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An update review on recent skin fillers

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ABSTRACT

Facial rejuvenation has changed over the last decade, evolving from the rhytidectomy to an approach that focuses on revolumization, due to a more complete understanding of the changes to bone and soft tissue that occur with the aging face. Soft tissue augmentation using various injectable filler agents has gained popularity due to their nonsurgical, non-invasive procedures, instant cosmetic outcomes and limited recovery time. The skin filler market is booming and the variety of available skin fillers is increasing, providing the plastic surgeons many choices. Nonpermenant, biodegradable, resorbable agents may induce little complications, but they will normally disappear soon after injection. Semipermenant, biodegradable, biostimulary, nonresorbable fillers may induce a bit more complications, but they will normally disappear spontaneously in a few months. Permanent, nonresorbable fillers usually give rise to severe complications or reactions which may not disappear spontaneous. They may appear several years after the injection, and treatment is often insufficient. Unfortunately, the ideal filler with lasting effect but without any complication has not been discovered yet. In this review, we give an update on currently available skin filler agents, and what is new in recent 5 years.

Key words:

Skin fillers; revolumization; biodegradable; biostimulory; nonresorbable; bovine collagen; hyaluronic acid; polyacrylamide

INTRODUCTION

The past decade has seen an evolution in the filler market for meaningful volume restoration in the aging face. There are now over 35 major filler product companies worldwide.[1] In 2014, there were 2.3 million soft-tissue filler procedures in the United States, an increase of 3% from 2013.[2] The days of treating a nasolabial fold with single skin filler injection is gone, and a new era of more sophisticated approach of thoughtful, restrained, and effective filler injection has come. Deep-volume increase, combinational approaches, natural looking outcomes, and safety measures are the most important considerations for filler use.

Skin fillers on the market today are categorized into transitory biodegradable or resorbable within months and years respectively, and permanent or nonresorbable fillers. Biodegradable agents can be divided into

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two categories: (1) nonpermanent fillers, also named replacement fillers (collagen, hyaluronic acid and biological fillers), which has a short duration with typical lengths of several months to one year and are eventually reabsorbed through macrophage activation; (2) semipermanent fillers, or stimulatory fillers (polylactic acid and calcium hydroxylapatite), which have a longer duration of aesthetic improvements lasting up to years with minimal side effects. They will typically result in a foreign body reaction that elicits fibroblast activation and collagenesis at the site of injection. Permanent implants (polymethylmethacrylate, silicone and hydroxyethylmethacrylate) could provide long-lasting revolumization results and could also induce fibrogenesis and collagen production, but with higher potential risk of complications. The skilled hands of the experienced plastic surgeons/dermatologists are required for injection.[3-5]

BIODEGRADABLE FILLERS

Biodegradable fillers are impermanent agents than can last for a limited time of volume augmentation, from months up to 12 months, but will eventually metabolized by the body. Some of the volume effect is due to a transient inflammatory response to skin fillers with associated edema. However, these volume effects will diminish soon after injection.[6,7] Subsequent fibroblast activation and neocollagenesis can be another two factors for volume augmentation, but they only result in partial filler engraftment into the surrounding tissue.[8-10] Current biodegradable fillers stimulate neocollagenesis for more sustained aesthetic improvements and carry a low risk of adverse events or serious complications. Although permanent agents offer significant clinical benefits, short-term of volume effect, ease of correction and often reversible in the event of adverse effects make biodegradable fillers attractive to patients and plastic surgeons worldwide.

Generally, biodegradable filler spread on the market currently includes: hyaluronic acid (HA), bovoine collagen, calcium hydroxylapatite (CaHA) and injectable poly-L-lactic acid (PLLA).

Bovine collagen

Bovine collagen is a resorbable filler. Bovine collagen was the first facial filler approved by the Food and Drug Administration (FDA) for the correction of contour irregularities in the USA,[11,12] which has been used as an injectable filler for almost 30 years. Originally, Bovine collagen was injected into the dermis and subcutaneous tissue to correct viral pockmarks, depressed acne scars, lipoatrophy, deep nasolabial folds, rhytides, and soft tissue augmentation. The duration of the augmentation effect is usually less than 6 months.[13,14]

Histopathologically, bovine collagen fibers are much thicker than human collagen, have a homogeneous appearance nearly devoid of spaces between them, with fewer fibroblasts, and fail to refract polarized light. Skin tests are required before the injection of bovine collagen products. Rare hypersensitive reactions, including foreign body granulomas and palisading granulomas to bovine collagen have been reported. Rare systemic complications include flulike symptoms, paresthesias or difficulty breathing, and severe anaphylactic shock have been reported after injections of bovine collagen.[15,16]

The requirement for skin testing before injection to identify patients at risk for allergic reactions and its short duration of effect, particularly in more mobile areas of the face have restricted the popularity of Bovine collagen's usage as a skin filler.[17] Although human-based collagen was subsequently developed to lessen the chance of hypersensitivity reaction, the demand for collagen rapidly declined in the face of emerging products that offered long-lasting effects with few side effects.

Human-derived bioengineered collagen implants

Human-based collagen implants have been developed in recent years, to avoid allergic reactions to bovine collagen. Autologen (Collagenesis, Beverly, MA) is an injectable autologous human tissue matrix primarily composed of intact collagen fibrils that are processed from the patient's own skin and harvested during elective surgery.[18,19] Human collagen implants are also obtained from human donor tissues that undergo extensive screening for infectious disease and the material is irradiated before use. The cosmetic effect lasts about 4 to 7 months, depending on the area of treatment, injection technique, and amount of injected collagen.[17] No skin test for hypersensitive reactions is required for human-derived collagen products. Local adverse reactions include bruising, erythema, and swelling at the site of injection. Granulomatous reaction at the site of the injection has also been reported in few cases.[20]

HA

Crosslinked animal or non-animal derived HA fillers have been introduced to the market for more than 20 years in the USA and even longer in different countries around the world. Today, HA-based dermal fillers are the fastest non-invasive esthetic procedure in the USA,[21] which still remains the most popular dermal filler[22] despite the new injectable fillers with different innovative compounds continues to expand.

HA was first discovered by Karl Meyer, who is considered the father of glycosaminoglycan chemistry, and his assistant John Palmer.[23] HA is a glycosaminoglycan disaccharide, which exists naturally in the body. Approximately 50% of total HA is found in the skin, and it is produced by dermal fibroblasts, endothelial cells, synovial cells, adventitial cells, smooth muscle cells, and oocytes, and is released into the surrounding extracellular space. The half-life of HA is three days or less.[4]

Injections of HA are used for correction the wrinkles of the face, for soft tissue augmentation, and for filling all types of defects. HA has become the most popular skin filler agent, and reached a high patient satisfaction with a low incidence of serious complications. The highly charged nature of HA

provides its high solubility and high water binding affinity, which also contributes to volume augmentation.[23] HA may also stimulate neocollagenesis which is another reason for volume augmentation.[8,24,25] The injected HA is eventually degraded and cleared by hepatic metabolism as thus the effect diminished.

HA has no organ or species specificity, and therefore in theory there is no risk of an allergic reaction. Very few adverse hypersensitivity reactions secondary to injections of HA used as filler have been reported; in histology, they consisted of a granulomatous foreign body reaction, with abundant multinucleated giant cells surrounding an extracellular basophilic amorphous material, which was the injected hyaluronic acid gel. One favorable character of HA is that it can be easily dissolved with hyaluronidase if there is an undesired or adverse effect. The duration of action averages 6 months with a residual effect lasting up to 2 to 3 years.[26] The short longevity is the primary limitation of HA.

Currently available HA dermal fillers, depending on HA concentration, cross-link density, and manufacturing process, has different hydration capacity at equilibrium. Below are some of the favorable HA products by the plastic surgeons and dermatologist.

(1) Restylane® was FDA-approved in December of 2003, which is now the most popular dermal filler. Restylane® has been proven to be safe and effective in the treatment of nasolabial folds in a pivotal multicenter, double-blind clinical study.[27] Perlane® is a more viscous version of Restylane®, which was FDA-approved in 2007. Both Restylane® and Perlane® are producted by Q-Med AB in Sweden and distributed in the USA by Medicis Pharmaceutical Corporation. They are based on "nonanimal stabilized hyaluronic acid" and produced from cultures of Streptococcus equi via a proprietary process crosslinked with 1,4-butanediol diglycidyl ether giving a final concentration of 20 mg/mL. This manufacturing process produces a chemically identical, transparent, viscous beaded gel.[28]

(2) Juvéderm™ Ultra and Juvéderm™ Ultra Plus, FDA-approved in September, 2006, are new injectable HA dermal fillers, which are distributed by Allergan, Inc. The FDA has granted a label extension for Juvéderm™ Ultra and Juvéderm™ Ultra Plus in June, 2007 (Allergan, Inc. 2007). Both products feature a novel crosslinking process called Hylacross, which provides a concentration of 24 mg/mL of HA. Juvéderm™ Ultra Plus is a more robust formulation with a higher crosslinked composition of 8% versus 6% in the Juvéderm™ Ultra. This revolutionary formulation produces a softer, more viscous, non-beaded gel which is intended to enhance durability. The clinical data demonstrates that the effects with a single treatment of Juvéderm™ Ultra or Juvéderm ™ Ultra Plus may last for up to 12 months.[22,29,30]

(3) Elevess™ is the latest HA approved by the FDA, in July 2007, which was manufactured by Anika Therapeutics, MA, USA, and was based on chemically modified non-animal HA proprietary technology which incorporates 0.3% lidocaine hydrochloride as a component of the treatment syringe. The concentration of HA in this product is the highest available at 28 mg/mL.[22,29,30]

(4) The HA dermal fillers on the horizon are Puragen, Puragen Plus, Prevelle, Prevelle Plus, Belotero, and Teosyal family of products. Puragen and Puragen plus are based on double crosslinked (DXL™) technology with non-animal HA chains. DXL™ technology increases the resistance to degradation once the product is implanted Hyaluronic acid dermal fillers to come and not yet available in the USA.

Despite its great popularity and satisfying aesthetic outcome, there are some advertise reactions of HA injection. Nonallergic local side effects at the sites of injections are frequent, including pain, bruising, and transient edema, but they disappear in a few days and usually do not need any treatment.[31] Too superficial placement of HA fillers or an uneven distribution of the injected product can lead to visible, pale nodules in the skin. Uncommon additional nonallergic reactions include bacterial infections, herpes reactivation, generalized scleromyxedema,[32] aseptic abscess,[33] scar sarcoidosis,[34] and interferon-induced systemic sarcoidosis in patients with chronic hepatitis C, who also developed sarcoidal granulomas around the injected HA filler[35] and necrosis and livedoid pattern after accidental arterial embolization.[36] Blood vessels-embolism by HA injection is the most severe complications, which may lead to organ necrosis, such as blindness, stroke, which sometimes could be irreversible.

Platelet-rich plasma

Platelet-rich fibrin matrices (Selphyl System; Aesthetic Factors, LLC, Princeton, N.J.), derived through the collection and centrifugation of blood, is approved by the FDA as a medical device designed for the safe and rapid preparation of autologous platelet-rich plasma (PRP) for use in orthopedic surgery. For cosmetic applications, PRP is injected into the face to stimulate cell proliferation via the release of growth-promoting proteins.[37] Histological examination shows activated fibroblasts and new collagen deposition at the site of injection.[38] Injection is an office-based procedure used to fill scars and rhytides with only minor transient ecchymosis and edema.[31,37] Additional studies are required to evaluate the efficacy and safety of platelet-rich fibrin matrices for soft-tissue augmentation.[3]

PLLA

Injectable PLLA is biocompatible, biodegradable, biostimulatory, synthetic filler that must be injected into the reticular dermis or subcutaneous fat. Polylactic acid as Sculptra® was licensed by FDA in July, 2009.[39,40] Sculptra® effects by stimulating neocollagenesis through fibroblast activation,[41] thus becomes popular as soft-tissue augmentation filler. Animal studies have revealed that PLLA are able to stimulate the proliferation of dermal fibroblasts with subsequent endogenous production of collagen.[41,42] Histological studies in humans have shown gradual dissolution of the injected PLLA and dermal in-growth of type I collagen over 8 to 30 months after injection.[43,44] PLLA is gradually degraded by nonenzymatic hydrolysis into water and carbon dioxide over approximately 9 to 24

restore facial volume and contours, but complications such as granulomas and paraffinomas years after treatment have restricted their use for aesthetic treatment.

Silicone

No silicone product for soft tissue augmentation has been approved by FDA. The major indication for FDA-approved products is retinal detachment with removal of the material after reattachment. In soft tissue augmentation, removal of silicone is not performed. The use of liquid silicon is off label.[80] For decades, horrendous complications have been reported from silicone injections into breasts, and its use has been banned by many authorities. Adverse effects have also been noted after use for facial tissue augmentation.[81-83] After illegal silicone injection, the silicone embolism syndrome has been observed with potential fatal outcome in 24% of patients. Symptoms and signs of the "silicone syndrome" include dyspnea, fever, cough, hemoptysis, chest pain, hypoxia, alveolar hemorrhage, and altered consciousness.[84] They have almost been abandoned nowadays.

PMMA

PMMA is rigid, transparent and colorless, thermoplastic permanent skin filler with low cost, easy accessibility, and potential to achieve lasting results. PMMA has been used as an injectable filler to treat hollows and reduce rhytids. PMMA injections have been associated with several side effects; especially they may lead to some undesirable effects in the eyelids and periocular region.

First-generation polymerized PMMA microspheres are purified with diameter greater than 20 μm, which may produced foreign body granulomas; Lemperle *et al*.[85,86] postulate that larger PMMA microspheres (30 to 50 μm) may resist phagocytosis. However, Bachmann *et al*.[87] demonstrated that a giant cell reaction still occurs with larger PMMA microspheres. Complications of PMMA injection were classified as nodular masses, inflammation, allergies and skin hypopigmentation. The most affected sides were the lips (46%), followed by periocular, nasolabial folds, forehead, and cheeks. PMMA injection to the periocular region may be lead to erythema, hardening of the local tissues, edema, and formation of nodules and eyelid malposition, which are associated with fibrotic nodules, giant cell inflammation. The best treatment for these PMMA injection complications remains uncertain. Corticosteroid injection may have limited efficacy while surgical debulking may achieve favorable results.[88]

Aquamid (polyacrylamide hydrogel)

Aquamid has been used extensively for soft tissue augmentation and body contouring for 2 decades.[89] Aquamid is a biocompatible and nonabsorbable hydrogel consisting of 97.5% water and 2.5% cross-linked polyacrylamide (PAAG). The gel is manufactured through polymerization of the acrylamide monomers and N, N'-methylenbisacrylamide.[89] Aquamid is currently approved in several countries in Europe, European Conformity marked in Europe in 2001 for facial augmentation and minor body contouring, PAAG is available in more than 40 countries worldwide (Europe, Asia, the Middle East, and Latin America) and awaiting FDA approval.

After injection, the implant is encapsulated and surrounded by fibroblasts and microphages, theoretically preventing migration. Many studies have supported the usage of Aquamid for the treatment of various rhytides, facial contouring, and correction of HIV lipoatrophy. PAAG has been evaluated in clinical trials for facial contouring, deep rhytides and folds,[90-92] and the correction of facial lipoatrophy[93,94] with efficacy similar to nonanimal stabilized hyaluronic acid and duration of at least 1 year when used for the treatment of nasolabial folds.[95-98]

For the past decade, Aquamid has gained popularity as injectable filler. Similar to other facial fillers, there have been reported cases of inflammation, nodule and granuloma formation, and delayed hypersensitivity reactions. Histologic analysis of Aquamid injected into the subcutaneous layer revealed bioactive product that underwent cell infiltration and integration into tissues between weeks 1 and 8.[99] In some instances, surgical extraction of the polyacrylamide product was necessary to correct the adverse event of nodule formation. Careful attention to injection technique and sterile precautions are necessary to minimize unwanted reactions. In addition, there have been recent recommendations for the usage of prophylactic antibiotics to minimize complications from bacterial injections and biofilm formation when injecting Aquamid.[100,101]

Polyvinylpyrrolidone-silicone suspension

This is a permanent filler comprised of particles of polymerized silicone elastomer, 100-600 μm in size, dispersed in a carrier of polyvinylpyrrolidone (Bioplastique; Uroplasty BV, Geleen, The Netherlands). The suspension has been mostly used for lip augmentation and the correction of facial rhytids. It should be injected in the subcutaneous tissue. They usually remain at the injected site and could avoid from being phagocytosed by macrophagesdue to the large size of the silicone particles. They would produce a local foreign body reaction and fibrosis, which contributes to the filling effect.[102] Local side effects include induration, swelling, and granuloma formation.[103-105]

Histopathologically, granulomas secondary to this filler consist of irregularly shaped cystic spaces containing translucent, jagged "popcorn" nonbirefringent particles of varying size dispersed in a sclerotic stroma surrounded by abundant multinucleated foreign body giant cells.[102-105]

Polyalkylimide gel

Polyalkylimide gel is a permanent hydrophilic translucent gel filler composed of a hydrophilic biopolymer with 96% sterile water and 45% polyalkylimide polymer (Bio-Alcamid; Polymekon, Brindisi, Italy), and different from polyacrylamide. It has been used to increase volume in the cheeks in HIV patients with facial lipoatrophy related to antiretroviral therapy and for gluteal augmentation, correction of irregularities after liposculpture, scar depressions, and posttraumatic subcutaneous atrophy and

filling of pectus excavatum or other malformations of the skeleton. Complications secondary to this filler include edema, bruising, nodules, and infections, but no granulomas have been described. Histopathologically, this filler appears as basophilic amorphous material with granular appearance surrounded by sparse numbers of epithelioid histiocytes, foreign body multinucleated giant cells, neutrophils, and red cells.[106-110]

Polyvinylhdydroxide microspheres suspended in polyacrylamide gel

This is a permanent filler composed of composed of a suspension of 6 polyvinylhydroxide microspheres suspended in 2.5% polyacrylamide gel (Evolution; ProCytech SA), and has been used mostly for lip augmentation. This is a rarely used filler, and there are not descriptions of adverse reactions to this filler, other that the observation made by Lemperle *et al*.[49] who, in their comparative paper on fillers, injected Evolution (and later excised it from the first author's forearm) and found the filler to give little local reaction and diminish slowly over 9 months.[4]

CONCLUSION

Although dermal fillers have been used for decades in aesthetic medicine, the ideal filler is still missing, because all of them known today may cause adverse reactions. Patients' safety is hampered by nonlicensed products and users. These side effects are tend to be less severe after injection with non-permanent or semi-permanant biodegradable skin fillers, which will mostly disappear spontaneously within a few months. Unfortunately, however, after injection with slowly or nonbiodegradable permanant fillers, sever adverse reactions may appear and need active treatment. Follow-up of patients by trained physicians is necessary to reduce risks and initiate early treatment in case of complications. Careful selection of patients and particular selection of products, matching particular needs, and skilled injector is the best way to perform safe three-dimensional rejuvenation and achieve high patient's satisfaction. In the future, individualized, specifically tailored filler with long-lasting effect but with fewer complications might become available.

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Conflicts of interest

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