Soft Tissue Augmentation

Ranella J. Hirsch, MD; Joel L. Cohen, MD

Recent additions to the soft tissue augmentation armamentarium have greatly increased the dermatologic surgeon's choices in optimizing facial contouring and the treatment of acne scars. In this article, we review the science of fillers and look at the future of dermal fillers.

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During the normal aging process, there is a loss of connective and subcutaneous tissue, most notably on the face, neck, and hands. Subcutaneous tissue augmentation with injectable fillers can fill lines, replace lost volume, and reposition sagging structures. Thus, these materials may be used for a rejuvenating effect to soften the appearance of aging, provide a fuller more youthful face, and recontour lines that form over time.

In addition to rejuvenation, fillers have an important role in repairing defects such as scars. Scars from acne, surgery, or trauma predominantly result from loss or contraction of tissue, and each also can be greatly improved with fillers. Scars best suited for therapy with filler materials are soft and easily distensible. A stretch test can be performed and is recommended preoperatively. According to Solish and Pollack,[1] "pinch the skin around the scar to be treated and observe the amount of correction to the scar…complete correction with taut stretch predicts successful treatment with fillers."

Recently, a plethora of new products and developments for soft tissue augmentation have been introduced. We review current treatment options and look at the future of soft tissue augmentation.

Optimizing Results With Fillers

To optimize results using fillers for soft tissue augmentation, the practitioner must be knowledgeable about several important variables, including preprocedural instructions, choice of filler material, proper placement in the desired location, amount of implant deposited, postprocedural instructions, and timing of repeat injections. Each filler has individual properties that must be considered when selecting the product that is appropriate for a given patient and his/her goals. Different fillers have different tissue residence times, ranging from months to years. Selection of the perfect product for a given indication in a particular patient does not guarantee a perfect outcome. Precise placement of any filling substance is critical, requiring anatomic knowledge of the areas being treated as well as an understanding of the intended depth of placement of the material being utilized. We also feel that to optimize results, it is important that patients obtain incremental benefit from reevaluation and touch-up injections before an implant is completely absorbed.

Other factors affecting filler selection include budget and time frame. Depending on the amount and type of filler used, it also is prudent to avoid soft tissue augmentation for approximately 10 to 14 days prior to an important business or social event, such as a wedding. Patients should be advised to avoid aspirin, nonsteriodal anti-inflammatory drugs, vitamin E, and other herbal supplements for

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Dr. Hirsch is from Skincare Doctors, Cambridge, Massachusetts. Dr. Cohen is from AboutSkin Dermatology and DermSurgery, Denver, Colorado.
Dr. Hirsch is a consultant and has received honoraria from Allergan, Inc, and Medicis Pharmaceutical Corporation. Dr. Cohen is a clinical trial participant, consultant, national trainer, and speaker for Allergan, Inc, and Medicis Pharmaceutical Corporation. He also is a consultant and trainer for Dermik Laboratories, a consultant for Inamed Corporation, and a clinical trial participant for Ipsen.
Reprints: Ranella J. Hirsch, MD, Skincare Doctors, 777 Concord Ave, Suite 206, Cambridge, MA 02138.

10 days prior to treatment with any fillers to decrease the risk for and degree of swelling and bruising.

Preprocedure and postprocedure photography is essential for documentation; it can help show patients the degree of correction achieved. Too often, patients forget what you made go away and simply focus on what is leftover. Prior to any injection with soft tissue augmentation products, makeup should be completely removed and the treatment area cleaned with alcohol. Subsequently, a chlorhexidine preparation of the area is recommended. Postprocedure, ice to the treatment site can be effective at decreasing swelling and minimizing bruising. We have patients ice treatment areas for 20 minutes in the office to ensure the icing process is understood and started. We also tell patients to avoid exercise for 12 hours to decrease augmentation of blood to the area and to refrain from putting on makeup until the following day because of the potential risk for transfer of any bacterial or viral products from makeup; contamination is more than just a theoretic risk.

Fillers can be classified in many different ways. Typically, products are classified as temporary, semipermanent, or permanent fillers. Determining whether the material is from an animal, nonanimal, or autologous source is another method of classifying fillers.

The Holy Grail of dermal fillers is permanence coupled with a lack of antigenicity.[2] At present, no filler substance exists that is permanent without some level of antigenicity and inflammation. With dermal filling, less inflammation represents an improved chance at longevity because less inflammation is associated with a longer-lasting fill effect. These criteria are not met by fat or collagen from any source (bovine or cadaver), all of which are resorbed by the body over time.[3]

Collagen Fillers

Many dermal fillers are available for soft tissue augmentation. Zyderm® 1, Zyderm 2, and Zyplast® are suspensions of bovine dermal collagen packaged with lidocaine. The anesthetic tempers the discomfort of the intradermal injection. Zyderm 1 is available in a concentration of 35 mg/mL in phosphate-buffered saline solution with lidocaine added for anesthesia. Zyderm 2 is twice as concentrated at 65 mg/mL.[4] Zyplast is a more stable product because it contains collagen cross-linked with 0.0075% gluteraldehyde, which strengthens the collagen fibers, rendering it more resistant to decomposition by the host.[5]

Zyderm 1 is used to treat fine lines, shallow scars, and thin-skinned areas.[6] Zyderm 2 is indicated for the treatment of moderate lines, wrinkles, scars, and thicker-skinned areas. Zyplast is best used for contouring and shaping and to treat pronounced scars, lines, and furrows, as well as to define the lip border. A widely accepted practice is the layering of Zyderm 1 over Zyplast when both volume fill and subtle contour are required for optimal correction. While Zyplast is placed in the mid dermis, the injection technique for Zyderm is to raise a papillary dermal bleb as the material flows along superficial lines. It is necessary to overcorrect by approximately 200% with Zyderm as it is diluted with saline. When using this product, it is necessary to explain to patients that the saline is reabsorbed over 24 hours. When treating the glabella, botulinum toxin chemodenervation frequently is combined with Zyderm injections to enhance and prolong the correction obtained. Cutaneous necrosis, however, has been associated with soft tissue augmentation of the glabella, most likely resulting from deep product placement, causing compression of the watershed branches of the supratrochlear vessels or direct intravascular injection of the material.[6]

The primary advantage of bovine collagen is its proven safety record over many years in expert hands. The largest drawback to therapy with bovine material is the risk for hypersensitivity in 3% to 5% of treated patients, which has been documented in the aesthetic dermatology literature.[6] Because a substantial number of patients with one negative skin test subsequently have developed a reaction at the treatment site, double skin testing is widely practiced (lowering the risk from 1% to less than 0.5%).[7] It is recommended that if a patient has not received treatment for more than one year, a single retest should be done with evaluation at 2 weeks.

There has been some concern about the possibility of bovine collagen inciting crossover autoantibodies to human collagen, with theoretic risk for subsequent induction of collagen vascular disease. Various studies and panels have indicated that this type of induction has not occurred and would be extremely remote.[6-8] Public opinion also has swayed practitioners away from some animal-based products. Practitioners should avoid treating patients who have a history of lidocaine sensitivity, an anaphylactoid event, beef allergy, and, of course, previous sensitivity to bovine collagen.

To reduce the risk for sensitivity to a bovine product, quell any possible concerns of potential risk for transferring some animal-hosted infectious processes, and obviate the need for skin testing, CosmoDerm® and CosmoPlast® human-derived collagen products were launched in early 2003. CosmoDerm is bioengineered human collagen

obtained from fibroblasts of neonatal foreskin. It is ideal for patients sensitive to bovine- and cadaver-based collagens. This human material has been extensively tested for viruses, tumorigenicity, and retroviruses, as well as known genetic diseases. The product etymology is similar to the respective bovine derivatives Zyderm and Zyplast. CosmoDerm and CosmoPlast have the additional advantage of requiring no pre-skin testing, so they can be used at the initial consultation visit. They provide immediate correction and are valuable adjuncts to the fillers category.[9] No important data have shown CosmoDerm and CosmoPlast to yield a measurably longer correction as compared with the bovine product, and our anecdotal experience has not suggested increased durability either.

Autologen™ is an autograft composed of collagen removed from the donor patient during harvesting.[10] The tissue is frozen and sent for processing, where it can be stored for up to 5 years. When needed, it can be directly processed so that 1 sq in of harvested skin produces about 3 cc of Autologen product. The syringes of this processed material are stable for up to 6 months. Because it is autologous collagen, no skin testing is required, and patient anxiety about use of animal or another person's material is alleviated. The product contains no anesthetic, so topical anesthesia is necessary, and sometimes local infiltration blocks also are necessary. The injection sessions usually are spaced at 2-week intervals until the desired correction is achieved. The main disadvantages are the need for large tissue harvesting (usually skin from abdominoplasty or a face-lift procedure), the delay required for tissue processing, and the high cost of the product. It is composed of intact human dermal collagen fibers with intact telopeptides still attached, thus rendering it very resistant to enzymatic degradation, with reports suggesting durability of the injected material up to 18 months.[10]

Isolagen™ is another autologous collagen product; however, harvesting requires only a small piece of tissue, typically a 3-mm punch biopsy harvested from the postauricular sulcus.[10] The harvested material is sent to the company where it is cultured and grown in vitro for 6 weeks. The material is then returned to the physician's office in 1- to 1.5-cc aliquots. The injections are similar to traditional collagen injections. Like Autologen, the material does not contain any anesthetic. Injections usually are spaced at 2- to 3-week intervals until the desired correction is reached. Since the material is autologous, there should not be any risk for allergic or immunologic reactions. Nevertheless, skin testing is recommended so that any by-product allergy can be detected. Finally, because viable fibroblasts, collagen matrix, and other materials required for replenishment of the dermal support structures are being injected, the Isolagen process offers the opportunity to have a durable correction, but there are few data on the exact duration of the product.[10]

Cadaver-Derived Implants

Cymetra® and Fascian® are alternative soft tissue augmentation products. Both are acellular freeze-dried dermal grafts processed from human cadaver dermis. No skin testing is required. Fascian is derived from human gastrocnemius (crural) fascia or fascia lata that is then processed, freeze dried, and ethylene-oxide–sterilized to insure sterility. Harvested from screened human donors, Fascian is an injectable formulation of the same substance that is applicable for soft tissue repair and augmentation. Fascian is prepared in accordance with US Food and Drug Administration (FDA) regulations for processing nonviable human tissue, though cadaver-derived implants Cymetra, Fascian, and AlloDerm® are not FDA approved.[11] Provided in preloaded syringes, all 3 products have several advantageous features. It does not require refrigeration, and, because of low allergenicity, test implantation is not required.

Five different particle sizes (0.10 mm, 0.25 mm, 0.50 mm, 1.0 mm, and 2.0 mm) of Fascian are available in preloaded syringes containing 80 mg. Each particle size treats problems of different sizes and types. The syringe content can be hydrated in anesthetic solution to a volume of 1 to 3 cc and then injected through a needle. The product tends to spread evenly through the tissues. It is easy to handle and is stored at room temperature.[12] The process of tissue particulation has not altered the inherent graft properties, and Fascian seems to evoke the same process of collagen replacement that routinely occurs in larger grafts.

Hyaluronic Acid–Based Fillers

Over the past 2 years, the limelight has been on hyaluronic acid (HA)–based fillers. HA is a universal component of the extracellular matrix that, unlike collagen, is chemically identical across species and thus confers less risk for antigenicity.[13] In the past 2 years, the FDA approved several HA fillers including Restylane® and Hylaform®, and, more recently, Hylaform Plus and Captique™. HA itself is a glycosaminoglycan polysaccharide composed of alternating residues of the monosaccharides d-glucuronic acid and N-acetyl-d-glucosamine

forming a long unbranched polyanionic chain. Glycosaminoglycans are abundant in fetal skin and are present in low levels in adulthood. The chains in these HA products are hydrated and coil upon themselves, giving the material both elasticity and viscosity.[14] The product is known to have exquisite water-binding capacity and thus is responsible for dermal hydration.[15]

Restylane and Captique are derived from the fermentation of specific strains of streptococci, which are then alcohol precipitated, filtered, and dried. Hylaform is another HA derivative made from rooster combs.[16] Captique was FDA-approved in November 2004 and is very similar to Hylaform. Like Hylaform, it has a concentration of 5.5 mg/mL, contains 500 μm particles, and is cross-linked by divinyl sulfone. It also is injected with a 30-gauge needle. Captique, aside from its bacterial source, so closely resembles Hylaform that it is considered to be an extension of it as a new manufacturing source rather than a new product. Captique seems to be a useful product for areas such as the lips, which require minimal edema.

Restylane, Perlane™, and Restylane Fine Lines are biocompatible biotechnologically manufactured gels of HAs.[17] Though all 3 of these Restylane products are available in much of the world, including Europe and Canada, currently only Restylane is FDA approved in the United States. Restylane is packaged with sodium chloride and a phosphate buffer and comes as a preloaded 0.4- or 1.0-mL syringe. Restylane is more viscous (20 mg/mL) than Hylaform gel (5.5 mg/mL); Hylaform is more elastic. Both comprise the ground substance and are extremely hydrophilic.[17]

All 3 of the Restylane products contain a concentration of 20 mg/mL. The difference between each of these products is their unique particle size. Restylane Fine Lines has the smallest particle size (200,000 gel particles/mL) and is the least viscous of the 3 products. It is injected through a 31-gauge needle and is intended for the correction of superficial defects. Restylane is of a larger particle size (100,000 gel particles/mL). It is injected through a 30-gauge needle and is intended for placement in the papillary dermis for correction of moderate rhytides. Perlane is of the largest particle size (10,000 gel particles/mL), is injected via a 27-gauge needle, and is best suited for deep rhytides and sculpting. With these products as well as other HA products, anesthesia can be provided through judicious use of ice, topical anesthetics, and nerve blocks.

It is common practice to combine the use of an HA product such as Restylane for deeper rhytides with CosmoDerm or Zyderm for more superficial wrinkles. In addition, many practitioners are utilizing both botulinum toxin type A and dermal fillers to take advantage of their synergistic effects in tissue. Botulinum toxin type A functions to disrupt the muscle's ability to move; thus, it effectively prevents dynamic wrinkles from forming by keeping the musculature from pulling and imprinting lines in the overlying skin. By contrast, filler substances add volume. Used together, the results of each product last longer and are enhanced. In a prospective randomized study comparing the use of Restylane alone to the use of Restylane and botulinum toxin type A to treat severe glabellar rhytides, Carruthers and Carruthers[18] reported a better response and longer maintenance of correction.

Current standard of care with HA does not include pretreatment allergy testing. Delayed reactions with Restylane, defined as occurring 14 days or more after the last injection, occur in 1 of every 25,000 injections.[19] Anecdotally, these reactions seem to be transient, lasting between 2 weeks and 2 months, and only rarely require the use of topical or injectable corticosteroids.

It is imperative for practitioners to comprehend the distinct difference between delayed hypersensitivity reactions and true allergy. Lupton and Alster[20] reported on a particular case of hypersensitivity secondary to an impurity of the bacterial fermentation of the modified HA gel. Fernández-Aceñero et al[21] reported a case of a foreign body reaction after injection of HA. Histologic examination confirmed the presence of a nodule in the subcutaneous fat that stained intensely with Alcian blue at pH 2.7, confirming the presence of HA.[21] There are, as of the writing of this piece, 3 reported cases of HA-related allergy, which represents an extremely low complication rate.[20-22] It is not clear if these cases were the result of impurities in the material injected or true allergies.

Restylane is a nonanimal stabilized HA (NASHA) with an adverse reaction profile of 0.15% in the pre-1999 material and 0.06% in the post-1999 product. A decrease in adverse incidents is attributed to the introduction of a more purified HA raw material post-1999.[19] Nonetheless, practitioners must review the risks of the rare hypersensitivity reaction and/or the very rare allergy with prospective patients during the informed consent process. Worldwide, HA is not only manufactured under the names of Hylaform and Captique but also Juvéderm™ and Rofilan®.

The full spectrum of Juvéderm products (Juvéderm 18, Juvéderm 24, Juvéderm 24HV, Juvéderm 30, Juvéderm 30HV) currently is marketed

in Europe and Canada. Recently, the FDA approved Juvéderm 24HV, Juvéderm 30, and Juvéderm 30HV.[23] Based on our experience, it is a promising agent.

Juvéderm, like Restylane and Captique, is a nonanimal-derived HA made from bacterial fermentation of streptococcus and cross-linked by butane-diol-diglycidyl ether. Juvéderm, however, is a homogeneous (nonparticulate) gel-based HA, in contrast to the other hyalurons that contain particles of different sizes. It is believed that the homogeneous structure of Juvéderm gel leads to increased longevity because there is less surface area available for host enzymatic processes to attack and degrade the HA. The homogeneous Juvéderm has less friction on injection (ie, more pliable and viscoelastic) and could be potentially less inflammatory than other HA products.

The recently FDA-approved products include Juvéderm 24HV, Juvéderm 30, and Juvéderm 30HV. Juvéderm 24HV is highly cross-linked for increased versatility in contouring and volumizing middermal defects, Juvéderm 30 is intended for the subtle correction of facial wrinkles and folds, and Juvéderm 30HV is more highly cross-linked for volumizing and correcting deeper folds and wrinkles.[23] Unlike Juvéderm 18, which is composed of 18 mg of cross-linked HA, Juvéderm 24 and 30 contain 24 mg of cross-linked nonanimal-derived HA.

These products also do not contain anesthetic and thus require either topical anesthetic or injectable anesthetic prior to treatment in most patients. As with other hyalurons, injection technique is variable with linear threading, serial puncture, and cross hatching being advocated by various skilled injectors.

Aquamid® gel is 2.5% polyacrylamide and 97.5% water. Given the lack of particles and a very high concentration of water, it is homogeneous, stable, and nonbiodegradable. Aquamid has been authorized for sale in Europe since March 2001. de Cassia Novaes and Berg[24] present experience with Aquamid in 59 subjects (43 subjects [72%] received lip augmentation and 8 subjects [13%] received cheekbone enlargement and nasolabial fold correction with high levels of patient satisfaction).

Currently, in the United States, HA-based products are favored fillers among dermatologic surgeons given their longevity, ease of use, and safety data.[25] The Federal Food, Drug, and Cosmetic Act allows any legally marketed FDA-approved product to be administered for any condition in a doctor-patient relationship.[26] The term for this is *off-label use* and it is a widely accepted practice in the United States.

Permanent and Semipermanent Fillers

Recently, there has been renewed interest in more permanent fillers. Worldwide, permanent and semipermanent skin implants include New-Fill™, Artecoll®, Dermalive®, and Evolence™. The rights to New-Fill, renamed Sculptra® in the United States, have been purchased and the product was fast-tracked through the FDA to gain approval for the treatment of facial lipoatrophy in patients with human immunodeficiency virus.[27] New-Fill is polylactic acid that occurs naturally and is known to stimulate the body's own collagen production. Safety data presently are lacking, as no large trials have been reported yet in the United States. The deeper level of placement, large volume of dilution, and longer reconstitution times seem to anecdotally be greatly reducing the fairly high rates of nodule formation reported in Europe.

Artecoll is a nonbiodegradable permanent filler containing polymethylmethacralate microspheres 25% of 30 to 40 μm in diameter suspended in bovine collagen solution with saline and lidocaine 0.3% to minimize discomfort during injection.[28] It is designed for implantation into the deep reticular dermis. It has a 2-fold function: (1) an immediate filler, and (2) an inert long-lasting scaffold to stimulate permanent deposition of autologous collagen around the microspheres. The bovine collagen suspension component has an expected lifespan of 3 to 6 months and necessitates skin testing. Artecoll has been widely used in Europe for the last 10 years.[28]

The bovine collagen in Artecoll is obtained from calves aged up to 6 months that only have been fed milk and vegetables.[28] The goal of this diet is to avoid administration of hormones or antibiotics. To prepare the solution, the collagen is washed with sodium hydroxide to protect against contamination with bovine spongiform encephalitis and other viruses. The telopeptide immunogenic ends then are removed and the material filtered to lower antigenicity.[28]

The promise of long-standing correction leads the list of advantages and disadvantages. While the notion of long-standing correction is appealing to both patients and practitioners, late-onset granulomas have been reported in the aesthetic and dermatologic literature. Alcalay et al[29] recently reported the case of a 54-year-old woman who presented with firm nodules at the site of an Artecoll injection 14 months prior. Histologic examination revealed histiocytic granulomas with giant cells and vacuoles. If the product is injected too superficially, blanching will be observed and there is a substantial risk for

palpable permanent beading. Also of note is the risk for delayed sensitization to the bovine collagen within Artecoll.[30]

Radiesse™ is a calcium hydroxylapatite injectable filler currently FDA approved for oral/maxillofacial defects, vocal fold insufficiency, and radiographic tissue marking.[31] Radiesse is the longest lasting nonpermanent wrinkle filler available with results that can last up to 2 to 5 years. Its effects are longer lasting than any other treatment available, but there is concern that it can interfere with the reading of dental x-rays. Long-term clinical studies on its use as a soft tissue filler are lacking.[31]

Of critical importance with any injectable material is both the skill of the injector and the reliability of the product that is injected. It is imperative that patients carefully inquire about who is injecting and the product that is being injected. In a report on the development of orofacial granulomas after the use of filler substances, only 3 of 11 patients involved knew what substance had been injected.[32]

Silicone

Silicone, a synthetic compound composed of long polymers of dimethysiloxanes, likely is the most commonly implanted material in all of medical practice.[33] It has existed in an assortment of incarnations over many decades and can possess a variety of physical characteristics depending on its chemical structure. Its consistency can range from a gel form to an expansive shell (used as a tissue expander) to a stable solid compound. Solid silicone facial implants are highly inert and resistant to degradation but by nature are hydrophobic and nonporous. Consequently, silicone does not allow for fibrovascular ingrowth that, when achieved, yields several important benefits, including immobility and infection resistance. Thus, part of the implantation process for dermal implants is the fenestration with a scalpel or large bore needle to incite fibrous ingrowth.[33]

In the United States, use of silicone for soft tissue augmentation is not FDA approved and constitutes an off-label use of the product.[34] Side effects include the development of granulomas and a variety of rare immunologic manifestations.[35] Currently, there are 2 FDA-approved medical-grade liquid injectables (approved for ophthalmic use to tamponade retinal detachment)—AdatoSil 5000™ and Silikon® 1000.

Polytetrafluorethylene in the form of the Softform™ implant has a fibrillar nature that permits fibrovascular ingrowth into a microporous surface, permitting its widespread use in both soft tissue and bony augmentation, including the lips, nasolabial folds, and malar areas. Its history is poor with a substantial complication profile since its introduction in 1997. The 4 most frequent postoperative complications are extrusion, movement of the product, infection, and granulomatous swelling necessitating 8% removal of the device after implantation.[34]

Autologous Fat Transplantation

Unlike dermal fillers such as collagen and HA that function by the replacement of volume to a dead space, autologous fat transplantation is the grafting of viable donor tissue. Fat transplantation has many potential dermatologic uses, including the augmentation of congenital defects, management of scarring disease such as morphea, and use in lipodystrophy in patients with human immunodeficiency virus.[36] Best recipient sites are distensible scars associated with subdermal atrophy.[37] It also is used for cosmetic purposes, including breast augmentation and rejuvenation of aging hands.[38]

Many techniques exist, but the precise conditions yielding the most favorable survival of the transplanted fat are poorly understood.[39] The distinct advantage is the lack of immune response and the fact that this product can be frozen and reused. Meticulous care to prevent clerical error between stored donor and recipient tissue is crucial. The main disadvantages are the time and procedure required for the harvest and the unpredictable correction secondary to irregular resorption.[39]

Comment

The skill of the injector and the reliability of what is injected are of supreme importance for optimum results with any filler material. It is imperative that patients are treated by qualified injectors who understand the precise anatomy to be treated and know exactly what is being injected. Practitioners are fortunate to have many choices available to treat patients with acne scars and scars from other dermatologic conditions. Judicious patient selection, appropriate product selection, and meticulous technique are the best ways to ensure high levels of patient satisfaction and optimize clinical improvement.

REFERENCES

1. Solish N, Pollack SV. Approaches to acne scarring: a review. *J Cutan Med Surg*. 1998;2(suppl 3):24-32.

2. Krauss MC. Recent advances in soft tissue augmentation. *Semin Cutan Med Surg*. 1999;18:119-127.
3. Allen O. Response to subdermal implantation of texturized microimplants in humans. *Aesthetic Plast Surg*. 1992;16:227-230.
4. Hirsch RJ, Lewis AB. Treatment of acne scarring. *Semin Cutan Med Surg*. 2001;20:190-198.
5. Bailin MD, Bailin PM. Case studies: correction of surgical scars, acne scars, and rhytids with Zyderm and Zyplast implants. *J Dermatol Surg Oncol*. 1988;14(suppl 1):31-34.
6. DeLustro F, Mackinnon V, Swanson NA. Immunology of injectable collagen in human subjects. *J Dermatol Surg Oncol*. 1988;14(suppl 1):49-55.
7. Elson ML. The role of skin testing in the use of collagen injectable materials. *J Dermatol Surg Oncol*. 1989;15: 301-303.
8. Klein AW. Bonfire of the wrinkles. *J Dermatol Surg Oncol*. 1991;17:543-544.
9. Klein AW. Tissue fillers [letter]. *J Drugs Dermatol*. 2003;2:617.
10. Fagien S. Facial soft-tissue augmentation with injectable autologous and allogeneic human tissue collagen matrix (autologen and dermalogen). *Plast Reconstr Surg*. 2000;105:362-373; discussion 374-375.
11. Burres S. Preserved particulate fascia lata for injection: a new alternative. *Dermatol Surg*. 1999;25:790-794.
12. Burres S. Soft-tissue augmentation with Fascian. *Clin Plast Surg*. 2001;28:101-110.
13. Larsen NE, Pollack CT, Reiner K, et al. Hylan gel biomaterial: dermal and immunologic compatibility. *J Biomed Mater Res*. 1993;27:1129-1134.
14. Comper WD, Laurent TC. Physiological function of connective tissue polysaccharides. *Physiol Rev*. 1978;58: 255-315.
15. Meyer LJ, Stern R. Age-dependent changes of hyaluronan in human skin. *J Invest Dermatol*. 1994;102: 385-389.
16. Harry C. A comparison of today's treatment options for soft tissue augmentation. *Skin & Aging*. March 1999;3:88.
17. Duranti F, Salti G, Bovani B, et al. Injectable hyaluronic acid gel for soft tissue augmentation. a clinical and histological study. *Dermatol Surg*. 1998;24:1317-1325.
18. Carruthers J, Carruthers A. A prospective, randomized, parallel group study analyzing the effect of BTX-A (Botox) and nonanimal sourced hyaluronic acid (NASHA, Restylane) in combination compared with NASHA (Restylane) alone in severe glabellar rhytids in adult female subjects: treatment of severe glabellar rhytids with a hyaluronic acid derivative compared with the derivative and BTX-A. *Dermatol Surg*. 2003;29:802-809.
19. Friedman PM, Mafong EA, Kauvar AN, et al. Safety data of injectable nonanimal stabilized hyaluronic acid for soft tissue augmentation. *Dermatol Surg*. 2002;28: 491-494.
20. Lupton JR, Alster TS. Cutaneous hypersensitivity reaction to injectable hyaluronic acid gel. *Dermatol Surg*. 2000;26:135-137.
21. Fernández-Aceñero MJ, Zamora E, Borbujo J. Granulomatous foreign body reaction against hyaluronic acid: report of a case after lip augmentation. *Dermatol Surg*. 2003;29:1225-1226.
22. Raulin C, Greve B, Hartschuh W, et al. Exudative granulomatous reaction to hyaluronic acid (Hylaform). *Contact Dermatitis*. 2000;43:178-179.
23. Allergan announces FDA approval of Juvéderm gel family of products for the treatment of facial wrinkles and folds [press release]. Irvine, Calif: Allergan, Inc; June 5, 2006.
24. de Cassia Novaes W, Berg A. Experiences with a new nonbiodegradable hydrogel (Aquamid): a pilot study. *Aesthetic Plast Surg*. 2003;27:376-380.
25. 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.
26. US Food and Drug Administration. Federal Food, Drug, and Cosmetic Act. Available at: http://www.fda.gov /opacom/laws/fdcact/fdctoc.htm. Accessed August 17, 2006.
27. Moyle G, Lysakova L, Brown S, et al. Polylactate (NewFill) injections subjectively and objectively improve appearance and reduce anxiety and depression scores in HIV positive persons with facial lipoatrophy: a randomized, open label, immediate vs. delayed therapy study. Poster presented at: 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy; September 27-30, 2002; San Diego, California.
28. Lemperle G, Romano JJ, Busso M. Soft tissue augmentation with Artecoll: 10-year history, indications, techniques, and complications. *Dermatol Surg*. 2003;29:573-587.
29. Alcalay J, Alkalay R, Gat A, et al. Late-onset granulomatous reaction to Artecoll. *Dermatol Surg*. 2003;29:859-862.
30. McClelland M, Egbert B, Hanko V, et al. Evaluation of Artecoll polymethylmethacrylate implant for soft-tissue augmentation: biocompatibility and chemical characterization. *Plast Reconstr Surg*. 1997;100:1466-1474.
31. Lemperle G, Morhenn V, Charrier U. Human histology and persistence of various injectable filler substances for soft tissue augmentation. *Aesthetic Plast Surg*. 2003;27: 354-356; discussion 367.
32. Rubin JP, Yaremchuk MJ. Complications and toxicities of implantable biomaterials used in facial reconstructive and aesthetic surgery: a comprehensive review of the literature. *Plast Reconstr Surg*. 1997;100:1336-1353.
33. Rapaport MJ, Vinnik C, Zarem H. Injectable silicone: cause of facial nodules, cellulites, ulceration, and migration. *Aesthetic Plast Surg*. 1996;20:267-276.

34. Brody HJ. Complications of expanded polytetrafluoroethylene (e-PTFE) facial implant. *Dermatol Surg*. 2001;27:792-794.
35. Lombardi T, Samson J, Plantier F, et al. Orofacial granulomas after injection of cosmetic fillers. histopathologic and clinical study of 11 cases. *J Oral Pathol Med*. 2004;33:115-120.
36. Moskowitz L. Treatment of facial hemiatrophy by transplantation of fat tissues. *Med Clin*. 1930;26:1472.
37. Pinski KS. Microlipoinjection and autologous collagen. *Dermatol Clin*. 1995;13:339-351.
38. Vita VT. Lipoinjection and aging hands. *Am J Cosmet Surg*. 1989;6:27-32.
39. Rohrich RJ, Sorokin ES, Brown SA. In search of improved fat transfer viability: a quantitative analysis of the role of centrifugation and harvest site. *Plast Reconstr Surg*. 2004;113:391-395.