

Combined Treatment for Skin Rejuvenation and Soft-tissue Augmentation of the Aging Face

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ABSTRACT

Multiple types of anti-aging treatments are required to address the various etiologies of facial aging. Soft-tissue augmentation provides a minimally invasive option for patients seeking to look younger. However, due to changes in facial skin, musculature, fat and bone, anti-aging treatment requires a multifaceted approach. Injectable fillers may be combined with neurotoxins to resolve superficial wrinkles and restore facial volume. These modalities may be used with laser resurfacing or chemical peels to address epidermal and superficial dermal problems. Combining injectable soft-tissue augmentation treatments allows clinicians and patients to take advantage of the benefits of each modality and to address the multiple effects of facial aging. This review is based on clinical experience and a MEDLINE search for articles about volume replacement and soft-tissue augmentation. It provides a rationale that supports the use of combination techniques/products for soft-tissue augmentation.

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INTRODUCTION

Changes to the aging face result from a dynamic process involving thinning of the skin and loss of collagen, fat redistribution, muscular recontouring and bone remodeling.¹⁻³ The rate of change differs in the major facial compartments (skin, muscle, fat and bone) and changes in one compartment affect all compartments.^{1,3} With increasing age, more prominent wrinkles, folds and furrows arise due to further loss of skin elasticity and structural organization.^{1,3}

Many patients require more than one type of aesthetic treatment to address these multiple etiologies and maximize treatment outcomes.^{2,4,5} The variety of available treatments has greatly expanded the ability to reverse the visual signs of facial aging. Because each modality has its own strengths and limitations, combinations of products may be required to achieve optimal outcomes. The purpose of this article is to briefly review available soft-tissue augmentation modalities and to discuss relevant clinical experience with possible combinations of products.

Head-to-head comparisons have not been identified for most combinations mentioned in this review. Further combinations of anti-aging treatments described herein have not been reviewed or approved by the U.S. Food and Drug Administration (FDA).

Anti-aging Treatments

Numerous treatments are available for soft-tissue augmentation (Table 1). Each treatment, used appropriately, can help restore the youthful appearance of the face; the selection of treatments with complementary modes of action may produce

a synergistic effect. Furthermore, application of different modalities can be varied either spatially or temporally, potentially optimizing outcomes and improving tolerability.

Botulinum Toxin Type A

Injection with botulinum toxin type A (BTX-A; Botox®, Allergan, Irvine, CA, and Dysport® [abobotulinum toxin A], Medicis, Scottsdale, AZ) results in temporary denervation and relaxation of injected muscles and reduction in dynamic furrows and lines.^{6,7} BTX-A has been used widely to treat the glabellar area, crow's feet and forehead.⁴ Overcorrection must be avoided, as the full effect may not be apparent for seven to 10 days post-injection and persists for 90–120 days with BTX-A;⁴ and up to 180 days with abobotulinum toxin A.⁷ The safety record of BTX-A is good and most adverse events (AEs) are reversible without long-term consequences;⁶ an AE profile similar to placebo was noted with abobotulinum toxin A.⁷ Botulinum toxins may be used with volumizing treatments to enhance outcomes.

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TABLE 1.

Comparison of Injectable Anti-aging Treatments^a

	Onset of Effect	Mode of Operation	Current Indicated Areas	Duration of Effect	Benefits	Adverse Events
Radiofrequency	4–12 weeks	Collagen contraction, collagen synthesis	Protuberant jowls, neck skin, nasolabial folds, eyebrows	Several months	Generally safe, limited downtime, depending on specific device	Common: pain Rare: fat atrophy
Neurotoxins	3–4 days	Muscular relaxation	Dynamic lines and wrinkles, mostly in glabella	3–4 months	Rapid results	Common: headache, respiratory infection, and blepharoptosis
Collagens	Immediate	Volume and collagen replacement	Soft-tissue contour deficiencies, including wrinkles and acne scars	3–6 months	Bovine: reliable, contains lidocaine, ease of administration Human: no allergy testing required	Bovine: hypersensitivity or allergic reactions, skin testing prior to use, reactivation of herpes possible with lip injection Human: rare but can include bruising, erythema, and swelling
Hyaluronic Acid Derivatives	Immediate	Water retention	Moderate to severe facial wrinkles and folds, including nasolabial folds	3–12 months, depending on formulation	Reliable, well tolerated, no allergy testing required. Longer lasting than bovine collagen	Common injection-site AEs: temporary pain, induration, bruising, tenderness, itching, edema, and erythema. Serious AEs rare
Intense Pulsed Light	1 month	Wavelengths between 550 and 1100 nm	Lentigines, telangiectasis	6–9 months	Improvement of skin texture and irregular pigmentation	Slight erythema and edema, immediately after treatment
Calcium Hydroxylapatite	Immediate	Hypothesized collagen stimulation	Moderate to severe facial wrinkles and nasolabial folds, facial lipoatrophy in people with HIV	12 months	Long-term results, no allergy testing required, no concern for antigenic or inflammatory reactions	Injection-site bruising, edema. Nodules rarely develop if injected superficially
Injectable PLLA	Gradual	Hypothesized foreign-body reaction, collagen stimulation	Shallow to deep nasolabial fold contour deficiencies and other facial wrinkles	Up to 2 years	Safe, long-term results	Most common AEs injection-related. Serious AEs infrequent; injection-site nodule, granuloma, erythema, pain, inflammation, edema, hypersensitivity, and pruritus
PMMA	Rapid to gradual	Collagen component gets absorbed over short term. PMMA microspheres form permanent scaffold	Deep defects, glabella, nasolabial folds	Permanent	Longevity	Reports of persistent erythema at injection site

TABLE 1 CONT'D.

Comparison of Injectable Anti-aging Treatments^a

	Onset of Effect	Mode of Operation	Current Indicated Areas	Duration of Effect	Benefits	Adverse Events
Ablative Laser	1–2 weeks	Thermal in superficial dermis; wound-healing response	Fine and some coarse wrinkles and overall dyspigmentation, dark discolored under-eye circles, and skin texture		Improved appearance of photoinduced rhytides and dyschromia	Oozing, bleeding, infections. Downtime. Potential serious AEs: postinflammatory pigmentary changes, scarring
Nonablative Laser		Primarily thermal, focused in dermis	Fine wrinkles and skin texture		Limited downtime. Superficial layers spared	Inconsistent. Common AEs usually transient: erythema, periocular edema, skin bronzing
Chemical Peels	Depends on depth of peel	Chemical exfoliant	Superficial: mild actinic damage, wrinkling, dyschromia, actinic keratoses, and active acne. Medium-depth: severe dyschromia, moderate rhytidosis, laxity, photoaged skin, actinic keratoses	Variable	Improved skin texture	Increased downtime with deeper peels

^aReferences 4,6,13,14,17,18,21,23-28,35,36,44,47-50.

AEs=adverse events; HIV=human immunodeficiency virus; PLLA=poly-L-lactic acid; PMMA=polymethyl methacrylate.

Chemical Peels

Glycolic, trichloroacetic and salicylic acid peels are commonly used for treating photodamage and other superficial skin problems.⁴ Superficial chemical peels exfoliate the top layers of skin, where they are generally well tolerated and require little, if any, recovery time. Deeper peels stimulate epidermal growth, and dermal synthesis of collagen and elastin fibers;⁸ they are used primarily to treat severe dyschromia, moderate rhytidosis, actinic keratoses, moderate to severe skin laxity and photoaged skin. Deeper peels require at least five days for recovery and require post-peel home care.⁴ Peels are very effective at improving overall skin appearance; their effect lasts for weeks to months, depending on the depth and chemical used.⁹

Short- and Long-acting Dermal Fillers

Availability of the treatment options listed in Table 1 increased the opportunities for clinicians to correct age-related contour deficiencies. Preclinical studies showed that, in addition to physically occupying space, dermal fillers stretch fibroblasts, stimulate growth factors, and inhibit collagen breakdown, leading to formation and deposition of new collagen.^{10,11} Typically, dermal fillers avoid many of the risks of surgery while restoring

volume, providing a more relaxed, natural facial appearance compared with traditional “face-lift” surgery.^{5,12}

Collagen loss is a cardinal feature of aging skin. Collagen replacement can restore a more youthful appearance. Bovine-derived collagen requires skin testing before use due to possible hypersensitivity reactions.^{13,14} Collagen-based fillers have been used to correct facial lines, wrinkles and contour deficiencies,¹⁴ with immediate effects that last three to five months.¹⁵

Hyaluronic acid is a natural component of skin that provides structure and volume;¹⁶ its loss leads to dermal dehydration and wrinkle formation.¹⁶ Hyaluronic acid-based fillers are commonly used in mid to deep dermal implantation for correction of moderate-to-severe facial wrinkles and folds, including nasolabial folds.^{17,18} The effect of hyaluronic acid injection is immediate, with an average duration of approximately nine months.^{19,20} The most common AEs are injection-site related;¹⁷ hyaluronidase can quickly correct many AEs.^{17,21}

CaHA is a biocompatible mixture of an aqueous gel carrier and synthetic CaHA microparticles.^{15,22-24} After injection, the gel is

absorbed and the microparticles form a scaffold for collagen formation;^{23,25} the effect is immediate and lasts for approximately 12–14 months.²³ It is indicated for subdermal implantation for correction of moderate-to-severe facial wrinkles and folds, including nasolabial folds, with a wide variety of off-label facial aesthetic applications and is generally well tolerated.²³

Injectable poly-L-lactic acid (PLLA; Dermik Laboratories, a business of sanofi-aventis U.S. LLC) contains microparticles of PLLA, which is a biocompatible biodegradable synthetic polymer.^{22,26,27} Implantation of solid particles in pre-clinical studies indicated that PLLA may induce a foreign-body response that is hypothesized to lead to gradual collagen formation with effects lasting up to two years.²⁸ Injectable PLLA must be reconstituted with 5 mL sterile water, allowed to hydrate for at least two full hours before use, and used within 72 hours.²⁶ Reconstitution volumes of up to 10–12 mL have been utilized for some off-label procedures, such as hand and neck augmentation.^{29,30} In clinical practice, it is also relatively common to add 1–2 mL of lidocaine with epinephrine with 3 mL of diluent to increase patient comfort during the procedure.²⁹ However, reconstitution of injectable PLLA with volumes greater than 5 mL, and with lidocaine, is considered off label. Reconstituted product should be agitated immediately before and during administration to maintain an even suspension throughout the procedure.²⁶

Injectable PLLA is approved for use in immune competent people as a single regimen for correction of shallow-to-deep nasolabial fold contour deficiencies and other facial wrinkles in which a deep dermal grid pattern injection technique is appropriate.²⁶ It has been used off label to increase volume and to reposition several facial areas, and on the hands, chest and neck.^{31,32} The most common AEs are injection-related;^{26,33} serious AEs are infrequent and include injection-site nodules and papules.^{26,33}

Injectable polymethyl methacrylate (PMMA, Artefill®, Suneva Medical, San Diego, CA) is a suspension of 20% PMMA smooth microspheres in bovine collagen.²¹ The collagen is degraded within about three months post-injection, after which collagen forms around the permanent microspheres.²¹ Injectable PMMA is indicated for treatment of nasolabial folds, but has been used off label for glabellar frown lines, radial lip lines and mouth corners. The most common AE in clinical trials with injectable PMMA was unevenness at the injection site that continued for more than one month.³⁴ Other AEs included persistent (more than 48 hours) swelling or erythema, increased skin sensitivity, and rash and pruritus.³⁴

Ablative Therapy

Ablative laser devices are considered the non-surgical standard for improving clinical features of aging.³⁵ Techniques vary by type of laser, amount of energy emitted, pulse mode, and number of passes.⁴ In general, ablative laser resurfacing vaporizes

the epidermis and portions of the papillary dermis. Induced wounds promote a healing response, resulting in collagen formation and deposition.³⁵ After re-epithelialization, wrinkles, scars and blemishes are removed.^{4,35} Prolonged downtime for healing may be problematic, depending on the patient's lifestyle and tolerance of the effects.

Non-ablative Laser and Other Treatments

Non-ablative therapies have become popular as patients and clinicians look for procedures that avoid the complications and downtime associated with ablative lasers. Non-ablative lasers induce dermo-thermal injury through a cascade reaction of molecular repair, collagen formation and deposition without epithelial damage; there is minimal healing time.^{4,35} However, aesthetic results are less consistent and predictable than with ablative devices,³⁵ although modest improvement in fine wrinkling and skin texture has been reported.⁴

Fractional resurfacing creates microscopic thermal zones that represent columns of photocoagulation spatially distinct from areas of unexposed skin that assist in rapid re-epithelialization.³⁶ The procedure has been used for a variety of indications, including facial and non-facial photodamage, atrophic acne scars, hypopigmented scars and dyspigmentation.³⁶ Common AEs are usually transient and include erythema, periorcular edema and bronzing of the skin.³⁶

Intense pulsed light (IPL) therapy uses broad-spectrum (both visible and infrared) light to treat pigmentation and vascular problems associated with chronic photodamage.³⁵ Vascular lesions such as rosacea, erythema, flushing, telangiectasias and postlaser erythema respond well to IPL therapy.⁴

FIGURE 1. Before (left) and after (right) a single treatment with a combination of abobotulinum toxin A in the mentalis (10 units), glabella (40 units), and crow's feet (50 units), and hyaluronic acid (Restylane) (1 mL divided between right and left nasolabial creases, and 1 mL divided between right and left marionette lines).



FIGURE 2. Before (left) the third fractionated laser treatment, followed one week later by 3 mL of hyaluronic acid (Perlane) divided between the zygoma, nasolabial folds, and the marionette lines. This was followed nine months later by further hyaluronic acid (3 mL divided between right and left zygoma, nasolabial folds, and marionette lines), and botulinum toxin A (mentalis, five units; glabella, 25 units; periorbital area, 25 units). The after photo (right) was taken after a further Fraxel treatment six weeks later.



FIGURE 3. Before (left) and after (right) combination treatment with calcium hydroxylapatite and cross-linked hyaluronic acid. Four treatments with calcium hydroxylapatite were given at intervals of two weeks, three months and three weeks (total volume 5.4 mL, divided between nasolabial folds and marionettes). The after photo was taken after treatment with cross-linked hyaluronic acid (0.8 mL into upper and lower lips and upper lip lines) seven weeks after the last treatment with calcium hydroxylapatite.



Radiofrequency (RF) devices use impedance to convert electrical energy into heat.³⁵ Therapeutic energy levels are unknown³⁵ the critical temperature for collagen shrinkage and repair ranges from 57–75°C, depending on duration of application.³⁵ The epidermis is cooled before RF administration to preserve superficial skin layers.³⁵ RF devices have been used for treatment of periorbital rhytids, as well as thermalifting of the face, neck and brows.⁴

Recently, infrared technology has proven safe and effective in reducing facial and neck skin laxity. In one study, mobile delivery of infrared (1100–1800 nm) light significantly improved skin laxity ($P < 0.0001$), with all subjects grading the procedure as “painless.” Erythema, which subsided within one to three hours, was the only reported AE.³⁷

FIGURE 4. Before (left) a combination of nonanimal-source hyaluronic acid, botulinum toxin A, and injectable PLLA injections, and six full-face Fraxel treatments spread over two years. Hyaluronic acid was injected into the nasolabial folds, cheeks, and perioral area; one vial of injectable PLLA was injected into the temples and cheeks (reconstituted with bacteriostatic water 4 mL, and 2% lidocaine without epinephrine 2 mL); botulinum toxin was injected into the glabella, frontalis, and periorbital areas (25 units per area). The after photograph (right) was taken 12 months after treatment with injectable PLLA.



Combining Anti-aging Therapies

When considering combination therapy, it is essential to formulate criteria for determining which combinations may benefit specific patients. This includes evaluating areas affected by the aging process, the extent and location of volume loss and/or severity of rhytids in each target area, and the AE profile of each considered agent. Equally important in the treatment plan is assessment of the patient's goals and expectations, timeframe, and tolerance for therapy; budgetary constraints should also be discussed and addressed before initiating treatment.²⁸

BTX-A has been used in combination with chemical peels, various dermal fillers and fractional resurfacing.⁸ One common combination is BTX-A injections for the upper face (including fine horizontal forehead lines and crow's feet) plus soft-tissue augmentation for the mid and lower face. Combined use of BTX-A and filling agents can restore facial appearance by complementary modes of operation; relaxation and volume enhancement.⁵ The devices are used in the same facial area, for example, to treat marionette or lipstick lines.^{38,39} BTX-A has been used in addition to fillers for adjustment of brow height, smoothing of forehead lines and nasojugal folds, and resetting of facial contours.⁵ The effect of combination of abobotulinum toxin A with hyaluronic acid (Restylane) is shown in Figure 1, and combination with fractionated laser resurfacing and hyaluronic acid is shown in Figure 2.

Non-ablative lasers, IPL and RF devices immediately following BTX-A injection have proven effective for treatment of either the glabellar area or crow's feet without loss of efficacy or other apparent negative effect.⁴⁰ BTX-A has also been used with laser resurfacing, RF and fractional ablative (CO_2) resurfacing.^{4,6}

CaHA and hyaluronic acid have been used synergistically to replace facial volume.⁴¹ In one study, CaHA was used in the nasolabial folds, perioral and vermillion lip borders, while

hyaluronic acid was used to complement the effect of CaHA as well as to augment the upper and lower lip body adjacent to the wet-dry border.⁴¹ Overall, subjects in the combination group tended to have higher immediate and overall treatment satisfaction scores than those receiving monotherapy.⁴¹ Combination of hyaluronic acid, collagen and injectable PLLA has been used to correct nasolabial folds, lips, the bridge of the nose and corners and body of the mouth.¹⁴ Combination of cross-linked hyaluronic acid (Juvéderm) and CaHA in a patient from this practice is shown in Figure 3.

Another combination for soft-tissue augmentation may be injectable PLLA—which provides a more gradual onset and greater longevity of effect—together with agents that provide immediate but short duration of effect, such as hyaluronic acid or collagens. In a case study,⁴² injectable PLLA was used as a foundation for correcting mid-facial and temporal atrophy; hyaluronic acid was used to augment the lips, oral commissures and nasolabial folds and BTX-A was used to reduce mid-facial vertical compression.⁴² Unfortunately, this report focused on the technique, and did not include outcomes. The effect of combination of injectable PLLA and a nonanimal-source hyaluronic acid is demonstrated in Figure 4. Injectable PLLA also may be combined with chemical peels; because the modalities stimulate collagen differently, synergistic effects are theoretically possible.

Dermal fillers combined with laser, IPL and RF treatments have the potential to restore tissue volume and improve facial firmness and texture.⁴³ Some physicians administer laser therapy before injecting filler material due to concern that the laser will degrade the filler. However, a small study in 36 patients suggests that laser, RF and IPL therapies may be administered immediately after hyaluronic acid injection with no AEs.⁴³

Similarly, a small study was designed to assess the safety of RF treatment in six subjects recently treated with both hyaluronic acid and CaHA in their upper inner arm.⁴⁴ One subject served as a control and did not receive any RF treatment. After two weeks all except the control subject received two non-overlapping passes of RF treatment; three days later several assessment techniques were unable to distinguish between active and control treatments.⁴⁴ Subjects who received fillers plus RF noted a significant short-term tenderness, whereas the control subject did not.⁴⁴ Additional studies are required to assess the potential impact of more passes, lower fluence and lidocaine, and the short- and long-term efficacy.

Potential Disadvantages of Combined Anti-aging Treatments

For combination treatments, it is generally recommended that individual procedures be performed at least one week apart to allow for resolution of any AEs. Reactions that may leave the skin tender and sensitive to further manipulation, for example,

could interfere with post-procedure recommendations (e.g., deep facial massage) following injection of CaHA or injectable PLLA. It is also recommended to wait at least one or two days between a chemical peel and injection of BTX-A to minimize complications, although some practitioners may administer both treatments simultaneously. Superficial glycolic acid peels are generally administered in six sessions at four-week intervals; the specific timing of peels in conjunction with fillers or BTX-A injections depends on the patient's responses and the practitioner's level of experience.⁸

One potential concern with combination of multiple products is the increased risk of AEs, and increased difficulty of determining causality when events do occur. Injection-site reactions (e.g., pain, bruising, erythema, swelling) and papule and nodule formation have been reported with all fillers; bovine-derived collagen is also associated with a risk of hypersensitivity reactions.^{14,15,42,45} Although there is currently no clinical evidence demonstrating higher rates of AEs in patients receiving combination treatment versus single therapies, it is good clinical practice to ensure that patients are informed about all possible AEs associated with each treatment and that appropriate steps are taken to minimize any such effects.⁴⁶

CONCLUSION

The availability of an ever-increasing variety of injectable agents has made selection of facial anti-aging treatments more complex. Patients appreciate the minimal invasiveness and shorter recovery times, while physicians appreciate the versatility of modalities and the multitude of areas that can be corrected. Combining modalities can enable physicians to take advantage of the benefit of each modality and address the entire spectrum of facial aging. In the hands of an experienced clinician, and in appropriately selected patients, prudent use of combination treatment for soft-tissue augmentation can tailor therapy to optimize aesthetic outcomes.

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Dr. Beer is a consultant, speaker and/or advisor for Allergan, Johnson & Johnson, Medicis Pharmaceutical Corporation and sanofi-aventis U.S. He is a shareholder and director of The

Cosmetic Bootcamp LLC, and of Theraplex LLC. At any given time, Dr. Beer may be a shareholder of Allergan, Inc., Bioform Medical, Inc., Johnson & Johnson and Medicis Pharmaceutical Corporation.

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