Treatment of Lymphangiomas With OK-432 (Picibanil) Sclerotherapy
A Prospective Multi-institutional Trial

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Objective: To describe and to determine the robustness of our study evaluating the efficacy of OK-432 (Picibanil) as a therapeutic modality for lymphangiomas.

Design and Setting: Prospective, randomized trial and parallel-case series at 13 US tertiary care referral centers.

Subjects: Thirty patients diagnosed as having lymphangioma. Ages in 25 ranged from 6 months to 18 years. Twenty-nine had lesions located in the head-and-neck area.

Intervention: Every patient received a 4-dose injection series of OK-432 scheduled 6 to 8 weeks apart unless a contraindication existed or a complete response was observed before completion of all injections. A control group was observed for 6 months.

Outcome Measures: Successful outcome of therapy was defined as a complete or a substantial (>60%) reduction in lymphangioma size as determined by calculated lesion volumes on computed tomographic or magnetic resonance imaging scans.

Results: Overall, 19 (86%) of the 22 patients with predominantly macrocystic lymphangiomas had a successful outcome.

Conclusions: OK-432 should be efficacious in the treatment of lymphangiomas. Our study design is well structured to clearly define the role of this treatment agent.


Lymphangiomas are localized malformations in the development of the lymphatic system that most frequently affect the head and neck. In approximately half of these patients, the lesion is present at birth, and in most, the diagnosis is made before 2 years of age. Although spontaneous resolution has been reported to be as high as 41%, this figure is much lower in most large series. Surgical excision is the recommended treatment standard, but the invaginating nature of lymphangiomas, typically consisting of multiple cysts with a gossamer-thin lining, makes surgery difficult. Complete extirpation without damage to vital structures is possible in only approximately one third of cases. With incomplete excision, disease recurrence is extremely high.

To reduce surgical morbidity and to decrease recurrence rates, a variety of non-surgical treatments have been proposed, including radiation, diathermy, and injection of a variety of agents such as bleomycin sulfate, triamcinolone acetonide, interferon-alfa, fibrin-fibronectin sealing systems, and alcoholic solution of zein (corn protein).

Because these treatment options have met with limited success and cause considerable local or systemic adverse effects, recent interest has focused on the sclerosant OK-432 (Picibanil; Chugai Pharmaceutical Co, Ltd, Tokyo, Japan), as an alternative therapy.

In the past 14 years, a number of reports have described the successful use of OK-432 for the treatment of lymphangiomas of the head and neck in children. This potent immunostimulant is a lyophilized mixture of a low-virulence strain (Su) of group A Streptococcus pyogenes incubated with benzylpenicillin. Many authors, predominantly from Japan, have recommended its use as primary therapy in the treatment of lymphangiomas. Their encouraging results and previously published data from our group suggest that carefully designed clinical studies should...
be conducted to examine the role of OK-432 as primary therapy for lymphangiomas.19,20 Three years ago, we designed and began conducting a multi-institutional, prospective randomized control study to assess the efficacy of this relatively new treatment. The purpose of this report is to describe our study design and to evaluate its robustness by assessing results in 30 patients.

**Patients and Methods**

Patients with the clinical diagnosis of a lymphangioma underwent evaluation to determine their eligibility for this prospective study. Pretreatment assessment included a complete history and physical examination, extensive laboratory analysis, medical photography, and computed tomography or magnetic resonance imaging. Lymphangiomas were required to be purely macrocystic (defined as cystic spaces ≥2 cm³) or mixed (macrocystic component ≥50% of the total disease). Lesions located in the neck were staged according to the clinical staging system for lymphangiomas proposed by de Serres et al.29 Based on disease extent and location, the system classifies the disease as follows: stage I, unilateral infrahyoid disease; stage II, unilateral suprahyoid disease; stage III, unilateral infrahyoid and suprahyoid disease; stage IV, bilateral suprathyroid disease; and stage V, bilateral infrahyoid and suprathyroid disease. Patients with a penicillin allergy were excluded.

Children and adolescents, aged 6 months to 18 years with lymphangiomas of the head and neck, were eligible to participate in the randomized arm of the study. Two thirds...
of the participants were randomized to an immediate-treatment group (ITG) in which they received OK-432 therapy shortly after enrollment, and one third were randomized to a delayed-treatment group (DTG) in which they underwent an initial 6-month observation, thereby serving as control subjects for the study. If regression of their lymphangiomas was not observed after 6 months, this group began OK-432 therapy.

Persons with life-threatening lymphangiomas were placed in a third, nonrandomized emergency-treatment group. Finally, persons who were younger than 6 months or older than 18 years, or who had lymphangiomas in sites other than the head and neck region were enrolled in a fourth nonrandomized open-label group.

A standard OK-432 protocol was followed for all patient groups. In general, treatments were administered with the patient under general anesthesia, although local anesthesia can be used in older patients. As described in our previous series, a solution of OK-432 was prepared by dissolving 0.1 mg of OK-432 in 10 mL of isotonic sodium chloride solution. Under sterile conditions, a 20-gauge angiocatheter needle was introduced into the cyst. After withdrawing the needle, cyst contents were aspirated through the angiocatheter. Cyst localization was aided by the use of fluoroscopy, ultrasonography, transillumination, or palpation.

After aspirating most of the cyst fluid and taking care not to dislodge the angiocatheter, OK-432 was injected. A maximum volume of 20 mL was used per treatment session to inject 1 or several cysts, depending on the characteristics of the lymphangioma. After the injection, patients were monitored in the postanesthesia care unit for several hours before discharge and by means of regular telephone calls during the first 2 weeks thereafter. A diary was used to record temperature, adverse effects, and antipyretic use. Injections were spaced at 6 to 8 weeks, with a total of 4 treatments, unless contraindication existed or a complete response was observed before completion of therapy.

The complete pretreatment history and physical examination with radiography was repeated at 6 months and 1 and 2 years after completion of therapy. Outcome was determined by calculating lesion volume, defined as the product of orthogonal dimensions on computed tomography or magnetic resonance imaging findings, before and after therapy by a single radiologist (Y.S.) masked to the clinical status, date of the radiographic study, and study site. Reduction of lymphangioma size was recorded in 10% decrements as complete (≥90%), substantial (60%-80%), intermediate (20%-50%), or none (<20%). Clinical success was defined as complete or substantial responses to therapy.

Tests of toxicity and sterility were performed on each new lot number of OK-432. Informed consent was obtained from patients or parents before each treatment. The study has been approved by the institutional review boards in each of the 13 participating sites. Contingency tables were analyzed using the Fisher exact test.

### Table 3. Patient Characteristics Grouped by OK-432 Therapy Outcome in the Intent-to-Treat Group

<table>
<thead>
<tr>
<th>Treatment Outcomes</th>
<th>No. of Patients</th>
<th>Age, mo*</th>
<th>Volume of Lesion, cm³</th>
<th>Mean No. of Treatments</th>
<th>Macrocytic</th>
<th>Mixed</th>
<th>Microcytic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>18</td>
<td>37†</td>
<td>150†</td>
<td>1.8</td>
<td>17 (94)</td>
<td>1 (6)</td>
<td>0</td>
</tr>
<tr>
<td>Substantial</td>
<td>1</td>
<td>1</td>
<td>100</td>
<td>4.0</td>
<td>1 (100)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
<td>27, 504</td>
<td>512, 140</td>
<td>4.0</td>
<td>1 (50)</td>
<td>1 (50)</td>
<td>0</td>
</tr>
<tr>
<td>No response</td>
<td>8</td>
<td>29†</td>
<td>252†</td>
<td>3.1</td>
<td>1 (12)</td>
<td>2 (25)</td>
<td>5 (62)</td>
</tr>
</tbody>
</table>

*Indicates mean age at first treatment.
†Indicates mean volume of the lesion before the first treatment.

### Table 4. Response to OK-432 Therapy by Stage of Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Intent-to-Treat Group</th>
<th>On-Protocol Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>Clinical Success, %</td>
</tr>
<tr>
<td>I</td>
<td>6/6</td>
<td>100</td>
</tr>
<tr>
<td>II</td>
<td>2/3</td>
<td>67</td>
</tr>
<tr>
<td>III</td>
<td>8/11</td>
<td>73</td>
</tr>
<tr>
<td>IV</td>
<td>0/2</td>
<td>0</td>
</tr>
<tr>
<td>V</td>
<td>1/3</td>
<td>33</td>
</tr>
</tbody>
</table>

*The clinical staging system was proposed by de Serres et al,29 and is explained in the “Patients and Methods” section. Clinical (treatment) success was defined as complete and substantial responses, explained in the “Patients and Methods” section. Groups are described in the “Results” section.
†P = .02 for stages I, II, and III vs IV and V disease (Fisher exact test).

To assess study design, we evaluated data from 30 persons (18 male patients) who completed OK-432 therapy (Table 1). These patients constituted the intent-to-treat group. The on-protocol group excluded from the intent-to-treat group 4 patients with macrocytic disease, 1 patient who did not have a lymphangioma, and 1 patient who withdrew from the study.

Our results show that patients with macrocytic lymphangiomas have a significantly better treatment outcome compared with patients with mixed or microcystic lesions (Table 2). Of note, total lesion volume was not predictive of a successful response (Table 3). Patients with stage I, II, or III disease had a significantly better clinical response to therapy than did those with stage IV or V disease (Table 4, Figure 1, and Figure 2). The ITG patients also had a significantly greater response rate than the DTG patients (10:12 vs 0:3). In total, 19 (86%) of the 22 on-protocol patients with macrocytic or mixed lymphangiomas were treated successfully with OK-432 (Table 5 and Table 6). Minor adverse effects, including erythema, swelling, discomfort at the site of the injection, and pyrexia, were noted by most patients, but these resolved within 5 to 6 days of treatment. Three major adverse effects also occurred. The first involved a patient (patient 19) in whom left-sided proptosis developed secondary to a spontaneous intracystic hemorrhage 4 weeks after OK-432 injection of a lymphangioma adjacent to the left orbit. An or-
bital decompression was required in this patient. The second major adverse effect was a case of cervical cellulitis (patient 7) 4 to 5 weeks after the first injection, and a short course of intravenous antibiotics was required. The third major adverse effect was the development of stridor and impending airway obstruction in a patient (patient 5) with a massive lymphangioma of the left side of the neck that extended intrathoracically. An urgent tracheostomy was performed in this patient (Figure 3 and Figure 4).

To assess study design before completing enrollment, we report data on 30 patients who have been enrolled in a prospective multi-institutional trial to evaluate the safety and efficacy of OK-432 in the treatment of lymphangiomas. To date, a smaller number of patients than expected have been randomized to the DTG. Malenrollment was determined to be the cause; physicians had included patients in our database who did not participate in the study. From the ran-
domized arm of the study, it appears that OK-432 treatment for head and neck lymphangiomas in children will be significantly more effective than observation alone, al-

though the small number of patients in the DTG and the incomplete data collection preclude an accurate estimate of the rate of spontaneous regression of lymphangiomas. In 1 patient in the ITG, spontaneous regression occurred before initiation of therapy, resulting in a minimum observed regression rate in the randomized arm of 1 (5%) of 22 patients.

Our overall success rate, defined as the complete and substantial response rates, was 19 (66%) of 29 patients in the intent-to-treat group, which is in keeping with results of retrospective studies on the efficacy of OK-43218 (Table 5). However, if we exclude patients with microcystic disease, 86% of patients in the on-protocol group had a successful response to therapy. Macrocystic lesions respond significantly better than mixed (P = .02) and microcystic (P < .001) lesions, to such a degree that among the 19 patients treated successfully, 18 (95%) had macrocystic disease. The 5 patients with microcystic lesions failed to demonstrate any response to the OK-432 treatment (Figure 5).

Only 1 subject enrolled in our clinical trial had a lesion involving a site other than the head and neck (Figure 6). Although we cannot draw conclusions based on this case alone, it appears that complete response to therapy may have been due to the macrocystic nature of the lesion.

In 1995, a clinical staging system for lymphangiomas was proposed by de Serres et al29 to predict prognosis and outcome of surgical intervention. Like de Serres et al, we found that patients with stages I, II, and III disease had significantly greater response rates to OK-432 than did patients with stages IV and V disease (P = .02). If we define successful outcome to therapy as complete responses only, our results compare favorably with the surgical results they reported. Current numbers are not sufficiently large in any of the stages for disease in the neck to permit a meaningful comparison

Table 5. Overall Success of OK-432 Therapy*

<table>
<thead>
<tr>
<th>Treatment Groups</th>
<th>Groups, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intent-to-Treat</td>
</tr>
<tr>
<td>ITG + DTG</td>
<td>13/21 (62)</td>
</tr>
<tr>
<td>ETG + OLG</td>
<td>6/8 (75)</td>
</tr>
<tr>
<td>Total</td>
<td>19/29 (66)</td>
</tr>
</tbody>
</table>

* Treatment success was defined as complete and substantial treatment responses. Treatment groups and responses are explained in the “Patients and Methods” section; intent-to-treat and on-protocol groups, in the “Results” section. ITG indicates immediate-treatment group; DTG, delayed-treatment group; ETG, emergency-treatment group; and OLG, open-label group.

Table 6. Response to OK-432*

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Total No. of Patients</th>
<th>Response, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C  S  I  NR</td>
<td></td>
</tr>
<tr>
<td>On-protocol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITG</td>
<td>12</td>
<td>10 (83) 0 1 (8) 1 (8)</td>
</tr>
<tr>
<td>DTG</td>
<td>3</td>
<td>3 (100) 0 0 0</td>
</tr>
<tr>
<td>ETG</td>
<td>5</td>
<td>4 (80) 1 (20) 0 0</td>
</tr>
<tr>
<td>OLG</td>
<td>2</td>
<td>1 (50) 0 1 (50) 0</td>
</tr>
<tr>
<td>Intent-to-treat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITG</td>
<td>18</td>
<td>10 (56) 0 1 (6) 7 (39)</td>
</tr>
<tr>
<td>DTG</td>
<td>3</td>
<td>3 (100) 0 0 0</td>
</tr>
<tr>
<td>ETG</td>
<td>6</td>
<td>4 (67) 1 (17) 0 1 (17)</td>
</tr>
<tr>
<td>OLG</td>
<td>2</td>
<td>1 (50) 0 1 (50) 0</td>
</tr>
</tbody>
</table>

* Treatment groups and responses are described in the “Patients and Methods” section; intent-to-treat and on-protocol groups, in the “Results” section. Abbreviations are explained in the first footnotes to Tables 2 and 5.

Figure 3. Patient 5. A, Photograph of patient with a massive left-sided neck lymphangioma extending into the mediastinum. B, Three-dimensional reconstruction of computed tomographic scan demonstrates marked deviation of the trachea (long arrow points to the endotracheal tube) and a vessel overlying the lymphangioma (short arrow). R indicates right side.
of the 2 treatment options. Patient 2 had a retropharyngeal lymphangioma that would have been extremely difficult to resect. With a pretreatment tracheotomy placed for airway protection, the patient’s lesion regressed completely after 2 injections of OK-432 (Figure 7).

In general, adverse effects were minor, short-lived, and self-limited. Of the major adverse effects, the development of proptosis 4 weeks after injection of a periorbital lymphangioma is worrisome. Based on its time of occurrence and the magnetic resonance imaging findings of fluid-fluid levels suggestive of intracystic hemorrhage, we believe that this complication is unlikely to be related to the OK-432 treatment. Other authors also have reported the successful use of OK-432 to manage orbital lymphangioma.30 Nevertheless, we advise caution in treating lymphangiomas located in this site. With massive cervical lymphangiomas, the potential for airway compromise after therapy also exists, and preventive measures such as pretreatment tracheotomy or close postinjection observation should be considered.

With additional patient accrual, we will be able to address the effect that confounding variables such as previous surgery have on the outcome of OK-432 treatment of lymphangiomas. Increased enrollment also will provide us with a more accurate determination of the rate of spontaneous regression. To evaluate whether responses to therapy are sustained, longer follow-up will be required. These limitations notwithstanding, based on the data we present, we believe that OK-432 will be efficacious in the treatment of lymphangiomas and that the design of this clinical study is sufficiently robust to clearly define its role.

Accepted for publication January 10, 2002.

This study was supported in part by grant FD-R-001774 from the US Food and Drug Administration, Rockville, Md (Dr Smith).
Figure 5. Patient 4. Magnetic resonance imaging scan of a mixed lymphangioma involving the right suprahoid region before (A) and after (B) 4 injection treatments demonstrates no change in the microcystic portion of the lesion.

Figure 6. Patient 29. Magnetic resonance imaging scan of a macrocystic lesion involving the right elbow before (A) and after (B) 2 OK-432 injections demonstrates a complete response to the treatment.

Figure 7. Patient 2. A. Magnetic resonance imaging scan of a large retropharyngeal lymphangioma causing upper airway obstruction. B. Complete resolution of the lesion after 2 injection treatments of OK-432 is seen.
REFERENCES


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