Rejuvenation of the Aging Lip With an Injectable Acellular Dermal Graft (Cymetra)

Anthony P. Sclafani, MD; Thomas Romo III, MD; Andrew A. Jacono, MD

Objective: To evaluate the effects of Cymetra (micronized AlloDerm tissue) in rejuvenating the aging and atrophic lip.

Patients: Forty-four patients aged 32 to 80 years who reported age-related changes in the size and contour of the upper lip.

Methods: Patients were randomized to treatment with either Cymetra or glutaraldehyde cross-linked bovine collagen (Zyplast). Standardized photographs of each subject were taken before and after treatment initially and 3, 6, 9, and 12 months after initial treatment. Patients were monitored for signs of hypersensitivity, infection, and inflammation.

Main Outcome Measures: Digital photographs were analyzed for changes in the nasolabial angle, percentage of the total lip accounted for by the exposed red lip in the midline and on the lateral view, the visible red upper and lower lip surface areas, and the anterior projection of the upper and lower lips.

Results: All patients tolerated treatment well without any significant local or systemic complications. Nineteen patients were treated with Cymetra and 25 with Zyplast. Cymetra-treated patients were more likely than Zyplast-treated patients at 12 months (3 months after the previous treatment) to have increased the percentage of red lip in the midline (84.6% vs 38.9%; P = .01), the vermilion height in the upper lip midline (84.6% vs 38.9%; P = .01), and the exposed red lower lip on the lateral view (69.2% vs 33.3%; P = .048) by at least 20%; increased the lower lip projection by 0.5 mm or more (69.2% vs 27.8%; P = .02); and decreased the nasolabial angle by at least 10° (46.2% vs 16.7%; P = .07).

Conclusions: Cymetra is a suspension of particulate dermal matrix that seems to increase the upper lip bulk, vermilion, and lower lip projection after a threshold of Cymetra has been administered. There are few differences in any measured long-term (3 months after treatment) variables until the 12-month visit, when there were statistically significantly more Cymetra-treated patients with improved lip aesthetics than those treated with Zyplast. With repeated treatments, Cymetra seems to accumulate, producing a long-term effect superior to Zyplast in many patients.

Arch Facial Plast Surg. 2002;4:252-257

INJECTABLE SOFT TISSUE augmentation producing long-term results is a goal that has thus far eluded surgeons. Bovine collagen, available for more than 20 years, can produce excellent but short-term results, persisting for no more than 4 to 6 months. Cymetra (LifeCell Corp) has been introduced with the hope that homologous human dermal proteins may persist longer or be integrated into the recipient tissue during the healing process.

In a previous article, we showed that Dermalogen was slightly more persistent at 12 weeks than glutaraldehyde cross-linked bovine collagen (Zyplast; Collagen Corp, Palo Alto, Calif), although the small difference was believed to be clinically insignificant. Dermalogen, composed of dissociated collagen fibers and other components of human dermis, was progressively digested. In another study,25 subcutaneous AlloDerm sheets (LifeCell Corp) were compared with intradermal Zyplast. During 1-year follow-up, Zyplast was progressively resorbed, with complete loss of clinical effect; AlloDerm also lost some clinical effect, which seemed to stabilize by 6 months after implantation. AlloDerm, with its macrostructure of intercalated collagen and elastin fibers, may have provided a better milieu for collagen deposition.

Cymetra is composed of particles averaging 123 µm that retain the protein matrix structure of AlloDerm. In theory, these particles of Cymetra should, to some de-
Visits, Cymetra was simply resuspended in the same diluent. However, by the 6-month posttreatment, Cymetra was reconstituted and filtered yielding an estimated dose of 150 mg suspended in 0.5% lidocaine with 1:20000 epinephrine immediately before use. Initially, Cymetra was reconstituted and filtered yielding an estimated dose of 150 mg suspended in 0.8 to 1.2 mL of diluent. However, by the 6-month visits, Cymetra was simply resuspended in the same diluent without filtration, with concentrations ranging from 150 to 375 mg/mL.

**METHODS**

**PATIENT SELECTION**

Patients with signs of aging of the upper lip were accepted into the study. Only patients previously treated with or who had negative skin test results to Zyplast were included.

**TREATMENT COURSE**

At each visit, photographs of the perioral complex of each patient were taken in repose in frontal and right lateral projections. After application of EMLA (Astra USA, Marlborough, Mass), patients were treated with either Zyplast (using a 32-gauge needle) or Cymetra (using a 26-gauge needle) in the upper lip to produce a slight overcorrection. Material was injected between the orbicularis oris muscle and the overlying mucocutaneous junction of the upper lip. Material was also injected intradermally along both philtral columns and just under the mucocutaneous junction of the lower lip to produce an aesthetic result (Figure 1). The relative amounts of material injected into different parts of each lip were determined by the desired result expressed by each patient, and the exact amounts were recorded separately. Posttreatment photographs were then taken. Ice compresses were then applied lightly to the lips for a minimum of 20 minutes, and patients were instructed to refrain from oral animation for at least 4 hours.

Patients returned 1 week later, and photographs were again taken. If the patient desired, an additional “touch-up” injection was administered at this time, and the amount of material injected into each lip was recorded.

This sequence was repeated 3, 6, and 9 months after the original treatment, and at 12 months patients were photographed and received a last treatment if desired. All patients were evaluated and treated by one of us (A.P.S.) at all visits. All patients who completed 12 months of follow-up were offered 1 additional treatment with their choice of Cymetra or Zyplast, regardless of the experimental treatment group to which they had been assigned.

At each visit, patients were assessed for adverse reactions. Minor adverse events were defined as tenderness or irritation of the treated areas for less than 24 hours.

**RECONSTITUTING CYMETRA**

Cymetra was provided as an aseptic freeze-dried powder that was reconstituted with 0.5% lidocaine with 1:20000 epinephrine immediately before use. Initially, Cymetra was reconstituted and filtered yielding an estimated dose of 150 mg suspended in 0.8 to 1.2 mL of diluent. However, by the 6-month visits, Cymetra was simply resuspended in the same diluent.

**PHOTOGRAPHIC DATA**

All pictures were digitally captured (Sony DCR-VX1000; Sony Corp, Tokyo, Japan, and Mirror Eyes, Kirkland, Wash). Standardized, camera-mounted lighting and a black background were used, and close-up frontal and right lateral images of the perioral complex were taken. A ruler was included in each image for calibration. All measurements on every photograph were made by one of us (A.A.J.) and verified by another one of us (A.P.S.), without knowledge of patient identity or treatment received. Figure 2 shows the measurements made on each frontal and lateral photograph.

Data were recorded and analyzed using a software program (Microsoft Excel 2000; Microsoft Corp, Redmond, Wash). Statistical significance between average values was determined using 2-tailed t tests and between groups of responders using χ² analysis. This study was approved by the institutional review board of The New York Eye and Ear Infirmary.

**RESULTS**

**CLINICAL RESULTS**

Forty-seven patients (20 receiving Cymetra and 27 receiving Zyplast) were enrolled. Two patients (1 with Cymetra and 1 with Zyplast) were withdrawn owing to minimal age-related changes of the lips, and one Zyplast patient withdrew voluntarily prior to any treatment.

Of the remaining 19 patients receiving Cymetra (average age, 52.5 ± 10.5 years), 13 (68%) completed all visits through 12 months, whereas 14 (74%), 16 (84%), and 17 (89%) completed the study through the 9-, 6-, and 3-month visits, respectively. Of the 25 patients who received Zyplast (average age, 55.7 ± 9.2 years), 18 (72%) completed all of the required study visits through 12 months, whereas 16 (64%), 20 (80%), and 22 (88%) were available at the 9-, 6-, and 3-month visits, respectively. Most patients were Fitzpatrick skin types 2 or 3 and Glogau scale 2 or 3, with no difference in these variables between the 2 treatment groups.

©2002 American Medical Association. All rights reserved.
Patients who were habitually unable to return for follow-up within 2 weeks of the scheduled 3-month intervals were electively terminated from the study. Other patients were excluded from further participation owing to onset of pregnancy, relocation, or intercurrent facial surgery.

Thirty-seven adverse reactions were directly observed or reported by patients after the initial injection, and substantially fewer were noted after the 3- and 6-month injections (3 and 7 events, respectively). No adverse events were reported or observed after the 9- or 12-month injections (Table 1).

At the conclusion of the study, 9 (69%) of the 13 Cymetra-treated patients chose to receive an additional injection of Cymetra, whereas 1 (8%) chose to be treated with Zyplast; 3 (23%) refused any further treatment. Of the 18 Zyplast-treated patients who completed the study, 2 (11%) chose additional treatment with Zyplast, whereas 9 (50%) requested Cymetra treatment; 7 (39%) refused any further treatment.

PHOTOGRAPHIC RESULTS

Photographs were analyzed and percentage changes from pretreatment values were calculated, except for measurements of the anterior projection of the upper and lower lips, which were referenced to an extrinsic standard. Average values are given in Table 2. A review of individual data confirmed our clinical perceptions that whereas Zyplast-treated patients generally showed uniform responses, Cymetra-treated patients displayed more heterogeneous responses.

After reviewing all the clinical photographs, thresholds of 20% change from pretreatment values for change in the percentage of upper lip composed of vermillion, in upper lip vermillion height and vermillion surface area of upper or lower lips; a 10° change from pretreatment values (nasolabial angle); or a 0.5-mm change from pretreatment values (upper and lower lip projection) were determined to represent minimum but clearly identifiable posttreatment changes. Using these threshold values, patients were categorized as either clinical “responders” (CRs) or “nonresponders” (CNRs) for each value at each point. The characteristics and distribution of CRs and CNRs are given in Table 2.

We observed a significantly higher percentage of nasolabial angle CRs among Zyplast-treated patients vs Cymetra-treated patients at 3 months but significantly more CRs among Cymetra-treated patients than Zyplast-treated patients at 12-month follow-up (Table 2). There were also significantly more CRs among Cymetra-treated patients at 12 months for the following vari-

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Initial Injection, No. (%)</th>
<th>3-mo Injection, No. (%)</th>
<th>6-mo Injection, No. (%)</th>
<th>Total, No.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zyplast (n = 25)</td>
<td>Cymetra (n = 19)</td>
<td>Zyplast (n = 22)</td>
<td>Cymetra (n = 17)</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>7 (28)</td>
<td>9 (47)</td>
<td>1 (5)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Irregularities/asymmetry</td>
<td>2 (8)</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Herpes labialis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tenderness</td>
<td>5 (20)</td>
<td>2 (11)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pain</td>
<td>3 (12)</td>
<td>3 (16)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Erythema</td>
<td>2 (8)</td>
<td>1 (5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Swelling</td>
<td>0</td>
<td>2 (11)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>18</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*Zyplast; Collagen Corp, Palo Alto, Calif. Cymetra; LifeCell Corp, Branchburg, NJ.
Table 2. Results of Photographic Analysis in Patients Taking Cymetra vs Zyplast

| Variable | Time After Initial Treatment, mo | Patients, Clinical Responders/Total, No. (%) | Average Values† | Doses of Cymetra given to CRs and CNRs for each variable were generally not significantly higher in CRs compared with CNRs. At no time was there both a significantly higher percentage of Cymetra CRs than Zyplast CRs and a significant difference in Cymetra or

| Change in vermilion percentage at philtrum from baseline, % (%Δ[100*{(b−a)/b}]) | 3 | 10.61 | 6.62 | NS | 7/22 (32) | 3/17 (18) | NS | 10.00 | 16.10 | NS | 5/20 (25) | 5/16 (31) | NS | 9 | 10.46 | 16.06 | NS | 4/16 (25) | 5/14 (36) | NS |
| Change in vermilion percentage at midline from baseline, % (%Δ[100*{(d−c)/d}]) | 3 | 7.75 | 26.60 | .02 | 5/22 (23) | 8/17 (47) | NS | 9.23 | 28.95 | .05 | 7/20 (35) | 10/16 (62) | NS | 9 | 23.88 | 24.46 | NS | 6/16 (38) | 7/14 (50) | NS |
| Change in vermilion height at midline from baseline, % (%Δd) | 3 | 47.0 | 73.3 | .02 | 5/22 (23) | 8/17 (47) | NS | 6 | 10.4 | 29.1 | .08 | 7/20 (35) | 10/16 (62) | NS | 9 | 24.6 | 27.5 | NS | 6/16 (38) | 7/14 (50) | NS |
| Change in vermilion surface area from baseline, % (%Δe) | 3 | 7.39 | 11.97 | NS | 7/22 (32) | 6/17 (35) | NS | 6 | 34.97 | 28.02 | NS | 13/20 (65) | 9/16 (56) | NS | 9 | 26.47 | 15.36 | NS | 9/16 (56) | 5/14 (36) | NS |
| Change in nasolabial angle from baseline,° (%Δm) | 12 | −4.98 | −1.91 | NS | 7/22 (32) | 1/16 (6) | .056 | 6 | −5.18 | −3.24 | NS | 4/19 (21) | 4/16 (25) | NS | 9 | −5.43 | −7.40 | NS | 3/16 (19) | 5/14 (36) | NS |
| Change in vermilion height from baseline, % (%Δh) | 3 | 17.50 | 12.18 | NS | 6/22 (27) | 6/17 (35) | NS | 6 | 8.54 | 6.21 | NS | 6/20 (30) | 5/16 (31) | NS | 9 | 5.51 | 13.42 | NS | 4/16 (25) | 5/14 (36) | NS |
| Change in vermilion percentage on lateral view from baseline, % (%Δl/(g+h)) | 3 | 10.87 | 7.92 | NS | 5/22 (23) | 2/17 (12) | NS | 6 | 11.89 | 13.44 | NS | 5/20 (25) | 4/16 (25) | NS | 9 | 8.13 | 10.32 | NS | 4/16 (25) | 5/14 (36) | NS |
| Change in vermilion surface area from baseline, % (lateral) (%Δl) | 3 | 5.96 | 7.24 | NS | 6/22 (27) | 5/17 (29) | NS | 6 | 30.58 | 10.63 | NS | 11/20 (55) | 5/16 (31) | NS | 9 | 19.34 | 6.00 | NS | 6/16 (38) | 5/14 (36) | NS |
| Change in anterior projection, mm (Δi) | 3 | 0.28 | 0.38 | NS | 11/22 (50) | 7/16 (44) | NS | 6 | 0.32 | 0.21 | NS | 7/20 (35) | 8/15 (53) | NS | 9 | 0.39 | 0.39 | NS | 6/16 (38) | 6/14 (43) | NS |
| Change in vermilion surface area from baseline, % (%Δk) | 3 | 8.68 | 35.45 | .04 | 6/22 (27) | 6/17 (35) | NS | 6 | 34.38 | 30.86 | NS | 6/20 (30) | 2/16 (12) | NS | 9 | 34.32 | 43.75 | NS | 4/16 (25) | 5/14 (36) | NS |
| Change in nasolabial angle from baseline,*° (%Δm) | 12 | −4.98 | −1.91 | NS | 7/22 (32) | 1/16 (6) | .056 | 6 | −5.18 | −3.24 | NS | 4/19 (21) | 4/16 (25) | NS | 9 | −5.43 | −7.40 | NS | 3/16 (19) | 5/14 (36) | NS |
| Change in vermilion height from baseline, % (%Δh) | 3 | 17.50 | 12.18 | NS | 6/22 (27) | 6/17 (35) | NS | 6 | 8.54 | 6.21 | NS | 6/20 (30) | 5/16 (31) | NS | 9 | 5.51 | 13.42 | NS | 4/16 (25) | 5/14 (36) | NS |
| Change in vermilion percentage on lateral view from baseline, % (%Δl/(g+h)) | 3 | 10.87 | 7.92 | NS | 5/22 (23) | 2/17 (12) | NS | 6 | 11.89 | 13.44 | NS | 5/20 (25) | 4/16 (25) | NS | 9 | 8.13 | 10.32 | NS | 4/16 (25) | 5/14 (36) | NS |
| Change in vermilion surface area from baseline, % (%Δl) | 6 | 30.58 | 10.63 | NS | 11/20 (55) | 5/16 (31) | NS | 9 | 19.34 | 6.00 | NS | 6/16 (38) | 5/14 (36) | NS | 12 | 20.84 | 6.74 | NS | 6/18 (33) | 5/13 (38) | NS |

*Formulas refer to measured values in Figure 2.
†By 2-tailed t test. Zyplast; Collagen Corp, Palo Alto, Calif. Cymetra; LifeCell Corp, Branchburg, NJ. NS indicates not significant.
‡By χ² test.

| Doses of Cymetra given to CRs and CNRs for each variable were generally not significantly higher in CRs compared with CNRs. At no time was there both a significantly higher percentage of Cymetra CRs than Zyplast CRs and a significant difference in Cymetra or

| Change in vermilion percentage at philtrum from baseline, % (%Δ[100*{(b−a)/b}]) | 9 | 11.9 | −3.28 | NS | 6/16 (38) | 7/14 (50) | NS | 12 | 13.78 | 30.43 | .09 | 7/18 (39) | 11/13 (85) | .01 |
| Change in vermilion percentage at midline from baseline, % (%Δ[100*{(d−c)/d}]) | 9 | 24.6 | 27.5 | NS | 6/16 (38) | 7/14 (50) | NS | 12 | 16.2 | 38.9 | .04 | 7/18 (39) | 11/13 (85) | .01 |
| Change in vermilion height at midline from baseline, % (%Δd) | 9 | 24.6 | 27.5 | NS | 6/16 (38) | 7/14 (50) | NS | 12 | 16.2 | 38.9 | .04 | 7/18 (39) | 11/13 (85) | .01 |
| Change in vermilion surface area from baseline, % (%Δe) | 9 | 24.6 | 27.5 | NS | 6/16 (38) | 7/14 (50) | NS | 12 | 16.2 | 38.9 | .04 | 7/18 (39) | 11/13 (85) | .01 |

©2002 American Medical Association. All rights reserved.
Zyplast dose received between CRs and CNRs for any variable.

**COMMENT**

The aging lip (Figure 3) can be rejuvenated with surgical techniques.4-7 Several researchers8-11 have described good results with acellular dermal graft (AlloDerm) for lip augmentation. This method requires a surgical procedure, with a postoperative period of swelling and lip stiffness that many patients find unacceptable. Experimentally, AlloDerm seems to undergo partial volume loss before stabilization.2,3 Based on encouraging results with micronized AlloDerm,3 we examined the utility of an injectable acellular dermal graft in reversing the measurable stigmata of aging lips.

We compared the clinical results of Cymetra with Zyplast. Cymetra was more difficult to localize to smaller areas because of the decreased viscosity of the form of Cymetra used, a byproduct of the experimental method of reconstitution.

The clinical effects of Cymetra differed significantly from those of Zyplast. With injections to similar degrees of overcorrection, lips 1 week after early treatments with Cymetra showed less correction than lips treated with Zyplast. At 3 and 6 months, significant differences were not seen between Cymetra- and Zyplast-treated patients. However, even at these early follow-up visits, there was significantly greater resistance to Cymetra reinjection than during previous treatments and compared with retreatment of Zyplast-treated patients, suggesting residual subclinical Cymetra.

By the 12-month visit, measurable differences from pretreatment values were observed in a significantly greater proportion of Cymetra- than Zyplast-treated patients. We found that use of Cymetra can achieve some measure of lip rejuvenation that, with increasing dosage, can become more long lasting than Zyplast. With administration of cumulative doses of 1100 to 1600 mg of Cymetra, greater percentages of patients maintained improvement in the lips 3 months after treatment compared with use of Zyplast (as evidenced by increased percentage and height of the vermilion at the midline upper lip, increased lower lip projection, and decreased nasolabial angle).

The particular method used for injections may also have confounded some results. Because we injected along the vermilion border, increasing doses may have increased projection but at the same time caused some relative “hooding” and disappointing vermilion enhancement. We have since modified the injection technique used in our practices to better augment the vermilion and enhance the “poutiness” of the lip (Figure 4).

Complications of Cymetra treatment were relatively minor; the most common complication, ecchymosis at the injection sites, was seen predominantly after the first visit, and no patient withdrew from the study because of this.

We believe that serial Cymetra injections are a viable option for aesthetic rejuvenation of the lips. Patients must understand and accept the gradual improvement in lip aesthetics seen with Cymetra treatments. With serial administration of Cymetra, however, improved aesthetics are maintained at least 3 months after treatment compared with Zyplast use.

Not all patients attain progressively better results with repeated Cymetra treatments. We postulate that there is a dynamic process of graft dispersion, invasion, resorption, and stabilization that occurs after Cymetra injection. A host response to Cymetra ensues, with vascular, inflammatory, and fibroblastic infiltration of each Cymetra particle. Smaller particles are likely to be predominantly resorbed, whereas larger particles become incorporated in a host fibroblastic response. The particular potencies of these responses seem to vary from patient to patient. Some patients seemed to retain progressively more clinical effect with use of increasing total doses of Cymetra, whereas others displayed no cumulative effect.

---

**Figure 3.** Aging (left) and youthful (right) lips. The fine lines, decreased bulk and volume of the vermilion, increasing white lip length, vermilion inversion, philtral flattening, and decreased prominence of the Cupid bow need to be reversed to rejuvenate the lips.

**Figure 4.** The technique used in this study concentrated injections along the vermilion border, which led to less than desired fullness of the vermilion. Current technique (shown) seeks to add volume to vermilion.
We attribute this finding to the relative degrees of graft resorption vs incorporation. Owing to the study design, we cannot determine whether the effect of repeated Cymetra injections leads to a permanent clinical effect or is merely a result that outlasts the 3-month interval defined by the experimental protocol. Clinical results in non-study patients suggest that in certain patients, clinical improvement and tissue augmentation can be permanent (Figure 5).

In conclusion, we described a technique of lip rejuvenation that offers long-lasting or permanent correction with human materials and does not require invasive surgery. Cymetra should be injected in a serial fashion for gradual dermal enhancement. Patients should be cautioned that several injections are required before a clear-cut advantage over Zyplast treatment is seen. However, in appropriate patients, Cymetra can produce aesthetic results with significant longevity. Results of Cymetra treatment elsewhere in the face also show promise.

Accepted for publication March 28, 2002.

This study was supported by a grant from LifeCell Corp, the producer of Cymetra.

We thank Aida Ramos, RN, without whose tireless efforts in coordinating patient treatments and collecting data this study would not have been possible.

Corresponding author and reprints: Anthony P. Sclafani, MD, Division of Facial Plastic Surgery, Department of Otolaryngology—Head and Neck Surgery, The New York Eye and Ear Infirmary, 310 E 14th St, North Building, Sixth Floor, New York, NY 10003 (e-mail: asclafani@nyee.edu).

REFERENCES