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

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) 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.

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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.

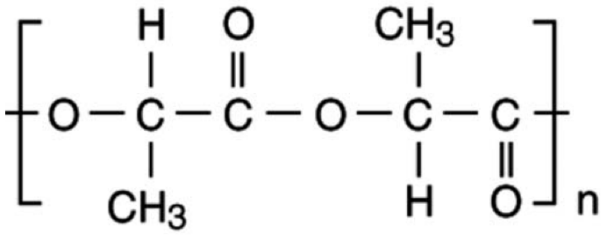
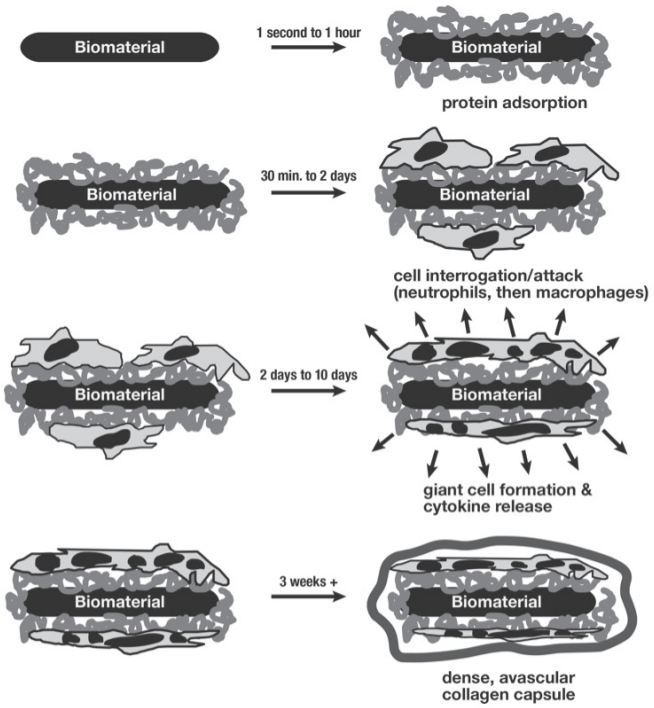
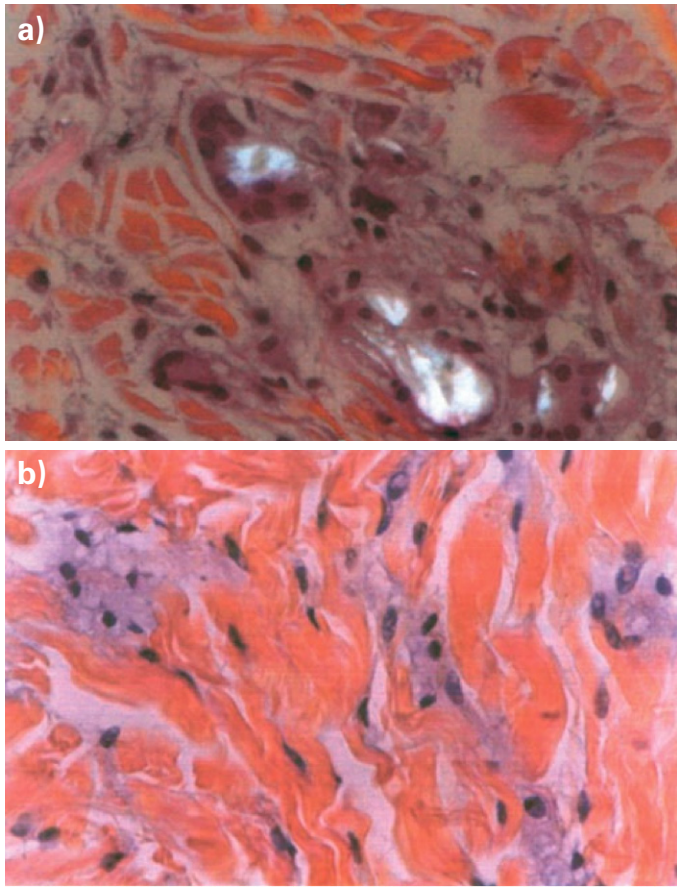


FIGURE 2. Foreign body reaction to a biomaterial.[5] Reprinted with permission from Buddy D. Ratner and Stephanie J. Bryant. Biomaterials: where we have been and where we are going. Annual Review of Biomedical Engineering, Volume 6, Pages 41-75. Copyright © 2004 by Annual Reviews.



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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AUTHOR CORRESPONDENCE

Rebecca Fitzgerald MD
E-mail:..... fitzmd@earthlink.net