Expert Review of Medical Devices

ISSN: 1743-4440 (Print) 1745-2422 (Online) Journal homepage: informahealthcare.com/journals/ierd20

Clinical data on injectable tissue fillers: a review

Claudette GJCA de Vries & Robert E Geertsma

To cite this article: Claudette GJCA de Vries & Robert E Geertsma (2013) Clinical data on injectable tissue fillers: a review, Expert Review of Medical Devices, 10:6, 835-853, DOI: 10.1586/17434440.2013.839211

To link to this article: https://doi.org/10.1586/17434440.2013.839211

Published online: 09 Jan 2014.

EXPERT REVIEWS

Clinical data on injectable tissue fillers: a review

Expert Rev. Med. Devices 10(6), 835–853 (2013)

Claudette GJCA de Vries* and Robert E Geertsma

Centre for Health Protection, National Institute for Public Health and the Environment (RIVM), P.O. Box 1, NL-3720 BA Bilthoven, The Netherlands
**Author for correspondence:*
Tel.: +31 30 2743496
Fax: +31 30 2744421
claudette.de.vries@rivm.nl

Treatment with injectable tissue fillers for aesthetic purposes is increasingly popular. In parallel with this success, questions related to the safety of these treatments and the products involved are being raised more prominently. To gain insight in the safety aspects of injectable tissue fillers, we performed a literature review to collect studies reporting clinical data of injectable tissue fillers. We found several case reports where serious complications after more than three years are described. However, there are only a limited number of well-defined prospective clinical studies available with follow-up periods longer than three years. Furthermore, causes of complications, that is, treatment or product related, are often not specified in literature. Considering the intended functional period of fillers in combination with the known occurrence of long-term complications, there is a need for well-defined prospective clinical studies. In order to be able to discriminate between product failure (a product safety issue) or application methodology (a physician expertise or training issue), better identification of observed complications and whether they are product or treatment related, is needed. For the safe use of the fillers it is important that treatment with injectable tissue fillers is performed by a trained physician, who knows the product specifications and its applications.

KEYWORDS: clinical data • complications • injectable tissue fillers • long-term follow-up • prospective clinical studies • safety

Injectable tissue fillers are increasingly popular for the treatment of facial wrinkles. According to the American Society for Dermatologic Surgery, soft tissue augmentation treatments showed a 130% increase between 2005 and 2007 [1]. Moreover, it is expected that due to increase in life expectancy, the demand for anti-aging treatments, like tissue augmentation with injectable tissue fillers, will grow [2]. Their success has been attributed to the fact that treatments with injectable tissue fillers are fast and appear to be relatively easy [2]. Only a relatively 'simple' subcutaneous injection is needed. Today, various injectable tissue fillers with different characteristics are available, for example, duration of the effect, material type and intended anatomical location.

Although the application of an injectable tissue filler seems to be relatively simple and safe, reports of serious adverse effects have appeared in the literature [2–8]. Estimates of the occurrence of severe complications after treatment with various types of injectable tissue fillers range between 1:80 and 1:50,000 patients [9,10]. Adverse side effects can be caused by incorrect injection techniques (treatment related) or by the characteristics of the products (product related) [11,12]. Short-, mid- and long-term complications can be discerned (TABLE 1) [2,13–15]. Short-term complications like pain, swelling, fever, immediate hypersensitivity reactions, occur immediately or within several days past treatment and disappear after several weeks. A more severe short-term complication is necrosis [5,16]. Necrosis occurs immediately or within a few days if blood vessels are obstructed by the filler material or if they are injured during the treatment [17]. Mid-term complications such as delayed inflammatory reactions, ulceration and granuloma reaction may occur after 2–12 months. If they do not disappear spontaneously, they can be treated with anti-inflammatory drugs (e.g., corticosteroids). Nodule formation, chronic inflammatory or delayed hypersensitivity reactions, and migration of the injected product are categorized as long-term complications, which occur after several years and can only be removed surgically. Delayed

 10.1586/17434440.2013.839211 ISSN 1743-4440

Table 1. Overview of the most frequently observed types of complications.

Short-term	Swelling, bruising, direct hypersensitivity, necrosis
Mid-term	Lumpiness, increased sensitivity, sensitization reaction, infection, granuloma or enlargement of implant, mild prominence of implant, occasional pain when scrubbing face
Long-term	Nodule formation, migration of the product, accumulation of the product, persistent swelling or redness, persistent pain, delayed hypersensitivity reactions after retreatment

hypersensitivity reactions are related to a triggering event, such as another operation or additional injection [16,18,19]. To gain insight in the safety aspects of injectable tissue fillers, we performed a literature review to collect studies reporting clinical data of injectable tissue fillers.

Literature review

Literature was identified through searches in electronic databases Scopus (Elsevier BV), Medline/PubMed (US National Library of Medicine) and the Food and Drug Administration (FDA) website, and supplemented with cross-references. Search strings, which were used, were 'skin filler,' 'injectable skin fillers,' 'facial tissue augmentation,' 'injectable filler skin effects,' 'complications of tissue fillers,' 'safety of tissue fillers' and product names. Only peer-reviewed articles and reports reviewed by the FDA were used for this literature review. Literature of the past decade, 2000–2012, with information on tissue fillers still used today on a large scale for facial tissue augmentation were reviewed. In additions, illustrative older and newer studies on facial application of permanent and semi-permanent injectable fillers were included. Studies on combination treatments with other products such as Botox were not included. Studies on biodegradable fillers, like collagen and non-cross-linked hyaluronic acid, were not included, because biodegradable fillers have a limited and waning role in the filler market due to their lack of longevity in the skin [20,21]. New and improved collagen and hyaluronic acid injectable tissue fillers, with a lasting result of more than six months, were included as semi-permanent injectable fillers. For this study, we reviewed available literature with clinical safety data for semi-permanent and permanent fillers. We distinguished prospective studies, retrospective studies and case reports. As prospective studies are most suitable to detect safety issues before products are used on a large scale, the focus of this review lies on prospective studies. From each study, we extracted the following data: filler material, study type, number of participants of the study, follow-up period, complications and cause of complication. Furthermore, we checked literature on duplicates by examining the content of the articles and the first author's name. Publications on follow-up studies of injectable fillers were indicated as such in the table.

Clinical data for semi-permanent & permanent tissue fillers

Injectable tissue fillers can be categorized according to the duration of their effect (Table 2). Examples of permanent filler materials are non-degradable fragments/microspheres in a resorbable matrix solution like collagen or hyaluronic acid, aqueous polymer solutions and silicone oil. Examples of semi-permanent filler materials are cross-linked hyaluronic acid or porcine collagen gel, polyvinyl alcohol 8%, carboxymethylcellulose and polyethylene oxide, non-animal derived poly-L-lactic acid (PLLA), and synthetic calcium hydroxyapatite suspension in a gel carrier. Permanent fillers will have a long-lasting effect, while semi-permanent and biodegradable fillers will be absorbed by the body after a certain period. To maintain the effects of the fillers, retreatment is needed for semi-permanent fillers after 7–24 months depending on the product, and for biodegradable fillers within approximately six months. Permanent fillers aim to provide a long lasting (>24 months) effect without the need for repeated treatment.

Semi-permanent tissue fillers

Semi-permanent tissue fillers are all relatively recent products, most of which have been evaluated in prospective studies with defined follow-up periods, varying from 6 to 38 months (Table 3). The number of studies and the size of the respective study populations vary considerably, when products are compared. Complications such as bruising or local hypersensitivity are usually transient or curable with minor treatment, for example, topical treatments with antibiotics and steroids [7,22]. However, there are also cases in which persistent inflammatory reactions after 24–60 months past treatment were observed [23,24]. We observed very large differences in the occurrence rate of complications with semi-permanent tissue fillers, between 0 and 56% (Table 3). Some authors did not specify the number of complications observed [25–28,201]. Moreover, in some cases the complications were described per injection site instead of per participant [29,202,203]. Although product as well as treatment related complications have been described in more than one-third of the studies, no specifications of the causes of the complications were given. Although this category of products is associated with an apparently minimal or low incidence of severe complications, knowledge of the product characteristics and training in specific injection techniques are necessary for the safe use of the products [2,15,30,204].

Most studies have a follow-up period ranging from six months to two years, which generally seems to correspond with the period that these products are intended to be present in the skin. However, there are cases known in which cross-linked hyaluronic acid fillers particles were found after two years [31]. Also, aesthetic effects up to four years with injectable PLLA have been observed, while the claimed aesthetic effect is approximately two years [32]. Between 2008 and 2012, some studies have been published with longer follow-up periods, that is, three to four years [32–36]. The need for this development is illustrated by two studies [37,38] in which it was found that semi-permanent injectable fillers remain in the skin longer than the period claimed by the manufacturer: 18 and 23 months, respectively, while the

Table 2. Type of injectable tissue fillers.

Type of filler	Duration of correction	Filler material
Biodegradable fillers	± 6 months	Bovine collagen
		Human-derived bioengineered collagen
		Hyaluronic acid
Semi-permanent fillers	7–24 months	Hyaluronic acid (cross linked)
		Polyvinyl alcohol 8%
		Porcine collagen gel (cross linked)
		Carboxymethylcellulose & polyethylene oxide
		Poly-L-Lactic acid, non-animal derived
		Synthetic calcium hydroxyapatite suspension in a gel carrier
Permanent fillers	>24 months	Polymethyl methacrylate
		Polyethyl methacrylate (copolymer of hydroxyethylmethacrylate and ethylmethacrylate in hyaluronic acid)
		Polyacrylamid solution
		Polyalkylimide solution
		Silicone

claims were 12 months. Experiences in the past with PLLA, also a biodegradable material, have already shown that late adverse effects may occur depending on the amount of material used, for example, PLLA bone plates and screws used in fixation of cheekbone fractures were found to be able to lead to swelling after about three to five years [39]. In this study, the total amount of PLLA was considered essential for the occurrence of the local persistent inflammation. Therefore, studies with a more extended follow-up period are needed for all semi-permanent fillers. A theoretical explanation for these late reactions possibly lies in that the cross-linked hyaluronic acid filler contain varying amounts of the hyaluronan-associated proteins [23].

Permanent tissue fillers

With regard to the safety and frequency of complications of permanent tissue fillers, a number of prospective studies, retrospective studies and various case reports were identified (Table 4). Silicone has been applied for over 50 years, and for a long time it was the only material used. Only since the late 1990s, products based on other materials have been developed. Four of the retrospective studies on silicone [40–43] are in fact just providing a set of anecdotal case reports without information on the period between injection and complication, or on possible causes of the complication. Therefore, they are only useful as an indicator for the occurrence of complications like severe granulomatous reaction and facial ulceration (Table 4) [44]. Only one relatively small prospective pilot study in which a silicone filler is used, with just six months follow-up, is available [45]. Descriptions of unpublished FDA approved studies for silicone fillers [10,46] are insufficiently detailed to draw conclusions.

For the more recent filler materials such as polymethyl methacrylate micro spheres in collagen, polyethyl methacrylate (copolymer of hydroxyethylmethacrylate and ethylmethacrylate) in hyaluronic acid, polyacrylamid solution, polyalkylimide solution, more data from prospective studies are available, with varying sizes of the study populations and follow-up periods for each product (Table 4). In the early 2000s, prospective studies stopped after 12 months or less [47–53]. Therefore, mainly short- or mid-term reactions, like immediate sensitivity reactions, formation of granulomas and swelling, could be picked up in these studies. In a number of case reports, long-term complications occurring after more than 12 months and even more than three years were described [8,16,19,44,54–60]. These case reports indicate that more extended follow-up periods are needed to determine long-term effects of permanent fillers.

In 2003, an advisory committee already provided advice to the FDA on a permanent tissue filler in which they formulated specific conditions for approval, including a post-marketing approval study for safety of not less than five years, a contraindication for lip augmentation, physician training and a patient educational brochure [205]. Results of this study were published by Cohen *et al.* [61,62].

Today, more and more prospective studies are published with follow-up periods exceeding three years [63–65]. In addition to the short term, often transient reactions, in these studies long-term complications, such as nodules, gel migration or accumulation, persistent redness or pain, swelling, infection and chronic inflammatory reactions are observed (Table 4). Similar to the situation with semi-permanent tissue fillers, very large differences in the reported occurrence rate of complications were found, while some authors did not specify the number of complications observed. Furthermore, in the various types of studies, both product- and treatment-related complications have been described, although the causes of complications were

Table 3. Type of studies and complications of semi-permanent tissue fillers.

Filler material[†]	Study, participants (n), follow-up	Complications	Cause of complication	Ref.
Hyaluronic acid (cross-linked)	Prospective study (n = 15), 6 months follow-up	All patients noted short-term complications	Not specified/ Not known	[25]
	Prospective study (n = 76), 6 months follow-up	Mild short-term complications, such as bruising, lumps and bumps, edema	Treatment related	[73]
	Prospective study (n = 150), 6 months follow-up[‡]	Short- and mid-term reactions. Treatment-related adverse events tended to occur more frequently on the non-animal-stabilized filler treated site	Treatment related	[74]
	Prospective study (n = 248), 6 months follow-up	Short-term complications were observed in more than half of the subjects. In 2 cases treatment of the adverse event was necessary	Treatment related	[75]
	Prospective study (n = 439), 6 months follow-up[‡,§]	Most mild or moderate adverse events, in 1 subject an abscess was reported after 4 months	Treatment related	[27,201]
	Prospective study (n = 56), 6 months follow-up	Mild injection site reactions	Treatment related	[76]
	Prospective study (n = 60), 6 months follow-up[‡]	Short term complications erythema, edema/swelling, bruising, pruritus, pain, tenderness	Treatment related	[77]
	Prospective study (n = ?), 6 months follow-up	No adverse events		[78]
	Prospective study (n = 40), 12 months follow-up[‡]	Mild adverse events: application site erythema was observed in approximately 40% of the subjects, hematoma, swelling, induration, numbness. Moderate adverse events: infection (5%), hematoma (5%), pain (5%). Severe adverse events pain (5%)	Treatment related	[79]
	Prospective study (n = 57), 12 months follow-up	Short-term complications in 30 cases	Treatment related	[80]
	Prospective studies (n = 72), 12 months follow-up	Short-term complications in 7 cases. In 2 cases migration and swelling was observed after 8 weeks	Treatment related	[81]
	Prospective studies (n = 709), 12 months follow-up	Delayed skin reaction in 3 cases	Product related	[82]
	Prospective study (n = 208), 12 months year follow-up[¶]	Short-term complications resolved in 7 days. Injection site cellulites occurred in 1 case	Treatment related	[207]

[†]Not all studies with the same filler material were performed with the same product from the same manufacturer.
[‡]Split face-design: clinical study in which subjects were randomized to contralateral treatment with two types of fillers.
[§]Pre-market clinical study.
[¶]Summary of Safety and Effectiveness data; follow-up of 12, 18, 24 and 36 months are available [209].
[#]Data of 30 months study not published yet
[††]The follow-up period was different for all the 36 subjects (e.g. for three subjects the follow-up period was 36 months or more, for nine subjects the follow-up was less than 12 months).
[‡‡]Anecdotal case reports.
[§§]Summary of Safety and Effectiveness data; follow-up of 12,18 and 24 months are available [210, 211]
[¶¶]Clinical study with HIV subjects.
Note: For polyvinyl alcohol 8% and carboxymethyl cellulose & polyethylene oxide injectable fillers no information on complications could be found.

Table 3. Type of studies and complications of semi-permanent tissue fillers (cont.).

Filler material[†]	Study, participants (n), follow-up	Complications	Cause of complication	Ref.
Hyaluronic acid (cross-linked)	Prospective study (n = 60), 18 months follow-up	No reported adverse events		[83]
	Prospective study (n = 75), 18 months follow-up[#]	Short-term complications	Treatment related	[26]
	Prospective study (n = 95), 18 months follow-up	Thirty-four adverse events were reported, only 1 was considered to be related to the treatment	Treatment related	[84]
	Prospective study (n = 36), 3–38 months follow-up[††]	Short-term complications in 3 subjects (lumpiness)	Treatment related	[35]
Hyaluronic acid (cross-linked)	Retrospective study (n = 5), 12 months follow-up	One patient experienced a vasovagal episode lasting 3 hours, 1 patient had postoperative pain. In 1 patient the gel migrated	Not specified/ not known	[85]
	Retrospective study (n = 4320), 12 months follow-up	Sixteen cases of acute and 18 cases of delayed hypersensitivity reactions	Product related	[86]
	Retrospective study (n = 155), follow-up not specified	Lumps or contour irregularities 11%, bruising 10%, color change 7% and accumulation of fluid 15%	Not specified/ not known	[29]
	Retrospective study (n = 286), follow-up not specified	Short-term complications in 14 subjects	Not specified/ not known	[87]
	Retrospective study 1999 (n = 144,000), follow-up not specified[‡‡]	Localized hypersensitivity reactions occurring in approximately 1 of every 1400 patients treated. Short-term complications 1 of every 650 patient	Product related	[12]
	Retrospective study 2000 (n = 262,000), follow-up not specified[‡‡]	Hypersensitivity occurred in 1 of every 5000 patients treated	Product related	[12]
Hyaluronic acid (cross-linked)	Various case reports (n = 27)	Granulomatous reactions 10 days to several months past treatment. Arterial embolization resulted in necrosis 2 weeks after treatment. Scleromyxedema 9 months past treatment. Persistent inflammatory reaction. Formation of nodules 5 months past treatment. Infection 1 day after injection. Several cases of inflammatory nodules 1–60 months past treatment	Product and treatment related	[5,22–24,88–92,208]
Porcine collagen gel (cross linked)	Prospective study (n = 149), 6 months follow-up[§,§§]	In 123 of the subjects injection site reactions were observed. Subjects were injected at multiple sites. 326 reactions were reported as mild, 18 as moderate and 3 severe	Product related	[202]

[†]Not all studies with the same filler material were performed with the same product from the same manufacturer.
[‡]Split face-design: clinical study in which subjects were randomized to contralateral treatment with two types of fillers.
[§]Pre-market clinical study.
[¶]Summary of Safety and Effectiveness data; follow-up of 12, 18, 24 and 36 months are available [209].
[#]Data of 30 months study not published yet
[††]The follow-up period was different for all the 36 subjects (e.g. for three subjects the follow-up period was 36 months or more, for nine subjects the follow-up was less than 12 months).
[‡‡]Anecdotal case reports.
[§§]Summary of Safety and Effectiveness data; follow-up of 12,18 and 24 months are available [210, 211]
[¶¶]Clinical study with HIV subjects.
Note: For polyvinyl alcohol 8% and carboxymethyl cellulose & polyethylene oxide injectable fillers no information on complications could be found.

Table 3. Type of studies and complications of semi-permanent tissue fillers (cont.).

Filler material[†]	Study, participants (n), follow-up	Complications	Cause of complication	Ref.
L-Polylactic acid (PLLA), non-animal derived	Prospective study (n = 96), 6 months follow-up	Mild transient bruising was observed in 15% of the patients. Formation of nodules was observed in 56% of the cases	Not specified/not known	[93]
	Prospective study (n = 14), 6 months follow-up[§§,¶¶]	No adverse events		[94]
	Prospective study (n = 30), 6 month follow-up[¶¶]	Short-term complications in 2 subjects	Treatment related	[95]
	Prospective study (n = 61), 6 months follow-up[¶¶]	Two patients developed persistent asymptomatic palpable intradermal papules	Treatment related	[96]
	Prospective study (n = 20), 7 months follow-up	Purpose of the study was to obtain preliminary data on efficacy and safety of the PLLA filler. Injections were given at 1-month intervals (total of 7 treatments). Injection sites were assessed after each treatment. No adverse events		[97]
	Prospective study (n = 50), 12 months follow-up[¶¶]	No adverse events		[98]
	Prospective study (n = 100), 12 months follow-up	Only 54 participants completed the 1 year follow-up. Device related subcutaneous papule at injection site was observed at 13 patients	Product related	[99]
	Prospective study (n = 30), 18 months follow-up	Mainly short-term complication, in some cases nodule formation	Treatment related	[100]
	Prospective study (n = 50), 24 months follow-up[¶¶]	In 22 patients, palpable but non-visible subcutaneous micronodules were observed	Not specified/not known	[101]
	Prospective study (n = 116), 25 months follow-up	Only 1 case of injection site bruising	Treatment related	[102]
	Prospective study (n = 10), 36 months follow-up	Short-term complications	Not specified/not known	[34]
	Prospective study (n = 65), 36 months follow-up	In only a few cases small subcutaneous papules were developed	Treatment related	[103]
Poly-L-Lactic acid (PLLA), non-animal derived	Retrospective study (n = 300), 12–24 months follow-up	Subcutaneous papules in 30 cases. These papules resolved, without treatment in 12–24 months	Treatment related	[104]
	Retrospective study (n = 281), 36 months follow-up	Transient side effects (e.g., bruising) and nodule formation	Treatment related	[105]

[†]Not all studies with the same filler material were performed with the same product from the same manufacturer.
[‡]Split face-design: clinical study in which subjects were randomized to contralateral treatment with two types of fillers.
[§]Pre-market clinical study.
[¶]Summary of Safety and Effectiveness data; follow-up of 12, 18, 24 and 36 months are available [209].
[#]Data of 30 months study not published yet
[††]The follow-up period was different for all the 36 subjects (e.g. for three subjects the follow-up period was 36 months or more, for nine subjects the follow-up was less than 12 months).
[‡‡]Anecdotal case reports.
[§§]Summary of Safety and Effectiveness data; follow-up of 12,18 and 24 months are available [210, 211]
[¶¶]Clinical study with HIV subjects.
Note: For polyvinyl alcohol 8% and carboxymethyl cellulose & polyethylene oxide injectable fillers no information on complications could be found.

Table 3. Type of studies and complications of semi-permanent tissue fillers (cont.).

Filler material[†]	Study, participants (n), follow-up	Complications	Cause of complication	Ref.
Poly-L-Lactic acid (PLLA), non-animal derived	Retrospective study (n = 100), up to 60 months follow-up[‡‡]	Papules observed in one case. Formation of nodules observed in another case after PLLA injections approximately 15 years after the use of silicone. In both case the problems resolved after treatment with triamcinolone injections. One case of diffuse hardening was observed, after treatment with intralesional steroids plus minocycline this was resolved	Treatment related	[32]
L-Polylactic acid (PLLA), non-animal derived	Various case reports (n = 21)	Only mild transient reactions were observed after injection, no adverse events were observed 12 and 48 months past treatment. Orofacial foreign body granulomas were observed 6 months to more than 12 months after treatment. Late-onset facial nodules 12–18 months past treatment	Product and treatment related	[3,54,106–109]
Synthetic calcium hydroxyapatite suspension in a gel carrier	Prospective study (n = 72), 15 months follow-up	Short-term complications occurred in 7 cases. Temporary visible product nodularity occurred in 15 patient, in 2 cases the product had to be removed from the skin	Treatment related	[110]
	Prospective study (n = 40), 18 months follow-up	Ecchymosis and hematoma occurred in 2 of the subjects	Treatment related	[111]
	Prospective study (n = 100), 18 months follow-up	Adverse events reported through 12 months were ecchymosis, edema, erythema, pain, and pruritus. Eighteen months safety data were not available at the time of submission	Not specified/not known	[28]
	Prospective study (n = 117), 6 months follow-up	Mainly short-term adverse events were observed. One nodule was observed	Treatment related	[112]
	Prospective study (n = 113), 6–12 months follow-up	Seven short-term adverse events were observed and resolved within 1 month	Not specified/not known	[113]
	Prospective study (n = 30), 12 months follow-up[¶¶]	Mainly short-term complications were observed, 1 incident of lumpiness	Not specified/not known	[114]
	Prospective study (n = 60), 12 months follow-up	Adverse events were hematomas (n=2) and 1 nodule. The hematomas resolved in a few days, the nodule was treated	Not specified/not known	[115]
	Prospective study (n = 100), 12 months follow-up[§]	Mid-term complications (e.g., contour irregularities, rash) were observed after 14 weeks on 89 injection sites	Not specified/not known	[203]

[†]Not all studies with the same filler material were performed with the same product from the same manufacturer.
[‡]Split face-design: clinical study in which subjects were randomized to contralateral treatment with two types of fillers.
[§]Pre-market clinical study.
[¶]Summary of Safety and Effectiveness data; follow-up of 12, 18, 24 and 36 months are available [209].
[#]Data of 30 months study not published yet
[††]The follow-up period was different for all the 36 subjects (e.g. for three subjects the follow-up period was 36 months or more, for nine subjects the follow-up was less than 12 months).
[‡‡]Anecdotal case reports.
[§§]Summary of Safety and Effectiveness data; follow-up of 12,18 and 24 months are available [210, 211]
[¶¶]Clinical study with HIV subjects.
Note: For polyvinyl alcohol 8% and carboxymethyl cellulose & polyethylene oxide injectable fillers no information on complications could be found.

Table 3. Type of studies and complications of semi-permanent tissue fillers (cont.).

Filler material[†]	Study, participants (n), follow-up	Complications	Cause of complication	Ref.
Synthetic calcium hydroxyapatite suspension in a gel carrier	Prospective study (n = 107), 12 months follow-up	Swelling (74%), redness (70%), bruising (63%), lumps or bumps (6.5%), nodules (2.8%)	Treatment related	[116]
	Prospective study (n = 609), 24 months follow-up	Nodule formation occurred in 48 cases	Not specified/not known	[117]
	Prospective study (n = 102), 36 months follow-up	Only short-term adverse events (e.g., edema, erythema)	Not specified/not known	[33]
Synthetic calcium hydroxyapatite suspension in a gel carrier	Retrospective study (n = 1000), 12–52 months follow-up	Mild and transient adverse events (e.g., edema, erythema)	Treatment related	[36]
Synthetic calcium hydroxyapatite suspension in a gel carrier	Case report (n = 1)	Granulomatous response	Product related	[118]

[†]Not all studies with the same filler material were performed with the same product from the same manufacturer.
[‡]Split face-design: clinical study in which subjects were randomized to contralateral treatment with two types of fillers.
[§]Pre-market clinical study.
[¶]Summary of Safety and Effectiveness data; follow-up of 12, 18, 24 and 36 months are available [209].
[#]Data of 30 months study not published yet
[††]The follow-up period was different for all the 36 subjects (e.g. for three subjects the follow-up period was 36 months or more, for nine subjects the follow-up was less than 12 months).
[‡‡]Anecdotal case reports.
[§§]Summary of Safety and Effectiveness data; follow-up of 12,18 and 24 months are available [210, 211]
[¶¶]Clinical study with HIV subjects.
Note: For polyvinyl alcohol 8% and carboxymethyl cellulose & polyethylene oxide injectable fillers no information on complications could be found.

unfortunately not always specified. Knowledge of different characteristics and limitations of injectable permanent tissue fillers, as well as training in specific injection techniques, have been reported; a necessary requirement to help a plastic surgeon to reduce the risk of complications and to increase the safe use of the product [2,15,30,206].

US soft-tissue fillers conference

Recently, the outcomes of a large conference on facial soft tissue fillers in the USA were published [66–69]. The conference was a joint effort of seven American professional societies, spanning the variety of clinicians applying these products. Issues of patient safety, efficacy and effectiveness were discussed, based on a literature review of data on details of the treatments. One of the key points was that there are major gaps in evidence related to the safety of soft-tissue fillers, and therefore more organized and systematic collection of safety data is needed. This key point on the need for greater availability of safety data correlates very well with our findings.

Expert commentary

In recent years the awareness of the need for well-defined prospective clinical studies with prolonged follow-up period before and after injectable fillers are placed on the market is growing. However, at the moment only a limited number of well-defined prospective clinical studies with sufficiently long follow-up periods are available for these products. Especially when the intended functional period is considered in combination with the known occurrence of long-term complications, such studies are clearly warranted. The various injectable tissue fillers have different characteristics, intended uses and limitations. Moreover, they each require specific injection techniques. Therefore, it is important that treatment with injectable tissue fillers is performed by a trained physician, preferably with a specialization in plastic surgery, who knows the product specifications and its applications. Observed complications can either be product-related or may be attributed to incorrect use. Therefore, it is important that both the safety of injectable tissue fillers and the way to apply these products are thoroughly evaluated by the manufacturer before they are placed on the market. Also afterwards post-marketing surveillance is needed including long-term clinical follow up. When describing results of such evaluations, it is necessary to specify the causes of observed complications as well as their frequency of occurrence. Before deciding on a treatment with injectable tissue fillers, the patient has to be informed on possible risks of such complications. In this context, it should be noted that risks cannot be excluded completely, not even when a product is injected in the right way by a trained doctor.

Five-year view

Because of the different characteristics of the various tissue augmentation treatments, a diverse range of injectable tissue fillers with different characteristics is available. Variations in

Table 4. Type of studies and complications of permanent tissue fillers.

Filler material[†]	Study, participants (n)	Complications	Cause of complication	Ref.
PMMA in collagen or carboxymethyl-cellulose	Prospective study (n = 14), 8 months follow-up	No adverse side effects		[48]
	Prospective study (n = 290), 12 months follow-up	Swelling after implantation, longer lasting redness and transparency of the product were observed. In one case an allergic reaction occurred	Product and treatment related	[47]
	Prospective study (n = 1008), 18 months follow-up[‡]	Preliminary results of this study with a 60 months follow-up period (start 2009) adverse events were observed (e.g., lumpiness, swelling, pain, granuloma)	Product and treatment related	[63]
	Prospective study (n = 119), 60 months follow-up	Twenty adverse events, e.g., lumpiness, granuloma, sensitivity at 15 subjects were observed. Previous results (results after 12 months) of this study are described by Cohen in 2004	Treatment related	[61,62]
	Prospective study (n = 118), follow-up period not specified	Acute side effects, like swelling and delayed side effects, e.g., persistent redness	Product and treatment related	[119]
PMMA or carboxymethyl-cellulose	Retrospective study (n = 72), mean follow-up 34 months	Four times nodule formation and once persistent lip pain was reported	Not specified/ not known	[120]
PMMA in collagen or carboxymethyl-cellulose	Various case reports (n=43)	Blindness after incorrect injection technique. Granuloma reactions immediate to 48 months past treatment. Necrosis immediate to 7 days after treatment. Nodule formation 1–10 years past treatment. Infection 12 months past treatment. Chronic inflammatory reaction 1–10 years past treatment. Formation of nodules, inflammatory reactions.6 months to 10 years past treatment	Product and treatment related	[16,19,54,55,58,59,121,122]
Polyethyl methacrylate (copolymer HEMA and EMA) in hyaluronic acid	Prospective study (n = 455), 36 months follow-up[§]	Swelling, formation of nodules, redness on average six months after the injection (percentage is not specified)	Not specified/ not known	[123]

[†]Not all studies with the same filler material were performed with the same product from the same manufacturer.
[‡]This study started in 2009. The interim results covers the 18-month period after treatments.
[§]Data from the 60 months follow-up are not yet available. An undefined part of the subjects was injected with another injectable. Results from this study are mixed with results from other studies.
[¶]Database: population-based registry for collecting adverse reactions to injectable fillers.
[#]Clinical study with HIV subjects.
[††]Information from questionnaires distributed along with the product and follow-up information from involved physicians was collected into a database.
‡‡Anecdotal case reports.

Table 4. Type of studies and complications of permanent tissue fillers (cont.).

Filler material[†]	Study, participants (n)	Complications	Cause of complication	Ref.
Polyethyl methacrylate (copolymer HEMA and EMA) in hyaluronic acid	Retrospective study (n = 19), mean follow-up 22.8 ± 18.9 months[¶]	Main adverse reactions were nodules, discoloration, erythema and swelling	Not specified/ not known	[124]
	Retrospective study (n = 118), mean follow-up 23.1 ± 22.8 months[¶]	Main adverse reactions were nodules, discoloration, erythema and swelling	Not specified	[125]
Polyethyl methacrylate (copolymer HEMA and EMA) in hyaluronic acid	Various case reports (n = 14)	Granuloma reactions 4–36 months past treatment, nodules 24 months past treatment Several cases of inflammatory nodules 7–48 months past treatment. Keratoacanthoma-like reaction	Product and treatment related	[59,126–130]
Polyacrylamid solution (PAAG)	Prospective study (n = 59), 9 months follow-up	Short-term reactions	Not specified/not known	[49]
	Prospective study (n = 31), 12 months follow-up[#]	Ecchymosis (58%) and small palpable but not visible nudules (29%)	Not specified	[131]
	Prospective study (n = 315), 12 months follow-up	Mild adverse events (e.g., bruising, redness), one infection	Treatment related	[51]
	Prospective study (n = 40,0000), 12 months follow-up[††]	Fifty-five cases of swelling at the injection site, often combined with tingling sensation, redness, pain, purulent secretion or cysts occurred	Treatment related	[50]
	Prospective study (n = 88), 24 months follow-up[#]	Of the initial study population (n= 115) 88 completed the 24 months follow-up. Subcutaneous nodules (n = 3), transient local inflammatory reactions (n = 3)	Product related	[132]
	Prospective study (n = 290), 24 months follow-up[#]	Treatment-emergent adverse events; product 18.3%, injection procedure 24.5%, injection-site nodules 8.3% and papules 8.6%	Treatment and product related	[133]
	Prospective study (n = 145), 48 months follow-up[#]	Small nodules, one serious adverse event (local infection) 32 months past treatment	Not specified/not known	[64]

[†]Not all studies with the same filler material were performed with the same product from the same manufacturer.
[‡]This study started in 2009. The interim results covers the 18-month period after treatments.
[§]Data from the 60 months follow-up are not yet available. An undefined part of the subjects was injected with another injectable. Results from this study are mixed with results from other studies.
[¶]Database: population-based registry for collecting adverse reactions to injectable fillers.
[#]Clinical study with HIV subjects.
[††]Information from questionnaires distributed along with the product and follow-up information from involved physicians was collected into a database.
‡‡Anecdotal case reports.

Table 4. Type of studies and complications of permanent tissue fillers (cont.).

Filler material[†]	Study, participants (n)	Complications	Cause of complication	Ref.
Polyacrylamid solution (PAAG)	Prospective study (n = 141), 60 months follow-up[#]	Acute adverse events: temporary swelling (18.42%), subcutaneous hematoma (7.9%), localized accumulation of the gel (2.6%). Late adverse events (after 1 year): localized permanent indurations (blebs: 10.52%), migration of the gel (7.9%). Of the initial study population (n= 314) 141 completed the 60 months follow-up. Adverse events in patient who did not complete the follow-up were also reported. These complications were: 8 patients developed localized infection. Two of these patients developed definite abscess 2 weeks after treatment	Treatment related	[134]
	Prospective study (n = 251), 60 months follow-up	A total of 104 adverse events (e.g., edema, gel accumulation, infection) in 73 patients were reported throughout the 60 months follow-up period. Previous results of this study are described by von Buelow (12 and 24 months)	Product and treatment related	[65,135,136]
Polyacrylamid solution (PAAG)	Retrospective study (n = 104), mean time since injection ± 47 months	In 30 subjects the injectable was palpable not visible in the lips. In 3 subjects the gel migrated and formation of edema occurred by 2 subjects	Not specified/ not known	[137]
	Retrospective study (n = 542), one day to 60 months follow-up	Abscess formation, displacement of the gel, infection, etc.	Not specified/ not known	[138]
Polyacrylamid solution (PAAG)	Various case reports (n = 7)	PAAG material migrated 36–60 months past treatment due to muscular activity or gravity and capsule was broken by incorrect massage or incidental force. Infection one week after injection. Extreme pain 18 months and edema 7 months past treatment. Inflammatory reactions more than 2–36 months after injection	Product and treatment related	[60,139,140]

[†]Not all studies with the same filler material were performed with the same product from the same manufacturer.
[‡]This study started in 2009. The interim results covers the 18-month period after treatments.
[§]Data from the 60 months follow-up are not yet available. An undefined part of the subjects was injected with another injectable. Results from this study are mixed with results from other studies.
[¶]Database: population-based registry for collecting adverse reactions to injectable fillers.
[#]Clinical study with HIV subjects.
[††]Information from questionnaires distributed along with the product and follow-up information from involved physicians was collected into a database.
‡‡Anecdotal case reports.

Table 4. Type of studies and complications of permanent tissue fillers (cont.).

Filler material[†]	Study, participants (n)	Complications	Cause of complication	Ref.
Polyalkylimide solution	Prospective study (n = 17), 11 months follow-up[#]	Four cases of complications, varying from capsule formation or gel migration to an infection at 1 injection site	Not specified/ not known	[52]
	Prospective study (n = 31), 12 months follow-up[#]	Only mild and transient adverse events	Not specified/ not known	[53]
	Prospective study (n = 11), 18 months follow-up[#]	Only mild and transient adverse events	Not specified/ not known	[141]
	Prospective study (n = 31), 22 months follow-up[#]	Only mild transient adverse events (e.g., bruising, pain, swelling)	Not specified/ not known	[142]
	Prospective study (n = 9), 24 months follow-up[#]	Only mild transient adverse events (e.g., modest inflammatory reaction, edema)	Treatment related	[143]
	Prospective study (n = 73), 36 months follow-up[#]	Only swelling after implantation	Treatment related	[144]
	Prospective study (n = 2,000), follow up not specified	In 12 cases staphylococcus infections occurred, of which 3 cases could be directly described to the implanted material	Product related	[145]
Polyalkylimide solution	Retrospective study (n = 4), 24–48 months follow-up[‡‡]	Abscess formation, infection, migration, inflammatory nodules	Product and treatment related	[146]
	Retrospective study (n = 3,196), 24–48 months follow-up	Inflammation and accumulation years after treatment, hardening of the capsule and migration	Not specified/ not known	[147]
Polyalkylimide solution	Various case reports (n = 63)	Abscess, late inflammatory reaction, migration of the filler 24 h to 36 months past treatment [148]. Infection, migration and capsule formation 12–36 months past treatment. Inflammatory reactions more than 12 months after injection. Foreign body granuloma 12 months past treatment. Infection to 36 months past treatment. Facial nodules and facial edema 6–52 months after injection with filler	Product and treatment related	[129,148–152]

[†]Not all studies with the same filler material were performed with the same product from the same manufacturer.
[‡]This study started in 2009. The interim results covers the 18-month period after treatments.
[§]Data from the 60 months follow-up are not yet available. An undefined part of the subjects was injected with another injectable. Results from this study are mixed with results from other studies.
[¶]Database: population-based registry for collecting adverse reactions to injectable fillers.
[#]Clinical study with HIV subjects.
[††]Information from questionnaires distributed along with the product and follow-up information from involved physicians was collected into a database.
‡‡Anecdotal case reports.

Table 4. Type of studies and complications of permanent tissue fillers (cont.).

Filler material[†]	Study, participants (n)	Complications	Cause of complication	Ref.
Silicone	Prospective study (n = 77), 6 months follow-up[#]	No adverse events		[45]
Silicone	Retrospective study (n = 179), 36–84 months follow-up	In 6.2% mild transient complications were observed, and in 2.2% small nodules were observed	Treatment related	[153]
	Retrospective study (n = 235), follow up not specified[‡‡]	Over a period of 20 years 2 cases of complications (local infections) were observed	Not specified/not known	[40]
	Retrospective study (n = 347), follow up not specified[‡‡]	Over a period of 20 years 1 complication (nodule formation) was observed	Not specified/not known	[41]
	Retrospective study (n = 916), follow-up not specified	Overcorrection 1 year past treatment, hyperpigmentation within a few months past treatment	Product related	[154]
	Retrospective study (n = 4,862), follow up not specified[‡‡]	Over a period of 22 years complications (e.g., migration) were observed due to large volumes and contamination. Due to decreasing the injection volume and purifying the silicone gel the incidence of complications decreased considerably over the years	Product and treatment related	[43]
Silicone	Various case reports (n = 586)	Development of pseudo-lymphoma beside silicone related granulomas 60 months past treatment. Severe granulomatous reaction and facial ulceration. Facial nodules, cellulites, ulceration and migration between 5 and 20 years after treatment with silicone injections	Product and treatment related	[44,56,57]

[†]Not all studies with the same filler material were performed with the same product from the same manufacturer.
[‡]This study started in 2009. The interim results covers the 18-month period after treatments.
[§]Data from the 60 months follow-up are not yet available. An undefined part of the subjects was injected with another injectable. Results from this study are mixed with results from other studies.
[¶]Database: population-based registry for collecting adverse reactions to injectable fillers.
[#]Clinical study with HIV subjects.
[††]Information from questionnaires distributed along with the product and follow-up information from involved physicians was collected into a database.
‡‡Anecdotal case reports.

characteristics lie in duration of the effect, material type and intended anatomical location. It is expected that due to the increasing life expectancy, the demand for anti-aging treatments like tissue augmentation with injectable tissue fillers will grow. As a result of this, manufacturers will place new or improved types of injectable tissue fillers on the market. According to Glogau *et al.*, currently more than 200 commercial products are available outside the United States [70]. Many of these products are variations on existing materials, for example, hyaluronic acid fillers with a higher degree of cross-linking. Also new products have recently emerged, containing a mix of different materials such as hyaluronic acid in combination with hypromellose and particles of cross-linked dextran [70]. Kablik *et al.* reported that, in recent years, hyaluronic acid-based tissue fillers have become

the material of choice for use in soft tissue augmentation [71]. However, the request for permanent correction by consumers is also likely to continue, leading to an expected market for permanent tissue fillers. The use of permanent tissue fillers is controversial. On the one hand, there is the consumer's pursuit of a lasting youthful appearance. On the other hand, there are important issues such as the nonreversible effects and problems like immune responses and delayed infections. No easy solutions for these issues are available. Semi-permanent tissue fillers hold promises to be safer alternatives for permanent fillers, however, they have their disadvantages too. For example, the enzyme hyaluronidase can be used to degrade hyaluronic acid fillers in the skin if overcorrection is performed or a strong immune response occurs. However, several cases have been reported where it seemed to be impossible to degrade the filler completely with the enzyme [72]. A possible explanation could be that the hyaluronic acid material is modified to such an extent that the enzyme does not recognize the hyaluronic acid filler [72]. If product safety and application methodology are not evaluated sufficiently thorough before as well as after introduction on the market, or if the products are injected by insufficiently trained physicians, an increase in the occurrence of complications with injectable fillers can be expected, especially in view of the expected increase in the number of treatments with a wider range of available products.

Acknowledgement

The authors would like to thank WH de Jong for critically reviewing the manuscript.

Financial & competing interests disclosure

This investigation has been performed by order and for the account of the Health Care Inspectorate of The Netherlands, within the framework of project V/360050 Supporting the Health Care Inspectorate on Medical Technology. The author have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Key issues

- All semi-permanent and permanent injectable tissue fillers may cause complications.
- Complications can occur long after the first treatment. Complications can be product- or treatment-related.
- Tissue filler products need to be thoroughly evaluated in clinical studies with sufficient long-term follow-up before and after they are placed on the market.
- Only trained physicians with knowledge of products and the intended use, who have evaluated the risks and benefits with the consumer, should perform treatment with tissue fillers.

References

1 Smith KC. Reversible vs nonreversible fillers in facial aesthetics: concerns and considerations. *Dermatol. Online J.* 14(8), 3 (2008).

2 Lowe NJ, Maxwell CA, Patnaik R. Adverse reactions to dermal fillers: review. *Dermatol. Surg.* 31(11 Pt 2), 1616–1625 (2005).

3 Dijkema SJ, van der Lei B, Kibbelaar RE. New-fill injections may induce late-onset foreign body granulomatous reaction. *Plast. Reconstr. Surg.* 115(5), 76e–78e (2005).

4 Vochelle D. The use of poly-L-lactic acid in the management of soft-tissue augmentation: a five-year experience. *Semin. Cutan. Med. Surg.* 23(4), 223–226 (2004).

5 Narins RS, Jewell M, Rubin M, Cohen J, Strobos J. Clinical conference: management of rare events following dermal fillers–focal necrosis and angry red bumps. *Dermatol. Surg.* 32(3), 426–434 (2006).

6 Nicolau PJ. Long-lasting and permanent fillers: biomaterial influence over host tissue response. *Plast. Reconstr. Surg.* 119(7), 2271–2286 (2007).

7 De Boulle K. Management of complications after implantation of fillers. *J. Cosmet. Dermatol.* 3(1), 2–15 (2004).

8 Sneistrup C, Holmich LR, Dahlstrom K. [Long-term complications after injection of permanent tissue-fillers to the lips]. *Ugeskr. Laeger.* 171(17), 1414 (2009).

9 Lemperle G, Rullan PP, Gauthier-Hazan N. Avoiding and treating dermal filler complications. *Plast. Reconstr. Surg.* 118(Suppl. 3), 92S–107S (2006).

10 Duffy DM. Liquid silicone for soft tissue augmentation. *Dermatol. Surg.* 31(11 Pt 2), 1530–1541 (2005a).

11 Lemperle G, Romano JJ, Busso M. Soft tissue augmentation with artecoll: 10-year history, indications, techniques, and complications. *Dermatol. Surg.* 29(6), 573–587, discussion 87 (2003).

12 Friedman PM, Mafong EA, Kauvar AN, Geronemus RG. Safety data of injectable nonanimal stabilized hyaluronic acid gel for soft tissue augmentation. *Dermatol. Surg.* 28(6), 491–494 (2002).

13 Duffy DM. Complications of fillers: overview. *Dermatol. Surg.* 31(11 Pt 2), 1626–1633 (2005).

14 Glavas IP. Filling agents. *Ophthalmol. Clin. North Am.* 18(2), 249–57, v–vi (2005).

15 Narins RS, Bowman PH. Injectable skin fillers. *Clin. Plast. Surg.* 32(2), 151–162 (2005).

16 Salles AG, Lotierzo PH, Gemperli R *et al.* Complications after polymethylmethacrylate injections: report of 32 cases. *Plast. Reconstr. Surg.* 121(5), 1811–1820 (2008).

17 Grunebaum LD, Bogdan Allemann I, Dayan S, Mandy S, Baumann L. The risk of alar necrosis associated with dermal filler injection. *Dermatol. Surg.* 35(Suppl. 35) 635–640 (2009).

18 De Boulle K. Critical reflections on ArteFill, a permanent injectable product for soft tissue augmentation: mechanism of action and injection techniques, indications, and

applications. *Aesthetic Plast. Surg*. 34(3), 287–289 (2010).

19 El Shafey SI. Complications from repeated injection or puncture of old polyacrylamide gel implant sites: case reports. *Aesthetic Plast. Surg*. 32(1), 162–165 (2008).

20 Dayan SH, Bassichis BA. Facial dermal fillers: selection of appropriate products and techniques. *Aesthet. Surg. J*. 28(3), 335–347 (2008).

21 Finn JC, Cox S. Fillers in the periorbital complex. *Facial Plast. Surg. Clin. North Am*. 15(1), 123–132, viii (2007).

22 Ghislanzoni M, Bianchi F, Barbareschi M, Alessi E. Cutaneous granulomatous reaction to injectable hyaluronic acid gel. *Br. J. Dermatol*. 154(4), 755–758 (2006).

23 Alijotas-Reig J, Garcia-Gimenez V. Delayed immune-mediated adverse effects related to hyaluronic acid and acrylic hydrogel dermal fillers: clinical findings, long-term follow-up and review of the literature. *J. Eur. Acad. Dermatol. Venereol*. 22(2), 150–161 (2008).

24 Bardazzi F, Ruffato A, Antonucci A, Balestri R, Tabanelli M. Cutaneous granulomatous reaction to injectable hyaluronic acid gel: another case. *J. Dermatolog. Treat*. 18(1), 59–62 (2007).

25 Carruthers J, Klein AW, Carruthers A, Glogau RG, Canfield D. Safety and efficacy of nonanimal stabilized hyaluronic acid for improvement of mouth corners. *Dermatol. Surg*. 31(3), 276–280 (2005).

26 Narins RS, Dayan SH, Brandt FS, Baldwin EK. Persistence and improvement of nasolabial fold correction with nonanimal-stabilized hyaluronic acid 100,000 gel particles/mL filler on two retreatment schedules: results up to 18 months on two retreatment schedules. *Dermatol. Surg*. 34(Suppl. 34), S2–S8, discussion S (2008).

27 Baumann LS, Shamban AT, Lupo MP *et al*. Comparison of smooth-gel hyaluronic acid dermal fillers with cross-linked bovine collagen: a multicenter, double-masked, randomized, within-subject study. *Dermatol. Surg*. 33(Suppl. 33) S128–S135 (2007).

28 Silvers SL, Eviatar JA, Echavez MI, Pappas AL. Prospective, open-label, 18-month trial of calcium hydroxylapatite (Radiesse) for facial soft-tissue augmentation in patients with human immunodeficiency virus-associated lipoatrophy: one-year durability. *Plast. Reconstr. Surg*. 118(Suppl. 3), 34S–45S (2006).

29 Goldberg RA, Fiaschetti D. Filling the periorbital hollows with hyaluronic acid gel: initial experience with 244 injections. *Ophthal. Plast. Reconstr. Surg*. 22(5), 335–341, discussion 41–43 (2006).

30 van Dam D, van der Lei B, Cromheecke M. Statements on the safety of permanent soft tissue fillers in Europe. *Aesthetic Plast. Surg*. 33(4), 479–481 (2009).

31 Farahani SS, Sexton J, Stone JD, Quinn K, Woo SB. Lip nodules caused by hyaluronic acid filler injection: report of three cases. *Head Neck Pathol*.6(1), 16–20 (2012).

32 Rendon MI. Long-term aesthetic outcomes with injectable poly-l-lactic acid: observations and practical recommendations based on clinical experience over 5 years. *J. Cosmet. Dermatol*. 11(2), 93–100 (2012).

33 Bass LS, Smith S, Busso M, McClaren M. Calcium hydroxylapatite (Radiesse) for treatment of nasolabial folds: long-term safety and efficacy results. *Aesthet. Surg. J*. 30(2), 235–238 (2010).

34 Salles AG, Lotierzo PH, Gimenez R, Camargo CP, Ferreira MC. Evaluation of the poly-L-lactic acid implant for treatment of the nasolabial fold: 3-year follow-up evaluation. *Aesthetic Plast. Surg*. 32(5), 753–756 (2008).

35 Liew S, Nguyen DQ. Nonsurgical volumetric upper periorbital rejuvenation: a plastic surgeon's perspective. *Aesthetic Plast. Surg*. 35(3), 319–325 (2010).

36 Tzikas TL. A 52-month summary of results using calcium hydroxylapatite for facial soft tissue augmentation. *Dermatol. Surg*. 34(Suppl. 1), S9–S15 (2008).

37 Monstrey SJ, Pitaru S, Hamdi M *et al*. A two-stage phase I trial of Evolence30 collagen for soft-tissue contour correction. *Plast. Reconstr. Surg*. 120(1), 303–311 (2007).

38 Bennett R, Taher M. Restylane persistent for 23 months found during Mohs micrographic surgery: a source of confusion with hyaluronic acid surrounding basal cell carcinoma. *Dermatol. Surg*. 31(10), 1366–1369 (2005).

39 Bergsma JE, de Bruijn WC, Rozema FR, Bos RR, Boering G. Late degradation tissue response to poly(L-lactide) bone plates and screws. *Biomaterials*16(1), 25–31 (1995).

40 Webster RC, Gaunt JM, Hamdan US, Fuleihan NS, Smith RC. Injectable silicone for facial soft-tissue augmentation. *Arch. Otolaryngol. Head Neck Surg*. 112(3), 290–296 (1986a).

41 Webster RC, Hamdan US, Gaunt JM, Fuleihan NS, Smith RC. Rhinoplastic revisions with injectable silicone. *Arch. Otolaryngol. Head Neck Surg*. 112(3), 269–276 (1986b).

42 Webster RC, Fuleihan NS, Hamdan US, Gaunt JM, Smith RC. Injectable silicone: Report of 17.000 Facial treatments since 1962. *Am. J. Cosm. Surg*. 3(2), 41–48 (1986c).

43 Aronsohn R. A 22 year experience with the use of silicone injections. *Am. J. Cosm. Surg*. 1(1), 21–28 (1984).

44 Mastruserio DN, Pesqueira MJ, Cobb MW. Severe granulomatous reaction and facial ulceration occurring after subcutaneous silicone injection. *J. Am. Acad. Dermatol*. 34(5 Pt 1), 849–852 (1996).

45 Jones DH, Carruthers A, Orentreich D *et al*. Highly purified 1000-cSt silicone oil for treatment of human immunodeficiency virus-associated facial lipoatrophy: an open pilot trial. *Dermatol. Surg*. 30(10), 1279–1286 (2004).

46 Prather CL, Jones DH. Liquid injectable silicone for soft tissue augmentation. *Dermatol. Ther*.19(3), 159–168 (2006).

47 Lemperle G, Gauthier-Hazan N, Lemperle M. PMMA-Microspheres (Artecoll) for long-lasting correction of wrinkles: refinements and statistical results. *Aesthetic Plast. Surg*. 22(5), 356–365 (1998).

48 Epstein RE, Spencer JM. Correction of atrophic scars with artefill: an open-label pilot study. *J. Drugs Dermatol*. 9(9), 1062–1064 (2010).

49 de Cassia Novaes W, Berg A. Experiences with a new nonbiodegradable hydrogel (Aquamid): a pilot study. *Aesthetic Plast. Surg*. 27(5), 376–380 (2003).

50 Christensen L, Breiting V, Vuust J, Hogdall E. Adverse reactions following injection with a permanent facial filler polyacrylamide hydrogel (Aquamid): Causes and treatment. *Eur. J. Plast. Surg*. 28(7), 464–471 (2006).

51 Narins RS, Coleman WP 3rd, Rohrich R *et al*. 12-Month controlled study in the United States of the safety and efficacy of a permanent 2.5% polyacrylamide hydrogel soft-tissue filler. *Dermatol. Surg*. 36(Suppl.), 31819–31829 (2010).

52 Karim RB, de Lint CA, van Galen SR *et al*. Long-term effect of polyalkylimide gel injections on severity of facial lipoatrophy and quality of life of HIV-positive patients. *Aesthetic Plast. Surg*. 32(6), 873–878 (2008).

53 Loutfy MR, Raboud JM, Antoniou T *et al*. Immediate versus delayed polyalkylimide gel injections to correct facial lipoatrophy in HIV-positive patients. *AIDS* 21(9), 1147–1155 (2007).

54 Lombardi T, Samson J, Plantier F, Husson C, Kuffer R. Orofacial granulomas

after injection of cosmetic fillers. Histopathologic and clinical study of 11 cases. *J. Oral Pathol. Med.* 33(2), 115–120 (2004).

55 Kim KJ, Lee HW, Lee MW, Choi JH, Moon KC, Koh JK. Artecoll granuloma: a rare adverse reaction induced by microimplant in the treatment of neck wrinkles. *Dermatol. Surg.* 30(4 Pt 1), 545–547 (2004).

56 Lee MW, Choi JH, Sung KJ, Moon KC, Koh JK. A case of cutaneous pseudolymphoma associated with silicone injection. *Acta Derm. Venereol.* 84(4), 312–313 (2004).

57 Rapaport MJ, Vinnik C, Zarem H. Injectable silicone: cause of facial nodules, cellulitis, ulceration, and migration. *Aesthetic Plast. Surg.* 20(3), 267–276 (1996).

58 Alcalay J, Alkalay R, Gat A, Yorav S. Late-onset granulomatous reaction to Artecoll. *Dermatol. Surg.* 29(8), 859–862 (2003).

59 Requena C, Izquierdo MJ, Navarro M *et al.* Adverse reactions to injectable aesthetic microimplants. *Am. J. Dermatopathol.* 23(3), 197–202 (2001).

60 Cheng NX, Xu SL, Deng H *et al.* Migration of implants: a problem with injectable polyacrylamide gel in aesthetic plastic surgery. *Aesthetic Plast. Surg.* 30(2), 215–225 (2006).

61 Cohen SR, Berner CF, Busso M *et al.* Five-year safety and efficacy of a novel polymethylmethacrylate aesthetic soft tissue filler for the correction of nasolabial folds. *Dermatol. Surg.* 33(Suppl. 33), S222–S230 (2007).

62 Cohen SR, Holmes RE. Artecoll: a long-lasting injectable wrinkle filler material: report of a controlled, randomized, multicenter clinical trial of 251 subjects. *Plast. Reconstr. Surg.* 114(4), 964–976, discussion 77–79 (2004).

63 Narins RS, Cohen S, Group aTF-YI. Novel polymethylmethacrylate soft tissue filler for the correction of nasolabial folds: interim results of a 5-year long-term safety and patient satisfaction study. *Dermatol. Surg.* 36766–36774 (2010).

64 Negredo E, Puig J, Aldea D *et al.* Four-year safety with polyacrylamide hydrogel to correct antiretroviral-related facial lipoatrophy. *AIDS Res. Hum. Retroviruses* 25(4), 451–455 (2009).

65 Pallua N, Wolter TP. A 5-year assessment of safety and aesthetic results after facial soft-tissue augmentation with polyacrylamide hydrogel (Aquamid): a prospective multicenter study of 251 patients. *Plast. Reconstr. Surg.* 125(6), 1797–1804 (2010).

66 Hanke CW, Rohrich RJ, Busso M *et al.* Facial soft-tissue fillers: assessing the state of the science conference—proceedings report. *J. Am. Acad. Dermatol.* 64(4 Suppl.), S53–S65 (2011).

67 Hanke CW, Rohrich RJ, Busso M *et al.* Facial soft-tissue fillers conference: assessing the state of the science. *J. Am. Acad. Dermatol.* 64(4 Suppl.), S66–S85 (2011).

68 Rohrich RJ, Hanke CW, Busso M *et al.* Facial soft-tissue fillers conference: assessing the state of the science. *Plast. Reconstr. Surg.* 127(4 Suppl.), 22S–S (2011).

69 Rohrich RJ, Hanke CW, Busso M *et al.* Facial soft-tissue fillers: Assessing the state of the science conference – Proceedings report. *Plast. Reconstr. Surg.* 127(Suppl. 4S), 9S–21S (2011).

70 Glogau RG. Fillers: from the past to the future. *Semin. Cutan. Med. Surg.* 31(2), 78–87 (2012).

71 Kablik J, Monheit GD, Yu L, Chang G, Gershkovich J. Comparative physical properties of hyaluronic acid dermal fillers. *Dermatol. Surg.* 35(Suppl.) 1302–1312 (2009).

72 Edsman K, Nord LI, Ohrlund A, Larkner H, Kenne AH. Gel properties of hyaluronic acid dermal fillers. *Dermatol. Surg.* 38(7 Pt 2), 1170–1179 (2012).

73 Rzany B, Cartier H, Kestemont P *et al.* Full-face rejuvenation using a range of hyaluronic acid fillers: efficacy, safety, and patient satisfaction over 6 months. *Dermatol. Surg.* 38(7 Pt 2), 1153–1161 (2012).

74 Carruthers A, Carey W, De Lorenzi C, Remington K, Schachter D, Sapra S. Randomized, double-blind comparison of the efficacy of two hyaluronic acid derivatives, restylane perlane and hylaform, in the treatment of nasolabial folds. *Dermatol. Surg.* 31(11 Pt 2), 1591–1598, discussion 8 (2005).

75 Dover JS, Rubin MG, Bhatia AC. Review of the efficacy, durability, and safety data of two nonanimal stabilized hyaluronic acid fillers from a prospective, randomized, comparative, multicenter study. *Dermatol. Surg.* 35(Suppl.) 1322–1330, discussion 30–31 (2009).

76 Kestemont P, Cartier H, Trevidic P *et al.* Sustained efficacy and high patient satisfaction after cheek enhancement with a new hyaluronic acid dermal filler. *J. Drugs. Dermatol.* 11(1 Suppl.), s9–s16 (2012).

77 Ascher B, Bayerl C, Brun P *et al.* Efficacy and safety of a new hyaluronic acid dermal filler in the treatment of severe nasolabial lines – 6-month interim results of a randomized, evaluator-blinded, intra-individual comparison study. *J. Cosmet. Dermatol.* 10(2), 94–98 (2011).

78 Cartier H, Trevidic P, Rzany B *et al.* Perioral rejuvenation with a range of customized hyaluronic acid fillers: efficacy and safety over six months with a specific focus on the lips. *J. Drugs Dermatol.* 11(1 Suppl.), s17–s26 (2012).

79 Prager W, Wissmueller E, Havermann I *et al.* A prospective, split-face, randomized, comparative study of safety and 12-month longevity of three formulations of hyaluronic acid dermal filler for treatment of nasolabial folds. *Dermatol. Surg.* 38(7 Pt 2), 1143–1150 (2012).

80 DeLorenzi C, Weinberg M, Solish N, Swift A. Multicenter study of the efficacy and safety of subcutaneous non-animal-stabilized hyaluronic acid in aesthetic facial contouring: interim report. *Dermatol. Surg.* 32(2), 205–211 (2006).

81 Lowe NJ, Grover R. Injectable hyaluronic acid implant for malar and mental enhancement. *Dermatol. Surg.* 32(7), 881–885, discussion 5 (2006).

82 Lowe NJ, Maxwell CA, Lowe P, Duick MG, Shah K. Hyaluronic acid skin fillers: adverse reactions and skin testing. *J. Am. Acad. Dermatol.* 45(6), 930–933 (2001).

83 Raspaldo H, De Boulle K, Levy PM. Longevity of effects of hyaluronic acid plus lidocaine facial filler. *J. Cosmet. Dermatol.* 9(1), 11–15 (2010).

84 Narins RS, Coleman WP 3rd, Donofrio LM *et al.* Improvement in nasolabial folds with a hyaluronic acid filler using a cohesive polydensified matrix technology: results from an 18-month open-label extension trial. *Dermatol. Surg.* 36(Suppl.) 31800–31808 (2010).

85 Malhotra R. Deep orbital Sub-Q restylane (nonanimal stabilized hyaluronic acid) for orbital volume enhancement in sighted and anophthalmic orbits. *Arch. Ophthalmol.* 125(12), 1623–1629 (2007).

86 Andre P. Evaluation of the safety of a non-animal stabilized hyaluronic acid (NASHA – Q-Medical, Sweden) in European countries: a retrospective study from 1997 to 2001. *J. Eur. Acad. Dermatol. Venereol.* 18(4), 422–425 (2004).

87 McCracken MS, Khan JA, Wulc AE *et al.* Hyaluronic acid gel (Restylane) filler for

facial rhytids: lessons learned from American Society of Ophthalmic Plastic and Reconstructive Surgery member treatment of 286 patients. *Ophthal. Plast. Reconstr. Surg.* 22(3), 188–191 (2006).

88 Fernandez-Acenero MJ, Zamora E, Borbujo J. Granulomatous foreign body reaction against hyaluronic acid: report of a case after lip augmentation. *Dermatol. Surg.* 29(12), 1225–1226 (2003).

89 Hoenig JF, Brink U, Korabiowska M. Severe granulomatous allergic tissue reaction after hyaluronic acid injection in the treatment of facial lines and its surgical correction. *J. Craniofac. Surg.* 14(2), 197–200 (2003).

90 Zimmermann US, Clerici TJ. The histological aspects of fillers complications. *Semin. Cutan. Med. Surg.* 23(4), 241–250 (2004).

91 Bisaccia E, Lugo A, Torres O, Johnson B, Scarborough D. Persistent inflammatory reaction to hyaluronic acid gel: a case report. *Cutis* 79(5), 388–389 (2007).

92 Dal Sacco D, Cozzani E, Parodi A, Rebora A. Scar sarcoidosis after hyaluronic acid injection. *Int. J. Dermatol.* 44(5), 411–412 (2005).

93 Engelhard P, Knies M. Safety and efficacy of New-Fill® (polylactic acid) in the treatment of HIV associated lipoatrophy of the face (HALF). *Proceedings of 14th International AIDS Conference*. Catalonia, Spain (2002).

94 Borelli C, Kunte C, Weisenseel P, Thoma-Greber E, Korting HC, Konz B. Deep subcutaneous application of poly-L-lactic acid as a filler for facial lipoatrophy in HIV-infected patients. *Skin Pharmacol. Physiol.*18(6), 273–278 (2005).

95 Moyle GJ, Lysakova L, Brown S *et al.* A randomized open-label study of immediate versus delayed polylactic acid injections for the cosmetic management of facial lipoatrophy in persons with HIV infection. *HIV Med.*5(2), 82–7 (2004).

96 Burgess CM, Quiroga RM. Assessment of the safety and efficacy of poly-L-lactic acid for the treatment of HIV-associated facial lipoatrophy. *J. Am. Acad. Dermatol.* 52(2), 233–239 (2005).

97 Beer K. A single-center, open-label study on the use of injectable poly-L-lactic acid for the treatment of moderate to severe scarring from acne or varicella. *Dermatol. Surg.* 33 (Suppl. 33), S159–S167 (2007).

98 Cattelan AM, Bauer U, Trevenzoli M *et al.* Use of polylactic acid implants to correct facial lipoatrophy in human immunodeficiency virus 1-positive individuals receiving combination antiretroviral therapy. *Arch. Dermatol.* 142(3), 329–334 (2006).

99 Humble G, Mest D. Soft tissue augmentation using sculptra. *Facial Plast Surg.* 20(2), 157–163 (2004).

100 Moyle GJ, Brown S, Lysakova L, Barton SE. Long-term safety and efficacy of poly-L-lactic acid in the treatment of HIV-related facial lipoatrophy. *HIV Med.* 7(3), 181–185 (2006).

101 Valantin MA, Aubron-Olivier C, Ghosn J *et al.* Polylactic acid implants (New-Fill) to correct facial lipoatrophy in HIV-infected patients: results of the open-label study VEGA. *AIDS* 17(17), 2471–2477 (2003).

102 Narins RS, Baumann L, Brandt FS *et al.* A randomized study of the efficacy and safety of injectable poly-L-lactic acid versus human-based collagen implant in the treatment of nasolabial fold wrinkles. *J. Am. Acad. Dermatol.* 62(3), 448–462 (2010).

103 Levy RM, Redbord KP, Hanke CW. Treatment of HIV lipoatrophy and lipoatrophy of aging with poly-L-lactic acid: a prospective 3-year follow-up study. *J. Am. Acad. Dermatol.* 59(6), 923–933 (2008).

104 Woerle B, Hanke CW, Sattler G. Poly-L-lactic acid: a temporary filler for soft tissue augmentation. *J. Drugs Dermatol.* 3(4), 385–389 (2004).

105 Lowe NJ, Maxwell CA, Lowe P, Shah A, Patnaik R. Injectable poly-l-lactic acid: 3 years of aesthetic experience. *Dermatol. Surg.* 35(Suppl.), 1344–1349 (2009).

106 Sadove R. Injectable poly-L: -lactic acid: a novel sculpting agent for the treatment of dermal fat atrophy after severe acne. *Aesthetic Plast. Surg.* 33(1), 113–116 (2009).

107 Beljaards RC, de Roos KP, Bruins FG. NewFill for skin augmentation: a new filler or failure? *Dermatol. Surg.* 31(7 Pt 1), 772–776, discussion 6 (2005).

108 Reszko AE, Sadick NS, Magro CM, Farber J. Late-onset subcutaneous nodules after poly-L-lactic acid injection. *Dermatol. Surg.* 35(Suppl.), 1380–1384 (2009).

109 Hamilton DG, Gauthier N, Robertson BF. Late-onset, recurrent facial nodules associated with injection of poly-L-lactic acid. *Dermatol. Surg.* 34(1), 123–126, discussion 6 (2008).

110 Godin MS, Majmundar MV, Chrzanowski DS, Dodson KM. Use of radiesse in combination with restylane for facial augmentation. *Arch. Facial Plast. Surg.* 8(2), 92–97 (2006).

111 Jacovella PF, Peiretti CB, Cunille D, Salzamendi M, Schechtel SA. Long-lasting results with hydroxylapatite (Radiesse) facial filler. *Plast. Reconstr. Surg.* 118(3 Suppl.), 15S–21S (2006).

112 Smith S, Busso M, McClaren M, Bass LS. A randomized, bilateral, prospective comparison of calcium hydroxylapatite microspheres versus human-based collagen for the correction of nasolabial folds. *Dermatol. Surg.* 33(Suppl. 33), S112–S121, discussion S21 (2007).

113 Sadick NS, Katz BE, Roy D. A multicenter, 47-month study of safety and efficacy of calcium hydroxylapatite for soft tissue augmentation of nasolabial folds and other areas of the face. *Dermatol. Surg.* 33(Suppl. 33), S122–S126, discussion S6–S7 (2007).

114 Carruthers A, Carruthers J. Evaluation of injectable calcium hydroxylapatite for the treatment of facial lipoatrophy associated with human immunodeficiency virus. *Dermatol. Surg.* 34(11), 1486–1499 (2008).

115 Moers-Carpi MM, Tufet JO. Calcium hydroxylapatite versus nonanimal stabilized hyaluronic acid for the correction of nasolabial folds: a 12-month, multicenter, prospective, randomized, controlled, split-face trial. *Dermatol. Surg.* 34(2), 210–215 (2008).

116 Moers-Carpi M, Storck R, Howell DJ, Ogilvie P, Ogilvie A. Physician and patient satisfaction after use of calcium hydroxylapatite for cheek augmentation. *Dermatol. Surg.* 38(7 Pt 2), 1217–1222 (2012).

117 Jansen DA, Graivier MH. Evaluation of a calcium hydroxylapatite-based implant (Radiesse) for facial soft-tissue augmentation. *Plast. Reconstr. Surg.* 118(3 Suppl.), 22S–30S, discussion 1S–3S (2006).

118 Sankar V, McGuff HS. Foreign body reaction to calcium hydroxylapatite after lip augmentation. *J. Am. Dent. Assoc.* 138(8), 1093–1096 (2007).

119 Lemperle G, Hazan-Gauthier N, Lemperle M. PMMA microspheres (Artecoll) for skin and soft-tissue augmentation. Part II : Clinical investigations. *Plast. Reconstr. Surg.* 96(3), 627–634 (1995).

120 Bagal A, Dahiya R, Tsai V, Adamson PA. Clinical experience with polymethylmethacrylate microspheres (Artecoll) for soft-tissue augmentation: a retrospective review. *Arch. Facial Plast. Surg.* 9(4), 275–280 (2007).

121 Silva MT, Curi AL. Blindness and total ophthalmoplegia after aesthetic polymethylmethacrylate injection: case report. *Arq. Neuropsiquiatr.* 62(3B), 873–874 (2004).

122 de Melo Carpaneda E, Carpaneda CA. Adverse Results with PMMA Fillers. *Aesthetic Plast. Surg.* 36(4), 955–963 (2012).

123 Bergeret-Galley C, Latouche X, Illouz YG. The value of a new filler material in corrective and cosmetic surgery: DermaLive and DermaDeep. *Aesthetic Plast. Surg.* 25(4), 249–255 (2001).

124 Bachmann F, Erdmann R, Hartmann V, Wiest L, Rzany B. The spectrum of adverse reactions after treatment with injectable fillers in the glabellar region: results from the Injectable Filler Safety Study. *Dermatol. Surg.* 35(Suppl.), 21629–21634 (2009).

125 Rossner M, Rossner F, Bachmann F, Wiest L, Rzany B. Risk of severe adverse reactions to an injectable filler based on a fixed combination of hydroxyethylmethacrylate and ethylmethacrylate with hyaluronic acid. *Dermatol. Surg.* 35(Suppl.), 1367–1374 (2009).

126 Sidwell RU, Dhillon AP, Butler PE, Rustin MH. Localized granulomatous reaction to a semi-permanent hyaluronic acid and acrylic hydrogel cosmetic filler. *Clin. Exp. Dermatol.* 29(6), 630–632 (2004).

127 Christensen L, Breiting V, Janssen M, Vuust J, Hogdall E. Adverse reactions to injectable soft tissue permanent fillers. *Aesthetic Plast. Surg.* 29(1), 34–48 (2005).

128 Furmanczyk PS, Wolgamot GM, Argenyi ZB, Gilbert SC. Extensive granulomatous reaction occurring 1.5 years after DermaLive injection. *Dermatol. Surg.* 35(Suppl.) 1385–1388 (2009).

129 Alijotas-Reig J, Garcia-Gimenez V, Miro-Mur F, Vilardell-Tarres M. Delayed immune-mediated adverse effects of polyalkylimide dermal fillers: clinical findings and long-term follow-up. *Arch. Dermatol.* 144(5), 637–642 (2008).

130 Gamo R, Pinedo F, Vicente J *et al.* Keratoacanthoma-like reaction after a hyaluronic acid and acrylic hydrogel cosmetic filler. *Dermatol. Surg.* 34(7), 954–959 (2008).

131 Rauso R, Gherardini G, Parlato V, Amore R, Tartaro G. Polyacrylamide gel for facial wasting rehabilitation: how many milliliters per session? *Aesthetic Plast. Surg.* 36(1), 174–179 (2012).

132 Mole B, Gillaizeau F, Carbonnel E *et al.* Polyacrylamide hydrogel injection in the management of human immunodeficiency virus-related facial lipoatrophy: results of the LIPOPHILL open-label study. *AIDS Res. Hum. Retroviruses* 28(3), 251–258 (2012).

133 Bassichis B, Blick G, Conant M *et al.* Injectable poly-L-lactic acid for human immunodeficiency virus-associated facial lipoatrophy: cumulative year 2 interim analysis of an open-label study (FACES). *Dermatol. Surg.* 38(7 Pt 2), 1193–1205 (2012).

134 De Santis G, Pignatti M, Baccarani A *et al.* Long-term efficacy and safety of polyacrylamide hydrogel injection in the treatment of human immunodeficiency virus–related facial lipoatrophy: A 5-year follow-up. *Plast. Reconstr. Surg.* 129(1), 101 (2012).

135 von Buelow S, von Heimburg D, Pallua N. Efficacy and safety of polyacrylamide hydrogel for facial soft-tissue augmentation. *Plast. Reconstr. Surg.* 116(4), 1137–1146, discussion 47–48 (2005).

136 von Buelow S, Pallua N. Efficacy and safety of polyacrylamide hydrogel for facial soft-tissue augmentation in a 2-year follow-up: a prospective multicenter study for evaluation of safety and aesthetic results in 101 patients. *Plast. Reconstr. Surg.* 118(3 Suppl.), 85S–91S (2006).

137 Breiting V, Aasted A, Jorgensen A, Opitz P, Rosetzsky A. A study on patients treated with polyacrylamide hydrogel injection for facial corrections. *Aesthetic Plast. Surg.* 28(1), 45–53 (2004).

138 Kalantar-Hormozi A, Mozafari N, Rasti M. Adverse effects after use of polyacrylamide gel as a facial soft tissue filler. *Aesthet. Surg. J.* 28(2), 139–142 (2008).

139 Manafi A, Emami AH, Pooli AH, Habibi M, Saidian L. Unacceptable results with an accepted soft tissue filler: polyacrylamide hydrogel. *Aesthetic Plast. Surg.* 34(4), 413–422 (2010).

140 Alijotas-Reig J, Garcia-Gimenez V, Miro-Mur F, Vilardell-Tarres M. Delayed immune-mediated adverse effects related to polyacrylamide dermal fillers: clinical findings, management, and follow-up. *Dermatol. Surg.* 35(Suppl.), 1360–1366 (2009).

141 Treacy PJ, Goldberg DJ. Use of a biopolymer polyalkylimide filler for facial lipodystrophy in HIV-positive patients undergoing treatment with antiretroviral drugs. *Dermatol. Surg.* 32(6), 804–808 (2006).

142 Antoniou T, Raboud JM, Kovacs C *et al.* Long-term efficacy and safety of polyalkylimide gel for the treatment of HIV-associated lipoatrophy. *AIDS Care* 21(10), 1247–1252 (2009).

143 Hoenig JF. Cheek augmentation with Bio-Alcamid in facial lipoatrophy in HIV seropositive patients. *J. Craniofac. Surg.* 19(4), 1085–1088 (2008).

144 Protopapa C, Sito G, Caporale D, Cammarota N. Bio-Alcamid in drug-induced lipodystrophy. *J. Cosmet. Laser Ther.* 5(3–4), 226–230 (2003).

145 Pacini S, Ruggiero M, Morucci G, Cammarota N, Protopapa C, Gulisano M. Bio-alcamid: a novelty for reconstructive and cosmetic surgery. *Ital. J. Anat. Embryol.* 107(3), 209–214 (2002).

146 Ross AH, Malhotra R. Long-term orbitofacial complications of polyalkylimide 4% (bio-alcamid). *Ophthal. Plast. Reconstr. Surg.* 25(5), 394–397 (2009).

147 Schelke LW, van den Elzen HJ, Canninga M, Neumann MH. Complications after treatment with polyalkylimide. *Dermatol. Surg.* 35(Suppl. 35), 1625–1628 (2009).

148 Goldan O, Georgiou I, Grabov-Nardini G *et al.* Early and late complications after a nonabsorbable hydrogel polymer injection: a series of 14 patients and novel management. *Dermatol. Surg.* 33(Suppl. 33), S199–S206, discussion S (2007).

149 Karim RB, Hage JJ, van Rozelaar L, Lange CA, Raaijmakers J. Complications of polyalkylimide 4% injections (Bio-Alcamid): a report of 18 cases. *J. Plast. Reconstr. Aesthet. Surg.* 59(12), 1409–1414 (2006).

150 Chrastil-LaTowsky B, Wesley NO, Mac Gregor JL, Kaminer MS, Arndt KA. Delayed inflammatory reaction to bio-alcamid polyacrylamide gel used for soft-tissue augmentation. *Arch. Dermatol.* 145(11), 1309–1312 (2009).

151 Akrish S, Dayan D, Taicher S, Adam I, Nagler RM. Foreign body granulomas after injection of Bio-alcamid for lip augmentation. *Am. J. Otolaryngol.* 30(5), 356–359 (2009).

152 Jones DH, Carruthers A, Fitzgerald R, Sarantopoulos GP, Binder S. Late-appearing abscesses after injections of nonabsorbable hydrogel polymer for HIV-associated facial lipoatrophy. *Dermatol. Surg.* 33(Suppl. 33), S193–S198 (2007).

153 Moscona RA, Fodor L. A retrospective study on liquid injectable silicone for lip augmentation: long-term results and patient

satisfaction. *J. Plast. Reconstr. Aesthet. Surg.* 63(10), 1694–1698 (2010).

154 Hevia O. Six-year experience using 1,000-centistoke silicone oil in 916 patients for soft-tissue augmentation in a private practice setting. *Dermatol. Surg.* 35(Suppl. 35), 1646–1652 (2009).

Websites

201 Inamed Corporation. Summary of safety and effectiveness data –Juvederm (2006). wwwaccessdatafdagov/cdrh_docs/pdf5/P050047bpdf (Accessed 7 January 2011)

202 ColBar LifeScience Ltd. Summary of Safety and Effectiveness Data – Injectable Collagen Filler for Aesthetic Use (2008). wwwaccessdatafdagov/cdrh_docs/pdf7/P070013bpdf (Accessed 7 January 2011)

203 BioForm Medical Inc. Summary of Safety and Effectiveness data – Radiesse (2006). wwwaccessdatafdagov/cdrh_docs/pdf5/P050052bpdf (Accessed 29 January 2010)

204 de Vries CGJCA, Geertsma RE. Injecteerbare semi-permanente rimpelvullers in Nederland. Inventarisatie van toepassing en complicaties RIVM-briefrapport 360050008 (2007). wwwrivmnl/bibliotheek/rapporten/360050008html (Accessed 3 December 2010)

205 FDA. Summary From the General and Plastic Surgery Devices Panel Meeting (2003). wwwfdagov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/GeneralandPlasticSurgeryDevicesPanel/ucm124761htm (Accessed 25 November 2010)

206 Geertsma RE, de Bruijn ACP, van Drongelen AW, Hollestelle ML, de Jong WH, van Tienhoven E. Mate van voorkomen en ernst van complicaties bij het gebruik van permanente vullers bij rimpelbehandelingen. RIVM-briefrapport 078 (2006). wwwrivmnl/bibliotheek/rapporten/360050003html (Accessed 3 December 2012)

207 Anika Therapeutics Inc. Summary of safety and effectiveness -Cosmetic Tissue Augmentation product (CTA) (2006). wwwaccessdatafdagov/cdrh_docs/pdf5/P050033bpdf (Accessed 7 January2011)

208 CORNEAL. MAUDE Adverse Event Report -CORNEAL JUVEDERM ULTRA- (2006). wwwaccessdatafdagov/scripts/cdrh/cfdocs/cfMAUDE/DetailCFM?MDRFOI__ID=897305 (Accessed 7 January 2011)

209 FDA. Post-Approval Study Commitment (2008). wwwaccessdatafdagov/scripts/cdrh/cfdocs/cfPMA/pma_pascfm?t_id=358603&c_id=74 (Accessed 2 February 2012)

210 FDA. Summary of Safety and Effectiveness Data (2008a). wwwaccessdatafdagov/cdrh_docs/pdf7/P070013bpdf.(2008a) (Accessed 7 January 2011)

211 FDA. Summary of Safety and Effectiveness Data (2004a). wwwaccessdatafdagov/cdrh_docs/pdf3/P030050bpdf (Accessed 7 January 2011)