ONLINE FIRST

Contemporary Review of Injectable Facial Fillers

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Perhaps the most significant change in facial rejuvenation in the last 10 years has been the introduction of nonsurgical treatments for the relaxation of facial wrinkles and for the restoration of lost volume. Fillers such as paraffin and silicone have been used in the past for volume restoration, but only recently have new fillers been developed whose safety and efficacy have been supported by clinical research. The introduction of hyaluronic acid (HA) fillers in 2003 began the filler revolution and paved the way for development of biostimulatory and permanent materials. There is an abundance of high-level evidence-based studies comparing the HA fillers, calcium hydroxylapatite, and poly(methyl methacrylate) with collagen and other HA formulations, but there is only limited high-level data evaluating poly-L-lactic acid.

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A new branch of aesthetic procedures was developed in the new millennium. Historically, silicones and paraffins were injected, with sometimes disastrous results including granulomas and paraffinomas, often seen many years after treatment.[1] Although collagen injections became available in the 1980s, because of the limited longevity of results and potential for hypersensitivity, combined with the social stigma of having injections performed, these treatments were predominantly used by the "rich and famous." The introduction of Botox (onabotulinum toxin A; Allergan Inc) and Restylane (hyaluronic acid [HA]; Medicis Aesthetics) in the early 2000s had particular appeal to the women of the baby boomer generation (born 1946-1964), who had become members of the workforce and were interested in rejuvenation procedures with minimal downtime. Since 1997, the number of nonsurgical procedures performed in the United States increased 356%, with Botox taking the lead, followed by HA fillers. The Aesthetic Society for Aesthetic Plastic Surgery reported that in 2011, there were 1.2 million patients injected with HA in the United States.[2]

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The market responded to the immense interest in nonsurgical treatments with the development of numerous new filling agents. Of the currently used dermal fillers, Sculptra (poly-L-lactic acid [PLLA]) (Valeant Pharmaceuticals) was approved by the US Food and Drug Administration (FDA) in 2004; Juvéderm (HA) (Allergan), Artefill (poly[methyl methacrylate] [PMMA]) (Suneva Medical), and Radiesse (calcium hydroxylapatite [CaHA]) (Merz Aesthetics) were approved in 2006; and Belotero (HA) (Merz Pharmaceuticals) and LaViv (human fibroblasts) (Fibrocell Technologies) were approved in 2011 (**Table 1**). Botulinum toxins are considered drugs by the FDA, but wrinkle fillers are considered medical devices. For this reason, the FDA assigned generic names to the botulinum toxins, but trade names are used to describe the different formulations of injectable fillers. The FDA specifically defines a cosmetic injectable device as a product used to improve appearance and does not impart any health benefits.[3] Wrinkle fillers are a subcategory of medical devices, defined as injectable implants used to improve wrinkles and smooth the face. Wrinkle fillers can produce either tempo-

Table 1. Injectable Fillers Listed by Dates of FDA Approval

Year of FDA Approval	Product Trade Name (Manufacturer)[a]	Product Description
1981	Zyderm 1 (Inamed/Allergan)	Bovine collagen (35 mg/mL)
1983	Zyderm 2 (Inamed/Allergan)	Bovine collagen (65 mg/mL)
1985	Zyplast (Inamed/Allergan)	Bovine collagen (35-mg/mL collagen cross-linked with glutaraldehyde)
2003	Cosmoderm (Inamed/Allergan)	Human collagen
	Cosmoplast (Inamed/Allergan)	Human collagen
	Restylane (Medicis Aesthetics)	HA
2004	Hylaform (Inamed Corp)	Animal-derived HA
	Captique (Genzyme Corp)	Nonanimal HA
	Sculptra (Valeant Pharmaceuticals)	PLLA
2005	Cosmoderm 2 (Inamed/Allergan)	Human collagen
2006	**Juvéderm Ultra** (Allergan)	Nonanimal HA
	Juvéderm Ultra Plus (Allergan)	Nonanimal HA
	Artefill (Suneva Medical)	PMMA
	Radiesse (Merz Aesthetics)	CaHA
2007	**Perlane** (Medicis Aesthetics)	Nonanimal HA
	Elevess (Anika Therapeutics)	Nonanimal HA
2008	Prevelle silk (Mentor Corp)	Nonanimal HA
	Evolence (ColBar LifeScience)	Porcine collagen
2009	Hydrelle (formerly Elevess) (Anika Therapeutics)	Nonanimal HA
	Sculptra Aesthetic (Valeant Pharmaceuticals)	PLLA
2010	**Juvéderm XC** (Allergan)	Nonanimal HA with lidocaine
	Restylane-L (Medicis Aesthetics)	Nonanimal HA with lidocaine
	Perlane-L (Medicis Aesthetics)	Nonanimal HA with lidocaine
2011	**Belotero** (Merz Pharmaceuticals)	Nonanimal HA
	LaViv (Fibrocell Technologies)	Autologous fibroblasts
Pending	Juvéderm Voluma (Allergan)	Nonanimal HA
	Juvéderm Voluma-XD (Allergan)	Nonanimal HA with lidocaine

Abbreviations: CaHA, calcium hydroxylapatite; FDA, US Food and Drug Administration; HA, hyaluronic acid; PLLA, poly-L-lactic acid; PMMA, poly(methyl methacrylate).

[a] Products in boldface are currently available.

rary or permanent results, based on their composition. The stringent FDA guidelines require that a new device demonstrates that it is safe and effective and equivalent or noninferior to a legally marketed device. Currently, FDA-approved temporary fillers are collagens, HA, CaHA, and PLLA, while the only permanent filler with FDA approval is PMMA. Silicone, although used for certain ophthalmic conditions, is not FDA approved for any cosmetic injection. Injectable filling agents are generally approved for improvement of moderate to severe nasolabial folds (NLFs), marionette lines, or facial lipoatrophy; however, Restylane was recently granted FDA approval for lip augmentation.

HYALURONIC ACID

Hyaluronic acid is a naturally occurring polysaccharide found in the skin dermis, umbilical cord, synovial joint fluid, hyaline cartilage, and connective tissues. Because it is biodegradable, biocompatible, and nonimmunogenic, it is an ideal filling agent. The chemical structure of HA consists of disaccharide units of glucuronic acid and N-acetylglucosamine connected by alternating β-1,3 and β-1,4 bonds. Hyaluronic acids work well as fillers because of their low potential for allergic reactions, their consistency across species, and their viscoelastic and hygroscopic (swelling by the absorption of water) properties. Some early HA fillers were derived from rooster combs; however, residual avian proteins caused allergic reactions in some patients. Nonanimal stabilized HAs were developed by the fermentation of *Streptococcus equi* bacterium and are currently the only class of HA fillers used today.[4]

Hyaluronic acid fillers differ from one another by their degree of cross-linking, gel consistency properties, and concentration. Cross-linking is required to stabilize the HA and prevent degradation when injected into the skin. Cross-linking transforms hylan fluid into a more cohesive gel. The most common cross-linking agent used is 1,4-butanediol diglycidal ether, which can be irritating or even toxic to skin. For this reason, any unlinked 1,4-butanediol diglycidal ether must be removed during the manufacturing process. Fillers may differ by both the amount of cross-linked HA as well as the degree of cross-linking within the gel.[5]

In addition, HAs can be classified as either monophasic or biphasic gels.[6] Biphasic gels such as Restylane and Perlane (Medicis Aesthetics) are particles of cross-linked HA suspended in a liquid. They differ by particle size: Restylane particles are roughly 250 μm in diameter, and Perlane, 550 μm, with concentrations of 100 000 particles/mL and 8000 to 10 000 particles/mL, respectively. Monophasic gels (Juvéderm Ultra and Juvéderm Ultra Plus [Allergan]) are cross-linked in 1 process (Hylacross technology) (Allergan), producing entirely stabilized smooth gel without particles. Belotero (Merz Pharmaceuticals) is also a monophasic gel cross-linked by cohesive polydensified matrix technology, which produces increased elastic and viscous properties.

Clinical trials for facial fillers focused on treatment of the NLFs. This particular anatomical area was ideal to

Table 2. Wrinkle Severity Rating Scale

Score	Description	Findings
0	Absent	No visible nasolabial fold; continuous skin line
1	Mild	Shallow but visible fold with a slight indentation; minor facial feature; filler implant will produce a slight improvement in appearance
2	Moderate	Moderately deep folds; clear facial feature visible at normal appearance but not when stretched; excellent correction expected with filler
3	Severe	Very long and deep folds; prominent facial feature; less than 2-mm visible fold when stretched; significant improvement expected from filler
4	Extreme	Extremely deep and long folds; detrimental to facial appearance; 2-4–mm V-shaped fold when stretched; unlikely to have satisfactory improvement with filler implant alone

Table 3. The Global Aesthetic Improvement Scale

Rating	Description
Very much improved	Optimal cosmetic result
Much improved	Marked improvement by not completely optimal; touch-up would slightly improve result
Improved	Obvious improvement but touch-up or retreatment is indicated
No change	Appearance essentially the same as the original condition
Worse	Appearance is worse than original condition

study for several reasons: it is an area not well treated by most aging face surgical procedures; it has a built-in side-by-side control; and it is easy to analyze and photograph. Before the introduction of HA fillers, collagen injections were the standard treatment for the correction of wrinkles and folds. For this reason, collagen was used as the control for early efficacy and safety studies of new injectable products.

The initial major US study of HA fillers was performed by Nairns et al[7] in 2003. They performed a double-blind, split-face, randomized controlled trial (RCT), which compared the efficacy of Restylane (HA) with Zyplast (collagen) (Inamed Corp) for the correction of NLFs (n = 138). By assessing the patients using both the 5-point Wrinkle Severity Rating Scale (WSRS [validated by Day et al[8]]) (**Table 2**) and the Global Aesthetic Improvement Scale (GAIS)[7] (**Table 3**), they found that at 6 months, approximately 60% of patients treated with HA retained improvement compared with only 9% of patients treated with collagen. In addition, less HA product was required to produce the optimal cosmetic effect compared with collagen. Adverse events (AEs) were similar for the 2 products. Lindqvist et al[9] performed a similar study in Europe, comparing Perlane with Zyplast; however, the patients were followed up for 1 year. Their results were similar to the study by Nairns et al[7] and showed that Perlane was superior to Zyplast at maintaining correction of the NLFs at 6 and 9 months; however, they noted that Perlane caused fewer local injection site reactions compared with collagen.

The superiority of Juvéderm in longevity and safety over collagen was studied in a multicenter RCT.[10] In this split-faced study, 439 subjects were injected on 1 NLF with 1 of 3 different preparations of Juvéderm (which differed by degree of cross-linking) and with Zyplast on the contralateral NLF. All fillers were well tolerated; however, all 3 HA products showed longer-lasting correction for at least 6 months compared with collagen. Lupo et al[11] confirmed the superiority of Juvéderm Ultra Plus over Zyplast in an RCT (n = 87) on the treatment of NLFs, showing correction in 81% of subjects for up to 1 year, with up to 2 touch-up treatments.

By 2008, the clear superiority of HA products over Zyplast collagen became evident. For subsequent studies, Restylane became the comparator because its efficacy and safety profiles had been validated by clinical trials. Clinical trials focused on determining clinical differences between the different HA types. Treatment of glabellar lines with single cross-linked HA (Restylane) compared with double cross-linked HA (Puragen, not FDA approved, similar to Prevelle [both Mentor Corp]) was reported in an RCT (n = 10), which showed equal effectiveness of both products. The longevity of the double cross-linked HA was superior to the single cross-linked HA at 12 months. There were no treatment-related AEs with either product.[12]

A pilot study comparing monophasic to biphasic HA preparations was recently performed by Nast et al.[13] In a prospective, double-blinded RCT (n = 60) comparing correction of the NLFs with Restylane (monophasic HA) with Teosyal (Teoxane Laboratories) (biphasic HA, currently not FDA approved), they found that both products showed good long-term results and were well tolerated. There was slight superiority of the mono-HA over the bi-HA in terms of durability, persistence, and participant preference.

The evaluation of long-term results and effects of differing retreatment schedules was studied in an RCT (n = 75) using Restylane treatment of the NLFs, which differed in injection intervals to determine the optimal retreatment schedule. They noted retreatment at either 4.5 or 9 months resulted in persistent nasolabial improvement for up to 18 months.[14]

In 2010, lidocaine hydrochloride was added to the HA preparations for comfort during injection. Levy et al[15] compared patient comfort using lidocaine-containing HA (Juvéderm Ultra 3 [Allergan]) with Restylane-Perlane. In this single-blind RCT (n = 126), 95% of patients preferred the

lidocaine-containing HA for overall injection comfort. Monheit et al[16] compared lidocaine-containing Prevelle Silk (Mentor Corp) with the same filler without lidocaine (Captique; Genzyme Corp) in 2009 and found in an RCT (n = 45) that pain was diminished by 50% using the lidocaine-containing HA.

Since their introduction in 2003, HA fillers have been shown to have excellent effectiveness and acceptable safety profiles. They have been used on label to improve the NLFs and lips, as well as off label to correct lines and wrinkles and to volumize the aging face.[17] They have been found to provide a longer-lasting improvement over both collagen-based products as well as animal-derived HA. Safety was reviewed from a worldwide data of 144 000 patients treated with HA (Restylane and Perlane) in 1999 and 262 000 patients treated in 2000.[18] The total AEs decreased from 0.15% to 0.06% after the introduction of a more purified HA raw material. The most common AE was hypersensivity reactions seen in 1 of every 5000 patients treated. Temporary events included redness, swelling, localized granulomas, and bacterial infections.

Safety has also been determined in darker-skinned patients.[19] An RCT of 160 patients treated with Juvéderm and Zyplast in the NLFs showed no hypersensitivity and a 6-month duration of effectiveness. There were no occurrences of keloid formation, hypertrophic scarring, hypopigmentation, or hypersensitivity; however, 3 patients developed mild hyperpigmentation.

The tolerability and efficacy of the newest HA, Belotero, was studied in an 18-month open-label trial. Belotero was injected into both NLFs, and touch-ups were allowed for optimal correction.[20] No significant AE or immunogenic reactions were noted, and correction was effective for at least 48 weeks in approximately 80% of subjects. Belotero was also compared with Restylane for correction of NLFs in a 4 week, split-face RCT (n = 25) and found improved evenness of NLFs for the Belotero-treated side compared with the Restylane-treated side at 4 weeks.[21]

The safety and efficacy of large particle HA for facial contouring was evaluated by DeLorenzi et al[22] in 2009 in a nonblinded, non-RCT study. Fifty-seven patients underwent cheek or chin augmentation with Restylane SubQ (Medicis Aesthetics) and were followed up for 12 months. Patients and investigators found approximately 50% aesthetic improvement at 12 months with more than 90% improvement at 6 months. Minimal AEs reported when the product was implanted subcutaneously or preperiosteally. A similar European study compared Juvéderm Voluma (Allergen) with patients previously treated with Restylane SubQ in the cheeks and chin. Also, in a nonblinded, nonrandomized, and noncontrolled study, 69% of injectors and 61% of patients preferred Voluma in terms of ease of use and aesthetic effects.[23]

CALCIUM HYDROXYLAPATITE

Calcium hydroxylapatite is an injectable product with ideal qualities for tissue implantation including longevity; low AE profile; and nonantigenic, nonirritating, nontoxic, and biocompatible properties. Prior to FDA approval as a dermal filler, CaHA had FDA approval for vocal fold augmentation and repair of oromaxillofacial defects and as a radiographic soft tissue marker. Injectable calcium hydroxylapatite (Radiesse [Merz Aesthetics], formerly Radiance FN [Bioform Medical Inc]) was FDA approved in 2006 as a filler for augmentation of moderate to severe NLFs. The product consists of synthetic bone with microspheres 25 to 45 μm in diameter, combined in a carboxymethylcellulose carrier gel. Radiesse injectable material consists of 35% CaHA microspheres suspended in a 70% gel carrier.[24] Within several weeks after injection, the carrier gel is absorbed. Unlike the HAs, Radiesse induces neocollagenesis with the microspheres serving as scaffolding for the new collagen fibrils. This product is nonimmunogenic, and no skin testing is required. Over time, the CaHA particles are degraded into calcium and phosphate ions and excreted by the body.

In an RCT in 2007 (n = 117), Smith et al[25] performed a split-face injection of the NLFs, comparing Radiesse with human collagen (Cosmoplast; Inamed/Allergan). At 6 months, results were graded by blinded evaluators, and they found that 79% of the Radiesse-treated folds had "superior" results compared with the collagen side. In addition, the amount of CaHA required for optimal correction was half that needed for collagen. Smith et al[25] found that the clinical results of Radiesse were superior to collagen at 3 and 6 months and was preferred over human collagen by more than 96% of injectors and patients. Adverse events were mild for both treatment groups and included erythema, edema, and ecchymosis.

Having shown clear superiority over collagen, Radiesse was then compared with the HAs. In a European study performed in 2008, Moers-Carpi et al[26] enrolled 60 patients in a 12-month, split-face RCT comparing NLFs treated with Radiesse and Restylane. At the 6-, 9-, and 12-month time points, CaHA was consistently superior to HA in aesthetic rating using the standard WSRS and GAIS tests. At 12 months, 79% of the NLFs treated with CaHA were still improved or better vs only 43% of the HA-treated folds. In a similar study, Radiesse was compared with 2 HA fillers, Juvéderm 24 (Juvéderm Ultra) and Perlane for NLF treatment.[27] In this multicenter trial, 205 patients randomly received either HA gel or CaHA injection to the NLF. At 8 months, GAIS evaluation demonstrated significantly more patients treated with CaHA showed improved GAIS scores compared with either HA.

The 2007 consensus recommendations confirmed efficacy of CaHA for the correction of volume loss in the midface and lower face. As such, it serves as an excellent elevator of a depressed oral commissure and restores lost volume to the marionette lines, pre-jowl sulcus, labiomental crease, chin, and midface.[28] However, because of the risk of necrosis and nodule formation, it is contraindicated for injection into the lips and glabella. Sadick and colleagues[29] conducted a 47-month safety and efficacy evaluation of CaHA and reported only 7 minor events in 113 patients, which resolved in 30 days.

Product safety of CaHA for injection in patients with darker skin types was studied in 2009 by Marmur et al.[30] In an open-label, nonrandomized, 5-center trial, 100 patients with Fitzpatrick skin types IV to VI were injected subdermally with CaHA and returned at 3 and 6 months to be assessed for the presence of keloids, hypertrophic

scarring, and hypopigmentation or hyperpigmentation. There were no signs of AEs at any time during this study, highlighting the safety of this product.

Although Radiesse mixed with lidocaine is not commercially available, a technique for mixing the product with lidocaine prior to injection was developed by Busso and Voigts[31] in 2008 and was FDA approved in 2009. Radiesse mixed with lidocaine, 2%, was shown to remain mixed for at least 24 hours without separating or settling. In an RCT of NLF injection of CaHA with and without lidocaine, subjects reported statistically significantly less pain in the fold treated with the mixture vs the plain control.[32] The mixing process was performed using 0.2 mL of lidocaine, 2%, mixed with 1.3-mL Radiesse. A female-to-female Luer lock syringe was used to mix the products using approximately 10 back-and-forth strokes.

INJECTABLE PLLA (SCULPTRA)

Approved in 2004 for the correction of facial lipoatrophy in patients with human immunodeficiency virus (HIV) and in 2009 for aesthetic volume replacement for cosmetic purposes, Sculptra (Valeant Pharmaceuticals) is a collagen stimulator. Poly-L-lactic acid is a synthetic polymer similar to absorbable suture material. It is reconstituted with sterile water to create a hydrogel with a methylcellulose carrier. Poly-L-lactic acid stimulates collagen formation by causing a foreign body reaction accompanied by dermal fibrosis. Several treatment sessions are required for optimal facial volume restoration, and patients must be counseled that the results are gradual. Poly-L-lactic acid is biodegradable and does not offer permanent correction. The longevity of the product varies but may be observed to last for several years, requiring a periodic touch-up procedure.

Poly-L-lactic acid is best injected into the superficial subcutaneous or preperiosteal tissues by a fanning, crosshatching grid or depot technique, followed by massage for several days to evenly disperse the product. Early experience with the product resulted in nodule formation; however, improvements in increasing particle size uniformity, combined with higher dilution ratios, have made AEs less frequent. Multiple studies have shown that patients injected with PLLA for HIV-associated lipoatrophy have had prolonged improvement in dermal thickness as well as improvement in quality of life.

The initial pilot study on PLLA ("New-Fill" in Europe) for HIV facial lipoatrophy was performed in the VEGA study by Valantin et al[33] in 2003. In this 96-week, uncontrolled, single-center, open-label study, 50 HIV-infected patients who were receiving antiretroviral therapy were treated with PLLA at 2-week intervals for 6 weeks. No severe treatment-related AEs were encountered; however, 52% of patients developed palpable but nonvisible and nonbothersome subcutaneous nodules. In addition, viral load and CD4 cell counts remained unchanged during the course of treatment. The PLLA was reconstituted with 3- to 4-mL of sterile water. For comfort, 1-mL lidocaine was injected locally. A total of 4 mL per cheek was injected at each treatment. Patients were evaluated by clinical examination, photographs, and ultrasonography, and results included significant increases in total cutaneous thickness with improved facial aesthetics and improved quality of life.

Immediate vs delayed PLLA treatments were studied in a 24-week, open-label, single-center randomized study in 2004 by Moyle et al[34] at the Chelsea and Westminster Hospital in London, England. In this study, 30 HIV-positive patients with facial lipoatrophy were treated with 3 PLLA injection sessions at 2-week intervals and were observed for a total of 24 weeks. In this study, all patients were treated at week zero, and then subsequent treatments were either immediate (weeks 2, 4, and 6) or delayed (weeks 12, 14, and 16). The product was reconstituted with water, and lidocaine was added, for a total volume of 4 to 5 mL per treatment. There were no serious AEs reported, although 1 patient developed a superficial local cellulitis that did not require antibiotic treatment. Most importantly, the percentage of patients who developed subcutaneous papules was 31%. In this study, the product was injected in the deep dermal plane.

In a 3-year study of non-HIV patients injected with Sculptra for aesthetic volumization, Lowe et al[35] evaluated nodule formation in 210 patients previously treated with PLLA. They concluded that most nodules resolved spontaneously and were related to placement of product and recommended not injecting around the eye or mouth. As more experience with the product was determined by clinical practice, it was found that increasing dilution and placement of the product in planes deeper than the dermis decreased the incidence of subcutaneous papules. A review of the literature by Kates and Fitzgerald[36] showed that the rates of papule formation had fallen to 0% to 13% using newer protocols for treatment.

In 2009, Sculptra was approved by the FDA for use in volumization of the aging face. Identical to Sculptra, the cosmetic product was packaged and sold as Sculptra Aesthetic. It was approved for the correction of shallow to deep NLFs, contour deficiencies, and other facial wrinkles and lines, which could be improved using a grid-pattern technique. Because there were no similar FDA-approved products for facial volume restoration, Sculptra did not need to prove equivalence to Restylane on a split-face trial—volumization studies were only needed to show efficacy and safety.

In their comprehensive review of facial volume with PLLA, Fitzgerald and Vleggaar[37] recommended dilution of the product with 5 mL or more of sterile water and the addition of lidocaine, 1% to 2%, to achieve a final dilution of 8 to 9 mL per vial. Injections were placed in the superficial subcutaneous or preperiosteal planes. Patients were instructed to massage the injected regions for 5 minutes, 5 times a day for 5 days after treatment. They also recommend resuspension of the product at least 2 hours, preferably overnight, before use.

POLY(METHYL METHACRYLATE)

ArteFill (Suneva Medical) is the only FDA-approved permanent filler used for treatment of the NLFs. Approved in 2006 (originally manufactured by Artes Medical Inc), its predecessors Artecoll and Arteplast had been used in Europe for the previous 10 years. The original formulations

produced granulomas at an unacceptably high rate; therefore, by changing the formulation process to remove negative charge on the particles and refining the process to produce a smooth sphere, the incidence of granuloma formation was resolved. Such modifications in the production of PMMA decreased the granuloma formation from 2.5% for Arteplast to less than 0.01% for ArteFill.[38]

ArteFill is a polymer of microspheres suspended in a bovine-based collagen, 3.5%, and lidocaine, 0.3%. The microspheres have a diameter of 30 to 45 μm and are smooth and round; there are approximately 6 million microspheres per 1 mL of product. Skin testing at least 1 month prior to injection is required because of the bovine collagen content. Since 2006, PMMA has been approved by the FDA for treating the NLFs. ArteFill is stored in the refrigerator until ready to use; it is allowed to come to room temperature before injection to ease the flow through the syringe. After injection, the initial correction is achieved by the collagen component, which is degraded in 1 to 3 months. During this time, PMMA becomes encapsulated with connective tissue, which results in volume improvement. The permanent microspheres are not degraded or phagocytized; the results cannot be reversed. Complications of beading or lumpiness can be seen when injected into the lips and around the eyes; therefore, injection is not recommended in these areas.

The initial FDA evaluation of ArteFill was a multicenter, double-blinded, randomized controlled study (n = 251) that compared Artefill with bovine collagen treatment in the glabella, NLFs, radial upper lip lines, and oral commissures.[39] Injections were placed by tunneling technique at the deep dermal-subcutaneous junction. Patients were evaluated using a 5-point photographic Facial Fold Assessment Scale.[40] At 12 months, significant wrinkle correction was noted for 87% of treated patients. Adverse events were uncommon, and redness, swelling, and lumpiness were more common in the collagen group. A subgroup of 69 patients were contacted 4 to 5 years later for further assessment and were evaluated for delayed AEs. Among these 69 patients, the total number of AEs was 6 of 272 wrinkles injected, for an AE rate of 2.2%. Two of the 6 AEs were severe (lumpiness that required excision for 1 patient and steroid injections in the other).

Cohen et al[41] reported on the 5-year safety and efficacy of PMMA. Patients in the original pivotal study for the FDA were contacted, and blinded observers graded the NLFs on a validated 6-point assessment scale. Compared with baseline, PPMA filler was noted to maintain the NLF correction over the 5 years. In addition, it was noted that the time frame between 1 and 5 years continued to show improvement. Of the 145 subjects in the study, there were 8.3% treatment-related AEs—1.4% moderate and 0.7% severe. The most common treatment-related AE was lumpiness, the majority of which were mild. The safety profile was reported to be consistent with other soft-tissue products including Restylane, Juvéderm, and Radiesse.

Gelfer et al[42] published the first series of complications seen after ArteFill or Artecoll injections. Delayed granulomatous reactions were reported in 10 patients. The authors concluded that the natural history of granulomas may be spontaneous resolution, and treatment is often not necessary. A significant number of nodules were reported after injection of the lips; therefore, injection for lip augmentation is not recommended.

AUTOLOGOUS FIBROBLASTS

Originally known as Isolagen technology (Isolagen Inc), tissue is harvested from patients by a postauricular punch biopsy and cultured to produce a fibroblast cell line. Because tissue is autologous, it is biocompatible and demonstrates a low incidence of hypersensitivity reactions. A pilot study (n = 10) was performed in 1999 by Watson et al[43] using intradermal fibroblast injections for facial rhytids and dermal depressions (3 injection sessions at 2-week intervals). At 6 months, they found that 90% of patients showed improvement of 60% to 100%, and a histologic study showed evidence of increased thickness and density of the dermal collagen.

In 2011, The FDA approved LaViv as a dermal filler for the correction of moderate to severe NLFs. Like Isolagen, a punch biopsy is harvested from the postauricular area and fibroblasts are produced for injection. In a phase 3 clinical trial, Weiss et al[44] conducted a double-blinded, randomized comparison of autologous fibroblasts with placebo (transport medium without living cells). They noted that dermal injection of fibroblasts improved wrinkles, acne scars, and other dermal defects compared with placebo. LaViv is still in clinical trials to determine longevity of correction.

CONCLUSIONS

The safety and efficacy of dermal fillers on the market today are clearly delineated by the current literature. The development of facial filling agents is an actively evolving process. Currently available filling agents have been refined to maximize results and minimize complications. As the world of facial-filling products continues to expand, it is evident that there are multiple opportunities for further research in these areas.

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