Update on Dermal Filling Agents: The University of Miami Department of Dermatology's Cosmetic Center Perspective

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Collagen and hyaluronic acid (HA), 2 of the key dermal constituents that are lost as a result of age and environmental stress, can be temporarily replaced with increasingly sophisticated products. In fact, dermal filling agents used in soft tissue augmentation procedures have steadily and significantly increased in popularity since their inception nearly 3 decades ago. For a while, bovine collagen implants were considered the standard-bearing agents but have recently been eclipsed by human-derived and HA fillers. This article presents an overview of the use of collagen, HA, and poly-L-lactic acid fillers in the dermal skin layer. We will also discuss the pros and cons associated with these fillers as well as their current application in soft tissue augmentation procedures as viewed and practiced by practitioners at the University of Miami Cosmetic Center, Florida.

Beauty is a characteristic that provides sensory pleasure and plays an integral and universal role within society.[1] More than ever, patients are demanding to look and feel beautiful. By applying the practical art and science of cosmetic dermatology, cosmetic dermatologists can restore, correct, and enhance the appearance of the body's most aesthetic organ, the skin. Although cosmetic dermatologists use numerous methods to achieve this goal, soft tissue augmentation has moved to the forefront of cosmetic procedures.[2] By the mid-1980s, injecting bovine-derived collagen fillers to treat wrinkles had entered popular consciousness in the United States.[3] At the same time, scientists in other countries began to generate human-derived dermal fillers and hyaluronic acid (HA) fillers to replace the dermal components that dissipated secondary to aging. Most recently, deeper, more volumizing, and longer-lasting fillers have been added to the armamentarium of cosmetic dermatologists. One of the most prominent of these fillers is poly-L-lactic acid (PLLA). Overall, these soft tissue fillers can be classified in many ways, including depth of injection, longevity, allergenicity, degree of correction, and cost. In addition, they can be implanted using various techniques, such as serial sticks, threading, and fanning. This article will discuss the chief dermal constituents that are targeted for replenishment in soft tissue augmentation procedures, the benefits and drawbacks of the fillers used for such procedures, and the tricks of the trade regarding their employment based

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on our experiences at the University of Miami Cosmetic Center (UMCC), Florida.

COLLAGEN

Collagen protein imparts crucial skin characteristics, such as strength, durability, and resilience. Type I collagen and type III collagen are the chief collagen components in the dermal layer of adult human cutis, comprising 80% to 85% and 10% to 15%, respectively.[4] As people age, the structural proteins and primary constituents of the skin (ie, collagen) decline. This decline correlates with a 20% decrease in dermal thickness and results in skin fragility and wrinkles.[5] Naturally aged skin histopathologically exhibits epidermal and dermal atrophy with fragmented and irregular collagen bundles.[6,7] Thus, injection of various forms of collagen into the dermal layer of skin can temporarily restore a youthful appearance.

BOVINE COLLAGEN

For more than a quarter of a century, bovine collagen has been the standard-bearing dermal implant used to safely, effectively, and temporarily correct some of the undesired results from cutaneous facial aging.[3] Zyderm I, Zyderm II, and Zyplast were the first injectable bovine collagen filling agents approved by the US Food and Drug Administration (FDA) during the 1980s. All 3 of these products contain 95% type I collagen and 5% type III collagen, along with lidocaine 0.3%.[8] Zyderm I is composed of 3.5% bovine dermal collagen, Zyderm II contains 6.5% bovine dermal collagen, and Zyplast is made up of 3.5% bovine dermal collagen cross-linked with 0.0075% glutaraldehyde. The higher concentration of bovine dermal collagen in Zyderm II causes it to be thicker and less flexible than Zyderm I and Zyplast.[8] The glutaraldehyde cross-linked with collagen in Zyplast reinforces the collagen fibers and extends the duration of the correction. All 3 bovine collagen implants are available in 0.5- to 2.0-cc preloaded syringes and must be kept refrigerated until use.[8]

Pros

Bovine-derived collagen implants are effective in temporarily diminishing facial wrinkles and scars. Zyderm I is indicated for the treatment of superficial wrinkles, and Zyderm II is indicated for the treatment of moderate to deep wrinkles (eg, glabellar lines, forehead furrows, crow's-feet, fine perioral lines, and scars). Zyplast is indicated for treating deeper lines (eg, nasolabial folds and atrophic scars) and for shaping the vermilion border of the lips.[9] In addition, Zyderm I is well-suited for use in combination with Zyplast as an overlay when treating deeper rhytides (Table). The cosmetic enhancement achieved with Zyderm I and Zyderm II typically lasts for approximately 3 months, whereas the cosmetic

Recommended Combination of Dermal Fillers: Approach of the University of Miami Department of Dermatology's Cosmetic Center, Florida

Indication	Agent
Eyebrow-lift	Juvéderm Ultra or Juvéderm Ultra Plus, Restylane, Perlane, Puragen, Prevelle
Glabella	CosmoDerm I, Zyderm I
Eyes (tear trough)	Juvéderm Ultra, Prevelle
Cheekbones and below	PLLA, Restylane, Perlane, Prevelle, Puragen, Juvéderm Ultra Plus
Nose (nose bridge and raising the tip)	CosmoPlast, Restylane, Perlane
Nasolabial fold/deep wrinkles	CosmoPlast, PLLA, Restylane, Juvéderm Ultra or Juvéderm Ultra Plus, Puragen, Prevelle, Perlane
Smoker's lines	CosmoDerm or Juvéderm Ultra
Lips' edge (vermilion border, philtrum, corners)	CosmoPlast, Restylane, Juvéderm Ultra
Lips' body (dumbbell look)	Hylaform, Prevelle, Prevelle Silk, Juvéderm Ultra
Marionette lines	CosmoPlast, Restylane, Juvéderm Ultra or Juvéderm Ultra Plus, Perlane
Jowls	PLLA, Restylane, Juvéderm Ultra or Juvéderm Ultra Plus
Acne scars	Zyderm II or CosmoDerm II, Restylane or Juvéderm Ultra

Abbreviation: PLLA, poly-L-lactic acid.

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Figure 1. Patient before (A) and after (B) CosmoPlast treatment of nasal tip.

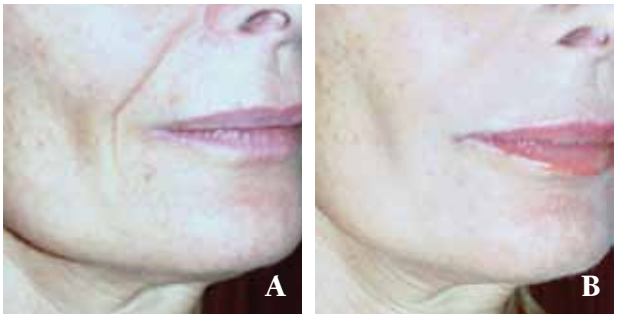

Figure 2. Patient before (A) and after (B) CosmoPlast treatment of nasolabial folds.

enhancement achieved with Zyplast lasts for up to 4 months.[9] To maintain optimal effect, bovine collagen implants can be safely reinjected 3 to 4 times per year, with a goal of overcorrection. Zyderm and Zyplast are the least expensive dermal fillers available and generally result in less bruising than HA agents.[10]

Cons

The injection of bovine-derived collagen filling agents can elicit 2 types of rare, but distinct, adverse reactions: nonhypersensitive and allergic.[8,9] Nonhypersensitive reactions include abscesses, bacterial infections, beading, cyst formation, ecchymoses, herpes virus infection, and local necrosis.[11] The risk of inducing such reactions can be reduced through various steps. If feasible, during the 10 days prior to the scheduled procedure, patients should be advised to avoid taking nonsteroidal anti-inflammatory drugs, aspirin, vitamin E, and other anticoagulants in order to reduce the risk of bruising. For patients with a history of oral herpes infections, the use of antiviral medications is recommended to lower the likelihood of recurrence. To reduce the risk of tissue necrosis, avoid injecting Zyplast into the glabellar region.[12] In a small percentage of patients (0.04%) treated with Zyderm or Zyplast prior to 1990, cysts were reported at the injection site. To prevent this adverse effect, injecting directly into the dermis is recommended.[12]

Prior to a patient being injected with bovine collagen products, 2 skin tests are performed at 6 and 2 weeks before the scheduled injections. These skin tests are necessary to lower the risk of hypersensitive or allergic reactions.[9] Sensitivity to bovine collagen is believed to be present in approximately 3% of the general population.[13] Although a patient is unlikely to experience an adverse reaction to bovine collagen agents after 2 negative skin tests, the risk (0.5%–6.2%) is never fully eliminated.[14,15] If unexpected allergic reactions do occur, they typically resolve within 4 to 24 months and can be successfully treated with topical or intralesional corticosteroids, a brief course of systemic corticosteroids, or topical tacrolimus and oral cyclosporine.[15-19]

The UMCC Experience

The fact that Zyderm and Zyplast are the most prevalent and least costly fillers on the market drives some patients at the UMCC to select these fillers. Also, patients who continue to use these implants because they perceive them as safe are reluctant to try alternatives. Therefore, we still use Zyderm I for fine lines, Zyplast for deeper furrows, and in rare cases, Zyderm II for acne scars (Table). However, the allergenicity and shorter duration of these agents make them less favored fillers.

BIOENGINEERED HUMAN COLLAGEN

Bioengineered human collagen implants include CosmoDerm I, CosmoDerm II, and CosmoPlast. These dermal filling agents, which contain human collagen types I and III, were approved by the FDA in 2003.[20]

CosmoDerm I, which contains 35 mg/cc of purified human-derived collagen with lidocaine 0.3%, is indicated for superficial wrinkles.[20] The concentration of collagen in CosmoDerm I is doubled in CosmoDerm II, whereas CosmoPlast contains the same concentration of collagen, but it is cross-linked with glutaraldehyde. Again, cross-linking reduces degradation by collagenase, thus making the filler a longer-lasting and firmer product.

Pros

The great advantage of human-derived versus bovine-derived fillers is that there is no skin testing requirement before using CosmoDerm and CosmoPlast, so these products can be administered during a patient's first visit. Longevity trials have not yet been performed with CosmoDerm and CosmoPlast, but the general consensus is that their cosmetic effects are immediate. CosmoDerm injections last approximately 3 months, and CosmoPlast injections last from 4 to 7 months, depending on the treatment area, injection technique, and amount of filling agent used.[20] Similar to the bovine-derived fillers, CosmoPlast and CosmoDerm contain lidocaine to reduce procedure-related discomfort as well as edema and ecchymoses by inhibiting the activation of eosinophils.[21]

Indeed, we observed that the swelling, bruising, and erythema associated with CosmoDerm and CosmoPlast have been minimal. These products usually result in less bruising than procedures involving HA fillers. In our experience, CosmoDerm and CosmoPlast are associated with the least amount of downtime following soft tissue augmentation procedures.

Cons

Like Zyderm and Zyplast, CosmoDerm and CosmoPlast require refrigeration and are contraindicated in patients allergic to lidocaine.[20] The longevity of their cosmetic effects are similar. CosmoDerm and CosmoPlast are very costly to manufacture; therefore, they are the more expensive filling agents.[10]

The UMCC Experience

The stiffness of CosmoPlast is more pronounced than that of HA products and provides constitutional strength, which enhances the vermilion border of the lips and the bridge of the nose and elevates the corners of the mouth (Table). At the UMCC, we commonly employ CosmoPlast to create a beautiful lip line (also known as the *Snow White line*) and the Cupid's bow shape of the lip borders and to upturn the tip of the nose in order to create a confident appearance (Figure 1). Although HA fillers are favored, CosmoDerm I can also be used to plump the body of the lip. CosmoDerm can be layered over CosmoPlast to achieve ideal contouring of deep lines, such as the nasolabial folds (Figure 2). In addition, we typically inject HA filler on top of CosmoPlast to treat medium and deep wrinkles. For human-derived collagen products, we use an average of 1 syringe for patients in their 20s, 2 syringes for patients in their 30s, 3 syringes for patients in their 40s, and a varying number of syringes as needed for older patients to correct age-related lines and folds. Although we very rarely use fillers to treat glabellar rhytides because of the potential risk of tissue necrosis, our preferred filler for glabellar rhytides is CosmoDerm I.

HYALURONIC ACID

HA is one of the most prevalent of the glycosaminoglycans and potently binds to and directs water into the skin, thereby volumizing, hydrating, and softening the skin to render a youthful appearance. HA also plays an influential role in cell growth, membrane receptor function, and adhesion, along with stabilizing intercellular structures and producing the elasticoviscous network for collagen and elastin fibers to bind together in the proper formation.[22] However, these connections dissolve with age, which may explain the disorganized clumps of collagen and elastin fibers characterizing older skin.[23] The elasticoviscous and volumizing qualities of HA make it an excellent dermal filling agent.[24]

HA filling agents pose less of a risk of inducing allergy and immunogenicity than bovine collagen products because HA is chemically identical across all species.[25] HA has a heparinlike effect that can cause a greater incidence of bruising than that caused by collagen fillers.[26] Presently, HA products used in the United States do not contain lidocaine, the lack of which is linked to increased patient discomfort.[8]

In recent years, HA agents have emerged as the novel gold standard products for soft tissue augmentation, greatly outperforming other filler products.[27,28]

Restylane

Restylane is a nonanimal stabilized HA gel produced by fermentation in bacterial cultures of equine streptococci.[28] This highly cross-linked transparent agent is a prominent HA product that was approved by the FDA in 2003 for treatment of nasolabial folds.[8] Restylane is the stiffest of all the currently available HA fillers because of the greater concentration (approximately 100,000 particles/mL in 20 mg/mL) and the method of cross-linking of HA.[28] Of the products in the Restylane line, only Restylane and Perlane are currently approved by the FDA.[29] Perlane, which has the same concentration of HA as Restylane but consists of larger gel particles, is used over deeper and larger areas, such as the cheeks and jowls.

Pros—Restylane products do not require refrigeration or skin tests prior to treatment.[29] Acute and delayed-type hypersensitivity reactions to Restylane occur less frequently than those associated with collagen products.[29] Rare events of sterile abscesses, nodules, granulomas, and tissue necrosis secondary to hylans have been reported.[29] The longevity of the cosmetic effects of Restylane averages 6 to 12 months, making Restylane more enduring than most of the other filling agents discussed so far.[29] The syringe design of Restylane is superior to that of other HA products, making Restylane easier to administer.

Cons—In addition to the bruising and pain associated with Restylane injections, erythema and edema are typical adverse effects lasting a few days after injection.[29] Since hylans are thicker materials, their rheology is different from that of the collagen fillers, requiring the clinician to use more pressure when administering these products.[29] Because poor injection technique when administering Restylane can result in bumps and blue blebs, proper training is recommended.[29] We noted that slower injections and postprocedure massage of Restylane may lower the risk of inflammation and nodules. The temporary administration of low-dose systemic prednisone can improve severe swelling.

The UMCC Experience—Restylane is ideal for injecting in the middermal layer to fill facial rhytides (nasolabial

and marionette lines, chin and jowl depressions, nasal deformities, and tip lift) as well as acne scars and uneven defects (Table). Although many practitioners do it, we do not like to use Restylane in areas with thin skin, such as the body of the lip or around the eyes. Now that Hylaform (a softer HA filler) is being taken off the market, we are looking forward to the launch of Restylane Lip, which is a softer and more pliable Restylane product designed especially for the lips.

Juvéderm

Approved by the FDA in 2006, Juvéderm is also a non-animal stabilized HA dermal filler.[30] Juvéderm products differ by the HA concentration and the level and regularity of cross-linking. Of the Juvéderm products, only Juvéderm 24 HV (Juvéderm Ultra) and Juvéderm 30 HV (Juvéderm Ultra Plus) are currently FDA approved and sold in the United States.[30] Both of these fillers are composed of 24 mg/cc of HA, but Juvéderm Ultra Plus has a higher proportion (11%) of cross-linked HA than Juvéderm Ultra, rendering it a deeper injection agent. Juvéderm is a homogenous gel with the highest cross-linking of any HA filler (90%), creating a smoother consistency.[29] Although the duration of correction achieved with Juvéderm has never been tested directly, it is reported to be similar to that of Restylane.[30]

Pros—Juvéderm products require no skin tests or refrigeration prior to their use and can be administered to patients during the initial visit.[29] These products are also immunologically inert, leading to less immune-mediated and granulomatous adverse effects compared with other fillers.[30] Overall, the adverse effect profile of Juvéderm is similar to that of Restylane.[29] We have found Juvéderm to be a slightly softer and easier HA to inject compared with other HA products, probably owing to its homogenicity.

Cons—Like all HA products without lidocaine, Juvéderm products can induce erythema, swelling, and bruising.[30] There is a theory that higher levels of Juvéderm cross-linking may increase inflammatory reactions in the skin, but this theory has not been proven.[29] Caution must be taken when injecting Juvéderm into thin skin areas to prevent a bluish Tyndall effect and nodules.[29]

The UMCC Experience—Juvéderm Ultra Plus is appropriate for deeply sunken areas, such as the malar prominences and jowl void (Table). It is also a softer workhorse for treating the area around the eyes as well as the tear trough and for building up the body of the lip and the nasolabial and marionette lines. Any of the HA fillers, including Juvéderm Ultra, Juvéderm Ultra Plus, Restylane, or Perlane, can be applied to raise the lateral aspects of the brows even better and more naturally than botulinum toxin type A.

POLY-L-LACTIC ACID

Derived from the α-hydroxy acid family, injectable PLLA is a synthetic, biodegradable, biocompatible, immunologically inert peptide polymer.[31-33] Given the size and slow degradation of the PLLA microspheres, this 3-dimensional substance is thought to foster neocollagenesis by stimulating fibroblasts and gradually restoring facial volume.[34-36] In the United States, PLLA is approved for the treatment of HIV-associated facial lipoatrophy, but it has been used off label for folds cosmesis.

The mechanism of action of PLLA and the proper technique of injecting it (with a larger-bore, 25-gauge needle, compared with the 30-gauge needle used for other dermal fillers) requires practitioners to restore volume to a selected treatment area over time rather than to a specific wrinkle.[37] In addition, specialized training to use PLLA is required.

Pros

PLLA imparts a minimally invasive and effective correction, with optimal cosmetic benefits of skin thickness and facial improvement in wrinkles, depressions, and laxity seen at 2 to 4 weeks posttreatment and lasting approximately 18 to 24 months.[35,37-39] Having been used successfully in various medical devices for more than 30 years, PLLA has an established safety record.[40] New product guidelines and injection techniques (eg, using a more dilute product, avoiding overcorrection, not injecting too superficially, and administering postinjection massage) have reduced the incidence of adverse effects (eg, granulomas and nodule formation) as compared to an earlier packaging of PLLA.[41]

Cons

Results from PLLA injections are not immediate, and multiple injections are required to achieve the optimal cosmetic effect, with the number of treatments depending on the volume of the defect being treated.[38] Adverse events are rare, but PLLA can cause more postinjection site pain, bruising, and swelling than other products, partly because of the larger needle used. Adding lidocaine to the diluent mitigates injection pain. Bruising can be reduced by mixing epinephrine into the PLLA solution and applying arnica gel, which has coagulant properties, to the affected areas postinjection or by taking bromelain supplements (500 mg twice daily). Hyperkinetic areas (eg, around the eyes and smoker's lines above the lips) should not be treated with PLLA because of small papules that can emerge in such areas. Nodule formation and hematoma formation are the other rare adverse effects reported, but are less likely if the new injection guidelines are followed.[42,43]

The UMCC Experience

PLLA must be injected with special caution, not too superficially, and not in excess at each location. We usually use 2 to 3 cc of the product for patients in their 30s and 4 cc for patients 40 years and older. Patients older than 50 years and postmenopausal women generally require more than 4 sessions spaced one month apart. The treatment areas of choice for PLLA are the malar prominences, cheeks, and nasolabial folds. Because of its tendency to form papules in hyperkinetic areas, PLLA should never be injected into the lip, above the lip, or in the crow's-feet area. After the procedure, the patient's skin should be vigorously massaged with arnica gel to reduce bruising, pain, and nodule formation. Restylane, Juvéderm, or Perlane can be layered over PLLA and can provide the immediate result desired by some patients.

SUMMARY

Soft tissue augmentation procedures have become increasingly popular since their mainstream introduction a quarter of a century ago. Research is ongoing to develop filler devices that overcome the limitations of current products, match their most advantageous characteristics, and exceed the duration and discomfort of correction. Because of consumer demand, several forms of collagen and HA filling agents are available in the United States, and others are on the horizon. As other fillers enter the arena, we shall soon determine their pros and cons from the UMCC perspective. Presently, the trend is to use collagen, HA, and PLLA in conjunction to achieve an optimal cosmetic result. It is the responsibility of skin practitioners to be aware of the expanding list of filling agent options in order to make the most appropriate treatment selections for their patients.

REFERENCES

1. Etcoff NL. Survival of the Prettiest: The Science of Beauty. New York, NY: Anchor Books; 2000.
2. Housman TS, Hancox JG, Mir MR, et al. What specialties perform the most common outpatient cosmetic procedures in the United States? *Dermatol Surg*. 2008;34:1-7.
3. Klein A, Elson M. The history of substances for soft tissue augmentation. *Dermatol Surg*. 2000;26:1096-1105.
4. Gniadecka M, Nielsen OF, Wessel S, et al. Water and protein structure in photoaged and chronically aged skin. *J Invest Dermatol*. 1998;111:1129-1133.
5. Fenske NA, Lober CW. Structural and functional changes of normal aging skin. *J Am Acad Dermatol*. 1986;15:571-585.
6. Lavker RM. Structural alterations in exposed and unexposed aged skin. *J Invest Dermatol*. 1979;73:59-66.
7. Lovell CR, Smolenski KA, Duance VC, et al. Type I and III collagen content and fiber distribution in normal human skin during ageing. *Br J Dermatol*. 1987;117:419-428.
8. Eppley BL, Dadvand B. Injectable soft-tissue fillers: clinical overview. *Plast Reconstr Surg*. 2006;118:98e-106e.
9. Clark DP, Hanke CW, Swanson NA. Dermal implants: safety of products injected for soft tissue augmentation. *J Am Acad Dermatol*. 1989;21:992-998.
10. Sengelmann RD, Tull S, Pollack SV. Soft tissue augmentation. In: Robinson JK, Hanke WC, Sengelmann RD, et al, eds. *Surgery of the Skin: Procedural Dermatology*. Philadelphia, PA: Elsevier Mosby; 2005:437-462.
11. Cooperman LS, Mackinnon V, Bechler G, et al. Injectable collagen: a six-year clinical investigation. *Aesthetic Plast Surg*. 1985; 9:145-151.
12. Hanke CW, Higley HR, Jolivette DM, et al. Abscess formation and local necrosis after treatment with Zyderm or Zyplast collagen implant. *J Am Acad Dermatol*. 1991;25:319-326.
13. Elson ML. The role of skin testing in the use of collagen injectable materials. *J Dermatol Surg Oncol*. 1989;15:301-303.
14. Castrow FF 2nd, Krull EA. Injectable collagen implant—update. *J Am Acad Dermatol*. 1983;9:889-893.
15. Siegle RJ, McCoy JP Jr, Schade W, et al. Intradermal implantation of bovine collagen: humoral immune responses associated with clinical reactions. *Arch Dermatol*. 1984;120:183-187.
16. Klein AW. In favor of double testing. *J Dermatol Surg Oncol*. 1989;15:263.
17. Klein AW, Rish DC. Injectable collagen update. *J Dermatol Surg Oncol*. 1984;10:519-522.
18. Moody BR, Sengelmann RD. Topical tacrolimus in the treatment of bovine collagen hypersensitivity. *Dermatol Surg*. 2001;27: 789-791.
19. Baumann LS, Kerdel F. The treatment of bovine collagen allergy with cyclosporin. *Dermatol Surg*. 1999;25:247-249.
20. Baumann L. CosmoDerm/CosmoPlast (human bioengineered collagen) for the aging face. *Facial Plast Surg*. 2004;20:125-128.
21. Okada S, Hagan JB, Kato M, et al. Lidocaine and its analogues inhibit IL-5-mediated survival and activation of human eosinophils. *J Immunol*. 1998;160:4010-4017.
22. Piacquadio D, Larson NE, Denlinger JL, et al. Hylan B gel (Hylaform) as a soft tissue augmentation material. In: Klein AW, ed. *Tissue Augmentation in Clinical Practice: Procedures and Techniques*. New York: Marcel Dekker; 1998:269-293.
23. Ghersetich I, Lotti T, Campanile G, et al. Hyaluronic acid in cutaneous intrinsic aging. *Int J Dermatol*. 1994;33:119-122.
24. Larsen NE, Pollak CT, Reiner K, et al. Hylan gel biomaterial: dermal and immunologic compatibility. *J Biomed Mater Res*. 1993;27:1129-1134.
25. Barbucci R, Lamponi S, Magnani A, et al. The influence of molecular weight on the biological activity of heparin like sulphated hyaluronic acids. *Biomaterials*. 1998;19:801-806.
26. Pandolfi M, Hedner U. The effect of sodium hyaluronate and sodium chondroitin sulfate on the coagulation system in vitro. *Ophthalmology*. 1984;91:864-866.
27. Cosmetic Surgery National Data Bank 2005 Statistics. The American Society of Aesthetic Plastic Surgery Web site. http://www.surgery.org/download/2005stats.pdf. Accessed June 7, 2006.
28. Narins RS, Brandt F, Leyden J, et al. A randomized, double-blind multicenter comparison of the efficacy and tolerability of Restylane versus Zyplast for the correction of nasolabial folds. *Dermatol Surg*. 2003;29:588-595.
29. Narins RS, Cohen JL, Michaels J. Hylans and soft tissue augmentation. In: Carruthers J, Carruthers A, eds. *Soft Tissue Augmentation*. 2nd ed. Philadelphia, PA: Saunders Elsevier; 2007:chapter 4. *Procedures in Cosmetic Dermatology*.
30. Monheit GD, Prather CL. Juvéderm: a hyaluronic acid dermal filler. *J Drugs Dermatol*. 2007;6:1091-1095.
31. Majola A, Vainionpää S, Vihtonen K, et al. Absorption, biocompatibility, and fixation properties of polylactic acid in bone

tissue: an experimental study in rats. *Clin Orthop Relat Res*. 1991; 268:260-269.
32. Gogolewski S, Jovanovic M, Perren SM, et al. Tissue response and in vivo degradation of selected polyhydroxyacids: polylactides (PLA), poly(3-hydroxybutyrate) (PHB), and poly (3-hydroxybutyrate-co-3-hydroxyvalerate) (PHB/VA). *J Biomed Mater Res*. 1993;27:1135-1148.
33. Viljanen JT, Pihlajamäki HK, Törmälä PO, et al. Comparison of the tissue response to absorbable self-reinforced polylactide screws and metallic screws in the fixation of cancellous bone osteotomies: an experimental study on the rabbit distal femur. *J Orthop Res*. 1997;15:398-407.
34. Burgess CM, Lowe NJ. NewFill for skin augmentation: a new filler or failure? *Dermatol Surg*. 2006;32:1530-1532.
35. Sherman RN. Sculptra: the new three-dimensional filler. *Clin Plast Surg*. 2006;33:539-550.
36. Thioly-Bensoussan D. A new option for volumetric restoration: poly-L-lactic acid. *J Eur Acad Dermatol Venereol*. 2006;20 (suppl 1):12-16.
37. Vleggaar D, Bauer U. Facial enhancement and the European experience with Sculptra (poly-l-lactic acid). *J Drugs Dermatol*. 2004;3:542-547.
38. Keni SP, Sidle DM. Sculptra (injectable poly-L-lactic acid). *Facial Plast Surg Clin North Am*. 2007;15:91-97.
39. Vleggaar D. Facial volumetric correction with injectable poly-L-lactic acid. *Dermatol Surg*. 2005;31:1511-1517.
40. Lowe NJ. Dispelling the myth: appropriate use of poly-L-lactic acid and clinical considerations. *J Eur Acad Dermatol Venereol*. 2006;20(suppl 1):2-6.
41. Vleggaar D. Poly-L-lactic acid: consultation on the injection techniques. *J Eur Acad Dermatol Venereol*. 2006;20(suppl 1):17-21.
42. Borelli C, Kunte C, Weisenseel P, et al. Deep subcutaneous application of poly-L-lactic acid as a filler for facial lipoatrophy in HIV-infected patients. *Skin Pharmacol Physiol*. 2005; 18:273-278.
43. El-Beyrouty C, Huang V, Darnold CJ, et al. Poly-L-lactic acid for facial lipoatrophy in HIV. *Ann Pharmacother*. 2006;40: 1602-1606.