Review article

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The role of fillers in the management of acne scars

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Summary

Acne scars are present in 95% of patients with acne, and can cause profound psychosocial morbidity. Fillers are commonly used for facial soft tissue augmentation, and there is increasing interest in their use for the treatment of acne scars, particularly for the atrophic subtype. We review the evidence for the use of temporary, semi-permanent and permanent fillers for acne scars. The use of permanent methylmethacrylate fillers for acne scarring is supported by a randomized controlled trial, and is approved by the United States Food and Drug Administration. There is initial evidence supporting the use of poly-L-lactic acid and hyaluronic acid fillers, but evidence is still lacking about the use of polyacrylamide and polyalkylimide fillers.

Introduction

Acne vulgaris (AV) affects 80% of adolescents. The subsequent scarring affects up to 95% of patients,[1] and can be the cause of significant psychosocial distress. Acne scars can be classified as hypertrophic or atrophic, with the latter being more common, and further subclassified as ice-pick, rolling and boxcar scars.

Following the inflammation associated with AV, the subsequent scarring is attributed to an interplay of several mechanisms, including inflammation, granulation tissue formation and matrix remodelling. Treatments used by dermatologists for acne scarring include chemical peels, dermabrasion, ablative and nonablative laser devices, punch excision, dermal grafting and fat transplantation.

We focus upon the emerging field of revolumization of acne scars using dermal fillers, either as monotherapy or in conjunction with other treatments.

Types of fillers

Fillers are classified as either temporary [effects lasting up to 18 months; e.g. hyaluronic acid (HA)], semi-permanent [effects lasting up to 2 years; examples include poly-L-lactic acid (PLLA) and calcium hydroxyapatite (CH)] or permanent [effects lasting for longer than 3 years; examples include polymethylmethacrylate (PMMA), silicone, polyacrylamide and polyalkylimide] (Table 1). Fillers are injected using various techniques, including droplet injection, linear threading, fanning or three-dimensional volumization. Postulated mechanisms of action of fillers include augmentation of dermal and subcutaneous tissue scaffolding alongside stimulation and enhancement of collagen and tissue formation.[2,3] Although human, bovine and porcine collagen-based fillers have previously been used, they have a short duration of action and they have now been supplanted by longer-lived fillers, so will not be discussed further.

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Temporary fillers

Hyaluronic acid

HA is a temporary filler, which is produced by streptococcal fermentation[4] and consists of a glycosaminoglycan polysaccharide. Multiple HA fillers have been approved by the United States Food and Drug Administration (FDA), and these differ in their concentration of HA and in their molecular and rheological properties.[5] FDA-approved HA fillers include Juvéderm (Allergan), Restylane and Perlane (Galderma), Prevelle (Mentor),

Table 1 Classification of fillers, with example trade names

Filler	Trade names
Temporary	
Hyaluronic acid	Belotero, Juvéderm, Perlane, Restylane
Semi-permanent	
Poly-L-lactic acid	Sculptra (Newfill)
Calcium hydroxylapatite	Radiesse
Permanent	
Polymethylmethacrylate	Bellafill (previously Artefill)
Polyalkylimide	Bio-Alcamid
Polyacrylamide	Aquamid
Silicone	

and Belotero (also known as Esthelis-Merz).[6] Beletero Balance has been FDA-approved since 2011 and Restylane since 2003[7] for moderate to severe wrinkles and folds. Juvederm Voluma has been FDA-approved for age-related volume loss since 2013.[8]

HA fillers are commonly used to lessen the prominence of facial folds, or for volumization of discrete areas, such as for lip augmentation. HA fillers, injected into the deep dermis, have been shown to stimulate fibroblasts to produce collagen, and therefore replace volume with minimal reported side-effects.[9] Four studies have investigated the use of HA fillers in acne scarring, one of which used HA filler microinjections as an adjunct following fractional laser resurfacing[10] (Table 2). Although the studies were limited by numbers (with sample sizes ranging from 2 to 12 subjects), all demonstrated improvement in acne scar appearance, with minimal or transient side-effects such as mild erythema.[10–13]

Semi-permanent fillers

Poly-L-lactic acid

PLLA is a synthetic biodegradable polymer, which was originally used to correct facial lipoatrophy secondary to human immunodeficiency virus (HIV). It has been shown to be safe, with long-lasting effects of up to 2 years, and was first approved for soft tissue augmentation in Europe in 1999.[14] Brand names include Sculptra, which was FDA-approved for treatment of HIV-associated lipoatrophy in 2004.[15]

There have been four studies on PLLA for acne scarring, conducted between 2007 and 2010, which had sample sizes ranging between 1 and 22 subjects, and all showed positive outcomes.[2,16–18]

In 2014, Waibel *et al.* proposed using topically applied PLLA following treatment with ablative fractionated carbon dioxide laser (CO_2) for the treatment of atrophic acne scars. This prospective study used four blinded dermatologists to objectively analyse before and after photographs of 80 participants, using the Modified Manchester scar scale, and found that at 3 months post-treatment, 95% of the scars showed improvement.[19]

Calcium hydroxylapatite

CH is a natural biocompatible substance found in human bone and tooth. Some physicians prefer its use because of its ability to create significant volume change instantly with minimal product, compared with (for example) PLLA, which tends to stimulate collagen weeks after injection without instant volumization. Although CH fillers cause immediate change in tissue augmentation, their effects can last up to 18 months, as the microspheres create a framework through which fibroblasts can infiltrate and enable neocollagenesisis.[20]

Radiesse is a brand of CH filler that has been FDA-approved for treatment of moderate to severe wrinkles and folds since 2006.[21,22]

To date, there has only been one small (n = 10) open trial on the use of CH fillers in acne, which demonstrated that CH fillers are beneficial for up to 12 months in atrophic acne scars, but there was no demonstrable benefit for ice-pick scars.[23]

Permanent fillers

Polymethylmethacrylate

PMMA is a synthetic, biocompatible, permanent filler. Complications seen with PMMA are uncommon, and include tissue necrosis, chronic inflammatory reactions, lymphoedema and infections. PMMA (now Bellafill, previously called Artefill) received FDA approval for soft tissue augmentation in 2006,[24] and is the only filler to be approved by the FDA for use in acne scarring since January 2015.[25]

There have been three studies demonstrating the benefit of PMMA in atrophic acne scars.[3,26,27] The largest double-blind, randomized-controlled trial (RCT) to date (n = 147) used two treatment sessions with a 6-month follow-up, and demonstrated that PMMA provided a statistically significant superior treatment for atrophic facial acne scarring of 64%, versus 33% in the control arm (P = 0.0005).[26] A single-centre, open-label, pilot study of 14 patients with atrophic acne scars undertook subcision prior to PMMA (Artefill) injection; 96% of scars demonstrated improvement

Table 2 Tabulated evidence of the use of fillers in acne scarring.

Study	Indication	Aim	Patients, *n*	Findings
HA (temporary)				
Goodman *et al.,* 2015[11]	HA to treat atrophic acne scarring in Fitzpatrick skin types I–IV. Brand name: Juvéderm Voluma (Allergan)	Pilot study, two treatments and follow-up interval: patient followed up for a total of 3 months from the second treatment	5	Mean scar count reduced from 48.8 to 15.4 after the second session. Static objective grading scale demonstrated improvement from 3.2 (prior to first treatment) to 2.6 (final review)
Patel *et al.,* 2015[12]	Pneumatic injections of HA in Fitzpatrick skin types IV–V. Brand name: Belotero Balance	Two treatments (at 4-week intervals) of needle-less injections of cross-linked HA. Follow-up interval: patients were followed up for a total 3 months with one follow-up visit.	2	Acne scar grade improvement as assessed by physician. Patient 1: score of 2–1; Patient 2: score of 3–2. No significant AEs even in darker skin types
Halachmi *et al.,* 2013[10]	Moderate to severe atrophic acne scars treated with HA postfractional ablative laser resurfacing. Brand name: Restylane	Microinjection of 20 mg/mL HA. Follow-up interval: patients were followed up for a total of 1–2 months, with one follow-up visit	12	Immediate visual improvement in all lesions. Retained scattered, deep, ice-pick scars. AEs included transient pinpoint bleeding at injection site
Hassone*t al.,* 2010[13]	HA to treat facial atrophic scars secondary to acne, dog bite, piercing, BCC and leishmaniasis, Brand name: Esthelis	Linear threading, serial puncture or both used in open trial. Follow-up interval: patients were followed up for a total of 1 month, with one follow-up visit immediately, 1 week and 1 month post-treatment.	12	Moderate (27%), good (57%) and excellent (17%) immediately, 1 week and 1 month post-treatment. AEs included mild erythema
PLLA (semi-permanent)				
Sapra *et al.,* 2015[16]	Single-arm, unblinded, open-label, phase II study. Brand name: Sculptra	3–4 treatments of PLLA at 4-week intervals. Follow-up interval: patients were followed up for a total of 16 months, with follow-up visits at treatments 2 and 4	22	45.5–68.2% reported 'much to excellent improvement' using photographs. Subject treatment satisfaction increased to 44%. AEs included one patient with palpable nodule that was not visible
Rkein *et al.,* 2014[19]	Treatment of atrophic scars with ablative CO_2 laser and topical PLLA immediately afterwards. Brand name: Sculptra	Uncontrolled prospective study. Follow-up interval: patients were followed up for a total of 3 months, with follow-up visits at 3 months only.	80	Blinded physicians reported that 95% of scars improved at 3-month follow-up, demonstrating synergistic effect of CO_2 laser and PLLA in atrophic scars
Sadick *et al.,* 2009[17]	Case study of 60-year-old white woman, who had undergone previous CO_2 laser and dermabrasion without effect on acne scars. Brand name: Sculptra	Seven treatments of injectable PLLA given to individual acne scars. Follow-up interval: the patient was followed up for a total of 14 months, with follow-up 6 months after the seventh treatment, and touch-up at 14 months after the seventh treatment.	1	Patient reported observable improvement. AEs include minimal swelling and bruising lasting 5–7 days
Sadove,2009[18]	PLLA used in macular atrophic acne scarring. Brand name: Newfill	3 treatment sessions over a 12-week period (in women). Follow-up interval: patients were followed up for a total of 4 years, with follow-up visits at 1 year and 4 years post-reatment.	2	Both patients 'extremely pleased with results'. AEs included minimal swelling and redness. No nodule/papule formation

Table 2. continued

Study	Indication	Aim	Patients, *n*	Findings
Beer, 2007[2]	Treatment for acne scars secondary to moderate/severe acne or varicella treated with PLLA. Brand name: Sculptra	Single-centre, open-label, prospective study, with seven treatments. Follow-up interval: patients were followed up for a total of six sessions, with follow-up at each treatment session. Time-scale of follow-up not stated.	20	Investigator assessed reduction in acne scar size and severity as significant ($P < 0.001$). Subject rated reduction in scar severity as significant ($P = 0.0078$)
CH (semi-permanent)				
Goldberg *et al.*, 2006[23]	Use of CH in acne scars. Brand name: Radiesse	Open study. Follow-up interval: patients were followed up for a total 12 months, with one follow-up visit post-treatment.	10	Depressed acne scars responded to treatment but no response from ice-pick scars. No significant AEs.
PMMA (permanent)				
Karnick *et al.*, 2014[26]	Treatment of atrophic facial acne scars with suspended PMMA microspheres. Brand name: Artefill	Double-blind, randomized, multicentre, controlled trial of 2 injection treatments in patients with moderate to severe rolling atrophic scars. Follow-up interval: patients were followed up for a total of 6 months, with one follow-up visit post-treatment.	147	Successful treatment in 64% versus 333% control arm, ($P = 0.0005$). AEs were minimal
Epstein *et al.*, 2010[27]	Treatment of atrophic acne scars with PMMA. Brand name: Artefill	Single centre, open-label, pilot study. Subcision preceded filler injection. Follow-up interval: patients were followed up for a total 8 months, with follow-up visits at 2,4 and 8 months post-treatment.	14	At 8 months, 96% of acne scars showed improvement. No AEs reported
Carvalho *et al.*, 2009[3]	PMMA to correct facial defects; this study included the review of PMMA in depressive acne scars. Brand name: Artefill	PMMA injected over 1–4 sessions with 40–60 days between applications. Follow-up interval: 53% of patients were followed up for a total of > 5 years [maximum follow-up 9 years (4.5%)], with follow-up visits at each session, and at 1 month and 6 months, then yearly thereafter.	25*	Found to be effective, long-lasting and safe
Silicone (permanent)				
Barnett *et al.*, 2005[30]	Review of safety and efficacy of silicone microdroplet injections over 30 years for acne scars	Multiple, microdroplet liquid silicone injections. Follow-up interval: patients were followed up for a total 30 years, with follow-up immediately and then subsequently at 10, 15 and 30 years post-treatment.	25	Improvement of depressed acne scars, even at follow-up of 10,15 and 30 years

AEs, adverse effects; BCC, basal cell carcinoma; CH, calcium hydroxyapatite; HA, hyaluronic acid; PLLA, poly-L-lactic acid; PMMA, polymethylmethacrylate. *Number of patients within the study (out of a total of 266 patients) with atropic acne scars.

at 8 months post-treatment, with no adverse effects reported.[27]

Silicone

Silicone fillers are considered to be a controversial choice for tissue augmentation. Issues regarding silicone purity and lack of long-term follow-up within trials to confirm safety has resulted in a decline in their use in soft tissue augmentation. Silicone-based fillers are occasionally used instead of PLLA to correct HIV-associated lipodystrophy, but this remains controversial because of the increased risk of adverse reactions, including granulomas and nodules.[28] To date,

there has only been one trial reviewing the use of silicone fillers in depressed acne scars; Barnet *et al.* followed up five patients who were treated with liquid injectable silicon, at 10, 15 and 30 years, and concluded that multiple injections with a microdroplet technique is safe and effective to treat depressed acne scars. However, given the paucity of data regarding the long-term safety of liquid silicone, the FDA has not approved it for augmentation tissues anywhere in the body.[29]

Polyalkylimide and polyacrylamide

There are no studies to date supporting the use of other permanent fillers (polyalkylimide and polyacrylamide) in the treatment of atrophic acne scars. The permanence of action and arguably more severe AES of migration of material, particularly with large boluses, may discourage their future use for this indication.

Conclusion

Fillers are commonly used in the treatment of facial tissue augmentation, but their role in the treatment of facial acne scars is yet to be fully exploited by dermatologists. To date, PMMA is the only FDA-approved filler for treatment of atrophic acne scars, with a large double-blinded RCT supporting its use. From the literature, it appears that dermal fillers should be considered for boxcar or rolling atrophic acne scars. There is insufficient evidence to support the use of fillers for deeper ice-pick scars, either as monotherapy or in combination with laser ablation. Categorizing fillers by duration of action may be a useful construct when determining which filler may be the most appropriate to use. Future developments may include increased use of ablative laser-assisted delivery of topically applied fillers.

Learning points

- A range of treatments is available for post-acne scarring, with varying degrees of success.
- Fillers, including temporary, semi-permanent and permanent, are used successfully in the treatment of facial soft tissue augmentation.
- Use of fillers for volumization of areas of tissue loss following acne scarring has recently become of interest to dermatologists.
- We comprehensively reviewed and summarized the literature underlying the use of fillers for acne scarring.
- Only one filler (PMMA; Bellafill) has been approved for use for post-acne scarring by the FDA, with its use supported by an RCT.
- Future use of fillers may include the use of laser-assisted delivery of topically applied fillers.

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Multiple choice questions

Learning objective

To demonstrate up-to-date knowledge in the management of Acne scars with temporary, semi-permanent and permanent fillers.

Question 1

The appearance of which subtype of acne scar is most likely to benefit from filler injection?

(a) Hypertrophic scars.
(b) Ice-pick scars.
(c) Keloid scars.
(d) Rolling scars.
(e) None of the above.

Question 2

Which dermal filler is classified as 'temporary' in its duration of effect?

(a) Calcium hydroxylapatite
(b) Hyaluronic acid.
(c) Poly-L-lactic acid.
(d) Polymethylmethacrylate.
(e) Silicone.

Question 3

Which fillers are approved by the United States Food and Drug Administration for treatment of atrophic acne scars?

(a) Hyaluronic acid.
(b) Poly-L-lactic acid.
(c) Polymethylmethacrylate.
(d) All of the above.
(e) None of the above.

Question 4

Which filler has been trialled for topical use following fractional ablative laser resurfacing?

(a) Hyaluronic acid.
(b) Poly-L-lactic acid.
(c) Polymethylmethacrylate.
(d) All of the above.
(e) None of the above.

Question 5

Which of the following fillers does not have any evidence of use for acne scars?

(a) Polymethylmethacrylate.
(b) Hyaluronic acid.
(c) Polyacrylamide.
(d) Poly-L-lactic acid.
(e) Calcium hydroxylapatite.

Instructions for answering questions

This learning activity is freely available online at http://www.wileyhealthlearning.com/ced

Users are encouraged to

- Read the article in print or online, paying particular attention to the learning points and any author conflict of interest disclosures
- Reflect on the article
- Register or login online at http://www.wileyhealthlearning.com/ced and answer the CPD questions
- Complete the required evaluation component of the activity

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