

Combined Therapy Optimizes Facial Rejuvenation

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PALM BEACH, FLA. — Technical tips to optimize use of injectable facial fillers and botulinum toxin were offered during a live patient demonstration at the annual meeting of the Florida Society of Dermatology and Dermatologic Surgery.

A natural-looking result is the goal. "We want to return patients to what they looked like when they were younger. That

is what our patients want," Dr. Mark S. Nestor said. "Really, the idea is combining [products], such as Botox and some of these fillers, to get optimal results."

An initial patient assessment should include realistic expectations. Know what fillers can and cannot achieve. "What you see as a physician may be different than what a patient is concerned about. When you have done this for a while, it's interesting to look at why something bothers patients," said Dr. Nestor of Aventura, Fla.

Along with Dr. James M. Spencer and Dr. Joely Kaufman, Dr. Nestor treated a series of volunteers at the meeting with combined treatments of injectable fillers and botulinum toxin.

Treatment was halted for one person who experienced an adverse reaction. She was tilted back in the chair while ice was applied to her forehead. "She is having a vasovagal response, which is not that uncommon," Dr. Nestor said. "This happened in South Beach [at a meeting in Feb-

ruary 2007]. Patients need to be laid back, and they will come out of it quickly."

The newest filler option is Perlane (hyaluronic acid, Medicis), which was approved by the Food and Drug Administration in May for correction of moderate to severe facial folds and wrinkles. Perlane's nonimmunogenic, stabilized hyaluronic acid gel particles are similar to Restylane (hyaluronic acid, Medicis) but larger. Perlane adds volume to restore surface contour in facial wrinkles and folds, including the nasolabial fold. The product should be injected into the deep dermis up to the superficial layer of the subcutis.

Dr. Nestor injected Perlane with a 27-G needle. "You can actually feel the filler going in. What you are seeing right away is the significant lift you get because this product is really robust."

After injecting the nasolabial folds, he massaged inside and outside of the mouth to get an even distribution, noting that "Perlane smooths out very, very nicely." The next step involved superficial injections of Restylane on top of the same area. He finished the treatment with botulinum toxin injections to the crow's feet area.

Perlane can also be injected to accentuate areas below the mouth, said Dr. Nestor, who disclosed a relationship with Medicis.

While treating another volunteer, he noted that Perlane can replace significant volume loss in the midcheek for an extended period. "It doesn't roll off. Studies have shown it can remain there 5 or 6 years."

In contrast, Dr. Nestor advised under-correction of volume loss when using Juvederm Ultra (hyaluronic acid gel, Allergan). "The idea here is that you can always inject more. You don't want to inject too much to begin with." He typically injects the filler as he withdraws the syringe. "You can feel it going into the deeper aspect of the dermis."

Dr. Kaufman injected another volunteer with Juvederm. Another option would be Sculptra (poly-L-lactic acid, Sanofi-Aventis). "By using Sculptra, you would need less hyaluronic acid in the nasolabial folds," said Dr. Kaufman of the University of Miami. The direction of product flow can make a big difference. For marionette lines, for example, she injects downward toward the center of the face below a patient's mouth. In addition, one little bolus of hyaluronic acid right under the vermilion border on either side of the mouth "really turns the lip up," she said.

Another combination approach uses injection of Radiesse (calcium hydroxylapatite, BioForm Medical) to restore facial volume and botulinum toxin to lift the corners of the mouth, said Dr. Spencer, who has a skin cancer and cosmetic dermatology practice in St. Petersburg, Fla.

Dr. Spencer used a 27-G needle and a 1.3-cc syringe during the demonstration. Radiesse is "more viscous, so it takes a little more effort to inject," he said. Threading or serial puncture down are the two technique options. "I always see them back in a week to make sure everything is okay." He estimated that the volume enhancement with Radiesse will last 1-2 years.

Dr. Kaufman and Dr. Spencer had no relevant disclosures regarding the products used in the demonstration. ■



BRIEF SUMMARY

For Dermatologic Use Only—Not for Ophthalmic, Oral, or Intravaginal Use
Rx only

CONTRAINDICATIONS

FINACEA® Gel, 15%, is contraindicated in individuals with a history of hypersensitivity to propylene glycol or any other component of the formulation.

WARNINGS

FINACEA® Gel, 15%, is for dermatologic use only, and not for ophthalmic, oral, or intravaginal use.

There have been isolated reports of hypopigmentation after use of azelaic acid. Since azelaic acid has not been well studied in patients with dark complexion, these patients should be monitored for early signs of hypopigmentation.

PRECAUTIONS

General: Contact with the eyes should be avoided. If sensitivity or severe irritation develops with the use of FINACEA® Gel, 15%, treatment should be discontinued and appropriate therapy instituted. The safety and efficacy of FINACEA® Gel, 15%, has not been studied beyond 12 weeks.

Information for Patients: Patients using FINACEA® Gel, 15%, should receive the following information and instructions:

- FINACEA® Gel, 15%, is to be used only as directed by the physician.
- FINACEA® Gel, 15%, is for external use only. It is not to be used orally, intravaginally, or for the eyes.
- Cleanse affected area(s) with a very mild soap or a soapless cleansing lotion and pat dry with a soft towel before applying FINACEA® Gel, 15%. Avoid alcoholic cleansers, tinctures, and astringents, abrasives, and peeling agents.
- Avoid contact of FINACEA® Gel, 15%, with the mouth, eyes and other mucous membranes. If it does come in contact with the eyes, wash the eyes with large amounts of water and consult a physician if eye irritation persists.
- The hands should be washed following application of FINACEA® Gel, 15%.
- Cosmetics may be applied after FINACEA® Gel, 15%, has dried.
- Skin irritation (e.g., pruritus, burning, or stinging) may occur during use of FINACEA® Gel, 15%, usually during the first few weeks of treatment. If irritation is excessive or persists, use of FINACEA® Gel, 15%, should be discontinued, and patients should consult their physician (See ADVERSE REACTIONS).
- Avoid any foods and beverages that might provoke erythema, flushing, and blushing (including spicy food, alcoholic beverages, and thermally hot drinks, including hot coffee and tea).
- Patients should report abnormal changes in skin color to their physician.
- Avoid the use of occlusive dressings or wrappings.

Drug Interactions: There have been no formal studies of the interaction of FINACEA® Gel, 15%, with other drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term animal studies have not been performed to evaluate the carcinogenic potential of FINACEA® Gel, 15%. Azelaic acid was not mutagenic or clastogenic in a battery of *in vitro* (Ames assay, HGPRT in V79 cells [Chinese hamster lung cells], and chromosomal aberration assay in human lymphocytes) and *in vivo* (dominant lethal assay in mice and mouse micronucleus assay) genotoxicity tests.

Oral administration of azelaic acid at dose levels up to 2500 mg/kg/day (162 times the maximum recommended human dose based on body surface area) did not affect fertility or reproductive performance in male or female rats.

Pregnancy: Teratogenic Effects: Pregnancy Category B

There are no adequate and well-controlled studies of topically administered azelaic acid in pregnant women. The experience with FINACEA® Gel, 15%, when used by pregnant women is too limited to permit assessment of the safety of its use during pregnancy.

Dermal embryofetal developmental toxicology studies have not been performed with azelaic acid, 15%, gel. Oral embryofetal developmental studies were conducted with azelaic acid in rats, rabbits, and cynomolgus monkeys. Azelaic acid was administered during the period of organogenesis in all three animal species. Embryotoxicity was observed in rats, rabbits, and monkeys at oral doses of azelaic acid that generated some maternal toxicity. Embryotoxicity was observed in rats given 2500 mg/kg/day (162 times the maximum recommended human dose based on body surface area), rabbits given 150 or 500 mg/kg/day (19 or 65 times the maximum recommended human dose based on body surface area) and cynomolgus monkeys given 500 mg/kg/day (65 times the maximum recommended human dose based on body surface area) azelaic acid. No teratogenic effects were observed in the oral embryofetal developmental studies conducted in rats, rabbits, and cynomolgus monkeys.

An oral peri- and postnatal developmental study was conducted in rats. Azelaic acid was administered from gestational day 15 through day 21 postpartum up to a dose level of 2500 mg/kg/day. Embryotoxicity was observed in rats at an oral dose that generated some maternal toxicity (2500 mg/kg/day; 162 times the maximum recommended human dose based on body surface area). In addition, slight disturbances in the postnatal development of fetuses was noted in rats at oral doses that generated some maternal toxicity (500 and 2500 mg/kg/day; 32 and 162 times the maximum recommended human dose based on body surface area). No effects on sexual maturation of the fetuses were noted in this study. Because animal reproduction studies are not always predictive of human response, this drug should be used only if clearly needed during pregnancy.

Nursing Mothers:

Equilibrium dialysis was used to assess human milk partitioning *in vitro*. At an azelaic acid concentration of 25 µg/mL, the milk/plasma distribution coefficient was 0.7 and the milk/buffer distribution was 1.0, indicating that passage of drug into maternal milk may occur. Since less than 4% of a topically applied dose of azelaic acid cream, 20%, is systemically absorbed, the uptake of azelaic acid into maternal milk is not expected to cause a significant change from baseline azelaic acid levels in the milk. However, caution should be exercised when FINACEA® Gel, 15%, is administered to a nursing mother.

Pediatric Use: Safety and effectiveness of FINACEA® Gel, 15%, in pediatric patients have not been established.

Geriatric: Clinical studies of FINACEA® Gel, 15%, did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ADVERSE REACTIONS

Overall, treatment related adverse events, including burning, stinging/tingling, dryness/tightness/scaling, itching, and erythema/irritation/redness, were 19.4% (24/124) for FINACEA® Gel, 15%, and 7.1% (9/127) for the active comparator gel at 15 weeks.

In two vehicle controlled, and one active controlled U.S. clinical studies, treatment safety was monitored in 788 patients who used twice daily FINACEA® Gel, 15%, for 12 weeks (N=333) or for 15 weeks (N=124), or the gel vehicle (N=331) for 12 weeks.

Table 3. Cutaneous Adverse Events Occurring in ≥1% of Subjects in the Rosacea Trials by Treatment Group and Maximum Intensity*

	FINACEA® Gel, 15% N=457 (100%)			Vehicle N=331 (100%)		
	Mild n=99 (22%)	Moderate n=61 (13%)	Severe n=27 (6%)	Mild n=46 (14%)	Moderate n=30 (9%)	Severe n=5 (2%)
Burning/ stinging/ tingling	71 (16%)	42 (9%)	17 (4%)	8 (2%)	6 (2%)	2 (1%)
Pruritus	29 (6%)	18 (4%)	5 (1%)	9 (3%)	6 (2%)	0 (0%)
Scaling/dry skin/xerosis	21 (5%)	10 (2%)	5 (1%)	31 (9%)	14 (4%)	1 (<1%)
Erythema/ irritation	6 (1%)	7 (2%)	2 (<1%)	8 (2%)	4 (1%)	2 (1%)
Contact dermatitis	2 (<1%)	3 (1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)
Edema	3 (1%)	2 (<1%)	0 (0%)	3 (1%)	0 (0%)	0 (0%)
Acne	3 (1%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)

*Subjects may have >1 cutaneous adverse event; thus, the sum of the frequencies of preferred terms may exceed the number of subjects with at least 1 cutaneous adverse event.

FINACEA® Gel, 15%, and its vehicle caused irritant reactions at the application site in human dermal safety studies. FINACEA® Gel, 15%, caused significantly more irritation than its vehicle in a cumulative irritation study. Some improvement in irritation was demonstrated over the course of the clinical studies, but this improvement might be attributed to subject dropouts. No phototoxicity or photoallergenicity were reported in human dermal safety studies.

In patients using azelaic acid formulations, the following additional adverse experiences have been reported rarely: worsening of asthma, vitiligo depigmentation, small depigmented spots, hypertrichosis, reddening (signs of keratosis pilaris), and exacerbation of recurrent herpes labialis.

Post-marketing safety—Skin: facial burning and irritation; Eyes: iridocyclitis on accidental exposure with FINACEA® Gel, 15%, to the eye (see PRECAUTIONS).

OVERDOSAGE

FINACEA® Gel, 15%, is intended for cutaneous use only. If pronounced local irritation occurs, patients should be directed to discontinue use and appropriate therapy should be instituted (See PRECAUTIONS).

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