



FACIAL ENHANCEMENT AND THE EUROPEAN EXPERIENCE WITH SCULPTRA™ (POLY-L-LACTIC ACID)

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Abstract

The primary reason patients seek aesthetic treatments is to combat the signs of aging. However, the majority of facial treatments and procedures fill specific wrinkles or pull-taught sagging skin, without returning the volume and contours of a youthful face. Injectable poly-L-lactic acid (Sculptra™) is a synthetic, biodegradable polymer, popular in Europe for the correction of lipoatrophy. The novel technique and mechanism of action of this product require physicians to adjust their practice of treating a specific line to returning volume to a facial area. Sculptra™ has been used successfully for the correction of nasolabial folds, mid and lower facial volume loss, jaw line laxity, and other signs of facial aging. Sculptra™ treatment provides a minimally invasive, effective, and prolonged (18-24 months) facial enhancement correction with a low frequency of side effects and no need for allergy testing.

Introduction

Numerous facial aesthetic treatments and procedures are available to the cosmetic physician. The majority of these aesthetic options are directed at the correction of wrinkles or folds as stand-alone detriments of aging. However, this focus on superficial wrinkles ignores the underlying volume loss and subsequent decrease in tissue connectivity and support that occurs with aging and as a side effect from disease therapies, such as with Highly Active Anti-Retroviral Therapy (HAART).

Indeed, a major factor in the visible signs of aging is progressive volume loss, which results from a combination of physiologic processes, including dermal dystrophy, bone resorption and lipoatrophy¹. With aging, the dermis becomes thinner as the dermoepidermal junction flattens and the stratum corneum loses its integrity. These dermal changes expose the aging skin to increased shearing forces as a result of lost connectivity¹³. The epidermis can instead thicken (with photoaging-induced inflammation) or thin (with sun-protected chronological aging)¹³. However, wrinkles can develop with either scenario^{4,5}. Skeletal

atrophy and redistribution also contribute to an aged appearance. For example, orbits may become larger and maxillae smaller, thereby reducing the available anchoring area and compacting the overlying tissue layers⁶.

In addition to these physiologic changes, the more substantial volume loss and predominant source of facial wrinkles is derived from lipoatrophy (fat loss) and an overall fat redistribution as associated with aging. The reduction in concentrated buccal and orbital fat pads along with the more global loss of fat within the facial hypodermis, diminish the youthful contours of the face while further reducing support for overlying dermal layers and allowing the skin to sag in accord with gravity. Combined, the result of these changes is frequently displayed as a concavity of the cheeks and temples along with the appearance of wrinkles, folds and deep furrows such as nasolabial folds⁷.

Sculptra™ (Dermik Laboratories, Berwyn, PA) has recently been approved by the Food and Drug Administration (FDA) for the restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus. This new injectable poly-L-lactic acid provides the treating physician with a novel approach to correcting contour deficiencies beyond filling a wrinkle. Outside of the United States, poly-L-lactic acid (marketed under the trade name New-Fill™) has been more broadly and cosmetically approved for use in large volume corrections of the signs of lipoatrophy since early 2004, and in the category of "wrinkle filler" since 1999, by the French Notified Body G-Med (Department of Evaluation of

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Medical Devices).

Poly-L-lactic acid has been used by an estimated 150,000 people in more than 30 countries throughout Europe and South America, and in Australia to treat a variety of facial volume and contour deficiencies, including signs of aging such as wrinkles, folds and sunken cheeks. This paper provides a brief background on this novel compound and offers a description of the European experience with injecting poly-L-lactic acid into individuals with varying degrees of lipoatrophy.

Lipoatrophy

Several variables can contribute to the degree of lipoatrophy, including: age, weight, genetics, personal habits (e.g., smoking, sun exposure², diet⁸) and compounding pathologies, such as HIV. There is presently no widely-used consensus scale of lipoatrophy severity and treatment. However, a rudimentary understanding of lipoatrophy can distinguish patients as exhibiting mild (chronological aging from 20 to 40 years of age), moderate (chronological aging from 30 years of age, which can be compounded by personal habits) or severe characteristics (typically associated with disease).

The novel activity of poly-L-lactic acid, as a volume enhancement for lipoatrophy, requires the treating physician to adjust their approach. Rather than filling a wrinkle, poly-L-lactic acid is best used to restore volume to a lipoatrophic area. With this treatment technique adjustment it becomes necessary to understand the variety of lipoatrophy presentations, which are not exhibited uniformly across all individuals.

Sculptra (Poly-L-lactic Acid)

Properties

Sculptra is an injectable medical device consisting of poly-L-lactic acid, sodium carboxymethylcellulose and non-pyrogenic mannitol. Poly-L-lactic acid is a synthetic biocompatible, biodegradable, absorbable polymer (Figure 1)^{9,10}. Allergy testing is not required before clinical use due to the synthetic, non-animal origin of the compound. The immunologically inert nature of poly-L-lactic acid is further emphasized by its polymers that have been used for several decades in various medical devices such as soft tissue anchors, absorbable sutures, surgical sealant meshes and solid implants, including screws, plates and pins^{9,11,12}. Poly-L-lactic acid microspheres have also been used as vectors embedding sustained-release injectable formulations¹³.

Mechanism of Action

After injection of poly-L-lactic acid, the microparticles in the site gradually degrade as the surrounding tissue continues to

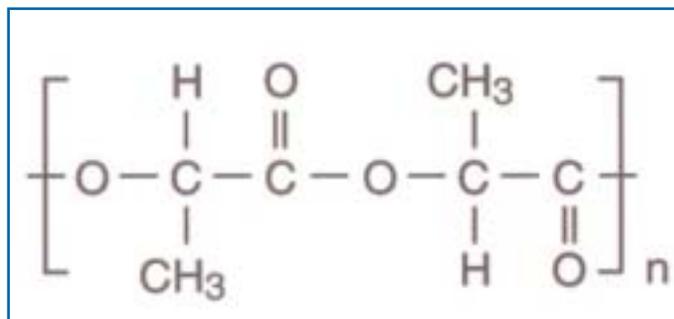


Figure 1. Structural formula of poly-L-lactic acid.

respond to the compound. Whereas the poly-L-lactic acid is eventually broken down into carbon dioxide and water¹⁴, the collagen production that occurs in response to the implant remains and provides the source of the long-term correction. The collagen production gradually and progressively increases the volume of the lipoatrophic areas over the course of weeks to months. One clinical implication of this gradual mechanism of action is the importance of avoiding over-correction during injections, which would otherwise provide undesired results.

Nasolabial biopsies, at 12 (Figure 2) and 30 months (Figure 3) after the last treatment, from a 55-year-old female patient injected with two sessions of poly-L-lactic acid approximately four weeks apart, showed a progressive dissolution of poly-L-lactic acid microparticles associated with a gradual ingrowth of type I collagen into the accumulations of the particles. These findings putatively indicate that the long-term mechanism of action of poly-L-lactic acid is responsible for the production of a fibrous tissue response that maintains volume correction after the implanted product is absorbed.

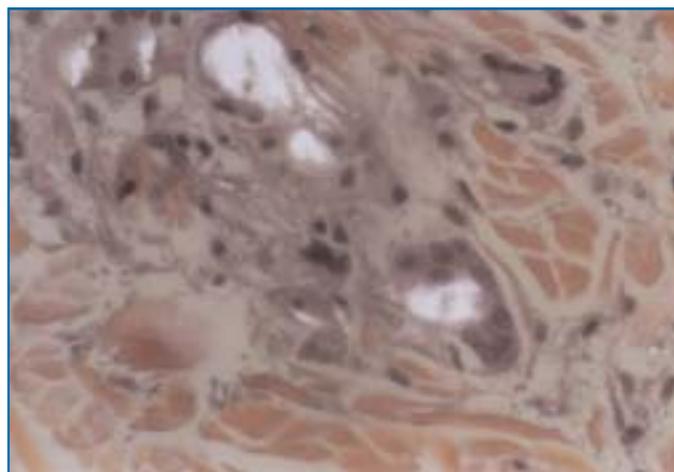


Figure 2. Histologic examination (H&E, original magnification x 400) exhibiting microparticles of poly-L-lactic acid at 12 months after last treatment, with adjacent aggregation of giant cells, histiocytes and collagen fibers.

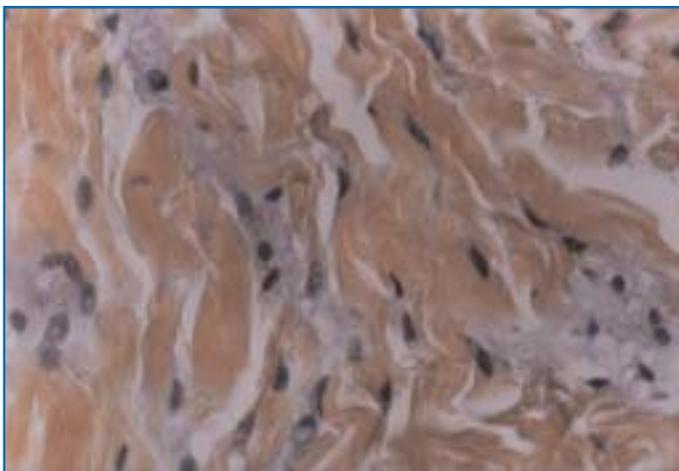


Figure 3. Histologic examination (H&E, original magnification x 400) of injected poly-L-lactic acid at 30 months after last treatment, showing the lack of PLLA microparticles and the abundance of collagen fibers.

Overview of Sculptra Studies

The tissue response and degradation of poly-L-lactic acid have been demonstrated in a preclinical murine model by Gogolewski et al.¹⁵ In their study, poly-L-lactic acid solids (and other polyhydroxy acids) were subcutaneously implanted in mice, who were then evaluated for tissue responses at 1, 3, and 6 months. Poly-L-lactic acid was shown to be well-tolerated with no acute inflammation, abscess formation or cytotoxicity at, or remote from, the implantation site. Throughout the duration of the study, the poly-L-lactic acid implant progressively degraded and an evolving tissue response was observed, with collagen fibers steadily but increasingly filling the space originally occupied by the implant. The results of more recent clinical studies further corroborate these findings¹⁶⁻¹⁹.

An initial open-label multicenter clinical study was conducted by Laglenne et al.²⁰ with 110 patients 23 to 78 years of age. Patient acceptability, tolerability and the aesthetic performance of poly-L-lactic acid in filling vertical wrinkles of the face were assessed over one year of treatment using no more than 1 mL of product per site of injection.

Patient acceptance, evaluated on a visual analog scale (VAS), was excellent with mean scores above 90%. Non-specific ecchymoses were noted in fewer than 10% of the patients and no immediate or delayed allergic or granulomatous reactions were reported. The efficacy of the treatment was considered to be very good by 70% of physicians and 75% of patients. The outcomes were consistent and comparable, regardless of the type of wrinkle; these results were maintained up to one year post treatment²⁰.

Recently, Valantin et al.²¹ reported on the efficacy and safety of poly-L-lactic acid in severely lipoatrophic patients with HIV. They enrolled 50 patients into this open-label, single-arm

study, who received four sets of injections at day 0 and weeks 2, 4, and 6 of a maximum of 4 mL of poly-L-lactic acid per cheek. Lidocaine (1 mL) was injected locally to prevent discomfort. Evaluations were conducted at weeks 6, 24, 48, 72, and 96, based on clinical examination, facial ultrasonography and photography. At the trial outset, the total cutaneous thickness (TCT) was 2.9 mm with no underlying facial fat. The change in TCT was shown to significantly increase ($p < 0.001$) with administration of poly-L-lactic acid by week 6 (+5.1 mm), 24 (+6.4 mm), 48 (+7.2 mm), 72 (+7.2 mm), and 96 (+6.8 mm) (Figure 4)²¹.

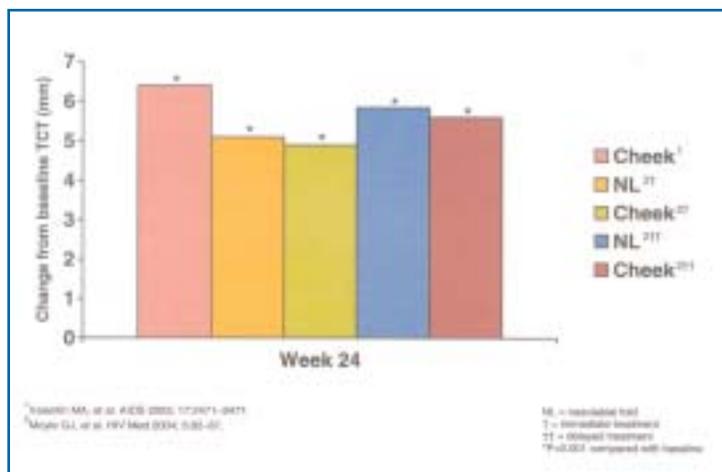


Figure 4. Change in total cutaneous thickness (TCT) in mm.

Expected minimal, localized edema was observed in patients at the injection site, spontaneously resolving within 24-48 hours. Minimal ecchymosis developed in 15 patients following injection, spontaneously resolving within two to three days. In addition, palpable but non-visible and non-bothersome subdermal papulae were observed in 22 patients, spontaneously resolving in six patients by week 96. No serious adverse events were observed during this high-dose study, with no interruptions of poly-L-lactic acid treatment in any patient²¹.

Additionally, Moyle et al.²² conducted an open-label, randomized, safety and efficacy, 24-week study of immediate versus delayed treatment with poly-L-lactic acid in severely lipoatrophic patients with HIV. Injections for those in the immediate treatment arm were administered at weeks 0, 2, and 4 compared with those in the delayed treatment arm administered at weeks 12, 14 and 16. In total 4-5 mL of poly-L-lactic acid was injected per cheek, per session. Evaluations were made at weeks 0, 12, and 24, for both groups, based on facial ultrasound, VAS, the Hospital Anxiety and Depression Scale (HADS) and by photographic assessment.

A significant increase ($p < 0.001$) from baseline in skin thickness was observed at week 12 in the immediate treatment group at the cheek and nasolabial region compared with the delayed treatment group. At 24 weeks both treatment arms were

observed to have significant increases ($p < 0.001$) over baseline skin thickness (Figure 4). A trend towards decreasing anxiety and depression scores was observed in both treatment groups from start of treatment through to week 24. Adverse events were uncommon and did not interrupt treatment².

Poly-L-lactic Acid Injection Technique: European Experience

The extent of changes due to facial aging demands a global approach to rejuvenation rather than filling a few individual lines. Restoration of soft tissue volume and contours, as well as the smoothing of wrinkles, must be accomplished in order to more closely approximate the youthful appearance sought by patients. Based on our experience in Europe, poly-L-lactic acid is the optimal compound to address this need. However, the mechanism of action for poly-L-lactic acid requires a physician to fully comprehend the technique differences between this product and fillers, before incorporating its use in practice.

Poly-L-lactic acid is provided as a vial containing 150 mg of lyophilized product. The authors recommend that the powder be reconstituted with 5 mL of sterile water for injection. Alternatively, it is acceptable to reconstitute poly-L-lactic acid with 4 mL of sterile water and 1 mL of lidocaine to reduce the discomfort from the procedure. After reconstitution, the mixture should be allowed to sit for at least two hours prior to use, in order to allow for full hydration; however, the product can also be prepared several hours in advance, for convenience. Following reconstitution, the product should be firmly shaken prior to application in order to ensure homogeneity of the suspension.

Alternative reconstitution proportions are acceptable including and upwards from 3 mL; however, the majority of patients are best served using 5 mL to reconstitute the compound. Stronger concentrations (up to 3 mL) should be used sparingly and only in severely lipoatrophic patients. A 5 mL dilution provides a controllable injection of the product with only a light-to-moderate pressure on the plunger. More importantly, the increased volume helps distribute the injected product evenly, increasing the opportunity to obtain the desired result. It has been our experience that uneven product distribution is a major contributory factor when disappointing results are obtained and should therefore be given particular attention by the treating physician. Furthermore, a 5 mL dilution reduces the incidence of needle blockages.

Poly-L-lactic acid is injected using a 26-gauge needle. Each injection should be at a spacing of 0.5-1.0 cm from the previous injection. Despite the small needle size, it should be expected that some patients will experience some minor discomfort with the initial injection, and should be warned of this.

Techniques differ somewhat with the area being treated and the severity of lipoatrophy. Unlike line fillers, overcorrection is not required and instead should be avoided to prevent undesired results. The mildly to moderately lipoatrophic lower face should require approximately 5 mL of product using a criss-cross and tunneling technique. Each injection should be roughly 0.1-0.2 mL into the deep dermis at the junction with the hypodermis and followed by massage after every 3-4 injections. The temple region should require only 3-6 injections per side with 0.1-0.2 mL per injection; however, this region is better served using a depot of product instead of tunneling, followed by massage. Unlike the lower face, injection into the temples should be deep to the dermis. More advanced techniques of injection around the orbits or into the perioral region should not be attempted without sufficient training and knowledge of the injection procedure. Complete treatment can range from three to five sessions, depending on lipoatrophy severity and patient response, separated by four to six weeks in-between injections, in order to adequately judge the full cosmetic effect of the previous treatments.

Case reports

Patient 1: Mild Lipoatrophy

Patient 1 was a 44-year-old female who presented with mild nasolabial folds and marionette lines (Figure 5A). The patient had no history of cosmetic augmentation and was considered a suitable candidate for poly-L-lactic acid based on the need for volumetric enhancement in these regions. A total of 5 mL was used per session, 2.5 mL injected per side. The three sessions were spaced as near to four weeks apart as possible. Deep dermal layer injections were administered using a tunneling technique in crisscross pattern. The product was injected seriatim using 0.1-0.2 mL per injection. The aesthetic effect was obvious at 12 months (Figure 5B) and persisted through the 24-month follow-up. This case represents typical mild lipoatrophy expression in younger aesthetic patients who are seeking longer-lasting volume enhancement, and in whom a filling mechanism of action would be inappropriate.



Figure 5A & B. Patient 1 mild lipoatrophy prior to (A) and after (B) injection of Poly-L-lactic acid.

Patient 2: Moderate Lipoatrophy

Patient 2 was a 39-year-old HIV positive female who was con-

cerned with the noticeable volume loss in her mid and lower face and the obvious nasolabial folds, despite her relatively young age (Figure 6A). There was no sign of severe photoaging or compounding dermatological problems. The patient did not have a previous history of aesthetic enhancement and needed a volume adjustment to improve her appearance that could not be adequately achieved by other minimally invasive treatments. With this more moderate lipoatrophy, the patient required four treatment sessions at approximately four weeks apart. The first two sessions required a total of 6 mL per session (3 mL per side) and the latter two sessions required 4 mL per session (2 mL per side). Injections were at the level of the deep dermis and administered using a tunneling technique in crisscross pattern, using 0.1-0.2 mL per injection. The aesthetic effect of the product was assessed at 15 months (Figure 6B) and the improved appearance was persistent through a 24-month follow-up. The dynamic expression in Figure 6B highlights the natural appearance of effects from poly-L-lactic acid in this patient that is consistent with the results across patients.

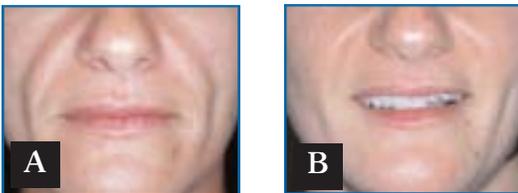


Figure 6A & B. Patient 2 moderate lipoatrophy prior to (A) and after (B) injection of Poly-L-lactic acid.

Patient 3: HAART-Related Severe Lipoatrophy

Patient 3 was a 55-year-old male with HAART-related severe lipoatrophy, presenting globally in the face, but with particular emphasis in the mid and lower face (Figure 7A). This patient received five treatment sessions of 6 mL per session (3 mL per side), due to the severity of the condition. With the near lack of hypodermal adipose tissue in this patient, it was important to focus injections into the deep dermis without intruding into the nearby perioral and periorbital musculature, inhibiting optimal product distribution. The age of this patient was also considered in planning a treatment regimen, as older patients may have a slower tissue response, and may therefore require more product to develop the desired result. Follow-up assessment of this patient at 24-months showed a sustained improvement in appearance (Figure 7B).

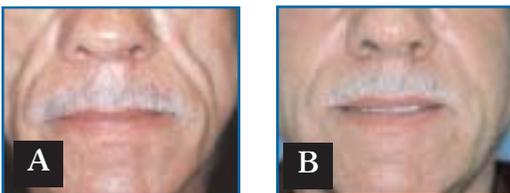


Figure 7A & B. Patient 3 Haart-related severe lipoatrophy prior to (A) and after (B) injection of poly-L-lactic acid.

Conclusions

Poly-L-lactic acid has been available for medical use for over 30 years in various polymer forms. The most recent compound, Sculptra, has been used in Europe since 1999 (under the trade name New-Fill™) for the cosmetic enhancement of wrinkles, folds and volume corrections, and is now available in the United States, for the restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with HIV. The presented case reports highlight typical cases of the range of lipoatrophy and the results of treatment with poly-L-lactic acid. Due to its volume-enhancing mechanism, this compound is able to cosmetically augment facial areas with volume deficits and in doing so reduces the outward appearance of wrinkles and folds. This effect is supported by several case reports in which the desired look was achieved with a series of injections over time, and maintained for 24-months even in dynamic expression. No adverse events were observed in this case series, but common procedural events for any injection should be communicated to the patient; these include mild edema and redness. Subacute events are uncommon and may be associated with overcorrection or uneven distribution of the product, therefore physician training is of importance. After 24 months, treatments may begin to slowly subside and should be retreated on a case-by-case basis and as necessary.

Sculptra is an attractive new treatment option for patients seeking longer-lasting facial volumetric enhancement. The novel action of poly-L-lactic acid places this product apart from injectable fillers as a unique approach to the augmentation of facial aesthetics with a broad range of applications.

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