>
<td>2</td>
<td>69 (50.0%)</td>
<td>59 (52.7%)</td>
<td>10 (38.5%)</td>
</tr>
<tr>
<td>Early latent</td>
<td>35 (25.4%)</td>
<td>32 (28.6%)</td>
<td>3 (11.5%)</td>
</tr>
<tr>
<td>Late latent</td>
<td>8 (5.8%)</td>
<td>4 (3.6%)</td>
<td>4 (15.4%)</td>
</tr>
<tr>
<td>Unknown duration</td>
<td>15 (10.9%)</td>
<td>11 (9.8%)</td>
<td>4 (15.4%)</td>
</tr>
<tr>
<td>Baseline RPR titre (RU)*</td>
<td>1083 (58.3–218.9)</td>
<td>1298 (60.6–247.5)</td>
<td>77.8 (53.6–113.1)</td>
</tr>
<tr>
<td>Baseline TPLA titre (TU)*</td>
<td>6109 (2933–17 918)</td>
<td>8234 (3325–23 571)</td>
<td>3435 (640–5272)</td>
</tr>
<tr>
<td>Treatment duration (week)*</td>
<td>4.5 (4–8)</td>
<td>4 (4–8)</td>
<td>6 (4–8)</td>
</tr>
<tr>
<td>Serological cure†</td>
<td>131 (94.9%)</td>
<td>105 (93.8%)</td>
<td>26 (100%)</td>
</tr>
<tr>
<td>Switch to other regimens</td>
<td>2 (1.4%)</td>
<td>0 (0%)</td>
<td>2 (7.7%)</td>
</tr>
</tbody>
</table>

*Median (IQR).
†Serological cure was defined as a ≥fourfold decrease in the RPR titre within 12 months in symptomatic early syphilis and 24 months in latent syphilis. RPR, rapid plasma reagin; TPLA, Treponema pallidum latex-agglutination.

### Table 2  Patients with treatment failure

<table>
<thead>
<tr>
<th>No</th>
<th>Age (years)</th>
<th>Sex</th>
<th>CD4 (µL)</th>
<th>HIV-RNA copies/mL</th>
<th>History</th>
<th>Stage</th>
<th>RPR (RU)</th>
<th>TPLA (TU)</th>
<th>Treatment duration (weeks)</th>
<th>Time to twofold decrease in RPR titre (months)</th>
<th>Time to fourfold decrease in RPR titre (months)</th>
<th>Second treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36</td>
<td>Male</td>
<td>530</td>
<td>&lt;20</td>
<td>Yes</td>
<td>2</td>
<td>79.8</td>
<td>6814</td>
<td>8</td>
<td>4</td>
<td>29</td>
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</tr>
<tr>
<td>2</td>
<td>47</td>
<td>Male</td>
<td>357</td>
<td>&lt;20</td>
<td>No</td>
<td>2</td>
<td>126.5</td>
<td>11435</td>
<td>8</td>
<td>9</td>
<td>–</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>Male</td>
<td>633</td>
<td>Undetectable</td>
<td>Yes</td>
<td>Early latent</td>
<td>56.7</td>
<td>4033</td>
<td>4</td>
<td>8</td>
<td>32</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>Male</td>
<td>270</td>
<td>10 000</td>
<td>Yes</td>
<td>Early latent</td>
<td>146</td>
<td>12 450</td>
<td>6</td>
<td>–</td>
<td>–</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>53</td>
<td>Male</td>
<td>452</td>
<td>Undetectable</td>
<td>No</td>
<td>Late latent</td>
<td>506</td>
<td>72 298</td>
<td>8</td>
<td>6</td>
<td>55</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>52</td>
<td>Male</td>
<td>495</td>
<td>Undetectable</td>
<td>Yes</td>
<td>Early latent</td>
<td>205.6</td>
<td>3249</td>
<td>8</td>
<td>11</td>
<td>25</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>49</td>
<td>Male</td>
<td>500</td>
<td>&lt;20</td>
<td>Yes</td>
<td>Early latent</td>
<td>72.6</td>
<td>9416</td>
<td>4</td>
<td>17</td>
<td>48</td>
<td>No</td>
</tr>
</tbody>
</table>

RPR, rapid plasma reagin; TPLA, Treponema pallidum latex-agglutination.

### DISCUSSION

Our findings indicate that treatment with 1.5 g/day of amoxicillin without probenecid is highly effective for the treatment of syphilis; comparable to the standard therapy. The current STD guidelines by the CDC recommend administering 2.4 million units of benzathine penicillin G intramuscularly in a single dose for early syphilis, and a total of 7.2 million units divided into three doses at 1 week intervals for late syphilis. In these regimens, the serological response rate of penicillin G was reported to be 88%–100% in early syphilis, and approximately 60% in late syphilis. Although the number of late syphilis cases in our study was small, it is noteworthy that 95.7% (22/23) of patients with late syphilis were successfully treated with the present oral regimen.

Compared with a previous report evaluating the efficacy and safety of 3 g/day amoxicillin with probenecid for syphilis in patients with HIV, 1.5 g/day amoxicillin without probenecid achieved comparable treatment efficacy but with a relatively low rate of treatment switching due to adverse events. In a previous report, 286 patients were treated with 3 g/day of amoxicillin with probenecid, and 273 patients (95.5%) achieved a ≥fourfold decrease in the RPR titre within 24 months regardless of stage. Nevertheless, 28 patients (9.8%) experienced adverse events, including skin rash, fever and diarrhoea. Among them, 21 patients (7.3%) switched to doxycycline and 7 patients discontinued treatment after a median of 10 days, while only 2 patients without HIV changed the treatment in our study, and none of the patients with HIV changed their treatment.

Pharmacokinetically, 1.5 g/day oral amoxicillin can achieve sufficient serum treponemicidal levels. To estimate the treponemicidal level of the antibiotics, the T. pallidum immobilisation assay has been used because of difficulties in culturing in vitro. The antibiotic level to inhibit 50% of T. pallidum immobilisation is reported as 0.003 µg/mL of penicillin and 0.070 µg/mL of amoxicillin. WHO determined the treponemicidal level of penicillin as 0.018 µg/mL (0.03 IU/mL) with safety margins based on these results. Following this, the estimated treponemicidal level of amoxicillin was extrapolated to be 0.42 µg/mL. Even a single dose of 0.5 g oral amoxicillin can achieve a treponemicidal level for 6–8 hours, therefore, we believe that 1.5 g/day amoxicillin is effective for syphilis. Recently, a culture system of T. pallidum in vitro has been developed, which is expected to provide a more accurate estimate of the minimum inhibitory concentration of antibiotics.
In the present study, although treatment duration varied between 4 and 14 weeks, treatment duration was not correlated with treatment efficacy. Japanese STD guidelines recommend 4–8 weeks of amoxicillin 1.5 g/day for early syphilis and 8–12 weeks for late syphilis. The need to take amoxicillin for at least 4 weeks is a disadvantage of this regimen. However, shorter treatment can be sufficient for early syphilis because one shot of benzathine penicillin G cannot achieve a treponemical level maintained for such a prolonged time. In addition, the regimen of 3 g/day amoxicillin with probenecid for 14 days was shown to be effective. Considering the multiplication time of *T. pallidum*, WHO recommends maintaining treponemical levels of antibiotics for 7–10 days with a maximum of 24–30 hours of subtreponemical intervals for early syphilis. Therefore, treatment with amoxicillin 1.5 g/day for 14 days may also be effective for early syphilis.

To the best of our knowledge, this is the first report evaluating the utility of a ≥twofold decrease in an automated RPR titre to assess the serological cure. Unlike other STIs, symptoms of syphilis can improve spontaneously without treatment and cause latent infection, including neurosyphilis. Hence, the evaluation of treatment efficacy depends on the improvement of symptoms and on the decrease of a non-treponemical titre. This time lag makes it difficult to assess the treatment efficacy. The automated RPR test, which is commonly used in Japan and Korea, has a strong correlation with the conventional manual RPR card test (Spearman’s r=0.931) in evaluating both the diagnosis and treatment efficacy of syphilis. The automated RPR titre tends to be faster than the manual RPR card test to achieve a ≥fourfold decrease, as shown in some studies. Although automated RPR tests may introduce some random error during sample dilution, it does not rely on interpretation by a technician, so a twofold change in the titre is a clinically meaningful difference in the automated RPR test. In our study, 77.5% of patients achieved a twofold decrease in the RPR titre within 3 months, and all achieved a fourfold decrease in the RPR titre. On the other hand, it is known that automated RPR titre could fluctuate in the first 6 months. Because the number of patients who failed treatment was too small in our study, additional research is needed to confirm whether the automated RPR test could make the assessment of treatment response quicker than the manual test.

Our study has some limitations. First, 21 patients treated with doses other than 1.5 g/day of amoxicillin were excluded and might have caused selection bias. In addition, some patients were treated with other antibiotics (oral benzylpenicillin 85; intravenous benzylpenicillin 7; minocycline 8; doxycycline 2). Intravenous benzylpenicillin was selected when neurosyphilis was suspected, and tetracycline was selected due to penicillin allergy, but the number of these patients were small. Oral benzylpenicillin is an old antibiotic that was previously used in Japan, but was considered to have low bioavailability and was gradually replaced by amoxicillin by 2015. Because the same clinicians tended to choose the same regimen, we believe that this is not a major selection bias. Second, there was a variety of treatment duration. As we discussed above, treatment duration was not related to the stage of syphilis and treatment efficacy, but treatment duration depended on the experience of clinicians. It is necessary to perform a prospective study to assess the efficacy and tolerability of 1.5 g/day amoxicillin with a uniform duration. Third, because this is an oral regimen, adherence to amoxicillin was unknown. However, we believe that adherence was high in patients with HIV because most of the patients received routine education about antiviral medicine from trained medical staff and were regularly administered oral medicines. As discussed above because the level of serum amoxicillin and the duration of treatment are sufficiently high, adherence is not expected to significantly affect the treatment outcome. Fourth, the reasons for treatment failure were not fully examined. In patient 4, an elevation of the RPR titre was seen after treatment. However, he was successfully treated with the same regimen. Consequently, we believe that this case was not neurosyphilis but reinfection. In the other cases, although lumbar puncture was not performed, clinicians regarded these cases as having a significant decrease in the RPR titre. In addition, the RPR titre decreased by ≥fourfold in the end after 24 months in five out of the six patients. These patients may have been successfully treated. Fifth, patients with a slow decrease in RPR titre might have been more likely to be excluded because of insufficient follow-up periods and treatment efficacy could be overestimated. However, the median observational period in these excluded patients was only 2 months, and clinicians were expected to follow the RPR titres when they assumed that the patients had treatment failures because of the slow decrease in the RPR. Therefore, we
believe these excluded patients had little effect on the rate of serological cure. Finally, not all patients were checked for an RPR titre regularly (eg, monthly), so the time to RPR decrease was not precise. Nevertheless, as it is likely to be overestimated, we were able to assess the treatment efficacy earlier than discussed above.

In conclusion, 1.5 g/day of amoxicillin without probenecid is highly effective with a low switch rate in patients with and without HIV. This regimen could serve as an alternative regimen in countries where benzathine penicillin G is not available.

**Key messages**

- A regimen of 1.5 g/day oral amoxicillin was highly effective against early and late non-neurosyphilis.
- This regimen was reliably tolerable compared with previously reported oral regimens.
- With the use of automated rapid plasma reagin (RPR) method, ≥twofold decrease of RPR titre within 3 months might be sufficient to determine the efficacy of treatment.

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**Provenance and peer review** Research ethics at our hospital (approval number: 1975). Ethic approval number 1975.

**Data availability statement** Data are available on reasonable request. Our patient data is available from fukushima-ori@umin.ac.jp.

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**REFERENCES**


