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Poly-L-Lactic Acid: A New Class of Collagen Stimulators

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Introduction

Original Articles

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INTRODUCTION

This supplement to the *Journal of Drugs in Dermatology* describes a new and exciting approach to noninvasive aesthetic age management employing poly-L-lactic acid (Sculptra). This product represents a new generation of products that both correct volume depletion associated with the aging process (volumizer) as well as induce long-term dermal remodeling changes (ie, neocollagenesis; bioactive stimulator). These clinical and pathophysiologic effects differentiate this product from the more conventional filler agents, which are used, for the most part, for localized filling of fine lines, folds, localized areas of volume depletion, and mucous membranes.

Poly-L-lactic acid is playing an emerging role in the clinicians' whole body nonablative therapeutic armentarium. From its early introduction in Europe and pivotal role in the management of HIV lipoatrophy to its present clinical aesthetic trials, American physicians have joined their European colleagues in better understanding the preferred clinical indications, optimal technique modifications, and potential adverse sequelae associated with this unique biologic agent.

This supplement outlines the clinical and scientific evolution of poly-L-lactic acid and its introduction into clinical practice in the US. Articles presented here document appropriate techniques of usage, indications in both the HIV as well as cosmetic venues, as well practical approaches as to how to incorporate this product into clinical practice. Finally, a detailed multicenter clinical experience is elucidated upon, which includes safety data as related to potential complications as well as management of adverse events in this clinical setting.

Understanding the importance of volume loss as an integral part of the photoaging process and recognizing the differences between poly-L-lactic acid and more traditional filling agents (ie, hyalurons and collagens) are the 2 major educational goals of the material presented in this supplement.

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Clinical Experience of Adverse Outcomes Associated with Poly-L-Lactic Acid

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Abstract

Background: Injectable poly-L-lactic-acid (PLLA) is used off label in cosmetic contouring and has US FDA approval for correcting facial lipoatrophy associated with HIV. There is little information available on the frequency of adverse events with semipermanent facial augmentation.

Objective: To utilize the authors' expertise to assess adverse effects with PLLA, and to offer insight on prevention and management of these adverse events.

Methods: The authors present data on adverse events associated with PLLA from their clinical practices, as well as an overview of the safety of semipermanent products from the literature.

Results: Data from 58 patients treated with PLLA in one practice showed that there were 9 occurrences of bruises, 6 of edema, one allergic reaction, and one occurrence of benign white nodules. Among 61 patients in the other practice, 2 patients developed intradermal papules and 5 patients developed minor bruising within 3 days of the treatment.

Conclusion: The risk of papules and nodules may be greatly reduced with correct reconstitution of the product and a proper injection technique along with massaging of the treatment area. Thus, the significant benefits of PLLA coupled with the low and manageable risks provide an acceptable benefit/risk profile.

Introduction

In 2005, approximately 8.4 million minimally invasive cosmetic procedures were performed in the US alone, a 53% increase from the year 2000. The majority of these procedures were nonsurgical and many involved the use of injectable soft-tissue fillers or volume enhancers. Despite this increase, collagen and fat injections have decreased by 58% and 13%, respectively, since 2004. However, facial augmentation with newer agents such as poly-L-lactic acid (PLLA; Sculptra®), hyaluronic acid (Restylane®, Hylaform®), and calcium hydroxylapatite (Radiesse™) have increased. According to the 2005 American Society of Plastic Surgeons USA Cosmetic Surgery Statistics,[1] this trend may be accounted for by the fact that bovine-based collagen and fat injections require time-consuming allergy tests and harvesting procedures, whereas the newer fillers can achieve similar results without these methods.

Poly-L-lactic acid is a synthetic, biocompatible, biodegradable molecule derived from the alpha-hydroxy-acid family. Initially developed in Europe as New-Fill™, PLLA has been effectively used for aesthetic indications since 1999 in more than 150,000 people worldwide. Poly-L-lactic acid is also approved by the US FDA for facial lipoatrophy associated with HIV.

The mode of operation by which PLLA creates volume augmentation is associated with a foreign body reaction that presents several weeks to months after injection, resulting in a gradual effect. As PLLA degrades, collagen production is stimulated, which increases volume and creates the aesthetic benefit (Figure 1).[2] Therefore, PLLA is categorized as a long-acting (up to 2 years), semipermanent volumizer.

The development of new injectable cosmetic products is driven by the desire to create an effective product with minimal adverse side effects compared to older agents. Generally, adverse side effects can be categorized as those that are caused by injection such as bruising, itching, erythema, pain, infection and soreness, and those related to the type of implanted product, such as papules, nodules, and systemic responses to the product. However, there is scant literature available presenting the frequency of adverse events over the long-term with the currently available products used for facial augmentation.

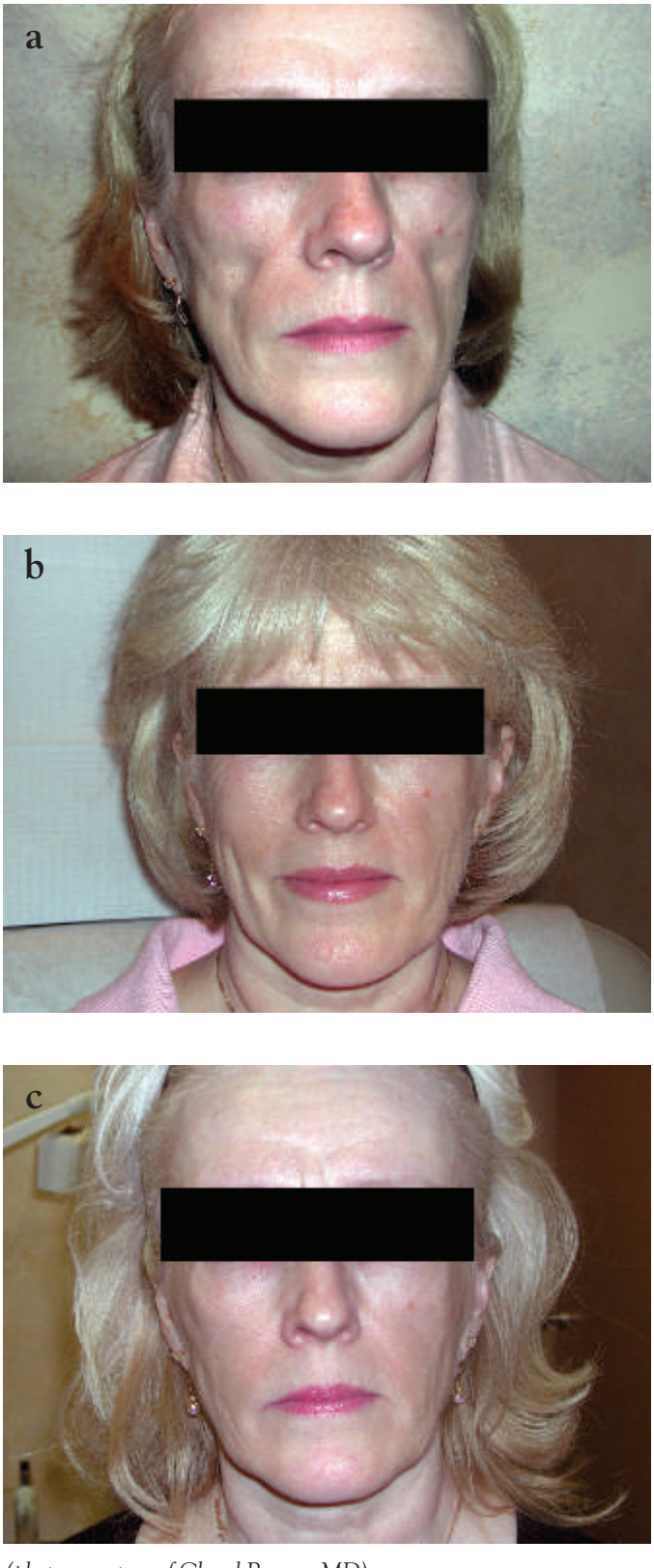
In this review, we will focus on our clinical experience of cosmetic device-related adverse events with PLLA and other semipermanent volumizers, and discuss the preventative techniques and best practices for management of adverse events with PLLA.

Device-Related Adverse Events Using Semipermanent Products

Semipermanent products are classed as those that have effects lasting from a few months to a few years. Calcium hydroxylapatite, PLLA, and autologous fat are in this category. Permanent products include silicon, polymethylacrylate, and polyacrylamide, whereas temporary products include fillers such as collagen and hyaluronic acids.

In terms of adverse events, the nature of the material in any device can impact the type of reaction. When a natural

Figure 1. Patient with lipoatrophy treated with poly-L-lactic acid: a) Pretreatment, b) Nine months posttreatment after 3 sessions (each 6 weeks apart), c) Eighteen months after last treatment.



(photos courtesy of Cheryl Burgess MD)

material is used, such as autologous fat, there is little chance of an immune response. However, excess fat injections may cause the local blockage of blood vessels, which can cause small clusters of cystic steatonecrosis,[3] skin necrosis, and even blindness in extreme cases.

Particle size is also important in terms of adverse events. For example, if the particle size is too small, the particles can migrate via the lymphatic system and lead to long-term complications and granulomatous reactions. To avoid phagocytosis, the ideal particle size should be 30 to 42 µm in diameter.[4]

Histologically, polyvinyl gel microspheres invoke a tissue reaction similar to that of polyacrylamide, which is a permanent facial augmentation product reported to have adverse events such as enlarged lymph nodes and gel migration.[5] Even 9 months postinjection, this tissue reaction can remain visible and palpable.[5] Future clinical research will reveal whether late side effects are as high as with acrylamides.[5]

Calcium hydroxylapatite, an inorganic compound that occurs in teeth and bones, has proven to be highly biocompatible.[6,7] However, this material can coalesce if injected into hyperkinetic facial muscles[7] and can exacerbate the development of a foreign body reaction. In a study involving 90 patients, 7 individuals (7.8%) developed nodules.[6]

Device-Related Adverse Events: Clinical Experience with Poly-L-Lactic Acid

Device-related adverse events are directly related to the device itself and vary greatly depending on the biocompatibility or nature of the device and how long it persists in the tissues. Occasionally, delayed hypersensitivity has been known to occur several years after injection and this may explain the formation of granulomas.[8] It should be noted that granulomas arising from a foreign body reaction should be differentiated from papules and nodules as these are more likely a result of uneven distribution of the product injected.[8,9] To date, the formation of nodules and papules has been of particular concern with PLLA, although no serious adverse events have been reported.

In pivotal studies for PLLA, subcutaneous papules were described in 44%, 31%, 6.1%, and 12.1% of the patients.[10-13] In one study, subcutaneous papules spontaneously resolved by week 96 in 6 of the 22 patients who developed them earlier in the trial.[10] High concentrations of localized PLLA (dilution with 3 mL sterile water for injection [SWFI]) and not enough time between treatments (less than 2 weeks) may be associated with nodule formation. Nonhomogeneous reconstitution of PLLA, or injection less than 2 hours after reconstitution, have both been associated with an increased risk of side effects. Numbers of subcutaneous papules were higher in early studies with PLLA use. However, when PLLA was diluted in 4 cc of sterile water and 1% lidocaine and subcutaneous injection used, nodules were relatively rare (<5%).[14]

Furthermore, our clinical experience of PLLA in patients receiving cosmetic augmentation has shown that the percentage of adverse events is similar to later PLLA study results. Data from 102 treatments (99 facial and 3 hand) in 58 patients were examined, of which there were 9 (9%) occurrences of bruises, 6 (6%) of edema, one (1%) allergic reaction, and one (1%) occurrence of benign white nodules (Table 1).

Our study in patients receiving PLLA for facial lipoatrophy related to HIV showed that of 61 immunocompromised HIV-infected patients with prior use of highly active antiretroviral therapy, there were no reported allergic reactions, infections, or adverse events after 18 months.[15] Two patients developed intradermal papules in the infraorbital region as a result of placement of PLLA and 5 patients developed minor bruising within 3 days of the treatment, which resolved within 7 days (Table 2).[15]

Additionally, published data have shown that in 2,131 patients receiving PLLA for facial augmentation and hand rejuvenation, as well as acne scar treatment, nonvisible subcutaneous papules (<5 mm) were noted in 66 patients (3.2%), of which 26.9% spontaneously resolved within 3 months. It was also found that a small number of patients developed visible subcutaneous papules after facial injections (26 patients or 1.2%) and injections into other parts of the body (8 patients or 0.38%; 5 injections into the neck and 3 into the hands).[16] Three patients had granulomas confirmed by histologic evaluation (0.1% of the total population).

Table 1. Adverse events in 102 treatments (in 58 patients) of poly-L-lactic acid in clinical practice (data courtesy of Neil S. Sadick MD).

Injection-related adverse event	Number of treatments (%)
Bruising	9 (9%)
Edema	6 (6%)
Allergic reactions	1 (1%)
Inflammation	2 (2%)
Device-related adverse event	
Injection site subcutaneous papule	1 (1%)

Table 2. Adverse events in 61 patients treated with poly-L-lactic acid.[15]

Injection-related adverse event	Number of patients (%)
Bruising	5 (8%)
Device-related adverse event	
Injection site subcutaneous papule	2 (3%)

Preventative Techniques for Adverse Events with Poly-L-Lactic Acid

Many adverse events, such as bruising, itching, erythema, pain, infection, and soreness, are related to the technique of the injection itself. Injection-related adverse events are similar among all injectable products since they are all introduced into the skin via a needle. Treatment using substances that require a heavy gauge needle may be more painful.[17] The risk of adverse events can be reduced if appropriate preinjection and injection techniques are employed.

The occurrence of adverse events associated with injectable PLLA may be minimized with correct patient assessment, product reconstitution, and administration techniques. A recommended technique is to dilute PLLA with 5 mL or more of SWFI and to allow it to reconstitute for more than 2 hours prior to use. Administration should be by deep dermal or subdermal injection. A minimal amount of product should be used for each injection (0.1-0.2 mL), and each injection site should be spaced at 0.5- to 1-cm intervals in order to avoid overcorrection, then followed by adequate massage of each treatment area.[18]

Foreign body reactions can be minimized if the material is evenly dispersed throughout the tissues, as uneven distribution can lead to papules/nodules. For example, material that is injected into tissue above hyperkinetic muscles, such as the orbicularis oculi and perioral muscles, can coalesce into large aggregations, triggering foreign body reactions. It is recommended that these areas only be injected by experienced injectors. In the authors' experience, to maximize the covalent bonding of the polymer when mixing PLLA, it is recommended that the vial be warmed gently after reconstitution to create a smooth gel for ease of distribution. An even distribution of material can be achieved by massaging the injection area post-treatment.

Injections can also cause localized skin discolorations. Red discoloration is caused by the inflammatory response,[19] whereas blanching at the injection site can be attributed to a temporary vascular reaction. If this is the case, the needle must be taken out and the area should be massaged immediately.

Management of Device-Related Adverse Events

Typically, papules are palpable, small (less than 5 mm), nonvisible, not bothersome, and are naturally alleviated over time without using any particular treatment. Many patients with papules that are not bothersome choose not to have treatment.

The management of chronic papules/nodules formed as part of the inflammatory response to devices can be challenging. Inactive and active papules and nodules should be differentiated to ensure appropriate treatment. Inactive

Table 3. Recommended treatment of nodules and papules arising with poly-L-lactic acid use.

Early onset papules and nodules	**Weekly:** Subcision (break-up) of nodules with 18-gauge needle Injection of sterile water to dilute poly-L-lactic acid at site Massage following injection
Late onset papules and nodules	**Every 1 to 2 weeks:** Intralesional injection of triamcinolone, 5-fluorouracil, or methylprednisolone **Plus daily:** Systemic therapy with low dose prednisolone, doxycycline, or tetracycline

papules/nodules are hard and not inflamed, while active ones are inflamed and tender. It must also be established whether they are confined to the treatment area. Histological examination should reveal whether histocytes or inflammatory cells are present (granulomas).

Once the papules/nodules have been characterized, a treatment regime can begin. For early onset nodules caused by the clustering of PLLA, treatment should occur weekly, using the following procedure: subcision of the nodules with an 18-gauge needle, injection of sterile water, and vigorous massage (Table 3). Papules can also be flushed out with normal saline at 0.9% solution to hydrate and redistribute the particles. Although an option, excision of nodules/papules is unnecessary because, as far as the authors are aware, the nodules/papules that have been reported for PLLA are not large enough to warrant this procedure.

Subcutaneous papules that appear several months after treatment should be treated every one or 2 weeks with intralesional injections of triamcinolone, 5-fluorouracil, or methylprednisolone together with daily systemic therapy using low-dose prednisolone, tetracycline, or doxycycline (Table 3).

Conclusion

Although all injectable products used for cosmetic augmentation are associated with some degree of risk, adverse events such as papules and nodules can be minimized with careful injection technique, correct reconstitution of the product, and massage of the injection area. In addition, a waiting period of at least 2 weeks between treatments allows the physician to properly assess the needs of the patient and the effects of the treatment. In our experience, we have seen that PLLA is safe and adverse effects are minimal. Thus, the significant benefits of PLLA coupled with the low and manageable risks provide an acceptable benefit/risk profile.

Few injectable devices have been investigated in long-term randomized, controlled clinical trials. The clinical studies that have been carried out often lack long-term follow-up data. This type of information is very important as adverse events, such as foreign body reactions, can appear many months or even years post-treatment. It is essential that physicians and patients are fully aware of the risks associated with facial volume augmentation so that they can provide the most appropriate treatment and utilize the best techniques to avoid adverse events.

To fully understand the risks associated with the injection of semipermanent devices, extended follow-up of treated patients is required. Follow-up studies investigating the long-term effects of PLLA are currently ongoing.

Disclosures

Dr. Sadick is an advisor/trainer for Dermik in the use of Sculptra, for which he receives an honorarium. Dr. Burgess is an advisor/trainer for Dermik in the use of Sculptra, for which she receives an honorarium. At the time of the research of the 61 patients in this article, she was not an advisor or trainer and did not receive any honorarium.

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Optimizing Patient Outcomes with Collagenic Stimulators

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Abstract
Volumetric expansion using poly-L-lactic acid (PLLA; Sculptra®) is a new method of restoring volume to the aging face. It has been used successfully for HIV-associated lipoatrophy and is now being utilized for various aesthetic indications. Techniques for reconstitution, injection, and postoperative considerations are important facets of successful treatment. Since the use of PLLA involves a gradual correction, setting realistic patient expectations and discussing the various risks and benefits associated with Sculptra injections during the patient consultation are also critical to obtaining optimal outcomes. Sculptra is reconstituted by the individual physician and variations in the amount and type of liquid added have an effect upon patient comfort and corrections obtained. The advent of PLLA adds a novel method of restoring facial volume.

Introduction

Poly-L-Lactic acid (PLLA; Sculptra®), also known as NewFill™ in Europe, was approved for the treatment of HIV-associated lipoatrophy in 2004. Since that time, it has become popular not only for that indication but also for off-label, cosmetic uses.[1] Its use for cosmetic issues relies upon volumetric expansions due to the formation of collagen and elastic fibers. This methodology is different than the direct replacement of volume by material injected under the skin, which is the method of action used for most presently approved cosmetic fillers. Successful use of PLLA requires a thorough understanding of the product, its mechanism of action, anatomy relevant to facial rejuvenation, effective approaches for patient consultations, technical considerations associated with its injection, and postoperative care and management.

Sculptra Composition and Reconstitution

Sculptra contains poly-L-lactic acid as an active ingredient. In addition to this, sodium carboxymethylcellulose (USP) and nonpyrogenic mannitol are also included. The product comes as a sterile, dry powder that must be reconstituted prior to injection. The need for reconstitution and the opportunity to vary the amount and type of liquid used for product dilution represents a significant difference from other filling agents that come prepackaged, offering no opportunity for physician modifications.

Reconstitution for the product begins with sterile preserved water. According to the package insert, between 3 to 5 mL of sterile water should be introduced into the bottle using an 18-gauge needle.[2] The mixture obtained should sit for a minimum of 2 hours in order to allow the PLLA to imbibe water. There is anecdotal evidence that longer amounts of time, such as 24 hours or longer, improve the outcome. At the present time, many injectors prefer to avoid the inconvenience associated with waiting for Sculptra to rehydrate and instead mix the product with water at the beginning of each week. These injectors let the prepared Sculptra remain refrigerated for up to 3 weeks. Prior to injection, most experienced physicians warm the product to body temperature by utilizing various parts of their bodies. Clinical trials on the optimal temperature for injection will be helpful in determining the optimal temperature for this product.

A second area of debate with respect to Sculptra reconstitution is the optimal type and amount of diluent. Experienced injectors add between 5 and 9 mL of liquid to the product and there is evidence that the dilutions of 6 mL and above are associated with decreased rates of papule formation. When injecting the hands, more dilute concentrations (7-9 mL of liquid) are recommended.

The fact that this product is not a solution but rather a suspension of particles in a liquid phase has important implications for its usage. PLLA suspension is dynamic and subject to gravitational forces. The practical implications of this fact are that the product precipitates out of suspension as time passes and, unless the syringe is gently agitated, different parts of the syringe will have different concentrations. Thus, various parts of the syringe, as well as different aspects of the facial injection, can contain more or less PLLA if the injector does not agitate the product or takes an unduly long time to complete the injection.

There is a general consensus among experienced injectors that the addition of lidocaine is beneficial to the patient although the amount and type of lidocaine is less well agreed upon. After adding water and waiting for the product to imbibe, lidocaine may be added to the bottle. The author adds either 1 or 2 mL of 1% lidocaine with 1:100 k epinephrine. Other experienced injectors add 1 to 2 mL of 2 % lidocaine. The advantage of adding the epinephrine-containing anesthetic is that it may decrease the incidence of bruising. Clinical trials comparing outcomes using various anesthetic additives will help determine which is optimal.

Mechanism of Action for Poly-L-Lactic Acid

Following an initial expansion due to the diluent, the PLLA incites a low-grade inflammatory reaction that creates new collagen and elastic fibers. Migration of fibroblasts occurs and a durable correction is created in the process. In studies evaluating the degree of correction in HIV lipoatrophy, increased dermal thickness of more than 3 times the

baseline value was shown. The correction lasted for at least 2 years in many patients.

The unique mechanism of action has implications that are important for both patient and physician. First and foremost, as has been previously stated, there is no way to predict who will make connective tissue briskly and who will do so slowly. However, because the volumetric expansion relies on the patients own collagen and elastic, there is very little risk of an allergic reaction. In addition, the correction obtained will be durable. It is likely that as dermatologists and plastic surgeons gain experience with this product, planned enhancement procedures will become incorporated into the treatment algorithm. This will ensure continuity of correction through additional fibroblastic stimulation. Finally, since a great deal of information regarding PLLA has been obtained in relation to its use for the treatment of HIV-associated lipoatrophy, long-term studies (including histopathology and immunostaining) of the use of this product for cosmetic uses in immunocompetent individuals will help to better elucidate the mechanisms of action, histology, optimal dilution, and ideal treatment scheduling for this population.

Patient Consultation for Treatment with Poly-L-Lactic Acid

Since the treatment schedule, mechanism of action, and time until correction is observed and potential risks are different than commonly used filling substances, an effective patient consultation regarding Sculptra is essential for optimal outcomes. Each patient consultation should begin with a discussion of the mechanism of action of PLLA and its contrast with materials that are direct volume replacement products. Although Sculptra is a new device, its active ingredient has been safely and effectively used in absorbable sutures for decades, and this discussion helps patients to understand the composition of PLLA.

As with any patient consultation, the establishment of a level of trust between physician and patient is of paramount importance. It is critical to spend enough time with each patient to form a rapport that will enable the patient to trust the physician and for the physician to trust the patient since each patient shares a large responsibility for his or her postoperative care. Screening for patients with body dysmorphic disorder should also occur during the consultation.

During the consultation, a candid discussion of realistic expectations for the procedure should also occur. Some patients will garner information that leads them to believe that all of their wrinkles will disappear following injections or that one injection with PLLA will restore them to the appearance they had when they were 18. For patients unable to have realistic expectations regarding their treatment, it is prudent to avoid any treatment. The use of photographs to demonstrate representative before and after results is also helpful in managing patient expectations. These photographs will help to reinforce the gradual nature of the correction over time. When photographs are used, a spectrum of outcomes should be presented and, whenever possible, the physician's own results should be presented in addition to those provided by other physicians.

Because the mechanism of action of PLLA is different than other fillers, it should be explained that a gradual restoration of volume, rather than the sudden one seen with direct volume replacement, will occur.[5] If patients do not expect dissipation of volume they will be disappointed as their pretreatment appearance returns. Furthermore, although there is an initial plumping of the skin associated with the injection of water, this is not a durable correction, nor is it predictive of the degree of correction that will ultimately be achieved. This last point must be discussed thoroughly since during the early experience with PLLA, some injectors told their patients to expect the correction to be visible immediately following injection. Given what we now know about the mechanism of action as well as the variations in volume used for reconstitution, this early notion should be disabused.

Since each patient forms collagen at a different rate, in consultations it should be explained that there is no way to predict the degree to which a given individual will respond to the product. It should be made clear that while some individuals may have a dramatic response (even to the degree of overcorrection), others may require multiple series of injections to notice a change. During my consultations, I discuss that while the average number of injections required for most patients is 3, some of my patients will require one treatment and others will require more than 5. The costs associated with each treatment session should also be discussed during the consultation to avoid any misunderstanding about the scope of expenses involved. For patients reticent to invest the time, effort, and money associated with this treatment, alternate modalities should be discussed.

During the consultation, it is important to discuss the need to "treat, wait and assess" required with the use of PLLA. The fact that immediate touch ups or enhancements that might be feasible with other materials are not typically useful with Sculptra since injections of the latter are not performed less than 2 weeks apart. This discussion may enable the physician to further triage patients desiring immediate results.

The potential long-term benefits of Sculptra should also be discussed during the consultation. Data from some studies suggests that the correction obtained may last for 22 months or longer.[4] For many patients, this part of the consultation facilitates a discussion of the available information and enables the patients to address questions and concerns they may have regarding the procedure.

Any discussion of fillers or volumizers should mention potential complications. For PLLA, this can include risks common to any injection including bruising, infection, intravascular placement of product with subsequent tissue necrosis and/or blindness, formation of scars, hypopigmentation, and hyperpigmentation. In addition, PLLA has

some unique risks such as formation of subcutaneous papules that warrant mention as well.[5]

Anatomic Considerations

The aging face is associated with 2 cardinal features: loss of volume and descent. Both of these may be addressed with judicious use of PLLA but this product requires a thorough understanding of the relevant anatomy of the face, its changes during the aging process and experience injecting products into a deep dermal/subcutaneous plane.

Volume loss in the aging face is associated with a diminution of soft tissue structures and bone recession. In addition, there is a lengthening of the muscles of facial expression that cause a stretching of the face. Volume loss is most typically manifest in the malar and temporal areas. Experience with HIV lipoatrophy has demonstrated the efficacy of PLLA in restoring volume to the malar area, and there is ample experience with injections into the temporal area as well.[6] For the aging face, injections of PLLA into the malar and temporal areas can effectively restore a more youthful appearance. As with other injections of PLLA, these injections should be made using a fanning technique into the deep dermis. Temporal volume loss may be corrected with injections made using a depot technique just above the periosteal plane (Figure 1).

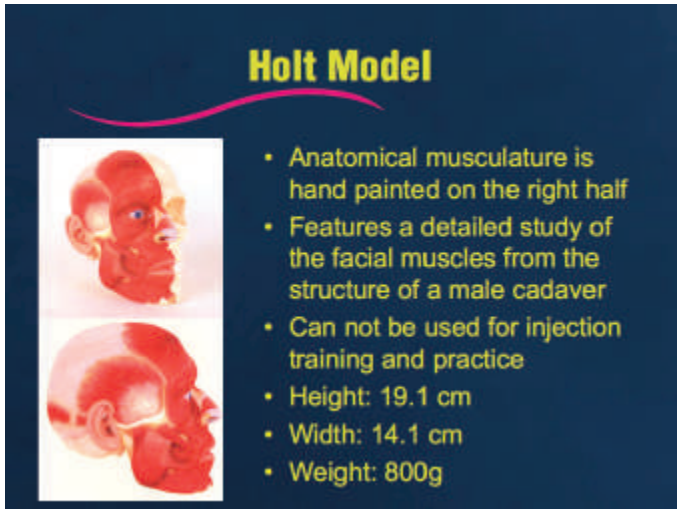
Facial ptosis, particularly mid-face descent, associated with aging is also well suited to treatment with Sculptra. The formation of innate collagen and elastic fibers can reposition facial anatomy to a more youthful pattern. This can successfully treat 3 of the cardinal features of the aging face: prominent nasolabial creases, jowls and mid-face descent. Prominent nasolabial creases are traditionally treated either surgically with a rhytidectomy or with direct soft tissue augmentation using fillers. Although each has its adherents and both are effective for many patients, neither repositions the face in an anatomically correct fashion. By creating new collagen and elastic fibers, PLLA can tighten the skin and subcutaneous tissues resulting in a cephalad movement. This movement restores a more youthful appearance to the face.

Injections of PLLA into the malar and zygomatic areas cause a tightening of the connective tissue. This adds volume and repositions the face, thereby improving the appearance of the nasolabial creases, reversing facial ptosis, and improving the appearance of the jowls. Volume may also be directly added to the nasolabial creases by direct placement of PLLA into this location.

Technical Considerations

Injections of Sculptra are undertaken in a manner different from any other filler. To begin with, one needs to inject the product in a timely manner to ensure that the suspension remains homogenous throughout the injection. It is vital that injections be placed in a deep dermal or subcutaneous plane. Placement too superficial will increase the incidence of subcutaneous papule formation. Although these papules may be treated with intralesional injections of steroids, they can be difficult to correct.

Figure 1. Holt model.



While all other filling agents may be injected with a 30- or 32-gauge needle, the particulate nature of the product will create clogging if a small needle is used. A 26-gauge or larger needle is recommended for Sculptra injections. Although a half inch needle may be utilized, the use of a one inch needle will not only facilitate use of the fanning technique but also the proper placement into the correct depth for injection. The package insert recommends that the bevel of the needle be oriented toward the skin but in practice many physicians orient the bevel medially or toward the deep tissue.

Once the needle is placed into the correct plane, small aliquots of material are deposited. These are typically 0.05 mL per injection but vary slightly based on the skill and experience of the injector. Prior to injection, particularly around areas that are very vascular, it is useful to aspirate the syringe to confirm placement of the needle port.

One area that requires particular technical consideration is the periorbital region. This location has extremely thin skin, prone to bruising and postinjection edema. In this location, injections should be beneath the orbicularis muscle and the depot technique should be used. As with other injections around the eye, the needle should never be pointed toward the globe and the nondominant hand should be utilized to protect the eye. When injecting in this location, it is imperative to constantly know the location of the orbital rim to avoid inadvertent intraocular injections.

PLLA may also be used to reposition the mid- and lower face. As bony recession and malar fat pad migration occur, visible stigmata of aging become apparent. Injections of Sculptra around the inferior border of the mandible can tighten this area and replace some volume loss. Injections into the zygomatic arch and malar areas can help to fill the hollows of the cheeks that are seen after loss of the malar

fat pad. The formation of new collagen can also reposition the mid-face to a more youthful position.

When injecting the malar hollow, a fanning technique should be utilized. Placement should be into the deep dermis. For injections of the zygomatic arch, depot injections into the periosteal plane should be utilized. Manual pressure may be used to spread the product.

The nasolabial crease may be affected by treatments in distant locations. Reversing mid-face descent with zygomatic arch injections may decrease the nasolabial crease. Injections directly into the nasolabial crease can also fill this area and produce dramatic results. When injecting the nasolabial crease, the needle should be inserted into the deep dermis and small aliquots (0.05 mL) deposited as the needle is withdrawn in a linear manner.

One unique aspect of treatment with PLLA is the degree to which massage must be employed in order to obtain an optimal outcome. Immediately following injections, the physician should massage the areas injected in a vigorous manner. A mild lubricant may be employed to facilitate this. Massaging the area helps to move the product into a homogenous plane and to reduce the aggregation of material. It is also an opportunity to reinforce the postoperative instructions, manage patient expectations, increase the bond with the patient, and to discuss future treatments. Printed instructions should be provided to each person instructing them to massage the treated areas for a minimum of 5 minutes, 5 times per day, for 5 days. While this is the most common recommendation at the present time, it is likely that the optimal schedule will be defined with clinical trials comparing different regimens. It is worthwhile to document the fact that post-treatment care instructions were provided following any cosmetic procedure.

Conclusions

Injections of poly-L-lactic acid present an opportunity for durable soft tissue correction and significant aesthetic enhancement. Successful patient outcomes depend upon a thorough understanding of the product, proper techniques for injection, and management of patient expectations. During the patient consultation, dermatologists and plastic surgeons should discuss the gradual nature of the correction achieved, potential complications, and the duration of correction. Post-treatment care should also be discussed. The unique aspects of this product present an opportunity for physicians to provide a durable correction using volumetric expansion.

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TECHNIQUE FOR INJECTING POLY-L-LACTIC ACID

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Abstract

Injectable poly-L-lactic acid (PLLA) or Sculptra® (Dermik Laboratories) is approved by the FDA for the correction of facial lipoatrophy in HIV infections. Cosmetic uses of PLLA are considered off label. PLLA is best suited for correction of stage 1 diffuse lipoatrophy normally observed in lean, aging patients, including those without HIV. Superficial or dermal defects should be corrected with temporary fillers such as hyaluronic acid or collagen rather than PLLA, which is designed for injection into the subcutaneous plane to cause gradual volume increase over time. Injecting PLLA into superficial layers may result in the development of linear granulomatous responses in the dermis. Reconstitution with 4 mL of sterile water at least 24 hours before use is recommended. Just before treatment the total volume is increased to 5 mL by adding 1 mL of lidocaine (1%) without epinephrine. This is standard procedure. For patients with significant stage 1 lipoatrophy 2 vials are prepared for each treatment session. The vial contents are withdrawn into a 1-mL tuberculin syringe and injected with a 2-inch, 25-gauge needle. The primary author (DHJ) uses a linear retrograde, cross-hatching technique through multiple puncture sites to inject the solution into the immediate subdermal plane or deeper. The easiest area to correct with PLLA is the mid-malar area, while the most difficult is the periocular area. The primary author uses PLLA to correct nasolabial folds only in patients with lipoatrophy in this area.

Introduction

Traditional modalities for correcting facial volume loss due to aging are alloplastic implantation and facial fat grafting.[1,2] Poly-L-lactic acid (PLLA) may be considered a nonsurgical equivalent to fat grafting. When injected into the subcutaneous plane, PLLA causes gradual volume increase in the treated areas over time, unlike dermal fillers or volumizers designed to correct lines, folds, and related deficiencies.[3]

PLLA is a well known component of medical products such as intrabone and soft tissue implants and the plates, pins, and screws for reconstructive surgery.[4-7] PLLA is believed to be immunologically inert and has been used widely as a vector for drugs injected intramuscularly or subcutaneously. Developed in Europe and introduced as NewFill™ (Medifill, London, UK; Biotech Industries SA, Luxembourg), injectable PLLA received European Union approval to increase the volume of skin creases, folds, wrinkles, and scars, and to correct large volume losses due to lipoatrophy. The FDA has approved PLLA, marketed as Sculptra® by Dermik Laboratories, for restoration and/or correction of the signs of facial lipoatrophy in HIV infections. A variety of studies have established the efficacy of injectable PLLA for this purpose.[8-10] At the time of this writing, other uses of Sculptra are considered off-label in the US, in contrast to Europe and Canada where the product is approved for cosmetic use. Experiences with injectable PLLA in Europe[11] and in the US[12] have been reported.

Injectable PLLA is a biocompatible, biodegradable, and resorbable synthetic polymer of crystalline microparticles 40 to 63 microns in diameter. The particles are small enough to permit injection by a 26-gauge needle and large enough to escape phagocytosis by macrophages and to not penetrate capillary walls.[13] The irregular shapes of the microparticles minimize mobility.[10] Resorption of PLLA occurs slowly over 2 to 3 years.[9]

PLLA facilitates volumetric correction by eliciting a foreign body giant cell reaction that takes place weeks or months after its injection. Injected PLLA polymers degrade by hydrolysis to monomeric lactic acid, which, in the presence of lactic dehydrogenase, is oxidized to pyruvic acid. Pyruvic acid may be converted to glucose or to carbon dioxide and water via the tricarboxylic acid cycle.[10,14] As PLLA degrades, fibroblast proliferation is stimulated resulting in collagen synthesis.[15] This collagen deposition is responsible for the gradual volume correction and cosmetic benefit of PLLA.[3,16] Patients treated successfully by the primary author (DHJ) report that correction dissipates in 6 to 12 months. Other reports indicate improvement lasting 18, 24, 30, and 40 months after the initial treatment.[10,13] Since PLLA is synthetic and not of animal origin, no allergy test is required before clinical use.[13]

The following discussion of the reconstitution, injection, and uses of PLLA reflects the personal experience and knowledge of the authors gained by treating patients with lipoatrophy, reading the medical literature, and communicating with colleagues. These techniques, though not identical to those recommended by the manufacturer, have provided the greatest benefits to the authors' patients.

Uses of Poly-L-Lactic Acid

The authors grade the severity of facial lipoatrophy with the Carruthers lipoatrophy scale (0 = no lipoatrophy, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe lipoatrophy).[17] Patients with stages 2 through 4 lipoatrophy are most effectively and economically treated with the permanent filler liquid injectable silicone,[18,19] whereas patients with stage 1 diffuse lipoatrophy (normally observed in lean, aging

patients without HIV) are often best suited for PLLA. Two European studies[8,9] evaluated the use of PLLA for the treatment of moderate to severe lipoatrophy in patients with HIV. The authors of both studies reported that changes in skin thickness were statistically significant after PLLA injection in patients with stage 2 through 4 facial lipoatrophy. However, the efficacy endpoint in these studies—a change in skin thickness—is often not the optimal correction sought by most HIV-infected patients with facial lipoatrophy. The author (DHJ) has evaluated many patients with stage 2 through 4 HIV facial lipoatrophy who have received 5 or more injections with 2 vials of PLLA per injection session without achieving optimal correction, and who were dissatisfied with the treatment. It appears that the volume loss in these patients is often too great for PLLA to be routinely effective. However, patients with milder stage 1 facial lipoatrophy, which by definition is often found in normal, healthy, lean individuals as well as patients with early HIV facial lipoatrophy, often achieve excellent results with PLLA. The author (DHJ) has successfully used PLLA to correct stage 1 volume loss in any cheek location—the mid-malar, premasseteric, temporal, and nasolabial fold areas as well as below the zygomaticus area. The author (DHJ) has also injected PLLA into lipoatrophied hands.

The author (DHJ) does not use PLLA to correct defects originating in the dermis. Temporary fillers, such as hyaluronic acid or collagen products, are best suited for these applications. Both authors of this paper agree that problems may occur if PLLA is placed in the superficial, mid-reticular, or papillary dermal layers. In the opinion of the coauthor (DV), however, there is no indication that placement of PLLA into the deep reticular dermal layer causes problems. Support for this lies in the results of 2 European studies[8,9] in which PLLA was placed into the deep dermal layer. The author (DHJ), however, argues that when injecting PLLA into the dermis even experienced dermatologists are never sure which layer (mid, reticular, or deep) they are injecting into. For this reason the author (DHJ) urges that physicians inject PLLA only into the immediate subdermal plane and never into the dermis as the probability is high that persistent granulomatous injection site reactions may result,[15] even in non-HIV patients.[20] This reaction may be understood by considering how PLLA is metabolized after injection. As PLLA degrades, the capacity of phagocytic cells in surrounding tissues may be exceeded, resulting in the accumulation of hydrolyzed polymeric chains. This reaction is even more important when the product is used in excessive amounts.[14] The accumulated polymeric debris may cause granulomatous reactions[15] that produce dermal papules. Such papules usually do not form if PLLA is injected evenly into the subcutaneous layer. Papules will form, however, when the quantity of PLLA placed into the subcutaneous layer (or any tissue) is excessive. Inactive (nongranulomatous) papules may also develop when small or moderate amounts of PLLA are placed into the mid-reticular or papillary dermis as a consequence of protrusion of collagen formation. Histologic studies do not reveal inflammation but they will show the expected mild histiocytic reaction associated with a cosmetically inappropriate outcome (unpublished data, DV).

Reconstitution

Sculptra is packaged as a sterile 367.5-mg lyophilized powder (150 mg PLLA) in a glass vial that requires no refrigeration. It must be reconstituted with sterile water (provided) before use. In addition to PLLA, Sculptra contains sodium carboxymethylcellulose (a suspending agent) and nonpyrogenic mannitol to enhance lyophilization.[3,10] Although the manufacturer recommends reconstituting the product at least 2 hours before use, the author (DHJ) recommends reconstituting with 4 mL sterile water at least 24 hours prior to use. The reconstituted vials are refrigerated until the day of use. Two vials are reconstituted for each treatment session.[2,21] The vials are placed at room temperature one hour before use. Heating of vials is not recommended as it is not known how heating affects the product. Lidocaine (1%, 1.0 mL) without epinephrine is added to each vial immediately before injection to minimize patient discomfort.[13] When ready for use, the 2 suspensions have an opaque, ground glassy appearance. If the reconstituted products are clear, particles have settled to the bottom and the vials must be shaken again. When patients fail to keep their appointment, the vials are refrigerated for several days for use on another patient. Although the manufacturer recommends using the reconstituted product within 72 hours, a recent study indicates that reconstituted Sculptra retains its 24-hour efficacy for 3 weeks.[22] The author (DHJ) typically stores a reconstituted vial up to 2 or 3 weeks with refrigeration.

Injection Technique

With injectable fillers of any sort, proper injection technique minimizes the possibility of device-related adverse events and maximizes the chance of optimal correction. Depending on the device being used, incorrect placement may cause unevenness, blanching, foreign body reactions, and localized destruction of tissues.[23]

The author (DHJ) usually uses a linear retrograde rather than a serial puncture technique for injecting Sculptra. Retrograde technique involves tunneling the needle in the subcutaneous plane and slowly injecting the material as the needle is slowly withdrawn. Retrograde technique reduces the possibility of injecting into a blood vessel. Performing a reflux maneuver before injection helps to avoid an intravascular injection. Furthermore, fewer punctures are less painful and less traumatic. The thumb should be removed from the plunger upon inserting and withdrawing the needle from the skin to avoid the possibility of tracking PLLA through the dermis, which may lead to inflammatory dermal papules.[15] Before injecting, the lipoatrophied areas are marked with a fine black water-soluble marker (Sharpie fine point). Depressions should be marked when the patient is smiling and when the patient is not smiling because smile-induced tissue motion may obscure resting lipoatrophy, potentially resulting in overcorrecting the volume-deficient area. Injections are made precisely into the area of the defect.

Figure 1. Non-HIV-infected man with stage I facial lipoatrophy associated with age and lean body habitus. **Left:** Patient before treatment with Sculptra. **Right:** Patient one month after the final of 4 treatment sessions (total of 8 vials) given over 3 months.

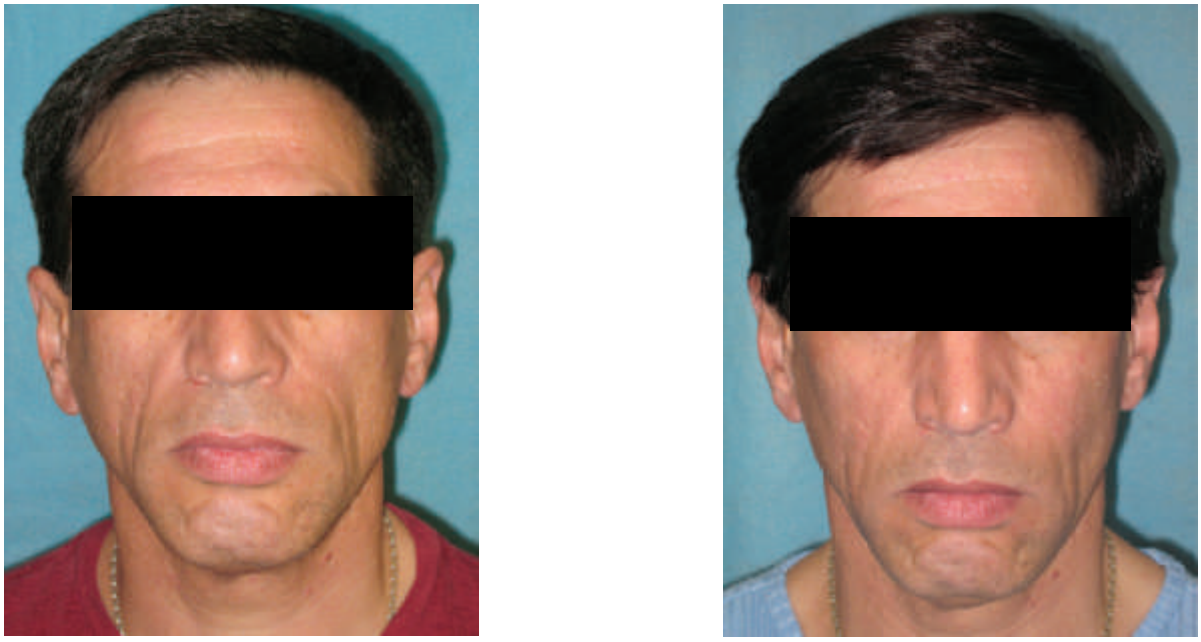
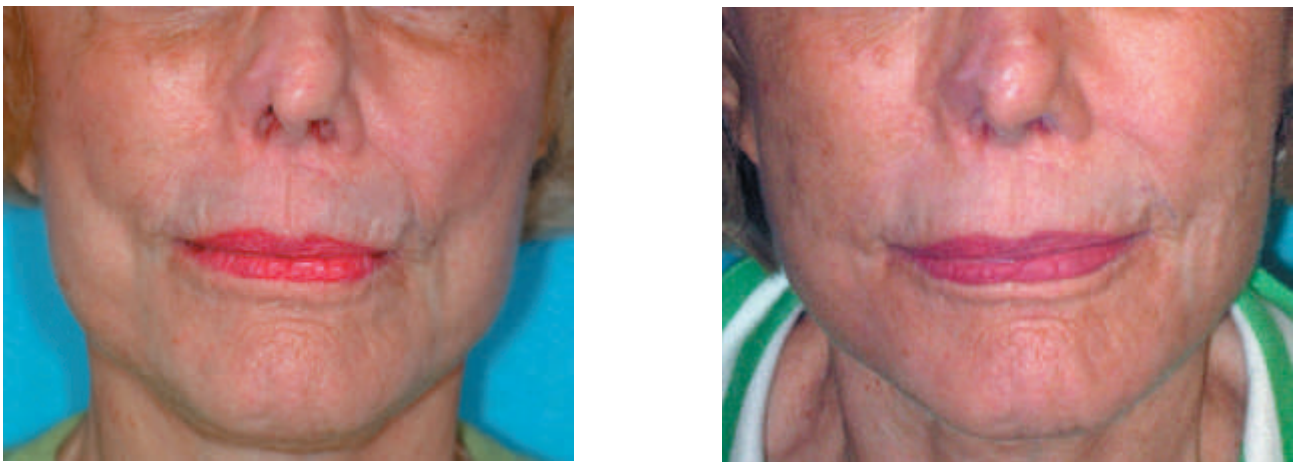
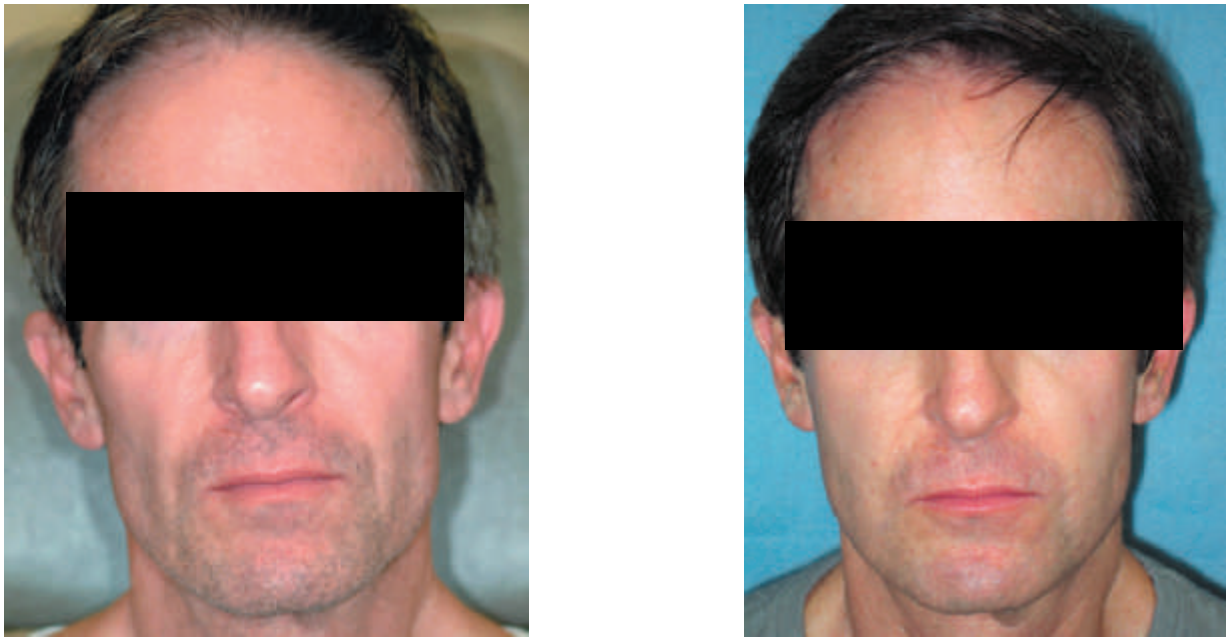


Figure 2. Non-HIV-infected woman with stage I facial lipoatrophy associated with age and lean body habitus. **Left:** Patient before treatment with Sculptra. **Right:** Patient 4 months after the final of 5 treatment sessions (total of 9 vials) given over 6 months.



The reconstituted vial must be shaken just before use to make certain the suspension is evenly dispersed.[13,21] The author (DHJ) withdraws the vial contents into a 1-mL tuberculin syringe, shakes the syringe to further ensure homogeneity, and injects the product with a 2-inch, 25-gauge needle. Occasional needle clogging will occur, in which case the needle should be replaced. The area to be corrected is anesthetized by injecting a small bleb of lidocaine (1%) with epinephrine intradermally at the entry site of the 25-gauge needle that is used to inject Sculptra. During insertion, the subcutaneous space is entered when the injector feels a sudden reduction in resistance to penetration. With the linear retrograde technique, the injector can determine that the immediate subdermal plane has been entered by pressing down on the completely inserted needle and observing that the overlying skin is *not* retracted; if the needle is still in the dermis, the overlying skin will be retracted and form a dimple. With the linear retrograde technique, Sculptra may be injected 5 to 15 times (with few puncture sites) in a single treatment session. Technique variations include serial fanning with retrograde injection and the more geometrical serial puncture grid technique. Fanning with multiple passes from one point, with or without perpendicular placement of 2 fanning maneuvers, seems to be more associated with (subdermal) nodule formation in novice hands than serial puncture single injections in a grid pattern (cross hatch).[24] The nodule may be due to accumulation or concentration of particles at the entrance point, especially when too many passes

Figure 3. Non-HIV-infected man with Stage I facial lipoatrophy associated with age and lean body habitus. **Left:** Patient before treatment with Sculptra. **Right:** Patient 8 months after the final of 5 treatment sessions (total of 10 vials) given over 4 months.



are made from one point. The author (DHJ) uses both crosshatching and fanning in the immediate subdermal plane or deeper with linear retrograde technique. Great care should be taken to avoid tracking PLLA through the dermis when the needle is inserted or removed (ie, there should be no pressure on the plunger). The volume injected (up to 1 mL) through each puncture site depends on the nature of the defect. The treated areas are swollen due to edema at the end of the treatment session.

After injecting serial parallel passes with the linear retrograde technique, the author (DHJ) often reinjects at a 90-degree angle to the initial injection. Such perpendicular crosshatching results in a more even distribution of filler than injecting in only one direction.[3] When treatment is completed, the treated area is given a 5-minute massage to distribute the product evenly and permit more precise facial contouring in the target location.[21] The patient is instructed to massage the area for 5 minutes, 2 to 3 times daily, for 2 to 4 weeks.[25]

Sculptra can be slowly injected into the periocular area but great caution is required to avoid lump formation. Very small (0.1 mL) serial puncture depot injections are placed beneath the orbicularis oculi in the immediate supraperiosteal plane beneath the muscle and above the periosteum of the bone. The area should be massaged to promote even dispersion.

For visible stage 1 lipoatrophy, 2 vials of Sculptra are usually required for optimum results on both sides of the face. Subtle lipoatrophy may require only a single vial. Three to 5 treatments at monthly intervals are usually necessary for complete correction (Figures 1-3).

The easiest area to correct with Sculptra is the mid-malar area, while the most difficult is the periocular area. Beginners should take special care to avoid injecting Sculptra into the superficial dermis because the product is designed to correct subcutaneous defects associated with fat loss. The author (DHJ) uses Sculptra to correct nasolabial folds only in patients with lipoatrophy in this area. If the nasolabial defect is of dermal origin, a hyaluronic acid filler may be layered over the Sculptra with excellent results.

Adverse Effects

The most common adverse effects—erythema, bruising, swelling, and hematoma—occur at the injection site.[21] Adverse effects observed in clinical trials of Sculptra have been reviewed in detail.[10] In the author's (DHJ) practice, edema is the most common adverse effect. The immediate appearance of dermal blanching indicates that the injection was superficial and did not penetrate the subcutaneous layer.[21] Such injections may also result in the formation of dermal papules. The goal is to create an even PLLA plane underneath the subcutaneous plane, which is why the treated area is massaged. Massaging spreads the product and prevents the formation of clumps (areas with accumulated product of high particle concentrations) and subsequent inflammatory reactions that produce even more clumps. Whether areas of high particle concentration cause inflammatory reactions with palpable nodules remains controversial.

Conclusion

Successful volume correction with Sculptra depends on the physician's ability to accurately differentiate between dermal defects and volume loss due to lipoatrophy and physician's skill in injecting the proper amount of PLLA filler into the subcutaneous plane. Sculptra has contributed significantly to the quality of life of HIV patients with facial

volume loss and promises to be equally effective in aging non-HIV patients.

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MECHANISM OF ACTION OF POLY-L-LACTIC ACID: A STIMULATORY DERMAL FILLER

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Abstract

Approved by the US FDA in August 2004, poly-L-lactic acid (PLLA) or Sculptra® (Dermik Laboratories) represents a new category of dermal filling agents for restoration, rejuvenation, and enhancement procedures. Termed *stimulatory fillers* for their primary mechanism of action (ie, products that achieve volumetric correction by virtue of the upregulation of neocollagenesis and/or fibroplasia), they represent a distinct category of dermal augmentation differing from replacement fillers. In this article, the mechanism of action of one such product, PLLA, is discussed.

History of Soft Tissue Augmentation

The history of facial and body contouring is well-documented in the medical literature and in fact probably dates back to prehistoric times as is evidenced by suggestive forensic anthropological findings demonstrating modifications of body morphology.

More recently, the concept of injecting materials into the body, and especially the face, to achieve a cosmetic enhancement has become well accepted in modern medicine and society. Beginning with fat transfer first reported in 1893 by Neuber,[1] followed by the use of high viscosity fluids in the 1970s, then collagen in the 1980s, an ever expanding list of biologic, synthetic, and combination products of various chemical polymer compositions are now being used to achieve various degrees and durations of correction.[2]

Classification of Dermal Fillers or Volumizers

Originally, the classification of these substances was somewhat artificially divided into temporary, semipermanent, and permanent groupings. While this stratification by duration was helpful, it never really addressed the more fundamental issue of mechanism of action. This was understandable as essentially all products, for various lengths of time, simply replaced lost volume or added desired volume by a mechanistic space occupying effect, much like pumping caulking into a crevice fills the void.[3,4]

As the palette of dermal fillers or volumizers has expanded worldwide, there has been a need to establish a classification schema that addresses their fundamental mechanisms of action. As there appears to be essentially 2 distinct types of activities leading to the clinical effect, the terms *stimulatory* and *replacement* were first proposed by Werschler and Narurkar in 2006.[5]

Essentially, in this classification system the product activity determines its class rather than its longevity. This addresses 2 challenges with the current duration of effect system. First, duration is a variable factor in each individual patient, even changing within a patient between injection sessions over time and by different injectors. Second, there is no universally agreed upon duration that qualifies a product as being temporary, semipermanent, or permanent. Commonly, a range is given for products such as temporary lasting 3 to 6 months, semipermanent 6 to 12 months (or in some literature 12 months to 2 or even 5 years), and permanent sometimes described as being over 5 years and at other times being lifelong (as in the case of silicone).[6]

As duration is a patient variable, consensus has not been reached on duration timelines. Products currently on the market exhibit 2 primarily different methods of achieving a clinical effect (ie, replacement and stimulatory), therefore the current system has, in the authors' opinion, severe limitations.

In the mechanism of action classification, each filler product is examined as to its actual biologic effect such as water binding, protein replacement, neocollagenisis, fibroplasia. The duration of action, usually expressed as a range of time, then becomes a product characteristic along with such features as storage, handling, dilution, pretreatment skin testing, adverse event profile.[5]

It is within this classification system that PLLA as a stimulatory dermal filling agent is reviewed.

Stimulatory Filling Agents

When a product being used as a dermal augmentation tool achieves a clinical effect through a dynamic biologic process, (eg, the initiation of soft tissue growth, an increase in the existing rate of growth, a reduction in soft tissue breakdown or some other mechanism other than the space occupying and volume creating effect of the product itself), it is classified as a stimulatory filler.

It is important to address the changes that can occur from reactive fibroplasia secondary to tissue trauma such as needle sticks, especially with subcision, which is a form of scarring, and differentiate them from true soft tissue ingrowth. In the case of the former, the changes are reactive, occur only in those areas directly injured, and are demonstrated in histologic examination as being distinct (ie, cicatrix) from surrounding tissue.

Stimulatory filling can be an exclusive method of action or can coexist in conjunction with replacement filling in var-

ious proportions. In some products available today, such as calcium hydroxylapatite microspheres (Radiesse, Bioform Medical), there exists a biphasic mechanism of action in which the initial space occupying effect is of replacement activity (gel carrier composed of carboxymethylcellulose), which is then followed by a gradual transition to stimulatory neocollagenesis/fibroplasia activity induced by the calcium microspheres, all of which is typically clinically transparent to the patient.

Soft tissue bioaugmentation, as in the case of PLLA, is felt to be a form of upregulation of endogenous tissue growth rates. This leads to the clinical and histologic effect of a net increase in tissue from what would normally be present without the effect of the stimulatory agent being introduced. This assumption has been reinforced by clinical trial data.

In the Vega study (N = 50), those areas being treated with PLLA were shown to develop an increase in dermal thickness. The median total cutaneous thickness, as measured by ultrasound, was 3 mm (range 2.4-3.6 mm). At various endpoints, the median total cutaneous thickness was measured at 5.2 mm at week 8, 6.4 mm at week 24, 7.2 mm at week 48, 7.2 mm at week 72, and 7 mm at week 96.

Similar results were found in the Chelsea and Westminster study where, starting with a baseline range of skin thickness of 2.1 to 2.7 mm, study participants achieved a mean thickness increase of approximately 4 to 6 mm, which was observed 12 weeks after the initiation of treatment for all patients (N = 41).[7-9]

In the aesthetic sense, this means a reduction in concavities, an increase in convexities, a reduction in surface wrinkles and creases from a volume expansion effect, and an overall 3 dimensional increase in the area being treated, usually the face.

Additionally, if the tissue ingrowth is composed of proportions of constituent tissue types, which are identical or similar to those of the native tissue, then the treated (stimulated) area will have clinical characteristics approximating the area at an earlier point in time (younger). In the case of the dermis of the face, the optical tone and texture, the tensile strength, and the vascularity appear to be restored to an earlier point in time.

Poly-L-Lactic Acid

Each vial of PLLA consists of a 367.5-mg anhydrous powder cake composed of microspheres of PLLA measuring 40 to 63 nm, sodium carboxymethylcellulose, and nonpyrogenic mannitol. It is reconstituted with sterile water (typically 5 to 10 mL) for a minimum of 2 hours before injection. The product is intended for injection into the deep dermal-fat interface. Superficial injections should be avoided as the product may create collagenesis at too superficial of a level clinically resulting in lumps, bumps, or ridges.

Once the reconstituted product is introduced into the dermal-fat interface, a stimulatory effect occurs through a mechanism(s) as of yet not completely understood. However, the long-term tissue ingrowth is composed of type I collagen, not any of the constituent ingredients of the PLLA vial. PLLA itself is a biocompatible, biodegradable, nonpyogenic natural synthetic, and eventually is broken down into CO_2, glucose, and water.[8]

As the product injected does not in and of itself provide any volumetric augmentation, and the clinical effect of dermal thickening is composed of type I collagen and not cicatricial fibrosis or injected polymer, its effect is considered to be purely stimulatory. In this case, the stimulatory effect appears to be exclusively or primarily neocollagenesis, rather than inhibiting natural tissue breakdown processes. It may be that the development of native tissue (type I collagen) is chiefly responsible for the longevity of action. It may also be other as of yet unrecognized factors. However, it does appear that the net increase in tissue induced by the PLLA microspheres is responsible for the clinical effectiveness.

As the PLLA particles undergo dissolution, the stimulus for neocollagenesis is decreased, leading to a gradual clinical loss of effect. Typically, this occurs after 18 to 24 months. Intermittent touch-up treatments may be administered to maintain the desired effect.

Understanding the various and complex geometric features of facial aging and descent will allow the PLLA injector to best understand and utilize the product. Because various degrees of dermal thickening may be selectively achieved in different areas of the face, a lifting, tightening, augmenting mixture of effects may be created by the experienced user to substitute, delay, or even complement surgical lifting procedures.

Since the mechanism of action of PLLA is stimulatory and the product is used to thicken the dermis rather than fill individual lines and wrinkles, PLLA is best used in the conceptual framework of *global* or *pan facial sculpting*.[10]

Facial Volumetric Restoration

As the face ages, it undergoes certain changes of biometric volume loss secondary to both hard and soft tissue resorption and atrophy. The dermis generally thins, although the upper dermis may thicken with extremes of photodamage, while the epidermis thins intrinsically. Severe photodamage may lead to epidermal hypertrophy. Fat tends to redistribute, generally accumulating in the lower face. The facial skeleton decreases in volume, especially the lower portion (mandible and maxilla) when combined with dental loss.[10,11]

Traditionally, with the exception of fat transfer, soft tissue augmentation has focused on filling creases, wrinkles, and furrows. This was in large part determined by the unique product characteristics of available filling agents such as collagen. As newer products have been developed and approved, a new conceptual framework of nonsurgical total facial restoration or rejuvenation has emerged based on the various clinical effects and mechanisms of action of highly divergent injectable products.[12]

With cosmetic denervation with neurotoxin, volumetric augmentation with dermal thickening, site specific

enhancement with various dermal replacement fillers, and various resurfacing regimens considerable and significant improvements from baseline both reconstructive and esthetic are obtainable for most patients.[12,13]

Combining Stimulatory and Replacement Filling Agents

With an ever expanding selection of products to choose from, the skilled injector can create a palette of combinations of products from all categories to satisfy even the most clinically challenging patient scenario. The use of PLLA as a foundational treatment for global thickening prior to the addition of other dermal filling agents, replacement or stimulatory, has the unique benefit of priming the tissue to become more robust and thus accepting of additional layers of differing products. Replacement fillers are generally preferred for lip augmentation, site specific enhancement, superficial lines and wrinkles, and naturally thin skinned areas such as the eyelids.

A Conceptual approach to treating the aging face with an array of products, each with unique mechanisms of action, unique attributes, and strengths and weaknesses in different areas, allows for ideal customization of treatment packages. Beginning with a stimulatory dermal filling agent, such as PLLA, to thicken and stabilize the aging dermis allows for amplified subsequent results with replacement filling agents, such as hyalurons.

Conclusion

In the macro level framework of nonsurgical restoration of the aging face, addressing the fundamental causes of the clinical appearance of the aged face is paramount. One of these changes, dermal atrophy, leads to a progressive decline in the structural framework of the collagen mask of the face. The loss of dynamic support ultimately leads to static changes such as facial descent, pleating of the lower face, loss of distinct facial units, an inversion of the "triangle of youth" to one of a "triangle of age" and the development of lines, creases, and wrinkles in repose.[14]

PLLA injections may be used to stimulate neocollagenesis, leading to a measurable and significant increase in skin thickness principally as a result of upregulation of production of native type I collagen. This increase in total cutaneous thickness results in an enhanced framework of structural support for facial units leading to more youthful facial proportions.

PLLA appears to be a true stimulatory dermal filler or volumizer in that its entire mechanism of action is independent of any replacement volume and completely dependent upon natural protein synthesis.

When dermal augmentation is considered for global sculpting, PLLA may be currently the best choice for pan facial correction as it is long lasting, appears to be well tolerated, and prepares the target tissue for additional treatments of various types and categories.

Disclosure

Dr. Werschler is a consultant, investigator, speaker, and senior advisory board member for Dermik Aesthetics, a division of Sanofi-Aventis, the manufacturer of Sculptra.

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SCULPTRA™ is an injectable implant that contains microparticles of poly-L-lactic acid, a biocompatible, biodegradable, synthetic polymer from the alpha-hydroxy-acid family. **SCULPTRA** is reconstituted prior to use by the addition of Sterile Water for Injection, USP (SWFI) to form a sterile non-pyrogenic suspension.

INTENDED USE / INDICATIONS
SCULPTRA is intended for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus.

CONTRAINDICATIONS
- **SCULPTRA** should not be used in any person who has hypersensitivity to any of the components of the product.

WARNINGS
- Use of **SCULPTRA** in any person with active skin inflammation or infection in or near the treatment area should be deferred until the inflammatory or infectious process has been controlled.
- Do not overcorrect (overfill) a contour deficiency because the depression should gradually improve within several weeks as the treatment effect of **SCULPTRA** occurs (see **IMPORTANT CONSIDERATIONS**).
- Injection procedure reactions to **SCULPTRA** have been observed consisting mainly of hematoma, bruising, edema, discomfort, inflammation, and erythema. The most common device related adverse effect was the delayed occurrence of subcutaneous papules, which were confined to the injection site and were typically palpable, asymptomatic and non-visible. Refer to **ADVERSE EVENTS** for details.
- Special care should be taken to avoid injection into the blood vessels. An introduction into the vasculature may occlude the vessels and could cause infarction or embolism.

PRECAUTIONS
- **SCULPTRA** should only be used by health care providers with expertise in the correction of volume deficiencies in patients with human immunodeficiency virus after fully familiarizing themselves with the product, the product educational materials, and the entire package insert.
- **SCULPTRA** vials are for single patient use only. Do not reuse or resterilize the vial. Do not use if package or vial is opened or damaged.
- Long-term safety and effectiveness of **SCULPTRA** beyond two years have not been investigated. Dermik® is conducting a post approval study to evaluate the safety and effectiveness of **SCULPTRA** beyond two years.
- **SCULPTRA** should be used in the deep dermis or subcutaneous layer. Avoid superficial injections. Special care must be taken when using **SCULPTRA** in areas of thin skin. Refer to **PATIENT TREATMENT** for instructions regarding injection techniques.
- Safety and effectiveness of treatment in the periorbital area have not been established.
- As with all transcutaneous procedures, **SCULPTRA** injection carries a risk of infection. Standard precautions associated with injectable materials should be followed.
- As with all injections, patients treated with anti-coagulants may run the risk of a hematoma or localized bleeding at the injection site.
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- After use, treatment syringes and needles may be potential biohazards. Handle accordingly and dispose of in accordance with accepted medical practice and applicable local, state and federal requirements.
- The safety of **SCULPTRA** for use during pregnancy, in breastfeeding females or in patients under 18 years has not been established.
- No studies of interactions of **SCULPTRA** with drugs or other substances or implants have been made.
- The safety and effectiveness data from clinical trials of **SCULPTRA** in non-Caucasians and women with human immunodeficiency virus are limited. Dermik® will conduct a post approval study in non-Caucasians and women with human immunodeficiency virus.
- The safety of using **SCULPTRA** in patients with increased susceptibility to keloid formation and hypertrophic scarring has not been studied. Dermik® will conduct a post approval study to determine the likelihood of keloid formation and hypertrophic scars in patients with human immunodeficiency virus receiving **SCULPTRA** injections.
- The patient should be informed that he or she should minimize exposure of the treatment area to excessive sun and UV lamp exposure until any initial swelling and redness has resolved.

ADVERSE EVENTS
Adverse event data from four clinical studies that included 277 patients are summarized in Tables 1 & 2 below.

TABLE 1:
NUMBER OF PATIENTS WITH TREATMENT-RELATED ADVERSE EVENTS OBSERVED IN CLINICAL STUDIES WITH TWO-YEAR FOLLOW-UP

	VEGA STUDY 50 Patients	C&W STUDY*** 29 Patients	AVERAGE DURATION (DAYS)
INJECTION PROCEDURE RELATED ADVERSE EVENTS			
Bruising	3(6%)	11(38%)	6
Edema	2(4%)	2(7%)	3
Discomfort	0	3(10%)	3
Hematoma	14(28%)	0	17
Inflammation	0	3(10%)	3
Erythema	0	3(10%)	3
DEVICE-RELATED ADVERSE EVENTS			**AVERAGE ONSET** (Months)**
Injection site subcutaneous papule*	26(52%)	9(31%)	7

*Subcutaneous papules refer to lesions of 5 mm or less, typically palpable, asymptomatic and non-visible.
**Onset data available from VEGA study only. Duration not noted for subcutaneous papules because most were ongoing at study completion.
*** Safety data were collected *post hoc* for 27 of the patients at approximately two years from study start.

TABLE 2:
NUMBER OF PATIENTS WITH TREATMENT-RELATED ADVERSE EVENTS OBSERVED IN CLINICAL STUDIES WITH ONE-YEAR FOLLOW-UP

	APEX 002 STUDY 99 Patients	BLUE PACIFIC STUDY 99 patients
INJECTION PROCEDURE RELATED ADVERSE EVENTS		
Bruising	1(1%)	30(30%)
Edema	3(3%)	17(17%)
Discomfort	19(19%)	15(15%)
Erythema	0	3(3%)
DEVICE RELATED ADVERSE EVENTS		
Injection site subcutaneous papule	6(6%)	13(13%)

The duration of the adverse events in Table 2 was not collected. The most common device related adverse effect was the delayed occurrence of subcutaneous papules, which were confined to the injection site and were typically palpable, asymptomatic, and non-visible. The study protocols did not include evaluation of treatment for subcutaneous papules, therefore, no information is available on how the papules were treated. In the VEGA study, the average onset of subcutaneous papules was 7 months after initial injection (range 0.3 – 25 months). Subcutaneous papules resolved spontaneously in 6/26 patients (24%) during the study. No information of onset and duration of papules is available from the Chelsea & Westminster study.

Treatment related adverse events, not included in Table 1 & 2, observed in clinical studies with a frequency of less than 5% were: injection site tenderness, injection site lesion, injection site bleeding, injection site induration, injection site infection and fever.

The following adverse events, which were not observed in the clinical studies, were detected from post-marketing surveillance outside of the US and literature reports: visible nodules with or without inflammation or dyspigmentation, malaise, injection site abscess, allergic reaction, injection site atrophy, Quincke's edema, injection site fat atrophy, photosensitive reaction, fatigue, injection site granuloma, hypersensitivity reaction, skin rash, skin roughness, lack of effectiveness, injection site reaction, hypertrophy of skin, hair breakage, colitis not otherwise specified, brittle nails, application site discharge, angioedema, aching joints, ectropion, and telangiectasias.

IMPORTANT CONSIDERATIONS
Post-treatment care. Immediately following an injection session with **SCULPTRA**, redness, swelling, and/or bruising may be noted in the treatment area. Refer to **ADVERSE EVENTS** for details. After the injection session, an ice pack (avoiding any direct contact of the ice with the skin) should be applied to the treatment area in order to reduce swelling. It is important to thoroughly massage the treatment area to evenly distribute the product. The patient should periodically massage the treatment area for several days after the injection session to promote a natural-looking correction.

Treat, Wait, Assess. During the first injection session with **SCULPTRA**, only a limited correction should be made. Do not overcorrect (overfill). The patient should be evaluated no sooner than two weeks after the injection session to determine if additional correction is needed. The original skin depression may initially reappear, but the depression should gradually improve within several weeks as the treatment effect of **SCULPTRA** occurs. The patient should be advised of the potential need for additional injection sessions at the first consultation.

STORAGE
SCULPTRA can be stored at room temperature, up to 30ºC (86ºF). DO NOT FREEZE.
Refrigeration is not required.

STERILITY
Each vial of **SCULPTRA** is packaged for single-use only. Do not resterilize.

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SCULPTRA® is contraindicated in those individuals who have shown a hypersensitivity to any of its components. SCULPTRA® should not be injected in areas with active skin infection or inflammation. Avoid injection into the blood vessels.

The most commonly observed adverse event was the delayed occurrence of subcutaneous papules, which were confined to the injection site and were typically palpable, asymptomatic, and non-visible. Visible nodules, with or without inflammation or dyspigmentation, have also been reported. Other adverse events include immediate and transient injection-related events such as bleeding from the injection site, discomfort, erythema or inflammation, ecchymosis, and edema.

Please see brief summary on following page.