

Choosing the Right Filler Comes With Experience

BY KERRI WACHTER

BOSTON — Cosmetic dermatologists have the knowledge and training to choose the right fillers that will garner the best results, according to Dr. Mary Lupo.

"Every FDA-approved filler, in my opinion, has an appropriate indication. You just need to know the relative strengths and weaknesses," said Dr.

Lupo, at the American Academy of Dermatology's Academy 2009 meeting.

Optimal results require an appropriate candidate, the choice of an appropriate product based on the patient's presentation, injection of a sufficient amount of product, the right complementing procedures, and maintenance of the effect with touch-ups, said Dr. Lupo, professor of dermatology at Tulane University in New Orleans.

Treating Older Patients

In general, older patients need more volume restoration, because their immune response is decreased. "So when one has an active filler, such as poly-L-lactic acid, the older patient may have less of an immune response to give you a final result," she said. However, the corollary is that the older patient may require so much volume with other fillers that it becomes financially unfeasible.

"Older patients always need complementing procedures to get a good result," she said.

When examining the defect being considered for correction, decide whether it is a line or a fold. Lines require less viscous fillers to avoid lumpiness. "When a skin fold is more redundant, however, you need a thicker, more structural filler in order to lift the fold." When working with folds, Dr. Lupo recommends improving the area superior to the fold in addition to filling the fold.

When talking with the patient, "it's important to point out that it really doesn't do much good to fill a line if the overall photoaging is so severe and the 'canvas of the skin' is so mottled and deformed that it will not give an overall improvement," she said. Fillers can be used adjunctively with other methods to achieve better results.

Filler Contraindications

Many of the hyaluronic acid (HA) fillers are manufactured from a streptococcal fermentation process, so ask about hypersensitivity to strep, she said. Some patients have sensitivity to lidocaine. If this

Continued on following page

ALDARA® (imiquimod) Cream, 5%

Brief Summary of Actinic Keratosis Prescribing Information See Package Insert for Full Prescribing Information

INDICATIONS AND USAGE: Actinic Keratosis: Aldara Cream is indicated for the topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp in immunocompetent adults. **Unvaluated Populations:** Safety and efficacy of Aldara Cream in immunosuppressed patients have not been established. Aldara Cream should be used with caution in patients with pre-existing autoimmune conditions. The efficacy and safety of Aldara Cream have not been established for patients with Basal Cell Nevus Syndrome or Xeroderma Pigmentosum.

CONTRAINDICATIONS: None.

WARNINGS AND PRECAUTIONS: Local Inflammatory Reactions: Intense local inflammatory reactions including skin weeping or erosion can occur after few applications of Aldara Cream and may require an interruption of dosing. Aldara Cream has the potential to exacerbate inflammatory conditions of the skin, including chronic graft versus host disease. Administration of Aldara Cream is not recommended until the skin is completely healed from any previous drug or surgical treatment. **Systemic Reactions:** Flu-like signs and symptoms may accompany, or even precede, local inflammatory reactions and may include malaise, fever, nausea, myalgias and rigors. An interruption of dosing should be considered. **Ultraviolet Light Exposure:** Exposure to sunlight (including sunlamps) should be avoided or minimized during use of Aldara Cream because of concern for heightened sunburn susceptibility. Patients should be warned to use protective clothing (e.g., a hat) when using Aldara Cream. Patients with sunburn should be advised not to use Aldara Cream until fully recovered. Patients who may have considerable sun exposure, e.g., due to their occupation, and those patients with inherent sensitivity to sunlight should exercise caution when using Aldara Cream. Aldara Cream shortened the time to skin tumor formation in an animal photocarcinogenicity study. The enhancement of ultraviolet carcinogenicity is not necessarily dependent on phototoxic mechanisms. Therefore, patients should minimize or avoid natural or artificial sunlight exposure. **Unvaluated Uses:** Safety and efficacy have not been established for Aldara Cream in the treatment of actinic keratosis with repeated use, i.e., more than one treatment course in the same area. The safety of Aldara Cream applied to areas of skin greater than 25 cm² for the treatment of actinic keratosis has not been established.

ADVERSE REACTIONS: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. **Clinical Trials Experience: Actinic Keratosis:** The data described below reflect exposure to Aldara Cream or vehicle in 436 subjects enrolled in two double-blind, vehicle-controlled studies. Subjects applied Aldara Cream or vehicle to a 25 cm² contiguous treatment area on the face or scalp 2 times per week for 16 weeks.

Table 1: Selected Adverse Reactions Occurring in >1% of Aldara-Treated Subjects and at a Greater Frequency than with Vehicle in the Combined Studies (Actinic Keratosis)

Preferred Term	Aldara Cream (n=215)	Vehicle (n=221)
Application Site Reaction	71 (33%)	32 (14%)
Upper Resp Tract Infection	33 (15%)	27 (12%)
Sinusitis	16 (7%)	14 (6%)
Headache	11 (5%)	7 (3%)
Carcinoma Squamous	8 (4%)	5 (2%)
Diarrhea	6 (3%)	2 (1%)
Eczema	4 (2%)	3 (1%)
Back Pain	3 (1%)	2 (1%)
Fatigue	3 (1%)	2 (1%)
Fibrillation Atrial	3 (1%)	2 (1%)
Infection Viral	3 (1%)	2 (1%)
Dizziness	3 (1%)	1 (<1%)
Vomiting	3 (1%)	1 (<1%)
Urinary Tract Infection	3 (1%)	1 (<1%)
Fever	3 (1%)	0 (0%)
Rigors	3 (1%)	0 (0%)
Alopecia	3 (1%)	0 (0%)

Table 2: Application Site Reactions Reported by >1% of Aldara-Treated Subjects and at a Greater Frequency than with Vehicle in the Combined Studies (Actinic Keratosis)

Included Term	Aldara Cream n=215	Vehicle n=221
Itching	44 (20%)	17 (8%)
Burning	13 (6%)	4 (2%)
Bleeding	7 (3%)	1 (<1%)
Stinging	6 (3%)	2 (1%)
Pain	6 (3%)	2 (1%)
Induration	5 (2%)	3 (1%)
Tenderness	4 (2%)	3 (1%)
Irritation	4 (2%)	0 (0%)

Local skin reactions were collected independently of the adverse reaction "application site reaction" in an effort to provide a better picture of the specific types of local reactions that might be seen. The most frequently reported local skin reactions were erythema, flaking/scaling/dryness, and scabbing/crusting. The prevalence and severity of local skin reactions that occurred during controlled studies are shown in the following table.

Table 3: Local Skin Reactions in the Treatment Area as Assessed by the Investigator (Actinic Keratosis)

	Aldara Cream (n=215)		Vehicle (n=220)	
	All Grades*	Severe	All Grades*	Severe
Erythema	209 (97%)	38 (18%)	206 (93%)	5 (2%)
Flaking/Scaling/Dryness	199 (93%)	16 (7%)	199 (91%)	7 (3%)
Scabbing/Crusting	169 (79%)	18 (8%)	92 (42%)	4 (2%)
Edema	106 (49%)	0 (0%)	22 (10%)	0 (0%)
Erosion/Ulceration	103 (48%)	5 (2%)	20 (9%)	0 (0%)
Weeping/Exudate	45 (22%)	0 (0%)	3 (1%)	0 (0%)
Vesicles	19 (9%)	0 (0%)	2 (1%)	0 (0%)

*Mild, Moderate, or Severe

The adverse reactions that most frequently resulted in clinical intervention (e.g., rest periods, withdrawal from study) were local skin and application site reactions. Overall, in the clinical studies,

2% (5/215) of subjects discontinued for local skin/application site reactions. Of the 215 subjects treated, 35 subjects (16%) on Aldara Cream and 3 of 220 subjects (1%) on vehicle cream had at least one rest period. Of these Aldara Cream subjects, 32 (91%) resumed therapy after a rest period. In the actinic keratosis studies, 22 of 678 (3.2%) of Aldara-treated subjects developed treatment site infections that required a rest period off Aldara Cream and were treated with antibiotics (19 with oral and 3 with topical). Of the 206 Aldara subjects with both baseline and 8-week post-treatment scarring assessments, 6 (2.9%) had a greater degree of scarring scores at 8-weeks post-treatment than at baseline. **Clinical Trials Experience: Dermal Safety Studies** Provocative repeat insult patch test studies involving induction and challenge phases produced no evidence that Aldara Cream causes photoallergenicity or contact sensitization in healthy skin; however, cumulative irritancy testing revealed the potential for Aldara Cream to cause irritation, and application site reactions were reported in the clinical studies. **Postmarketing Experience:** The following adverse reactions have been identified during post-approval use of Aldara Cream. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. **Body as a Whole:** angioedema. **Cardiovascular:** capillary leak syndrome, cardiac failure, cardiomyopathy, pulmonary edema, arrhythmias (tachycardia, atrial fibrillation, palpitations), chest pain, ischemia, myocardial infarction, syncope. **Endocrine:** thyroiditis. **Hematological:** decreases in red cell, white cell and platelet counts (including idiopathic thrombocytopenic purpura), lymphoma. **Hepatic:** abnormal liver function. **Neuropsychiatric:** agitation, cerebrovascular accident, convulsions (including febrile convulsions), depression, insomnia, multiple sclerosis aggravation, paresis, suicide. **Respiratory:** dyspnea. **Urinary System Disorders:** proteinuria. **Skin and Appendages:** exfoliative dermatitis, erythema multiforme, hyperpigmentation. **Vascular:** Henoch-Schönlein purpura syndrome.

USE IN SPECIFIC POPULATIONS: Pregnancy: Pregnancy Category C: Systemic embryofetal development studies were conducted in rats and rabbits. Oral doses of 1, 5 and 20 mg/kg/day imiquimod were administered during the period of organogenesis (gestational days 6–15) to pregnant female rats. In the presence of maternal toxicity, fetal effects noted at 20 mg/kg/day (57X MRHD based on AUC comparisons) included increased resorptions, decreased fetal body weights, delays in skeletal ossification, bent limb bones, and two fetuses in one litter (2 of 1567 fetuses) demonstrated exencephaly, protruding tongues and low-set ears. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 5 mg/kg/day (98X MRHD based on AUC comparisons). Intravenous doses of 0.5, 1 and 2 mg/kg/day imiquimod were administered during the period of organogenesis (gestational days 6–18) to pregnant female rabbits. No treatment related effects on embryofetal toxicity or teratogenicity were noted at 2 mg/kg/day (1.5X MRHD based on BSA comparisons), the highest dose evaluated in this study, or 1 mg/kg/day (407X MRHD based on AUC comparisons). A combined fertility and peri- and post-natal development study was conducted in rats. Oral doses of 1, 1.5, 3 and 6 mg/kg/day imiquimod were administered to male rats from 70 days prior to mating through the mating period and to female rats from 14 days prior to mating through parturition and lactation. No effects on growth, fertility, reproduction or post-natal development were noted at doses up to 6 mg/kg/day (87X MRHD based on AUC comparisons), the highest dose evaluated in this study. In the absence of maternal toxicity, bent limb bones were noted in the F1 fetuses at a dose of 6 mg/kg/day (87X MRHD based on AUC comparisons). This fetal effect was also noted in the oral rat embryofetal development study conducted with imiquimod. No treatment related effects on teratogenicity were noted at 3 mg/kg/day (41X MRHD based on AUC comparisons). There are no adequate and well-controlled studies in pregnant women. Aldara Cream should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers:** It is not known whether imiquimod is excreted in human milk following use of Aldara Cream. Because many drugs are excreted in human milk, caution should be exercised when Aldara Cream is administered to nursing women. **Pediatric Use:** AK is not a condition generally seen within the pediatric population. The safety and efficacy of Aldara Cream for AK in patients less than 18 years of age have not been established. Aldara Cream was evaluated in two randomized, vehicle-controlled, double-blind trials involving 702 pediatric subjects with molluscum contagiosum (MC) (470 exposed to Aldara; median age 5 years, range 2–12 years). Subjects applied Aldara Cream or vehicle 3 times weekly for up to 16 weeks. These studies failed to demonstrate efficacy. Similar to the studies conducted in adults, the most frequently reported adverse reaction from 2 studies in children with MC was application site reaction. Adverse events which occurred more frequently in Aldara-treated subjects compared with vehicle-treated subjects generally resembled those seen in studies in indications approved for adults and also included otitis media (5% Aldara vs. 3% vehicle) and conjunctivitis (3% Aldara vs. 2% vehicle). Erythema was the most frequently reported local skin reaction. Severe local skin reactions reported by Aldara-treated subjects in the pediatric studies included erythema (28%), edema (8%), scabbing/crusting (5%), flaking/scaling (5%), erosion (2%) and weeping/exudate (2%). Systemic absorption of imiquimod across the affected skin of 22 subjects aged 2 to 12 years with extensive MC involving at least 10% of the total body surface area was observed after single and multiple doses at a dosing frequency of 3 applications per week for 4 weeks. Among the 20 subjects with evaluable laboratory assessments, the median WBC count decreased by 1.4*10⁹/L and the median absolute neutrophil count decreased by 1.42*10⁹/L. **Geriatric Use:** Of the 215 subjects treated with Aldara Cream in the AK clinical studies, 127 subjects (59%) were 65 years and older, while 60 subjects (28%) were 75 years and older. Of the 185 subjects treated with Aldara Cream in the superficial basal cell carcinoma clinical studies, 65 subjects (35%) were 65 years and older, while 25 subjects (14%) were 75 years and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. No other clinical experience has identified differences in responses between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

OVERDOSAGE: Topical overdosing of Aldara Cream could result in an increased incidence of severe local skin reactions and may increase the risk for systemic reactions. The most clinically serious adverse event reported following multiple oral imiquimod doses of >200 mg (equivalent to imiquimod content of >16 packets) was hypotension, which resolved following oral or intravenous fluid administration.

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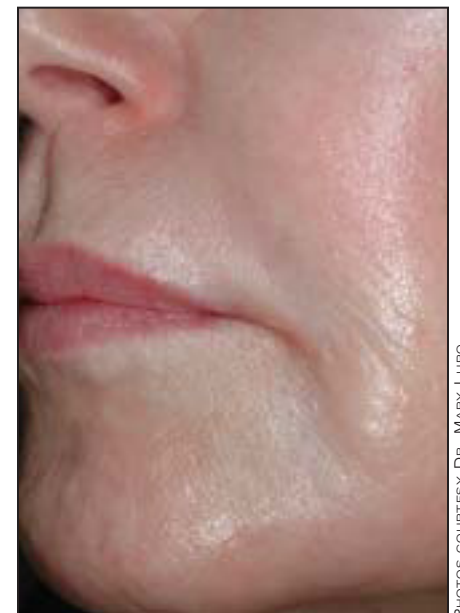
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A patient is shown before treatment with one syringe of Restylane.



The effect was prolonged for 3.5 years by performing periodic touch-ups.

Continued from previous page

is the case, avoid using Prevelle Silk, CosmoDerm, and CosmoPlast. Poly-L-lactic acid is a component of Vicryl sutures, so if a patient has a history of allergic reaction to these sutures, avoid using Sculptra.

The use of anticoagulants by a patient is not necessarily a contraindication, "but it certainly behooves you to discuss the incidence of bruising that might be significant in these patients," Dr. Lupo said. For smokers wanting fillers, she uses a consent form to make these patients aware of the increased risk of necrosis.

Managing Expectations

The issue of cost also should be part of the discussion. Older patients will need more filler, meaning that temporary fillers may not be as cost effective over time. Semipermanent fillers may offer more benefit and it might be worth considering permanent.

To get the most out of a filler, complementing procedures should be considered. Such procedures can include onabotulinumtoxinA (Botox), intense pulsed light, chemical peel, nonablative laser, and ablative laser. "At the end of the day, the more procedures that a patient can afford, the better they will look," Dr. Lupo noted.

The Fillers

► **CosmoDerm and CosmoPlast (human collagen).** These products are the best choice for immediate results. They are great for lining the lips and for fine perioral lines, and both are fairly painless. They have a short duration, however, and both will be discontinued in 2010, according to Dr. Lupo.

► **Restylane (HA gel).** The filler is versatile and can be reversed by using hyaluronidase. It also can be injected with a finer-gauge needle, which reduces pain and allows treatment of finer lines. One injection lasts about 6 months, but it can last longer with touch-ups. Swelling and bruising should be considered, she said.

► **Perlane (HA gel).** This filler is a larger-particle gel suspension of HA. It is typically used for nasolabial folds and cheeks, and it can be used for lips with good technique to avoid lumping. "I have not found that the duration is any better than with Restylane," said Dr. Lupo.

► **Juvéderm Ultra and Juvéderm Ultra Plus (cross-linked HA).** This product is malleable and soft. It is also great for lips; however, because it is so malleable, it is not the best choice for defining the lip border. This filler is also reversible. "It is a little bit harder to get through a 1-inch needle," she said. Duration is 7-9 months without touch-ups.

Juvéderm Ultra Plus is the same as Juvéderm Ultra, although increased crosslinking of HA results in improved longevity—up to 1 year without touch-ups. "It's never to be used in fine lines, in my opinion," Dr. Lupo said. It is best injected with a 30-gauge needle. This filler is extremely good in skin of color.

► **Prevelle Silk (cross-linked HA and lidocaine).** The added lidocaine decreases patient discomfort. There is very little swelling because of the low HA

concentration, but as a result it does not last as long—3 months or less. "It's inexpensive, and it's a good introductory filler for the hesitant patient," she said.

► **Eleveess (cross-linked HA and lidocaine).** Eleveess has the highest concentration of HA available on the market. "My personal opinion, based on my limited experience with it, is that it tends to be highly inflammatory as a result of this high concentration of HA," she said.

► **Radiesse (calcium hydroxylapatite).** This structural filler is great for men. It does cause a lot of same-day redness. "I do routinely mix it with lidocaine, and

that is now FDA approved and has been found not to decrease its longevity," she said. It's a good choice for marionette lines and the pre-jowl sulcus, but avoid using it for the lips, she said.

► **Sculptra (poly-L-lactic acid).** The FDA cleared Sculptra this year for cosmetic purposes—correction of mild-to-severe nasolabial folds and wrinkles and contour irregularities. "The optimal patient for this is a younger lipoatrophy patient, because these patients still have enough of an immune response to actually get a good bang for the buck," she said. This filler is not reversible. The

most common problem with Sculptra is the presence of nodules if it is injected too superficially, said Dr. Lupo.

► **Evolence (porcine collagen).** "In my opinion, it's a stiffer, more structural filler," she said. It works well in the nasolabial folds. Dr. Lupo always mixes it with lidocaine, though this makes it flow more quickly, so she uses a 30-gauge needle. It is a good choice for men with thick skin. Evolence has a low incidence of bruising and swelling.

Dr. Lupo reported significant financial relationships with a number of pharmaceutical and skin care companies. ■

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Parameter	Day 7	Day 14
Scaling	~68	~88
Cracking	~50	~82
Itching	~40	~45
Dryness	~42	~55
TEWL	~18	~35

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