

# The history and journey of dermal fillers

With nearly 100 dermal filler brands on the market today, Danielle Meagher delves into their history and clinical uses to help readers gauge which is the best choice for different treatments



*Dr Danielle Meagher graduated in dentistry from Trinity College Dublin; she also holds an Honours degree in Aeronautical Engineering from UMIST, Manchester. Danielle is CEO, principal dentist and director of facial aesthetics at DermaDental, Ireland's first combined facial aesthetics and dental clinic. Danielle completed all of her training in facial aesthetics at Harley Street in London, alongside other dentists, doctors and plastic surgeons.*

Before exploring the use of third generation dermal fillers at the facial aesthetic dental interface, let us look back at the early dermal fillers, as well as examining some of the key brand names available on the market today. We will look at their individual derivation (bovine/human), their gel particle size, degree of cross-linking and percentage of cross-linking within that degree of cross-linking.

However, let us first look back a little at the early dermal fillers, their FDA approval, and indeed the relevance of FDA approval or non-approval, as well as off-label use (including any legal ramifications of off-label use) before critically analysing the use of dermal fillers within any aesthetic practice.

Bovine-derived collagen Zyplast 1 was the first FDA-approved dermal filler; this was nearly 30 years ago, back in 1981. Zyderm 1 had the potential to cause an allergic reaction as a result of its bovine collagen, plus its effects didn't last very long (less than two months) and it gave disappointing results for deep folds and scars. As a result, two

years later Zyderm 2 and Zyplast were FDA-approved and introduced into the market. Zyplast gave significantly improved results for deeper folds. These dermal fillers were then the sole FDA-approved fillers for over a decade (Murray, 2005).

## **Bovine-derived collagen fillers**

Collagen is the major structural component of the skin, and as such it seemed a natural deduction that the dermis could be replenished with bovine-derived collagen. Indeed, bovine collagen is still used today.

According to Lowe et al (2005), there is a risk of allergy from bovine-derived collagen fillers. Numerous reports also describe skin necrosis, especially with the use of Zyplast in the glabellar region (Hanke et al, 1991). Two negative skin tests are required prior to treatment, and although two negative tests make the likelihood of an allergic reaction low, it does not eliminate the risk fully. There is a delay of up to six weeks from first testing the product on the patient's skin to actually having dermal filler treatment, and

today's discerning facial aesthetic patient will most likely be unwilling to wait this duration for treatment.

## **Eliminating the bovine element**

As a result of the risk of allergy to bovine-derived collagen fillers, companies were motivated to develop human-derived collagen dermal fillers. Since these agents do not contain any bovine element, no allergy test is required.

In March 2003, the FDA approved three bio-engineered human collagen dermal fillers: CosmoDerm 1, CosmoDerm 2 and CosmoPlast. These resulted in reduced patient downtime and, similar to the bovine-derived collagen products, the CosmoDerm family contained lidocaine. The incorporation of lidocaine into dermal filler product reduces pain during treatment, but also reduces oedema and ecchymosis by inhibiting the activation of eosinophils, thus reducing the risk of bruising.

## **The porcine-derived range**

The next type of filler to consider in brief is that of the porcine-derived (pig tendons)

family of dermal fillers. The common brand is Evolence, which has been used outside the United States since 2004. Porcine collagen resembles human collagen so closely that the risk of allergy is remote and no skin testing is required prior to treatment.

Note that Evolence is not cross-linked with glutaraldehyde, unlike Zyderm and CosmoPlast. Instead, Evolence is cross-linked with a natural sugar, D-ribose. It is recommended that Evolence is injected into mid-to-deep dermis, and results last longer than either human- or bovine-derived collagen fillers – reportedly up to six months (US Food and Drug Administration 2008).

### Introducing hyaluronic acid

Next in the history of dermal fillers, and indeed possibly the most important advancement, was the introduction of hyaluronic acid-based dermal fillers.

Hyaluronic acid (HA) is found naturally in the body; it is the most prominent glycosaminoglycan in the skin. Hyaluronic acid is a hydrophilic substance, and as such binds to water when injected into the skin. In addition to volumising, softening and hydrating the skin, HA plays a role in cell growth, repair and adhesion.

In February 2003, the FDA approved Restylane, a cross-linked non-animal source hyaluronic acid (NASHA). Restylane was found to be longer-lasting, have minimal adverse reactions, be easy to use, did not require refrigeration, and was cost-effective. In addition, very importantly, it did not require skin testing, so there was no delay in having treatment.

However, these FDA-approved hyaluronic acid dermal fillers did not contain lidocaine, and so were more painful on injection than the previous bovine or human predecessors. Also initially, due to the heparin effect of HA, there was a greater incidence of bruising than we had seen previously with collagen fillers.

Despite these shortcomings, hyaluronic acid has fast emerged as the market leader of dermal fillers due to the predictable superior cosmetic results they achieve.

In 2006, the FDA approved Juvéderm, another HA-based dermal filler. In the USA only two types of Juvéderm dermal fillers are FDA-approved (Monheit, 2007). Both Juvéderm Ultra and Juvéderm Ultra Plus have similar indications to Restylane and Perlane, and do not require refrigeration or skin allergy testing. Allergan has now launched a Juvéderm product that contains lidocaine, so it would seem the only shortcoming in the HA family of dermal fillers has now been eliminated.

Although unwanted side-effects are rare with use of HA dermal fillers, correction is possible with the use of commercially available hyaluronidase. Hyaluronidase breaks down unwanted HA dermal fillers. Hyaluronidase preparations are clear, concentrated liquids that are stored in a refrigerated vial; they are reconstituted with saline or lidocaine (with or without adrenaline). Prior to treatment with hyaluronidase, a skin test can be performed. Once the refrigerated vial is reconstituted with saline/lidocaine, the mixture in the vial is gently swirled. Before use it is advisable to do a test area. By injecting 0.06-0.1ml of reconstituted solution into the superficial dermis at the antecubital fossa, the area can be monitored for a positive hypersensitive reaction, which typically consists of a weal appearing within five minutes with associated itching, the effects lasting up to half an hour.

In 2003, Q-Med's Restylane and Perlane received FDA approval for treatment of nasolabial folds. This NASHA-based dermal filler is produced by fermentation in a bacterial culture of equine streptococci. Restylane contains 100,000 particles per ml; these particles are highly cross-linked. Restylane has been used in the

correction of nasolabial folds, tear troughs, glabellar frown lines and marionette lines, as well as for lip and cheek augmentation. It can also be used to correct nasal deformities, as an alternative to rhinoplasty surgery.

Perlane is a NASHA-based dermal filler manufactured by Q-med; the only difference is that it contains larger particles, and as such is suitable for the correction of deeper folds and can also be used for cheek enhancement. Also in the Q-med range is Restylane SubQ, which gives excellent cheek enhancement outcomes. Restylane Lipp, as the name suggests, is an excellent choice for lip enhancement treatment.

### NASHA adverse effects

The adverse effects of NASHA-based hyaluronic acid dermal fillers such as Restylane and Perlane (both Q-MED) and all products included in each respective brand are minimal, but do exist.

If injected too superficially, a bluish Tyndall effect can be seen (Carruthers et al, 2006); this represents visible hyaluronic acid seen through the translucent epidermis (Rayleigh effect). However, a nick with a small 30 gauge needle is usually sufficient to allow the expression of this superficially-placed dermal filler. There is, of course, the possibility of more bruising and pain compared to collagen fillers (due to the lack of lidocaine in NASHA-derived dermal fillers).

On occasion, palpable nodules have been reported under the skin. To minimise the risk of such nodules, a linear threading technique is best used.

Peter and Menne (2006) also reported various cases of retinal branch artery occlusion following injection of hyaluronic acid: 'The potential for retrograde embolisation of substances from the face in the retinal vascular territory exists, as there are multiple anastomoses between the vascular supply of the face and orbit.'

### Botulinum toxin

Ideally, dermal filler is used in the lower one-third of the face and/or malar region; the upper third of the face benefits from treatment with Botulinum toxin A. On occasion and in order to achieve optimum relaxation of glabellar frown lines, Botulinum toxin A treatment is followed two weeks later by some dermal filler into the glabellar region. This protocol is only for stubborn glabellar frown lines; Botulinum toxin A normally yields excellent results in this area.

### Additional types of filler

There are, in fact, many dermal types of filler on the market today. Many are FDA-approved. Some are FDA-approved for certain uses only. Some are not FDA-approved at all.

Examples of other brands of filler include Hyalafarm, Captique, Teosyal, Puragen, and Prevelle Silk. Artefill was FDA-approved for use in the USA in 2007. Radiesse was FDA-approved at the end of 2006 for the correction of facial wrinkles and folds, and for the correction of HIV-associated facial atrophy. Radiesse is composed of 30% calcium hydroxylapatite and 70% carrier gel. Treatment of the lips has resulted in cyst formation and as such it is wise to avoid treating the lips with Radiesse (Alam, 2008).

The next significant introduction to the dermal filler market was Sculptra (Poly-L-lactic acid). Sculptra differs from all other agents in several ways, in that the effects are not immediate and more than one treatment is required. Sculptra is not a true dermal filler, and works differently by stimulating fibroblasts to produce more collagen, therefore increasing facial volume (Butterwick, 2007). Sculptra is a biodegradable, biocompatible and immunologically inert peptide so the risk of allergy is minimal, however post-treatment dermal nodules have been reported. In the USA Sculptra is FDA-approved for the treatment of HIV-associated lipodystrophy, although it is commonly used

to treat advanced nasolabial folds. This off-label use is common, much in the same way that Botulinum toxin A has been used off-label to treat glabellar frown lines.

Sculptra relies on neocollagenesis to stimulate the dermis. Results are not seen for four to six weeks and up to three treatments will be necessary (every four to six weeks).

Dermal nodules have been reported, but the risk of such nodules can be reduced with vigorous post-treatment massage, as well as by reconstitution of the product with 6ml or greater of sterile water.

### **Best for your patients**

With such regular and rapid advancements in the area of dermal fillers, one can be forgiven for becoming easily confused regarding the best choice for patients.

An ideal dermal filler product will need to satisfy many requirements, such as biocompatibility, non-reactivity, and reversibility/minimally invasive delivery, while also allowing for pain-free delivery.

In addition, patients will no longer tolerate a six-week lead time in between skin testing and treatment. Yet they require dermal filler products that last a minimum of six months. Patients also require 'no downtime' dermal filler treatments.

Cost-effective products with good predictable aesthetic results (every treatment) are also favoured by the patient, and indeed the aesthetic practitioner.

### **Incorporating lidocaine**

The final 'icing on the cake', according to many practitioners, is the incorporation of lidocaine into the HA dermal filler product. As a Trinity graduate in dentistry, whether or not the dermal filler product contains lidocaine is of absolutely no consequence to me. In fact, even if the brand contains lidocaine, I will always use some dental block initially.

In 2008 Allergan launched a dermal filler product that contains lidocaine: Juvéderm Ultra. This suits many non-dental practitioners, because often the administration of 'dental block' seems somewhat elusive to achieve. So the idea of having a dermal filler containing lidocaine would suggest there is no need for dental block. I would disagree with this; I believe the benefit of incorporation of lidocaine is that it reduces oedema and ecchymosis by inhibiting the activation of eosinophils, thus reducing the risk of bruising. After the initial couple of injections of Juvéderm Ultra there will be a good degree of anaesthesia achieved, but as a keen practitioner of 'pain-free' facial aesthetics I always use some local dental block before ever proceeding with any lip injections. Excellent dental block, in my mind, is still the key to pain-free facial aesthetics.

### **The fillers of choice**

It is my opinion that the family of NASHA dermal fillers are the fillers of choice. They satisfy all the safety and aesthetic requirements of both the discerning facial aesthetic practitioner and, indeed, the discerning facial aesthetic patient.

The benefits of using dermal fillers within a facial aesthetic practice are well documented. According to Maio (2004): 'This minimal approach offers a faster, less painful, and less costly alternative or complement to surgical facelifts.'

This area of biodegradable dermal fillers is a rapidly growing field, wrote Maio (2004): 'According to the American Association of Plastic Surgeons, more than 356,000 surgical rhinoplasties and 128,000 face-lifts were performed in 2003, representing an increase of 1% and 9% respectively, over those performed the year before. However, during the same period the real growth in cosmetic procedures was in dermal injections treatments, which increased by 30%.'

The traditional face-lift is not yet obsolete. But with many patients opting for minimally invasive procedures (no down time/none of the risk that is associated with general anaesthetic) involving the use of Botulinum toxin A and, indeed, dermal fillers, the need for a face-lift can be postponed almost indefinitely with regular visits to a facial aesthetic clinic.

Many surgeons also find that following face-lift surgery there may be some final 'tweaking' required, and it is easier to make any final adjustments with dermal filler. In addition, dermal filler can be used to fill tear troughs.

Malar augmentation using dermal filler can be carried out to define the cheek bones; a HA product such as Restylane Sub Q is an excellent choice for this area. Also, while rhinoplasty is usually considered the treatment of choices to reshape noses, dermal fillers are proving to be an excellent option when correcting small defects or concave nose bumps. HA dermal fillers can also be injected into the base of the nose to ensure a more delicate downturn, or indeed to reduce the drooping effect that occurs with age. It is also possible to increase a nostril flare by using HA products with a smaller particle size.

According to Maoi (2004), it is possible 'for a more extensive nose reshaping, filling the anterior nasal spine and the columella basis with collagen opens the nasolabial angle' [90-110°]. This is in addition to the benefit of combined treatment with Botulinum toxin A, where by injecting the depressor of the septum excessive nose tip drooping can be corrected.

While the above suggestions may simply be 'food for thought' for the novice injector, there is no denying that on a daily basis there are more and more nasolabial folds, oral commissures, marionette lines and lips being treated with one or more dermal filler products.

### **Other uses**

Within the dental arena, the benefits of dermal filler in the correction of both cleft lip (Schweiger et al, 2008) and mandibular prognathia must not go unmentioned (Reytan et al, 2007).

Also, an *Irish Dentist* article (Meagher, 2008) presented a case study of a young caucasian female with an asymmetric upper lip. This lip was successfully treated with a hyaluronic acid dermal filler product.

The type of dermal filler to be used should be at the discretion of the individual practitioner, within reason. There are about 100 different types of dermal fillers on the market today.

The author favours NASHA-based dermal fillers, such as Restylane (Q-Med). Juvéderm and Hydrofill are excellent options for the novice injector, but with skill growth and experience the Q-Med product range is a firm favourite of many facial aesthetic practitioners.

Finally, as always, informed consent is paramount to using dermal filler products in any aesthetic practice. According to Dendy et al (2005): 'Obtaining informed consent is a crucial component in minimising legal complications. This consent represents a vital part of patients' education and can serve as a legal document demonstrating the patients' understanding of the risks associated with the procedure.'

Finally, one must be aware of the legal ramifications of off-label filler use (Goldberg, 2006). Many clinicians use a variety of drugs in an off-label manner. Botulinum toxin A is an obvious example.

Some dermal filler products are used off-label from their FDA approval. An example of off-label use would be Sculptra. According to Goldberg (2006), Poly-L lactic acid is FDA cleared for use in HIV lipoatrophy. However, this agent is more commonly used for off-label, non-FDA cleared facial volume enhancement in non-HIV patients.

The use of dermal fillers in any aesthetic practice is a key part of the clinician's armoury to combat the natural ageing process that we are all subject to. With the Baby Boomers now in their 50s and 60s, there is an increased demand for anti-ageing treatments in order to offset or even delay the loss of youth. This demand is particularly in response to the forces responsible for facial ageing, which include: sun damage, gravity, soft tissue maturation, reduced collagen and elastin, and changes due to environmental factors

The journey and history of the facial aesthetic dermal filler, and indeed the clinical benefits, have been highlighted in this paper. After critically analysing the use of dermal fillers in an aesthetic practice with contemporary evidence, the author considers that the benefits of use of dermal

fillers within any aesthetic practice are undisputed. This is not just in regard to true cosmetic enhancement, but also in the area of cleft or asymmetric lip, non-surgical rhinoplasty, and correction of prognathic mandibles. [7](#)

### References

Alam et al (2008) Injectable fillers. *Dermatol Surg* **34 Suppl 1**: S115-48

Butterwick (2006) Understanding injectable Poly-L-lactic acid. *Plast Reconstr Surg* **118(3 Suppl)**: 46S-54S

Caruthers et al (2006) Management of injected hyaluronic acid induced Tyndall effects. *Lasers Surg Med* **38(3)**: 202-4

Goldberg (2006) Legal ramifications of off-label filler use. *Dermatologic Therapy* **19**: 189-193

Hanke et al (1991) Abscess formation and local necrosis after treatment with Zyderm or Zyplast collagen implant. *J Am Acad Dermatol* **25**: 319-326

Lowe et al (2005) Adverse reactions to dermal fillers: review. *Dermatol Surg* **31(11 Pt 2)**: 1616-25

Maio (2004) The minimal approach: an innovation in facial cosmetic procedures. *Aesth Plast Surg* **28**: 295-300

Meagher (2008) Treating lip asymmetry with filler. *Irish Dentist* **11(8)**: 35-38

Monheit et al (2007) Juvéderm: a hyaluronic acid dermal filler. *J Drugs Dermatol* **6(11)**: 1091-5

Murray et al (2005). The evolution of soft tissue fillers in clinical practice. *Dermatol Clin* **23(2)**: 343-63

Peter S, Mennel S (2006) Retinal branch artery occlusion following injection of hyaluronic acid (Restylane). *Clinical and Experimental Ophthalmology* **34**: 363-364

Reytan et al (2007) Aesthetic correction of the upper lip in a patient with mandibular prognathia with a novel long-lasting collagen filler: a case report. *Dermatol Surg* **33**: 1274-1276

Schweiger et al (2008) Successful treatment with injected hyaluronic acid in a patient with lip asymmetry after surgical correction of cleft lip. *Dermatol Surg* **34**: 717-719

US Department of Health and Human Services (2008) *US Food and Drug Administration. Device Approval*