Injectable Fillers in Aesthetic Dermatology

a report by

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Europe's population is ageing and this, in conjunction with fashionable chronic sun exposure, has greatly amplified normal cutaneous intrinsic ageing. In addition, looking young and feeling fit is considered the norm in our present way of life. Consequently, it is of no surprise that demand for aesthetic treatments is high and continuing to grow.

Dermatology has evolved enormously in recent years with the arrival of many new, non-invasive out-patient aesthetic techniques that help to improve appearance. Although wrinkles remain the major sign of ageing, the restoration of facial volumes and contours and the creation of a balanced, natural look must also be taken into account when treating the ageing face today. Injectable filler products have greatly evolved and are used worldwide. However, it must be emphasised that these techniques should be used according to the results of evidence-based studies, bearing in mind that successful aesthetic treatments also require a minimum of 'artistic' talent in order to achieve an overall natural look.

Long-term safety concerns encourage us always to choose biodegradable fillers, because any complications that arise will usually resolve themselves spontaneously. Using non-resorbable, permanent fillers, on the other hand, could give rise to long-term, hard-to-treat complications; patients must therefore be fully informed of the risks involved and a consent form should be signed. We believe that non-degradable fillers should be reserved for treating certain pathologies, such as HIV-related lipoatrophy, scars, etc.

Biodegradable Products

Bovine-derived collagen (Collagen Corp., US) was the first widely accepted filler agent, even though it was short-lasting and some patients experienced allergic reactions.[1] More recently, a human-derived collagen (Cosmoderm®, US) has been marketed that decreases the allergic potential of the product, but longevity is still only a few months. A new porcine-derived collagen (Evolence®, Johnson & Johnson) does not require prior allergy testing and the effects have been reported to last longer.

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Hyaluronic acid (HA) is an hydration molecule that occurs naturally in the dermis and has become the new 'gold standard' of safe, injectable filler products. It is used for wrinkle treatment, volume augmentation and mesotherapy. In a non-modified natural form its turnover in skin is rapid (24–48 hours) due to the actions of endogenous hyaluronidase, free radicals and temperature.

Injectable HA[2] is derived essentially from either of two sources: animals (rooster combs) or bacterial fermentation (*Streptococcus*), the latter of which does not require prior skin allergy testing. The duration of action of HA fillers is variable and mostly depends on stabilisation techniques such as cross-linking, which prolong efficacy from days to months, or even years.

There are two major categories of HA products:

- 'biphasic' – the result of different sizes of HA microspheres in an HA suspension (e.g. Q-Med products); and
- 'monophasic' – homogeneous: the preferred HA manufactured by most other companies.

Certain HAs have been developed that last for years before enzymatic removal (Sub-Q® and Macrolane® from Q-Med; Voluma® from Corneal). The use of HAs with different viscosities and molecular weights now allows for a novel combination approach to creating an aesthetically pleasing, more youthful face.

The following two biodegradable products have a very long duration of action and can in some circumstances last for many years. They should

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Table 1: Best Known Biodegradable Agents

Collagen: bovine (Zyderm®), porcine (Evolence®), autologous (Isolagen®), isogenic (Cymetra®), human (Cosmoderm®)
Gelatin powder and aminocaproic acid: Fibrel®
Human cadaver tissue: Fascian®
Hyaluronic acid: animal-derived (Hylaform®), non-animal-derived (Restylane®, Juvederm®, Hydrafill®, Surgiderm®, Hyaluderm®, Matridex®, Teosyal®, Anteis®, Captique®, Idune®, Isogel®)
Polyoxyethylene, polyoxypropylene: Profill®
Polyvinyl alcohol: Bioinblue®
Synthetic calcium hydroxyapatite: Radiesse®, Beautifill®

Table 2: Best Known Non-biodegradable Agents

Polydimethylsiloxane: Fluid silicone 350cs, Silskin® 1,000cs
Dimethylsiloxane: Bioplastic®
Polymethyl metacrylate in collagen: Artecoll®, Artefill®
Polymethyl metacrylate in hyaluronic acid: Dermalive®, Dermadeep®
Polyacrylamide gel: Aquamid®, Outline®
Polyalkylimide gel: Bio-alcamid®
Polyacrylamide and polyvinyl acid gel: Evolution®

not be used to treat superficial rhytids or the lips. Hydroxyapatite[3] (Radiesse® from Bioform) as microspheres in a carboxymethylcellulose excipient must be injected deeply – into the hypodermis or deeper – in order to avoid visible nodules. No prior allergy testing is required and the product may last for years. Microparticles of polylactic acid[4] (Newfill® and Scuptra® from Aventis) require an excellent injection technique and appropriate dilution in order to avoid visible or palpable nodules. No prior allergy testing is required and the product can last for many years.

A French product based upon polyoxyethylene (Profill®) is no longer used as it caused the delayed appearance of a characteristic lipoatrophy[5] (see *Figure 1*).

Non-biodegradable Fillers

Medical-grade 350cs silicone had been used for a long time[6] and the microdroplet technique was considered the best. However, at present this product is not legally available for aesthetic therapy. In the US, a silicone product used in ophthalmology with a higher molecular weight of 1,000cs – Silskin® – is currently used 'off-label' and does not require prior allergy testing.

Polyacrylamide gels[7] may be injected deeply for volume augmentations; polyalkylimide[8] (Bioalcamid®) is also used for volume augmentation. This particular product creates some sort of endoprosthesis surrounded by a fibrous capsule. However, these two products should be used with caution to avoid infectious complications.

A suspension of microspheres of polymethylmetacrylate (PMMA) in bovine collagen was developed in Germany as Arteplast® and Artecoll® and caused severe, delayed (sometimes for years) granulomatous

Figure 1: Lipoatrophy After Profill® Injection

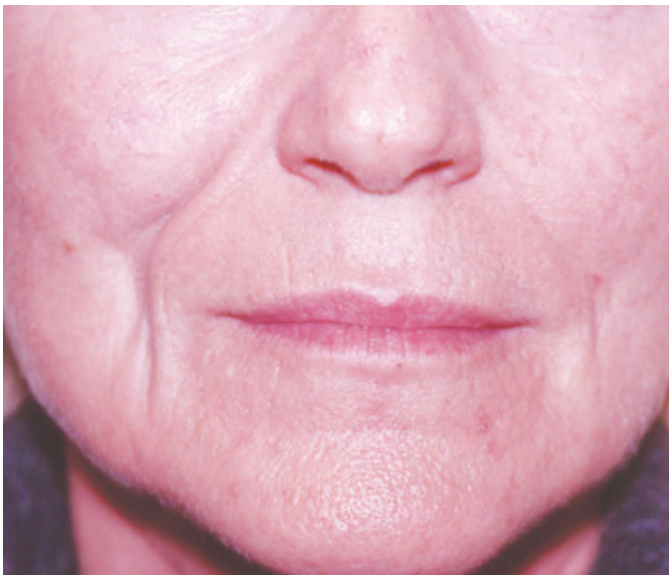
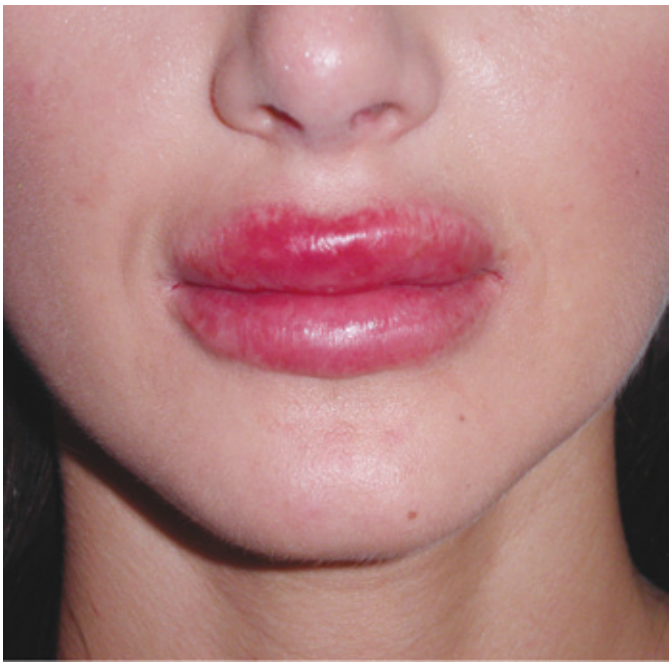


Figure 2: Granulomatous Reaction After Dermalive® Implantation



reactions[9]: an allergy test is required. The latest version of this product, Artefill®, is marketed as a much less reactive product due to better purification procedures. Time will tell.

Polyethylmetacrylate (PEMA; Dermalive®, France) is a suspension of multi-faceted microparticles in an HA suspension and also caused serious, delayed-onset inflammatory granulomatous reactions (see *Figure 2*). This product should not be used anymore.

As aesthetic specialists we are still seeing too many patients with complications due to filler injections[10] and often they do not know the exact nature of the product used. Histopathology[11] can be of assistance, especially in a medico-legal context, in identifying the causal agent. As an ideal filler does not yet exist, difficulties in treating severe side effects caused by non-resorbable fillers should encourage us all to utilise only

100% degradable products. Lipo-filling and fat-grafting give excellent volume contouring results – but should not be used for the lips or for nasolabial folds – and the suggested mode of action is the grafting of preadipocytes and, eventually, the presence of pluripotent stem cells.

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Conclusion

The market for facial rejuvenation has vastly expanded over the past few years and more and more doctors from all disciplines, as well as from medical device laboratories, are being enticed into entering the field. New products and 'miracle treatments' are continuously presented to aesthetic practitioners; however, as Dr Arnold Klein wrote, "remember that everything that is obsolete was once new, which indicates that everything that is new is not necessarily better."[12] We must always use our analytical sense of judgment and maintain the highest ethical standard of integrity in order to maintain our credibility.

In Europe, the majority of injectable fillers on the market have not been subjected to pre-distribution clinical studies; their only legal requirement is to have a CE marking, which does not guarantee that there are no short- or long-term side effects.

We hope that the various European government agencies responsible for overseeing the medical device market will try to improve the present situation in order to better protect both the physician and, most importantly, the consumer, who still resembles in some circumstances a clinical 'guinea pig'. Looking to the future, maybe the ideal filler product for restoring a youthful appearance while correcting rhytids and volume defects will be based upon pluripotential stem cell technology. ■

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