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Treatment Options in Facial and Nonfacial Volumization: An Introduction to Poly-L-Lactic Acid

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EDITORIAL

ORIGINAL ARTICLES

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EDITORIAL Journal of Drugs in Dermatology

The Need for Consensus Recommendations on the Use of Injectable Poly-L-Lactic Acid for Facial and Nonfacial Volumization

The primary reason patients seek aesthetic treatment from dermatologists or plastic surgeons is to combat the signs of aging.[1] Increased interest in this goal has been driven by the development of newer treatment options that help restore a more youthful visage, as well as the increasing societal emphasis on the value of an appearance that conveys youth, vitality, and fecundity.[2,3]

An enhanced understanding of the dynamic anatomical and physiological changes associated with the aging face has, in turn, allowed a more sophisticated appreciation of the interdependent nature of such changes and how they work in concert to affect overall facial aesthetics.[4] As our knowledge and experience have grown, it has become possible to more specifically tailor treatment approaches to the individual needs of each patient.

Soft tissue augmentation is one important option in aesthetic enhancement, and it continues to grow in popularity for a number of reasons. These include practical considerations such as its minimally invasive nature[5] and its ability to directly nullify volume loss, which is now appreciated as a key root cause of the declining aesthetics associated with facial aging.[4]

> "Soft tissue augmentation is one important option in aesthetic enhancement, and it continues to grow in popularity for a number of reasons."

Agents that replace collagen are effective tools for addressing volume loss.[2] Among these, poly-L-lactic acid (PLLA) carries great potential as a cosmetic treatment. Poly-L-lactic acid is a stimulator of host collagen synthesis; this neocollagenesis acts to volumize soft tissue in a gradual, progressive, and predictable manner.[4] The patient photographs found in the "Facial Volumization with PLLA: Representative Results" portion of the "Consensus Recommendations on the Use of Injectable Poly-L-Lactic Acid for Facial and Nonfacial Volumization" section of this supplement[6] demonstrate the ability of PLLA to provide natural-looking restoration of lost facial volume.

Despite the considerable value conveyed by its mechanism of action, the full clinical potential of PLLA was not initially realized, as its use was associated with the frequent occurrence of adverse events, such as nodules and papules.[7-11] These results were due, in large part, to inadequate recommendations regarding the methodology of PLLA use[12] and patient selection, and a somewhat common misunderstanding of the clinical implications of its underlying mechanism. However, our understanding of the use of injectables, including PLLA, for cosmetic enhancement is in a continual state of evolution and refinement. Considerable time has passed since the introduction of PLLA for soft tissue augmentation, and the collective experience of innumerable clinicians and investigators now forms a requisite knowledge base that can better inform its appropriate clinical utilization.

An international group of experts, each with more than a decade of experience in the use of PLLA, was convened in 2013 to discuss the evolving literature on PLLA, share their personal experiences and perspectives, and synthesize consensus recommendations on the appropriate use of PLLA for soft tissue augmentation.[6] The objective of these recommendations is to enhance the use of this agent in order to decrease adverse events and improve patient outcomes.

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ORIGINAL ARTICLE Journal of Drugs in Dermatology

Composition and Mechanism of Action of Poly-L-Lactic Acid in Soft Tissue Augmentation

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ABSTRACT

Poly-L-lactic acid (PLLA) is a synthetic, biocompatible, biodegradable polymer. For its use in soft tissue augmentation, it is supplied as a lyophilized powder containing PLLA microparticles, the size and chemical attributes of which are tightly controlled. As a biocompatible material, PLLA generates a desired subclinical inflammatory tissue response that leads to encapsulation of the microparticles, stimulation of host collagen production, and fibroplasia. Over time, the PLLA degrades, the inflammatory response wanes, and host collagen production increases. This response leads to the generation of new volume and structural support that occurs in a gradual, progressive manner, and which can last for years. Coupled with consistent, optimized injection methodology, the use of PLLA in soft tissue augmentation can result in a predictable cosmetic effect that is completely controlled by the treating clinician.

J Drugs Dermatol. 2014;13(suppl 4):s29-s31.

INTRODUCTION

Poly-L-lactic acid (PLLA) (Figure 1)[1] is a synthetic, biocompatible, biodegradable polymer that has been used in various medical applications for more than 3 decades.[1,2] For its use in soft tissue augmentation, it is supplied in a sterile glass vial as lyophilized powder, which includes nonpyrogenic mannitol, sodium carboxymethylcellulose, and PLLA microparticles.[3] The diameter of the microparticles is tightly controlled, measuring on average between 40 µm to 63 µm; particle size is key to product performance, as particles in this range are large enough to avoid both passage through capillary walls and phagocytosis by dermal macrophages, but small enough for easy injection.[1] Prior to use, reconstitution of the lyophilized product through the addition of sterile water forms a hydrocolloid suspension.[1,3]

Poly-L-lactic acid is a relatable example of the clinical utility of biocompatible materials. The biocompatibility of a product pertains to its ability to generate a beneficial cellular or tissue response in a particular clinical application.[4] Implanted polymeric biomaterial results in an inflammatory response (Figure 2), the nature of which is determined by many factors that can be broadly classified into 3 categories: the biomaterial's properties, the host's characteristics, and the methodology by which the biomaterial is introduced into the host.[5] Consistency in each of these 3 parameters leads to a predictable host response and, in the case of collagen stimulators, to a predictable cosmetic effect that is completely controlled by the clinician.

The impact of the methodology of biomaterial introduction, as it relates to PLLA, will be explored in detail in "The History Behind the Use of Injectable Poly-L-Lactic Acid for Facial and Nonfacial Volumization: the Positive Impact of Evolving Methodology" section of this supplement.[6]

The properties of a biomaterial implant that affect host response include both physical attributes (shape, size, surface area) and chemical attributes (pH, charge, hydrophilic vs hydrophobic), in both its initial and degraded forms.[5] The importance of such properties can be illustrated briefly by looking at one well-established example, the refinement of microparticle size during the development of polymethylmethacrylate (PMMA)-based collagen stimulators. Arteplast®, the first generation of injectable PMMA, had a broad range of particle sizes and a high level of particles below 20 µm, resulting in an unpredictable amount of inflammation and high incidence of granulomas.[7] The second-generation agent, Artecoll®, had greater uniformity in particle size, and while the results with this agent were improved, further refinement was necessary to produce the third-generation product, Artefill®, the first to meet the United States Food and Drug Administration's rigorous quality requirements.[7]

As this example illustrates, a great deal has been learned over time regarding how the many characteristics of collagen stimulators can affect their clinical behavior. With the tight control over the physical and chemical attributes of injectable PLLA microparticles, the tissue response with its use follows a controlled and predictable pattern.[8] Although the injection of PLLA into the subcutaneous or the supraperiosteal plane creates the appearance of immediate volumization due to mechanical

FIGURE 1. Structural formula of poly-L-lactic acid in Sculptra.[1] Reprinted with permission from Danny Vleggaar. Facial volumetric correction with injectable poly-L-lactic acid. Dermatologic Surgery, Volume 31, Issue 11 (Pt 2), Pages 1511-1518. Copyright © 2005 by the American Society for Dermatologic Surgery, Inc. Published by John Wiley and Sons.

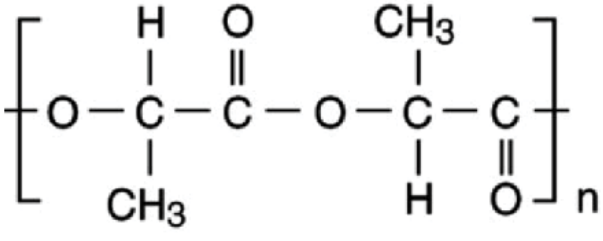
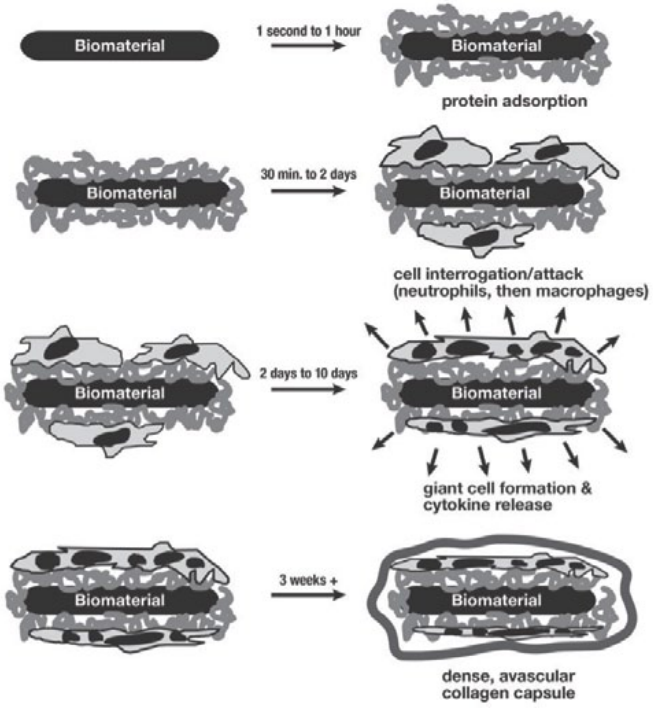
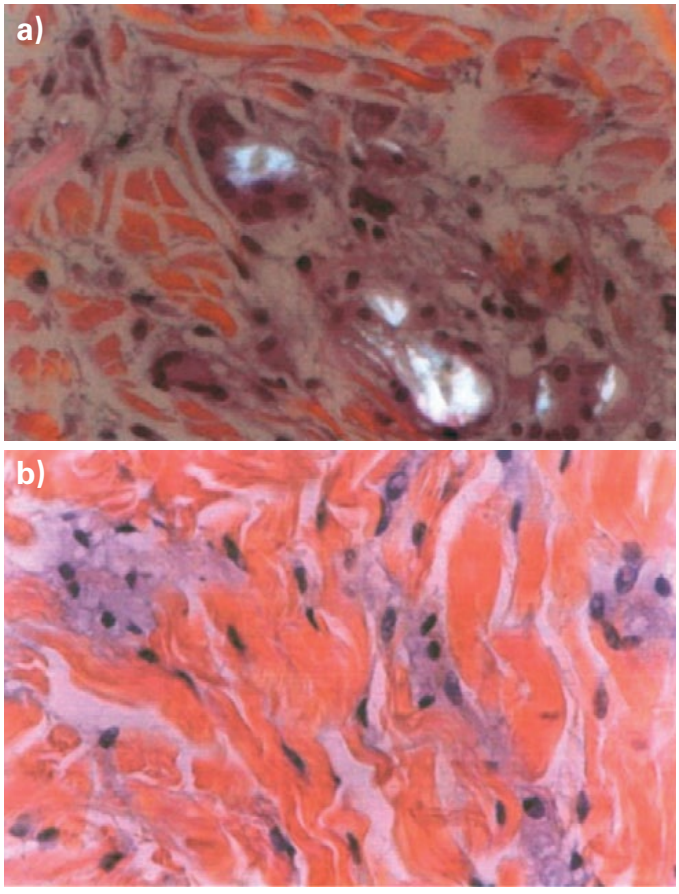


FIGURE 2. Foreign body reaction to a biomaterial.[5] Reprinted with permission from Buddy D. Ratner and Stephanie J. Bryant. Biomaterials: where we have been and where we are going. Annual Review of Biomedical Engineering, Volume 6, Pages 41-75. Copyright © 2004 by Annual Reviews.



expansion of the surrounding tissue, this effect is transient.[9] The cosmetically relevant mechanism of action (MOA) of PLLA involves the initiation of a desired subclinical inflammatory tissue response to the polylactides.[8] This inflammatory response leads to encapsulation of the microparticles, stimulation of host collagen production, and fibroplasia.[10] Over time, the PLLA degrades, the inflammatory response wanes, and host collagen production increases (Figure 3),[1] generating new volume and structural support in a gradual, progressive manner.[1,8,11,12] Due to the prolonged nature of its activity, the

FIGURE 3. Biopsy samples from poly-L-lactic acid (PLLA)-injected patients demonstrate a waning inflammatory response, PLLA degradation, and collagen accumulation over time.[1] **a)** Histological examination at 12 months post-PLLA injection, showing PLLA microparticles with adjacent aggregation of giant cells, histiocytes, and collagen fibers (Hematoxylin-eosin stain; x 400 original magnification). **b)** Histological examination at 30 months post-PLLA injection, showing an absence of PLLA particles microparticles and an abundance of collagen (Hematoxylin-eosin stain; x 400 original magnification). Reprinted with permission from Danny Vleggaar. Facial volumetric correction with injectable poly-L-lactic acid. Dermatologic Surgery, Volume 31, Issue 11 (Pt 2), Pages 1511-1518. Copyright © 2005 by the American Society for Dermatologic Surgery, Inc. Published by John Wiley and Sons.



cosmetic benefits of PLLA can last for several years.[13,14] It should be noted that the prolonged activity of PLLA is also a key consideration in the avoidance of overcorrection with its use in soft tissue augmentation.[1]

The MOA of PLLA contrasts with the MOA of products that directly augment tissue volume. However, neocollagenesis is not unique to PLLA. Even hyaluronic acid has been shown to stimulate collagen production,[15] although at a level lower than that seen with PLLA. Both injectable calcium hydroxylapatite (CaHA) and, as previously mentioned, PMMA, act primarily through the stimulation of collagen production.[16,17] Compared with PLLA, the scaffold provided by CaHA microspheres is degraded relatively quickly

over time, with a quicker loss of correction, while PMMA is not biodegradable and theoretically results in permanent effects.[16] However, a permanent effect may not be ideal, as cosmetic deficits often fluctuate with the increasing age of the patient.[8]

Studies Supporting the Mechanism of Action of Poly-L-Lactic Acid

In a murine model, a tissue response to and degradation of PLLA has been demonstrated.[18] In one study, at 1 month post-implantation, PLLA microparticles became surrounded by mononuclear macrophages, mast cells, foreign body cells, and lymphocytes.[18] At 3 months, increased collagen fiber deposits and a substantial decrease in cell numbers were observed, and at 6 months collagen production continued to increase with reductions in the number of fibrocytes and mononuclear macrophages. PLLA degradation continued throughout this time period, with decreases of 6%, 32%, and 58% at 1, 3, and 6 months, respectively.[18] In guinea pigs, the subcutaneous implantation of PLLA powder resulted in a very mild inflammatory response with evidence of a foreign body reaction at 1 week, marked fibroblastic activity and proliferation at 2 weeks, and gradual ingrowth of tissue fibers at 4 weeks, with no further indication of inflammatory reaction.[19] These preclinical findings are consistent with human histologic observations showing progressive dissolution of PLLA over 9 months,[16] a significant increase in mean levels of type I collagen at 6 months with an inflammatory response similar to baseline,[20] and gradual ingrowth of type I collagen 8 to 24 months post-injection.[1]

SUMMARY

Poly-L-lactic acid is a biocompatible, biodegradable polymer with established efficacy in numerous medical applications. The formulation of PLLA for use in soft tissue augmentation has been enhanced through inclusion of specific excipients and tight control over the physical and chemical attributes of PLLA microparticles.

When evaluating the clinical utility of biocompatible materials, PLLA provides a relatable example because it exerts its effects through the induction of a desired host response. This response leads to encapsulation of the microparticles, fibroplasia, PLLA degradation, and prolonged collagen synthesis, which generates new volume and structural support in a gradual, progressive manner. The consistent nature of the PLLA microparticles, coupled with an optimized injection technique, allows clinicians to achieve a controlled, predictable cosmetic effect.

DISCLOSURES

Danny Vleggaar MD has been a medical consultant for Sinclair IS Pharma, France; PharmaSwiss SA, Switzerland; Valeant Eastern Europe; and Cutanea Life Sciences, Inc. He also has been a trainer for Valeant Pharmaceuticals International, Inc./Medicis Corporation.

Rebecca Fitzgerald MD has been a consultant and speaker for Valeant Pharmaceuticals North America LLC/Medicis Corporation; Merz Aesthetic, Inc; and Allergan USA, Inc.

Z. Paul Lorenc MD has been a consultant for Johnson & Johnson; La Lumiere, LLC; Medicis Corporation; Merz Corporation; and Mentor Corporation. In addition, he holds the following patents: US Patent 5/611,814–Resorbable Surgical Appliance for Use in Supporting Soft Tissue in a Superior Position; US Patent 60/950,423–Composition and Method of Use for Soft Tissue Augmentation/Drug Delivery; US Patent 12/797,710–Method for Measuring Change in Lip Size After Augmentation; and US Patent 13/604,012–Light Therapy Platform System.

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The History Behind the Use of Injectable Poly-L-Lactic Acid for Facial and Nonfacial Volumization: The Positive Impact of Evolving Methodology

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ABSTRACT

Poly-L-lactic acid (PLLA) was first approved for soft tissue augmentation in Europe in 1999 for the cosmetic correction of scars and wrinkles. Due, in part, to inadequate usage recommendations that included those related to product reconstitution and hydration, injection sites, techniques, and timing, and patient selection, PLLA use was initially associated with suboptimal cosmetic benefit and a high rate of specific adverse events, such as the formation of nodules. As clinical experience with PLLA has increased, the implementation of specific methodological changes has allowed greater, more consistent cosmetic effects to be achieved, with a low rate of adverse events. This enhanced PLLA methodology, coupled with an evolving understanding of the interplay between structures in the aging face, now allows predictably favorable results across a broad range of patient types.

J Drugs Dermatol. 2014;13(suppl 4):s32-s34.

INTRODUCTION

Poly-L-lactic acid (PLLA) has been used in a variety of medical applications, such as absorbable sutures, fixation devices in orthopedic and plastic surgery, and vectors for sustained release of bioactive compounds for more than 30 years, during which time it has demonstrated excellent safety and biocompatibility.[1-5]

Poly-L-lactic acid was first approved for soft tissue augmentation in Europe in 1999, for the cosmetic correction of scars and wrinkles.[3] The initial recommendations for its use, including those related to product reconstitution and hydration, injection sites, techniques, timing, and patient selection, were, in retrospect, inadequate or suboptimal.[6,7] As a result, the full potential of PLLA was not immediately realized; instead, its clinical use was associated with a high rate of specific adverse events (AEs), such as nodules and papules.[6-8] Although usually remaining nonbothersome, nonvisible, and small, nodules can sometimes necessitate additional interventions, such as surgical excision.[9,10]The early experience with PLLA caused clinicians to become disenchanted regarding its clinical utility, with many specialists remaining wary and/or skeptical to this day.[6]

Over the past decade of clinical experience with the use of PLLA in soft tissue augmentation, much insight has been garnered regarding the specific shortcomings of those initial approaches. Evolution of specific aspects of PLLA methodology by clinicians and investigators has helped to decrease the frequency of AEs and improve the cosmetic benefits associated with its use.[9,11-25]

Taking a specific, historical look at the evolving methodology of PLLA injection can inform current practice with the use of this agent, as the accumulated experience provides a requisite dataset for the establishment of new recommendations. Upon the initial European approval of PLLA for soft tissue augmentation, a reconstitution in ≤3 mL of sterile water 3 minutes prior to injection was recommended.[3,6] In clinical use, PLLA was often injected superficially (as with a dermal filler), at high concentrations, and with short intervals between treatments.[6] In addition, injection sites were often chosen with less discrimination than was warranted, including facial areas where there was a risk of the material coalescing, such as the hypermobile perioral and periocular regions.[6,7] Early studies with PLLA reflected the shortcomings of these practices, which were associated with a high incidence of PLLA injection-site subcutaneous papules (Table 1).[3,11,18,26-32]

In 2004, the European indication for PLLA was extended to include large volume corrections of lipoatrophy. Coincident with this labeling expansion, modifications to the methodology of PLLA reconstitution and injection were largely adopted. Reconstitution volume was increased to 5 mL, hydration times were increased from minutes to hours (and eventually to overnight), the interval between injections was increased to 4 to 6 weeks, postinjection massage was introduced into the regimen, and clinicians began to avoid the injection of PLLA into the dermis.[9,14,16,19,22,23,30,31,33-36] Although it is impossible to determine which of these methodological changes had the greatest impact, a significant decrease

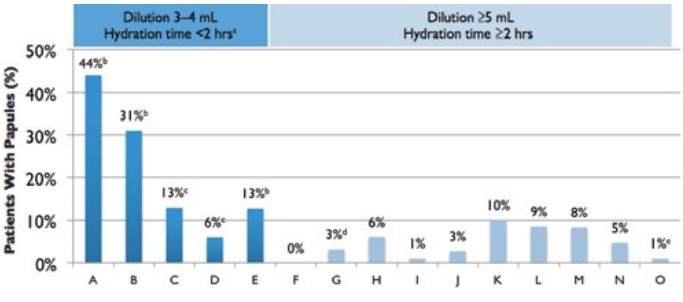
TABLE 1.

Summary of Early Human Immunodeficiency Virus–Associated Facial Lipoatrophy Studies With Poly-L-Lactic Acid[3,11,18,26-32]

Study (year)	Patients (N)	Treatment Interval (week)	Reconstitution Volume (mL)	Hydration Time	Incidence of Papules n (%)
VEGA (2003)	50	2	3–4	Not specified[a]	22 (44%)
Chelsea and Westminster (2004)	30[b]	2	2 (+1 mL lidocaine)	Not specified[a]	9 (31%)
Blue Pacific (2004)	99	3	3	Not specified[a]	13 (13.1%)
APEX002 (2004)	99	3	3–5	Minutes[c]	6 (6%)
Lafaurie (2005)	94	2	3 mL (+1 mL lidocaine)	Minutes[c]	12 (12.8%)

[a]Not specified; manufacturer's instructions at the time were to reconstitute 3 minutes prior to injection.
[b]Data for 29/30 patients were included in the analysis.
[c]Not explicitly stated; injections were carried out per manufacturer's instructions, which indicated reconstitution should occur 3 minutes prior to injection.

FIGURE 1. Incidence of papules in select clinical studies of poly-L-lactic acid 2003-2012.[3,9,11,14,16,18,19,22,23,26-36]

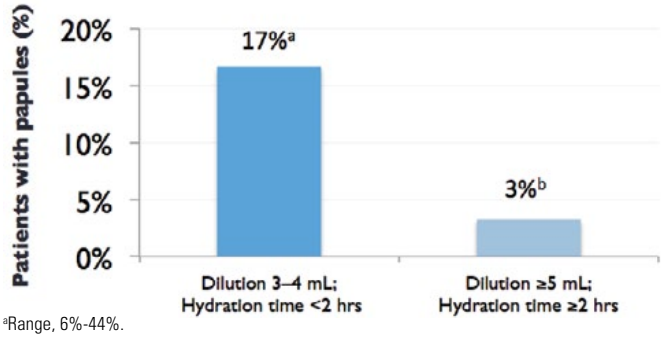


Earlier studies also had shorter treatment intervals: [a]Hydration time was not formally reported—manufacturer's instructions at the time were to reconstitute 3 minutes prior to injection. [b]2-week treatment interval. [c]3-week treatment interval. [d]Hydration occurred overnight, except during the first month, for which only 30 minutes were allotted. [e]Hydration time was not formally reported. Studies included: A: VEGA 2003 (N=50); B: Chelsea & Westminster 2004 (N=30; data for 29/30 patients were included in the analysis); C: Blue Pacific 2004 (N=99); D: APEX002 2004 (N=99); E: Lafaurie 2005 (N=94); F: Borelli 2005 (N=14); G: Vleggaar 2006 (N=2131); H: Levy 2008 (N=65); I: Redaelli 2009 (N=568); J: Mazzuco 2009 (N=36); K: Lee 2010 (N=40); L: Narins 2010 (N=116); M: Palm 2010 (N=130); N: Schierle 2011 (N=106); O: Rendon 2012 (N=100).

in the incidence of papule formation was observed with their implementation (Figures 1 and 2).[3,9,11,14,16,18,19,22,23,26-36]

Two groups of investigators have reported on the impact of a methodology modification on the incidence of subcutaneous papules in their own practices.[12,25] In the first report, which included observations on approximately 300 patients across a 5-year period, PLLA was reconstituted in 3 mL sterile water and hydrated for 2 to 12 hours prior to injection in the first 2 years of observation.[12] With this protocol, 10% of patients developed subcutaneous papules, the majority of which resolved in 12 to 24 months without treatment. The protocol was modified about halfway into the 5-year period, in which 3 key methodological factors were altered: hydration time was increased to 36 to 48 hours, 2 mL lidocaine was added to the suspension immediately before injection (for a total volume of 5 mL), and PLLA was injected into the uppermost portion of the subcutaneous fat rather than the lower dermis. With these protocol modifications in place, the incidence of subcutaneous papules decreased to <1%.[12]

FIGURE 2. Pooled data on incidence of papules in select clinical studies of poly-L-lactic acid (2003-2012) stratified by dilution volume and hydration time.[3,9,11,14,16,18,19,22,23,26-36]



[a]Range, 6%-44%.
[b]Range, 0%-10%.

The second group of investigators injected approximately 3,000 patients with PLLA from 1999 to 2006, using a micropuncture technique.[25] From 1999 to 2002, about 1,500 patients received injections in which PLLA was reconstituted in 3 mL sterile water, with an incidence of late-onset inflammatory nodules of 1%. In the latter 4 years of this time period, the reconstitution volume was increased to 5 mL (or even greater, on occasion), with the other methodological factors held constant. In this second cohort of approximately 1,500 patients, the incidence of late-onset nodules was greatly reduced to 0.13%.[25]

Our understanding of how best clinically to use PLLA continues to evolve based on clinical trials and real-world experience, as well as through a deeper appreciation of the interplay between facial structures throughout the aging process. These advancements have enabled more subtle distinctions to be made regarding the use of PLLA, such as injection techniques for specific facial areas, and the correlations between treated surface area and per-session product volume and between the volumetric correction and number of sessions required.[37] These and other more nuanced observations will be more specifically described in the "Consensus Recommendations on the Use of Injectable Poly-L-Lactic Acid for Facial and Nonfacial Volumization" section of this supplement.[38]

SUMMARY

With the initial use of injectable PLLA in soft tissue augmentation, inadequate usage guidelines coupled with a lack of clinical experience resulted in a high incidence of nodules and papules, compromising its image as a viable clinical option. Over time, as experience grew, alterations in methodology revealed several factors critical to effective PLLA utilization. Increased reconstitution volume, hydration time, and duration of the interval between treatments, along with a better appreciation of the appropriate sites and depth for PLLA injection, have greatly improved clinical outcomes. Our understanding and techniques continue to evolve, allowing predictably favorable results across a broad range of patient types.

DISCLOSURES

Danny Vleggaar MD has been a medical consultant for Sinclair IS Pharma, France; PharmaSwiss SA, Switzerland; Valeant Eastern Europe; and Cutanea Life Sciences, Inc. He has also been a trainer for Valeant Pharmaceuticals International, Inc./Medicis Corporation.

Rebecca Fitzgerald MD has been a consultant and speaker for Valeant Pharmaceuticals North America LLC/Medicis Corporation; Merz Aesthetic, Inc; and Allergan USA, Inc.

Z. Paul Lorenc MD has been a consultant for Johnson & Johnson; La Lumiere LLC; Medicis Corporation; Merz Corporation; and Mentor Corporation. In addition, he holds the following patents: US Patent 5/611,814–Resorbable Surgical Appliance for Use in Supporting Soft Tissue in a Superior Position; US Patent 60/950,423–Composition and Method of Use for Soft Tissue Augmentation/Drug Delivery; US Patent 12/797,710–Method for Measuring Change in Lip Size After Augmentation; and US Patent 13/604,012–Light Therapy Platform System.

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ORIGINAL ARTICLE Journal of Drugs in Dermatology

Understanding, Avoiding, and Treating Potential Adverse Events Following the Use of Injectable Poly-L-Lactic Acid for Facial and Nonfacial Volumization

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ABSTRACT

Injection-related adverse events (AEs) may occur with the use of any injectable substance, including all commercially available fillers. The most common of these AEs include discomfort, bruising, edema, and erythema, which are generally transient and resolve spontaneously. The majority of AEs widely felt to be associated with poly-L-lactic acid (PLLA) are papules, nodules, and granulomas. Papules and nodules, which are histologically distinct from granulomas, tend to arise several weeks after injection, are generally palpable, asymptomatic, and nonvisible, and will typically resolve on their own, but can be camouflaged with the use of hyaluronic acid. They generally result from suboptimal product reconstitution or placement and, as such, their incidence can be minimized by improved injection methodology. In contrast, true inflammatory granulomas are very rare (incidence 0.01%-0.1%), seem to be systemic in nature, and represent an overabundance of host reaction to PLLA. Granulomas may become apparent months or years post-injection and may persist and grow over time. Their treatment is geared toward halting the increased secretion of interstitial substances and invasion of cells, and may include the administration of steroids and antimetabolites such as 5-fluorouracil.

J Drugs Dermatol. 2014;13(suppl 4):s35-s39.

INTRODUCTION

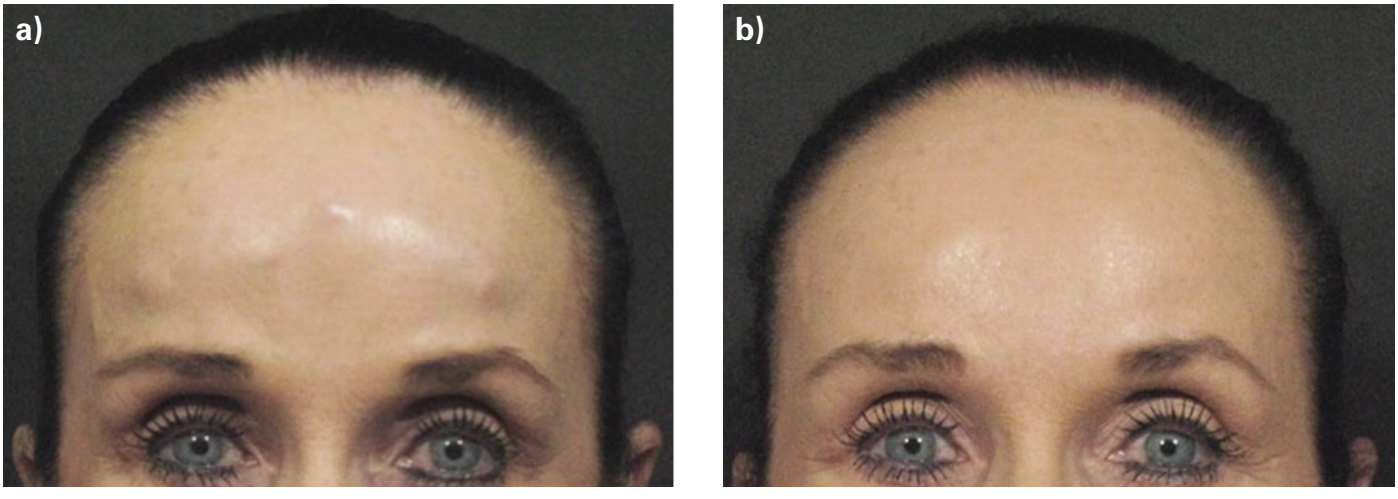
Injection-related adverse events (AEs) may occur with the use of any injectable substance, including all currently commercially available fillers. The most common of these AEs include discomfort, bruising, edema, and erythema, which are generally transient and resolve spontaneously.[1-5] Potentially far more serious, and fortunately far less common, injection-related AEs can also include tissue necrosis, including rare cases of blindness.[6,7] This may be caused by inadvertent intravascular injections, and has also been described in the literature with all injectable fillers. The ability to reflux to ensure the needle is not in a vessel prior to injection of poly-L-lactic acid (PLLA) is technically possible because it is a very low viscosity suspension injected with a large (25 or 26) gauge needle, and thus may offer some advantage. Another potentially injection-related AE described with many injectable fillers, including PLLA, is infection.[8] This may highlight the importance of proper facial cleansing and preparation prior to multiple injection sites with long-lasting fillers. Finally, the majority of AEs widely felt to be associated with PLLA are papules, nodules, and granulomas. These terms have been used interchangeably, although they are, in fact, clinically very distinct. This distinction merits clarification as it has caused a fair amount of confusion, and will be discussed below.

Papules and Nodules

These are typically palpable, asymptomatic, and nonvisible, tend to arise several weeks after injection, and frequently remain the same size until they are resorbed, treated, or removed.[9] They have been noted to occur more frequently around the hypermobile perioral and periocular regions.[10]

An incidence rate of 6% to 44% for papules/nodules with the use of PLLA was reported in early studies.[2,4,5,11-17] This frequent occurrence may have had a disproportionately large impact on the perception of PLLA safety, as each was classified as a serious AE by regulatory bodies such as the US Food and Drug Administration.[18] Currently, clinical experience has taught us that the occurrence of papules and nodules stems from suboptimal product reconstitution or placement and can be minimized if proper techniques are implemented during the preparation and injection of PLLA.[9,19] Indeed, a review of the literature confirms that these AEs occur infrequently when optimal modalities are used.[20] The simple yet critical techniques to ensure even distribution and proper placement of the implanted PLLA to maximize outcomes and minimize the occurrence of nodules are reviewed in the preceding article of this supplement[21] and again in the final article.[22]

FIGURE 1. Poly-L-lactic acid–associated nodules in the forehead from microparticles clumped in the frontalis muscle, before and after treatment with hyaluronic acid placed around the nodules in order to camouflage their appearance. Photographs courtesy of Rebecca Fitzgerald MD.



Histologically, papules and nodules consist of an overabundance of microparticles (often surrounded by skeletal muscle) surrounded by a normal foreign body reaction including foreign body giant cells.[9] It is important to note that the presence of foreign body giant cells constitutes a histopathological diagnosis of "granuloma," initially implicating these lesions to be inflammatory lesions. This implication led to early treatment of this problem with steroid injections. However, injection of steroids or anti-mitotics such as 5-fluorouracil (5-FU) have little clinical effect on these lesions because the majority of the lesion is product and not host reaction to product. Additionally, injection of steroids may lead to atrophy of adjacent tissue, actually accentuating the visibility of the nodule. Most nodules associated with PLLA injection will resolve on their own.[23] Many patients simply need reassurance that they are not dangerous, will not grow in size or number, and will resolve on their own. Excision is an option, but resolves a transient problem with a permanent scar.[23,24] Camouflage of these lesions with hyaluronic acid (HA) gel until they resolve may offer a more gratifying treatment (Figure 1).

"Most nodules associated with poly-L-lactic acid injection will resolve on their own."

Finally, the location of papules and nodules may suggest their origin. Proper dilution, reconstitution, and deep placement are critical. Superficial placement leads to visible papules. Placement in or through active muscles, particularly under the eye or near the corners of the mouth, leads to localized overcorrection and nodules (representing product trapped in muscle fibers). These may even be seen in a patient with a strong zygomaticus major muscle. Diffuse papules/nodules are likely to be an issue with reconstitution (ie, shaking the vial immediately after adding water; crystals on the sidewalls of the vial won't hydrate), inadequate hydration time (leading to in vivo hydration), or poor suspension immediately prior to injection (leading to uneven distribution of particles). Lastly, focal papules/nodules may be an issue of placement (ie, redeposition at the apex of a "fan" when using the fanning technique).

Granulomas

First, it should be noted that the term "granuloma" has been used in reference to papules and nodules as well as to large inflammatory lesions in the medical literature,[3] which has resulted in considerable challenges in the interpretation of granuloma incidence and, in turn, to the overall safety profile associated with the use of injectable products such as PLLA.[3] In contrast to the low power histopathology of a nodule showing an overabundance of product with a "normal" foreign body reaction consisting of a few foreign body giant cells, histopathology of a true granuloma shows a smaller amount of product with an overabundance of host reaction to product and "wall-to-wall" foreign body giant cells (Figure 2).[19] This is in contrast to the purposeful stimulation of a subclinical inflammation, which is, in fact, the mechanism of action of stimulatory products like PLLA, calcium hydroxyapatite, and polymethylmethacrylate. With the injection of collagen stimulators in a normal host, subclinical granulomatous inflammation is a natural and desired tissue response that follows a predictable course.[19] A form of chronic inflammation, granulomatous inflammation occurs to prevent the migration of bodies that cannot be removed by phagocytosis or enzymatic breakdown; it is histologically distinctive for its accumulation of epithelioid cells, a type of modified macrophage.[3] In a "normal" response, the encapsulation of the product and the subsequent fibroplasia is

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FIGURE 2. Nodule vs granuloma.[19] **a)** Low-power histopathology of a nodule with an overabundance of product trapped in the skeletal muscle. **b)** Low-power histopathology of a true clinical granuloma showing an overabundance of host reaction to a small amount of product. Reprinted with permission from Rebecca Fitzgerald, Danny Vleggaar. Facial volume restoration of the aging face with poly-L-lactic acid. Dermatologic Therapy, Volume 24, Pages 2-27. Copyright © 2011 Wiley Periodicals, Inc.

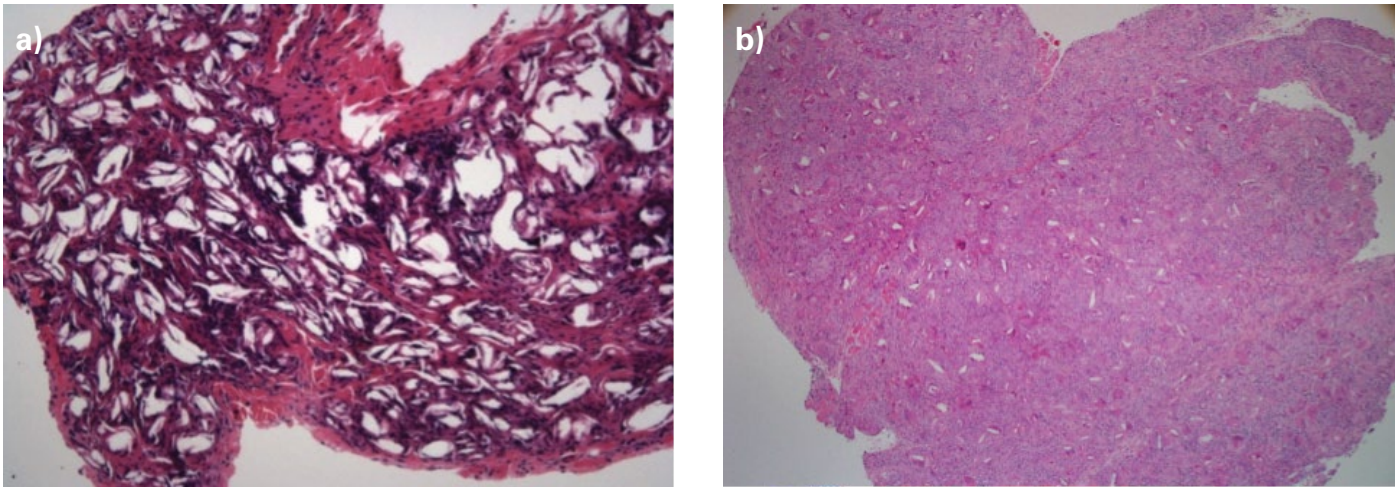

TABLE 1.

Differences Between Granulomas and Nodules[25]

	Granulomas	Nodules
Time of appearance	Suddenly, 6–24 months after injection	1–2 months after injection, after swelling vanishes
Location	At all injected sites at the same time	Single nodules, close to facial muscles, particularly in the lips
Size	Growing to the size of a bean, with skin discoloration, edema	Remain the size of a lentil or a pea
Borders	Grow fingerlike into surrounding tissue	Well confined by fibrous capsule
Persistence	If untreated, they disappear after 1–5 years	Until absorption (or permanent)
Histology	Foreign body granuloma; particles or microspheres are scattered	Foreign body reaction; particles or microspheres form aggregates
Treatment	React well to intralesional or systemic corticosteroids	Little effect from corticosteroids; must wait for absorption or excision
Cause	Still unknown	Technical error

Adapted with permission from Gottfried Lemperle, Nelly Gauthier-Hazan, Marianne Wolters, Marita Eisemann-Klein, Ute Zimmermann, David M. Duffy. Foreign body granulomas after all injectable dermal fillers: part 1. Possible causes. Plastic and Reconstructive Surgery, Volume 123, Pages 1842-1863. Copyright © 2009 by the American Society of Plastic Surgeons.

predictable in amount and volumizes the tissue to produce the desired cosmetic result.

Lemperle et al[25] have tabulated some well-defined clinical differences between true inflammatory granulomatous reactions and papules/nodules (Table 1).[25] The most striking clinical difference is that a true granulomatous reaction seems to be a systemic response (ie, the reaction is seen in all treated areas at the same time). In contrast to nodules, granulomas may become apparent months or years post-injection[9] (Table 1). They typically have poorly defined borders and may persist and grow over time, although they too are capable of spontaneous resolution.[9]

All injectable dermal fillers have the potential, in some patients, to cause a foreign body–type reaction that may develop into a granuloma.[19,24,26] However, the incidence of visible, clinically significant granulomas with injectables, including PLLA, in actual clinical practice is very low (0.01%–0.1%),[3,27,28] and their occurrence is currently unpredictable.[19] A recent review of the literature and new case reports summarized the clinical features of 56 biomaterial-induced granulomas involving oral and perioral tissues and is shown in Table 2.[28] In this review, there were 4 reports of granulomas with PLLA use, less than the number reported with silicone, collagen, HA, and acrylic hydrogel suspended in HA; however, this may reflect which of these fillers is most commonly used.[28]

TABLE 2.

Clinical Features of Biomaterial-Induced Granulomas (56 Reported Cases)[28]

Material Injected	No. of Reported Cases[a]
Silicone	18
Collagen	13
Hyaluronic acid	7
Acrylic hydrogel suspended in hyaluronic acid	6
Poly-L-lactic acid	4
Polymethylmethacrylate	2
Polytetrafluoroethylene	2
Not specified	7
Site	
Upper lip	19
Nasolabial fold	16
Lower lip	12
Cheek/buccal mucosa	9
Both lips	7
Clinical Presentation	
Single nodule	17
Diffuse swelling	15
Multiple nodules	13
Mass	6
Other	5

[a]Some patients presented with multiple lesions, multiple augmentation materials were employed, or patients underwent multiple treatment modalities. Reprinted with permission from Bruno C. Jham, Nikolaos G. Nikitakis, Mark A. Scheper, John C. Papadimitriou, Bernard A. Levy, Helen Rivera. Granulomatous foreign-body reaction involving oral and perioral tissues after injection of biomaterials: a series of 7 cases and review of the literature. Journal of Oral and Maxillofacial Surgery, Volume 67, Pages 280-285. Copyright © 2009 American Association of Oral and Maxillofacial Surgeons.

In the treatment of granulomas, surgical excision is not recommended due to their poorly defined borders and the potential for this approach to lead to fistulas, abscesses, or scars.[9] Treatment is geared toward stopping both the increased secretion of interstitial substances and the invasion of cells.[24] Approaches include the administration of steroids (intralesional, intramuscular, or systemic) with or without the coadministration of immune-modulating medications.[9] Intralesionally injected 5-fluorouracil, alone or in combination with triamcinolone acetonide or betamethasone, are among other approaches demonstrated to be highly effective (Table 3[24]; Figure 3). In addition, intense pulsed light can be a useful adjunct for the treatment of engorged capillaries.[9] Recurrence following the successful treatment and resolution of granulomas is rare.[9]

TABLE 3.

Proven Treatments for Granulomas[24]

Proven Treatment
• Triamcinolone (Kenalog, Volon-A) 20–40 mg intralesionally
• Triamcinolone (1 mg/mL) + 5-fluorouracil (50 mg/mL) intralesionally
• Prednisolone (Depo-Medrol) 20–40 mg undiluted
• Betamethasone (Diprosone) 5–7 mg intralesionally
• 1:3 Betamethasone (Diprosone) 3.5 mg + 1:3 5-fluorouracil (1.6 mL) + 1:3 lidocaine intralesionally

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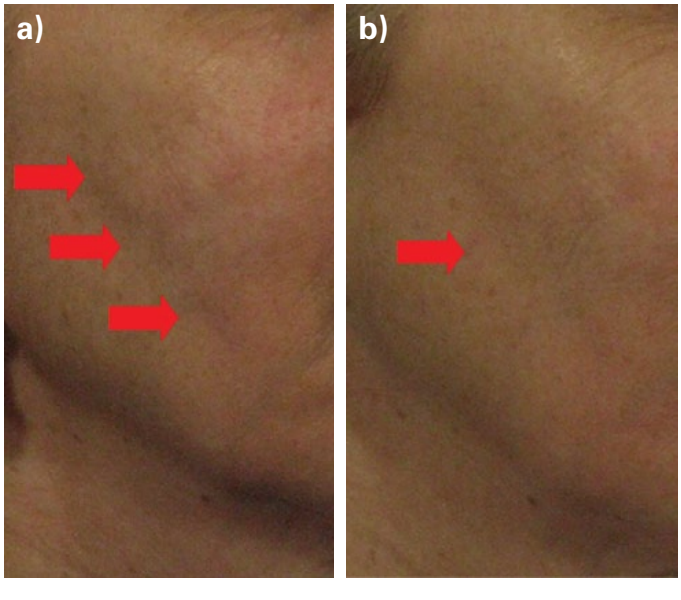
FIGURE 3. Histologically confirmed granuloma: **a)** before treatment; and **b)** after treatment with a mixture of 0.9 cc 5-fluorouracil (50 mg/mL) and 0.1 cc triamcinalone (40 mg/mL) for a total concentration of 4 mg/mL triamcinalone. One cc injected into granuloma every 2 weeks x 2 with subsequent resolution. Photographs courtesy of Rebecca Fitzgerald MD.



SUMMARY

Injection-related AEs with the use of PLLA are generally transient and typically resolve spontaneously. Most patients simply need reassurance that the AEs will resolve on their own. To summarize simply, papules and nodules represent an overabundance of product with a predictable host reaction and granulomas represent a profound overabundance of host reaction to product. The occurrence of nodules, which are generally nonvisible and asymptomatic, has been minimized through improved methodology; if desired, they can be camouflaged via the injection of HA or surgically excised.

True inflammatory granulomas are rare (incidence <0.1%) and have been reported with many currently available injectable fillers. They can be addressed clinically with injections of steroids and antimetabolites such as 5-FU and rarely recur after treatment.

DISCLOSURES

Danny Vleggaar MD has been a medical consultant for Sinclair IS Pharma, France; PharmaSwiss SA, Switzerland; Valeant Eastern Europe; and Cutanea Life Sciences, Inc. He also has been a trainer for Valeant Pharmaceuticals International, Inc./Medicis Corporation.

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Satisfying Patient Expectations With Poly-L-Lactic Acid Soft Tissue Augmentation

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ABSTRACT

Patient interest and physician use of soft tissue augmentation have increased significantly in recent years, especially among younger patients. A recent consumer survey conducted on behalf of the American Society of Plastic Surgeons found that the majority of respondents would rather have a facial injectable treatment than a surgical treatment. In another recent survey, consumers gave the highest overall satisfaction ratings to injectable filler treatments (92%), including poly-L-lactic acid (PLLA), and injectable wrinkle relaxers (92%), with injectable fillers receiving the highest "extremely satisfied" rating (45%). Long-lasting benefit is a desirable attribute in soft tissue augmentation, making PLLA a favorable alternative for many patients. When considering the use of PLLA, clinicians should ensure that their patients understand its benefit profile, and that these benefits are consistent with the patients' cosmetic goals. The implementation of the latest recommendations on methodological approaches in the use of PLLA will minimize the occurrence of adverse events, further enhancing patient satisfaction.

J Drugs Dermatol. 2014;13(suppl 4):s40-s43.

INTRODUCTION

There has been significant growth in both patient interest and physician use of soft tissue augmentation in recent years, especially among younger patients. Patients' motivation behind this increased interest is complex. Studies using digitally enhanced photographs[1] and those conducted using botulinum toxin type A injections[2] have shown that improvement in facial appearance increases overall attractiveness, reduces perceived age by up to 5 years,[2,3] and promotes a positive effect on mood[4] and self-esteem.[5]

A 2006 Harris Interactive Survey involving nearly 800 women aged 35 to 69 years, conducted on behalf of the American Society of Plastic Surgeons, found that the reasons women consider cosmetic interventions include: looking younger, improving intimate relationships, and increasing their confidence.[6] Sixty-three percent of the respondents reported that they would much rather have a facial injectable treatment than a surgical treatment. The facial signs of aging that women are most likely to be very concerned or extremely concerned about are wrinkles (44%) and sagging skin (41%).[6]

Recently, the first ever American Society for Dermatologic Surgery (ASDS) Consumer Survey on Cosmetic Dermatologic Procedures solicited feedback from over 6,300 consumers.[7] While 6.4% of those surveyed had previously had a cosmetic treatment, 53% said they were considering injectable fillers in the future.[7,8] Consumers gave the highest overall satisfaction ratings to injectable filler treatments (92%), including poly-L-lactic acid (PLLA), and injectable wrinkle relaxers (92%),[9] with injectable fillers receiving the highest "extremely satisfied" rating (45%).[7]

Another study conducted by the ASDS found that among women considering using medical anti-aging treatments, 89% and 75% would prefer gradual results lasting 2 years, compared with immediate results lasting 6 months or 1 year, respectively (Figure 1).[10] It is interesting to note that long-lasting effects were more important than cost as a factor in treatment decisions, particularly among women who had already used an injectable product.[10]

To optimize outcomes, cosmetic treatment must be tailored for each patient; communication is thus paramount. Clinicians need to understand their patients' treatment goals, including areas for correction and the desired timeframe for cosmetic benefit.[11] The cosmetic deficits of patients considered for PLLA should match its benefit profile of increased soft tissue volume. If PLLA is agreed upon, patients should be educated on the nature of their underlying deficits (eg, volume depletion), the gradual onset of cosmetic improvement, the need for multiple sessions, and the long-lasting benefits of the approach.[11] Clinicians should also take measures to minimize the occurrence of adverse events, such as nodule formation, through the implementation of the latest recommendations on methodological approaches.[11,12]

There is a growing trend in the use of injectable dermal fillers for soft tissue augmentation in patients 35 to 50 years of age (Figure 2)[11]; in fact, in 2012, about 75% of respondents receiving

FIGURE 1. Paired comparison analysis of factors impacting women's medical anti-aging treatment decisions.[10] Adapted with permission from Susan Weinkle, Mary Lupo. Attitudes, awareness, and usage of medical antiaging treatments: results of a patient survey.The Journal of Clinical and Aesthetic Dermatology. 2010;3(9):30-33. Copyright © 2010 Matrix Medical Communications. All rights reserved.

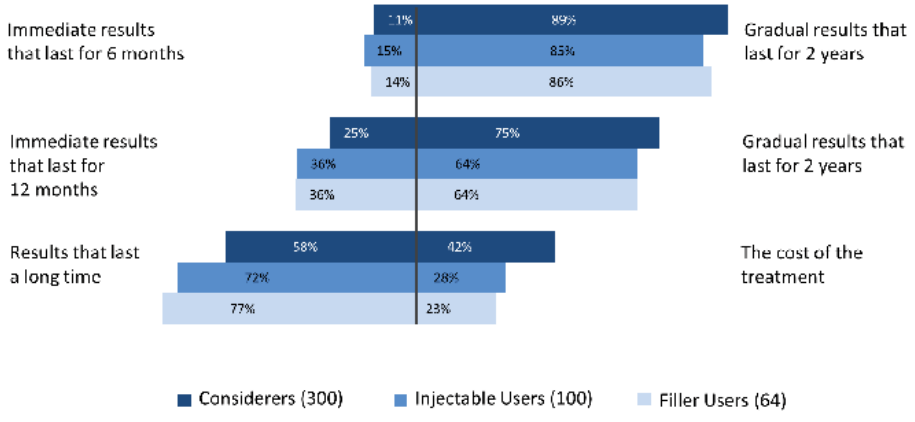
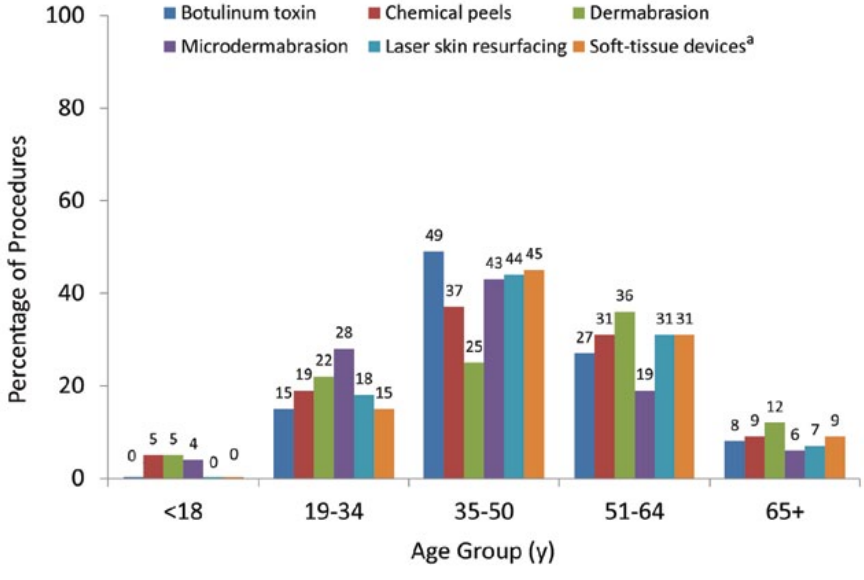


FIGURE 2. Use of cosmetic procedures across different age groups.[11] Reprinted with permission from Stephen H. Mandy. Satisfying patient expectations with soft-tissue augmentation. Dermatology Online Journal, Volume 15, Pages 1-16. Copyright © 2009.



[a]Soft-tissue devices include autologous fat, calcium hydroxylapatite, bovine-derived and human-derived collagen, hyaluronic acid, and poly-L-lactic acid.

PLLA were 54 years of age or younger.[13] In light of this trend, it may behoove the clinician who has limited experience with the use of PLLA to begin with a younger patient. The selection of a younger patient, with less complex cosmetic deficits, may result in greater patient satisfaction, with the added benefit of increasing the familiarity and comfort level of the practitioner.

Studies Reporting on Patient Satisfaction With Poly-L-Lactic Acid for Soft Tissue Augmentation

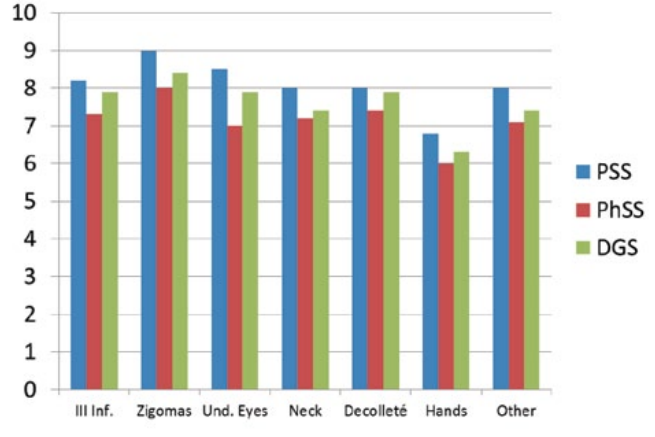
There are several published studies and surveys on the use of PLLA in soft tissue augmentation in non-HIV patients that included patient satisfaction as an endpoint.[14-22]

The largest such study included 2,131 patients, 95.9% of whom were seeking cosmetic augmentation.[14] Treatment satisfaction was based on patient-physician discussions and aided by a retrospective review of photographs taken during and at the conclusion of the treatment. Approximately 95% of patients were satisfied with the achieved cosmetic result.[14]

In a large retrospective case history review of 568 patients receiving PLLA for cosmetic problems, patient and physician satisfaction were scored on a scale of 1 to 10.[15] A Definitive Graduated Score (DGS) was also calculated using both photographic results and the average patient/physician scores. Overall, the

DGS averaged 7.6 (range, 6.3-8.4 depending on area treated), with average patient satisfaction scores higher than those of physicians (Figure 3).[15] The most favorable results were achieved from treatments to the cheekbones and malar areas.[15]

FIGURE 3. Average patient and physician satisfaction scores with poly-L-lactic acid, with definitive graduated scores, stratified by facial region.[15] Reprinted with permission from Alessio Redaelli, Riccardo Forte. Cosmetic use of polylactic acid: report of 568 patients. Journal of Cosmetic Dermatology, Volume 8, Pages 239-248. Copyright © 2009 Wiley Periodicals, Inc.



DGS, Definitive graduated score; III Inf, lower third of the face; PhSS, physician satisfaction score; PSS, patient satisfaction score; Und, under.

In a retrospective survey, 130 respondents who received PLLA for cosmetic enhancement across a 5-year period rated the results of their treatment.[16] Although not stratified by duration since treatment, 55% of patients overall indicated that they had "good" or "excellent" correction of their cosmetic issues. Patient assessment correlated roughly to the number of treatment sessions, with 75% of patients having 5 or more sessions reporting at least "good" correction.[16] In another retrospective survey with 40 respondents who had been treated with PLLA for facial atrophy, 80% of patients were satisfied with their cosmetic outcome (*P*=.0001) in relation to their expectations prior to treatment.[17]

In a study that included both non-HIV (n=38) and HIV (n=27) patients, satisfaction with PLLA was assessed on a 5-point scale.[18] Ninety-one percent of patients overall, and 89.5% of the non-HIV patients seeking cosmetic enhancement, were "very satisfied" with their treatment at study end. In a 3-year follow-up investigation, satisfaction with PLLA proved durable; 86% of non-HIV patients (n=35) remained "very satisfied" or "somewhat satisfied" with the results of their treatment.[19]

A small study investigated the satisfaction of women treated with PLLA for sunken nasolabial folds.[20] Each patient received 1 injection per month for 3 consecutive months. Patient satisfaction was assessed on a 4-point scale at each application, at 6 months, and 36 months after treatment. After 6 months, 60% of patients initially indicated that they were "satisfied" or "very satisfied" with the results, but this increased to 80% when the patients were shown the clinical photographs of their improvement. Even 3 years after their injections, 60% of patients remained at least "satisfied."[20]

In a study in which 36 patients with varying degrees of cutaneous aging in the neck and chest (presternal area) were treated with PLLA, 92% indicated that they were pleased with the results and would choose to do it again.[21] Those patients treated in the presternal region reported optimal improvement and high satisfaction.[21]

"To optimize outcomes, cosmetic treatment must be tailored for each patient; communication is thus paramount."

SUMMARY

Patients seek cosmetic enhancement for a number of reasons and soft tissue augmentation is increasingly viewed as an attractive option, especially among younger patients. Long-lasting benefit is a desirable attribute, making PLLA a favorable alternative for many patients. A high level of patient satisfaction with PLLA has been established in a rigorous series of clinical studies and surveys.

To improve the likelihood of satisfaction with PLLA treatment for individual patients, it is important for clinicians to select patients appropriately, have a firm grasp on their cosmetic goals, and calibrate their expectations regarding its benefit profile.[12] Clinicians should take every measure to minimize adverse events, and for those with little prior PLLA experience, selection of a younger patient with a less complex array of cosmetic deficits may enhance patient satisfaction, as well as afford clinicians the opportunity to increase their experience and comfort level.

DISCLOSURES

Danny Vleggaar MD has been a medical consultant for Sinclair IS Pharma, France; PharmaSwiss SA, Switzerland; Valeant Eastern Europe; and Cutanea Life Sciences, Inc. He also has been a trainer for Valeant Pharmaceuticals International, Inc./Medicis Corporation.

Rebecca Fitzgerald MD has been a consultant and speaker for Valeant Pharmaceuticals North America LLC/Medicis Corporation; Merz Aesthetic, Inc; and Allergan USA, Inc.

Z. Paul Lorenc MD has been a consultant for Johnson & Johnson; La Lumiere, LLC; Medicis Corporation; Merz Corporation; and Mentor Corporation. In addition, he holds the following

patents: US Patent 5/611,814–Resorbable Surgical Appliance for Use in Supporting Soft Tissue in a Superior Position; US Patent 60/950,423–Composition and Method of Use for Soft Tissue Augmentation/Drug Delivery; US Patent 12/797,710–Method for Measuring Change in Lip Size After Augmentation; and US Patent 13/604,012–Light Therapy Platform System.

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Consensus Recommendations on the Use of Injectable Poly-L-Lactic Acid for Facial and Nonfacial Volumization

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ABSTRACT

Poly-L-lactic acid (PLLA) was approved for use in Europe in 1999. In the United States, it was approved by the Food and Drug Administration in 2004 for the treatment of facial lipoatrophy associated with human immunodeficiency virus, and in 2009 for cosmetic indications in immune-competent patients. The need for consistent, effective PLLA usage recommendations is heightened by an increased consumer demand for soft tissue augmentation and a shift toward a younger demographic. Over the past 14 years, considerable experience has been gained with this agent, and we have come to better understand the clinical, technical, and mechanistic aspects of PLLA use that need to be considered to optimize patient outcomes. These consensus recommendations regarding patient selection, proper preparation and storage, optimal injection techniques, and other practical considerations reflect the body of evidence in the medical literature, as well as the collective experience of this author group.

J Drugs Dermatol. 2014;13(suppl 4):s44-s51.

INTRODUCTION

Poly-L-lactic acid (PLLA) was approved for use in Europe in 1999. In the United States, it was approved by the Food and Drug Administration in 2004 for the treatment of facial lipoatrophy associated with human immunodeficiency virus (HIV),[1] and in 2009 for cosmetic indications in immune-competent patients.[2] Over the past 14 years, considerable experience has been gained with PLLA; and its safe and effective use has been well documented.[3-24]

The need for consistent, effective usage recommendations is heightened by an increased consumer demand for soft tissue augmentation, and a shift toward a younger demographic that may have a lower tolerability for adverse events.[25,26] The demonstrated preference of patients for gradual, long-lasting effects[27,28] is well matched to the mechanism of action of PLLA,[7,29-31] which provides distinct clinical advantages over other available options, including cosmetic benefits lasting 2 years or more.[1,29]

Our detailed review of the literature reveals that most of the early problems encountered with PLLA resulted from suboptimal methodology, including inadequate reconstitution volumes, short hydration times, injection of large volumes of highly concentrated product with short intervals between treatments, and injection into the dermis and in locations that were not optimally chosen vis-à-vis its mechanism of action.[5,6,9,12,18,32] As clinical experience has grown, we have come to better understand the technical and mechanistic aspects of PLLA use that need to be considered to optimize patient outcomes (Table 1). With this enhanced understanding, PLLA utilization can now achieve predictable cosmetic benefits that are completely controlled by the treating clinician.

The consensus recommendations that follow reflect the body of evidence in the medical literature, as well as the collective experience of this author group, each of whom have more than a decade of experience in the clinical utilization of PLLA.

Patient Selection

As with all cosmetic procedures, it is important that there be clear communication between physician and patient (Table 1). In addition, patients should be well matched to the mechanism of action and clinical effects of the treatment.

- Patients should have realistic treatment goals, be educated on aging-associated volume loss and the gradual nature of PLLA cosmetic benefits, and understand the need for multiple treatment sessions and periodic maintenance for an enduring effect.
- Experience with facial augmentation has taught us that patients with very empty faces or those with a very elastotic outer skin envelope may be challenging to volumize, requiring a substantial amount of product, any product, to achieve a desirable result. This should be expected in this patient population and discussed prior to any filler treatment to prevent unnecessary frustration on the part of both the patient and the physician.
- Patients are starting cosmetic treatments earlier than they have traditionally done. The 2012 American Society of Plastic Surgeons statistics revealed that 66% of cosmetic patients are now between the ages of 30 and 54, while only 26% are age 55 or older. This younger group often needs less product and fewer treatment sessions than the older group, and is gratifying to treat.[33]
- Patients with permanent fillers, or active auto-immune or connective tissue disease (eg, multiple sclerosis, lupus) may be less predictable hosts.
- Active granulomatous disease should be considered a contraindication to PLLA use.

Poly-L-Lactic Acid Preparation and Storage

Recommendations on the preparation and storage of PLLA focus on ensuring complete and homogenous dispersion and hydration of PLLA in sterile water for injection (SWFI) or bacteriostatic water, in a volume that facilitates injection (Table 2).

- Reconstitution/Dilution
  - Prior to reconstitution, tap the vial to ensure there is no powder sticking to the top of the vial or rubber stopper.
  - Use an antiseptic to clean the rubber stopper.
  - Add 7–8 mL SWFI or bacteriostatic water slowly to the powder.
    - Dilution in this volume range leads to:
      - Even PLLA distribution.
      - Easier injection, with reduced risk of needle blockage.
      - Decreased incidence of papules and nodules.
- Hydration
  - Hydrate at room temperature for ≥24 hours.
    - Adequate powder hydration allows the avoidance of injecting dry PLLA microclumps, which will hydrate in vivo and potentially lead to nodule formation.
  - Do NOT shake the vial during hydration.
    - Shaking can result in the deposition of dry PLLA clumps on the vial wall.
- Storage of reconstituted PLLA
  - Prior to use, reconstituted PLLA can be stored for up to:
    - 48 hours at room temperature.
    - 3–4 weeks in a refrigerator (4°C) [with bacteriostatic water]

Final Poly-L-Lactic Acid Preparation

Final steps prior to injection should ensure a hygienic approach and a smooth injection process.

- Patient/Clinician (Table 1)
  - Patients should wash their face with soap and water.
  - The clinician should wipe the areas for injection with chlorhexidine/alcohol immediately prior to injection to reduce risk of infection or biofilm formation.
- PLLA preparation
  - Warm the PLLA solution to room temperature (if stored at 4°C).
  - Dilute to final injection volume.
    - For facial injections, a final dilution of 9 mL is recommended, and may be achieved by the addition of 1–2 mL lidocaine (with or without epinephrine).
    - For décolletage injections, a final dilution of 11–16 mL is recommended, and may be achieved by further dilution with addition al SWFI or bacteriostatic water and 1–2 mL lidocaine (with or without epinephrine).
  - Ensure product is evenly suspended by slowly rolling the vial; do not shake. Shaking can create foam, which may clog the needle.

Poly-L-Lactic Acid Injection and Aftercare

Key factors in the utilization of PLLA include site selection (Table 1); injection depth, quantity, and frequency; and aftercare, as well as other practical considerations (Table 3).

Injection Site Selection

Injection sites associated with the most favorable outcomes are dynamically stable, with sufficient dermal thickness to allow a proper depth of injection.

TABLE 1.

Optimizing Results With Poly-L-Lactic Acid

Category	Tip
Patient Interactions	• Reinforce the goals of PLLA use (eg, deep, global volumization), as compared with other treatments. • Use diagrams to demonstrate expected cosmetic changes. • Calibrate expectations regarding the gradual nature of the cosmetic enhancement. • Document cosmetic changes with photographs (at baseline and each subsequent visit).
Product Handling	• Warm PLLA to body temperature before injection to facilitate injection. • Avoid agitation immediately prior to injection to decrease risk of clogging. • If foaming is an issue, remove the rubber stopper and slowly draw product out of the vial.
Injection Techniques	• Understand facial anatomy to avoid injection in or too close to blood vessels. • Apply a thin, uniform coating to entire surface of the treatment region. • Treat, wait, and assess; avoid over-application within a single session to decrease risk of overcorrection.

PLLA, poly-L-lactic acid

TABLE 2.

Poly-L-Lactic Acid Preparation and Storage

Step	Recommendations
Reconstitution/Dilution	• Ensure there is no powder sticking to the top of the vial or rubber stopper. • Use an antiseptic to clean the rubber stopper. • Slowly add 7–8 mL sterile water for injection or bacteriostatic water.
Hydration	• Hydrate at room temperature for ≥24 hours. • Do NOT shake the vial during hydration.
Storage of Reconstituted Poly-L-Lactic Acid	• 48 hours at room temperature. • 3–4 weeks in a refrigerator (4°C).
Final Injection Volume for Facial Treatment	• 9 mL, achieved by the addition of 1–2 mL lidocaine (with or without epinephrine) immediately prior to injection.
Final Injection Volume for Décolletage Treatment	• 11–16 mL, achieved by further dilution with additional SWFI or bacteriostatic water and 1–2 mL lidocaine (with or without epinephrine) immediately prior to injection.

SWFI, sterile water for injection.

TABLE 3.

Practical Considerations for Poly-L-Lactic Acid Injection

- The viscosity of PLLA is very low compared with hyaluronic acid gel; therefore, caution should be exercised to avoid inadvertent overcorrection.
- A 25-gauge, 1.5-inch needle is recommended for PLLA injection; the syringe needle should be primed prior to injection.
    - o A 22-gauge, 50-mm cannula may also be considered.
- Excessive foam in the syringe may lead to needle clogging; this may be addressed by removing the needle from the syringe and pushing the plunger until the foam is expelled through the syringe hub. A new needle can then be attached.
- Any product remaining after a patient's session should be discarded.

PLLA, poly-L-lactic acid.

- The authors have achieved optimal results in the following areas:
  - Temporal fossa
  - Malar/submalar areas
  - Chin and mandible
  - Décolletage
- Potentially problematic areas include:
  - Areas of hyperdynamic muscle movement (eg, perioral and periocular regions)
    - This may lead to microparticle clumping, localized overcorrection, and nodules/papules.
  - Neck and hands
    - The thin skin in these areas requires superficial injections, increasing the possibility of nodule and papule formation.

Injection Techniques

Favorable injection techniques allow slow, safe, uniform dispersion of PLLA at the proper depth for optimal cosmetic benefit.

General considerations include:

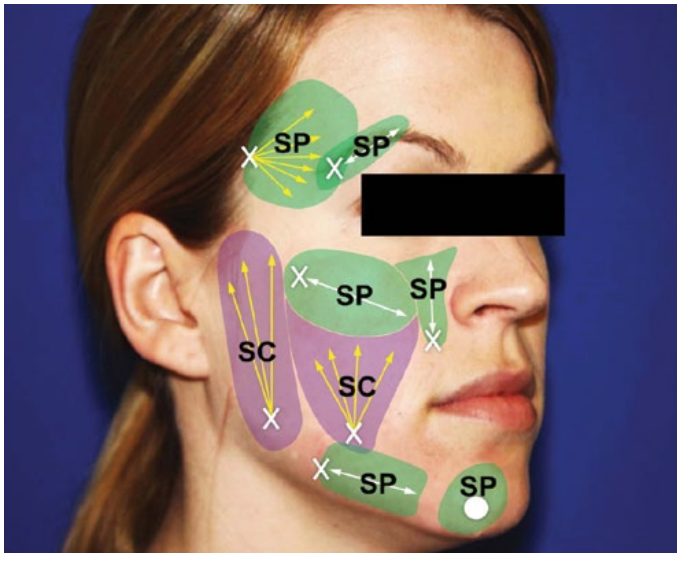
- Injection should be into the subcutaneous or supraperiosteal plane.
  - Superficial injection (ie, into the dermis) should be avoided, as this may lead to visible neocollagenesis.
- A reflux maneuver should be performed routinely to eliminate any risk of inadvertent intravascular injection.
- Injection should be performed slowly.
- If the needle clogs, it should be removed and the foam pushed out of the syringe hub. A new needle should then be affixed and primed prior to injection.
- Injection technique can generally be selected based on the experience and comfort level of the clinician, with consideration given to the anatomic area being treated (see below).
  - A cross-hatch pattern should be considered, especially while becoming familiar with PLLA.
  - With more experience, fanning, cross-fanning, and depot approaches are also commonly utilized.
    - Fanning has the advantage of fewer needle sticks; however, vigilance is required to avoid multiple deposits at the apex of the fan.

Site-specific recommendations on the injection of PLLA for facial soft tissue augmentation include (Figure 1)[34]:

- Medial cheek/Mid-face
  - Inject supraperiosteally over the zygoma, maxilla, and canine fossa/pyriform aperture.
  - Inject into the deep subcutaneous plane in the submalar/mid-cheek, where bony background is absent.
- Lateral face
  - Inject in the superficial subcutaneous fat above the parotid gland and masseter muscle.

FIGURE 1. Site-specific recommendations for the injection of poly-L-lactic acid (PLLA).[34]

- Potential areas amenable to correction with PLLA are indicated on this model. Recommended points of entry for each anatomic site are marked with a white X.
- Injectable PLLA should be placed supraperiosteally in the temples, lateral brow, zygomatic area, maxillary area, mandibular area, and mental area (green areas marked with "SP").
- Injectable PLLA should be placed in the subcutaneous fat in the mid-cheek regions and preauricular area (purple areas marked with "SC").
- Depending on the anatomic area, recommended techniques include fanning (yellow arrows), retrograde linear threading (white arrows), or depot (white circle) injection.



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- Mandible/Chin
  - Inject supraperiosteally over the menton, pre-jowl sulcus, and antegonial notch
- Temporal fossa/Lateral brow
  - Inject supraperiosteally at the origin of the temporal muscle.
  - Inject supraperiosteally at the tail of the brow.
- Periorbital supraperiosteal injections approached through the orbicularis oculi muscle should be avoided.
  - This approach may lead to papule formation, perhaps resulting from extrusion of PLLA along the needle tract during muscular contraction.

Injection Quantity and Frequency

- The amount of surface area to be treated is the sole determinant of the amount of PLLA used during a session.
  - The vast majority (~98%) of patients should receive 1-2 vials per session if treating the whole face (0.5–1 vial per side).
    - Up to 3 vials may be required for a patient requiring treatment over a very large surface area.

- A uniform distribution of product should be ensured for each treated region (ie, coat the region); injection should not vary by particular focal areas or based on specific cosmetic deficits.
- The final volumetric correction is determined by the number of treatment sessions.
- Treatment can continue until the patient is satisfied with the results.
    - Most experts find 3–5 sessions to be optimal.
    - Younger or fuller faces need less product and fewer sessions.
- An interval of at least 4 weeks between sessions is recommended.
- Subsequent courses of treatment (ie, "top-up" courses) typically occur 2 years after the initial course.
    - During these courses, less PLLA per session, and a fewer number of sessions, are generally required.
    - Some patients prefer once-a-year, single-session maintenance treatments to keep pace with the aging process.

Post-treatment Massage

- Although data to support post-treatment massage are limited, massaging the injected area for a few minutes after treatment is recommended.
- Continued self-massage by patients may be left to the discretion of the treating physician.

"As clinical experience has grown, we have come to better understand the technical and mechanistic aspects of poly-L-lactic acid use that need to be considered to optimize patient outcomes."

SUMMARY

These recommendations are consistent with the authors' perspectives on "best practices" with the use of PLLA for soft tissue augmentation. It is our hope that these recommendations will both increase clinicians' confidence in the use of this agent and lead to predictable, consistent, and favorable outcomes across the range of patients seeking cosmetic enhancement.

Facial Volumization With Poly-L-Lactic Acid: Representative Results

Due to an increasing societal emphasis on the importance of a youthful appearance, as well as the development of new treatment options, there is a rising consumer demand for procedures that can reverse the signs of aging. For many patients with facial volume loss, poly-L-lactic acid (PLLA) is an excellent treatment choice. Its mechanism of action results in cosmetic effects that have a gradual onset and last 2 years or more, which is well-matched with reported patient preference for durable benefits. Refined PLLA methodology, along with a better understanding of the structures in the aging face and how they interrelate, now allows for favorable and predictable results across a range of patient types.[31]

In the above consensus recommendations, we detail procedures for the proper administration and aftercare of PLLA including: careful patient selection and education, proper preparation and storage, optimal injection techniques, and after-injection massage. Here, we provide some representative before-and-after photographs of several of our patients, which illustrate how the implementation of these recommendations during PLLA soft tissue augmentation can replace lost facial volume and sustain this restoration.

Figure 2 shows a 34-year-old patient before and after her PLLA therapy, with injected areas indicated. Figure 3 demonstrates the progression of PLLA enhancement in a 38-year-old female patient at 6 months and 1 year after beginning therapy. In Figure 4, a 30-year-old female patient is shown at baseline, 2 months, and 2 years after PLLA therapy was initiated. In this patient, PLLA was injected in the supraperiosteal space to enhance the jaw line.

FIGURE 2. Thirty-four-year-old female patient with early signs of facial volume loss. The image on the left **a)** shows the patient prior to beginning poly-L-lactic acid (PLLA) therapy. The image on the right **b)** was taken 5 months after the initial PLLA injection session. One vial of PLLA was injected monthly at 3 sessions (3 vials total). Injection areas included the temple, cheek, preauricular area, pyriform fossa, and marionette line/chin area. Photographs courtesy of Melanie D. Palm MD MBA.

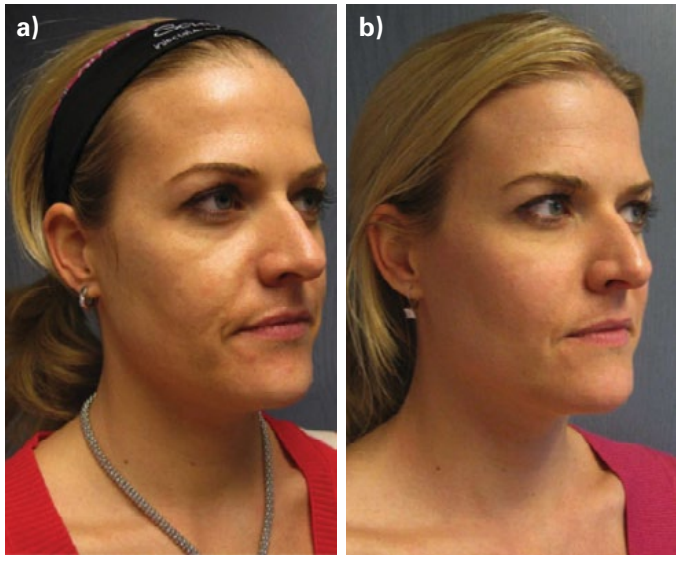

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FIGURE 3. The progression of the restoration of facial volume loss and correction of facial asymmetry with poly-L-lactic acid (PLLA) injections in a 38-year-old female patient. This patient had 3 sessions of PLLA injections, 2 vials per session, spaced 1 month apart. The first photograph **a)** shows the patient before the administration of PLLA, and the "after" photographs show the results at **b)** 6 months and **c)** 1 year after beginning therapy. Photographs courtesy of Rebecca Fitzgerald MD.

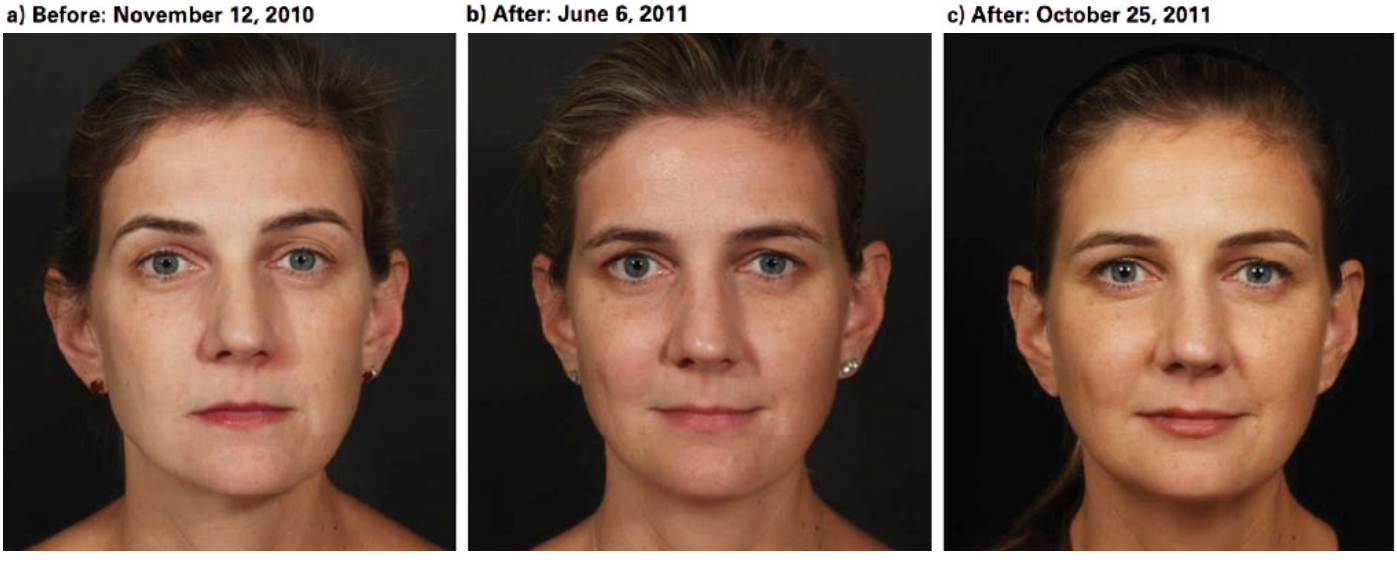
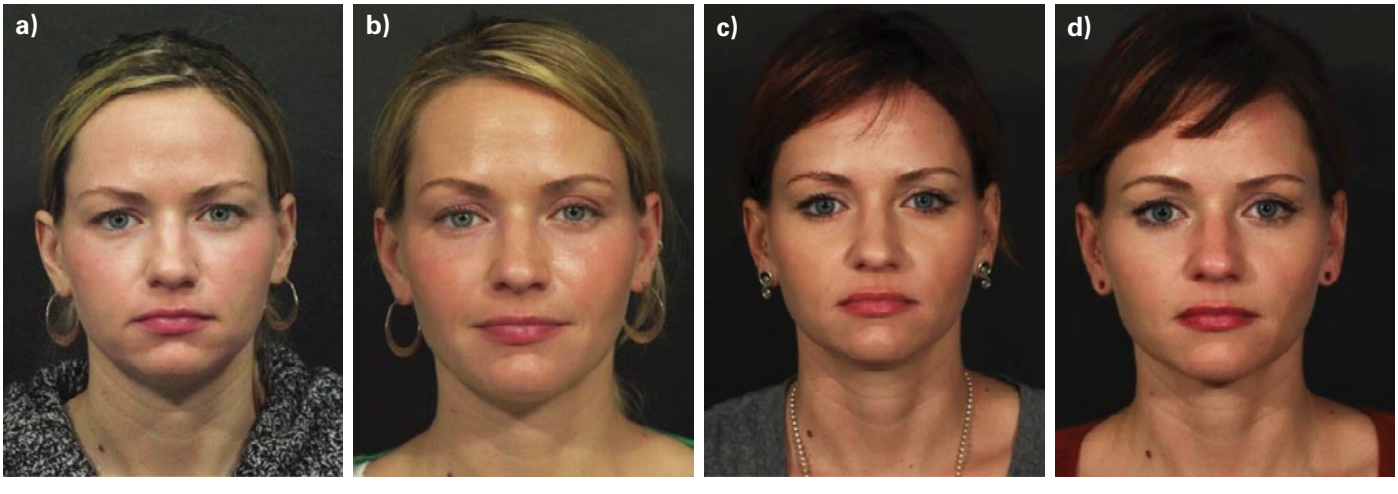


FIGURE 4. These are photographs of a 30-year-old female patient treated with poly-L-lactic acid (PLLA), 2 vials/session, 2 sessions spaced 1 month apart over a period of 29 months. **a)** Baseline; **b)** 3 months after treatment was initiated; **c)** 27 months after initial treatment; and **d)** 1 month following touch-up with 1 vial of PLLA. The patient received no other treatment. Note the brow elevation and change in the perioral area with supraperiosteal injections along the supraorbital rim, zygoma, maxilla, and mandible. Photographs courtesy of Rebecca Fitzgerald MD.



DISCLOSURES

Danny Vleggaar MD has been a medical consultant for Sinclair IS Pharma, France; PharmaSwiss SA, Switzerland; Valeant Eastern Europe; and Cutanea Life Sciences, Inc. He also has been a trainer for Valeant Pharmaceuticals International, Inc./Medicis Corporation.

Rebecca Fitzgerald MD has been a consultant and speaker for Valeant Pharmaceuticals North America LLC/Medicis Corporation; Merz Aesthetic, Inc; and Allergan USA, Inc.

Z. Paul Lorenc MD FACS has been a consultant for Johnson & Johnson; La Lumiere, LLC; Medicis Corporation; Merz Corporation; and Mentor Corporation. In addition, he holds the following patents: US Patent 5/611,814–Resorbable Surgical Appliance for Use in Supporting Soft Tissue in a Superior Position; US Patent 60/950,423–Composition and Method of Use for SoftTissue Augmentation/Drug Delivery; US Patent 12/797,710–Method for Measuring Change in Lip Size After Augmentation; and US Patent 13/604,012–Light Therapy Platform System.

J. Todd Andrews MD has been a medical consultant for Sinclair IS Pharma, France. He has also been a consultant and trainer for Valeant Pharmaceuticals North America LLC/ Medicis Corporation, and Allergan USA, Inc.

Kimberly J. Butterwick MD has served as an Advisory Board member for Allergan, Inc. and has received honoraria as a consultant for Allergan, Inc., Merz Corporation, and Valeant Pharmaceuticals International, Inc.

Jody A. Comstock, MD has been a physician trainer, speaker, and consultant for Allergan, Inc., Lumenis, and Valeant Pharmaceuticals International, Inc. He has also been a speaker and consultant for Obagi Medical Products, Inc., a division of Valeant Pharmaceuticals North America LLC and SkinCeuticals International.

C. William Hanke MD has served as a consultant for and has received clinical research grants from Valeant Pharmaceuticals International, Inc. to conduct studies on poly-L-lactic acid.

T. Gerald O'Daniel MD FACS serves as a physician trainer for Sculptra for Valeant Pharmaceuticals International, Inc.; he receives no support or financial assistance. He has no other relationships to disclose.

Melanie D. Palm MD MBA has served as a physician trainer, speaker, and consultant for Valeant Pharmaceuticals.

Wendy E. Roberts MD has served as a consultant, speaker, and Advisory Board member for and has received honoraria from: Allergan Medical, Allergan Cosmetic, Kythera Biopharmaceuticals, La Roche-Posay, L'Oréal, MELA Sciences, NeoStrata Company, SkinMedica, Top MD, Theraplex, and Valeant Pharmaceuticals International, Inc.

Neil Sadick MD has received research grants from Allergan, Inc. and Valeant Pharmaceuticals North America LLC, and is a member of the Advisory Board for Merz Pharmaceuticals and Valeant Pharmaceuticals North America LLC.

Craig F. Teller MD has conducted research for Allergan, Inc. and Amgen Inc., and has received consultant honoraria from and served as a member of the Advisory Board and/or Speakers' Bureau for AbbVie Inc., Allergan, Inc., Amgen Inc., Celgene Corporation, Merz Corporation, Taro Pharmaceuticals U.S.A., Inc., and Valeant Pharmaceuticals International, Inc./Medicis Corporation.

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