Clinical outcomes of Ghanaian Buruli ulcer patients that defaulted from antimicrobial therapy

Sandor Klis, Riemer Kingma, Richard O. Phillips, Tjip S. van der Werf, Ymkje Stienstra

Submitted
Abstract

Objectives
Buruli ulcer (BU) is a tropical skin disease caused by infection with Mycobacterium ulcerans, which is currently treated with 8 weeks of streptomycin and rifampicin. The evidence to treat BU for a duration of 8 weeks is limited; a recent retrospective study from Australia suggested that a shorter course of antimicrobial therapy might be equally effective. We studied the outcomes of BU in a cohort of Ghanaian patients who defaulted from treatment and as such received less than 8 weeks of antimicrobial therapy.

Methods
Charts from a cohort of BU patients that were treated at Nkawie-Toase hospital between 2008–2012. Number of days of antimicrobial therapy and patient and lesion characteristics were recorded.

Results
One hundred thirty seven out of 316 patients defaulted from therapy or wound care. Forty-seven defaulters with follow-up completed had received less than 56 days of antibiotics. 81% of these patients healed after 32 days or less of antibiotics. There was a significantly increased rate of healing in smaller lesions; 94% of WHO category I lesions had healed after 32 days or less of antibiotics.

Conclusion
Although numbers were small, and a potential for bias exists, our findings suggest that a reduction of the duration of antimicrobial therapy in BU in small, early lesions is feasible. These findings can serve as a basis for future well-designed studies.
Introduction

Buruli ulcer (BU) is a neglected tropical disease caused by infection with *Mycobacterium ulcerans*. It has been reported in 33 countries, but is currently most prevalent in West-Africa. After an incubation period of several months, the disease typically starts with a painless nodule that progresses into an ulcer over the course of several weeks (1). Delayed or inadequate treatment can result in extensive scarring and disabilities.

Treatment with antibiotics has been available for over a decade, and has replaced surgical excision as the primary treatment modality (2). The current WHO-recommended antibiotic regimen is 8 weeks of daily oral rifampicin and intramuscular streptomycin. High rates of cure are achieved with this regimen, but the associated pain, loss of productivity, and toxicity are a concern, and can lead to large numbers of defaulters and loss to follow-up (3–6).

Shortening the duration of therapy reduces toxicity, costs, discomfort, and treatment-related loss of productivity (4). In addition, it is likely to improve adherence (7, 8). Other mycobacterial diseases are also treated with lengthy antimicrobial regimens. The duration of drug therapy for multi-bacillary leprosy – formerly, a life-long treatment – was reduced to 12 months in 1997, and recently the addition of clofazimine to multidrug treatment for *Mycobacterium tuberculosis* has been shown to potentially halve treatment duration in the mouse model (9, 10). The currently advocated 8 weeks of therapy for *M. ulcerans* infection are largely based on a small, WHO-sponsored pilot study (11). In this study BU lesions were surgically excised after 0, 2, 4, 6, and 8 weeks of streptomycin-rifampicin combination therapy. Lesions excised after 0 or 2 weeks were culture positive, whereas lesions excised after 4 weeks or more were culture negative. However, as *M. ulcerans* is a slow-growing organism, a safety margin of an additional 4 weeks was chosen, based on expert opinion.

A recent observational study in an Australian BU cohort demonstrated that a shorter duration of antibiotic therapy in patients with side-effects of the treatment resulted in high rates of cure in patients who also underwent surgery, and in a small number of patients who did not have surgery (6). Most patients with Buruli ulcer live in West-Africa, with less favorable circumstances with limited access to surgery and with less antimicrobial treatment options, that potentially benefit more from shorter treatment duration. In the current study, we describe the clinical and functional outcomes of a cohort of BU patients in Ghana who defaulted from treatment, and as such received less than 8 weeks of antimicrobial therapy without additional surgery.
Clinical outcomes of Ghanaian Buruli ulcer patients that defaulted from antimicrobial therapy

Method

Design

We reviewed patient records at the BU clinic of Nkawie-Toase Hospital, Ashanti region, Ghana, between 2008 and 2012. Some of these patients that had visited the clinic between 2008 and 2012 had defaulted from antibiotic therapy or wound care; we followed these individuals by searching and visiting their last known address, or, if available, by telephone contact, in the context of a study specifically designed to study default from antimicrobial therapy or wound care (5). Patients were followed-up between July and October 2013. All of the retrieved patients that had persisting lesions or severe functional limitations were counseled and referred for further treatment or physiotherapy. A lesion was considered healed if complete epithelialization had been ascertained. In the event of a non-healed lesion, a swab was taken for BU disease confirmation by PCR, and the patient was asked to come back to the BU clinic for further treatment.

Procedures

The WHO defines completed therapy for BU as 56 doses of antibiotics within a time frame of 70 days. For this retrospective study, we included all patients that had not completed antimicrobial therapy according to this definition. From the records, patient and lesion characteristics, WHO category, the number of days of streptomycin and rifampicin administration, and Buruli Ulcer Functional Limitations Scale (BUFLS) scores were retrieved. The WHO has defined three categories of BU as a measure of size and severity. A category I lesion is defined as a single lesion < 5cm in cross-sectional diameter, a category II lesion as a single lesion between 5cm and 15cm in diameter, and a category III lesion as a single lesion > 15cm in diameter, multiple lesions, lesions at critical sites (e.g. around the eye, genitalia), and osteomyelitis. The BUFLS is a previously validated scale designed to measure functional limitations in former BU patients by measuring perceived difficulties with daily activities (12). We also retrieved information on actual drug treatment from the records, with detailed information about any missing reporting dates and drug dosages.

Ethics

The study protocol was approved by the Committee on Human Research, Publication, and Ethics of the Kwame Nkrumah University of Science and Technology and the Komfo Anokye Teaching Hospital, Kumasi (reference number CHRPE/AP/133/12). Written informed consent was obtained from all participants aged ≥ 12 years, and consent from
parents, or legal representatives of participants aged ≤ 18 years. Patient records were reviewed anonymously, and all reported procedures, i.e. lesion and disability assessment, are part of local routine care for BU.

Figure 1. Frequency distribution of days of antimicrobial therapy (N = 316). SR = Streptomycin – Rifampicin combination therapy.

Results

A total of 316 patients had visited the clinic between 2008 and 2012 with a clinical diagnosis of BU. Of these, 46% completed antimicrobial therapy for BU by the WHO definition. The frequency distribution of number of days of antimicrobial therapy is shown in figure 1. Of 140 patients that we attempted to find, 56 were retrieved. The median (IQR) duration between start of therapy and follow-up for these 56 patients was 203 (94–240) weeks. Forty seven of these patients had not completed antimicrobial therapy, the remainder had defaulted from wound care. Six of these 47 patients had sought treatment of various forms (surgery or different antibiotics than SR) at another hospital. An additional 9 patients had died of unknown causes. Patient and lesion characteristics are shown in table 1.
Table 1. Patient and lesion characteristics. *Significant difference between retrieved and non-defaulted ($p < 0.02$ by Mann-Whitney U). All other between group differences ns by Chi-square or Mann-Whitney U. PCR = Polymerase Chain Reaction, ZN = Ziehl-Neelsen staining.

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Retrieved ($N=173$)</th>
<th>Not retrieved ($N=143$)</th>
<th>Total ($N=316$)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex (%male)</strong></td>
<td>32.1%</td>
<td>42.1%</td>
<td>52.2%</td>
</tr>
<tr>
<td><strong>Median Age (IQR)</strong></td>
<td>28 (15–54)</td>
<td>34 (15–57)</td>
<td>33 (13–56)</td>
</tr>
<tr>
<td><strong>Median weeks of illness before seeking care (IQR)</strong></td>
<td>4 (2–7)</td>
<td>4 (2–8)</td>
<td>5 (3–16)</td>
</tr>
<tr>
<td><strong>Use of traditional treatment</strong></td>
<td>44.6%</td>
<td>39.7%</td>
<td>40.3%</td>
</tr>
</tbody>
</table>

**Clinical form**

- **Ulcer**: 80.4% (85.7%) 72.4% 79.1%
- **Plaque**: 8.9% (6.3%) 12.7% 9.5%
- **Edema**: 7.1% (5.6%) 11.9% 8.5%
- **Nodule**: 3.6% (1.6%) 3.0% 2.5%

**WHO Category of Lesion**

- **I**: 35.7% (32.5%) 30.6% 32.5%
- **II**: 28.6% (24.6%) 29.1% 27.4%
- **III**: 35.7% (42.1%) 39.6% 40.1%

**PCR or ZN**

- **Positive**: 41.1% (29.4%) 41.8% 36.7%
- **Negative**: 32.1% (33.3%) 20.1% 27.5%
- **Not performed**: 26.8% (37.3%) 38.1% 35.8%

**Median Days of SR (IQR)**

- 28 (19–33) 29 (16–47) 56 (56–57) 55 (28–56)

The main reported reasons for defaulting by the retrieved patients were lack of money for transportation (35%), the fact that their lesion had already healed before planned end of treatment (19%), drug side effects (mainly dizziness and red urine; 14%), diversion to other modes of treatment (mainly herbal; 14%), and various others (pregnancy, drug shortage, moving abroad, low mobility).
The median (IQR) BUFLS score was 11 (0–22). Those that were healed at follow up had a median (IQR) score of 0 (0–15), whereas those that were not healed had a median (IQR) score of 24 (20–29) \((p < .001\) by Mann-Whitney U test).

**Table 2.** Rates of healing by WHO Lesion category. \(p = \) test of significant difference between WHO Categories by Chi-Square for trend (linear-by-linear association). PCR + = Confirmed by polymerase chain reaction at initiation of treatment.

<table>
<thead>
<tr>
<th>WHO Category</th>
<th>Duration &lt; 32 days ((N = 42))</th>
<th>Duration &lt; 56 days ((N = 47))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCR+</td>
<td>All patients</td>
</tr>
<tr>
<td>Category I</td>
<td>7/7 (100%)</td>
<td>16/17 (94%)</td>
</tr>
<tr>
<td>Category II</td>
<td>3/4 (75%)</td>
<td>8/10 (80%)</td>
</tr>
<tr>
<td>Category III</td>
<td>5/6 (83%)</td>
<td>10/15 (67%)</td>
</tr>
<tr>
<td>Total</td>
<td>15/17 (88%)</td>
<td>34/42 (81%)</td>
</tr>
<tr>
<td>(p)</td>
<td>.35</td>
<td>.05</td>
</tr>
</tbody>
</table>

The diagnosis of BU was only confirmed by polymerase chain reaction (PCR) in a proportion of patients. The rates of healing of patients defaulting from antimicrobial therapy per WHO lesion category, both for PCR confirmed lesions and for all lesions combined, are listed in table 2. We chose to display rates of healing both for a total dose of less than 56 days, and less than 32 days. The cut-off of 32 days was chosen to reflect a clinically relevant shortening of therapy duration and including all patients who decided to stop their medication after one month of use. The median (IQR) number of doses of SR administered to followed-up patients that had healed, or had not healed was 28 (15–30), and 28 (14–30) respectively \((ns\) by Mann-Whitney U test). Patients that had healed did not differ from patients that had not healed by age, gender, or clinical form at baseline.

An open wound was seen in a total of 9 patients during the follow up visits. Patient and lesion characteristics and number of days of antimicrobial therapy for these patients are shown in Table 3. All non-healed lesions were located on the lower limb.
Clinical outcomes of Ghanaian Buruli ulcer patients that defaulted from antimicrobial therapy

Table 3. Patient and lesion characteristics of non-healed defaulters. Duration = time since onset of lesion in months, SR = Streptomycin–rifampicin combination therapy, BUFLS = Buruli Ulcer Functional Limitation Score, PCR = Polymerase Chain Reaction result at baseline, + = positive, – = negative, ? = unknown.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Gender</th>
<th>Category</th>
<th>Size (cm²)</th>
<th>Duration</th>
<th>Days of SR</th>
<th>BUFLS Baseline</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>F</td>
<td>3</td>
<td>5</td>
<td>48</td>
<td>27</td>
<td>26,3</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>46</td>
<td>F</td>
<td>1</td>
<td>2,6</td>
<td>44</td>
<td>0</td>
<td>31,6</td>
<td>?</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>F</td>
<td>3</td>
<td>3,5</td>
<td>19</td>
<td>28</td>
<td>21,1</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>M</td>
<td>3</td>
<td>24</td>
<td>19</td>
<td>28</td>
<td>15,8</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>22</td>
<td>F</td>
<td>2</td>
<td>4,2</td>
<td>22</td>
<td>42</td>
<td>26,3</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>M</td>
<td>3</td>
<td>17,6</td>
<td>61</td>
<td>30</td>
<td>38,2</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>15</td>
<td>F</td>
<td>2</td>
<td>3,5</td>
<td>58</td>
<td>30</td>
<td>18,4</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>43</td>
<td>M</td>
<td>2</td>
<td>11</td>
<td>13</td>
<td>14</td>
<td>23,7</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>71</td>
<td>M</td>
<td>3</td>
<td>18</td>
<td>15</td>
<td>14</td>
<td>21,4</td>
<td>–</td>
</tr>
</tbody>
</table>

Discussion

Here we present follow-up data from a cohort of Ghanaian BU patients who defaulted from antimicrobial therapy. More than half of the patients seen at the clinic over the study period did not complete therapy. A considerable proportion of patients that received incomplete therapy had healed lesions at follow-up. In patients with small lesions, rates of healing were excellent, and were similar to rates of healing found in drug trials and observational studies that also looked at small, early lesions, and in recent large cohort studies (13–16). In addition, recurrence was not reported nor observed. Compared to the Australian cohort, our cohort featured a larger proportion of large lesions (60% vs 8% non-Category I), and the rate of healing of these larger lesions appeared to be less than in small lesions.

The effect of lesion size on rate of healing was significant in patients receiving less than 32 days of therapy. This might be caused by both lesion and drug characteristics. A smaller lesion might harbor a smaller number of bacteria that are cleared in a shorter period of time. In addition, antibiotic penetration in larger lesions might be worse due to larger amounts of poorly vascularized necrotic tissue. Alternatively, larger lesions might benefit more from a high standard of wound care, and defaulters from antimicrobial therapy also ceased to receive specialized wound care from the BU treatment center, causing a delay in healing.
The patients that had not healed at follow-up had long standing lesions, most of which were not confirmed by PCR at baseline, and were PCR-negative at follow-up. The BUFLS scores were high in these patients, indicating the significant functional limitations caused by BU. However, though clinically suspected BU, these lesions might have another etiology such as tropical ulcer, cutaneous leishmaniasis, cutaneous tuberculosis or pyoderma gangrenosum. Also co-morbidities such as sickle cell disease, but especially HIV infection have been shown to cause large, non healing ulcers (17–19), and HIV tests were not performed routinely on the patients in our cohort.

The current study suffers from several limitations. Only a small proportion of defaulters were retrieved during the follow-up project. Although those retrieved and not retrieved did not differ in baseline characteristics, this might have introduced significant bias. Further bias may have been introduced since a healed lesion was one of the reasons to default from therapy. In addition, the number of patients was relatively small, with an even smaller number of PCR confirmed lesions. Due to the retrospective nature of the study, the sample size could not be increased. Nevertheless, the same pattern of results—decreasing rates of healing with increasing size was observed in both the PCR confirmed cases and the entire cohort. Lastly, those who stopped due to side effects of the drugs might have experienced these side effects due to higher plasma levels of the drugs, leading to an enhanced antimicrobial effect, although rifampicin levels are already well above the minimally inhibitory concentration in most cases (20).

The potential for bias in both this study and the Australian cohort is significant, and the option of shortened therapy duration in small, early BU lesions should preferably be studied in a well-designed randomized controlled trial. Newly developed laboratory monitoring techniques such as viability PCR and mycolactone detection might aid in ensuring patient safety and interpretation of results (21, 22). Our data are based on streptomycin-rifampicin combination therapy, which is likely to be replaced in the near future by completely oral therapy with clarithromycin-rifampicin (23). As streptomycin is bactericidal and clarithromycin is bacteriostatic, it is possible that a shorter duration of therapy is not feasible with clarithromycin. However, Cowan et al. also found shorter therapy to be effective in patients receiving antibiotic combinations that did not contain streptomycin, and the need for complete sterilization is unclear as previous studies have reported cure in patients whose lesions were culture positive after 8 weeks of antimicrobial therapy (3, 13, 14).

Our data suggest that shorter therapy for BU in small, early lesions is feasible in a cohort of Ghanaian patients that did not undergo surgery. Shortened treatment might have significant benefit in terms of toxicity, costs and discomfort, but needs to be carefully evaluated in well-designed studies.
Financial Disclosure

SK was supported by an MD/PhD grant of the Junior Scientific Masterclass, Groningen University. RK was supported by the BUG foundation. YS was supported by a VENI grant from the Netherlands Organisation for Scientific Research. The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter discussed in this manuscript. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.
References


