CME

Injectable Soft-Tissue Fillers: Clinical Overview

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Learning Objectives: After studying this article, the participant should be able to: 1. Know the composition and biology of injectable fillers. 2. Understand the advantages and disadvantages of each injectable filler. 3. Understand the U.S. Food and Drug Administration regulatory status of each type of injectable filler, including their indications.

Background: The use of injectable filling agents for soft-tissue facial defects has a long history of successful use based on xenogeneic collagen materials. New materials of differing compositions for injection treatments either are now available or will soon be available for clinical use.

Methods: A review of the medical literature was performed to provide chemical compositions, methods of preparation, biological behavior, and clinical outcomes for every known injectable filler material that is either currently used or being evaluated in clinical trials.

Results: Hyaluronic acid–based materials have now replaced animal or human-derived collagen as the standard injection materials. Synthetic alternatives offer the potential of longer lasting results, but the long-term outcome with their use in large numbers of patients is not yet known.

Conclusions: As there is no single injectable filler that has all of the desired characteristics, understanding the advantages and disadvantages of one filler over another is extremely helpful in guiding the patient to an informed decision. Although all of the reviewed injectable fillers are safe, the concepts of their long-term volume persistence and how they compare with each other remain largely anecdotal, with few prospective controlled clinical trials. (*Plast. Reconstr. Surg.* 118: 98e, 2006.)

The placement of high-flow, low-viscosity materials for soft-tissue enhancement has a long history of use in aesthetic facial alteration. Although bovine collagen injections have long been dominant, the past 5 years have seen the emergence of numerous new fillers of differing compositions. When combined with the increasing popularity of injectable Botox and other office-based procedures, the role of injectable soft-tissue augmentation continues to expand. With the advent of various new injectable fillers, it is important to assess their compositions and characteristics to make the optimal selection to achieve the patient's goals.

Ideally, an injectable implant should have a lack of any significant inflammatory response (be highly biocompatible), be easily introduced into the recipient site by injection (have good flow behavior through a small-gauge needle), and produce an acceptably long period of volume retention (i.e., months to years). Each current U.S. Food and Drug Administration–approved filler and those under U.S. Food and Drug Administration application/study exhibit differences in these three basic characteristics. It is incumbent on the physician to understand the physical and biological properties of the intended filler before its clinical use.

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Received for publication September 26, 2005; accepted November 1, 2005.

DOI: 10.1097/01.prs.0000232436.91409.30

XENOGENEIC MATERIALS

Zyderm/Zyplast

The first widely used injectable filler, whose clinical use continues to decline, remains the standard to which all other injectable fillers continue to be compared.

Its animal derivation and short longevity have led to its decrease in popularity.[1] In U.S. Food and Drug Administration clinical trials, however, its long history of clinical use and data make it the frequently used control.

Composition

Zyderm I and II and Zyplast (Inamed Aesthetics, Santa Barbara, Calif.) are derivatives of bovine

collagen. Zyderm I was U.S. Food and Drug Administration approved in 1981, whereas Zyderm II gained U.S. Food and Drug Administration approval in 1983. Zyplast was U.S. Food and Drug Administration approved in 1985. Zyderm I is 96 percent type I collagen, with the remainder being type III collagen. It is 3.5 percent bovine dermal collagen by weight, suspended in phosphate-buffered physiologic saline.[2] Zyderm II is 6.5 percent bovine dermal collagen by weight. Zyplast is 3.5 percent bovine dermal collagen cross-linked by glutaraldehyde, which makes it more resistant to biodegradation. It is more viscous than Zyderm but less immunogenic.

Clinical Characteristics

Zyderm and Zyplast are prepackaged in 1- or 2-ml syringes. They are opaque and are typically injected with a 30-gauge needle. Zyderm I is injected in the papillary dermis and is U.S. Food and Drug Administration approved for fine lines and shallow acne scars. Zyderm II, which also comes in 0.5-ml syringes, is injected in the papillary dermis and is U.S. Food and Drug Administration approved for moderate lines and deeper acne scars. Zyplast is injected into the mid to deep dermis and the subcutaneous region and is best used for deep folds and lines. Overcorrection is necessary with Zyderm because it is diluted with phosphate-buffered physiologic saline, which is reabsorbed. Results typically last 2 to 3 months.

Advantages

With a 25-year history of clinical use, Zyderm and Zyplast are known to be safe, with very few local complications. Their clinical effectiveness and versatility are well established. Also, they come diluted with 0.3% lidocaine, which may reduce the pain on injection.

Disadvantages

Because Zyderm and Zyplast are bovine derivatives, they require skin testing and thus should not be used on the day of consultation, unless it is an established patient. Two skin tests are administered 2 weeks apart, with the second test being 4 weeks before the procedure. Of note, 3 percent of patients develop a sensitivity reaction even with a normal skin test.[3] Local adverse effects include erythema, induration, pruritus, and skin discoloration. Furthermore, a systemic hypersensitivity reaction can occur 48 to 72 hours after injection. This is manifested by fever, malaise, and urticaria, which are treated with short-term oral steroids. Granulomas have also been reported with Zyderm/Zyplast. Reactivation of herpes is possible with lip injections; thus, patients with a positive history need antiviral prophylaxis. Other complications include necrosis of the overlying skin and unilateral vision loss caused by retinal artery occlusion. They are also contraindicated in patients with lidocaine allergies. The material starts to be degraded immediately after injection, with clinical effects observable for a few months. The reduction in injection volume is essentially linear over time.

ALLOGENEIC MATERIALS (COLLAGEN-BASED HOMOLOGUES)

Cosmoderm/Cosmoplast

In an eventual response to the concerns and problems with bovine-derived collagen, the introduction of human-based collagen homologues has occurred more recently. Similarly named, they offer the promise of decreased immunogenicity and longer lasting results.

Composition

CosmoDerm I and II and CosmoPlast (Inamed) are injectable implants derived from highly purified human collagen. Both CosmoDerm and CosmoPlast were U.S. Food and Drug Administration approved for use in facial aesthetic surgery in March of 2003 and are the only U.S. Food and Drug Administration–approved dermal fillers made from human collagen.

The collagen is cultured from a single cell line of human dermal fibroblasts that has been used for over 10 years to manufacture human-based tissues; these cells produce natural collagen that is then isolated and purified for injection. The cell line undergoes extensive testing for viruses, retroviruses, and tumorigenicity. CosmoDerm II contains approximately twice the concentration of collagen as CosmoDerm I.

Clinical Characteristics

CosmoDerm and CosmoPlast are prepackaged in 1-ml syringes. They are opaque and should be refrigerated but must not be frozen. They are typically injected with 30-gauge needles. CosmoDerm is U.S. Food and Drug Administration approved for shallow wrinkles or acne scars and is injected into the superficial papillary dermis. CosmoPlast is injected into the mid to deep dermis for the correction of more pronounced wrinkles or scars. However, the safety and efficacy of CosmoDerm use in lip augmentation has not been established. Its flow characteristics are similar to Zyderm and, like Zyderm, overcorrection is necessary with CosmoDerm because it is diluted with saline, which is reabsorbed. The use of CosmoDerm I should be limited to 30 cc per patient per year. CosmoDerm II and CosmoPlast should

be limited to 15 cc per patient per year. Results typically last 3 to 6 months.

Advantages

The Inamed Human Collagen Immunogenicity Clinical Study demonstrated that the 95 percent upper confidence interval for experiencing a hypersensitivity reaction against CosmoDerm and CosmoPlast is less than 1.3 percent. This is less than the incidence of immunologically related adverse events reported with Zyderm/Zyplast in treated patients who initially had a negative skin test. Unlike bovine collagen implants, these dermal fillers do not require a pretreatment skin test before treatment. This has been established through their preapproval U.S. Food and Drug Administration application study. Thus, patients may undergo treatment at the time of their initial consultation. They come diluted in 0.3% lidocaine, which may have some benefit in reducing pain on injection.

Disadvantages

The use of these products is contraindicated in patients with a known allergy to lidocaine. In a study to evaluate sensitization to CosmoDerm and CosmoPlast, 428 patients were injected with CosmoDerm I into the forearm and followed for 2 months; the more common adverse side effects included the following: cold-like symptoms, 4.1 percent; flu-like symptoms, 2.0 percent; and urinary tract infection, 1.0 percent.[3]

The longevity of this material appears to be similar to bovine collagen. No prospective study has been reported that conclusively demonstrates superior volume persistence.

Cymetra

AlloDerm has many indications in reconstructive and aesthetic surgery. The conversion of these materials into an injectable form is a logical extension of their subcutaneous use.[4]

Composition

Cymetra (LifeCell Corp., Palo Alto, Calif.) is the injectable form of micronized AlloDerm, a decellularized processed dermal allograft[5] that was U.S. Food and Drug Administration approved in 2000. The material is originally obtained from tissue banks compliant with the guidelines of the American Association of Tissue Banks and the U.S. Food and Drug Administration. First, the epidermis is completely removed, followed by the removal of dermal cells and stabilization of the dermal matrix through the inhibition of metalloproteinases. The material is then cryofractured, breaking down the acellular dermal matrix into micronized particles that are packaged into syringes. At the time of clinical use, it is necessary to hydrate the powder.

Clinical Characteristics

Cymetra is presented as a 330-mg dry particulate in a 5-cc syringe. It is reconstituted with 1 cc of 1% lidocaine and is injected through a 26-gauge needle into the subcutaneous space. Its more viscous consistency after hydration requires a large-caliber needle for introduction. Cymetra is indicated for use in nasolabial folds, lips, and acne and depressed scars. Results typically last 3 to 9 months.

Advantages

No immune response is elicited because cells exhibiting major histocompatability complexes I and II have been removed. Patients can be treated at initial consultation because no skin testing is needed.

Disadvantages

Because of Cymetra's large particle size (>100 μm), injections are less smooth than most other implants and can be more painful because of the size of the needle. Patients should also be made aware of postinjection edema. Furthermore, its use should be avoided in periocular line correction and glabellar contouring to avoid the risk of intravascular injection and migration. Cymetra is supplied in an antibiotic-supplemented medium; thus, patients with sensitivities to the antibiotic should not receive this material. The size of the hydrated particles and the needle do not allow intradermal injection, limiting its use to the subcutaneous space.

As this is a tissue bank material, formal U.S. Food and Drug Administration clinical trials and comparisons to other materials have not been conducted. Reported clinical outcomes are largely anecdotal. There are no clinical trials that demonstrate its longevity to be superior to other collagen-based implants.

Fascian

Tissue bank collagen material, other than from the dermis, is possible from numerous other sources. Fascia, with a very tight fibrillar collagen weave, offers the potential for a more dense form of collagen implant. Fascian was introduced in April of 1999.

Composition

Fascian (Fascia Biosystems, Beverly Hills, Calif.) is preserved, particulate fascia lata derived from human cadavers obtained from an American Association of Tissue Banks Guideline–compliant

tissue bank.[6] Preserved fascia lata has been used for a long time as a sheet graft material but has only recently become available in injectable form.[7]

Clinical Characteristics

Fascian is freeze-dried, irradiated, and then processed into particle sizes of 0.25, 0.5, 1.0, or 2 mm, of which 80 mg of volume is inserted into each syringe. The material may be stored at room temperature for years. Clinically, Fascian is indicated for deep wrinkles, scars, fat atrophy, and prominent nasolabial folds.[8] At the time of injection, the fascia particles are initially hydrated in 3 to 5 cc of 0.3% lidocaine solution. This produces a thick paste that can be extruded through a large-bore needle. The injected area is preundermined with a 20-gauge needle and the material injected into the preformed tunnel with a 16- to 25-gauge needle, depending on the size of the particles used. Fascia Biosystems reports the duration of results to be 6 to 8 months, but other anecdotal reports show Fascian's duration to be 3 to 6 months.

Advantages

In a study by Burres, 81 patients receiving 109 injections of Fascian over a period of 6 to 9 months experienced no infections, allergic reactions, or acute rejections; there have been no reports of disease transmission.[9] No skin testing is necessary, so the patient may the receive injection at the time of initial consultation.

Disadvantages

Trace amounts of polymyxin B sulfate, bacitracin, or gentamicin are present in Fascian implants; patients with known allergies to these antibiotics should avoid Fascian accordingly. The large size of the needle needed for introduction results in the potential for increased bruising. In addition, local anesthesia infiltration into the recipient or nerve blocks may be needed for patient comfort during the procedure. Documentation of the longevity of the material has not been reported in any prospective or controlled patient series.

SYNTHETIC MATERIALS

Restylane

The long-term use of this synthetically derived material in Europe and the very favorable clinical results represented a fundamental change in injection technology.[10] The transition from a protein-based material to one of an extracellular matrix composition is a paradigm shift from two decades of previous clinical experience.

Composition

Restylane (Medicis, Scottsdale, Ariz.) is produced today by fermentation in cultures of equine streptococci. The fermented material is then stabilized by means of epoxidic cross-links of the glycosaminoglycan chains. As a result of this processing method, the hyaluronic acid, or hyaluronan, does not cause immunologic sensitization and there is virtually no risk of allergic reactions.[11] Hyaluronan is a polysaccharide that is an essential component of the extracellular matrices in which most tissues differentiate. In certain tissues, such as the vitreous cavity of the eye and synovial joint fluid, it is the major constituent. Unlike collagen, it is identical across all animal species and microbes. The largest amount of hyaluronan resides in skin, where it is present in both dermis and epidermis. Hyaluronan's high capacity for holding water and high viscoelasticity give it some unique properties that are useful in various medical and pharmaceutical applications.[12] Because it retains moisture, hyaluronan is used in some cosmetics to keep skin young and fresh-looking. As we age, the water-holding capacity of our skin decreases as hyaluronan depolymerizes. Therefore, the retention or insertion of hyaluronan into the skin is theoretically helpful in wrinkle reduction.

Hyaluronic acid can be rather rapidly degraded and is ultimately metabolized in the liver. Modern processing methods have produced more stable forms of hyaluronic acid that have much longer in vivo retention times. As degradation occurs over time, water is attracted to the material at the site of implantation. As the hyaluronic acid concentration decreases, more water bonds to it, thus helping with cosmetic persistence. This feature is what probably accounts for its longer volume retention effects than bovine collagen (isovolemic degradation).

Clinical Characteristics

A variety of differing grades of transparent gels are available, based on the same type of gel from highly concentrated (20 mg/ml) stabilized hyaluronic acid, which varies in particle size and subsequent indication. Restylane has a particulate size of 100,000 gel particles per milliliter, flows through a 27-gauge needle, and is U.S. Food and Drug Administration approved for mid-dermal applications such as deeper wrinkle reduction and for lip augmentation, nasolabial folds, and glabellar creases.[13] Restylane has even been successfully used in the treatment of tear trough deformities.[14] Restylane Fine Lines has the highest concentration at 200,000 gel particles per milliliter, can be injected through a 30-gauge needle, and is indi-

cated for thin superficial wrinkles. The lowest concentration gel is Perlane at 8000 gel particles per milliliter, which is injected through a 27-gauge needle and is intended for shaping facial contours and correcting deep folds, and for lip augmentation.[15] Restylane was U.S. Food and Drug Administration approved in December of 2003, Restylane FN and Perlane await eventual U.S. Food and Drug Administration clearance.

Advantages

Its universal hyaluronic acid composition makes the need for preinjection skin testing unnecessary, as the risk for hypersensitivity reactions is minimal.[16] It is easily injected and flows nicely through small-gauge needles. Although not permanent, its persistence is reported to exceed that of bovine collagen, with estimates of between 6 and 12 months after injection.[17]

Disadvantages

In a study comparing Restylane with Zyplast, there was an overall higher incidence of severe bruising (3.6 percent versus 0.7 percent), severe swelling (3.6 percent versus 1.4 percent), and severe pain (3.6 percent versus 1.4 percent) with Restylane. The increased pain is partly because Restylane does not come mixed with local anesthetic. Common side effects include injection-site inflammation, with an incidence of 0.02 percent, and local hypersensitivity reactions (i.e., swelling, erythema, and induration), with an incidence of 0.02 percent, lasting a mean of 15 days.[18] Its cost is more than that of collagen-based materials.

Captique

Composition

Captique (Inamed) is a nonanimal, stabilized, hyaluronic acid–based material derived from the same nonanimal source as Restylane. It was U.S. Food and Drug Administration approved in December of 2004. As a competitive analogue to Restylane, it offers what appears to be a very similar hyaluronic acid–composed injection material from a different manufacturing source. Marketing information states that it is a "softer" hyaluronic acid than Restylane, although that exact meaning of that is not clear. One can speculate that this means it has less gel particles per milliliter.

Clinical Characteristics

Similar to Restylane, it is a clear, colorless gel that is indicated for fine lines and wrinkles. It comes in 1-cc syringes and is typically injected with a 30-gauge needle, although flow through a 30-gauge needle is also possible. The longevity of the injection is reported to be 3 to 6 months.

Advantages

No skin test is necessary, as with other hyaluronic acid materials.

Disadvantages

What, if any, differences exist between it and Restylane are not known. It is assumed that its clinical performance, in terms of incidence of postinjection reactions and longevity of volume persistence, is similar. No controlled clinical trial comparing it to Restylane and any other injectable has been reported, although anecdotally, Captique is felt to last significantly shorter than Restylane.

Hylaform

Composition

Hylaform (Inamed) is a sterile, colorless gel implant that consists of cross-linked molecules of hyaluronic acid derived from an avian source.[19] Extracts of the rooster comb have been widely used in orthopedic surgery as a viscoelastic injection into symptomatic joints since 1996. This is a more dense form of avian-derived hyaluronic acid because of its intraarticular use. As a facial soft-tissue injection, its density is decreased. It gained U.S. Food and Drug Administration approval in April of 2004. Hylaform Plus, which is also a clear, colorless gel, consists of larger mean hyaluronic acid particles than Hylaform. Hylaform Plus was U.S. Food and Drug Administration approved in October of 2004.

Clinical Characteristics

Hylaform is indicated for moderate to severe facial wrinkles and folds, but not for lip augmentation.[12] Hylaform comes in prepackaged sterile syringes that should be stored at room temperature. It is injected into the mid to deep dermis using a 30-gauge needle. Hylaform Plus is U.S. Food and Drug Administration approved for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds. Subdermal injection will lead to inferior results, and if it is injected too superficially, it may cause skin discoloration. Linear threading, serial puncture injections, or a combination of the two have been demonstrated to be effective. However, overcorrection should be avoided. Patients should be limited to 20 cc of Hylaform gel per 60-kg body mass per year. The safety of injecting greater amounts has not been established. Results typically last 3 to 4 months.

Advantages

No skin test is necessary; thus, it can be used at the initial consultation.

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