How MSF operational research in a neglected disease (Buruli ulcer) treatment programme can impact international management guidelines

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Introduction

The main burden of Buruli Ulcer (BU) is in West and Central Africa (Figure 1). However this also corresponds to regions with high HIV prevalence (Figure 1), and all 15 countries in West and Central Africa reporting BU cases have an HIV prevalence of 1-5%. Therefore there is a significant potential for BU and HIV to occur in the same individual and BU-HIV coinfection is an important emerging management challenge for BU disease.

Despite this, there is little known about the interaction between BU and HIV. For example, is the prevalence of HIV increased in BU patients? Are there any clinical implications of HIV infection in BU patients such as when to start antiretroviral therapy and what are the optimum BU treatment regimens to use?

Limited by the paucity of scientific studies, guidance for management of this disease challenge for BU disease.

Here we describe how analysis of data from the BU treatment programme of Médecins Sans Frontières in Akonolinga, Cameroon provided some of the scientific basis for development of guidance principles for BU/HIV coinfection.

Figure 1. Global distribution of HIV and BU estimated prevalence.

Figure 2. A global view of HIV infection in the world, Barwon Health, Geelong, Australia.

MSF-Akonolinga, Cameroon

• This was a BU treatment programme based in a District Ministry of Health Hospital.
• Prospective data was collected on all BU treated patients.
• The analysis included 1130 patients with a first episode of BU treated from 1/1/2002 to 27/3/2013

Results:

The prevalence of HIV in BU patients

<table>
<thead>
<tr>
<th></th>
<th>Female with BU</th>
<th>Female regional (15-49yrs)</th>
<th>Men with BU ≥15yrs</th>
<th>Men regional (15-49yrs)</th>
<th>Children with BU ≥15yrs</th>
<th>Children regional</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All BU patients</td>
<td>37% (52/141)</td>
<td>8%</td>
<td>20% (24/123)</td>
<td>4.7%</td>
<td>4% (5/114)</td>
<td>0.68%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCR confirmed BU patients</td>
<td>39% (34/87)</td>
<td>8%</td>
<td>17% (15/88)</td>
<td>4.7%</td>
<td>5% (4/73)</td>
<td>0.68%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The effect of HIV on the clinical presentation.

<table>
<thead>
<tr>
<th></th>
<th>Single lesion</th>
<th>Multiple lesions</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV + (n=83)</td>
<td>63 (76%)</td>
<td>20 (24%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HIV – (n=376)</td>
<td>333 (88%)</td>
<td>41 (11%)</td>
<td></td>
</tr>
</tbody>
</table>

• HIV+ patients tended to have larger BU lesions: diameter 5.5 (IQR 3-12) vs 5.0 cm (IQR 2-9.5; p=0.12)
• A higher proportion of HIV+ patients had ulcerated lesions (93% vs 86%; p=0.12)

The effect of immunosuppression on the size of a BU lesion

<table>
<thead>
<tr>
<th>CD4&lt;500</th>
<th>CD4≥500</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cat 1</td>
<td>21 (55%)</td>
</tr>
<tr>
<td>Cat 2/3</td>
<td>44 (48%)</td>
</tr>
<tr>
<td>28 (30%)</td>
<td>&gt;500 cells/ mm³</td>
</tr>
</tbody>
</table>

The level of immune suppression at diagnosis of BU/HIV patients

• 92/121 (76%) HIV+ patients tested since 2002 had CD4 data
• 20 (22%): ≥500 cells/ mm³
• 44 (48%): 201-500 cells/ mm³
• 28 (30%): >500 cells/ mm³

The effect of HIV on mortality

• Mortality rate higher among HIV+ than HIV- BU patients [8/83 (11%) vs 5/376 (1%); p<0.001]
• Median CD4 cell count among the eight deceased HIV patients: 229 cell/mm³ (IQR 98-378)
• Median duration until death: 41.5 days (IQR 16.5-66.5 days)
• None were on antiretroviral therapy

The effect of HIV immune suppression on time for BU wound healing

<table>
<thead>
<tr>
<th></th>
<th>HIV+ patients</th>
<th>HIV- patients</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 cells/mm³</td>
<td>39 (47%)</td>
<td>27 (64%)</td>
<td>0.002</td>
</tr>
<tr>
<td>200 cells/mm³</td>
<td>22 (27%)</td>
<td>23 (42%)</td>
<td>0.04</td>
</tr>
<tr>
<td>500 cells/mm³</td>
<td>6 (7%)</td>
<td>9 (15%)</td>
<td>0.19</td>
</tr>
<tr>
<td>&gt;500 cells/mm³</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Recommendations of BU/HIV expert panel influenced by results from Akonolinga

• All BU patients should be offered quality provider-initiated HIV testing and counselling
• Combination antibiotic treatment for BU should be commenced before starting ART
• ART should be initiated in all BU/HIV infected patients with symptomatic HIV disease (WHO clinical stage 3 or 4) regardless of CD4 cell count and in those asymptomatic individuals with CD4 count ≤500 cells/mm³
• If CD4 count is not available, those in WHO category 2 or 3 BU disease should be offered ART.
• Patients with CD4 2000 cells/mm³ do not commence ART until CD4 has fallen below 500 cells/mm³ or other criteria for ART have been met
• For eligible individuals, ART should be commenced as soon as possible after the start of BU treatment, preferably within 8 weeks, and as a priority in those with advanced HIV disease (CD4 <350 cells/mm³ or WHO stage 3 or 4 disease).

Conclusions

An MSF programme focused on the neglected tropical disease of BU through clinical practice and study of observational data, allowed acquisition of important knowledge regarding the clinical and epidemiological interactions between BU and HIV disease. This was important in building simple ‘common sense’ preliminary international guidelines for the management of BU/HIV coinfection.

Acknowledgements

• MSF, MoH staff and patients Akonolinga, Cameroon
• MSF, Geneva: A. Artières, L. Rossel, O. Akroba
• Departments of NTD and HIV WHO: K. Asiedu, M. Vitoria