Next-Generation Dermal Fillers and Volumizers

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Since the introduction of dermal fillers to the US market in 1981, a number of advances in composition, production, and application of the products have been made. For years, European clinicians have had access to more fillers than their US counterparts because of different product approval processes. Although the vast majority of these products will not see regular use in the United States, some of today's most popular fillers were first tested in Europe. This article reviews the characteristics of the ideal filler, how manufacturers have come to satisfy some of those characteristics in products currently approved by the US Food and Drug Administration (FDA), and the characteristics that are still missing from those products. We also review a number of next-generation fillers that may be approved by the FDA in the near future; data and reports from European studies on these products also are presented for review.

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Since the introduction of the first dermal fillers to the US market in 1981, the practice of minimally invasive facial rejuvenation using these products has grown exponentially.[1] In 2010, US physicians performed more than 1 million injectable hyaluronic acid (HA) treatments alone, with only more botulinum toxin injections in the hierarchy of nonsurgical cosmetic procedures.[2] The global market for dermal fillers is estimated to be just under $850 million per year.[3] This widespread acceptance of dermal fillers would not have been possible without the advances in formulation and delivery since the first collagen filler, Zyderm (Allergan, Inc), was introduced in 1981.

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For more than 20 years, bovine collagen–based fillers (Zyderm and Zyplast, Allergan, Inc) were the only available US Food and Drug Administration (FDA)–approved fillers.[4] Although they were demonstrated to be effective for the correction of fine lines and scars, these bovine protein–based compounds required allergy testing in each patient prior to use. The advent of human-based collagen fillers (Cosmoderm and Cosmoplast, Allergan, Inc) ended the need for allergy testing, which was a notable improvement; unfortunately, these fillers achieved only moderate correction in deeper folds and results often were short lived (3–4 months). Results of lip correction with these early collagen fillers lasted an even shorter amount of time.[5]

Advances in technology and application techniques as well as the development of a better understanding of patients' aesthetic needs have led practitioners to think differently about fillers. The term *dermal fillers* does not even capture the breadth of products that have emerged to volumize and contour the face.

It is important to consider the properties of the ideal filler when evaluating the progression of fillers. The ideal filler would be composed of an easily injectable

hypoallergenic substance that could be naturally incorporated into the patient's tissue without risk for adverse reactions. Additionally, the ideal filler would be inexpensive; painless; and provide consistent and long-lasting yet reversible results.

So far, no product has been manufactured to satisfy all of the ideal filler criteria; however, great strides have been made since the first bovine collagen–based fillers of the 1980s. First approved by the FDA in 2003, HA fillers fulfill a number of properties of the ideal filler where collagen products once fell short. Because HA is homologous across species, the need for allergy testing is obviated.[4] Additionally, HA fillers produce results that last for 6 months or more, and some HA products indicated for the correction of nasolabial folds last for 9 months or more. The effects of HA-fillers can be reversed with hyaluronidase in the event of unwanted results. Nodules, which are among the most troublesome side effects associated with injectable fillers, are quite rare with HA fillers, occurring in only 0.01% to 0.1% of cases.[6]

Currently, a number of HA- and non-HA–based fillers exist in the US market (Table 1). All collagen fillers have been removed from the market, primarily due to their shorter duration compared to HA fillers. This absence of collagen fillers has left a notable gap in the armamentarium for treating fine lines.

The molecular structure of the HA monomer is identical across all HA fillers regardless of its source (bacterial or animal).[7] When injected into human tissue, the raw HA monomer quickly is broken down in the enzymatic degradation of endogenous hyaluronidase; to overcome this response, manufacturers add cross-linkers, such as 1,4-butanediol diglycidyl ether (BDDE) or divinyl sulfone, to un–cross-linked HA to create an HA gel that imposes both a physical and chemical barrier to enzymatic breakdown. A greater degree of cross-linking corresponds to a harder gel and more longevity in the treated tissue[4]; however, as the gel becomes harder and more cohesive, more force is required during injection and the possibility of eliciting an immune response is increased.[7] Thus manufacturers strive to produce fillers that are both easy to administer and are nonimmunogenic, while also being efficacious and long lasting in tissue.

Many different aspects of the manufacturing process can create substantially different end products, and for this reason, all HA fillers are not the same. Key differences include length of the polymer chain, degree of water solubility, type of cross-linker used, degree and efficiency of cross-linking, gel hardness, gel viscosity, extrusion force, gel consistency, and total HA concentration. The unique interaction of these characteristics defines a product's efficacy, longevity, ease of injection, and safety profile. Understanding these differences in characteristics is critical to choosing the right filler in an ever-expanding complex market.

Hyaluronic acid fillers are the most frequently injected dermal fillers in the United States,[2] but there are a variety of other filler materials that currently are FDA approved, including calcium hydroxylapatite (Radiesse, Merz Aesthetics, Inc), poly-L-lactic acid (Sculptra Aesthetic, sanofi-aventis US LLC), and polymethylmethacrylate (Artefill, Suneva Medical, Inc). Radiesse, which is priced lower for a given volume of product than HA fillers, has been used fairly extensively as a volumizer for several years. Based on data available from the American Society for Aesthetic Plastic Surgery[2] and the Manufacturer and User Facility Device Experience (MAUDE) database,[8] adverse events are reported more frequently for Radiesse than HA-based fillers; reports also indicate that Radiesse should not be injected near the lips.

With the growing popularity of dermal fillers, there continues to be a demand for a more ideal filler. Volume deficits from facial fat loss, fat movement, and skeletal remodeling are becoming increasingly recognized as integral contributors to facial aging.[9,10] Accordingly, a trend toward a more volumizing filler that can replace these deficits and recontour the face has emerged.[11] Interestingly, a lifting effect may be achieved by volumizing the midface, resulting in improvement of the midface and nasolabial folds.

Patients continue to seek products that create longer-lasting effects and minimize the need for repeat treatments. Some manufacturers have attempted to achieve these results in part by stimulating natural collagen production with adjuvants to the filler.

We review a variety of dermal fillers that may soon be available for use in the United States. The majority of the preliminary data come from European reviews and trials of the respective products. More than 70 filler products are approved for use in Europe where European Conformity (CE mark) approval for fillers falls under the medical devices category, often with no clinical data required, allowing for faster approval than the FDA in the United States. The focus of this review is to reveal products that show promising results, minimal complications, and possibility of FDA approval in the near future (Table 2).

JUVÉDERM VOLUMA

Approved by the FDA in 2006, Juvéderm (Allergan, Inc) is a line of HA-based products that have achieved marked commercial success in the United States and have become the most globally utilized dermal fillers.[3] Juvéderm Voluma, the newest product in this line, is

Patient at baseline (A) and after treatment with Juvéderm Voluma (Allergan, Inc)(B). Photographs courtesy of Jean and Alastair Carruthers, MD, Vancouver, Canada.

currently under FDA review and may be approved in 2012. Juvéderm Voluma is a viscous, highly cohesive, fully reversible, 20-mg/mL HA filler used to restore facial volume (Figure). Its use as a volumizer makes it quite different from the traditional wrinkle filler.

Unlike Juvéderm Ultra XC, which primarily is composed of high-molecular-weight HA, Juvéderm Voluma is composed of 90% low-molecular-weight HA and only 10% high-molecular-weight HA. Juvéderm Voluma is optimally cross-linked with BDDE, with more efficient cross-linking for a given amount of BDDE versus the original Juvéderm line.[12] The combination of the high cross-linking and low-molecular-weight formula gives the product a high viscosity and cohesiveness while still remaining smooth and easily injectable.[14] Rheologic comparisons with other products in the Juvéderm family have shown an increase in viscosity in the Voluma formulation.[29] Juvéderm Voluma also has prospectively been shown to be efficacious and well-tolerated in both age-related volume loss[14] and lipodystrophy associated with human immunodeficiency virus (HIV).[13] In the HIV group, facial improvement was still noted 12 months later in 76% (16/21) of patients.[13] Additionally, no product migration was noted in either study. Juvéderm Voluma also is preferred by both patients and practitioners in patients who have previously been treated with Restylane (Medicis Aesthetics, Inc).[15]

EMERVEL

Emervel (Galderma SA) is a new family of BDDE cross-linked HA-based dermal fillers that was launched in Europe in January 2011. All 5 products (Emervel Classic, Emervel Deep, Emervel Touch, Emervel Lips, Emervel Volume) have the same concentration of HA (20 mg/mL) but vary in the degree of cross-linking and gel calibration; all but Emervel Touch are available with and without lidocaine.

Emervel Classic is designed for mid dermal injection to treat moderate facial wrinkles such as nasolabial folds. In a European split-face, randomized, evaluator-blinded study, Emervel Classic demonstrated similar efficacy to Restylane. Local erythema, edema, and tenderness were significantly less severe and resolved faster after treatment with Emervel Classic ($P<.05$), indicating overall better tolerability compared to Restylane.[16]

Emervel Deep is formulated for the correction of more severe wrinkles. In another study, comparison to Perlane (Medicis Aesthetics, Inc) showed that Emervel Deep demonstrated a significantly greater improvement in wrinkle severity rating scale ($P=.002$) and was well-tolerated, with only mild local injection-site reactions reported.[17]

Six-month interim data from a 170-participant, evaluator-blinded, split-face, multicenter US comparison of Emervel Classic Lidocaine and Juvéderm Ultra XC demonstrated comparable efficacy and safety profiles.[30]

RESTYLANE SUBQ

Restylane was the first HA filler to be approved in the United States in 2003. Recently, it also has become the first HA filler to be approved for lip enhancement. Restylane SubQ (Q-Med, a Galderma Division) is a large-particle, stabilized HA gel containing 1000 gel particles per 1 mL, as opposed to 100,000 particles per 1 mL in Restylane.[19] It has been utilized in Europe since 2006,[18]

Table 1

FDA-Approved Dermal Fillers

Product (Filler Type)	Manufacturer	Indication
Artefill (polymethylmethacrylate)	Suneva Medical, Inc	Correction of nasolabial folds
Belotero Balance (hyaluronic acid)	Merz Aesthetics, Inc	Correction of moderate to severe facial wrinkles and folds, such as nasolabial folds
Elevess (hyaluronic acid)	Anika Therapeutics, Inc	Treatment of facial wrinkles and folds
Hylaform (hyaluronic acid)	Genzyme Corporation	Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds, such as nasolabial folds
Juvéderm Ultra XC (hyaluronic acid)	Allergan, Inc	Injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds, such as nasolabial folds
Prevelle Silk (hyaluronic acid)	Mentor Corporation	Treatment of moderate to severe facial lines, folds, and wrinkles
Radiesse (calcium hydroxylapatite)	Merz Aesthetics, Inc	Subdermal implantation for correction of moderate to severe facial wrinkles and folds, such as nasolabial folds
Restylane/Restylane-L; Perlane/Perlane-L (hyaluronic acid)	Medicis Aesthetics, Inc	Mid to deep dermal implantation for correction of moderate to severe facial wrinkles and folds, such as nasolabial folds; lip enhancement (Restylane only)
Sculptra Aesthetic (poly-L-lactic acid)	sanofi-aventis US LLC	Correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles

Abbreviation: FDA, US Food and Drug Administration.

and it is currently under FDA review. The product is intended for facial contouring by subcutaneous or supraperiosteal injection. Physicians must be trained by the manufacturer prior to use.

In a review of 57 patients who received Restylane SubQ injections through a 16-gauge blunt cannula, 58% (33/57) of patients observed improvement in their appearance that persisted 12 months after treatment. Product migration did occur, and in 5% (3/57) of participants, the migrated product was still present at 12 months posttreatment.[19] Restylane SubQ also has achieved good long-term aesthetic results in patients with HIV-associated lipoatrophy; however, lumped product was observed in 23% (3/13) of participants 24 months into the study.[20] Overall, Restylane SubQ has not had commercial success in those countries where it currently is available, and to

Table 2

Next-Generation Dermal Fillers

Product	Manufacturer	Characteristics	Studies (Year)
Juvéderm Voluma	Allergan, Inc	Viscous and highly cohesive 20-mg/mL HA filler; 90% low-molecular-weight HA; used for deep dermal injections to restore age- or HIV-associated volume loss	Raspaldo[12] (2008); Bechara et al[13] (2008); Hoffmann[14] (2009); Fischer[15] (2010)
Emervel (Classic, Deep, Touch, Lips, Volume)	Galderma SA	Family of five 20 mg/mL HA filler formulations with varying degrees of cross-linking and gel calibration; all formulations, except Emervel Touch, are available with and without lidocaine	Rzany et al[16] (2011); Ascher et al[17] (2011)
Restylane SubQ	Q-Med, a Galderma Division	Large-particle, stabilized HA gel containing 1000 gel particles per 1 mL, as opposed to 100,000 particles per 1 mL in Restylane; used for facial contouring by subcutaneous or supraperiosteal injection	Lowe and Grover[18] (2006); DeLorenzi et al[19] (2009); Skeie et al[20] (2010)
Atlean	Stiefel, a GSK Company	Combination of β-TCP particles suspended in an HA gel; immediate results from HA and sustained effects from β-TCP–stimulated collagen production	
Belotero (Soft, Basic, Intense)	Merz Aesthetics UK	Family of 3 monophasic polydensified HA filler formulations; varying densities theoretically allow optimal tissue spread	Prager and Steinkraus[21] (2010); Pavicic[22] (2011)
Teosyal (Meso, First Lines, Global Action, Touch Up, Deep Lines, Kiss, Ultra Deep, Ultimate)	Teoxane Laboratories Geneva	Family of 8 monophasic HA filler formulations ranging from 15 to 25 mg/mL; boasts what the manufacturer claims to be the lowest level of contaminants, thus minimizing inflammation	Nast et al[23] (2011)
Revanesse (Pure, Ultra, Lips, Contour)/ ReDexis (Ultra)	Prollenium Medical Technologies Inc	Family of 5 monophasic nonparticulate HA fillers; ReDexis products contain dextranomer beads, which are claimed to attract collagen and elastin and provide lasting augmentation	
Aquamid	Contura International A/S	Permanent non-HA filler composed of 2.5% polyacrylamide gel and 97.5% water; used in Europe since 2000; higher rate of adverse reactions compared to HA fillers	Negredo et al[24] (2009); Pallua and Wolter[25] (2010)
Puragen/ Prevelle Lift	Mentor Worldwide LLC	Double cross-linked 20 mg/mL (Puragen) and highly viscous 22 mg/mL (Prevelle Lift) lidocaine-containing HA fillers	Kono et al[26] (2008); Onesti et al[27] (2009); Monheit et al[28] (2010)

Abbreviations: HA, hyaluronic acid; HIV, human immunodeficiency virus; β-TCP, β-tricalcium phosphate.

our knowledge, there is no plan to launch the product in the United States, likely because of the increased rate of migration or lumps relative to other HA fillers. Generally, the more cohesive the product, the longer it lasts, but there also is a greater potential for these types of side effects. It is unknown if specific injection techniques may reduce the occurrence of such side effects.

ATLEAN

Atlean (previously being developed by Stiefel, a GSK Company) was introduced in Europe in 2007 by the same group of French pharmacists who developed the poly-L-lactic acid filler Sculptra Aesthetic. Atlean is a combination of β-tricalcium phosphate (β-TCP) particles suspended in an HA gel. β-TCP is a nonimmunogenic, biologically compatible, biodegradable material with a long history of safe use as a bone substitute.[31] The manufacturer claims that the HA portion provides an immediate yet temporary volumizing effect, while the β-TCP particles produce sustained effects by stimulating endogenous collagen production. Although anecdotal reports indicate good results from treatment with Atlean, there have been no published studies in the literature. Our understanding is that Stiefel is no longer developing this product, and it is unclear if another company will attempt to do so.

BELOTERO

Belotero (Merz Aesthetics UK) is a family of 3 HA-based fillers (Belotero Soft, Belotero Basic, Belotero Intense) first launched in Germany in 2005. Belotero is a monophasic polydensified HA-based filler, which contrasts other biphasic and monophasic monodensified fillers. The difference between these groups of fillers lies in the manner in which cross-linking is performed during the manufacturing process.[32] In biphasic products, cross-linked HA is sieved through a screen to isolate cross-linked HA particles of uniform size.[33] Monophasic fillers are not sieved and contain a mixture of randomly sized and shaped pieces.[34] Monophasic monodensified HA gels mix and cross-link the HA particles in a single step, while monophasic polydensified fillers add additional HA and further cross-linking after the initial mix.[32] The manufacturer claims that this process creates a gel with different zones of densities, theoretically allowing for optimal spreading throughout the tissue, while conventional HA fillers would not be able to fill the smallest gaps.[35,36] Blinded punch biopsy studies comparing the 3 classes of HA fillers showed that a monophasic polydensified HA distributed more evenly in the dermis, while the biphasic and monophasic monodensified products resulted in clumping.[32]

In a blinded, split-face, randomized prospective trial, Belotero Basic (22.5 mg/mL HA) demonstrated substantially greater improvement in nasolabial fold correction when compared to Restylane.[21] The evaluations in this study were conducted using a Phase-shift Rapid In-vivo Measurement of Skin (PRIMOS) system designed to assess the mean depth of target areas in the treatment of nasolabial folds. Both fillers were equally well-tolerated with no serious adverse effects.[21] A retrospective review of 149 patients treated with Belotero Intense (25.5 mg/mL) demonstrated significant ($P<.001$) lasting improvement of deep and very deep wrinkles.[22]

Belotero Balance (Merz Aesthetics, Inc) was FDA approved in November 2011 for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds.

TEOSYAL

Teosyal (Teoxane Laboratories Geneva) is a line of 8 monophasic BDDE cross-linked HA fillers that were introduced in Europe in 2004 and have been used in more than 1.5 million injections. The product line ranges from a 15 mg/mL HA composition designed for mesotherapy to a 25 mg/mL HA formula intended for subdermal injection and facial remodeling. Similar to other monophasic HA fillers, Teosyal is reputed to be less elastic and more cohesive when compared to biphasic products.[23] These products boast the lowest protein and bacterial endotoxin levels, theoretically reducing swelling, inflammation, and hypersensitivity reactions.[37]

A blinded, split-face, randomized trial of 60 patients compared the results of Teosyal Deep Lines (25 mg/mL) to the biphasic filler Restylane Perlane.[23] Both products demonstrated good and comparable efficacy both immediately after injection and 6 months posttreatment. The authors did not comment on any differences in edema or inflammatory reactions but did note that both products were well-tolerated with no severe adverse effects.[23]

REVANESSE/REDEXIS

Revanesse (Prollenium Medical Technologies Inc) is a family of monophasic nonparticulate HA-based products with 5 formulations (Revanesse, Revanesse Pure, Revanesse Ultra, Revanesse Lips, Revanesse Contour) that have been available for use in Canada since 2010. Two products, marketed under the names ReDexis and ReDexis Ultra, include dextranomer beads that are dissolved into the HA gel base. The positive charge of the beads is thought to attract naturally occurring, negatively charged collagen and elastin, which then bind together and provide natural augmentation that lasts after the HA has been broken down.[38] According to the manufacturer,

this design gives the products greater filling power and decreases degradation in tissue, with results lasting 18 months on average for ReDexis and up to 24 months for ReDexis Ultra. Marketing materials for the products include a prospective, blinded, randomized comparison of Revanesse Ultra to Restylane, which showed equivalent results and a good safety profile.[38]

AQUAMID

Aquamid (Contura International A/S) is a non-HA filler that has been in use in Europe since 2000. A premarket approval application was submitted to the FDA in April 2010. Aquamid consists of 2.5% polyacrylamide gel and 97.5% water and is used for the treatment of deep wrinkles and HIV-associated lipoatrophy. Unlike HA-based fillers, Aquamid is permanent filler, similar to Sculptra Aesthetic and Artefill, which currently are FDA approved. The polyacrylamide material has proven to be nontoxic,[39] nonallergenic, nonembryotoxic, and essentially nonresorbable.[40]

In a prospective noncomparative study of Aquamid in 251 patients, aesthetic results were rated as good or very good.[25] The study aimed to assess long-term safety, with 116 patients following up at 60 months. Throughout the study period, a total of 53 treatment-related adverse events were reported, including edema, gel accumulation, hematoma, infection, and pain. Thirteen reports of blebs or indurations, a common concern for permanent fillers, occurred during 60 months of follow-up. Two serious treatment-related adverse events occurred, both infections, but both resolved during the study period.[25] A review of 145 patients with HIV-associated lipoatrophy treated with Aquamid reported only 1 serious adverse event (infection) in patients with at least 4 years of treatment.[24]

PURAGEN/PREVELLE LIFT

Puragen (Mentor Worldwide LLC) is a double cross-linked, HA-based filler currently approved as a CE-marked Class III medical device in Europe for the correction of facial wrinkles, folds, and lip enhancement. In a 6-month prospective, blinded comparative study with Captique (Inamed Corporation), Puragen demonstrated increased durability in the correction of nasolabial folds.[27] Similar results were obtained in a smaller 12-month comparison of Puragen and Restylane.[26] US Food and Drug Administration approval of Puragen currently is pending.

Prevelle Lift (Mentor Worldwide LLC), also known as Dermal Gel Extra, is a sister product to Prevelle Silk (Mentor Corporation), which was approved by the FDA in 2008 to treat moderate to severe facial lines, folds, and wrinkles. Prevelle Lift is highly cross-linked and cohesive and designed to target deeper lines and wrinkles. In a randomized, split-face, 9-month comparative study with Restylane in 140 participants, Prevelle Lift demonstrated equivalent efficacy but required significantly less volume ($P<.001$) and fewer touch-ups ($P=.005$). Adverse effects for the 2 products were equivalent.[28] Prevelle Lift is already approved for use in Canada.

CONCLUSION

The dermal filler market is expanding more and more rapidly each day. As the demand for fillers continues to grow, manufacturers will introduce new products to satisfy practitioner and patient needs. Long-term safety and efficacy data for new products should be evaluated as the data are released to help guide practitioners in their selections. When considering which product to choose, it is important to remember that there is still no ideal filler, and each patient must be assessed on an individual basis to determine which product will best fulfill his/her needs.

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