Supplement

Physiochemical Characteristics of Poly-L-Lactic Acid (PLLA)

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Abstract

Poly-L-lactic acid (PLLA) is a synthetic, biocompatible, biodegradable polymer. For soft-tissue augmentation, the size and chemical attributes of the PLLA microparticles are central to this agent's ability to promote a subclinical inflammatory response that stimulates deposition of collagen in the extracellular matrix. The resultant restoration of facial volume occurs in a controlled, predictable manner and is long lasting. The unique physiochemical and biostimulatory properties of PLLA differentiate it from other available treatments and are the foundation of the unique treatment methodology required for optimal results.

Editorial Decision date: January 10, 2018.

Poly-L-lactic acid (PLLA) is has been safely used in an array of clinical applications for over 30 years including dissolvable sutures, intrabone implants, and soft-tissue implants. It was first introduced as an agent for "facial filling" of lipotrophic HIV patients in 2004,[1] after having been available in Europe since 1999. In the years since its initial US approval in this difficult-to-treat population, clinical experience has led to development of treatment strategies that minimize the incidence of adverse events observed in the initial clinical trials.[2] Technical advances, coupled with an improved understanding of the contribution of volume loss to facial aging,[2] has led to the emergence of PLLA as a safe and effective treatment for the volume loss that is known to lead to a sagging or deflated appearance,[3] one of the hallmarks of facial aging. Soft-tissue augmentation is an option in facial rejuvenation that has grown considerably in popularity, as it is an efficient means to correct volume loss and is minimally invasive.[4] When assessing patients for whom revolumization with fillers is appropriate, the physiochemical properties of each treatment option should be considered to inform treatment selection. Here, the physiochemical characteristics that differentiate PLLA from hyaluronic acid (HA) fillers, as well as other biostimulatory agents such as calcium hydroxyapatite (CaHA) and polymethyl-methacrylate (PMMA), are reviewed.

PLLA Composition and Biostimulatory Properties

PLLA is a biocompatible, biodegradable synthetic polymer that is safely degraded along the same metabolic pathway as lactic acid. PLLA microparticles are able to stimulate subclinical inflammation in the host, which in turn promotes collagen synthesis. Over the course of treatment, which may include several sessions, the controlled and gradual deposition of collagen provides a natural-looking outcome desired by patients.

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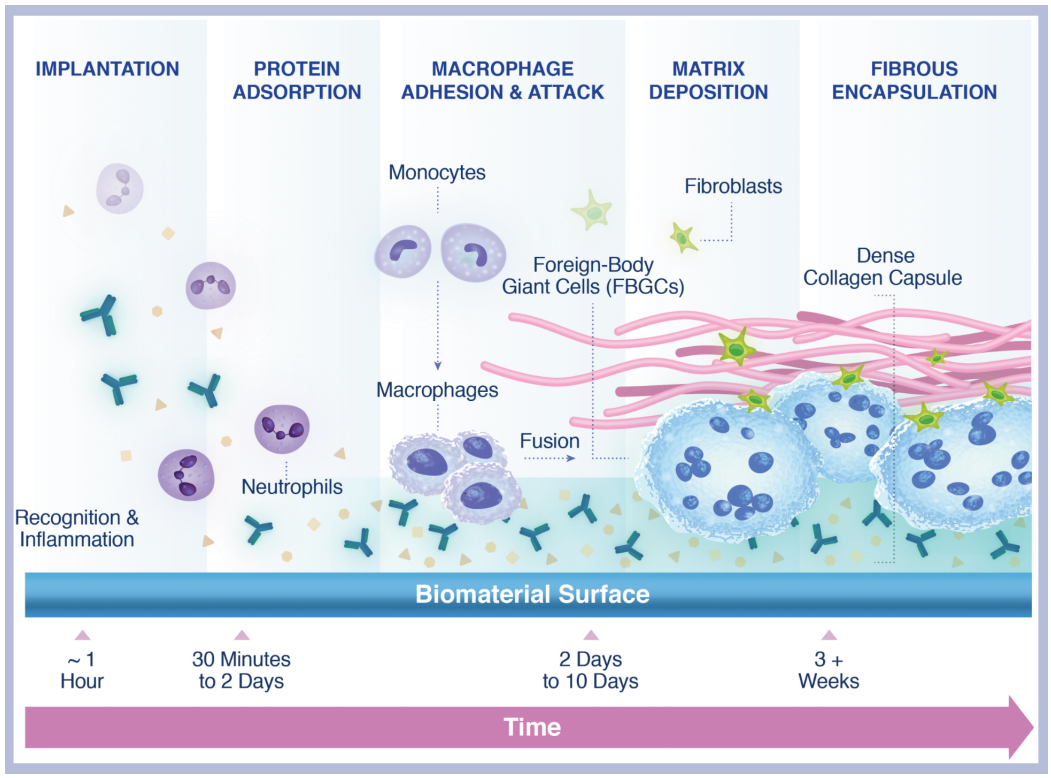

Figure 1. Foreign body reaction to a biomaterial (figure provided by X-Medica, LLC, Alpharetta, GA).

When used as an injectable implant for soft-tissue volumization, PLLA is supplied as a lyophilized powder, which includes PLLA microparticles, carboxymethylcellulose, and nonpyrogenic mannitol.[5] Following reconstitution with sterile water and appropriate hydration time, the hydrocolloid suspension can be easily injected into the appropriate area.

The PLLA microparticles measure between 40 and 63 µm in diameter. This particle size ensures that the particles are large enough to avoid phagocytosis by dermal macrophages or passage through capillary walls, but small enough to be easily injected by needles as fine as 26 gauge.[6,7]

PLLA Mechanism of Action

Once injected, the PLLA microparticles elicit a subclinical foreign body inflammatory response, resulting in encapsulation of the microparticle, followed by fibroplasia and resultant collagen type I deposition in the extracellular matrix (Figure 1).[8] The course of collagen stimulation following injection with PLLA has been explored both in animal models and in human studies,[6,9-11] and preclinical studies with animal models mirror and support the findings of subsequent human studies.[9,10] Both preclinical and human studies of tissue response to PLLA illustrate a waning inflammatory response, PLLA degradation, and collagen accumulation over time.[6] Protein adsorption occurs immediately following injection, followed by infiltration by neutrophils and then macrophages (Figure 1).[8]

Though an increase in volume may be visible in the patient's face immediately following injection, this is due to mechanical distention from the suspension of the microparticles and resolves within several hours to a few days. The degree of distention may be used as an approximation of how the patient will appear following ~3 treatments, allowing for a prediction of the number of treatments that will be required to achieve the desired results.[2] Within 3 weeks, the microparticles are encapsulated, and at 1 month postinjection, PLLA microparticles are surrounded by mast cells, mononuclear macrophages, foreign body cells, and lymphocytes.[9] At 3 months, the waning of the inflammatory response is indicated by the reduction in cell number. At this time, an increase in the number of collagen fibers is also apparent.[12] At 6 months, the number of macrophages and fibrocytes continues to dwindle as collagen production continues to increase. At this 6-month mark, the inflammatory response has returned to baseline.[13] Significant increases in type I collagen are observed around the periphery of the PLLA encapsulation up to between 8 and 24 months postinjection, as collagenesis continues,[6] and more recent work has demonstrated the presence of type III collagen adjacent to the PLLA particles.[11] Over the course of 9 months, the PLLA microparticles are degraded,

with a 6%, 32%, and 58% reduction at 1, 3, and 6 months, respectively, and are metabolized by the same metabolic pathway as lactic acid.[9]

PLLA Physiochemical Properties

Over the last decade, an appreciation for how the physiochemical properties of all fillers, including collagen stimulators, are tied to their clinical performance has been in a state of constant evolution and refinement. The chemical properties, such as pH, charge, or affinity for water, and physical properties, such as size, shape, texture, and surface area, of the intact product (as well as its degraded form) contribute to the performance of any biomaterial.[14] With HA fillers, differing rheologic characteristics may make one product well suited for deep placement, while another may have more utility as a superficially placed "line filler."

With biostimulatory products, refinement of particle size in the development of first-to-market PMMA-based collagen stimulators represents a critically important advancement in the use of these types of agents. The initial presence of heterogeneous particle size (between 20 and 100 μm) in the first-generation Arteplast (Artes Medical, Inc., San Diego, CA) resulted in a higher degree of inflammation, leading to a higher incidence of granulomas than was desired or expected.[7] Adjustments to the manufacturing process produced a more tightly controlled particle size (25 to 40 μm), leading ultimately to the development of Artefill (Suneva Medical, Inc., San Diego, CA), a US Food and Drug Administration (FDA)-approved agent.[7] Likewise, the tightly controlled size of the PLLA microparticles (40 to 63 μm) contributes greatly to the predictability of treatment with this agent. When coupled with correct dilution, adequate hydration, and optimal injection techniques, the PLLA microparticles elicit a predictable host response and therefore a predictable cosmetic effect that may be completely controlled by the clinician.[2,15] Additionally, proper patient selection will maximize results and decrease frustration for both the patient and the clinician (ie, fillers of any kind may be a suboptimal choice for patients with advanced skin laxity, poor craniofacial support, and high volume loss). Such patients may be better served with surgical options such as lifts, fat augmentation, and implants.

PLLA is a Unique and Long-Lasting, but not Permanent, Agent

The primary differences between HA fillers and biostimulatory agents are conceptually simple but critically important for the correct application of treatment. Though HA fillers have been shown to stimulate a comparatively small degree of collagen deposition,[16] their efficacy is based upon their ability to directly fill soft tissue, not collagen stimulation. More volumization can be obtained by using more product at any one session with this direct filling agent. In contrast, CaHA, PLLA, and PMMA are known to act through the stimulation of collagen.[10,17] As PLLA depends exclusively on the host response to the product, rather than a direct fill, the amount of product used at any one session is determined by the surface area to be treated at that session, while the final volumetric correction is determined by the number of treatment sessions. These treatment sessions are spaced 4 to 6 weeks apart to allow time for the host response to develop between sessions.

CaHa and PLLA are durable, but ultimately biodegradable, products. The microparticles in CaHA injections are more readily degraded than those in PLLA, lasting for up to 12 to 18 months.[18] PLLA is the most durable of all currently FDA-approved biodegradable products, with results from studies used to garner initial FDA approval showing full correction still present in 80% of subjects at 24 months (the cut-off date of the original study).[5] Unlike CaHa and PLLA microparticles, PMMA is not biodegradable, making it theoretically permanent.[10] The advantages and disadvantages of this are controversial, as some clinicians express concern that permanent agents may have permanent adverse events.

PLLA as an Approach to Volume Restoration

Over recent years, a growing understanding and appreciation for the contribution of volume loss to facial aging has supported targeted use of fillers.[19] PLLA's unique mechanism of action underlies the requirement for specific treatment methodologies that are outlined below and presented in more detail elsewhere.[2,20] High patient satisfaction has been achieved with this long-lasting approach to volume restoration.[4]

PLLA provides long-lasting results exclusively through stimulation of the body's own collagen synthesis. As noted above, because the effects of PLLA collagen stimulation are not immediate, volume restoration with PLLA may require several sessions that are at least 4 weeks apart.[2] It is important to remember that the amount of PLLA injected in a single treatment is dictated by the surface area covered at that treatment session and not by the final degree of volumetric correction desired. Rather, the final degree of volumetric correction is addressed by the number of treatments.[2] A firm grasp of this concept is critical for avoiding overcorrection, especially in light of PLLA's durability.

Appropriate product reconstitution, hydration, handling, and placement are central to avoiding adverse events. Higher reconstitution volumes and longer hydration times

(up to 48 hours) have been shown to reduce the risk of nodule formation.[21] Consensus recommendations further describe the procedures for optimal patient selection, product handling (including preparation and storage), and injection techniques. These consensus guidelines provide the information needed for current and best treatment practices.[20,21] By increasing hydration time to between (24 and 48 hours) and volume to between 5 and 9 mL, as well as careful selection of the injection plane of PLLA (the uppermost portion of subcutaneous fat rather than lower dermis, and supraperiosteally), the incidence of nodules was lowered from 10%—the comparatively higher incidence reported in initial clinical studies—to 0.15%.[22,23]

DISCUSSION

PLLA is a biocompatible, biodegradable implant that acts by stimulating a host response leading to fibroplasia, which provides volume. The widely accepted William's definition of biocompatibility is the ability of a material to perform with an appropriate host response in a specific application.[24] Therefore, the biocompatibility of this material is contingent upon the manner in which it is used (ie, how, where, and how much of the product is used may greatly influence the type and intensity of the host response). A subclinical inflammatory response followed by encapsulation and fibroplasia is the desired endpoint for application of this product as a tissue augmentation device.

In the application of tissue augmentation, a predictable response correlates with a "predictable" host (no active immunogenic issues), as well as a "predictable" amount of biomaterial (the concentration of material introduced). A predictable amount of biomaterial is easily achieved by following the guidelines outlined here in terms of preparation (dilution, hydration time) and administration (amount and level of injection). As noted above, this product is not a "passive" filler, but relies upon the host response to the product for its effect, and this is a process that takes 4 to 6 weeks. Therefore, the amount of product used at any single treatment session should be determined solely by the surface area treated at that session (using approximately 0.2 to 0.3 mL/cm^2), while the patient's final volumetric correction is determined by the number of treatment sessions.

It is interesting to note that our initial global experience with this product was in very wasted faces (human immunodeficiency virus-associated lipoatrophy), which required a large amount of product and many sessions to correct. Of course, very wasted faces are now recognized to need a large amount of product—any product—to correct. This early experience was also tainted by suboptimal techniques, leading to the development of an unacceptably high number of papules and nodules, a problem that resolved as a true understanding of how to use biostimulatory devices such as PLLA evolved. We now recognize that optimizing outcomes and minimizing adverse events with this product are not difficult, but simply require awareness and attention to the methodology guidelines presented herein. The subtle, natural appearing results attainable with this product have been associated with high patient satisfaction.

CONCLUSIONS

PLLA provides clinicians with a powerful tool for providing long-lasting correction of facial volume loss. As experience has been gained with this product and technical issues have evolved, it has been found to be a safe and effective product with predictable and reproducible results. Subtle, natural, and pleasing results of long duration can be obtained with a reasonable amount of product utilizing the emerging concepts of the pathophysiology of facial aging in order to optimize site-specific corrections.

Evaluate each patient individually and determine prior to the start of treatment if fillers are a cost-effective choice for the patient. Remember that very empty and very elastotic faces are very difficult to fill (regardless of product choice), requiring considerable product which may be expensive for the patient. A patient with severe global lipoatrophy and a thin body with no fat donor sites may have limited choices for rejuvenation and may therefore choose fillers regardless of cost. This may be accomplished more successfully in a patient with good skin elasticity. A patient with an outer skin envelope that is no longer able to accommodate any underlying volume loss should be made aware that replacement of volume may not give the results desired without also addressing the excess skin with a surgical lift.

As with all filler agents, less PLLA is required in younger or fuller faced patients to achieve desirable results. Treatments done over several sessions with PLLA, or even HA fillers, are appealing to many patients who prefer a slower, more subtle approach to rejuvenation. With PLLA, the patience required to go through several sessions is rewarded by the durability and longevity of the product.

Disclosures

Dr Fitzgerald has served as a speaker trainer for Galderma, and consultant for Allergan and Merz. Dr Bass has served as a consultant and investigator for Endo Phamaceuticals, Cynosure Inc., Merz Pharmaceuticals, and Neothetics. Dr Goldberg has participated in the Merz speakers' bureau, and has been awarded research grants by Allergan, Galderma, and Merz. Dr Graivier has served as a consultant for Merz and as an investigator for Galderma. Dr Lorenc has served as a consultant for Allergan, Galderma, and Merz.

Funding

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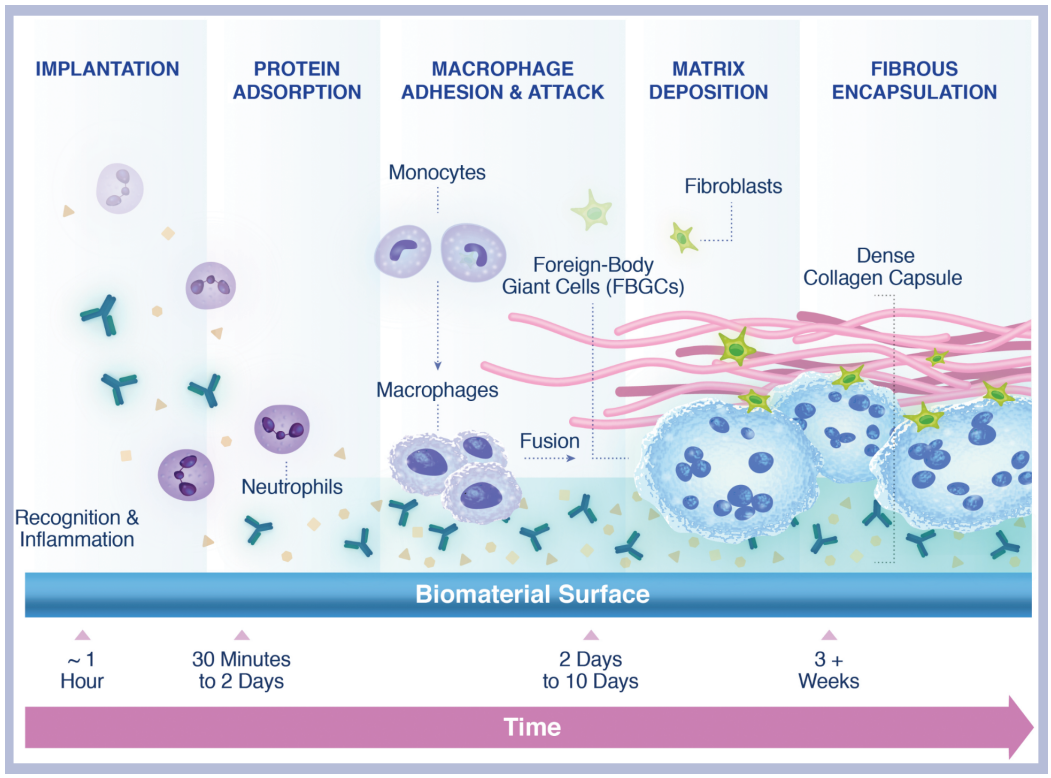

Figure 1. Foreign body reaction to a biomaterial (figure provided by X-Medica, LLC, Alpharetta, GA).

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DISCUSSION

PLLA is a biocompatible, biodegradable implant that acts by stimulating a host response leading to fibroplasia, which provides volume. The widely accepted William's definition of biocompatibility is the ability of a material to perform with an appropriate host response in a specific application.[24] Therefore, the biocompatibility of this material is contingent upon the manner in which it is used (ie, how, where, and how much of the product is used may greatly influence the type and intensity of the host response). A subclinical inflammatory response followed by encapsulation and fibroplasia is the desired endpoint for application of this product as a tissue augmentation device.

In the application of tissue augmentation, a predictable response correlates with a "predictable" host (no active immunogenic issues), as well as a "predictable" amount of biomaterial (the concentration of material introduced). A predictable amount of biomaterial is easily achieved by following the guidelines outlined here in terms of preparation (dilution, hydration time) and administration (amount and level of injection). As noted above, this product is not a "passive" filler, but relies upon the host response to the product for its effect, and this is a process that takes 4 to 6 weeks. Therefore, the amount of product used at any single treatment session should be determined solely by the surface area treated at that session (using approximately 0.2 to 0.3 mL/cm^2), while the patient's final volumetric correction is determined by the number of treatment sessions.

It is interesting to note that our initial global experience with this product was in very wasted faces (human immunodeficiency virus-associated lipoatrophy), which required a large amount of product and many sessions to correct. Of course, very wasted faces are now recognized to need a large amount of product—any product—to correct. This early experience was also tainted by suboptimal techniques, leading to the development of an unacceptably high number of papules and nodules, a problem that resolved as a true understanding of how to use biostimulatory devices such as PLLA evolved. We now recognize that optimizing outcomes and minimizing adverse events with this product are not difficult, but simply require awareness and attention to the methodology guidelines presented herein. The subtle, natural appearing results attainable with this product have been associated with high patient satisfaction.

CONCLUSIONS

PLLA provides clinicians with a powerful tool for providing long-lasting correction of facial volume loss. As experience has been gained with this product and technical issues have evolved, it has been found to be a safe and effective product with predictable and reproducible results. Subtle, natural, and pleasing results of long duration can be obtained with a reasonable amount of product utilizing the emerging concepts of the pathophysiology of facial aging in order to optimize site-specific corrections.

Evaluate each patient individually and determine prior to the start of treatment if fillers are a cost-effective choice for the patient. Remember that very empty and very elastotic faces are very difficult to fill (regardless of product choice), requiring considerable product which may be expensive for the patient. A patient with severe global lipoatrophy and a thin body with no fat donor sites may have limited choices for rejuvenation and may therefore choose fillers regardless of cost. This may be accomplished more successfully in a patient with good skin elasticity. A patient with an outer skin envelope that is no longer able to accommodate any underlying volume loss should be made aware that replacement of volume may not give the results desired without also addressing the excess skin with a surgical lift.

As with all filler agents, less PLLA is required in younger or fuller faced patients to achieve desirable results. Treatments done over several sessions with PLLA, or even HA fillers, are appealing to many patients who prefer a slower, more subtle approach to rejuvenation. With PLLA, the patience required to go through several sessions is rewarded by the durability and longevity of the product.

Disclosures

Dr Fitzgerald has served as a speaker trainer for Galderma, and consultant for Allergan and Merz. Dr Bass has served as a consultant and investigator for Endo Phamaceuticals, Cynosure Inc., Merz Pharmaceuticals, and Neothetics. Dr Goldberg has participated in the Merz speakers' bureau, and has been awarded research grants by Allergan, Galderma, and Merz. Dr Graivier has served as a consultant for Merz and as an investigator for Galderma. Dr Lorenc has served as a consultant for Allergan, Galderma, and Merz.

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ORIGINAL ARTICLE

Optimizing injectable poly-L-lactic acid administration for soft tissue augmentation: The rationale for three treatment sessions

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U Bauer, MH Graivier. Optimizing injectable poly-L-lactic acid administration for soft tissue augmentation: The rationale for three treatment sessions. Can J Plast Surg 2011;19(3):e22-e27.

BACKGROUND: The availability and variety of different injectable modalities has led to a dramatic increase in soft tissue augmentation procedures in recent years. Injectable poly-L-lactic acid (PLLA) is a synthetic, biodegradable polymer device approved in the United States for use in immunocompetent patients as a single regimen of up to four treatment sessions for correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles. Injectable PLLA is also approved for restoration and/or correction of signs of facial fat loss (lipoatrophy) in individuals with HIV.

METHODS: The present article provides an overview of previous studies with injectable PLLA, and specifically focuses on the number of recommended treatment sessions and intervals between treatment sessions. The authors also provide two case studies to support their recommendations for an average of three treatment sessions.

RESULTS: Although the specific mechanisms remain hypothetical, injections of PLLA are believed to cause a cascade of cellular events that lead to collagen repair and subsequent restoration of facial volume. Because the development of a response to injectable PLLA is gradual and its duration of effect is long lasting, sufficient time between treatment sessions should be allocated to avoid overcorrection.

CONCLUSION: Studies of injectable PLLA support the hypothesized mode of operation, and the experience and clinical recommendations of the authors that suggest that three treatment sessions are an optimal regimen for use of injectable PLLA in the majority of patients.

Key Words: *Collagen; Cosmetic; Dermal fillers; Injectable devices; Injectable PLLA*

L'optimisation de l'administration d'acide L-polylactique injectable pour augmenter les tissus mous : la justification de trois séances de traitement

HISTORIQUE : La disponibilité et la variété de différentes modalités injectables a donné lieu, ces dernières années, à une augmentation considérable des interventions d'augmentation des tissus mous. L'acide L-polylactique (PLLA) injectable est un polymère biodégradable synthétique approuvé aux États-Unis auprès des patients immunocompétents, sous forme de schéma posologique unique d'un maximum de quatre séances de traitement pour corriger les anomalies du contour des sillons nasolabiaux légers à profonds et d'autres rides faciales. Le PLLA est également approuvé pour restaurer ou corriger les signes de perte lipidique (lipoatrophie) faciale chez les personnes atteintes du VIH.

MÉTHODOLOGIE : Le présent article propose un aperçu d'études antérieures sur le PLLA injectable et s'attarde sur le nombre de séances de traitement recommandées et sur les intervalles entre ces séances. Les auteurs présentent également deux études de cas pour étayer leur recommandation de prévoir une moyenne de trois séances de traitement.

RÉSULTATS : Même si les mécanismes précis demeurent hypothétiques, on pense que les injections de PLLA provoquent une cascade d'événements cellulaires qui suscitent la réparation du collagène et une restauration subséquente du volume facial. Puisque la réponse au PLLA injectable est graduelle et que son effet est de longue durée, il faut prévoir une période suffisante entre les séances de traitement afin d'éviter une surcorrection.

CONCLUSION : Les études sur le PLLA injectable appuient le mode d'utilisation postulé ainsi que l'expérience et les recommandations cliniques des auteurs selon lesquelles trois séances de traitement constituent la posologie optimale d'utilisation du PLLA chez la majorité des patients.

The availability and variety of nonsurgical soft tissue augmentation options led to a 90% proportionate increase in minimally invasive cosmetic procedures from 2000 to 2008 (1). Age-related alterations to the face result from normal physiological processes (ie, facial skeletal resorption), dermal dystrophy, dermal thickening owing to photoaging or thinning resulting from chronological aging, loss (facial lipoatrophy) or redistribution of facial fat, and the appearance of facial wrinkles (2,3). Facial volume loss can also occur in patients receiving antiretroviral therapy for HIV, and can be the result of other diseases involving inherited or acquired lipodystrophies such as familial partial lipodystrophy (Dunnigan or Köbberling variety), Parry-Romberg syndrome and Barraquer-Simons syndrome (4-6).

A wide range of injectable devices for soft tissue augmentation is available in Europe and the United States (7) including hyaluronic acids, calcium hydroxylapatite, polymethylmethacrylate microspheres, injectable poly-L-lactic acid (PLLA) and silicone oil (8). Hyaluronic acid and collagen preparations are safe and effective; however, the results only typically last between three and 12 months (7,9-13). The use of bovine-derived collagen requires allergy testing and is generally effective for approximately three months. Human-derived collagen does not require allergy testing (14), and the effects can last up to four to seven months (15). Newer silicone oils have been shown to be effective for facial lipoatrophy; however, no long-term follow-up studies of adverse effects have been reported, particularly with regard to the incidence of severe foreign body reactions – a complication that was associated with the older formulations (16). Calcium hydroxylapatite has a suggested duration of approximately 12 months and a favourable safety profile (17). Injectable PLLA has demonstrated effectiveness for the correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles (18), and in restoring facial fat loss due to HIV-associated lipoatrophy; its effects last up to 25 months (19-22).

The purpose of the present article was to offer a rationale for the use of three treatment sessions, on average, of injectable PLLA (Sculptra Aesthetic, Dermik Laboratories, sanofi-aventis, USA) to obtain long-lasting and gradual correction of facial folds and wrinkles such as nasolabial folds in immunocompetent patients (ie, those without HIV-associated facial lipoatrophy). Two case studies are presented to illustrate this approach. The recent approval of injectable PLLA in the United States for use in immunocompetent individuals as a single regimen of up to four sessions for the correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles provides further support for the three-treatment approach (18). Injectable

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PLLA is also approved for the restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with HIV (19). Injectable PLLA is a synthetic, biocompatible, biodegradable, polymeric device. Because its effects develop gradually and are sustained for up to 25 months (18,19), clinicians need to understand the dynamics of the product to ensure its optimal use in soft tissue augmentation and minimize the occurrence of adverse events.

INJECTABLE PLLA: THE RATIONALE FOR THREE INJECTION SESSIONS

Studies in animals have shown that the implantation of solid PLLA particles, plates, discs, pins or screws produces a cascade of events that results in the formation of new tissue (23-28). In humans, Lemperle et al (25) observed a cellular response (involving macrophages, lymphocytes and giant cells), which was similar to that seen in mice after reconstituted PLLA (New-Fill, Biotech Industry SA, Luxembourg) was injected into the volar skin of the forearm. Treatment with injectable PLLA has also been reported to result in the gradual growth of type I collagen for eight to 24 months (2). Although additional studies in humans are necessary to more accurately determine the mode of operation of injectable PLLA, the studies described above provide a logical framework to guide the use of the device for the correction and/or restoration of nasolabial fold wrinkles.

Based on the hypothesized mode of operation discussed above, injections of PLLA into the deep dermis or subcutaneous layer are believed to induce a local tissue reaction that may lead to the redevelopment of the collagenous network lost due to aging or disease and, ultimately, the restoration of collagenous scaffolding within the tissue (29,30). Because this cellular cascade occurs over time, injectable PLLA has a gradual treatment effect, and the application of additional treatments before the results of the previous treatment are apparent can result in overtreatment of the area. The time to response and ensuing signs of correction depend on the individual, owing to interpersonal differences in age, skin type and skin quality; moreover, results may not be evident for up to several weeks after treatment – an effect that is unlike that of collagens and hyaluronic acids (29,31). Therefore, it is important to wait for the underlying biological response (ie, cellular cascade) to occur between each treatment; a limited correction should be made with the first treatment session (19). It is also crucial to assess the effects of each previous series of injections to determine what refinements are needed before proceeding with additional treatment. This has been previously described in the literature as the 'treat-wait-assess' approach, and has been successfully applied in the correction of HIV-related facial lipoatrophy and for volume restoration in antiaging treatment (32,33).

Each treatment with injectable PLLA potentially elicits the cellular cascade of events that is believed to lead to collagen formation, in which the magnitude of response is dependent on the volume of injectable PLLA used. Because of variations in the severity of the nasolabial fold volume deficits among patients, the volume of injectable PLLA used for each patient will differ. However, this volume should never be in excess of the initial loss in facial volume or the severity of the facial wrinkle, nasolabial line or fold, which is overcorrection, and is not recommended. The first treatment with injectable PLLA elicits an observable response because of mechanical tissue expansion from the injected volume (reconstituted with sterile water for injection), facilitating a noticeable correction of contour deficiencies (29,31). This initial effect will likely subside owing to partial resorption of the carrier solution, although the first stages of the underlying dermal structural restoration are believed to begin here (2,31). Consequently, it is common for the initially observed correction of the contour deficit to return to pretreatment status a few days after the first injection; thickening of the soft tissue usually increases again after the first several weeks (19,31). Subsequent injections, in theory, provide continued stimulation of the tissue response, resulting in further refinement of volume replacement for long-term improvement of facial contour deficits (34). Thus, based on the hypothesized foreign body response to the injected microparticles of PLLA (or other injected fluids or particles) (35,36), each treatment is believed to result in the formation of collagen that replaces lost volume (21). The extent of volume restoration and collagen formation, however, may be dependent on the volume of injectable PLLA used in each treatment and on interindividual differences.

Because the proposed mode of operation of injectable PLLA involves a tissue response, sufficient time needs to be allowed for that response to occur. Consequently, based on our experience, we recommend that patients be re-evaluated at an interval of no less than three weeks before the second treatment and three months before the third treatment. These intervals will allow sufficient time for the underlying tissue processes involved in the correction to take place and become observable following treatment with injectable PLLA. In our experience, patients with greater overall skin thickness may require a longer period between treatment sessions (up to several months) before the full effect of treatment becomes apparent (20,37,38).

The use of three treatment sessions of injectable PLLA is supported by earlier studies evaluating the efficacy and safety of injectable PLLA in patients with HIV-associated facial lipoatrophy. The VEGA study (20) used an average of four treatment sessions, the Chelsea and Westminster trial (21,22) involved three treatment sessions and the Blue Pacific Group study (39) used up to six treatment sessions with injectable PLLA at three- to six-week intervals. Although HIV-associated facial lipoatrophy may be mechanistically distinct from the volume loss and contour deficiencies encountered in the typical patient with age-related volumetric loss, the above studies support the need for more than two injection sessions to achieve optimal, fully visible effects with injectable PLLA. The recent approval of injectable PLLA in the United States for use in immunocompetent individuals (18) allows its use for aesthetic purposes in a wider range of patients. This approval was based on a single study of injectable PLLA (40), which is discussed later in the present article.

OPTIMIZING INJECTABLE PLLA RESULTS FOR SOFT TISSUE AUGMENTATION

Based on the hypothesized mode of operation of injectable PLLA, and supported by the authors' clinical experience, three treatment sessions are recommended to gradually restore facial volume in the typical cosmetic patient. The authors' experience with injectable PLLA began in 1999 and, since that time, approximately 4000 patients have been treated with this injectable device. Most patients favour gradual aesthetic change so that their friends and family remain unaware of their soft tissue augmentation treatments (41). For a new patient, at least four weeks should separate the first two treatments, and the patient should wait least three weeks before the third treatment. Moreover, the authors' clinical experience with injectable PLLA has indicated that six months should elapse after the third treatment before any further assessments. The observations suggest that this time interval is sufficient to determine the extent of the correction achieved by the first three treatment sessions and to assess the need for additional treatments. At the same time, this approach minimizes the risk of overcorrection of the injected area and reduces the risk of adverse events including development of papules and nodules. Finally, the total injection volume will vary, depending on the area of the deficit requiring correction, the patient's age and skin quality. The treatment area should be massaged periodically during and following each injection to ensure even distribution of the product (19). Most importantly, patients should be instructed to massage the treatment area following the 'three five rule' – massage the area for 5 min, five times a day, for at least five days (34,42,43). Using the injection technique described in the package insert is also recommended for minimizing the occurrence of adverse events.

CASE STUDIES

According to the package insert, injectable PLLA should stand for at least 2 h after reconstitution to ensure complete hydration. However, in

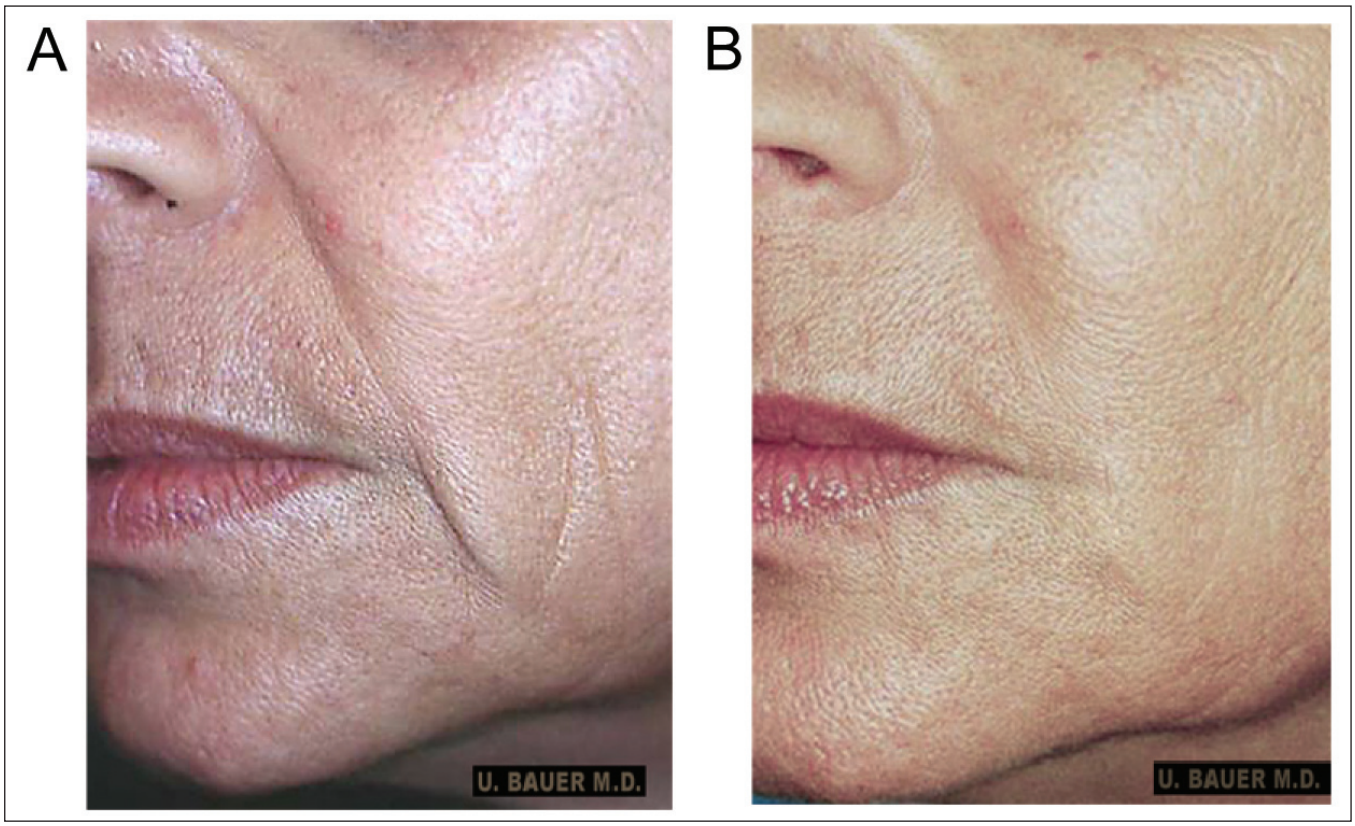

Figure 1) *Patient 1: A 55-year-old Caucasian woman, before (***A***) and 12 months after (***B***) the third injectable poly-L-lactic acid treatment. Notice the degree of correction in the nasolabial fold region and in the marionette line*

the authors' experience, a better suspension is achieved when reconstitution is performed at least 12 h before use (44). Five millilitres of sterile water for injection should be added to each vial, although many clinicians, including the authors, reconstitute PLLA with 4 mL of bacteriostatic water for injection and add 1 mL to 3 mL of lidocaine to minimize injection pain (45). The reconstitution volume, however, is not the same as the injection volume; approximately 20 aliquots of 0.1 mL to 0.2 mL (2.0 mL to 4.0 mL total injected volume) of reconstituted injectable PLLA may be necessary to cover the targeted area (19). It is recommended that injectable PLLA be administered using 26-gauge needles and be injected into the deep subdermis or subcutaneous layer. Firm massage is used to evenly distribute injectable PLLA. In older patients, maxillary bone and soft tissue changes may result in elongation of upper lip length and change in the proportion of the lower one-third of the face (46). In these patients, injection into the supraperiosteal plane helps to elevate the soft tissue and can positively modify the lower facial proportion (46), although this use of injectable PLLA has not been approved by the United States Food and Drug Administration. Additionally, in patients with deep nasolabial folds (wrinkle rating severity scale of 3, 4 or 5) (47), supraperiosteal injection at the pyriform aperture will give improved correction (46). After reconstitution, vials of injectable PLLA can be stored at room temperature for up to 72 h before use (18,19).

Patient 1 was a 55-year-old Caucasian woman who was a smoker. She had thin skin, which remained void and pinched when tested before treatment. The poor quality of her skin was typical of smokers who generally have reduced microcirculation in their skin; furthermore, less nutrition is provided to the outer dermal layer, thus drying the skin layers, creating fine wrinkling and promoting faster aging. In addition, the nicotine deposited in the patient's skin diminished its colour, giving the skin a grayish pallor (48,49).

Lossof facial fat and resultant hollowing contributed to the patient's tired and older appearance. In the authors' experience, extreme care with injections into very thin skin layers is needed because even a minor error, such as an uneven distribution of injectable material, may cause irregular results. In these instances, lower injection volumes (ie, one injection of less than 0.1 mL) of more dilute injectable PLLA are used, with a reconstitution volume of up to 6 mL to 7 mL. The authors also insist that the patient performed regular aftercare massage of the injected area. Based on the hypothesized mode of operation, injectable PLLA provides structural support by inducing a tissue response leading to collagen development, thus creating a suspended net under the entire area of the deficit or fold. Therefore, with older patients, such as the present 55-year-old woman, injectable PLLA should be injected just above the area of the nasolabial fold and extended widely outside the defect to create a lifting effect. In addition, PLLA should be injected into the deep dermal layer or subcutaneous layer (19), but never into the dermis. In fact, some physicians, including the authors, elect to inject the device into the supraperiosteal layer, although this method is considered to be off label (46).

After the initial consultation, the patient was interested in a gradual, long-lasting, minimally invasive corrective procedure, and requested treatment with injectable PLLA to soften and fill out her nasolabial folds (Figure 1A). The use of hyaluronic acid-based products was also discussed, but was discounted because of their shorter duration of effect compared with injectable PLLA, and the need for a large amount of filler material to correct the patient's deficit. The reconstituted product was injected bilaterally into the area slightly above the nasolabial folds. The patient received three treatments over 12 weeks. Because of her poor skin quality, four weeks were allowed between her first and second treatment, thus giving sufficient time for the collagen restoration and repair processes to begin. Four weeks after her first treatment, the patient was assessed as having little or no observable cosmetic improvement. This result was not unexpected because the initial observable improvement was largely due to mechanical expansion of the carrier and mostly subsided to pretreatment

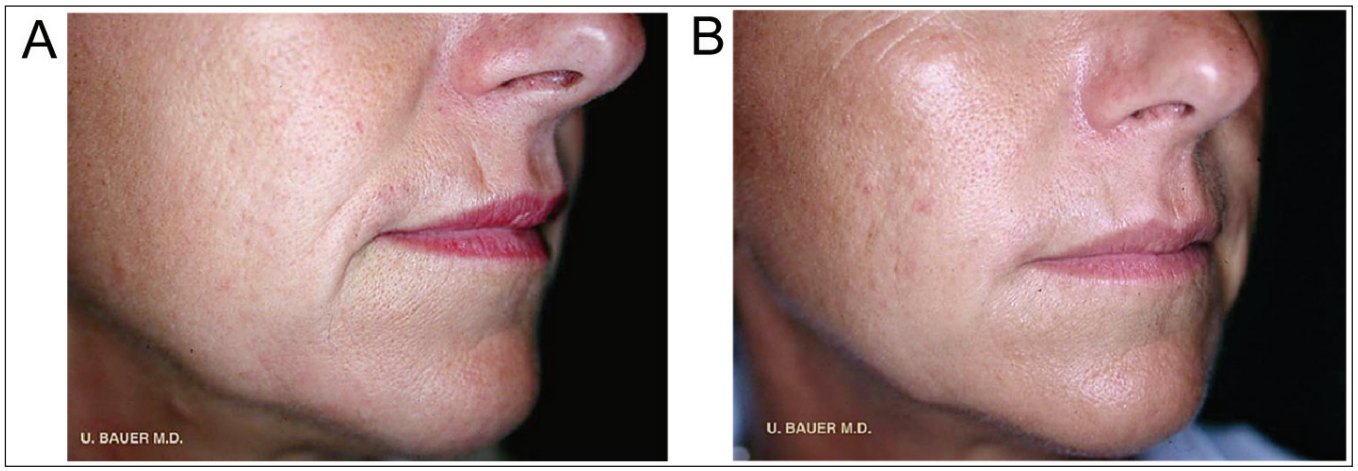

Figure 2) *Patient 2: A 45-year-old Caucasian woman, before (**A**) and 24 months after (**B**) the third injectable poly-L-lactic acid treatment. Hyaluronic acid in superficial lines. Reproduced from reference 56*

levels in approximately one week (29,31). After the second treatment, a 20% to 30% improvement in tissue quality and growth was noted, based on the authors' clinical experience, comparison of the patient's photographs before and after treatment and the patient's opinion regarding the treatment results. A third treatment was administered eight weeks after the second treatment to continue the restorative collagenous repair and refine the improvement in the nasolabial region. Each treatment was well tolerated, with no adverse events reported.

After completing her treatment, the patient presented with good correction of the nasolabial fold and marionette lines, and improvement in her skin quality, with an enormous gain in elasticity; this was based on visual inspection by the physician and patient as well as through comparison with pretreatment photographs. Figure 1B shows the area of injection 12 months after the third and final treatment with injectable PLLA. For this patient, improved skin quality led to an increase in the fibrotic layer in the dermis and subdermal layer, which could be manually ascertained in the skin layer overlying the site treated with injectable PLLA. A thicker skin layer also reflects light better as the deep shades disappear because of the improved convexity of the facial contours (50). With restoration and repair of the underlying collagen in the nasolabial fold region, the patient's face and skin appeared healthier, her pores were reduced and the overall roundness (convexity) in the middle of her face gave her a more youthful appearance. The patient has returned for yearly follow-up assessments. In the five years since her initial treatment with injectable PLLA, the patient has maintained the underlying correction without any adverse events. She has also reported very high satisfaction with her treatment. Since her treatment with injectable PLLA, the patient has returned for two additional Fraxel laser treatments (Thermage, Solta Medical Inc, USA). She also received two treatments with hyaluronic acid to address her more superficial wrinkles.

Patient 2 was a 45-year-old, healthy, nonsmoking, active Caucasian woman. The patient's objective for treatment was to lose the 'negative expression' on her face (Figure 2A). She had previously tried hyaluronic acid-based fillers and now desired a longer lasting and more overall correction. Based on discussions with the patient concerning the degree of correction she desired, it was agreed that treatment with injectable PLLA would provide her with the correction she sought. Because lost or damaged collagen likely contributed to her 'negative expression' (51), there was a four-week interval between her first and second treatments with injectable PLLA to allow for the effects of the treatment to take place. After assessing the improvements of the second treatment, the authors waited eight weeks before administering the third treatment. In each treatment session, injectable PLLA was reconstituted to a final dilution of 5 mL (4 mL of sterile water for injection plus 1 mL of lidocaine) and was allowed to stand for up to 48 h before use, as previously discussed. Bilateral injections of 2 mL of injectable PLLA were made above the nasolabial fold region. Each treatment was well tolerated. For this patient, the areas of improvement included the nasolabial fold region, marionette lines and the area above the lip (Figure 2B). After three treatments, the convexity of her nasolabial fold region had been restored, virtually eliminating the fold and marionette line. She maintained very good improvement in the nasolabial fold region for 24 months following the final treatment (Figure 2B). She remains very satisfied with her treatment and has not reported any adverse events. The patient was assessed 36 months after her final treatment session and has returned annually for the past four to five years for follow-up. She continues to show very good correction and has required additional treatment with injectable PLLA only in the zygomatic area. She, however, continues to receive treatment with one vial of hyaluronic acid yearly for superficial wrinkles.

DISCUSSION

Interest in delaying the visible signs of aging, such as progressive volume loss, thinning of the dermis and a loss of continuity caused by lines, wrinkles and deep furrows, combined with the greater availability and variety of noninvasive injectable fillers, likely account for the increased interest in soft tissue augmentation procedures (52). Injectable PLLA has been shown to be safe and effective in the management of facial lipoatrophy, in patients with and without HIV who are seeking soft tissue augmentation. The cases presented in the present article show that injectable PLLA is an appropriate nonsurgical option for soft tissue augmentation.

Our clinical experience with injectable PLLA suggests that three treatment sessions provide an optimal regimen for most immuncompetent patients. This practice is based on the treat-to-repair, wait-to-restore and assess-to-refine concept (32,33), wherein each series of injections is believed to contribute to a foreign body response. Because each patient responds differently to treatment with injectable PLLA, it is important to allow sufficient time between treatments to avoid overcorrection of the original deficit. Overcorrection of the injected area may produce an unwanted visual effect, and may contribute to the formation of subcutaneous nodules (31,53,54). It should be emphasized that the effects of treatment with injectable PLLA are gradual and long lasting (55). A minimum of three- to four-week intervals between treatment sessions allows for the effect of injectable PLLA, namely the cellular cascade responsible for collagen repair and restoration, to occur. Providing the time for the cellular processes for collagen repair and restoration to occur also minimizes the risk of overcorrection.

Our treatment approach is supported by earlier studies (20-22,39), in which patients with HIV-associated facial lipoatrophy were successfully treated with injectable PLLA using an average of three treatment sessions. Although HIV-associated facial lipoatrophy and the development of wrinkles due to facial fat loss or redistribution due to aging are

different pathophysiological processes and may not be completely comparable in terms of severity, the cases discussed in the present article provide clinical confirmation of the benefits of three treatment sessions with injectable PLLA administered in at least three- to four-week intervals or longer (eg, eight weeks). Both patients experienced clinical improvement in the nasolabial fold regions and in the alleviation of marionette lines. It is also noteworthy that the injection volume for each treatment session and for the overall treatment was different for each of the cases presented, thus underscoring the need to carefully consider each patient's age, severity of deficit and treatment goals before beginning treatment. Furthermore, such practice helps to avoid overcorrection of the treatment area. We hope that the examples presented in the present article will help clinicians achieve a greater understanding of how best to use injectable PLLA in soft tissue augmentation.

Since the patients described above were treated, a clinical trial in which subjects were treated with injectable PLLA or human collagen (CosmoPlast, Allergan-Inamed, USA) at three-week intervals has been completed (40). In this study, there were three weeks between treatments; a mean of 3.2 injection sessions were required by subjects in the injectable PLLA group. Within three weeks of the final treatment with injectable PLLA, there were significant ($P<0.001$) improvements in wrinkle assessment scores compared with baseline; the improvements continued to increase until the 13-month assessment period, and were maintained at the 19- and 25-month assessment periods. The safety profiles of injectable PLLA and human collagen were similar, with a higher incidence of adverse events in collagen recipients; the incidences of nodules and papules following injectable PLLA were 7% and 9%, respectively. Additional studies may help to support the value of administering injectable PLLA in three sessions for the aesthetic correction of facial contour deficits, and to determine appropriate patient selection criteria for use of this approach.

CONCLUSION

In our experience with injectable PLLA in immunocompetent individuals, soft tissue augmentation over the course of a mean of three treatment sessions, at three- to four-week intervals, has produced optimal results. It is important to carefully evaluate the patient after each treatment session and to individualize follow-up injections and timing because each patient will respond differently to the use of injectable PLLA.

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