Minimizing the risk of adverse events with injectable poly-L-lactic acid

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Citation

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Abstract

Injectable poly-L-lactic acid (Sculptra®) is an effective and durable treatment for volume correction/restoration (in people with human immunodeficiency virus treatment-related facial fat loss [lipoatrophy]) and is well tolerated when administered correctly. Incorrect administration technique and suboptimal preparation of poly-L-lactic acid can lead to the formation of papules and nodules. In order to minimize the risk of development of these lesions, poly-L-lactic acid should be reconstituted correctly and injected subcutaneously at the junction of the dermis and subcutaneous fat using the appropriate technique tailored to both the patient and area of correction. Here we overview the best administration techniques for poly-L-lactic acid in order to minimize the potential for adverse effects and optimize treatment outcomes. Used correctly, poly-L-lactic acid is associated with a favorable risk–benefit profile.

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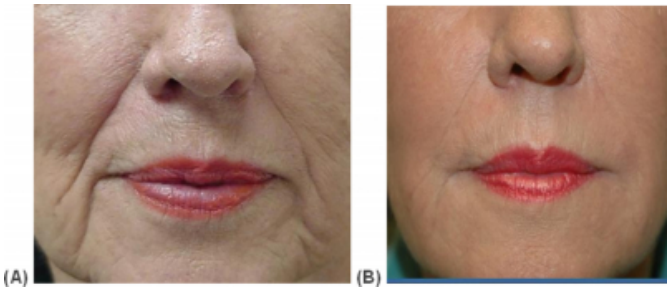
INTRODUCTION

Polymers of lactic acid have been used safely for decades in medical devices, including screws, resorbable sutures, pins and implants. Injectable poly-L-lactic acid (PLLA; Sculptra ® ; also known in Europe as Sculptra and New-Fill ® ; Dermik Laboratories, a business of sanofi-aventis US LLC., Bridgewater, NJ) is a synthetic, biocompatible, biodegradable, immunologically inert device that has been shown to elicit substantial increases in dermal volume following injection into the face [1,2,3,4] . Injectable PLLA received CE Mark accreditation in Europe in 1999 where it is licensed for cosmetic use and for correction of associated facial fat loss (lipoatrophy) in patients with human immunodeficiency virus (HIV) [4] . It was approved by the United States Food and Drug Administration for the latter indication in 2004, and is currently undergoing review for the cosmetic indication for use in the correction of wrinkles, such as nasolabial folds.

Increases in dermal thickness following injection of PLLA are thought to be the result of the production or recruitment of new fibroblasts, which subsequently produce collagen, as observed in animal studies [5] . This mode of operation is thought to lead to the observed gradual and substantial increases in dermal thickness, that can be sustained for up to 24 months (Figure 1) [6,7,8] . One study of PLLA in patients with HIV-associated facial lipoatrophy demonstrated significant increases in median cutaneous thickness at all post-treatment timepoints up to Week 96 ($p<0.001$ versus baseline) [7] .

Figure 1

Figure 1: Patient before (A) and after (B) three treatments with poly-L-lactic acid (17-month follow-up period)



Three treatment sessions with poly-L-lactic acid were undertaken (six vials in total), each separated by approximately 8 weeks. Patient was also treated with Radiesse ® in the marionette lines and Botox ® in the depressor anguli oris muscle

As with all injectable products, injection of PLLA can be associated with the risk of adverse events (AEs). Procedure-

and injection-related AEs, such as erythema, bruising and discomfort, are relatively common for all injectable devices and are generally mild, resolving spontaneously over several days [9,10,11]. Device-related AEs, such as allergic reactions, hypersensitivity or inflammatory reactions, as well as the formation of papules and nodules, are less common among injectable devices [8,9,11]. Of device-related AEs, the formation of papules and/or nodules has been reported as a potential AE with PLLA use (Table 1) [7,12,13,14]. Data from pivotal clinical trials of PLLA in the correction of HIV-associated facial lipoatrophy highlighted the development of asymptomatic and non-visible subcutaneous papules (lesions of ?5 mm, usually palpable) at the injection site [7,12,13,14]. The prevalence of these papules varied widely (from 6–52%) in these studies (Table 1). As the studies were conducted among similar populations, these differences may be attributable to variation in preparation and/or injection technique.

Figure 2

Table 1: Adverse reactions observed in clinical studies [,,,]

	VEGA study N=50	Chelsea and Westminster study[a] N=30	APEX study N=99	Blue Pacific study N=99
	2-year follow-up studies		1-year follow-up studies	
Injection–procedure-related adverse reactions				
Bruising	3 (6%)	11 (38%)	1 (1%)	30 (30%)
Edema	2 (4%)	2 (7%)	3 (3%)	17 (17%)
Discomfort	0	3 (10%)	19 (19%)	15 (15%)
Hematoma	14 (28%)	0	0	0
Inflammation	0	3 (10%)	0	0
Erythema	0	3 (10%)	0	3 (3%)
Device-related adverse reactions				
Injection site subcutaneous papule[b]	26 (52%)	9 (31%)	6 (6%)	13 (13%)

[a]Safety data was collected post hoc for 27 of the patients at approximately 2 years from the start of the study; [b]Subcutaneous papules refer to lesions of 5 mm or less, typically palpable, non-bothersome and non-visible

A number of physicians who are experienced with PLLA have highlighted the importance of correct preparation and application techniques for minimizing the occurrence of subcutaneous nodules and papules [8,9,15,16,17]. Indeed, the use of proper injection technique for PLLA has been noted to result in a marked decrease in nodule/papule formation without compromising treatment efficacy [18]. This article describes the appropriate injection technique and dilution factors for PLLA in order to prevent the appearance of nodules and papules.

INJECTION TECHNIQUE

Engelhard et al advise that each treatment should be tailored to the individual [12]. It is important to take into account factors such as age and the area for correction when planning a treatment regimen. Additionally, patients should be instructed to avoid non-steroidal anti-inflammatory medications or aspirin for 1 week before injection to minimize bruising. The number of injections per session and the total volume of PLLA used is determined by the area and severity of correction required. Burgess et al recommended that PLLA injections be performed using a 3-mL syringe with a 25-gauge, 1.5-inch needle [16]. Based on the author's clinical experience, a 1-mL syringe with a 25-gauge, 1-inch needle is an optimal combination. The product information for PLLA does not recommend injecting with needles smaller than 26-gauge [1].

RECONSTITUTION OF POLY-L-LACTIC ACID

Injectable PLLA is supplied in a glass vial as a lyophilized powder and the manufacturer recommends that it be reconstituted with 3–5 mL sterile water for injection (SWFI) before use [1]. Specifically, it must be reconstituted at least 2 hours prior to injection and then agitated immediately prior to injection to ensure even distribution of PLLA in the solution. In addition, the manufacturer recommends that the product be used within 72 hours after reconstitution.

Several authors have reported that more concentrated suspensions of PLLA (<5 mL total volume) result in greater incidences of papules/nodules [9,15,17,19]. During two large HIV studies, relatively high rates of nodule formation were observed (>30%) and, in both studies, PLLA was reconstituted with 3–4 mL SWFI [6,7]. Conversely, in studies where PLLA was reconstituted into a more dilute suspension (?5 mL total volume), a noticeably reduced incidence of nodule formation has been observed (<5%) [8,15,16]. The author's clinical experience suggests that dilution with 6 mL SWFI is optimal for injections into the face. Furthermore, the author finds that slight warming of the product with bodily contact (such as in the palm of the hand) prior to injection can help increase the consistency of the suspension.

INJECTION PROCEDURE WITH POLY-L-LACTIC ACID

Depending on the area being treated, there are two types of injection technique that should be utilized; tunneling and

depot. The most appropriate technique for the mid and lower face is threading or tunneling. The needle is inserted deeply at a 30- to 40-degree angle, followed by lowering of the needle to inject parallel to the skin. Prior to depositing PLLA, a reflux maneuver should be performed to ensure that a blood vessel has not been entered. PLLA is injected at the junction of the dermis and subcutaneous fat as the needle is withdrawn. For other areas, such as the temples, it is recommended that PLLA be injected in a depot fashion (0.05 mL per injection) and be placed into the temporal fascia.

Injections into the mid and lower face should be spaced approximately 0.5–1.0 cm apart, with 0.1–0.2 mL of reconstituted product per injection [20,21]. Some authors have suggested that in most cases, a maximum of two vials should be injected per session (one vial per cheek) to minimize the potential for AEs [16]. Treatment sessions should be spaced at 4–6-week intervals to allow for the full volumizing effects of PLLA to be realized. Overcorrection with injectable PLLA is not recommended and injection of excessive quantities in one treatment session may result in an increased rate of papules/nodules [17].

DEPTH OF INJECTION

Visible/palpable nodules have been associated with superficially injected PLLA; the incidence of nodules can be substantially diminished by injection into the deeper subcutaneous tissue rather than the lower dermis [9,15,16,17,19]. The depth at which any injectable device is injected is critical to achieving optimal results. For example, superficial placement of hyaluronic acid fillers can lead to visible, pale nodules in the skin [9]. Generally, more permanent devices need to be injected more deeply. As the effects of PLLA are sustained for up to 24 months [6,7,8], it is generally recommended that PLLA be injected at the junction of the dermis and subcutaneous plane or the subcutaneous fat.

POST-INJECTION MASSAGE

Massage of the treated area has been found to reduce the formation of subcutaneous papules and nodules [18,22]. In a study by Borelli et al, no nodule formation was observed following the deep subcutaneous application of PLLA, with subsequent massage [18]. It is recommended that physicians should thoroughly massage the cheek for 2–5 minutes after every 3–4 injections [23]. The author advises patients to massage their cheeks inside and out, twice daily for up to 1 month after treatment. A rule of ‘five' may also be a useful reference for patients to adhere with. Specifically, this would include massage for 5 minutes, five times a day for 5 days post-injection, followed by once-a-day massage for an additional month. Compliance with regular post-treatment massage is especially important following injections into the temple area.

CONCLUSION

PLLA exhibits many desirable characteristics; it is synthetic, biocompatible, biodegradable, immunologically inert and provides versatile, durable correction for up to 24 months [4,6,7,8]. When injected correctly, it is associated with a very favorable risk–benefit profile [8,12,15,16]. Physicians treating patients with PLLA have the benefit of many years' collective experience with the product. Refining the technique by which PLLA is injected, specifically, utilizing optimal dilution concentrations, correctly placing PLLA at the junction of the dermis and subcutaneous fat, thorough post-injection massage by the physician, and advising patients about the importance of post-treatment massage, have been shown to greatly reduce the risk of AEs, including papules and nodules. Overall, appropriate injection technique and dilution factors for PLLA help to achieve optimum results and prevent the occurrence of unwanted AEs.

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