Exploring the effectiveness of a new generation of collagen-stimulating fillers

Volume loss is one of the first signs of facial ageing and dermal fillers have become an increasingly popular cosmetic intervention for this indication. Collagen-stimulating fillers are a safe and effective treatment for restoring shape and redefining contours. Ian Strawford explains the mechanism of action of the Ellansé dermal filler range and shares three patient case studies.

In recent years, the recognition of the importance that facial volume loss plays in the ageing process has shifted the focus of treatment from isolated problem areas, such as the nasolabial folds, to the entire face, to restore shape for a more harmonious and natural effect (Lupo, 2008). Dermal fillers have become a popular means of addressing volume loss and contour defects resulting from ageing, disease or trauma. The most widely used dermal fillers are the ones based on hyaluronic acid (HA) gels (Smith, 2008; Carruthers et al, 2015); however, non-permanent collagen-stimulating dermal fillers have become an increasingly important and popular treatment over the last decade, with over 4 million treatments worldwide (Pavicic, 2013).

Since the introduction of calcium hydroxyapatite and poly-L-lactic acid collagen-stimulating dermal fillers in 2006 and 2004, respectively, the role of collagen stimulation in facial aesthetics has been studied extensively (Lacombe, 2009; Pavicic, 2013). In this article, the author examines a newer range of dermal fillers containing polycaprolactone (PCL) (Ellansé, Sinclair Pharma UK). More specifically, the author will discuss the products’ unique properties, the indications for their use, their safety record and clinical evidence to support its use in practice.

Later in the article, the author will demonstrate the extensive use of Ellansé dermal fillers in his personal practice by sharing three patient case studies. These case studies will show the potential of collagen-stimulating dermal fillers to produce safe and natural long-lasting results.

How collagen-stimulating fillers work

On injecting any dermal filler or biostimulatory agent/biomaterial, such as PCL, into human tissue, there will always be an initial foreign body response to the product in the host’s tissues (Nicolau, 2007). It is important for injectors to understand the mechanism of this foreign body response to comprehend why collagen stimulation occurs and how it is part of the body’s normal healing response.

Normal healing starts within 2 hours of injury. Healing starts with an initial inflammatory phase, followed by the production of macrophage cells, which in turn stimulate fibroblast cells to form type III collagen or scar tissue. This rapid production of type III collagen allows for a quick initial healing phase to be completed. When a material, such as PCL, is implanted, following the initial inflammatory phase and within 2 weeks, the microparticles within the tissues will become encapsulated by fibroblasts, leading to fibroplasia (a natural protective mechanism of the body to isolate the ‘harmful’ foreign particles). This gradual process of encapsulation produces a stable capsule of mainly type I or non-scar tissue collagen around each of the particles. Encapsulation will last as long as the foreign body or biomaterial remains within the tissues (Nicolau, 2007; Williams, 2008; Kim and Van Abel, 2015).

Multiple factors affect encapsulation of the material, including the site of implantation and the host response, which is dependent on their health status and age. Equally as important is the physical properties of the biomaterial implanted, notably the size and shape of the particles.

Simply put, the effect of a biomaterial on the host is to stimulate an inflammatory/immune response, and the effect of the host’s response on the biomaterial is to attempt to eliminate or encapsulate the foreign material (Ratner and Bryant, 2004; Nicolau, 2007). Biomaterial particle size and shape is a significant factor on predicting the response to the implanted material. Particles sizes <20 µm in size are phagocytosed by macrophages and eliminated from the body (Morhenn et al, 2002). Particle sizes of between 25 and 50 µm that are spherical in shape produce the most fibrosis or new collagen when implanted due to the higher surface area per mass of any biomaterial used (Gelb et al, 1994). Particle sizes 50-50 µm in size are more likely to produce a prolonged inflammatory reaction producing only type III collagen (Morhenn et al, 2002; Nicolau, 2007).

In essence, an effective biostimulatory material needs to induce a predictable host response when implanted. In the case of collagen-stimulating dermal fillers, this is to produce type I collagen in response to the biomaterial for as long as it is present in the body. Thus, the ideal collagen-stimulating product should consist of smooth microparticles no larger than 50 µm, that are stable in both size and shape, as well as being long-lasting before degradation and full elimination from the body (Nicolau, 2007).
Biocompatibility of polycaprolactone and carboxymethyl cellulose gel

PCL is a polymer that was first synthesised in the early 1930s by the Carothers Group, which led to the initial biomedical applications for its use in medicine. PCL has been used for many decades in a variety of bioresorbable device applications in medical, cosmetic and pharmaceutical industries, and has been shown to be one of the safest medical polymers in use today. It has been a key component of bioresorbable sutures, medical implants, three-dimensional scaffolds and controlled drug delivery systems, including contraceptives (Hutmacher et al, 1996; Breitenbach et al, 2000; Agrawal and Ray, 2001; Aberturas et al, 2002).

Carboxymethyl cellulose (CMC) gel is a polysaccharide and plant-based derivative of cellulose. It has been used widely in the pharmaceutical, food and cosmetic industries for many decades (McElligott and Hurst, 1968; Leonardis and Palange, 2015). CMC gel has not only been deemed non-toxic and non-carcinogenic, but also it has been shown to have a bactericidal effect within tissues (Keipert and Voigt, 1979).

**Ellanse dermal fillers**

Ellanse dermal fillers comprise of 70% CMC gel carrier and 30% PCL synthetic polymer microspheres (Figure 1). The microspheres in Ellanse fillers are all 25–50 µm in size with a smooth surface and spherical shape, which contribute to the products’ biocompatibility. The PCL microspheres’ characteristics also explain the regular distribution of the type I collagen around them, forming a scaffold with minimal inflammatory reaction (Laeschke, 2004; Kim and Van Abel, 2015; Fanovich et al, 2016).

The PCL microspheres in Ellanse are homogeneously suspended in the aqueous-based CMC gel carrier, which enables a uniform distribution, prevents clumping, and allows a greater surface area for stable encapsulation and collagen formation. After injection, the CMC gel carrier is gradually resorbed by macrophages over a period of up to 6 weeks, as the particle sizes are <20 µm. The CMC gel carrier has been shown to have an elastic modulus, represented by G prime (G’), of approximately 1000 Pa, which is significantly higher than the values reported for all HA fillers (Stocks et al, 2011). In the author’s experience, when Ellanse is injected it has a significant lifting and volumising effect with only small volumes used, allowing for accurate placement of the PCL microspheres.
Unlike most HA dermal fillers, the CMC gel carrier particles in Ellansé are not cross-linked, and thus the filler is easy to inject. The CMC gel displays significant shear thinning properties, which means it has a smooth and acceptable extrusion force and a 27 gauge needle or cannula can be used (de Melo and Marijnissen-Hofsté, 2012).

The initial volumising effect seen following the injection of Ellansé is due to the CMC gel carrier. After approximately 12 weeks the PCL microspheres have stimulated neocollagenesis and the production of new collagen around the microspheres. This results in the replacement of the volume of the gel carrier, which is lost through bioreosorption. Thus, the volumising effect seen following the injection of Ellansé is maintained (Nicolau and Marijnissen-Hofsté, 2012). (Figure 2).

Longevity

Ellansé’s PCL microspheres degrade slowly through hydrolysis of the polymer ester linkages. The products of PCL degradation are hydroxycaproic acid and water, which are excreted from the body as CO$_2$ and H$_2$O (Pitt et al, 1981; Gunatillake and Adhikari, 2003).

Ellansé range consists of four products where the microspheres last 1, 2, 3 and 4 years due to the different chain lengths of PCL present within the filler’s microspheres (Moers-Carpi and Sherwood, 2013; Kim and Van Abel, 2015). Commercially, these products are referred to as Ellansé-S, Ellansé-M, Ellansé-L and Ellansé-E, respectively.

The chain lengths and number of ester bonds increase in each of the products, which progressively halve themselves until they reach the final degradation size. Only at that moment do the microspheres collapse, losing their scaffold affect and therefore the volume connected to the neocollagenesis. Maintaining their shape and size of 25–50 µm means that there is no ongoing inflammatory process to risk complications of nodules or granuloma formation (Laeschke, 2004).

Ellansé PCL microspheres are the only injectable collagen-stimulating product shown to maintain the microsphere shape and size throughout the duration of the product of 1–4 years (Figures 3 and 4), as evidenced by animal and human histological studies (Nicolau, 2013; Kim and Van Abel, 2015).

A 24-month, prospective, randomised controlled study of 40 patients, evaluated the efficacy, safety and longevity of the 1- and 2-year Ellansé products (Ellansé-S and -M), with a sustained improvement in 90% and 91% of patients, respectively. Both products were found to be safe and very well-tolerated (Moers-Carpi and Sherwood, 2013).

A similar study using Ellansé-M for forehead contouring in combination with botulinum toxin injections showed a significant improvement in the Global Aesthetic Improvement Scale (GAIS) over the first 3 months due to neocollagenesis, which was maintained for the 24-month period (Bae et al, 2016).

Further evidence of prolonged neocollagenesis was shown in a randomised, prospective, blinded, split-face, single-centre study involving 40 patients treated with Ellansé-S on one side of the face and Perlane HA on the other side in the nasolabial folds. After 6, 9 and 12 months post treatment, nasolabial folds treated with the PCL-based dermal filler showed statistically significant improvements on the Wrinkle Severity Rating Scale and greater improvements on the GAIS compared to those treated with a non-animal stabilised HA dermal filler. Both products were found to be equally safe and well-tolerated (Galadari et al, 2015).

Biostimulation

Ellansé can be used for biostimulation, improving the volume in the hypodermal fat layer if needed. Small amounts of Ellansé can be placed in this layer using a 25 gauge cannula with a retrograde fanning technique and multiple passes in different directions (Iozzo, 2016). It is vitally important to control the amount of PCL being used and the author recommends no more than 0.05 ml of product per linear thread of 2” to avoid overstimulation and nodule formation when the PCL is placed closer to the dermis with a higher concentration of subdermal fibroblasts. Usually a maximum of 0.5–1 ml is used per side of the face.

The collagen stimulation following this biostimulation reliably shows a volumisation of the hypodermal fat layer with an improvement in dermal thickness and elasticity similar to traditional HA skin boosters, but with results lasting in excess of 2 years (lozzo, 2016). The author often uses this biostimulation technique to improve the hypodermal layer 3 months before using suspension sutures in patients with significant hypodermal volume loss and dermal thinning and laxity. This is done to improve the outcome and reduce complications of suture lifting.

Injection techniques

Local anaesthetic (lidocaine) can be mixed with PCL-based dermal fillers without negatively changing the physical properties of the filler (de Melo and Marijnissen-Hofsté, 2012). A maximum of 0.2 ml of either 1% or 2% lidocaine should be used, using a female-to-female Luer-Lock connector, with at least 15 mixing strokes, to yield a 0.3% concentration of local anaesthetic. This will allow a relatively pain-free injection of the product (de Melo and Marijnissen-Hofsté, 2012).
In the author’s opinion, due to the significant collagen-stimulating properties of PCL in Ellansé, its use is best suited to advanced practitioners experienced in using both needle and cannulae, to obtain optimum results and reduce the risk of complications. It is important to have a thorough understanding of the facial ageing process and anatomy to make a suitable assessment of the patient and use facial mapping, which helps practitioners to identify the areas to be augmented, to avoid danger zones, and to plan the overall injection strategy (Cotofana et al, 2016; Solish, 2016; Wilson et al, 2016; Woodward, 2016).

Ellansé fillers can be used within the whole face for both volumisation and reshaping, placing the product deep in the subcutaneous or preperiosteal plane. In the author’s experience, only small amounts of product are needed to achieve correction compared with HA-based dermal fillers, when placed in the correct plane, due to the product’s very high G’, as previously mentioned (Stocks et al, 2011).

Either the 0.75” 27 gauge needle (supplied) or a 25 gauge 1.5” or 2” cannula can be used for placement. The author prefers to use a cannula in most situations as it has been shown to be less traumatic and safer than a needle (Hexsel et al, 2012).

When using a needle for deep placement, single boluses should be no more than 0.2 ml. For injectors using a cannula, each retrograde linear fan should be 0.1–0.2 ml of product. Overcorrection is to be avoided; the author prefers to undercorrect to allow time for the neocollagenesis process to have an effect, especially in younger patients. A review 3 months following treatment is appropriate and a further top-up treatment can be undertaken at this point, but not before.

Chin and nose augmentation

Highly-cohesive and collagen-stimulating fillers have been shown to be excellent for augmenting the chin and jawline (Rho et al, 2015). Nose augmentation or non-surgical rhinoplasty using dermal fillers have also been found to be safe and effective using both temporary and more long-term products (Chen et al, 2014). However, the risk of vascular compromise is much higher in the nose than the rest of the face and the author recommends the use of Ellansé for non-surgical rhinoplasty only by practitioners who are trained and experienced on this procedure. In the author’s experience, only small amounts of Ellansé need to be used to achieve a long-lasting correction of over 4 years.

Side effects and complications

As with any dermal filler, short-term swelling, bruising and discomfort can occur and are often dependent on the experience of the practitioner, as well as patient-related factors (e.g. age and medical history). The use of blunt-tipped cannulae can significantly reduce the risk of bruising and discomfort (DeJoseph, 2012; Lazzeri et al, 2012; van Loghem et al, 2016).

It is well-recognised that there is a risk of blindness associated with the injection of dermal fillers to the face with needles. However, the consensus is that this significant risk can be reduced with a good knowledge of facial anatomy and the use of cannulas, especially in the mid-face and around the periorbital region (Lazzeri et al, 2012).

Sinclair Pharma has a robust vigilance system in place, which ensures close follow-up and reporting of adverse events to the appropriate regulatory authorities including the Medicines and Healthcare Products Regulatory Agency in the UK. From a review following the launch of Ellansé in the UK to December 2015, there were 155 cases reported for 323 726 syringes sold, which gives an adverse event rate of 0.048% or one adverse event per 2089 syringes. The adverse rate for lumps/nodules was 0.016%, while the adverse rate for oedema/swelling was 0.017% and inflammation/infection 0.002% (Christen, 2016).

A review of the adverse events by the medical vigilance team suggested that most cases of nodules and lumps were associated
with technical errors related to the injector rather than the product, such as using boluses of more than 0.2–0.4 ml, too superficial placement, or injecting within the muscles of the lips and eyelids, which are to be avoided (Christen, 2016).

Numerous publications have described the modalities of complications seen with dermal fillers in general and the management and treatment of them (Lemperle et al, 2006; Bailey et al, 2011; Beleznay et al, 2015; Heppt et al, 2015). For the treatment of nodules, the use of corticosteroids injected in very small volumes is often proposed, strictly within the nodules, to break down the excess collagen (Aguilera et al, 2016). Other papers have shown that radiofrequency can have an impact on reducing nodules (Hong et al, 2017).

Case studies
Case study one
A 44-year-old woman presented having not had any previous cosmetic treatment. On consultation, she expressed concerns about looking tired and her under-eye hollows and nasolabial lines (Figure 5). The author used a 25 gauge 38 mm cannula to inject Ellansé-S (the 1-year product) supraperiosteal along the malar groove in the deep malar fat pad, as well as the suborbicularis oculi fat to correct the malar volume loss and medial tear trough. The author also treated the mental crease and prejowl sulcus. A total of 2.2 ml of Ellansé-S was injected.

Treatment of the deep malar fat pad lifted and enhanced the nasolabial folds. The ‘after’ photo (Figure 5) was taken at the patient’s follow-up appointment at 4 months when full correction had taken place due to the new collagen formation.

Case study two
A non-smoking 57-year-old woman was concerned about the deep nasolabial and marionette creases beneath her mouth and the loss of volume in her cheeks, which was making her feel tired and look sad (Figure 6). It was agreed the best approach would be to use a combination of Ellansé-M (2-year product), to correct the volume loss, and Silhouette Soft sutures, to lift and correct the laxity of the jowls and improve the jawline contours. First, the Silhouette Soft sutures were applied, followed by the injection of Ellansé-M after 6 weeks. The author injected a total of 3 ml of with a cannula.

A year after treatment, the patient is still showing an excellent result with correction of her mid-cheek volume loss and reduction in her nasolabial folds and perioral lines, which can be expected to last over 2 years (Figure 6).

Case study three
This 58-year-old female had been a long-term smoker and was suffering with significant volume loss, poor-quality skin and laxity. She presented a challenge, but it was agreed that she would be a good candidate for combination treatment using Ellansé-S/-M and Silhouette Soft sutures. However, in her case, it was important to improve the hypodermal fat layer at least 3 months prior to inserting the suspension sutures, to improve the outcome and reduce complications of sutures. This was done using a 25 gauge 50 mm cannula with a retrograde fanning technique in the subdermal plane, using very small amounts of product (0.05 ml) with each pass. In total, 0.5 ml of Ellansé-S was injected for biostimulation in the submalar and subzygomatic areas.

Deep placement of Ellansé-M (2 ml) was also undertaken using the cannula in the deep malar fat pads and along the jawline and prejowl sulcus. After 3 months, when collagen stimulation was achieved, Silhouette Soft sutures were inserted without

Figure 5. Before (top) and after (bottom) the injection of 2.2 ml Ellansé-S to correct malar volume loss and the medial tear trough, and treat the mental crease and prejowl sulcus
facial complications. At 6 months, the patient was very happy with the correction of the volume loss in the mid-cheeks, nasolabial folds, pre-jowl sulcus and marionette lines. The quality of her skin significantly improved following the bio-stimulation treatment.

Figure 6. Before (left) and after (right) the application of Silhouette Soft sutures, to lift and correct jowl laxity, and the injection of 3 ml of Ellansé-M, to correct the volume loss in her cheeks

Figure 7. Before (left) and after (right) the injection of 0.5 ml of Ellansé-S for biostimulation, placement of 2 ml of Ellansé-M to treat the deep malar fat pads and the prejowl sulcus, and application of Silhouette Soft sutures to correct laxity
and was considering surgical blepharoplasty to correct her significant upper- and lower-eyelid laxity (Figure 7).

**Conclusion**

Collagen-stimulating dermal fillers have been popular with patients and practitioners for over a decade, following the initial use of poly-L-lactic acid in patients with severe facial lipoatrophy associated with HIV. All dermal fillers, whether HA-derived or collagen-stimulating, induce a foreign body reaction to this ‘implant’ when injected into human tissue, and it is important to understand the biological process that occurs following this.

Collagen-stimulating dermal fillers exert their long-term effect by producing encapsulation of the product, which, if stable, will produce healthy type I collagen and not an inflammatory reaction producing type III, scar tissue. The ideal collagen-stimulating dermal filler needs to be smooth and spherical in shape, with particles between 25 and 50µm in size. The PCL microspheres in Ellansé, which fit these criteria, have been shown to produce results of between 1 and 4 years, depending on which one of the four products are used. This tunable longevity allows aesthetic practitioners to tailor the treatment to the specific needs and outcomes desired.

PCL and CMC are both biocompatible, biodegradable and biorosorbable and have been shown to have excellent safety records in human use. In the author’s practice, many patients are seeking natural and long-lasting results. Ellansé has therefore become the main tool the author uses to achieve these desired outcomes due to its unique properties and the ability to safely stimulate collagen to replace lost volume, reshape facial contours or improve the dermis through biostimulation. With increasing concerns regarding the long-term safety of cross-linked HA-based dermal fillers, collagen-stimulating dermal fillers are likely to become an increasingly popular cosmetic facial treatment for discerning patients and practitioners alike.

**References**


McElligott TF, Hurst EW (1968) Long-term feeding studies of methyl ethyl cellulose ('Edifas' A) and sodium carboxymethyl cellulose ('Edifas' B) in rats and mice. *Food Cosmet Toxicol* 6: 449–60