 ORIGINAL ARTICLE Journal of Drugs in Dermatology

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

Danny Vleggaar MD,[a] Rebecca Fitzgerald MD,[b] and Z. Paul Lorenc MD FACS[c]

[a]Head of Cosmetic Dermatology in Private Practice, Geneva, Switzerland
[b]Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA
[c]Lorenc Aesthetic Plastic Surgery Center, New York, NY, USA

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

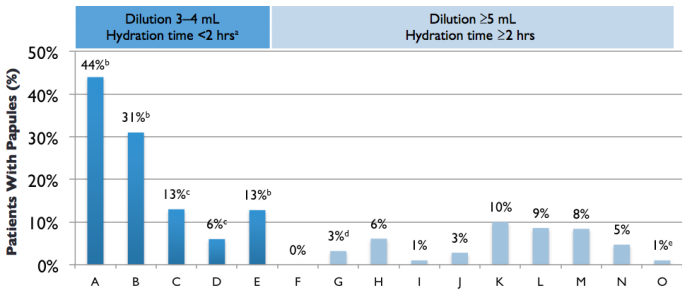
TABLE 1.

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]

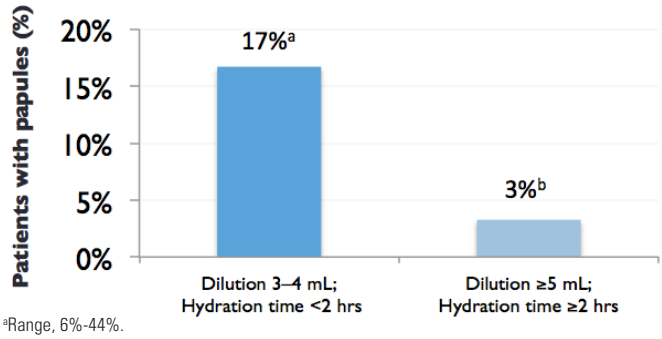


Earlier studies also had shorter treatment intervals: [a]Hydration time was not formally reported—manufacturer's instructions at the time were to reconstitute 3 minutes prior to injection. [b]2-week treatment interval. [c]3-week treatment interval. [d]Hydration occurred overnight, except during the first 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.

REFERENCES

1. Kulkarni RK, Pani KC, Neuman C, Leonard F. Polylactic acid for surgical implants. *Arch Surg.* 1966;93(5):839-843.
2. Kulkarni RK, Moore EG, Hegyeli AF, Leonard F. Biodegradable poly(lactic acid) polymers. *J Biomed Mater Res.* 1971;5(3):169-181.
3. Valantin MA, Aubron-Olivier C, Ghosn J, et al. Polylactic acid implants (New-Fill) to correct facial lipoatrophy in HIV-infected patients: results of the open-label study VEGA. *AIDS.* 2003;17(17):2471-2477.
4. Simamora P, Chern W. Poly-L-lactic acid: an overview. *J Drugs Dermatol.* 2006;5(5):436-440.
5. Matsusue Y, Yamamuro T, Oka M, Shikinami Y, Hyon SH, Ikada Y. In vitro and in vivo studies on bioabsorbable ultra-high-strength poly(L-lactide) rods. *J Biomed Mater Res.* 1992;26(12):1553-1567.
6. Lowe NJ. Dispelling the myth: appropriate use of poly-L-lactic acid and clinical considerations. *J Eur Acad Dermatol Venereol.* 2006;20(suppl 1):s2-s6.
7. Beljaards RC, de Roos KP, Bruins FG. NewFill for skin augmentation: a new filler or failure? *Dermatol Surg.* 2005;31(7 Pt 1):772-776.
8. Vleggaar D, Fitzgerald R, Lorenc ZP. Understanding, avoiding, and treating potential adverse events following the use of injectable poly-L-lactic acid for facial and nonfacial volumization. *J Drugs Dermatol.* 2014;13(suppl 4):s35-s39.
9. Vleggaar D. Soft-tissue augmentation and the role of poly-L-lactic acid. *Plast Reconstr Surg.* 2006;118(suppl 3):s46-s54.
10. Lam SM, Azizzadeh B, Graivier M. Injectable poly-L-lactic acid (Sculptra): technical considerations in soft-tissue contouring. *Plast Reconstr Surg.* 2006;118(suppl 3):s55-s63.
11. Mest DR, Humble G. Safety and efficacy of poly-L-lactic acid injections in persons with HIV-associated lipoatrophy: the US experience. *Dermatol Surg.* 2006;32(11):1336-1345.
12. Woerle B, Hanke CW, Sattler G. Poly-L-lactic acid: a temporary filler for soft tissue augmentation. *J Drugs Dermatol.* 2004;3(4):385-389.
13. Lowe NJ, Maxwell CA, Lowe P, Shah A, Patnaik R. Injectable poly-l-lactic acid: 3 years of aesthetic experience. *Dermatol Surg.* 2009;35(suppl 1):s344-s349.
14. Levy RM, Redbord KP, Hanke CW. Treatment of HIV lipoatrophy and lipoatrophy of aging with poly-L-lactic acid: a prospective 3-year follow-up study. *J Am Acad Dermatol.* 2008;59(6):923-933.
15. Burgess CM, Quiroga RM. Assessment of the safety and efficacy of poly-L-lactic acid for the treatment of HIV-associated facial lipoatrophy. *J Am Acad Dermatol.* 2005;52(2):233-239.
16. Borelli C, Kunte C, Weisenseel P, Thoma-Greber E, Korting HC, Konz B. Deep subcutaneous application of poly-L-lactic acid as a filler for facial lipoatrophy in HIV-infected patients. *Skin Pharmacol Physiol.* 2005;18(6):273-278.
17. Hanke CW, Redbord KP. Safety and efficacy of poly-L-lactic acid in HIV lipoatrophy and lipoatrophy of aging. *J Drugs Dermatol.* 2007;6(2):123-128.
18. Engelhard P, Humble G, Mest D. Safety of Sculptra: a review of clinical trial data. *J Cosmet Laser Ther.* 2005;7(3-4):201-205.
19. Narins RS, Baumann L, Brandt FS, et al. A randomized study of the efficacy and safety of injectable poly-L-lactic acid versus human-based collagen implant in the treatment of nasolabial fold wrinkles. *J Am Acad Dermatol.* 2010;62(3):448-462.
20. Carey D, Baker D, Petoumenos K, et al. Poly-l-lactic acid for HIV-1 facial lipoatrophy: 48-week follow-up. *HIV Med.* 2009;10(3):163-172.
21. Carey DL, Baker D, Rogers GD, et al. A randomized, multicenter, open-label study of poly-L-lactic acid for HIV-1 facial lipoatrophy. *J Acquir Immune Defic Syndr.* 2007;46(5):581-589.
22. Lee JY, Schulman MR, Skolnik RA. Modified poly-L-lactic acid injection technique: safety and efficacy of "cross-fanning" in non-HIV-related facial atrophy. *Ann Plast Surg.* 2010;64(4):435-441.
23. Palm MD, Woodhall KE, Butterwick KJ, Goldman MP. Cosmetic use of poly-l-lactic acid: a retrospective study of 130 patients. *Dermatol Surg.* 2010;36(2):161-170.
24. Rossner F, Rossner M, Hartmann V, Erdmann R, Wiest LG, Rzany B. Decrease of reported adverse events to injectable polylactic acid after recommending an increased dilution: 8-year results from the Injectable Filler Safety study. *J Cosmet Dermatol.* 2009;8(1):14-18.
25. Hamilton DG, Gauthier N, Robertson BF. Late-onset, recurrent facial nodules associated with injection of poly-L-lactic acid. *Dermatol Surg.* 2008;34(1):123-126.
26. Moyle GJ, Lysakova L, Brown S, et al. A randomized open-label study of immediate versus delayed polylactic acid injections for the cosmetic management of facial lipoatrophy in persons with HIV infection. *HIV Med.* 2004;5(2):82-87.
27. Lafaurie M, Dolivo M, Porcher R, Rudant J, Madelaine I, Molina JM. Treatment of facial lipoatrophy with intradermal injections of polylactic acid in HIV-infected patients. *J Acquir Immune Defic Syndr.* 2005;38(4):393-398.
28. Sculptra [package insert]. 2012.
29. Sculptra [package insert]. 2004.
30. Moyle GJ, Brown S, Lysakova L, Barton SE. Long-term safety and efficacy of poly-L-lactic acid in the treatment of HIV-related facial lipoatrophy. *HIV Med.* 2006;7(3):181-185.
31. Engelhard P, Knies M. Safety and efficacy of New-Fill (polylactic acid) in the treatment of HIV-associated lipoatrophy of the face (HALF) [abstract]. Presented at: XIV International AIDS Conference; July 7-12, 2002; Barcelona, Spain.
32. Mest DR, Humble G. Safety and efficacy of intradermal poly-L-lactic acid (Sculptra™) injections in patients with HIV-associated facial lipoatrophy [abstract 59]. *Antiviral Therapy.* 2004;9:L36-L37.
33. Redaelli A, Forte R. Cosmetic use of polylactic acid: report of 568 patients. *J Cosmet Dermatol.* 2009;8(4):239-248.
34. Mazzuco R, Hexsel D. Poly-L-lactic acid for neck and chest rejuvenation. *Dermatol Surg.* 2009;35(8):1228-1237.
35. Schierle CF, Casas LA. Nonsurgical rejuvenation of the aging face with injectable poly-L-lactic acid for restoration of soft tissue volume. *Aesthet Surg J.* 2011;31(1):95-109.
36. Rendon MI. Long-term aesthetic outcomes with injectable poly-l-lactic acid: observations and practical recommendations based on clinical experience over 5 years. *J Cosmet Dermatol.* 2012;11(2):93-100.
37. Fitzgerald R, Vleggaar D. Facial volume restoration of the aging face with poly-l-lactic acid. *Dermatol Ther.* 2011;24(1):2-27.
38. Vleggaar D, Fitzgerald R, Lorenc ZP, et al. Consensus recommendations on the use of injectable poly-L-lactic acid for facial and nonfacial volumization. *J Drugs Dermatol.* 2014;13(suppl 4):s44-s51.

AUTHOR CORRESPONDENCE

Rebecca Fitzgerald MD

E-mail:..... fitzmd@earthlink.net