Treatment of Chancroid

YUSUF DANGOR,* RONALD C. BALLARD, STEVEN D. MILLER, AND HENDRIK J. KOORNHOF
Emergent Pathogen Research Unit of the South African Medical Research Council, School of Pathology, University of the Witwatersrand, and South African Institute for Medical Research, P.O. Box 1038, Johannesburg 2000, South Africa

INTRODUCTION

The finding that sexually acquired genital ulcer disease, in particular chancroid, is a major cofactor in the heterosexual transmission of human immunodeficiency virus (HIV) (14, 35) has increased the urgency for the implementation of simple, effective, and inexpensive treatment regimens for chancroid which could be incorporated into HIV-control programs in developing countries.

Prior to the Vietnam war, the sulfonamides, tetracycline, and, in some regions, penicillin were accepted as adequate therapy for chancroid (43). Treatment failures with these antimicrobial agents which correlated with in vitro resistance were subsequently recorded in both the Far East (24) and Africa (11). At the present time, multidose therapy with either erythromycin or co-trimoxazole is regarded as the treatment of choice for the disease in most endemic areas. However, recently, single-dose therapies with compounds exhibiting suitable pharmacokinetic properties and good in vitro activity against Haemophilus ducreyi have yielded cure rates in excess of 90% (34, 38).

CORRELATION OF IN VITRO TEST RESULTS WITH IN VIVO EFFICACY

Although animal models for chancroid infection have been described (33, 41), they have not been used routinely for evaluating the efficacy of various treatments for the disease. Thus, the validity of in vitro susceptibility testing techniques has to be confirmed almost exclusively by human clinical trials. Lack of standardization of methodology for antimicrobial susceptibility testing of H. ducreyi is potentially an important variable. However, despite inconsistencies in the techniques used, a good correlation between in vitro results and clinical outcome has been obtained by using conventional breakpoint values (5, 8, 11; R. C. Ballard, H. G. Fehler, and B. S. Msikinya, Proc. 13th Int. Congr. Chemother., p. 16/21–16/24, 1983). However, occasional treatment failures, e.g., with spectinomycin, have occurred, even when the organism appears to be fully susceptible to the antimicrobial agent used (S. D. Miller, M. O. Duncan, H. G. Fehler, R. C. Ballard, and H. J. Koornhof, Proc. 15th Int. Congr. Chemother., p. 1338–1340, 1987).

CRITERIA FOR CLINICAL RESPONSES

Important objectives that have been found to correlate best with clinical outcome include rapid sterilization of the ulcer and early epithelialization of the ulcer base. Ideally, cultures of ulcer material should become sterile within 72 h (3, 25, 26) and clinical cure should ultimately be based on reepithelialization, which is usually complete by day 10 (5) but may be delayed up to 28 days (2). The majority of patients who do not show improvement of ulcers within 7 days (4, 5, 26, 40) should be regarded as treatment failures and therefore require therapy with an alternative agent. In general, clinical improvement has been associated with a decrease in pain at the ulcer site, disappearance of the purulent base of the ulcers, onset of epithelialization, and failure to reisolate H. ducreyi. Apart from the action of the antimicrobial agent, the rate of healing of ulcers appears to be affected by the initial size and site of the lesions (3, 9, 19).

In contrast, resolution of inguinal buboes should not be used as a criterion for the clinical efficacy of an antimicrobial agent since temporary progression of existing buboes with or without fluctuation may occur during the course of adequate antimicrobial chemotherapy. Aspiration of fluctuant buboes is frequently required to prevent spontaneous rupture and formation of inguinal or femoral ulcers. In such cases, culture of bubo material should be performed to exclude microbial persistence.

THERAPEUTIC TRIALS

The results of therapeutic trials of various antimicrobial agents in which cure rates of ≥90% have been obtained are summarized in Table 1. The emergence of β-lactamase-producing strains of H. ducreyi (16) suggests a limited role for the treatment of chancroid with penicillin or other β-lactamase-susceptible antibiotics. However, treatment of chancroid with amoxicillin plus clavulanic acid has yielded cure rates of over 90% in patients in Kenya (12, 30). Among the other beta-lactam antibiotics tested, ceftriaxone, which has a long half-life, gave excellent results following single-dose administration in two studies in Kenya and Thailand (5, 40) and was recently accepted as one of the treatments of choice for the disease by the Centers for Disease Control (7).

Erythromycin has proved to be consistently effective in the treatment of chancroid (6, 9, 20, 28) and has been accepted as one of the treatments of choice for chancroid worldwide. However, no significant difference in cure rates could be detected when patients in Johannesburg, South Africa, were treated with erythromycin stearate (500 mg four times daily) for 7, 14, or 21 days (9), indicating that a shorter duration of therapy could be effective. In a subsequent dose-finding study, single-dose erythromycin (1,500 mg) and other short-course regimens proved to be unsatisfactory in the treatment of the disease but good clinical and microbiological responses were recorded (>90% cure rates) when patients were treated with 500 mg three times daily for 3 days (3). Later in an open, controlled, comparative study, no treatment failures were recorded among 57 patients treated with such a 5-day course of erythromycin base (Miller et al., 15th ICC).

The quinolones roxocin, ciprofloxacin, enoxacin, norfloxacin, and fleroxacin have all proved to be effective in the treatment of chancroid (1, 3, 4, 15, 23, 25, 26). Although some of these agents have been found to be effective following single-dose administration, the efficacy of such...
TABLE 1. Treatment of culture-proven chancroid with antimicrobial agents with cure rates of ≥90%

<table>
<thead>
<tr>
<th>Country</th>
<th>Yr</th>
<th>Antibiotic</th>
<th>Dosagea</th>
<th>Cure rate (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenya</td>
<td>1981</td>
<td>Cefotaxime</td>
<td>1 g i.m.i. + 1 g of probenecid for 3 days</td>
<td>95</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>1986</td>
<td>Amoxicillin-clavulanic acid</td>
<td>500/250 mg t.i.d. for 3 days</td>
<td>95</td>
<td>27</td>
</tr>
<tr>
<td>Thailand</td>
<td>1984</td>
<td>Ceftiraxone</td>
<td>250 mg i.m.i., single dose</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>Kenya</td>
<td>1983</td>
<td>Erythromycin</td>
<td>500 mg q.i.d. for 10 days</td>
<td>100</td>
<td>28</td>
</tr>
<tr>
<td>South Africa</td>
<td>1983</td>
<td>Erythromycin</td>
<td>500 mg q.i.d. for 7 days</td>
<td>98</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>1987</td>
<td>Erythromycin</td>
<td>500 mg t.i.d. for 5 days</td>
<td>97</td>
<td>Miller et al., 15th ICC</td>
</tr>
<tr>
<td>Kenya</td>
<td>1981</td>
<td>TMP-SMX</td>
<td>160/800 mg b.i.d. for 7 days</td>
<td>100</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>1983</td>
<td>TMP-SML</td>
<td>160/800 mg b.i.d. for 5 days</td>
<td>96</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>1985</td>
<td>TMP-SMO</td>
<td>160/800 mg b.i.d. for 5 days</td>
<td>100</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>1987</td>
<td>TMP-SMX</td>
<td>160/800 mg b.i.d. for 3 days</td>
<td>96</td>
<td>26</td>
</tr>
<tr>
<td>South Africa and Zimbabwe</td>
<td>1989</td>
<td>TMP-SMP</td>
<td>1,000/800 mg, single dose</td>
<td>93</td>
<td>3</td>
</tr>
<tr>
<td>Kenya</td>
<td>1984</td>
<td>Rosoxacin</td>
<td>150 mg b.i.d. for 3 days</td>
<td>95</td>
<td>15</td>
</tr>
<tr>
<td>Thailand</td>
<td>1987</td>
<td>Ciprofloxacin</td>
<td>500 mg, single dose</td>
<td>100</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>500 mg, two doses, 12 h apart</td>
<td>98</td>
<td>4</td>
</tr>
<tr>
<td>South Africa</td>
<td>1988</td>
<td>Ciprofloxacin</td>
<td>500 mg, single dose</td>
<td>96</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1,000 mg, single dose</td>
<td>100</td>
<td>3</td>
</tr>
<tr>
<td>Thailand</td>
<td>1987</td>
<td>Norfloxacin</td>
<td>800 mg, single dose</td>
<td>94</td>
<td>1</td>
</tr>
<tr>
<td>Kenya</td>
<td>1983</td>
<td>Rifampin</td>
<td>600 mg daily for 3 days</td>
<td>100</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>1987</td>
<td>Spectinomycin</td>
<td>2 g i.m.i., single dose</td>
<td>94</td>
<td>13</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>1981</td>
<td>Thiamphenicol</td>
<td>2.5 g followed by 1.25 g 1 wk later</td>
<td>94</td>
<td>21</td>
</tr>
<tr>
<td>South Africa</td>
<td>1982</td>
<td>Minocycline</td>
<td>100 mg b.i.d. for 10 days</td>
<td>91</td>
<td>Ballard et al., 13th ICC</td>
</tr>
</tbody>
</table>

a Abbreviations: TMP, trimethoprim; SMX, sulfamethoxazole; SML, sulfamethole; SMO, sulfamoxole; SMP, sulfamethopyrazine.
b Abbreviations: i.m.i., intramuscular injection; t.i.d., three times a day; q.i.d., four times a day; b.i.d., two times a day.

single-dose regimens in populations with high rates of HIV type 1 infection remains to be confirmed. Recently, fleroxacin in a single oral dose was found to be effective therapy for microbiologically proven chancroid in Kenya in the absence of HIV infection. However, among HIV-infected men, a single dose of 200 or 400 mg of the antibiotic proved to be inadequate therapy for the disease (3 of 11 HIV-infected men [27%] had bacteriological failures) (23). Sulphonamide-trimethoprim combinations have also become established as one of the treatments of choice for the disease in many areas. In particular, multidose therapy with sulfamethoxazole-trimethoprim has been widely used (12, 19). Single-dose administration of combinations containing longer-acting sulphonamides was also evaluated in Kenya (30) and South Africa and Zimbabwe (3) with encouraging results. However, failure rates of 22 and 45% with sulphonamide-trimethoprim combinations were recently recorded in Kenya (25) and Thailand, where in vitro trimethoprim resistance has become widespread (39, 40). Sulphonamides alone are no longer recommended for the treatment of the disease in Africa or the Far East (12, 40).

The clinical efficacy of rifampin alone (600 mg once daily for 3 days) or combined with trimethoprim (600/160 mg as a single dose or daily for 3 days) was evaluated in Nairobi, Kenya (31). The respective cure rates recorded were 100, 91 and 94%.

Single-dose therapy with spectinomycin gave encouraging results in Kenya (13), but somewhat less favorable responses were recorded in South Africa (Miller et al., 15th ICC). Interestingly, spectinomycin appears to prevent progression of buboes more efficiently than either erythromycin base (Miller et al., 15th ICC) or co-trimoxazole (13), but the mechanism remains unknown. Although kanamycin and streptomycin have also been used successfully for the treatment of the disease (24, 42), treatment failures with these agents have been reported in Singapore (32), and failures with gentamicin have also been recorded in The Netherlands (37).

Thiamphenicol was found to be effective for the treatment of chancroid in Harare, Zimbabwe, where one initial oral dose of 2.5 g followed by 1.25 g given 7 days later yielded a cure rate of 94% (21). Subsequently, two doses of 2.5 g given on consecutive days were found to be equally effective (22).

The results obtained following tetracycline therapy have varied from good to poor (2, 17, 18, 24, 36). The longer-acting tetracycline derivatives minocycline and doxycycline have also been evaluated in a comparative study in South Africa. Significantly higher cure rates were obtained following treatment with minocycline than with doxycycline given at the same dosage (Ballard et al., 13th ICC). In this study, treatment outcome showed good correlation with in vitro susceptibilities of the isolates to the two tetracycline analogs.

SUMMARY AND PROSPECTS

Since the emergence of resistance to penicillin, tetracycline, and sulfonamides, erythromycin (500 mg three times daily for 7 days) or trimethoprim-sulfamethoxazole (160/800 mg twice daily for 7 days) has become established as the treatment of choice for chancroid. However, the duration of treatment with these agents could be shortened to 5 and 3 days, respectively, with a substantial saving in costs. Based on in vitro susceptibility testing, the most active drugs against H. ducreyi are ceftriaxone, ciprofloxacin, and roxithromycin. The former two agents are effective in single-
dose regimens, while the optimal dosage and duration of treatment of roxithromycin remain to be established. These agents may well emerge as acceptable alternatives for routine use, but problems may be encountered in populations with high rates of HIV infection. Other considerations, such as cost, patient compliance, and toxicity, are important factors in the choice of future regimens. The possibility of emergence of resistance to rifampin and the fact that this very active drug should probably be reserved for use in patients with tuberculosis mitigate against its acceptance for routine use in the treatment of chancroid. In the light of the experience of emergence of resistance in H. ducreyi, antimicrobial susceptibilities to drugs used routinely at present or in the future should be monitored closely.

With regard to the assessment of prospective antimicrobial agents, standardization of the criteria used for bacteriologic and clinical cure is desirable. Based on the experience of several workers (3, 26, 31), sterilization of the ulcer within 72 h should constitute a bacteriologic cure and persistence of viable organisms in ulcers or subsequent aspirates of fluctuant buboes should constitute evidence treatment failure. Although complete epithelialization of primary ulcerations may take up to 28 days, in the majority of cases it is achieved within 10 days. Lack of improvement with regard to pain at the ulcer site, purlulence of the ulcer base, and lack of epithelialization by day 7 after the onset of therapy also constitute evidence for treatment failure. Allowance should also be made for temporary progression in size of buboes and development of fluctuation despite initiation of effective therapy. In rare cases, concomitant infection with herpes simplex virus may result in apparent clinical relapse.

While nontherapeutic measures, such as elective circumcision, may play an important role in control of chancroid, the prompt use of effective affordable therapy for the disease should be a high priority among measures which could be introduced to control the heterosexual transmission of HIV in developing countries.

LITERATURE CITED


