ent dilutions (100.0, 33.3, 20.0, or 10.0 U/mL) in the glabella. New studies with higher numbers of patients are needed to confirm these preliminary results and perhaps demonstrate changes in techniques to increase the FE of botulinum toxin type A and allow treatments with fewer injections.

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Longitudinal Evidence of Increasing In Vitro Tolerance of Scabies Mites to Ivermectin in Scabies-Endemic Communities

Scabies remains a prominent cause of morbidity in remote Aboriginal communities in northern Australia. Secondary bacterial infection of skin lesions caused by scabies is linked to high rates of rheumatic fever and rheumatic heart disease in affected communities. Because the sustainability of community scabies eradication programs using topical permethrin, 5%, is problematic, oral ivermectin has been proposed as an alternative acaricide for mass drug administration.

While ivermectin is used routinely for the management of crusted scabies (CS) in northern Australia, reports of clinical and in vitro resistance indicate that prospective monitoring is required to detect the further emergence of ivermectin resistance. Herein, we report the results of a longitudinal study of in vitro acaricide sensitivity of Sarcoptes scabiei to ivermectin in a region under increasing drug selection pressure.

Methods. Specimens were obtained by gently scraping the skin of patients infected with CS who were admitted to the Royal Darwin Hospital. The scrapings were then examined for the presence of S scabiei using a dissecting microscope. If numerous live mites were found in the sample, acaricide sensitivity assays were performed using methods previously described. To maintain mite viability for the duration of the assay, mites were tested within 3 hours of collection and incubated at 28°C. From 1997 through 2006, sufficient mite numbers for analysis were obtained from 16 individual patients on 31 occasions (Table). Through a statistical comparison of data, we tested the null hypothesis that survival curves between years were identical.

Results. Survival times of mites exposed to ivermectin increased from 1997 through 2006 (P < .001) (Table), while survival times remained unchanged over 10 years.

Table. Aggregate Ivermectin In Vitro Survival Times, 1997-2006

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients Tested, No. (N=31)</th>
<th>Mites Assayed, No. (N=514)</th>
<th>Median Mite Survival Time, min</th>
<th>P Valuea</th>
<th>Excluding Patients With Documented Clinical Resistance</th>
<th>Median Mite Survival Time, min</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>5</td>
<td>20</td>
<td>60</td>
<td>&lt;.001</td>
<td>20</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>1998</td>
<td>3</td>
<td>20</td>
<td>60</td>
<td>&lt;.001</td>
<td>20</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>2</td>
<td>11</td>
<td>60</td>
<td>&lt;.001</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>4</td>
<td>209</td>
<td>210</td>
<td>&lt;.001</td>
<td>180</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>4</td>
<td>58</td>
<td>120</td>
<td>NS</td>
<td>120</td>
<td>NS</td>
<td></td>
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<tr>
<td>2002</td>
<td>3</td>
<td>27</td>
<td>145</td>
<td>NS</td>
<td>162</td>
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<td></td>
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<tr>
<td>2003</td>
<td>2</td>
<td>12</td>
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<td></td>
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<tr>
<td>2004</td>
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<td>NS</td>
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<td></td>
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<tr>
<td>2006</td>
<td>5</td>
<td>81</td>
<td>120</td>
<td>NS</td>
<td>150</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NA, no data available; NS, not significant.
aLog-rank test compared with other years combined.
bClinical treatment failure observed in 2 patients.

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for the negative control emulsifying ointment. Even when we excluded the 2 patients with previously documented resistance from the analysis, we found that the trend for increasing ivermectin survival time remained significant ($P=.006$) (Table). Results from a single patient with recurrent CS and previously documented ivermectin resistance are of note (Figure). When this patient was treated again in 2006 with 3 doses of ivermectin (200 µg/kg), no noticeable reduction in mite numbers was observed (unpublished observations). A significant increase in mite survival time was observed when mites collected after 8 days and 3 doses of ivermectin were compared with those collected prior to the commencement of ivermectin therapy ($P=.003$).

**Comment.** Mite survival times in the presence of in vitro ivermectin doubled over the 10-year study period. Furthermore, sequential data collected from a single patient over a course of ivermectin treatment confirms that selection for ivermectin-tolerant mites can occur rapidly and persist once established. These observations support concerns regarding the sustainability of mass drug administration scabies control programs using ivermectin. Surveillance of CS is important, not only to the individual but also to the community as a whole. As ordinary and crusted scabies are caused by the same variety of mite, patients with CS serve as core transmitters in many communities and may limit the success of community control programs. We are concerned by the potential for core transmitters serving as reservoirs of mites with increasing ivermectin tolerance, thus threatening the success of mass drug administration programs based on ivermectin.

Increased monitoring for the development of drug resistance is urgently needed within the community setting. Because the applications of in vitro assays are limited, the development of molecular-based diagnostic techniques that are more sensitive and amenable to community application is imperative. It should also be recognized in Australian Aboriginal communities and elsewhere that addressing the underlying causes of persisting high rates of scabies (eg, overcrowding, socioeconomic disadvantage, poor sanitation facilities) will effect a broader improvement in health as well as assist in control of scabies.

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**Acquired Lymphangiectasia Associated With Treatment for Preceding Malignant Neoplasm: A Retrospective Series of 73 Japanese Patients**

*Acquired lymphangiectasia (AL), previously called acquired lymphangioma, was first described in 1956 by Plotnick and Richfield as a complication of radical mastectomy. Like lymphangiosarcoma, which may arise as a complication of chronic lymphedema, AL mainly occurs after surgery and radiation therapy for malignant neoplasms such as breast carcino-

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**Figure.** Kaplan-Meier survival analysis of mites exposed to ivermectin. The data were collected from a patient with recurrent crusted scabies during an 8-day treatment regimen in 2006 and show significantly increasing median survival times ($P=.003$ by treatment day 8) over the course of ivermectin treatment, indicating selection for subpopulations of ivermectin-tolerant mites. “n” indicates number of mites used in each in vitro assay.