REVIEW ARTICLE

Systematic Review of Clinical Trials of Small- and Large-Gel-Particle Hyaluronic Acid Injectable Fillers for Aesthetic Soft Tissue Augmentation

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BACKGROUND Hyaluronic acid (HA) is the most frequently injected filler for soft tissue augmentation in the United States.

OBJECTIVE To systematically review published evidence for aesthetic use of small- and large-gel-particle HA.

METHODS AND MATERIALS Clinical data on anatomic area, level of evidence, patient population, trial design, endpoints, efficacy, and safety were extracted from PubMed.

RESULTS Fifty-three primary clinical reports were analyzed. The highest-quality efficacy evidence was for the nasolabial folds (NLFs), with 10 randomized, blind, split-face, comparative trials. Several randomized, blind trials supported treatment of the glabella, lips, and hands. Lower-level evidence (from studies with nonrandomized, open-label, or retrospective designs) was recorded for the nasojugal folds (tear troughs), upper eyelids, nose, infraorbital hollows, oral commissures, marionette lines, perioral rhytides, temples, and cheeks. Common adverse events (AEs) across anatomic areas were pain, bruising, swelling, and redness. Serious AEs were uncommon (8 events in 8 patients of 4,605 total patients) and were considered to be unrelated (7 events) or probably unrelated (1 event) to treatment.

CONCLUSION The efficacy and safety of small- and large-gel-particle HA are well established for NLFs; evidence for the glabella, lips, and hands is more limited. Preliminary reports in other anatomic regions suggest efficacy without major complications.

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The overwhelming majority of aesthetic treatments performed in the United States are nonsurgical or minimally invasive aesthetic procedures. This represents a dramatic shift from almost 15 years ago. In 1997, 46% of aesthetic procedures were surgical, whereas in 2010, 83% of patient treatment sessions were nonsurgical.[1] Injectable products are used in 52% of these minimally invasive procedures; the rest are mostly chemical, mechanical, or laser techniques to rejuvenate the skin or remove hair.[1] In 2004, the first full year after approval of the first non–animal-based hyaluronic

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acid dermal filler Restylane (for North America: Medicis Pharmaceuticals. Scottsdale, AZ) (otherwise, Galderma/Q-Med. Upsulla, Sweden) in the United States, the majority of aesthetic injection procedures involved botulinum toxin A (2,837,346) and fewer procedures involved injection of HA gels (882,469).[2] In 2010, botulinum toxin A injections have decreased (2,437,165 procedures), and HA injections have increased (1,315,121 procedures). Strong growth in demand for minimally invasive procedures has continued despite recent economic weakness,[3] possibly because of lower per-procedure costs than for surgery and increased patient awareness.[4]

The ongoing proliferation of injectable materials for soft tissue augmentation in the United States in recent years has generated many questions about optimal use of these products for aesthetic applications. Hyaluronic acid products available in the United States or awaiting U.S. approval include Restylane (approved in 2003), Juvéderm (Allergan, Santa Barbara, CA; 2006), Perlane (Medicis Pharmaceuticals, Scottsdale, AZ; 2007), Prevelle Silk (Mentor Worldwide, Santa Barbara, CA; 2008), Belotero Balance (Merz Aesthetics, Inc., Frankfurt, Germany; 2011), and Emervel (Galderma, Lausanne, Switzerland; currently approved in Europe and undergoing clinical trials in the United States). U.S. Food and Drug Administration (FDA)-approved HA products are indicated for nasolabial fold (NLF; all products) and lip (Restylane) augmentation; all other uses of these products are considered off label. HA fillers are the most frequently used class of injectable products for soft tissue augmentation, accounting for 85% of such procedures in 2010.[1] In the rapidly advancing field of aesthetics, the development of new techniques involving HA fillers in clinical practice has expanded far beyond the labeled indications. As a result, the range of anatomic areas now treated using HA fillers has, in some cases, outpaced rigorous confirmation of efficacy and safety in clinical trials. Most randomized controlled HA clinical studies have been limited to injections of the NLFs, at least in part because there are validated scales for this area (Wrinkle Severity Rating Scale [WSRS],[5] Modified Fitzpatrick Wrinkle Scale [MFWS],[6] Wrinkle Assessment Scale [WAS][7]), although nonvalidated scales have often been used (Global Aesthetic Improvement Scale (GAIS), Numerical Rating Scale (NRS), Global Improvement Assessment (GIA), Phaseshift Rapid In Vivo Measurement of Skin (PRIMOS), and others). Few or no studies of similar quality have been reported for the lips, oral commissures, cheeks, and other areas. The level of evidence for efficacy and safety data in these other areas is often low, based mostly on practical experience and extrapolations from studies of NLF correction.

Small-gel-particle HA (SGP-HA; Restylane) was the first HA gel that the FDA approved (in 2003[8]). In this article, we focus on the safety, efficacy, reliability, and degree of patient satisfaction of reported aesthetic applications of SGP-HA and large-gel-particle HA (LGP-HA; Perlane). No recent article has focused on examining the extensive evidence that has accumulated for SGP-HA and LGP-HA. Thus, there is a need for an update that systematically synthesizes the current state of knowledge about the aesthetic use of SGP-HA and LGP-HA.

HA agents may be differentiated based on their physical properties, which are an important factor in determining appropriate clinical uses.[9–12] Variations exist in the methods for producing and purifying the starting material, cross-linking, and generating particles. SGP-HA and LGP-HA consist of well-defined gel particles that are formed by passing stabilized, cross-linked gel through screens with a specific pore size. They are well-characterized fillers that differ only in their particle sizes, not in their manufacturing processes or formulations. Both products are stiffer yet more elastic than other HA fillers, with viscoelastic properties that permit manipulation immediately after injection to optimize distribution, contour, and smoothness while maintaining

resistance to deformation and migration.[9–11] Greater stiffness and elasticity also aid in providing lift, volume, structural support, and definition to the injected area.[9]

Objective

The objective of this effort was to prepare a systematic review of published medical literature on aesthetic uses of SGP-HA and LGP-HA formulated with lidocaine, which are available in the United States. The review includes comparisons of anatomic area, level of evidence, patient population, trial design, endpoints, efficacy, and safety.

Methods

Articles indexed in PubMed were searched on June 21, 2011, using the following string: "hyaluron* AND (*esthetic* OR dermal OR aging OR rejuven* OR sculpt* OR contour* OR trough* OR lines OR rhytid OR rhytids OR rhytides OR creases OR crow's feet OR frown OR facial contouring OR facial sculpting OR glabella* OR commissure* OR lip OR lips OR augmentation OR cheek OR chin OR folds OR scar OR scars OR scarring OR hand OR prejowl sulcus OR marionette OR brows OR nose) NOT (joint OR knee OR *arthriti* OR adhesion* OR review [pt])." Results were limited to humans, clinical trial, letter, randomized controlled trial, case reports, clinical trial phase II, clinical trial phase III, clinical trial phase IV, comparative study, controlled clinical trial, and multicenter study. No limit based on year or language of publication was applied. The search returned 404 articles.

Manual review of the abstracts was performed to remove review articles and publications related to topics other than aesthetics (e.g., gastroenterology, oncology, ophthalmology). Articles that reported results of treatment with SGP-HA or LGP-HA were retained if they described clinical trials, letters, case reports, or case series. Additional references were identified by reviewing citations within the articles already retrieved and from the extensive bibliography of a recent proceedings report[13] and the authors' existing collections. Three manuscripts known to the authors to be in preparation or in press were also included. All selected articles were analyzed in detail. Levels of evidence were assigned according to criteria established by the Oxford Centre for Evidence-Based Medicine (Table 1).[14]

Results

Results of the literature extraction are summarized in Table 2. Overall, the levels of evidence ranged from high (1b, representing good quality randomized controlled trials) to low (4; e.g., case reports). The majority of patients were women (range 71–100%) in all studies but one, which was a trial of SGP-HA for cheek augmentation in men with facial lipoatrophy due to human immunodeficiency virus (HIV) infection.[15] The average age of the study populations was generally 45 to 55, with occasional participants outside that range. Few studies specifically examined treatment in patients with skin of color.[16–18] Prospective studies often employed a split-face design in areas of the face with contralateral symmetry, such as the NLFs; otherwise, a parallel-group design was more common. Randomized and blinded trials were common

TABLE 1. Oxford Centre for Evidence-Based Medicine Levels of Evidence (LOEs)[14]

LOE	*Criteria*
1b	Individual RCT (with narrow confidence interval)
2b	Individual cohort study (including low-quality RCT; e.g., <80% follow-up)
4	Case series (and poor-quality cohort and case–control studies)

RCT, randomized controlled trial.
Only LOEs assigned in this analysis are shown.

TABLE 2. Summary of Literature Survey Results

Anatomic Sites	N	*Level of Evidence*[14]	*Design*	*Duration*	*Age, Mean ± Standard Deviation*	*Female, n (%)*	*Treatment, n*	*Comparator Treatments, n*	*Efficacy Outcome Measures*	*Common AEs (%) in SGP-HA or LGP-HA Group*
Nasolabial folds										
Beer 2007[46]	15	1b	Randomized, patient and evaluator blind, split face*	6 months	53 ± 12	15 (100)	SGP-HA, 15*	Hylan B plus, 15*	WSRS, GAIS	Bruising, redness, swelling, pain, itching, nodules; no SAEs
Brandt 2010[47]	60	1b	Randomized, patient, treater, and sponsor blind, split face*	2 weeks	53.4 ± 8.0	56 (93.3)	LGP-HA-L, 60* LGP-HA, 60*	NA	GAIS	LGP-HA vs LGP-HA-L (patient reported): tenderness (82 vs 83), swelling (65 vs 70), bruising (55 vs 60), redness (52 vs 57), itching (20 vs 27); no SAEs
Carruthers 2005[48]	150	1b	Randomized, patient and evaluator blind, split face*	12 months	51.9 ± NR	140 (93.3)	LGP-HA, 150*	Hylan B, 150*	WSRS, GAIS, number of sessions, treatment volumes	Swelling (23), pain (20), redness (14); no SAEs
Levy 2009[44]	126	1b	Randomized, patient blind, split face*	NR	53 ± NR	122 (96.8)	LGP-HA, 126	24 mg/mL cohesive HA with 0.3% lidocaine, 126	None (British Pain Scale)	Redness (36), swelling (25), bruising (9); no SAEs
Lindqvist 2005[23]	68	1b	Randomized, patient and evaluator blind, split face*	12 months	49.4 ± NR	65 (95.6)	LGP-HA, 68*	Bovine collagen, 68*	WSRS, GAIS, NRS	Redness (11), pruritus (9), swelling (7); no SAEs

TABLE 2. Continued

Anatomic Sites	N	*Level of Evidence*[14]	*Design*	*Duration*	*Age, Mean ± Standard Deviation*	*Female, n (%)*	*Treatment, n*	*Comparator Treatments, n*	*Efficacy Outcome Measures*	*Common AEs (%) in SGP-HA or LGP-HA Group*
Moers-Carpi 2007[37]	205	1b	Randomized, evaluator blind, parallel	12 months	52 ± NR	185 (90.2)	LGP-HA, NR	24 mg/mL cohesive HA, calcium hydroxylapatite	WSRS, GAIS, patient satisfaction	NR; no SAEs
Moers-Carpi 2008[49]	60	1b	Randomized, evaluator blind, split face*	12 months	50.5 ± NR	52 (86.7)	SGP-HA, 60*	Calcium hydroxylapatite, 60*	WSRS, GAIS	Extrusion (2); no SAEs
Narins 2003[43]	138	1b	Randomized, patient and evaluator blind, split face*	6 months	54.3 ± NR	128 (93.4)	SGP-HA, 138*	Bovine collagen, 138*	WSRS, GAIS, number of sessions, treatment volumes	Swelling (87), redness (85), tenderness (78), pain (57), bruising (52), itching (30); no SAEs
Narins 2007,[24] Narins 2008a[25]	149	1b	Randomized, patient and evaluator blind, split face*	12 months	55.7 ± 8.3	137 (91.9)	SGP-HA, 149*	Porcine collagen, 149*	MFWS, GIA	Erythema (50), edema (28), induration (28), bruising (23); no SAEs
Narins 2008b[50]	75	1b	Randomized evaluator blind, split face*	18 months (interim report of 36-month study)	53.8 ± 8.4	70 (93.3)	SGP-HA touch-up at 4.5 vs 9 months, 75*	NA	WSRS, GAIS	Swelling (23), bruising (20); no SAEs
Nast 2011[40]	60	1b	Randomized, patient and evaluator blind, split face*	7 months	54.8 ± 8.8	52 (86.7)	LGP-HA, 60*	25 mg/g monophasic HA, 60*	WSRS, GAIS, patient satisfaction	Erythema (73), edema (43), combined for both treatments; no SAEs

TABLE 2. Continued

Anatomic Sites	N	*Level of Evidence*[14]	*Design*	*Duration*	*Age, Mean ± Standard Deviation*	*Female, n (%)*	*Treatment, n*	*Comparator Treatments, n*	*Efficacy Outcome Measures*	*Common AEs (%) in SGP-HA or LGP-HA Group*
Goldman 2007[53]	36	1b	Randomized, evaluator blind, split face*	8 weeks	50 ± 10	33 (91.7)	SGP-HA, 36* SGP-HA + laser, 36*	NA	WSRS, GAIS	Myocardial infarction (3), anemia (3), herpes virus reactivation (3), erythema (3), bruising (3), lump (3); 1 SAE (unrelated to treatment)
Narins 2010[51]	315	1b	Randomized, patient and evaluator blind, parallel group	12 months	55 ± NR	287 (91.1)	SGP-HA, 105	Polyacrylamide hydrogel, 210	WAS, GAIS	Edema (79), bruising (76), redness (58), tenderness (55), pain (34), itching (23); 1 SAE (unrelated to treatment)
Narins 2011[56¶]	52	1b	Randomized, evaluator blind, split face*	18 months extension (final report of 36-month study)	NR	NR	SGP-HA retreatment at 18 months (after touch-up at 4.5 vs 9 months), 40	NA	WSRS, GAIS	Nasopharyngitis (4); no SAEs
Prager 2010[26]	20	1b	Randomized, patient and evaluator blind, split face*	4 weeks	45.8 ± NR	19 (95.0)	SGP-HA, 20*	Cohesive polydensified matrix HA, 20*	PRIMOS, VAS for pain, patient recommendation of treatment	Erythema (30), ecchymosis (10); no SAEs
Rao 2005[52]	8	1b	Randomized, patient and evaluator blind, split face*	12 weeks	"Adult"	8 (100)	SGP-HA, 8*	Hylan B, 8*	Unnamed 5-point scale	Erythema, edema, ecchymosis, pinpoint bleeding; no SAEs

TABLE 2. Continued

Anatomic Sites	N	*Level of Evidence*[14]	*Design*	*Duration*	*Age, Mean ± Standard Deviation*	*Female, n (%)*	*Treatment, n*	*Comparator Treatments, n*	*Efficacy Outcome Measures*	*Common AEs (%) in SGP-HA or LGP-HA Group*
Yan 2009[54,55]	86	2b	Open label	6 months	43 ± NR	82 (95.3)	SGP-HA	NA	WSRS, GAIS	Injection-related reactions (16% of injections); no SAEs
Weiss 2010[57]	60	2b	Randomized, double blind, split face*	2 weeks	52.1 ± 6.6	58 (96.7)	SGP-HA, 60* SGP-HA-L, 60*	NA	GAIS, VAS for pain	Swelling (60 vs 67), tenderness (65 vs 68), bruising (52 vs 58); no SAEs
Hedén 2010[45]	42	2b	Randomized, double blind, split face*	12 months	54 ± NR	40 (95.2)	LGP-HA, 42* LGP-HA-L, 42*	NA	None (VAS for pain)	LGP-HA vs LGP-HA-L: swelling (86 vs 88), tenderness (72 vs 58), redness (58 vs 60), bruising (58 vs 49), itching (28 vs 26), postprocedural pain (23 vs 19); no SAEs
Arsiwala 2010[58]	30	4	Open-label case series	9 months	52 ± NR	22 (73.3)	SGP-HA, 15 LGP-HA, 10 Both, 5	NA	Persistence of correction by baseline wrinkle severity (modified WAS)	Transient erythema, and needle marks (80), bruising (8); no SAEs
Bosniak 2004[31]	1446	4	Open-label consecutive series	9 months	50.5 ± 10.2	1,029 (71.2)	SGP-HA, 1,020	NA	Unnamed 4-point scale (physicians), patient satisfaction	Transient erythema, infrequent bruising; no SAEs
Dayan 2010[41]	22	4	Blinded photographic observers	6–8 weeks	52.5 ± 9.6	21 (95.5)	SGP-HA, 19	NA	Positive first impression (various categories)	NA

TABLE 2. Continued

Anatomic Sites	N	*Level of Evidence*[14]	*Design*	*Duration*	*Age, Mean ± Standard Deviation*	*Female, n (%)*	*Treatment, n*	*Comparator Treatments, n*	*Efficacy Outcome Measures*	*Common AEs (%) in SGP-HA or LGP-HA Group*
Nasolabial folds with or without oral commissures										
Dover 2009,[75] Glogau 2008[59]	283	1b	Randomized, patient and evaluator blind, parallel	24 weeks	54 ± NR	266 (94.0)	SGP-HA, 142 LGP-HA, 141	NA	WSRS	Swelling (91 vs 92), tenderness (85 vs 92), redness (79 vs 81), bruising (74 vs 82), mass formation (55 vs 52), itching (45 vs 32); no SAEs
Taylor 2009,[17] Taylor 2010[18]	150	1b	Randomized, patient and evaluator blind, split face*†	24 weeks	NR	140 (93.3)	SGP-HA, 150* LGP-HA, 150*	NA	WSRS	Swelling (>50), tenderness (>50), redness (~50), bruising (~50), pain (~50); serious injuries (1)
Nasolabial folds, lips, and glabella										
Kanchwala 2005[42]	976	2b	Evaluator blind, retrospective chart review	≥ 12 months	43‡ ± NR	NR	SGP-HA, 86	Autologous fat, 697 Calcium hydroxyapatite, 141 Hylan B, 52	Longevity, touch-up rate, economic cost	Ecchymosis, swelling; no SAEs

TABLE 2. Continued

Anatomic Sites	N	*Level of Evidence*[14]	*Design*	*Duration*	*Age, Mean ± Standard Deviation*	*Female, n (%)*	*Treatment, n*	*Comparator Treatments, n*	*Efficacy Outcome Measures*	*Common AEs (%) in SGP-HA or LGP-HA Group*
Nasolabial folds, oral commissures, lips, and glabella										
Duranti 1998[76]	158	4	Open-label, consecutive series	8 months	36.8 ± NR	158 (100)	SGP-HA	NA	Unnamed 5-point scale	Transient redness (100), swelling (8); no SAEs
Nasolabial folds, oral commissures, marionette lines, and perioral rhytides										
Brandt 2011[61]	20	4	Open-label cohort	4 weeks	59.6 ± NR	20 (100)	SGP-HA, 20 LGP-HA, 18	NA	GAIS	Bruising (95), tenderness (50), swelling (40), redness (20); no SAEs
Oral commissures										
Bosniak 2004[31]	1446	4	Open-label, consecutive series	9 months	50.5 ± 10.2	1,029 (71.2)	SGP-HA, 352	NA	Unnamed 4-point scale (physicians), patient satisfaction	Transient erythema, infrequent bruising; no SAEs
Carruthers 2005[60]	15	4	Open-label cohort	6 months	40.5‡ ± 7.9	15 (100)	SGP-HA, 15	NA	Unnamed 4-point scale	Pain (100), redness (100), swelling (100), canker sore (20); no SAEs

TABLE 2. Continued

Anatomic Sites	N	*Level of Evidence*[14]	*Design*	*Duration*	*Age, Mean ± Standard Deviation*	*Female, n (%)*	*Treatment, n*	*Comparator Treatments, n*	*Efficacy Outcome Measures*	*Common AEs (%) in SGP-HA or LGP-HA Group*
Lips										
Downie 2009[22]	79	1b	Randomized, patient and evaluator blind, parallel	12 months	NR	79 (100)	LGP-HA, 23	Cross-linked porcine collagen, 19 Highly cross-linked porcine collagen, 19 Bovine collagen, 18	Lip volume, Catherine Knowles-Clark Scale, patient satisfaction	Cold sore (6); 1 SAE (unrelated to treatment)
Glogau 2011[62]	180	1b	Randomized, evaluator blind, parallel	9 months	47.6 ± 10.6	179 (99.4)	SGP-HA, 135	No treatment, 45	MLFS, GAIS	Swelling (58), contusion (bruising or ecchymosis; 44), tenderness (22), pain (21), erythema (17); 4 SAEs (3 unrelated to treatment, 1 probably unrelated)
Bousquet 1999[32]	192	4	Prospective, open-label, consecutive series	NR	46 ± NR	192 (100)	SGP-HA, 192	NA	Investigator opinion, patient satisfaction	Swelling (86), redness (52); no SAEs
Bosniak 2004[31]	1446	4	Open-label, consecutive series	9 months	50.5 ± 10.2	1,029 (71.2)	SGP-HA, 685	NA	Unnamed 4-point scale (physicians), patient satisfaction	Transient erythema, infrequent bruising; no SAEs
Jacono 2008[35]	66	4	Open-label, consecutive series	9 months	45.8 ± NR	62 (93.9)	SGP-HA, 66	NA	Patient satisfaction	Transient erythema, infrequent bruising; no SAEs

TABLE 2. Continued

Anatomic Sites	N	*Level of Evidence*[14]	*Design*	*Duration*	*Age, Mean ± Standard Deviation*	*Female, n (%)*	*Treatment, n*	*Comparator Treatments, n*	*Efficacy Outcome Measures*	*Common AEs (%) in SGP-HA or LGP-HA Group*
Glabella										
Carruthers 2003[27]	38	1b	Randomized, blinded, parallel	32 weeks	49 ± 8 and 52 ± 8	38 (100)	SGP-HA, 19 SGP-HA + onabotulinumtoxinA, 19	NA	FWS, GAIS	Tenderness, swelling; no SAEs
Kono 2008[65]	10	1b	Randomized, evaluator blind, split face	12 months	NR	10 (100)	SGP-HA, 10*		Unnamed 4-point scale, "Which side is better?"	NR; no SAEs
Bosniak 2004[31]	1446	4	Open-label, consecutive series	9 months	50.5 ± 10.2	1,029 (71.2)	SGP-HA after onabotulinumtoxinA, 185	NA	Unnamed 4-point scale (physicians), patient satisfaction	Transient erythema, infrequent bruising; no SAEs
Nasojugal fold (tear trough) and infraorbital hollows										
Steinsapir 2006[68]	164	4	Independent evaluator, retrospective chart review	2–3 weeks	Women, 43 ± 9 Men, 46 ± 10	130 (79.3)	SGP-HA, 164	NA	Unnamed 5-point scale	Focal fullness (6); no SAEs
Viana 2011[69]	25	4	Independent evaluator	8–15 months	46.1 ± 8.8	25 (100)	SGP-HA, 25	NA	Unnamed 4-point scale	Bruising (52), erythema (40), swelling (8); no SAEs
Kane 2005[36]	24	4	Case series	NR	41 ± NR	24 (100)	SGP-HA, 23	Hylan B, 1	Patient satisfaction	Temporary surface irregularities (100), erythema, swelling; no SAEs

TABLE 2. Continued

Anatomic Sites	N	*Level of Evidence*[14]	*Design*	*Duration*	*Age, Mean ± Standard Deviation*	*Female, n (%)*	*Treatment, n*	*Comparator Treatments, n*	*Efficacy Outcome Measures*	*Common AEs (%) in SGP-HA or LGP-HA Group*
Goldberg 2006[33]	155	4	Retrospective case series	≤16 months	53 ± NR	114 (73.5)	SGP-HA, 155	NA	Patient satisfaction	Bruising (27), lumpiness (15), fluid build-up (15), color change (10); no SAEs
Berros 2010[30]	26	4	Open-label case series	6 months	NR (range 36–53)	21 (80.8)	SGP-HA (via foam-tipped cannula)	NA	Patient satisfaction	Edema (21), lumpiness (14), ecchymosis (13); no SAEs
Upper eyelids										
Morley 2009[39]	27	4	Independent evaluator, retrospective case series	Mean, 13 months	51 ± NR	24 (88.9)	SGP-HA	NA	Unnamed 3-point scale, patient satisfaction	Bruising (100), swelling (100); no SAEs
Nose										
Han 2006[34]	11	4	Case series	>1 year (6 patients)	NR (range 25–57	NR	SGP-HA + fibroblasts, 11	NA	VAS scale for patient satisfaction	NR; no SAEs
Bray 2010[70]	8	4	Case series	NR	NR	NR	SGP-HA, 8	NA	None	Bruising, edema, swelling, tenderness, redness; no SAEs
Lambros 2011[73]	40	4	Case series	NR	NR	NR	SGP-HA, NR	24 mg/mL cohesive, highly cross-linked HA	None	Bruising (~30); no SAEs
Moradi 2011[38]	20	4	Case series	NR	48 ± NR	20 (100)	SGP-HA, 20	NA	Patient satisfaction	Tenderness, bruising; no SAEs

TABLE 2. Continued

Anatomic Sites	N	*Level of Evidence*[14]	*Design*	*Duration*	*Age, Mean ± Standard Deviation*	*Female, n (%)*	*Treatment, n*	*Comparator Treatments, n*	*Efficacy Outcome Measures*	*Common AEs (%) in SGP-HA or LGP-HA Group*
Midface or cheeks										
Bertucci 2012[21]	40	2b	Open-label, evaluator-blind cohort	24 weeks	53.1 ± 7.0	34 (85.0)	LGP-HA-L, 40	NA	MMVS, GAIS	Upper respiratory tract infection (18), headache (13), injection site mass (10), injection site pain (5); no SAEs
Denton 2007[15]	18	4	Open-label, evaluator-blind consecutive series	12 months	47.2 ± NR	0 (0)	LGP-HA, 18	NA	5-point lipoatrophy scale, 7-point physician- and patient-rated improvement	Erythema (29), discomfort (29), implant palpability (29), telangiectasia (14); no SAEs
Face in general[§]										
Odunze 2007[16]	60	4	Retrospective patient series	≥6 months	56 ± NR	56 (93.3)	SGP-HA, 60	NA	Incidence of and time to touch-up	Lip angioedema (2), inclusion cyst (2); no SAEs
Olenius 1998[74]	113	4	Open-label cohort	6 months (12 months [some patients])	NR	106 (93.8)	SGP-HA, 113	NA	VAS for degree of correction or satisfaction (physicians and patients)	Redness, red spots, and swelling (7); no SAEs
Hands										
Man 2008[28]	10	1b	Randomized, patient and evaluator blind, split hand*	6 months	NR	10 (100)	SGP-HA, 10*	Human collagen, 10*	5-point VAS for vein clearance, patient tolerability and satisfaction	Pain, tingling, bruising; no SAEs

TABLE 2. Continued

Anatomic Sites	N	*Level of Evidence*[14]	*Design*	*Duration*	*Age, Mean ± Standard Deviation*	*Female,* n *(%)*	*Treatment,* n	*Comparator Treatments,* n	*Efficacy Outcome Measures*	*Common AEs (%) in SGP-HA or LGP-HA Group*
Brandt 2012[29]	16	4	Open-label cohort	12 months	60.1 ± 5.3	16 (100)	SGP-HA, 16	NA	4-point scales for prominence of veins, tendons, and bones, and loss of skin turgor; GAIS; patient satisfaction; patient self-perceived hand age	Itching (6); no SAEs

AE, adverse event; FWS, Facial Wrinkle Scale; GAIS, Global Aesthetic Improvement Scale; GIA, Global Improvement Assessment; HA, hyaluronic acid; LGP-HA, large gel particle HA; LGP-HA-L, large gel particle HA formulated with lidocaine; MLFS, Medicis Lip Fullness Scale; MFWS, Modified Fitzpatrick Wrinkle Scale; MMVS, Medicis Midface Volume Scale; NA, not applicable; NR, not reported; NRS, Numerical Rating Scale; PRIMOS, Phaseshift Rapid In Vivo Measurement of Skin; SAE, serious AE; SD, standard deviation; SGP-HA, small gel particle HA; SGP-HA-L, small gel particle HA formulated with lidocaine; VAS, visual analog scale; WAS, Wrinkle Assessment Scale; WSRS, Wrinkle Severity Rating Scale.

*Each patient received study treatment on 1 side and active comparative treatment on the other side.

†This study was originally planned to use blinded evaluators but then changed to use nonblinded investigator assessments for efficacy.

‡Median.

§Including cheek, forehead, glabella, lips, marionette lines, nasolabial folds, oral commissures, perioral areas, infraorbital areas, and tear troughs.

¶This study is a continuation of the 75 patients in Narins 2008b,[50]

Generic and proprietary names of filler products other than SGP-HA and LGP-HA: bovine collagen (Zyplast), calcium hydroxylapatite (Radiesse), 24 mg/mL cohesive, highly crosslinked HA (Juvéderm Ultra), 24 mg/mL cohesive, highly crosslinked HA with 0.3% lidocaine (Juvéderm Ultra 3), 24 mg/mL cohesive, more highly crosslinked HA (Juvéderm Ultra Plus), cohesive polydensified matrix HA (Belotero Basic), double-crosslinked HA (Puragen), human collagen (CosmoPlast), hylan B (Hylaform), hylan B plus (Hylaform Plus), less crosslinked porcine collagen (called PRI 1), 25 mg/g monophasic HA (Teosyal 27G Deep Lines), more crosslinked porcine collagen (called PRI 2), polyacrylamide hydrogel (Aquamid Hydrogel), porcine collagen (also called Dermicol P-35; Evolence).

for the NLFs but were less common in other areas. Follow-up periods ranged from 2 weeks to 36 months.

Comparative and noncomparative studies were found during the systematic review; the majority of evidence supporting the use of HA products focuses on augmentation of NLFs, with less evidence for use in other anatomic areas (e.g., hands, nasojugal fold, temples, upper eyelids) (Table 2).

Challenges in synthesizing results of different studies included wide variation in the endpoints used (Table 3), timing of patient assessments, and how results were reported. In addition, in a number of studies, it was unclear what primary efficacy endpoint was intended. Validated scales included the WSRS,[5] MFWS,[6] WAS,[7] the Medicis Lip Fullness Scale (MLFS),[19] the Medicis Midface Volume Scale,[20,21] and the Catherine Knowles-Clark scale.[22] Nonvalidated scales included the widely accepted GAIS and less-commonly encountered instruments such as the NRS,[23] GIA,[24,25] PRIMOS,[26] and Facial Wrinkle Scale (FWS).[27] However, even the widespread use of the GAIS was confounded by variation in its implementation; for example, some studies did not report worsening as a possible outcome, assigned slightly different names for numerically equivalent scores, or had different numbers of available steps for rating improvement. Ad hoc 3-, 4-, 5- and 8-point scales were used in some studies, as well as simple queries such as "Which side [of the 2 corresponding treated areas] is better?" For the hands, efficacy was assessed using 4- and 5-point scales that were intended to measure visibility of subcutaneous features such as veins, tendons, bones, and overall loss of turgor, as well as patient satisfaction and perception of their hands' apparent age.[28,29] For the lips, direct measurement of volume has been used to assess efficacy.[22] Patient satisfaction was an endpoint in many studies.[22,28–40] A unique endpoint in one study was "first impressions" of a panel of lay assessors who viewed photographs of patients after treatment.[41]

Treatment durability was measured by endpoints such as number of sessions in a given period and frequency of touch-up[42,43]; related to this was analysis of economic efficiency.[42] Two studies reported solely on level of pain rather than aesthetic efficacy.[44,45]

Findings are described below according to anatomic area. Commonly anticipated adverse events (AEs) were similar in the studies surveyed (Table 2); these AEs included local reactions at the injection sites such as swelling (induration, edema), bruising (ecchymosis, contusion [sometimes termed "hematoma"]), pain (tenderness, discomfort), redness (erythema), and itching (pruritus). These kinds of AEs, which are expected with filler injections,[13,44] were not reported in all of the studies surveyed.

Nasolabial Folds

Most studies evaluated the safety and efficacy of correction of the NLFs; these studies generally had a split-face design, in which each patient received one treatment on the left side and a different treatment on the right side. The NLFs alone were treated in 21 unique studies (24 articles),[23–26,37,41,43,44,46–55] including 17 randomized controlled trials with level 1b evidence[23–26,37,40,43–53,56,57] and four studies with level 2b or 4 evidence.[31,41,54,55,58] Treatment arms included 14 SGP-HA alone, one SGP-HA plus laser therapy, one SGP-HA formulated with lidocaine, eight LGP-HA, two LGP-HA formulated with lidocaine (LGP-HA-L), and one SGP-HA plus LGP-HA. Additional evidence supporting the use of HA products for the treatment of NLFs alone or in combination with other anatomic areas in the upper (e.g., glabella) and lower (e.g., oral commissures, lips, others) face is summarized in Table 2.

Adverse effects of treatment were generally those expected to occur, including needle marks or pinpoint bleeding; erythema or redness; itching or pruritus; swelling, edema, or induration; pain or tenderness; injection-related reactions; and bruising or ecchymosis. Several articles made no mention of

TABLE 3. Efficacy Assessment Methods Used in the Studies

Assessment	*Used for*	*Possible Score (best to worst)*	*Validated*
Wrinkle Severity Rating Scale[17,23,37,43,46,48–50,53–55,59,75]	Nasolabial folds with or without oral commissures	1 = Absent 2 = Mild 3 = Moderate 4 = Severe 5 = Extreme	Yes[5]
Modified Fitzpatrick Wrinkle Scale[24,25]	Nasolabial folds	0 = No wrinkle 0.5 = Very shallow yet visible wrinkle 1 = Fine wrinkle 1.5 = Visible wrinkle and clear indentation 2 = Moderate wrinkle 2.5 = Prominent and visible wrinkle 3 = Deep wrinkle	Yes[6]
Global Aesthetic Improvement Scale*[21,23,27,29,37,40,43,46–51,53–57,61,62]	Nasolabial folds, glabella, oral commissures, marionette lines, lips, lower face, midface, and hands	+4 = Complete improvement +3 = Substantial improvement +2 = Definite improvement +1 = Some improvement 0 = Unchanged −1 = Slight worsening −2 = Moderate worsening −3 = Marked worsening −4 = Very marked worsening	No
Global Improvement Assessment[24,25]	Nasolabial folds	1 = Much better 2 = Better 3 = No change 4 = Worse	No
Numerical Rating Scale[23]	Nasolabial folds	100–0% Improvement	No
Wrinkle Assessment Scale[51]	Nasolabial folds	0 = No wrinkles 1 = Just perceptible wrinkles 2 = Shallow wrinkles 3 = Moderate deep wrinkles 4 = Deep wrinkles, well-defined edges 5 = Very deep wrinkles, redundant fold	Yes
Facial Wrinkle Scale[27]	Glabella	0 = None 1 = Mild 2 = Moderate 3 = Severe	No
Phaseshift Rapid In Vivo Measurement of Skin[26]	Nasolabial folds	Mean wrinkle depth	No
Medicis Lip Fullness Scale[62]	Lips	5 = Very full 4 = Full 3 = Medium 2 = Thin 1 = Very thin	Yes[19]

TABLE 3. Continued

Assessment	*Used for*	*Possible Score (best to worst)*	*Validated*
Medicis Midface Volume Scale[21]	Midface	1 = Fairly full midface 2 = Mild loss of fullness 3 = Moderate loss of fullness 4 = Substantial loss of fullness	Yes
Lip volume[22]	Lips	NA	No
Catherine Knowles-Clark scale[22]	Lips	*Size* 2 = Extremely full 1 = Full 0 = Medium −1 = Thin −2 = Very thin *Vermilion body* −1 = Tight, almost unlined 0 = Rounded, natural lines 1 = Less rounded, fine lines 2 = Flattening, moderate wrinkles 3 = Severe wrinkles *Vermilion border* −1 = Protruding 0 = Distinct and intact 1 = Distinct but broken by fine lines 2 = Indistinct and broken by moderate lines 3 = Indistinct and severely lined	No
"Which side is better?"[65]	Glabella	Left Right	No
"Would you recommend treatment of one side, the other side, both sides, or neither side?"[26]	Nasolabial folds	Yes No	No
Unnamed 4-point scale[65]	Glabella	3 = Significant improvement 2 = Moderate improvement 1 = Mild improvement 0 = No improvement	No
Unnamed 5-point scale[52]	Nasolabial folds	5 = Complete disappearance 4 = Moderate disappearance 3 = Minimal disappearance 2 = No change 1 = Worse	No
Unnamed 5-point scale[76]	Nasolabial folds, oral commissures, lips, and glabella	Overcorrection Marked improvement Moderate improvement Slight improvement No improvement	No

TABLE 3. Continued

Assessment	*Used for*	*Possible Score (best to worst)*	*Validated*
Unnamed 4-point scale[60]	Oral commissures	4 = Superb improvement 3 = Moderate improvement 2 = Slight improvement 1 = No difference	No
Unnamed 5-point scale[68]	Nasojugal fold (i.e., tear trough)	4 = Very remarkable 3 = Remarkable difference 2 = Moderate difference 1 = Slight difference 0 = No difference	No
Unnamed 4-point scale[69]	Nasojugal fold (i.e., tear trough)	0 = Best result 1 2 3 = Worst result	No
Unnamed 3-point scale[39]	Upper eyelids	1 = Improved 0 = No change −1 = Worse	No
Unnamed 8-point scale[15]	Midface	7 = Dramatic improvement 6 5 4 4 3 1 0 = No improvement	No
5-point VAS[28]	Hands	5 = Complete clearance of veins 4 = Moderate disappearance 3 = Minimal disappearance 2 = No change 1 = Worse	No
Patient satisfaction and tolerability[28]	Hands	*Satisfaction* 5 = Complete clearance of veins 4 = Moderate disappearance 3 = Minimal disappearance 2 = No change 1 = Worse *Tolerability* 0 = No discomfort 1 = Mild discomfort 2 = Moderate discomfort 3 = Severe discomfort	No
4 Different visual severity scales[29] Vascular prominence Bony prominence Tendon prominence Loss of skin turgor	Hands	0 = Undetectable 1 = Mild 2 = Moderate 3 = Severe	No
Patient self-perception of age of the hands[29]	Hands	Mean values	No

TABLE 3. Continued

Assessment	*Used for*	*Possible Score (best to worst)*	*Validated*
No. of sessions and treatment volumes[43,48]	Nasolabial folds	Mean values	No
Longevity, touch-up rate, economic cost[42]	Nasolabial folds, lips, and glabella	Mean values	No
Incidence of and time to touch-up[16]	Face in general	Mean values	No
Positive first impression (various categories)[41]	Nasolabial folds	10 = Strongest agreement to 1 = Strongest disagreement for social skills, academic performance, dating success, occupational success, attractiveness, financial success, relationship success, and athletic success	No
British Pain Scale[44]	Nasolabial folds	1 = No pain to 10 = Extreme pain	No
VAS for pain[26]	Nasolabial folds	0 = No pain to 10 = Maximum imaginable pain	No
Patient satisfaction[37]	Nasolabial folds	Yes or no for various categories (would you recommend, beneficial to you, feel more attractive, emotional well-being better, more confidence)	No
Patient satisfaction[40]	Nasolabial folds	1 = Very satisfied 2 = Satisfied 3 = Moderately satisfied 4 = Dissatisfied 5 = Very dissatisfied	No
Patient satisfaction[36]	Nasojugal folds	NR	No
Patient satisfaction[33]	Infraorbital hollows	Satisfied Not satisfied	No
Patient satisfaction[39]	Upper eyelids	Satisfied Not satisfied	No
Patient satisfaction[31]	Nasolabial folds, glabella, lips, oral commissures	Very satisfied Satisfied Unsatisfied	No
Patient satisfaction[32]	Lips	Very satisfied Satisfied Unsatisfied	No
Patient satisfaction[35]	Lips	5 = Most satisfied 4 3 2 1 = Dissatisfied	No

TABLE 3. Continued

Assessment	*Used for*	*Possible Score (best to worst)*	*Validated*
Patient satisfaction[34]	Nose	5 = Excellent 4 3 2 1 = Unsatisfied	No
Patient satisfaction[38]	Temples	NR	No
Patient satisfaction[22]	Lips	Very satisfied Satisfied Neither satisfied or dissatisfied Dissatisfied Very dissatisfied	No
Patient satisfaction[33]	Infraorbital hollows	Yes or no	No
Patient satisfaction[39]	Upper eyelids	Yes or no	No

NA, not applicable; NR, not reported; VAS, visual analog scale.
*Implementation varied in number of categories, names of categories, and whether worse appearance was reported as a possible outcome.

such events.[37,49,53,56] Nodules were noted in one study of SGP-HA and hylan B gel, although the incidence was not reported, and the product(s) that caused the effect was (were) not identified.[46] An SGP-HA injection rate greater than 0.3 mL/min was found to increase the risk of AEs significantly.[59] Two serious AEs (myocardial infarction and osteoarthritis of the thumb) were observed in patients treated with SGP-HA, but neither was considered treatment related.[51,53] Two of 150 patients in a study of SGP-HA and LGP-HA experienced serious injuries, but the types of injury and their relationship to treatment were not described.[17]

Oral Commissures, Lips, Marionette Lines, and Lower Face

Oral commissures were treated using SGP-HA in three studies[31,60,61] that had only level 4 evidence, although one of those studies included a large number of patients (n = 352) injected in this area.[31] Efficacy in the oral commissures was assessed using the GAIS, unnamed 4-point scales, and patient satisfaction. Safety in this area was good; the most common AEs were expected injection-related pain, redness, and bruising. Three of 15 patients in a study of SGP-HA reported "canker sores" after injection around the oral commissures.[60]

The lips were more extensively examined in five studies,[22,31,32,35,62] including two randomized controlled trials with level 1b evidence[22,62] and three studies with level 4 evidence.[31,32,35] Treatment arms in studies of the lips included SGP-HA (4 studies)[31,32,35,62] and LGP-HA (1 study).[22,62] Pain, swelling, and bruising were common. "Cold sore" was reported as the most frequent AE in the study of LGP-HA.[22] The authors proposed that disruption of the dermis during injection may have increased the likelihood of herpes virus infection. Similar sores have not been commonly reported elsewhere with use of SGP-HA and LGP-HA, except the previously mentioned canker sores in the oral commissures,[60] although labeling for SGP-HA and LGP-HA includes precautions that injection in patients with a history of previous herpetic eruption may be associated with reactivation of the herpes virus.[63,64] Five of the 1,101 patients injected in the lips had serious treatment-emergent AEs that did not appear directly attributable to the filler injections; four events (diverticulitis, lumbar spinal stenosis, miscarriage, and pneumococcal pneumonia) were judged to be

unrelated to treatment, and one event (mild, transient ischemic attack) was considered to be probably unrelated.[22,62]

Glabella

Three studies included treatment of the glabella: one of SGP-HA monotherapy,[65] one of SGP-HA concurrent with onabotulinumtoxinA,[27] and one of SGP-HA after onabotulinumtoxinA therapy.[31] Two of the studies were randomized controlled trials with level 1b evidence,[27,65] although the number of patients was small for each of these (36 and 10 patients); the other study had level 4 evidence.[31] The authors concluded in one article that injection of onabotulinumtoxinA followed by SGP-HA was more effective than SGP-HA alone in this area of vigorous muscular activity.[27] In these studies of the glabella, only expected AEs, such as erythema, swelling, tenderness, and occasional bruising, were observed, and no serious AEs were reported,[27,31,65] although glabellar necrosis due to accidental arterial embolization or compression is a significant concern with any type of filler[66] and has been reported with SGP-HA, although rarely.[67]

Nasojugal Folds and Upper Eyelids

The nasojugal folds, also called tear troughs, and infraorbital hollows were treated using SGP-HA in five studies with level 4 evidence.[30,33,39,68,69] Injection of SGP-HA in the upper eyelids was reported in a single interventional case series with level 4 evidence.[39] AEs such as erythema, swelling, fullness, edema, fluid build-up, and lumps were often reported. Lumpiness resulting in contour irregularities could be reduced using massage, hyaluronidase injections, or touch-up with more HA.[30,33,36,68,69] Bruising was common,[33,69] but was reported to be reduced with the use of a special foam-tipped cannula for injection of SGP-HA in the infraorbital hollows.[30] This 25-g cannula is designed with a rigid base to permit ease of handling and contains a foam end designed to decrease the amount of trauma associated with delivery of HA product. Persistent malar swelling, although not common (5/155 patients), was a troublesome complication in some patients in the largest study of nasojugal fold treatment[33]; AEs of color change (darkening) in the injected area were reported in 3% to 10% of patients.[30,33] Other occasional complications (<1% of patients) in one study included asymmetry, cellulitis, and migraine, without clarification of the relationship to treatment.[68] Cellulitis resolved within a few days after administration of warm compresses and oral antibiotics. Bruising was universal in the 27 patients injected in the upper eyelid but was easily managed and resolved within days; in contrast to previously mentioned reports, no discoloration was reported.[39] One patient injected in the upper eyelids had blepharoplasty 5 months later and 1 month after that developed acute, bilateral swelling, possibly related to swimming with goggles; the swelling resolved after hyaluronidase was injected.[39] No serious AEs were reported when the nasojugal folds and upper eyelids were treated with SGP-HA.

Nose

Evidence for treatment of the nose was limited to two small case series with level 4 evidence.[34,70] In one study, patients received SGP-HA alone[70]; in the other study, they received injections of SGP-HA with fibroblasts.[34] In one study, anticipated redness, swelling, edema, tenderness, and bruising were reported[70]; the other study mentioned only mild dorsal deviation in one patient, which the authors suggested resulted from asymmetric injection.[34] No serious AEs were reported in these small studies, although it has been proposed that the nasal ala may be susceptible to necrosis based on a case series of patients injected with HA for facial augmentation.[71] Furthermore, two cases have been published of ischemic complications after nasal tip HA injections in patients after rhinoplasty; it was suggested that the previous surgery may have diminished blood flow to the nose, rendering it susceptible to ischemia.[72]

Temples, Cheeks, Midface, and Face in General

Injection of SGP-HA to volumize the temples was reported in two studies with level 4 evidence.[38,73]

Volumizing of the midface or cheeks was performed using LGP-HA-L in one study (level 2b evidence)[21] and with LGP-HA in another study in the setting of HIV-associated facial lipoatrophy (level 4 evidence).[15] Multiple facial areas were injected with SGP-HA in two studies with level 4 evidence.[16,74] AEs commonly reported in the studies included redness, erythema, swelling, edema, tenderness, discomfort, and bruising; red spots (noted at 6/285 injection sites in 106 patients) were attributed to entrapment of hemoglobin. Telangiectasia and implant palpability were noted in two and four of 18 treated patients, respectively, after injection of LGP-HA in the cheeks[15] but were not observed with any injections in the other anatomic areas. No serious AEs were reported in these studies.

Hands

Two studies of SGP-HA injection in the hands were found,[28,29] one of which was a randomized controlled trial with level 1b evidence,[28] but the number of patients was small in both studies (10 and 16, respectively). Common AEs include pain, itching, tingling, and bruising; no serious AEs were reported. Although transient swelling is commonly observed with injection of dermal fillers, it was not reported in either of these two small studies related to hand augmentation.

Patients With Skin of Color

Four reports (3 clinical studies) analyzed results separately in patients with skin of color.[16–18,62] A study of SGP-HA augmentation in multiple facial areas concluded that efficacy and safety were comparable in patients with fair (Fitzpatrick type I–III; $n = 40$) and dark (Fitzpatrick type IV–VI; $n = 20$) skin.[16] No keloids or dyspigmentation occurred; the authors suggested that their consistent use of a middermal depth for injection of the fillers may have enhanced tolerability in dark-skinned patients.[16] Another study examined SGP-HA and LGP-HA correction of NLFs with and without oral commissures in 150 patients with Fitzpatrick skin type IV to VI.[17,18] The authors concluded that the efficacy in their study of dark-skinned patients was similar to that in the registration studies of SPG-HA and LPG-HA, in which most patients were fair skinned.[17,18] None of the 150 patients developed keloids; postinflammatory hyperpigmentation developed in three patients and resolved in two of them[17]; there was no difference in the pattern of commonly reported AEs between patients with skin of color and white patients.[17] A study of SGP-HA for lip augmentation found a similar pattern of MLFS response in patients with Fitzpatrick skin type I to III and type IV to VI.[62]

Discussion

This systematic review of the medical literature on aesthetic applications of SGP-HA and LGP-HA identified a large number of treated anatomic areas of the face and hands. Effective treatment was demonstrated for the NLFs, glabella, hands, and lips; preliminary evidence of effectiveness was available for other areas. The overall safety profiles were mostly similar in the different treated areas, although care must be taken when injecting areas where vascular occlusion or bruising are concerns. HAs have the additional advantage over other fillers that implantation can be reversed with injection of hyaluronidase, which may be more convenient than surgical excision. Results with SGP-HA and LGP-HA appeared reliable and predictable for different anatomic areas and regardless of skin color.

As expected, the strongest evidence for use of SGP-HA and LGP-HA was in the NLFs, which were studied in an overwhelming majority of published randomized controlled trials. This is partly because the symmetry of the NLFs facilitates implementation of blinded studies in which the patients serve as their own controls and partly because the long, prominent crease of the NLF is easily scored to assess treatment effect. SGP-HA and LGP-HA have been used in this area with good success. On validated scales (WSRS, MFWS, WAS) and the widely accepted, nonvalidated GAIS, most patients were responders (had

improvement of at least 1 step on the scale 6 months after treatment in all studies, indicating good persistency in this anatomic area). WSRS response rates ranged from 70% to 85% for SGP-HA[18,43,46,54,55,75] and 63% to 75% for LGP-HA.[18,48,75] The MFWS response rate in a single study of 149 patients was 98% for SGP-HA[24]; in another study of SGP-HA, 88% of 315 patients were responders on the WAS.[51] Response rates for the GAIS were 73% to 90% for SGP-HA[49,51,54,55] and 64% for LGP-HA.[37]

Treatment of the lips, glabella, and hands is also supported, with one or two randomized controlled trials for each area, although studies of the hands involved small numbers of patients. SGP-HA is the only HA approved for lip augmentation and has been used in all three areas,[27–29,31,32,35,42,62,76] and LGP-HA has been studied for lip augmentation.[22] The validated MLFS has been used to score responses in the lips, with encouraging results for SGP-HA at 6 months (70% of patients with improvement of ≥ 1 grade) in an area of high mobility and in which treatment goals are more sophisticated than simply filling a crease.[62] SGP-HA has recently received FDA approval for submucosal implantation to achieve lip augmentation in patients aged 21 and older; it is the only HA with this indication.[63] For the glabella, it appears that SGP-HA is best combined with injection of botulinum toxin type A. This is not surprising considering the strong muscular contractions that occur in this region and was reflected in a relatively rapid rate of relapse (in this case, defined as return to baseline FWS score) when SGP-HA was used without the myoparetic agent.[27] In addition, fillers must be used judiciously in the densely muscular glabellar complex owing to the risk of ischemia and resultant necrosis because this is a watershed area of blood supply; thus, the total filler injection volume that may be safely injected is limited.[66] Necrosis associated with injection of a dermal filler has also been reported for the nasal alar region.[77] Necrosis can occur from external pressure on arterioles from the filler agent superseding the pressure flow through the vessel or from frank intravascular injection. For these reasons, it is necessary not only to use low volumes of filler in the glabella but also to watch carefully for any sign of blanching during the injection process.

Evidence for injections in other areas of the face is not as robust, but preliminary reports appear to indicate some level of effectiveness, with commonly reported AEs related to the injection procedure generally similar to those in other anatomic regions. SGP-HA was used more often than LGP-HA around the eyes and nose; SGP-HA also was used for the temples, sometimes in a highly diluted, high-volume form.[38,73] Duration of effect appeared particularly long for injections to the nose (18–30 months),[56,70] perhaps reflecting the mechanically static nature of this area or low rate of tissue turnover, and might be a subcision effect of the needle itself separating fibrous and muscular banding, as has been observed in separate reports when subcision alone was used to treat a nose scar and forehead wrinkles[78] or when subcision was used with a filler to correct skin defects after Mohs micrographic surgery.[79] Nevertheless, even for the more-mobile NLFs, recent data from Narins and colleagues have shown that some patients (21/63 [33%] patients who completed the study) injected with SGP-HA maintained full correction through 18 months or longer with two to three treatments.[50] Furthermore, the volumes used at subsequent sessions were lower than for the initial treatment.[56] A possible reason suggested for this persistence was de novo collagen biosynthesis initiated by stretching of the tissue (observed in an earlier study[80]) that received the implant.

Simultaneous treatment of multiple areas in some studies and the use of numerous different assessment tools, many of which are not validated, complicate comparisons of effectiveness between treatment areas. Comparisons of safety between anatomic areas are likewise difficult. Nonetheless, the safety profiles of SGP-HA and LGP-HA, other than the exceptions noted in the Results section above, appear consistent across anatomic areas and exhibit a low incidence of serious complications. The vast majority of the AEs were those that would be expected after injection of

any filler material (bruising, swelling, tenderness, redness, and itching). Some reports appear to have omitted these types of AEs entirely. Rapid injection rates, injection techniques that increased the dissection of the subepidermal plane (e.g., fanlike injection), and higher volumes of material used were demonstrated to increase the risk of AEs in a prospective analysis in 283 patients randomized to receive injections in the NLFs and oral commissures with SGP-HA or LGP-HA.[59] As the product instructions for use recommend, decreasing injection rates to a speed of no more than 0.3 mL/min may help reduce the occurrence of local AEs after injection.[63,64] Lumps or irregularities occurred most often in areas where the skin is thin, particularly in the nasojugal folds and infraorbital hollows.[30,33,36] These are sensitive areas that require special care to minimize not only lumps, but also bruising and color changes (e.g., blue discoloration) that may occur when injections are too superficial. In vitro testing has shown that SGP-HA is more readily degraded than a 24-mg/mL HA gel (Juvéderm Ultra; for North America: Medicis Pharmaceuticals. Scottsdale, AZ; otherwise, Galderma/Q-Med. Upsulla, Sweden). using exogenous ovine hyaluronidase.[81] In theory, this would mean that problematic SGP-HA injections could be more easily reversed than injections of the 24-mg/mL gel, but confirmation through well-designed studies is needed. Serious AEs were rarely reported (8 events in 8 patients out of 4,605 total patients)[17,51,53,62] and were judged to be unrelated to treatment (7 events)[17,51,53,62] or probably unrelated to treatment (1 event).[62]

Conclusions

SGP-HA and LGP-HA have been injected in a wide variety of anatomic regions with the goal of aesthetic improvement. Heterogeneity in study designs and assessment methods complicate comparisons of studies. Robust multistudy synthesis of efficacy data will be possible only if there is greater uniformity in assessment methods and reporting of results in the future. Efficacy and safety are well established for the NLFs; corresponding data exist for the glabella, hands, and lips but are considerably more limited. Rigorous evidence is lacking in other anatomic regions, but initial reports suggest efficacy without major complications. Serious AEs were uncommon. Treatment of young patients, elderly adults, and patients of color is not well characterized, although HA products are not FDA approved for use in patients younger than 18, and elderly patients are less likely to seek out these treatment options. Good-quality clinical studies are needed to clearly demonstrate the relative benefits and risks of SGP-HA and LGP-HA (as well as their lidocaine formulations) in areas other than the NLFs.

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