Understanding Injectable Poly-L-lactic Acid

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Injectable poly-L-lactic acid (PLLA) creates new volume by stimulating collagen production. PLLA compensates for age-related changes in tissue shape, with correction enduring for up to 2 years. A defined injection technique is necessary to maximize product efficacy, depending on the area of the face requiring correction. PLLA has a good safety profile, and common device-related adverse events include the formation of delayed, nonvisible, palpable subcutaneous papules. These can be alleviated by using a less concentrated preparation of PLLA, correct placement of PLLA, and postprocedure massage for up to 1 month after injection.

A substantial expansion in the number of available injectable devices approved for use in the cosmetic market has occurred in the past several years. Much of this expansion has been driven by growing consumer demand for cosmetic products that do not require invasive surgery.[1] In addition, there is a more diverse range of products to treat a greater variety of aesthetic deficits. Whereas previously many "fillers" were solely intended to fill rhytides of different severities, some new agents are designed to restore volume and recreate youthful facial contours. With the wide range of products available, it is important for the treating physician to understand the benefits and limitations of each product so that the most appropriate agent is selected for each procedure and each patient.

The physical and chemical attributes of a product directly influence both injection technique and the results that can be obtained. In this article, the author examines the properties of injectable poly-L-lactic acid (PLLA), how these properties influence injection technique, and approaches to patient treatment.

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INJECTABLE PLLA

Injectable PLLA is currently licensed in the European Union for correcting human immunodeficiency virus (HIV)–associated facial lipoatrophy and for increasing the volume of depressed facial areas, such as wrinkles, folds, and scars, and atrophic areas, such as the eyes, cheeks, temples, and perioral areas. PLLA is approved by the US Food and Drug Administration (FDA) for the restoration and correction of the signs of facial lipoatrophy in people infected with HIV. The manufacturer is seeking approval for a cosmetic indication, anticipated in 2007. Use of injectable PLLA in patients not infected with HIV is off label in the United States; therefore, the clinical experience in healthy cosmetic patients is relatively limited.

PLLA is a synthetic, biocompatible, biodegradable, and immunologically inert polymer derived from lactic acid. Although the injection of PLLA is novel, polylactides and their derivatives have been safely used for more than 30 years in a variety of medical devices, including sutures, pins, plates, and screws for reconstructive surgery; intrabone and soft tissue implants; and vectors for sustained release of bioactive compounds.[2]

Injectable PLLA is supplied as 40.8% PLLA (40- to 63-µm diameter microspheres), 24.5% sodium carboxymethylcellulose, and 34.7% nonpyrogenic mannitol and is reconstituted to form an injectable suspension with sterile water for injection (SWFI). To minimize patient discomfort, many physicians use lidocaine in addition to SWFI before injecting the product.

MODE OF OPERATION

The mode of operation of many injectable products is direct tissue augmentation by immediate volume replacement (eg, collagen and hyaluronic acid [HA]). New volume can also be created by the carrier substance used in the product. This is true for PLLA and, to a lesser extent, calcium hydroxylapatite (CaHA) and polymethylmethacrylate (PMMA). However, once the product is implanted, it degrades (except for PMMA, which is permanent), and the duration of correction is limited by the rate at which the body responds and breaks down the material.

In contrast to tissue-augmentation products that increase volume directly after injection, PLLA adds volume indirectly over time (its water base is absorbed after injection). An animal study further suggests that PLLA generates new volume by stimulating collagen production through a normal foreign-body reaction.[3] It is new endogenous collagen, rather than PLLA, that adds volume to depressed areas. Postinjection, PLLA is gradually broken down into smaller components, which are first hydrolyzed into lactic acid monomers and then into carbon dioxide and water.[3,4] After all of the PLLA has been absorbed, the process of neocollagenesis is thought to continue, since volume remains for many months after the active ingredient should have been metabolized. Indeed, PLLA correction has been reported to endure for up to 2 years before it starts to diminish.[5,6]

Within this class of device, neocollagenesis is not unique to PLLA. For example, injectable PMMA and CaHA also stimulate the production of collagen, which encapsulates PMMA or CaHA microspheres, respectively.[7] The scaffold provided by CaHA microspheres is degraded relatively quickly over time with the subsequent loss of correction, compared with PLLA, which provides correction for a longer time. Conversely, PMMA is not biodegradable and theoretically provides permanent correction. However, permanency may not be ideal as the patient ages. Areas requiring correction often change over time with volume and laxity.

INFLUENCE OF MODE OF OPERATION

Neocollagenesis is the mechanism by which PLLA is thought to create volume and dictates the slightly unusual approach to treatment with this injectable. The treating physician should treat, wait, and assess. Based on clinical experience, a period of time (usually 4 to 6 weeks) should elapse following initial treatment and before an assessment is made of the initial correction and before subsequent correction sessions.

In contrast, it is recommended that one-to-one correction is provided with PMMA and CaHA, and the results seen a few days postprocedure will approximate the final result achieved once the carrier is absorbed and collagen has been synthesized.[8] The immediacy of results achieved with PMMA and CaHA can be viewed as an advantage by patients who desire instant rejuvenation. However, many patients find a social advantage in returning for repeat sessions with PLLA. The progressive improvement in volume is unlikely to draw as much attention as a more dramatic, instant transformation. Undercorrection is recommended for PLLA, with the expectation that the patient should return for a number of subsequent sessions spaced 4 to 6 weeks apart.[8]

In addition, undercorrection provides the opportunity to modify or amplify results until both patient and physician are satisfied with the augmentation achieved. Further, as the inability to predict how an individual will respond to treatment is a contributory factor to unwanted side effects, the cautionary "treat, wait, and assess" approach offers some protection. This flexibility means that injectable PLLA is able to correct a wide range of defects, from minor volume loss to substantial correction involving multiple sessions.[5,9] The volume of other products that can be injected into the correct dermal plane limits the degree of correction that can be obtained with fillers such as CaHA or PMMA after 1 treatment session.[10] As the vehicle of these products is absorbed, repeat sessions are often needed to obtain a full correction. This may be less than ideal from the perspective of the patient because volume would appear to rise and fall over time, rather than improve gradually and less detectably. A gradual increase in volume is a feature of PLLA treatment.

INJECTION TECHNIQUE

Injection technique is largely dictated by the physicochemical properties of a product and its predicted reaction in situ. It is crucial that appropriate consideration is given to the way that injection with PLLA differs from the techniques used with other injectable products.

RECONSTITUTION

PLLA is supplied in glass vials as a lyophilized powder that must be reconstituted with SWFI for at least 2 hours before use and preferably overnight at room temperature. For most patients, a dilution of 1 vial PLLA per 5 mL SWFI is recommended to avoid adverse events such as nodules and papules.[10] For patients with severe HIV-associated lipoatrophy, a more concentrated (3 mL) suspension was used years ago,[11] although adverse events such as papule formation were more likely at this concentration.[12] For most patients undergoing facial correction, the author prefers diluting 1 vial with 5 mL SWFI and 1.5 mL lidocaine 1% with epinephrine. This dilution ensures at least 6 mL per vial, as some volume is lost in the mixing process.

The diluted material must be left to reconstitute for at least 2 hours, but preferably longer (eg, overnight),

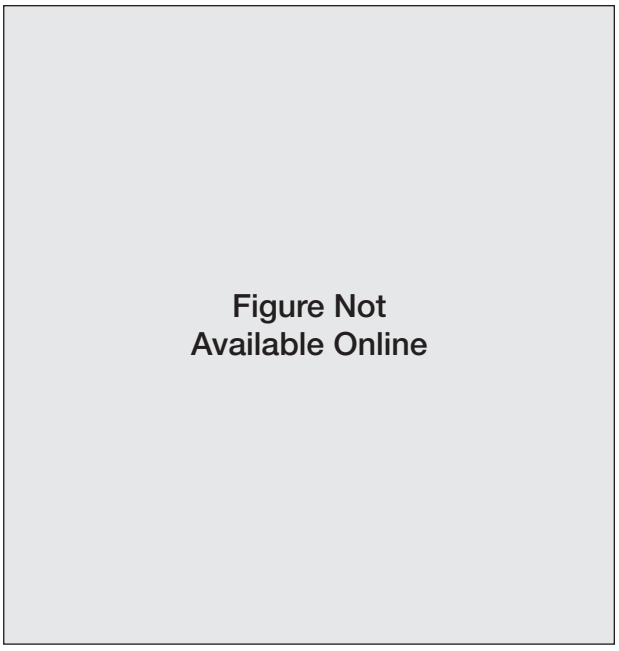

Figure 1. The level at which poly-L-lactic acid should be injected when using the tunneling technique (represented by the horizontal lines).[13] Adapted with permission from: Vleggaar D, Forte R, Cosmetic injectable devices: a review of the injection techniques, *J Drugs Dermatol*, 2006, 5; 951-956.

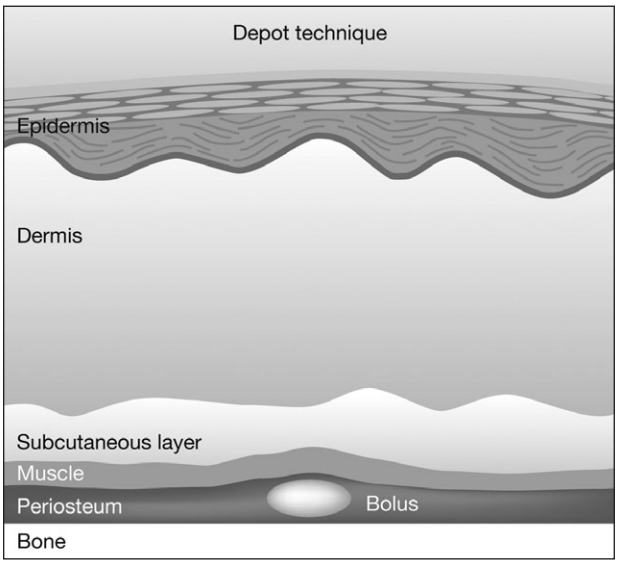

Figure 2. When injecting poly-L-lactic acid using the depot technique, the product is deposited just above the periosteum in a small bolus.

prior to injection to facilitate full hydration. During the reconstitution process, the product should not be shaken. However, directly before use, the vial should be thoroughly agitated.[10,12]

INJECTING PLLA

It is recommended that a 26-gauge needle be used for injection to avoid blockages and facilitate good flow control. Depending on the area of the face requiring correction, 2 techniques for the administration of PLLA are recognized: tunneling (threading) (Figure 1) and depot-type injections (Figure 2).[13,14] The tunneling technique is familiar to most physicians as it is one of the means by which many products can be injected. A point of divergence from HA-based products is the level at which PLLA is injected. Generally, longer-lasting products are deposited at a deeper level than are more temporary products.[15] PLLA is introduced at the junction of the dermis and subcutis, with the author favoring the uppermost subcutaneous plane versus the deep dermis as described below.

The tunneling technique should be used for the mid and lower face. The needle should be introduced into the skin, with the beveled edge facing up at an angle of 30° to 40°, until the deep dermal subcutaneous plane is reached (Figure 1). The transition from dermis to subcutaneous plane is made obvious by a sudden reduction in tissue resistance to the passage of the needle. If the needle is inserted at too shallow an angle, the bevel of the needle will be visible. Should immediate or slightly delayed blanching of the injected area occur, this is further confirmation that the needle angle is incorrect. If blanching is observed, the needle should be removed and the area gently massaged.

When the high subcutaneous plane has been reached, the needle angle is lowered and then advanced along this same level. Prior to depositing PLLA in the skin, a reflux maneuver should be performed to ensure that a blood vessel has not been entered. As the needle is withdrawn, a thin trail of PLLA is deposited in the tissue in a retrograde fashion, amounting to 0.1 to 0.2 mL of product per injection, leaving a subtle visible and palpable elevation of the skin. To avoid injecting the product upon withdrawal through the dermis, a brief pause should be taken before exiting.

Injections should be placed approximately 0.3 to 0.6 cm apart, and following every 3 to 4 injections, the site should be massaged vigorously. Subsequent injections should be made into areas adjacent to the initial treatment area in a grid or cross-hatched pattern. Some prefer a fanlike pattern, with care to avoid excess deposition at the apex of the fan. It is important to emphasize to patients that they must continue to massage the treatment site daily for several days posttreatment to minimize the possibility of nodule or papule formation and to ensure even distribution of the product. The "rule of 5s" is a helpful mnemonic for patients: massage 5 times per day, for 5 minutes, for 5 days.

When treatment of the upper face is required, the depot technique is more appropriate for the temples, tear trough, and malar regions. The depot technique involves inserting the needle at an angle of approximately 45° and

penetrating the dermis, subcutaneous layer, and muscle, before depositing the product just above into the periosteum in a small bolus of approximately 0.05 mL per injection (Figure 2). To ensure that a blood vessel has not been entered, a reflux maneuver should be performed before each injection. Depressions in the temples can be treated by injecting a bolus through the temporalis muscle. The upper zygoma and especially the periorbital regions are less forgiving of improper injection technique with PLLA, so appropriate training and experience should be sought before attempting correction in these areas. According to the author, more dilute solutions of product with 8 to 10 mL of SWFI are sometimes recommended for these areas, although one must be cautious, as there is more dispersion with a more dilute solution.

AVOIDING ADVERSE EVENTS

Injection-site–related adverse events, such as bruising, edema, discomfort, and pain, are to be expected in a proportion of patients. Rarely (<5% of patients), treatment-related adverse events such as erythema, fever, induration, papules, nodules, and infection occur at the site of injection.[10] These reactions tend to be temporary and self-limiting in nature. When reconstituting the product, one may add lidocaine in combination with epinephrine to ease some discomfort, prolong the duration of the local anesthetic, and help minimize bruising. Adherence to the correct injection technique also minimizes the risk of such events occurring; however, care must be taken to avoid intravascular injection.

Based on the results of 4 investigator-initiated clinical studies of patients with HIV-associated facial lipoatrophy, the most common device-related adverse event associated with PLLA was the formation of delayed palpable, nonbothersome, nonvisible subcutaneous papules at the injection site.[16] Patients should be warned of the possibility of nodule formation at the treatment site.[9] However, since the initial trials of PLLA were conducted, the injection technique has been refined on the basis of accrued experience. Three key points have emerged from adverse event reporting: uneven product distribution, incorrect placement of PLLA, and the use of an overly concentrated product are all thought to be major contributory factors to unsatisfactory results.[11,12,17]

Irrespective of the area of the face to be treated, palpable and occasionally visible papules or blanching can occur if PLLA is not injected at deep enough levels, so correct placement in the subcutaneous deep dermal plane is of paramount importance. Observance of these guidelines has been shown to dramatically reduce the incidence of papules and nodule formation.[11,16] Two areas are of special concern. The lips are prone to nodule formation and should not be treated with this product. Additionally, nodules tend to be most visible in the periorbital area. Very conservative treatment with strict adherence to guidelines is advised in this area.

In the event of nodule formation, treatment should be targeted at breaking down the lump. For example, early, noninflammatory nodules may require subcision with a needle and dilution of the PLLA with sterile water or saline, or another technique to break down the lump. If the nodule is unresponsive to subcision, injection of HA around the nodule has been recommended to camouflage its appearance. It is recommended that late-onset, active nodules receive treatment with localized anti-inflammatory therapy, systemic anti-inflammatory therapy such as intralesional corticosteroids and 5-fluorouracil, or both. If conservative measures fail, surgical excision may be considered.

COMMENT

PLLA can be used in most areas of the face to generate volume replacement. Furthermore, because of its mode of operation, PLLA can be used to provide progressive volume restoration. Indeed, if the appropriate training is undertaken and the correct injection technique is applied, PLLA can be used to treat a wide range of defects in any given patient. One exception to this is volume restoration of the lips because of the increased risk of adverse events in this area, due to both the highly dynamic nature and the anatomy of this tissue. Very superficial lines and wrinkles, and skin requiring resurfacing, also clearly lend themselves to other treatments, such as collagen, HA, or microdermabrasion. Physicians need to be mindful that PLLA is approved by the FDA only for HIV-related facial lipoatrophy. Many physicians will feel more comfortable awaiting FDA approval and further clinical studies in patients not infected with HIV before using the product to treat these patients.

Patients should be informed of the risks and benefits of PLLA, as well as alternative products. If the physician chooses to offer the product off label, this choice should be openly discussed with the patient. The initial patient consultation process is critical to optimizing patient satisfaction with PLLA, since those familiar with cosmetic interventions may be disappointed if results are not immediate. Serial photographs help demonstrate treatment progress to the patient, who can view the results in a mirror after half of the face has been injected. This is also very helpful in establishing realistic expectations. Furthermore, patients should be made aware of how long the correction is likely to remain. PLLA provides full correction for up to 24 months (and may not require further treatment for 2.5 years) and is more durable than are devices based on HA or collagen.[11] Unlike permanent products, correction will not be maintained indefinitely, but this allows for adjustments later on.

Acknowledgment—Editorial support for this article was provided by Dermik Laboratories, a business of sanofi-aventis U.S. LLC.

REFERENCES

1. Werschler WP, Weinkle S. Longevity of effects of injectable products for soft-tissue augmentation. *J Drugs Dermatol.* 2005;4:20-27.
2. Simamora P, Chern W. Poly-L-lactic acid: an overview. *J Drugs Dermatol.* 2006;5:436-440.
3. Gogolewski S, Jovanovic M, Perren SM, et al. Tissue response and in vivo degradation of selected polyhydroxyacids: polylactides (PLA), poly(3-hydroxybutyrate) (PHB), and poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHB/VA). *J Biomed Mater Res.* 1993;27:1135-1148.
4. Kronenthal RL. Biodegradable polymers in medicine. In: Kronenthal RL, Oser Z, Martin E, eds. *Polymers in Science and Surgery.* New York, NY: Plenum Press; 1975:119-137. *Polymer Science and Technology*; vol 8.
5. Valantin MA, Aubron-Olivier C, Ghosn J, et al. Polylactic acid implants (New-Fill) to correct facial lipoatrophy in HIV-infected patients: results of the open-label study VEGA. *AIDS.* 2003;17:2471-2477.
6. Bauer U. Improvement of facial aesthetics at 40 months with injectable poly-L-lactic acid (PLLA). Presented at: 17th Congress of the International Society of Aesthetic Plastic Surgery; August 28-31, 2004; Houston, Tex.
7. Lemperle G, Morhenn V, Charrier U. Human histology and persistence of various injectable filler substances for soft tissue augmentation. *Aesthetic Plast Surg.* 2003;27:354-366.
8. Lowe NJ, Maxwell CA, Patnaik R. Adverse reactions to dermal fillers: review. *J Derm Surg.* 2005;31:1616-1625.
9. Moyle GJ, Lysakova L, Brown S, et al. A randomized open-label study of immediate versus delayed polylactic acid injections for the cosmetic management of facial lipoatrophy in persons with HIV infection. *HIV Med.* 2004;5:82-87.
10. Sculptra [package insert] Berwyn, Pa: Dermik Laboratories; 2006.
11. Vleggaar D, Bauer U. Facial enhancement and the European experience with Sculptra (poly-L-lactic acid). *J Drugs Dermatol.* 2004;3:542-547.
12. Burgess CM, Quiroga RM. Assessment of the safety and efficacy of poly-L-lactic acid for the treatment of HIV-associated facial lipoatrophy. *J Am Acad Dermatol.* 2005;52:233-239.
13. Vleggaar D, Forte R. Cosmetic injectable devices: a review of the injection techniques. *J Drugs Dermatol.* 2006;5:951-956.
14. Vleggaar D. Poly-L-lactic acid: consultation on the injection techniques. *J Eur Acad Dermatol Venereol.* 2006;20(suppl 1):17-21.
15. Duffy DM. Complications of fillers: overview. *Dermatol Surg.* 2005;31:1626-1633.
16. Engelhard P, Humble G, Mest D. Safety of Sculptra: a review of clinical trial data. *J Cosmet Laser Ther.* 2005;7:201-205.
17. Woerle B, Hanke CW, Sattler G. Poly-L-lactic acid: a temporary filler for soft tissue augmentation. *J Drugs Dermatol.* 2004;3:385-389.