Calcium Hydroxylapatite Filler:  
An Overview of Safety and Tolerability

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ABSTRACT

Soft tissue fillers are becoming increasingly important as nonsurgical treatment options for facial rejuvenation. Calcium hydroxylapatite (CaHA) is an injectable dermal filler that contains uniform CaHA microspheres suspended in an aqueous carboxymethylcellulose gel carrier. It is considered a long-lasting, but non-permanent filler, and is highly biocompatible with human tissue. No osteogenesis has been reported in extensive literature describing the use of CaHA in a variety of soft tissue applications. Injection of CaHA into the oral mucosa and the lips is an unapproved indication and may result in nodule formation. This occurs soon after injection and is a result of accumulated particles and not a granulomatous reaction. As with all biodegradable dermal fillers, CaHA can be associated with rare incidences of foreign body reactions, but only a handful of case reports have been documented in 10 years of clinical use. CaHA can be associated with local, short-term, injection-related adverse events, which are generally mild and resolve within a few days. Clinical trials that have followed patients for up to 3 years post-injection report no long-term or delayed-onset adverse events. CaHA is an effective and safe treatment option for a variety of aesthetic indications. This paper focuses on common safety concerns of patients and aesthetic physicians, including unfounded fears of osteogenesis and foreign body granulomas, providing an up-to-date overview of the tolerability and long-term safety of CaHA for aesthetic indications.


INTRODUCTION

Facial rejuvenation procedures, which are minimally invasive and provide a long-lasting visible improvement, are rapidly increasing in popularity. In recent years, the recognition that facial volume loss plays an important role in the aging process, has shifted the focus of treatment from a concentration on isolated problem areas to targeting the entire face for a more harmonious and natural effect. Dermal fillers give the face a fuller, more youthful appearance and have become a popular means of addressing volume loss and contour defects resulting from ageing, disease, or trauma. As their popularity increases, so too has the number of products available. However, regulation of the industry varies considerably between countries. Pharmaceutical products achieve their principal action by pharmacological, metabolic or immunological changes within or on the body. Dermal fillers are classified as medical devices by most regulatory agencies, including the US Food and Drug Administration (FDA) as their primary intended action is mechanical (filling effect) and not pharmacological. In Europe, dermal fillers are also considered as medical devices, but they only require a European CE Mark that does not demand the conduction of clinical studies for approval to commence sales. In contrast, prescription only medicines such as botulinum toxin require a marketing license from the Medicines and Healthcare products Regulatory Agency (MHRA). In the USA, FDA approval is based on the review of data collected from controlled clinical studies of at least 6 months duration that have evaluated the safe and effective use of dermal fillers when injected into specified areas of facial tissue and in comparison with an established FDA-approved agent.

Benefit versus safety is a key consideration for any therapeutic product. Calcium hydroxylapatite (CaHA [Radiesse®]; Merz Pharmaceuticals GmbH, Frankfurt, Germany) received FDA approval in 2006 for facial soft tissue augmentation including the correction of moderate to severe nasolabial folds, and the restoration and correction of the signs of HIV-associated facial lipodystrophy. In Europe, CaHA received a CE mark in 2004 for plastic and reconstructive surgery, including deep dermal and subdermal soft tissue augmentation of the facial area. Since then it has been extensively used for the correction of moderate to severe facial lines and folds and to replenish lost volume. It is one of the most well-studied dermal fillers with more than 4 million syringes injected worldwide. This paper focuses on common safety concerns of patients and aesthetic physicians, including unfounded fears of osteogenesis and foreign body granulomas, providing an up-to-date overview of the tolerability and long-term safety of CaHA for aesthetic indications.

Mechanism of Action

CaHA is a biodegradable filler composed of synthetically produced smooth, uniform CaHA microspheres (diameter of 25−45 μm) suspended in a sodium carboxymethylcellulose gel carrier combined in a ratio of 30% microspheres to 70% gel by volume. The gel carrier suspends the particles and allows them to be de-
livered readily by injection needle. The other components of the gel are sterile water and glycerin; the product does not contain any animal or human derived components. The gel ingredients are US Pharmacopeia–grade pharmaceutical excipients that are classified ‘generally recognized as safe’ (GRAS) by the FDA. CaHA is found in nature as the mineral component of human bony structures. Synthetic CaHA shares the same biocompatibility profile of the natural compound, and therefore poses a low risk of being recognized as foreign by the immune system. The CaHA spheres are composed of calcium and phosphate ions, which are bonded together in a synthetic process to form calcium hydroxyapatite microspheres.

CaHA injection provides immediate and long-lasting volume enhancement. In the first part of its two-staged mechanism of action, the soluble carrier gel evenly distributes the CaHA microspheres at the injection site providing 1:1 correction. The spherical shape and uniform CaHA particulate size creates space between the microspheres, which prevents them from becoming packed too tightly together. The interstitial space between the microspheres is initially filled by the carrier gel. The gel gradually dissipates leaving the CaHA microspheres at the injection site where they induce long-term collagenesis. The microspheres are thus anchored at the injection site, preventing translocation of CaHA and ensuring a long-lasting cosmetic correction with an average duration of effect of around 15 months, in some cases even longer than 30 months. The longevity of correction is dependent on a number of factors, including the area in which the material is placed, the age of the patient, their ability to synthesize new collagen, and their rate of metabolism.

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Histological examination of CaHA after deep intradermal injection into human forearm revealed almost no foreign body reaction during 9 months of observation. In this manner, the CaHA microspheres are gradually broken down into calcium and phosphate ions and eliminated through the body's normal excretory processes. All of the components in the CaHA dermal filler are therefore fully metabolized over time. The end result is a highly biocompatible, long-lasting implant with similar characteristics to adjacent tissue. Radiographic and computed tomographic studies of CaHA have shown that in many patients the aesthetic corrections persist despite no CaHA being visible. Thus, the long-term correction provided by CaHA is not due to the continued presence of the microspheres, but to collagen production.

Clinical Applications of CaHA

Prior to its use in the aesthetic field, CaHA had been extensively used in dentistry and reconstructive surgery with a well-established safety record. An injectable form of CaHA received FDA approval for soft tissue augmentation in 2003 with indications including soft tissue marking, vocal cord augmentation and correction of maxillofacial defects. The efficacy and favorable safety profile of CaHA in these soft tissue indications led to the adoption of its off-label use in facial rejuvenation. In the USA, injectable CaHA (Radiesse®) was approved by the FDA in 2006 for facial soft tissue augmentation including the correction of moderate to severe nasolabial folds, and the restoration and correction of the signs of HIV-associated facial lipodystrophy. It is also widely used off-label to treat multiple areas of the face including nose, and hands. The earliest injections of CaHA for off-label facial soft-tissue augmentation date back to 2002.

In Europe, Radiesse® received a CE-mark in 2004 for plastic and reconstructive surgery, including deep and sub-dermal soft tissue augmentation of the facial area. The EU label also covers hand rejuvenation for which CaHA has proven effective and safe.

Since its approval for soft tissue applications over 10 years ago, CaHA has seen widespread use in multiple indications and significant safety data are available. As this publication goes to press, more than 3000 patients have received CaHA in controlled clinical studies and more than 4 million syringes of Radiesse® have been sold for a variety of aesthetic indications without any safety concerns.

Biocompatibility

CaHA is a biocompatible material that has the important qualities of being latex-free, non-toxic, non-mutagenic, and physiologically inert. As CaHA is identical to the major mineral component of human bony structures, it provokes little immune response. Extensive preclinical testing has shown that CaHA is inert and non-antigenic. No patient sensitivity testing is required prior to treatment with CaHA.

If correct injection procedures are followed, CaHA should not and practically cannot be implanted between periosteum and the bone. Accordingly, as progenitor cells for osteogenesis do not exist in soft tissue, no bone formation has been detected with CaHA in extensive clinical studies when injected in soft tissues. Animal studies have shown that when CaHA particles are placed in soft tissue separate from periosteum (for exam-
After subdermal injection into human forearm. a) At 3 months, the CaHA microspheres appear packed and the interstitium is filled with fibrin and scattered fibroblasts and macrophages. b) At 9 months, the microspheres appear degraded. Reproduced with permission from Lemperle et al, 2003.

Evidence that CaHA is degraded over time is provided by two studies. The first examined tissue specimens from healthy volunteers after subdermal injection of CaHA. At 3 months the CaHA microspheres were clearly visible, spherical and tightly packed, with newly formed interstitial tissue in and between the microspheres. At 9 months, the microspheres appeared partly degraded and diminished in volume (Figure 1). The second examined computed tomographic (CT) scans of individuals who had received CaHA for the treatment of HIV-associated facial lipoatrophy and correction of nasolabial folds. At 12 months after an initial injection of 25 ml, only residual amounts of CaHA could be observed on the scan. However, in a scan taken immediately after an additional injection of 9.1 ml, CaHA was clearly visible. Reproduced with permission from Carruthers et al, 2008.

Antigenicity

All filler substances are foreign bodies and have the potential to cause foreign body reactions with the host response ranging from limited macrophage infiltration to an intense foreign body reaction with fibrosis. The end result of a foreign body granulomatous reaction is the formation of mature fibrous tissue which encapsulates and isolates the foreign material from the body. The clinical presentation depends on the tissue response to the foreign body, composition and quantity of the material involved. The shape and size of the injected particles is an important factor, with granulomatous reactions occurring less frequently after injection of smooth, spherical particles than irregular and sharp-edged particles. In both rabbit and canine models, histological examination at intervals from 4 to 78 weeks after injection of large particle size CaHA (diameter > 75 μm, compared with a Radiesse® diameter of 25–45 μm) shows minimal inflammatory cell infiltrations including lymphocytes around injected particles, which had disappeared by 3 months. Furthermore, Lemperle et al. have shown that Radiesse microspheres stimulate almost no foreign body reaction in humans at 1, 3, or 9 months after deep intradermal injection. Biopsies taken from retroauricular areas in humans 4 and 9 months after a single injection of Radiesse® show that the grade of lymphohistiocytic infiltration present in the dermis is very low and comparable with baseline, which indicates the absence of an inflammatory response after Radiesse® administration (Prof Yana Yutskovskaya, personal communication).

Granulomas are a result of an excessive immunological reaction to a foreign body. The function of such reactions is to isolate and prevent the migration of foreign bodies that cannot immediately be removed by enzymatic breakdown or phagocytosis by enclosing them in a capsule of monocytes and macrophages. The engulfed material may resist degradation and remain sequestered in the macrophages. These activated macrophages secrete a variety of cytokines and other inflammatory products that attract additional macrophages and blood monocytes. Individual macrophages may become larger (epithelioid histiocytes) or fuse to form multinucleated foreign

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body giant cells. These cells are characteristic of granulomas, and a biopsy should be obtained for histological confirmation of a true granulomatous reaction.

Clinically, foreign body granulomas appear as red papules, nodules or plaques (with or without ulceration) and any material expressed is culture negative. The lesions become firmer over time due to fibrosis. They occur after a latent period, which can be several months to years after injection, and should be differentiated from non-inflammatory nodules, which occur early after the procedure (days to weeks) and are a result of poor technique or use of a filler for an incorrect indication.

A pilot histological study demonstrated that when CaHA is injected into the nasolabial folds, both standard light and electron microscopy revealed CaHA microspheres with minimal to no cellular inflammation or fibrosis. There have been no confirmed reports of granuloma formation in studies injecting CaHA for aesthetic use, even after more than 30 months after Radiesse® injection. A small case series in which large particle size CaHA was injected for correction of facial wrinkles and depressions was also not associated with granuloma formation. Two case reports in the literature have documented foreign body reactions with CaHA. The first described lip nodules in a woman who had previously received CaHA for lip augmentation. However, the woman had also been treated with several other fillers in the past, and a biopsy could not confirm that the reaction was due to CaHA. The second reported two incidental findings of a foreign body reaction to CaHA. In one case, injection of CaHA had provoked a nodule on the columella, which was discovered during rhinoplasty. The second case was discovered after histopathological examination of the deep section of a surgically removed basal-cell carcinoma. Histopathology showed a foreign body reaction with numerous giant cells and histiocytes. A similar incidental finding of a foreign body reaction without clinical relevance has been reported after excision of a nodular basal cell carcinoma from the nasolabial fold of a 66-year-old woman previously treated with Juvederm for nasolabial fold augmentation. A case series of eight individuals with inflammatory nodules suspected to have been caused by injection of CaHA was retrieved from a US diagnostic biopsy database. Microscopic examination of the nodules revealed characteristics consistent with CaHA-induced granulomatous reactions. It should be pointed out that foreign body granulomas generally appear after a latent period, which can be several months to years after injection. However, in each of the eight cases in this series, the biopsies were either performed very soon after injection, or the time from injection to biopsy was not noted. Indeed, the biopsy findings were consistent with a normal tissue response to an injected product, and in some cases accumulation of product, rather than a true foreign body granuloma occurring months to years after injection. In this report, all nodules were restricted to the lips and the mandibular labial vestibule. CaHA is not indicated for injection into highly mobile areas such as the lip mucosa or above the orbital rim, where accumulation of material from movement might result in nodule formation. Neither should CaHA be placed submucosally when injecting the mental crease, as it can again be displaced with facial movement and result in nodules in the oral mucosa. In all of these cases, the foreign body reactions observed were likely a normal tissue response to a mass of accumulated product, which probably occurred because of poor injection technique including over correction, too superficial placement of a filler, or use of a filler for an incorrect indication.

Any dermal filler can cause a foreign body reaction with clinical manifestations. Granulomatous reactions have been reported following injection of a number of commonly used dermal fillers including hyaluronic acid (Restylane®, Prevelle Silk), poly-L-lactic acid (Sculptra®), acrylic hydrogel particles with hyaluronic acid (Dermalive®), and polyacrylamide hydrogel (Acquamid®). With CaHA there are a very limited number of case reports over a decade of use with no cases of granulomatous reactions reported in numerous clinical trials. Injectors should be able to clinically and histologically differentiate nodules from granulomas as their treatment approaches differ. Nodules may respond to vigorous massage, with or without disruption with lidocaine or saline. A recent paper reports successful resolution of nodules after misplaced CaHA in the inferior eyelid with saline injections and erbium laser treatment.

Radiological Impact

As CaHA is radio-opaque, investigators have examined its potential for X-ray or computer tomography (CT) scan distortion. Fifty-eight patients who had been treated with CaHA for HIV-associated lipoatrophy or correction of nasolabial folds underwent radiographic and CT imaging studies over an extended period of time (up to 427 days after injection) and with varying amounts of CaHA (from 1.3 ml to 34.1 ml in total). Although, CaHA appeared inconsistently on the radiographs, it was clearly distinguishable from bones and adjacent structures on CT scans in almost all patients, with no obscuration of underlying structures and no evidence of migration.

Safety in Clinical Applications

Short-term safety results

Consistent with the use of dermal fillers in general, injection of CaHA can be associated with local, short-term, adverse events at the injection site. These events are minor in nature and degree (e.g. bruising, edema), limited to the injection site and resolve spontaneously after a few days. For the most part, they are the result of the injection procedure and not a result of the product itself. In the pivotal clinical trial that led to FDA approval of CaHA for aesthetic correction, 117 subjects...
with moderate to deep nasolabial folds received CaHA on one side of the face and human collagen on the other; up to two touch-up injections were permitted.47 There was no significant difference in adverse event rates or duration between the CaHA- and collagen-treated patients.

A second study followed 113 patients injected with CaHA for a variety of facial aesthetic applications over a 47-month period.27 Only seven subjects reported adverse events all of which were minor and resolved within 1 month: transient ecchymosis (n=3), non-granulomatous submucosal nodules of the lip (n=2), and inflammation and edema (n=2). The lip nodules were successfully treated with triamcinolone injection (1 mg injected into each lesion). However, it should be remembered that CaHA is not recommended for injection in the highly mobile lip area as constant activity of the orbicularis oculi can clump the material so that it becomes visible as nodules at the mucosa or vermilion border.

A three-arm study randomized 205 subjects with moderate to severe nasolabial folds to treatment with CaHA or one of three hyaluronic acid products (Juvederm 24, Juvederm 24HV, and Perlane).28 No serious adverse events were observed and there was no significant difference between treatments in rates of minor adverse events.28

**Long-term Safety Results**

Long-term safety of CaHA has been evaluated in an extension of the FDA approval study, which offered re-treatment with CaHA between 6 and 12 months after the initial injection in both folds to balance asymmetry.10 A total of 102 of the initial 117 subjects were enrolled and evaluated at intervals of up to 3 years after their last CaHA injection. Forty percent of the folds evaluated were graded as improved or better on the Global Aesthetic Improvement Scale (GAIS) at least 30 months after the last CaHA treatment. There were no long-term or delayed-onset adverse events in 99 patients followed for 3 years, including no reports of nodules, foreign body granulomas, or infections.10

A retrospective review of the safety and persistence of CaHA in a large cohort of 1000 patients treated for a variety of aesthetic applications has provided efficacy and safety data up to 1 year.48 Rare lip nodules were reported, but this outcome can be prevented by avoiding the use of CaHA in the lips as per the manufacturer’s recommendations. The most frequently reported adverse events were erythema and ecchymosis.

In a prospective, randomized, controlled, study to assess CaHA for cheek volumizing, 86 patients were randomized to immediate treatment with CaHA and 30 to the control group who received delayed treatment at 3 months.29 Patients received a maximum of 10 mL per cheek via linear threading. Treatment was to full correction, with as many strands as necessary. Side effects reported through 12 months were mild in nature, short in duration, and typical of dermal filler injections and included swelling, redness, and bruising.

In a comprehensive review, Lemperle stated that CaHA appears to cause the lowest rate of foreign body granulomas among all filler substances.49

**Safety in Combination With Other Treatments**

Modern cosmetic dermatology takes into consideration all aspects of skin aging including wrinkles and lines, loss of volume and contour, and skin surface and texture. As a result patients may require treatment with more than one product. CaHA has been used in combination with a number of different treatment modalities with no adverse effects.

**Monopolar radiofrequency treatment**

Radiofrequency treatment is commonly used to reduce cutaneous sagging and wrinkling. Radiofrequency selectively heats the deep dermis and fibrous septa, causing breakage of collagen hydrogen bonds and thus collagen denaturation. Subsequent wound healing promotes new collagen formation. These collagen changes produce skin tightening both immediately and over the next several months. Animal studies indicate that multiple passes of monopolar radiofrequency treatment directly over dermal filler-injected skin at treatment levels typically used in the clinical setting is associated with an increase in the inflammatory, foreign body, and fibrotic responses associated with the filler substances, but does not promote immediate adverse tissue responses, nor adversely affect filler longevity.50,51

In a pilot study in humans, radiofrequency treatment was applied to the upper inner arm of five patients over areas injected with CaHA or a hyaluronic acid 2 weeks previously.52 One control patient was not treated with radiofrequency. Punch biopsies were taken for histological analysis. The results showed that neither CaHA nor hyaluronic acid were disrupted or denatured after radiofrequency treatment. There was no associated hemorrhage, nodularity or filler spread.

**Hyaluronic acid fillers**

The popularity of dermal fillers means that more and more patients are using them in combination to achieve their desired effect. Among a group of 72 consecutive patients who underwent facial augmentation with CaHA, 29 requested additional augmentation at sites that had already been treated with CaHA and were treated with a hyaluronic acid (Restylane®).53 Of the 29 patients, six were treated concurrently, and the remaining patients were treated, on average, within 103 days of their CaHA treatment. CaHA-treated patients were followed for an average of 15 months, and combination patients for an average of 11.5 months. Patients treated with CaHA and hyaluronic acid in com-
bination had a similar safety profile to those treated with CaHA alone.54 In the CaHA group, bruising was the most frequent adverse event, occurring in 21 patients (46%). In the combination treatment group, swelling was the most common adverse event, reported by seven patients (47%). Two patients developed persistent nodules that required removal: in one patient, material was placed in too superficial location in the area of the right nasolabial fold, and in the other too generous an amount of CaHA was placed in the right lower lip vermilion border.

**Botulinum neurotoxin**

Botulinum toxin is increasingly used in conjunction with other minimally invasive cosmetic procedures and has been shown to enhance and prolong the effects of soft tissue augmentation. A new approach combines dermal fillers and botulinum toxin in a layered approach to address the three-dimensional changes of facial aging.54 At three separate visits, subjects received injections with botulinum toxin (Bocouture®), CaHA and finally a hyaluronic acid (Belotero® Soft, Belotero® Basic and/or Belotero® Intense) to treat dynamic lines, replace lost volume and fill deeper lines and folds, and treat finer lines, with impressive aesthetic results.

Combination therapy with botulinum toxin type A and CaHA may also increase the duration of response. It is recommended to start with botulinum toxin and wait for at least a week before proceeding with CaHA.54 It has been suggested that the paralysis afforded by the toxin allows the scaffolding of the CaHA to remain relatively immobile and may help to improve the ingrowth of fibroblasts and collagen.54 Similarly, there is less risk of nodule formation when dermal fillers are injected into highly mobile areas of the face if botulinum toxin has been injected previously.

**CONCLUSIONS**

Each dermal filler has its own unique profile in terms of associated risks, injection technique, and applications that should be considered by the patient and clinician when planning treatment. CaHA is a highly effective agent for many areas of facial soft-tissue augmentation and is associated with a high and well-established safety profile. Administration of CaHA provides immediate 1:1 correction as a result of its two-stage mechanism of action: immediate correction with the carrier gel followed by longer-term development of collagen matrix surrounding the CaHA microspheres. The adverse events associated with CaHA are typical of those observed with hyaluronic acid fillers. Thus patients may experience mild erythema, ecchymoses and swelling immediately after treatment.

As the medical literature supporting the efficacy and safety of CaHA accumulates, past misconceptions surrounding CaHA can be laid to rest. The biocompatibility of CaHA with human tissue means that the risk of an inflammatory reaction is extremely small. When CaHA is administered as per the manufacturer’s recommendations, avoiding injection into the lips, oral mucosa and periorbital area, there is no evidence of granuloma formation in any of the clinical trials or with over 4 million syringes injected in clinical practice. New tissue growth at the injection site mimics the surrounding tissue and there is no evidence of osteogenesis when CaHA is injected into soft tissue. As with all dermal fillers, experience, proper indication and skilled injection technique by the practitioner injector play an important role in the safety of CaHA. Training physicians in the use of particular products may provide better product placement in the skin and hence reduce technique-dependent complications.

**DISCLOSURES**

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**REFERENCES**