SPECIAL ISSUE

Fillers

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Retreatment with Injectable Poly-L-Lactic Acid for HIV-Associated Facial Lipoatrophy: 24-Month Extension of the Blue Pacific Study

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BACKGROUND  Facial lipoatrophy occurs in HIV-positive patients taking highly active antiretroviral therapy and during natural aging. Injectable poly-l-lactic acid (PLLA) is a device approved internationally for restoration and correction of the signs of HIV-associated facial lipoatrophy.

OBJECTIVE  To evaluate the long-term safety, duration of effect, and satisfaction with serial injections of PLLA for HIV-associated facial lipoatrophy.

METHODS AND MATERIALS  In this single-site, open-label, retreatment study, 65 HIV-positive patients were treated with injectable PLLA every 5 weeks (until optimal correction). Presenting degree of lipoatrophy based on the James scale (1 = mild, 4 = severe) was reviewed. Skin thickness was measured at fixed points with calipers. Patients completed a post-retreatment satisfaction questionnaire.

RESULTS  Nearly 10% of patients had persistent correction > 36 months, based on patient report. Approximately 50% required three or fewer retreatments to maintain satisfactory correction (determined by patient and physician). Milder lipoatrophy on initial presentation required fewer retreatments and had more sustained correction. Time to first retreatment varied according to James scale score: 1 (21.4 months) and 4 (13.0 months). The mean patient satisfaction score was 4.9 (1 = dissatisfied, 5 = very satisfied) at study end. No serious adverse events were reported.

CONCLUSION  Injectable PLLA is a safe and effective long-term treatment option for HIV-associated lipoatrophy.

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Facial contouring has become an important means of combating the potentially devastating effects of HIV-associated lipodystrophy syndrome associated with highly active antiretroviral therapy (HAART). Facial lipoatrophy can be a physically and emotionally disturbing consequence of HIV-associated lipodystrophy syndrome.1 Patients experiencing facial lipoatrophy report low self-esteem, depression, and stopping their HAART to avoid fat wasting and its psychosocial consequences.1-7 There are numerous approaches to facial contouring, including surgery and autologous fat transfer, as well as minimally invasive procedures, such as the use of the injectable devices calcium hydroxylapatite and poly-l-lactic acid (PLLA).

Injectable PLLA is a device approved in Europe and the United States for the treatment of HIV-related facial lipoatrophy. PLLA is a biodegradable, biocompatible, immunologically inert polymer of non-animal origin, eliminating the need for pretreatment allergy testing.8 Although the exact mode of operation is not fully understood, research has demonstrated that PLLA injections lead to the production of a fibrous-tissue response that persists over time.8 Tissue augmentation with injectable PLLA affords results that are clinically comparable with those obtained through fat grafting, although the results with injectable PLLA are more consistent and longer lasting, and the treatment itself is far less involved.8

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The facial contour improvements resulting from treatment with injectable PLLA have been shown to alleviate the emotional ramifications of facial wasting associated with HAART and to improve the quality of life for people who are HIV positive. Clinical trials in patients with HIV-associated facial lipoatrophy have demonstrated that initial treatment with injectable PLLA results in significant and prolonged increases in skin thickness and is associated with high patient satisfaction. The open-label VEGA study demonstrated significant correction of facial lipoatrophy as early as week 6 after treatment initiation with PLLA injections. This correction increased progressively through week 48 and was sustained at week 96. Burgess and Quiroga demonstrated that multiple treatments with injectable PLLA over a 5-month period led to substantial and sustained improvements in dermal thickening in 61 HIV-infected male patients. A similar study by Cartelat and colleagues also demonstrated high efficacy, safety, and patient satisfaction rates in 50 HIV-infected patients receiving between four and six PLLA injections or sessions over a 3-month period. The patients in this study reported statistically significant improvements from baseline in their self-perception of well-being as a result of the treatments.

The long-term psychological effects of injectable PLLA in the management of HIV-associated facial lipoatrophy were recently demonstrated in a follow-up study that used visual analog scales to record patient satisfaction approximately 2 years after initial participation in an open-label, single-center study. Results from the original study demonstrated improvements in patient self-perception, anxiety, and depression after treatment with injectable PLLA that persisted and increased through the recall visit.

We previously reported the results of the single-center, open-label Blue Pacific study in which 97 patients (95 men, 2 women) with HIV-associated facial lipoatrophy received up to six treatment sessions of injectable PLLA. Most patients (65 of 97) had James scale scores of moderate (3) to severe (4) (Table 1). Of the 97 patients, 75 returned for measurement at month 12 and therefore were eligible for inclusion in the data analysis regarding the efficacy on skin thickness. All patients experienced an increase in skin thickness (a mean increase of 65.1% from baseline through the end of treatment; the skin thickness continued to increase post-treatment and was maintained at 78% at the month-12, treatment-free, follow-up visit. At all time points, the increases in skin thickness were statistically significant (p < .001). At the conclusion of the 12-month, treatment-free follow-up, patients who completed the study were eligible for retreatment as participants in a 24-month injectable PLLA retreatment (extension) study. This report describes the results of this retreatment study.

### Methods and Materials

#### Study Objectives

The primary objective of the study was to continue the evaluation of the safety and quantifiable improvement in facial wasting (lipoatrophy) and duration of effect (after serial deep dermal or subcutaneous injections) of PLLA. Secondary objectives focused on the evaluation of the long-term acceptance of injectable PLLA as a treatment option for HIV-associated facial lipoatrophy.
**Informed Consent**

The study was conducted in compliance with the Western Institutional Review Board and informed consent regulations set forth in the U.S. Code of Federal Regulations (CFR) 21, Part 56, and CFR 21, Part 50. This study was conducted according to International Conference on Harmonization standards of Good Clinical Practice guidelines and in agreement with the latest revision of the Declaration of Helsinki, as well as applicable local regulations.

**Patient Selection**

Patients were eligible for inclusion in the retreatment study if they had completed the Blue Pacific study (completed on-site measurement at the month-12, end-of-study, follow-up visit), had HIV-associated facial lipoatrophy with clinically significant facial wasting after previous treatment with injectable PLLA in the Blue Pacific study, and desired maintenance of facial correction. All patients were willing to participate in the study, as supported by signed, written informed consent. Inclusion and exclusion criteria for patients in the original Blue Pacific study have been described in detail previously.13

**Study Design**

This was a single-site, open-label, 24-month retreatment study initiated after the 12-month, treatment-free, follow-up phase of the Blue Pacific study. The design for the initial Blue Pacific study has been described elsewhere.13 Based on the design of this study, all eligible patients had a screening evaluation on day 1 of their retreatment phase that included a clinical evaluation, with history and limited physical examination, facial digital photography, and an initial caliper skin-thickness measurement. The original, presenting degree of facial lipoatrophy according to the James scale (1 = mild, 4 = severe) was recorded. A study intake questionnaire was completed before retreatment and included the following clinical data: time from last treatment completion, patient weight, recent weight change, viral load and T-cell counts (within the prior 2 months), concurrent anabolic steroid use, concurrent recreational drug use, and current medications.

One of the two study investigators administered each treatment. Injectable PLLA was reconstituted with 5 ml of sterile water for injection 2 hours before injection, as described in the package insert, and was injected into target treatment areas in the deep dermal or subcutaneous layer. A total of 1 to 10 ml of the product was given using a cross-fanning injection technique; using a 25-gauge 1.5-inch needle, 0.1- to 0.2-ml threads of PLLA were placed per injection in a retrograde manner. Similar injections were then placed at approximately 90° to the original injections in the treatment areas. This technique differs from that described in the prescribing information.13 No more than 10 ml of reconstituted product was injected at any single treatment session. Patients were treated at 3-week intervals (maximum deviation of 10 days) until full correction was obtained. Patients could receive a maximum of 12 treatment sessions over the 24-month study period if the treating physician and the patient mutually agreed on the need (Figure 1).

Caliper skin thickness was measured, and serial digital photographs were taken before each subsequent treatment session to assess the continued efficacy of injectable PLLA. Baseline caliper skin thickness for each patient was determined at bilateral fixed points located at the intersection of the vertical axis through the lateral canthus of the eye and the horizontal axis of the nares. While seated, patients were photographed using an anterior–posterior and lateral–oblique technique at a distance of 3 feet. Digital photographs were also taken in case of an adverse event.

Before their first retreatment session, patients were asked to complete a questionnaire in which they ranked the relative importance of the following factors with respect to desire for retreatment: social, sexual, employment, self-worth, and cost of treatment. At each retreatment session, patients were asked to rate their satisfaction with the overall
treatment on a scale of 1 to 5 (5 = very satisfied). Patients were contacted by telephone within 48 to 72 hours after each treatment session to monitor for any adverse events. The investigator recorded all events on the case report form. Treatment was stopped in the case of local skin reaction, infection, patient intolerance, or patient request.

Results

Study Population

Seventy-five patients completed the month-12 follow-up visit in the original Blue Pacific study and were eligible for inclusion in the retreatment study. Of those 75 patients, 65 (63 male and 2 female) required retreatment and consented to participate in the retreatment study (Table 2). Of the 10 eligible patients who did not enter the retreatment study, nine continued to have persistent correction after 36 months and did not require retreatment during the extension phase, and one was treated at 30 months by his local physician. The mean age of the patients was 45.9 (range 34–66), 85% of the patients were white, and 97% were male. The patients had been HIV positive for a mean of 14.7 years (range 3–23 years) and had been taking antiretroviral therapy for a mean of 10.4 years (range 3–23 years).

Retreatment Outcomes

Table 3 demonstrates the study results according to severity of original (presenting) facial lipoatrophy by the James scale: 1 (n = 8), 2 (n = 11), 3 (n = 32), and 4 (n = 14). The time to first retreatment varied according to the original James scale score: 1 (21.4 months), 2 (15.7 months), 3 (14.0 months), and 4 (13.0 months). Patients with mild (James scale score 1) facial lipoatrophy had a mean of 1.9 retreatments, whereas those with moderate to severe facial lipoatrophy required more retreatments; for James scale score 2, 3, and 4, the mean number of retreatments were 3.4, 4.4, and 4.8, respectively. Approximately 50% of patients (n = 34) required three or fewer retreatment sessions to maintain satisfactory correction as determined by patient and physician.

<table>
<thead>
<tr>
<th>Demographic measures</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Age, mean (range)</td>
<td>45.9 (34–66)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>63 (97)</td>
</tr>
<tr>
<td>Female</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>55 (84.6)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (4.6)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>6 (9.2)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Number of years with HIV, mean (range)</td>
<td>14.7 (3.0–23.0)</td>
</tr>
<tr>
<td>Number of years taking antiretrovirals, mean (range)</td>
<td>10.4 (3.0–23.0)</td>
</tr>
</tbody>
</table>
Table 3. Distribution of Treatments and Retreatments

<table>
<thead>
<tr>
<th>Original James scale classification</th>
<th>1 (n = 8)</th>
<th>2 (n = 11)</th>
<th>3 (n = 32)</th>
<th>4 (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of treatments in original Blue Pacific study</td>
<td>3.3</td>
<td>4.3</td>
<td>5.2</td>
<td>5.5</td>
</tr>
<tr>
<td>Mean skin thickness change before first retreatment (mm)*</td>
<td>0.2</td>
<td>0.0</td>
<td>-0.5</td>
<td>+0.3</td>
</tr>
<tr>
<td>Mean time to first retreatment (months)</td>
<td>21.4</td>
<td>15.7</td>
<td>14.0</td>
<td>13.0</td>
</tr>
<tr>
<td>Mean number of retreatments over the 24-month study</td>
<td>1.9</td>
<td>3.2</td>
<td>4.4</td>
<td>4.8</td>
</tr>
</tbody>
</table>

*Change from end of treatment in the Blue Pacific study to time of first retreatment. Includes one patient who presented for initial retreatment with areas of overcorrection and irregular growth. Exclusion of this patient yielded -0.2 mm.

Figure 2 depicts a patient with mild lipoatrophy who underwent his first retreatment at month 36 after his initial treatment series. Figure 3 depicts a patient with more severe lipoatrophy (James scale score 3) who had a total of four retreatments over the course of the follow-up study. In both patients, end-of-treatment photos in the original study were taken 3 weeks after the final treatment (per protocol), although a longer time interval may allow better assessment of the continued augmentation that has been observed after treatment with injectable PLLA.

The mean skin thickness change before first retreatment generally varied according to presenting James scale score: 1 (+0.2 mm), 2 (0), and 3 (-0.3). The mean increase (+0.3 mm) in skin thickness observed in patients with severe facial lipoatrophy (James scale score 4) was solely attributed to areas of overgrowth in one patient, which skewed the results. Mean change for all other patients with James scale scores of 4, excluding this patient, was -0.2 mm.

Patient Satisfaction

Patient satisfaction with retreatment was extremely high. The mean satisfaction score after the first retreatment, recorded at the 5-week follow-up visit, was 5.0 (1 = dissatisfied, 5 = very satisfied). At the conclusion of the retreatment study, the mean satisfaction score was maintained at 4.9.

Adverse Events

There were no serious adverse events, and none of the patients discontinued the study because of an adverse event. Most patients experienced localized injection-site swelling for a few days that was related to underlying treatment technique. All but one of the small (<3 mm) papules that formed during the original study had resolved by the end of the retreatment study. In addition, in five (7.7%) of the 65 patients, a total of five new, small (<3 mm), non-visible papules were reported, all occurring within 2 to 7 months after retreatment. Four resolved spontaneously; one patient elected surgical excision of an infraorbital papule that was resistant to conservative treatment measures (including needle decontamination and dilution and retreatment with intraskeletal 5-fluorouracil steroid injection). Another patient presented at retreatment with areas of relative overcorrection. This patient had severe lipoatrophy (James scale score of 4) in the original study; the overgrowth was believed to be secondary to an overaggressive original treatment dosage per area. The patient responded to treatment that was administered in adjacent areas of the face to minimize the contour irregularities.

Discussion

The results of this 24-month retreatment study demonstrate that retreatment with injectable PLLA was effective and well tolerated, with most patients requiring 1 to 4 retreatments to maintain correction of HIV-associated facial lipoatrophy. Patients with milder facial lipoatrophy (James scale score 1–2) on initial presentation (before any treatment) required fewer retreatment sessions and had more sustained correction.

There was a low incidence (7.7%) of small (<3 mm) non-visible papules in this retreatment period, which was less than that observed in the original study.
period (13.1%). The incidence reported in other studies varies from less than 5% to greater than 40%. Higher incidence rates may reflect study design differences; the authors of the Chelsea and Westminster and VEGA studies specifically searched and palpated for papules, which may have contributed to the relatively higher incidence than in other studies, such as ours, that relied on patient reports. Although the mechanism underlying papule formation is not completely understood, product preparation and injection techniques may be contributing factors. Increasing the dilution time to a minimum of 2 hours and preferably to longer than 24 hours, increasing the dilution volume to 5 mL, and using postprocedure massage have been recommended to minimize adverse events. In the retreatment study, we increased the dilution volume from 3 mL, used in the original study, to 5 mL.
At our clinic, we increased the time interval between reconstitution to administration from 30 minutes in the original study to the manufacturer-recommended 2 hours in the retreatment study. In addition, patients received postinjection massage in the retreatment study but not during the original study. Finally, the clinicians who performed the injections were far more experienced with the injection technique by the time of the retreatment phase. The treatment interval in the retreatment study was comparatively longer than in the original trial (5 weeks vs 3 weeks) and also may have been an important factor in reducing adverse reactions that may result from overtreatment. Lengthening the interval between injections from 3 to 5 weeks may have allowed the investigators and patients to more accurately determine the need for additional treatments. Our collective experience supports that it is essential to wait and assess a
patient after treatment with injectable PLLA, because the effect is gradual, and the patient may respond well to smaller amounts of product. Use of excess product may lead to overcorrection in the future. It is also important to note that 12 of the 13 papules reported in the original Blue Pacific study resolved spontaneously over the 36-month combined study period. This observation is encouraging in that the vast majority of papules appear to be self-liniting.

The absence of a prespecified threshold to determine the need for retreatment limited the study design. This may have contributed to the large number of patients (36 of 73) opting to have their first retreatment at the time of their month-12 on-site follow-up from the original Blue Pacific study. These patients were already at the study site, were eligible for retreatment, and may have elected to undergo retreatment with the goal of maintaining correction rather than waiting for a decrease in the degree of correction before retreatment. In addition, the study protocol did not limit treatment to areas previously treated. A few patients did not objectively require retreatment because they had the same or greater caliper measurements but requested treatment mainly in areas not previously treated in the Blue Pacific study; because they were undergoing treatment, they also requested retreatment in areas previously treated for fear of loss of correction (Figure 4). Consequently, an exact answer to the rate of loss of correction over time is not possible from this study, although we feel that the data provide a clinical picture of when and how many retreatments are required for various patients with HIV-associated facial lipoatrophy included in this study.

This study was a continuation study of the Blue Pacific study. The manufacturer provided all study material, and patients paid a reduced injection fee. Although 12 treatments was the maximum available to each patient, only three patients with the most severe facial wasting at the start of the Blue Pacific study required all 12 treatments. The majority of patients required or asked for four treatments or less over a period of 24 months. In general, in the authors' experience, non-HIV patients require significantly fewer total treatments, including...

Figure 4. Representative patient who received injectable poly-L-lactic acid at month 12 mainly in previously untreated areas. During the Blue Pacific study, treatment was in the buccal fat pad and periorbital areas, but at month 12 follow-up, he mainly needed treatment in the nasolabial folds and lower cheeks (but also received retreatment in the originally treated areas); at month 28 after last retreatment, he received treatment in the infraorbital, lower face, nasolabial folds, and buccal fat pad areas. Labels (A) to (D) indicate progression of photographs.
retratments, than HIV-positive patients. Therefore, direct cost comparisons for other patient populations are not possible based on the results of this study.

This was an investigator-initiated trial conducted in a small, non-university-based clinic office. As such, we did not have access to other, validated means of objectively measuring efficacy, such as cutaneous ultrasound or three-dimensional photography. The use of skin calipers during the initial efficacy trial led us to continue using this measurement throughout the retreatment (extension) study. Nevertheless, the photographic and patient satisfaction data were all consistent with the skin-caliper measurements in support of the beneficial effects of injectable PLLA over the duration of the retreatment study. Furthermore, although potential bias might have been avoided by having one individual perform the skin-caliper measurements and another perform the injections, using the same individual to consistently obtain his or her own patient's measurements ensured intrapatient consistency in measurement technique.

Nine of the 10 eligible patients who did not enroll in the retreatment study reported persistent correction (>36 months) when contacted over the telephone for assessment of adverse events, and the additional patient was treated privately at month 30. The study protocol did not require patients to return to the site for final measurement. Because these patients were not measured physically, their data could not be included in the quantitative final results, but their continued correction and satisfaction would only tend to further support the longevity of results with injectable PLLA. In fact, according to patient report, approximately 10% of the patients who took part in the original Blue Pacific study had more than 36 months of persistent satisfaction and, therefore, presumed sustained correction. Finally, the demographics of this trial (heavily weighted to white men) is similar to the demographics reported in other studies of HIV-associated facial lipoatrophy. A 5-year manufacturer-sponsored registry study is currently underway to better elucidate response to injectable PLLA and the rate of side effects in women and people of color.

In conclusion, injectable PLLA was shown to be a safe and effective long-term treatment option for HIV-associated facial lipoatrophy. The results may not be completely generalizable to a non-HIV-infected population because host response may partially affect treatment outcome. Patients with milder facial lipoatrophy required fewer injections and had more sustained correction than those with severe facial lipoatrophy. All patients receiving treatment of facial lipoatrophy with injectable PLLA were highly satisfied with the results of the therapy.

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References


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