



Controversies and Conversations in Laser and Cosmetic Surgery

Hear from international experts on how they typically (and sometimes controversially) tackle skin rejuvenation, hair removal, acne, vascular lesions and other common dermatologic conditions.

Support provided by DUSA Pharmaceuticals, Inc., Laserscope, Medicis and Thermage, Inc.

Introduction

For the past 16 years, we've offered a yearly seminar that covers controversial issues surrounding cutaneous laser and cosmetic surgery. This conference, known as Controversies and Conversations in Laser and Cosmetic Surgery, boasts a faculty of distinguished international physicians, scientists, researchers and other experts who hold back nothing when sharing their candid views and engaging in spirited discussions with others. This year, as always, the 3-day symposium offered a unique opportunity for attendees to discuss controversial topics and current issues in a congenial and collegial atmosphere.

This conference is quite valuable because new instruments, technologies, techniques and products emerge every year. Reliable information about emerging therapies lags months to years behind aggressive marketing, and each new development has proponents and opponents, enthusiasts and skeptics. These gatherings have always been stimulating, exciting and enjoyable, and the information and opinions that surface are essential to those who have an interest in lasers, light sources, neurotoxins, soft tissue fillers and aesthetic procedures in their practices.

That Controversies has grown from a relatively intimate meeting to a larger gathering of colleagues reflects several realities:

- the evolution, growth and acceptance of laser and other energy sources in medicine and their ability to bring about unique benefits
- the growth in breadth and depth of the science and technology in these and related areas
- the marked increase of interest and capabilities in aesthetic medicine.

We hope you find the selections from the presentations that we've chosen for this supplement to *Skin & Aging* magazine to be as intellectually stimulating and interesting as we did. (Next year's meeting will be held at the Four Seasons Resort Aviara, North San Diego, from August 11 to 13. For more information, go to the "Controversies" link at www.skincarephysicians.net.)

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Fillers: Making the Best Choice

How to sort through the available fillers and those on the horizon.

By Rhoda S. Narins, M.D., Murad Alam, M.D.,
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Fillers are safe, biocompatible materials that are injected *in vivo* to correct volume loss skin abnormalities. They are a useful adjunct to lasers and light sources, which tend to be relatively more effective at correcting color and fine (rather than coarse) texture. A variety of fillers (more now than ever) are available that produce the results that patients desire. Hyaluronic acid products such as Restylane, Hylaform, Hylaform Plus and Captique; hydroxylapatite (Radiesse); and injectable poly-L-lactic acid (Sculptra) are available (and U.S. FDA approved) in addition to a patient's own fat and collagen. So far, only the latter has any anesthetic; that is, only Zyderm, Zyplast bovine collagen, CosmoDerm and CosmoPlast human collagen have lidocaine in the syringe.

Sculptra is FDA approved for the restoration and/or correction of the signs of facial fat loss in people who have HIV. Radiesse has 510(k) approval from the FDA for use in oral maxillofacial defects, for soft tissue vocal fold augmentation and as a tissue marker.) If filling for volume such as in the nasolabial folds and in hollow cheeks, these latter two fillers are well-suited for the job. Sometimes a combination of fillers suits a situation, especially if more than one area is being filled. In addition to considering the treatment area, a physician must also consider pain, the price of the chosen product, the duration of effect and potential side effects. This article will discuss these issues, as well as review the different filler options available.

What are the Controversies?

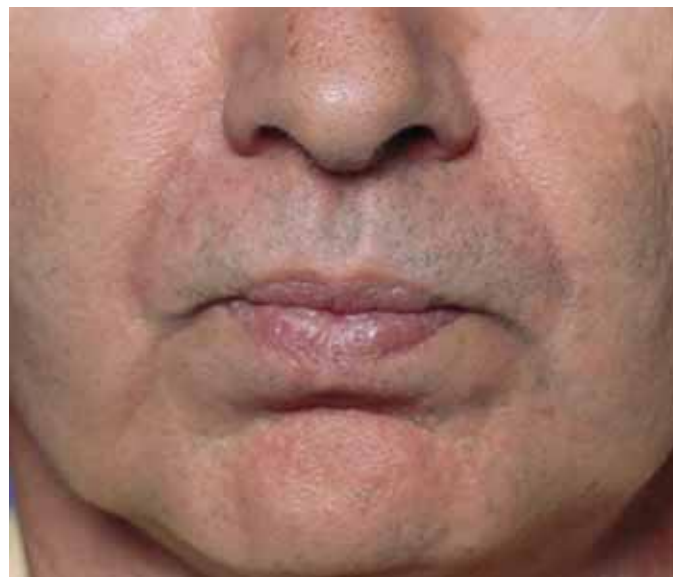
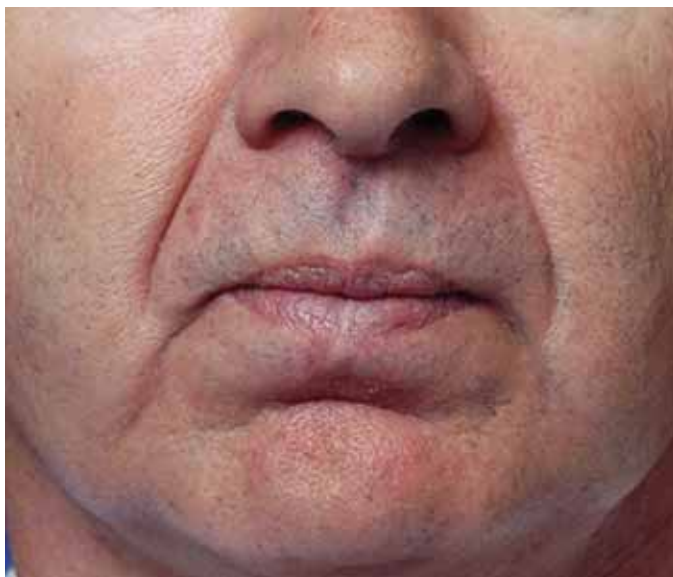
- 1. Are we getting closer to a filler that will do it all?**
- 2. Should we focus our efforts more on combining fillers for better outcomes?**
- 3. Do the newer fillers offer substantial benefits over some of the older filler agents?**

When deciding what product to use, consider into which area you will inject the chosen product as well as the result the patient desires. For example, hyaluronic acid fillers are ideal for filling the lip and lip margin, while Sculptra or Radiesse produce more imprecise filling and potentially too much fullness in the lips. (Use of these fillers for this purpose is not approved by the FDA.

Pick a Few Favorites

When discussing fillers in the initial patient consultation, choose a few favorite fillers on which to focus. (The time required to discuss the pros and cons of every filler is prohibitive and can become confusing for the patient.) Select these favorites based on:

- your expertise
- anatomic location
- size and depth of the defect (some defects are more superficial, linear, barely perceptible lines, and some are deeper crevices; likewise, some fillers are better with one type than another because some fillers are more linear while others are more volumetric)
- the cost-convenience trade-off
- the desire for persistence. While general persistence ranges may not hold for particular patients, they can be used to compare the relative persistence of fillers in general. The briefest-acting fillers last 2 to 3 months; the longest-acting, nonpermanent fillers last 1 to 2 years. The only



Note the patient's nasolabial folds at presentation (photo on left) and approximately 2 weeks after receiving three 1-mL syringes of Restylane (photo at right). *Photos courtesy of Medicis Aesthetics.*

FDA-approved, permanent, pre-packaged injectable filler currently available for facial augmentation is fat, although Artefill may be approved in the spring and Silikon is available off-label. See "Persistence of Filler Materials" on page 4 for information on how long some common fillers last.

- patient preference.

cost-sensitive, others may prefer convenience. If a patient is interested in a low-cost single procedure, consider a short-acting, less expensive filler. However, if a patient prefers less frequent visits, then consider a longer-lasting filler. Many patients prefer the longer-acting fillers.

Reviewing the Rules

The following "rules of thumb" can help guide what filler to select, and some of these are applicable to all fillers, regardless of their specific type.

Deeper fillers last longer. In general, the deepest fillers are placed in the superficial fat and last the longest, and the most superficial of these products is placed high in the dermis and has the shortest duration.

Safety is important and various fillers have different short-term problems. Some are more likely to cause long-term problems, which are often not well understood.

Short-term fillers can prove helpful for novice patients. Patients who have never had fillers before may benefit from one that lasts a brief period of time so they can determine whether they like the result. If they are satisfied with the effect, then that result can be locked in with a longer lasting filler.

Some anatomic areas are inherently more tricky to fill (e.g., the lips, periorbital areas and possibly fine marionette lines peripheral to the mouth). Regardless of the filler you use, watch out for lumpiness and bruising in these areas.

Patients may have a variety of preferences. Some are more

What Fillers Fill

- rhytids and folds
 - nasolabial folds and marionette lines
 - glabellar and periorbital rhytids
 - hollows under the eyes
- acne scars
- other scars
- enhance lips, chin, cheek and eye hollows, cheek bones, mid-face = "mini facelift"

Keep in mind that cosmetic concern involves both superficial and deep components. **Do you use two fillers, or just one?** If you only use one filler, remember that some of the most helpful fillers for this indication are the hyaluronic acid fillers (e.g., Restylane). You can also use fillers in combination; for example, layer one product for the deeper part of the defect and layer another product that works better for finer defects on top of that. If you use multiple fillers, keep in mind that each filler must be used with a specialized technique. There are commonalities in learning how to inject any prepackaged filler, but you do need to have knowledge of the product, the package insert, attend hands-on courses and talk extensively with knowledge-

able, clinical field representatives and colleagues who often can guide you in the precise injection technique of a specific filler.

It's also important to *carefully ask what the patient desires from the procedure*, as this can guide filler selection. Find out what actually bothers your patient, and then choose the filler that best works to treat that problem.

Using enough filler is crucial — especially with older patients and those who have significant defects. You might wish to decrease the cost, but if doing so is at the cost of less efficacy, then you really haven't done them a service. It is important to discuss the cost element early on, and if they can only afford a short-term filler, then use more of that rather than using a small quantity of a more expensive, long-term filler that doesn't provide the needed benefit.

Be aware of non-FDA-approved fillers. Some patients might prefer fillers that are FDA approved for cosmetic indications or FDA-approved fillers used for off-label purposes. Do what's usual and customary in your community. Using fillers that are not approved for any indication in the United States is something you should do only after careful disclosure to the patient (and your lawyer).

The most *common adverse effects* are similar for all of the fillers and include transient redness, swelling and bruising. Less common side effects include early and late allergic reactions, nodules, granulomas and skin necrosis. Some fillers are more prone to causing these adverse events, especially if they are injected too superficially.

Recent studies suggest that you can safely use Thermage monopolar radiofrequency over almost all of these fillers without altering the fillers in an adverse manner. These reassuring results have been demonstrated in both an animal model and in live patients.¹⁻³

The Scoop on Specifics

In this section, we share our thoughts on specific fillers. Hopefully our comments will help guide you in your selection of a filler for each patient.

Restylane works well for many applications and its effects are quite predictable. There's a bit of a learning curve, but after a couple of months of using it, you can make everybody look the way that they are capable of looking. Restylane has gotten at least as close to fat as we're going to get with a manufactured product. You can inject it in thin sheets, and it thickens and strengthens the skin and makes it more resistant to the deforming forces underneath it. That's something you can't do with any other filler.

If a new patient doesn't want a hyaluronic acid product, consider Cosmoderm or Cosmoplast human collagen because, as with hyaluronic acid, you can inject it without skin testing and swelling is minimal. Although Hylaform doesn't last as long as Restylane, it produces less swelling, especially in the lips. If a patient wants a hyaluronic acid that causes less swelling, Hylaform might be the choice. Juvéderm HV (high viscosity) is another hyaluronic acid filler that is not approved in the United States. It appears to last as long as Restylane and in some studies produces less swelling than Restylane.

One problem with silicone is that it works too well. You need to be able to say to a patient that enough is enough because they love it and want more. (Of course, most people are rational.) You potentially get the best of both worlds with silicone. It is versatile, the results are permanent and you can get the same volume effects that you do with Sculptra. Some physicians have used silicone for years without a problem. However, it is tricky to learn the micro-droplet technique, which must be used to maximize safety and efficacy. The office of Drs. Arndt, Dover and Kaminer

Persistence of Filler Materials

Material	Brand Name	Duration of Aesthetic Effect
Bovine Collagen	Zyplast, Zyderm	2-3 months
Human Collagen	Cosmoderm, Cosmoplast	2-3 months
Hyaluronic Acid	Restylane, Hylaform, Hylaform Plus, Captique	6-12 mos. (Restylane), 3-4 mos. (Hylaform) and 3-4 mos. (Hylaform Plus and Captique)
Poly-L-Lactic Acid	Sculptra	1-2 years
Calcium Hydroxylapatite	Radiance/Radiesse	9-12 months
Polymethylmethacrylate	Artefill	Permanent
Polymethylsiloxane	Silikon 1000	Permanent

was one of three sites that conducted an FDA-monitored, split-face, single-blinded study comparing silicone to Zyplast collagen for nasolabial folds. In 100% of the volunteers, 18 months after the first treatment, the results in the side filled with silicone were better than the side filled with Zyplast collagen. The risk, of course, is that permanent materials cause permanent side effects in some patients. On the other hand, silicone is ideal for people who have HIV lipodystrophy, who need a lot of material injected and need it to last for a long time.

For those who don't perform liposuction in their offices, and consequently aren't doing the fat transfer techniques, Sculptra can make a big difference. Injected several times over several months, it can flesh out a thin face.

Radiesse is an especially effective volume filler. For example, in the nasolabial fold, it lasts 9 to 12 months and provides an aesthetically pleasing result with few side effects. However, you do need to inject it a little bit deeper, but it may require only one treatment to obtain the desired results. The company recommends one treatment and a touch-up 6 weeks later. It's relatively inexpensive for patients now that the cost has come down, and it can be administered safely.

Many New Choices

It used to be that physicians belonged to one of two filler worlds: those in the surgery world would inject fat, and those in the non-surgery world would use bovine collagen.

At no other time in the history of dermatology have we had the variety of new products that have broadened our range of therapeutic options. Fillers such as hyaluronic acid derivatives, hydroxylapatite and human collagen can be adapted to any depressed line or scar on the face. Depending on anatomic location, side effects and preferred duration of effect, one or another filler may be appropriate. Volumetric fillers such as poly-L-lactic acid can plump up diffuse areas. For patients desiring long-term correction, careful use of injectable silicone has been shown to be effective.

Most physicians agree that volume replacement is a central part of restoring a natural, youthful look to the face. These new products help us do that much better than ever before, as long as the correct product is chosen. Learning how to use these materials, and what defect they are best suited for, is the first step in mastering the use of fillers. ■

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Filler Flaws

Collagen has a short duration of effect and doesn't provide volume effect.

Hyaluronic acid may be associated with bruising and some patient discomfort.

Radiesse is expensive, but has recently decreased in price. Its duration is also less than expected (9–12 months) and it requires pain management.

Silicone requires multiple treatments and adverse events can be permanent.

Sculptra also requires multiple treatments, is expensive and needs reconstituting for at least 2 hours (and preferably overnight) before injection. It also requires pain management.

Fat first needs harvesting, and in some areas (e.g., the cheeks) will last a long time, but not in heavy movement areas such as the lips and perioral area. Pain management is also required.

Artefill is a permanent filler and should be FDA-approved in the spring of 2006. Some reports of granulomas have surfaced, but these usually melt away and a dermatologist can often treat them with intralesional cortisone injections.

New Options in Skin Tightening: How Do They Stack Up?

A discussion of common issues surrounding this procedure, as well as a review of available technologies.

By Kevin C. Smith, M.D., F.R.C.P.C., A. Jay Burns, M.D., Michael S. Kaminer, M.D., and Brian S. Biesman, M.D.

Not only are skin-tightening technologies improving, but so is our understanding of how to use them as well as our patient selection criteria, which are all contributing to better results. Despite these improvements, many of us agree that problems exist with skin tightening, independent of the device you use, and we often get inconsistent results. So, where are we overall with this technology and what improvements are still needed?

Here, we'll discuss which patient types respond best to skin-tightening treatment, review the current technologies and offer some suggestions on how to bridge the gap from where we are now to a place where we're more knowledgeable and comfortable with these technologies. ("Mechanisms of Tightening" on page 8 provides the basics behind this technology.)

What are the Controversies?

1. What patient types respond best to skin-tightening treatment?
2. Can a new treatment algorithm produce markedly improved results?
3. Could some people be considered non-responders to skin-tightening treatments?

Ideal Candidates

In general, younger patients respond to tightening treatments faster and better than older patients. They're also often able to go longer between maintenance treatments. Non-smokers usually

do better than smokers, and people who protect themselves from the sun often do better than those who have sun damage. We also know that healthy people generally respond better and more completely to skin tightening than do people who have systemic diseases. But even taking all of those facts into account when we're looking at our patient selection criteria (e.g., age, past and present sun exposure, smoking, etc.), similar-looking patients can have considerably different responses to standard skin-tightening treatments. So how much improvement do our patients see?

A Closer Look at Patient Response

On average, patients improve by as little as 5% to 9% in some categories, and by 25% in others. To some people, 10% to 25% improvement doesn't look like much, while to others (such as our patients), it looks like a lot. Our challenge is to figure out how to improve these numbers.

Food for Thought

Fortunately for us, we don't have to choose what type of facelift we should give a patient because they basically choose for us. They say they don't want any downtime, so you consider taking the Thermage route. If they say they really want a home run and it has to look perfect, then consider a facelift, but a poor result cannot be 100% avoided. And if they want something in between, and we want them to look a little bit better than what we can give them with Thermage without actually giving them a facelift, then consider the thread option. (A small percentage of contour thread patients may develop scar tissue that's ridged and visible. If this happens, you can remove the threads, but doing so takes effort.) As far as the mini-facelift, patients hear minimum downtime and cost, but they don't want minimal result.

Radiofrequency (RF) produces clear improvements and results.

We shouldn't rely on photographs to reflect improvement because it's sometimes impossible to show 10% improvement. Therefore, we need to find other ways to measure efficacy. The effectiveness of a procedure is inversely proportionate to the effort required to convince the patient of that effectiveness. So judge for yourself. Look at the pictures. See how much time you're spending on these cases. How we age isn't all about tightening. Surgery meets many practitioners' idea of a gold standard result. Going forward into the review of technologies, a good rule of thumb to follow is to attack gravity with surgery and to attack skin conditions with laser or non-ablative resurfacing.

Comparing the Available Technologies

How do the new skin-tightening technologies stack up? They all have a substantial learning curve — even those with which we have experience. We have to learn how to counsel our patients better as to exactly what these technologies can and cannot accomplish. There are four skin-tightening technologies currently available:

1. Monopolar RF by Thermage (ThermaCool)
2. Cutera infrared light source (Titan) with most of the energy in the 1000–1300nm range
3. Syneron bi-polar RF and laser
4. Orion has an IR broadband light device that produces infrared light in the 800–1000 nm range.

Monopolar. With Thermage's new algorithm using multiple passes and pulses at comfortable, relatively low fluences, we can get efficacy in about 90% of patients. Sometimes results are dramatic and some patients respond beautifully, other patients respond less, but once you know what to look for and how to choose your patients, you can get reliable reproducible results in a patient who is willing to accept a substantially lesser result than they'd get from a surgical procedure. Thermage so far has been primarily a single session. Compared to other skin-tightening devices, Thermage stacks up quite well in terms of profit to a practice. It is a single-treatment procedure, has a relatively low cost to purchase the device and compares favorably to other notable revenue generators such as Botox and Restylane.

The disadvantage of using a Thermage device is the small (in some studies less than 6%) potential for patients to get limited results despite spending several thousand dollars. Touch-up treatments really are not practical due to the cost of the treatment tip, as well as the potential for limited benefit from a second procedure. The cost of a second session is high, so you have to justify the cost to the patient for the results that you're going to deliver. Once you open those disposables, you're stuck with that cost.

So why are they referring themselves and why are they send-

ing their friends for Thermage treatments and for tightening? Because many of these patients are getting results. And if you carefully choose your patients and carefully explain to them what the expectations are, then I think patients will generally be accepting and reasonably happy with the result, as long as one is careful in terms of what those expectations should be. Problems and difficulty with scarring and hypopigmentation do not exist with the new Thermage treatment algorithm.

Cutera. Tightening with this light source can prove costly because of the length of time necessary for procedures. There is a cost for each pulse because the treatment head has about 10,000 pulses, so you can divide that by the cost of the head, which is somewhere in the \$3,000 range. And there's the cost per pulse, but you're not obligated to use a specific number of pulses.

It takes 6 seconds for a pulse as opposed to about 1.9 seconds with Thermage. So it becomes more cumbersome to treat large areas. The spot size is about 1.5 cm². Some use this device in single sessions, some use it in multiple sessions.

Syneron. With regard to the bi-polar RF plus 900-nm diode laser, we're still waiting to hear what the synergy is between RF and the light. As per the company's thermal profile of this device, we should be able to get reasonable results. It is intended for use in multiple treatment sessions. However, some may view the learning curve with this bi-polar device as significant.

Mechanisms of Tightening

- 1) Collagen shrinkage reformation via thermal mechanisms
 - a. Ablative laser resurfacing
 - b. Non-ablative
 - Radiofrequency
 - Cool Touch, SmoothBeam
- 2) Removal of excess skin through surgery
- 3) Collagen shrinkage through vascular absorption of light and subsequent cascade
 - a. Pulsed dye, other vascular lasers

Orion. The Orion handpiece is about 4.5 cm², which makes it quite efficient, but there are some unresolved issues. How many sessions should we perform? How far apart? If you've completed an initial session and you want to do another one, what's the optimum time? Who is likely to respond? Also, if a patient is going to have a surgical procedure over one part of her upper face, can you do this simultaneously or not?



The photos above show the progress of skin tightening treatment with Thermage. The photo at left is pre-treatment; middle photo shows 2 weeks post-treatment and the photo at right is 6 months post-treatment.

Optimizing Outcomes

If you do multiple passes at a low fluence with many of these devices, you get better results with tightening in three directions. More passes at lower fluences makes the procedure less painful,

Could Some People be Non-Responders?

Could there be one or more temperature-dependent variants in collagen and/or elastic tissue or a temperature-dependent variable in the systems responsible for the production of cytokines and other variables such as heat shock proteins such that some individuals respond well to a given thermal load administered in a standard, non-ablative treatment? Or, could apparently similar individuals have protein structures or other biological subsystems that are relatively thermal-stable with the range of thermal loads imposed during typical non-ablative treatment and so they're poor responders?

Could there be some individuals whose recurrent regenerative processes are called into action by a moderate thermal insult of the type that we ordinarily give, while other, similar-appearing people are thermal-stable or even thermal-resistant or are thermophiles and are condemned to existence as non-responders? If the above speculations prove to be clinically relevant, perhaps some day we will have a set of genetic probes or other markers. ■

but it takes much longer and the results are reproducible about 90% of the time. The new Thermage 3.0-cm² tip should help considerably with the time element.

Researchers have done a lot of work on skin tightening technology and as a result, many different devices are available. It is, of course, important that we know how to use these available devices properly. Plus, we have more to learn with regard to use off the face (e.g., abdomen, arms). Skin tightening does not replace or produce the same results as face lift surgery, but it does have a role in facial rejuvenation. It is a tool that we can use effectively, but only if we, and our patients, have a good understanding of expected outcomes.

Just remember that the patients are most important, and when you bring out their before-and-after pictures, that's when they see improvement. Scientists want numbers; clinicians want happy patients. ■

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Photodynamic Therapy: Overcoming the Next Challenge

Can we ensure reproducible results?

By George Hruza, M.D., Mitchel P. Goldman, M.D.,
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Photodynamic therapy in conjunction with the use of 5-aminolevulinic acid (ALA) (Levulan) is now a widely accepted modality for the treatment of actinic keratoses, and in Europe and Australia it is also used for removing superficial basal cell carcinomas. More recently, this therapy has been shown to be effective for treating photodamage, acne, and a variety of other inflammatory dermatologic diseases. But the main benefit of topical photodynamic therapy (PDT) is that it has a very low level of invasiveness and excellent cosmetic outcomes.

Yet, a big question remains: *Can we obtain reproducible results?* In order to answer this question, we must first understand what is unpredictable about treating patients with ALA/PDT. In short, variability in treatment outcomes is due to many different things such as incubation times of the ALA, different types of light sources, different exposure times to the light and variable post-treatment regimens, to name a few.

A Closer Look at These Challenges

The great thing about ALA/PDT is that we can use it for many different diagnoses, from actinic keratoses, which is the only FDA cleared indication, to other non-cleared indications such as acne, photodamage, molluscum contagiosum, sebaceous hyperplasia, cutaneous T-cell lymphoma, and many others.

However, not one clinician seems to perform ALA/PDT the same exact way. Pre-treatment regimens can vary. We now know that it's important to de-grease the skin with acetone before applying ALA; also, microdermabrasion helps the ALA to penetrate. Preparing the skin to achieve maximum absorption of the ALA is a very important part of the success equation.

Application time is also critical. If Levulan incubates for longer than an hour, the nerve endings will become affected and the

What are the Controversies?

- 1. Is there a way to reproduce outcomes for ALA/PDT among practitioners?**
- 2. Are there certain conditions that we shouldn't treat with ALA/PDT?**
- 3. Is there one optimum light source we should use for ALA/PDT?**

patient may experience pain during the procedure. High-dose (long incubation) PDT produces pain and phototoxic reactions that can last from 1 to 2 weeks. Depending on the condition being treated, the incubation time may be longer than 1 hour.

The type of light or laser device that is used and its exposure time also figure into the variability of outcomes. We're not just using the BLU-U, which is an intense source of blue light, but also many other light sources. Doses delivered by the different devices for ALA/PDT range anywhere from the pulsed dye laser at 595 nm, 7 J/cm², one pulse, which equates to an activating light dose that's equivalent to about one-fortieth that of the BLU-U at 10 J/cm².

Post-treatment regimens also vary greatly, which again adds to variable outcomes of treatment. Some of this relates to what we may apply to our patient's skin, but it also has to do with how well our patients adhere to our post-treatment recommendations such as the necessity of staying out of the sun for at least 24 hours.

Reporting on the Research

Widespread studies have not yet been published that would make across-the-board treatment comparisons of ALA-PDT regi-



BEFORE (left) AND AFTER FOUR TREATMENTS (right): ALA and ClearLight: Acetone scrub; ALA incubation: 30 minutes; ClearLight: 4 minutes. Photos courtesy of Amy Taub, M.D.

mens foolproof. However, a look at the literature did provide some elementary insight into the success rates of ALA/PDT in treating some of the following conditions.

The Basics of ALA/PDT

Presently, two photosensitizers are FDA approved:

The first, topical 5-aminolevulinic acid (ALA) 20% (Levulan Kerastick) was developed by DUSA Pharmaceuticals and first approved in the United States in 1999. It is indicated for the treatment of non-hyperkeratotic actinic keratoses (AKs) of the face and scalp but is used for many off-label purposes. The original protocol called for applying Levulan to lesions and allowing it to remain in contact with skin for 14 to 18 hours before exposure to blue light for 16.7 minutes. This protocol caused patients pain, burning, crusting and peeling, which required healing time of 1 to 2 weeks. However, lesions infrequently recurred after 4 years. Today, many practitioners are favoring short-contact therapy of 1 hour with Levulan, followed by application of one of a number of laser or light devices to treat conditions ranging from photodamage to sebaceous disorders and hidradenitis suppurativa.

The second agent is methyl aminolevulinate (MetVix), which was developed by PhotoCure. It is the methyl ester of ALA. This drug is also approved for treating AKs. The drug is layered about 1-mm thick to the affected area and immediate surrounding area. The area is then covered with an occlusive dressing for 3 hours. After this incubation time, a red light with continuous spectrum of 570 nm to 670 nm and a total light dose of 75 J/cm² is delivered to the lesion's surface. ■

Skin cancer. ALA/PDT hasn't achieved 100% clearance rates. The success rate is anywhere from 48% to 93% effectiveness with one to two treatments. Skin cancer can recur in up to 31% of cases. This success rate is about as good as what you get with 5-fluorouracil or imiquimod (Aldara) or perhaps cryosurgery. So ALA/PDT works well, but it's not the Holy Grail.

Bowen's disease. The rate of clearance was reported to be as high as 91%, with some much lower rates. The recurrence rate was 52%.

Superficial basal cell carcinoma. With ALA/PDT, physicians have achieved up to a 97% clearance rate. With cases of nodular basal cell carcinoma, the rate has been less than 50%. Recurrence rates are up to 31%.

Squamous cell carcinoma. ALA/PDT does not clear this type of cancer, neither Levulan nor methyl aminolevulinate (MetVix).

Acne. One study by Goldman and Boyce¹ evaluated 22 patients; 12 of these patients received 6 minutes of BLU-U during two sessions that were 1 week apart. The remaining 10 patients received 20% ALA plus BLU-U for 6 minutes with only a 15-minute incubation for two sessions, 2 weeks apart. At evaluation 2 weeks following the last treatment, patients who received treatment with ALA and BLU-U had a 32% reduction in their acne versus BLU-U alone, for which 25% of patients had a reduction in acne papules. These results are almost less than what you get with placebo.

[[However, as noted by Dr. Goldman during the conference, the results of his study described above were 4 years ago when he used a 15-minute application of ALA followed by 6 minutes of Blue-U, with no prepping of the patients skin ahead of time with an acetone scrub or microdermabrasion. According to Dr. Goldman, he's presently getting "phenomenal results" in treating

acne by first doing microdermabrasion and an acetone scrub and then letting ALA incubate for 1 hour followed by 10 minutes of BLU-U light.]]

In another study, Santos did a split-face study in 13 patients comparing ALA-IPL to IPL alone.² Patients underwent two sessions, 2 weeks apart. At 4 weeks the acne was reduced more on the ALA-IPL side, and at 8 weeks that side was still reduced while the acne was back to baseline on the side treated with IPL alone. For acne, ALA-IPL offered some modest benefit, probably equivalent to a topical preparation.

Photorejuvenation. Alster performed a split-face study in 10 patients to evaluate ALA-IPL versus IPL alone.³ Patients underwent two treatment sessions. Erythema and edema were much greater on the ALA side, and desquamation as well as a little bit of blistering. But the results were also better. Using a quartile scale, the ALA was in the 25% to 50% range on average. IPL alone was in the less than 25% range.

Dover performed a split-face study on 20 patients that's just been published in the *Archives of Dermatology*.⁴ Patients underwent three treatments, 3 weeks apart of either ALA-IPL or IPL alone. Patients then also underwent two more treatments with just IPL alone. The study found that global improvement was significantly better on the ALA-IPL side, hyperpigmentation improved more, and fine lines were slightly better improved, although this result was not statistically significant. In addition, there was no difference in telangiectasia or roughness.

In conclusion, ALA-PDT seems to have good results in treating photodamage.

Some Basic Treatment Guidelines Developed by a New ALA/PDT Society

The American Society for Photodynamic Therapy (www.aspdt.org) was formed last year by a group of experts who use ALA/PDT for a variety of medical and cosmetic dermatologic treatments. The society is dedicated to education and research, and this group has developed some early basic protocols and guidelines that provide a good starting point for performing ALA/PDT procedures. These are non-FDA cleared guidelines, but they're based on advice from dermatologists who have extensive experience using this type of therapy. **Some of the society's recommendations for optimizing outcomes with Levulan PDT include the following:**

- You don't need to stop a patient's topical medications before treatment with ALA/PDT.
- Wash the patient's skin with soap and water or an alcohol swab before applying ALA, and have the patient undergo microdermabrasion or have an acetone scrub to help increase the absorption of the ALA.

Should ALA/PDT Be Used to Treat Skin Cancers?

Arielle Kauvar, M.D., Ph.D.: Photodynamic therapy should not be used to treat skin cancers. A large body of literature exists using MetVix in Europe with red light. The results have been approximately equivalent to that of cryotherapy or 5-fluorouracil therapy for superficial basal cell carcinomas (BCCs) — not for nodular BCCs or squamous cell carcinomas (SCCs).

Most of the literature in the last decade is really with red light sources and high-dose PDT as opposed to what we're doing now with pulsed dye lasers and IPLs, which I think are excellent modalities for photodamage and actinic keratoses. I'd like to see high-dose ALA-PDT for conditions such as acne but with epidermal sparing at the same time.

Mitchel Goldman, M.D.: I don't have a lot of faith in most of the studies that have been published. I've standardized the pre-treatment regimen I use, and I have had great success in treating my own squamous cell *in situ* lesions. It's been 2 years since I've treated them, and they haven't come back. I'm not going to undergo Mohs surgery when I can use ALA and get a great cosmetic result.

Jeffrey Dover, M.D., F.R.C.P.C.: I recall a patient who came to see me from Toronto who had extensive actinic keratoses. He had had several SCCs that had been excised, but wanted another treatment option. We applied ALA for 30 minutes and used a pulsed dye laser. He drove 12 hours back home to Toronto on a cloudy day following this therapy. He had an extensive phototoxic reaction; yet, he's had no actinic keratoses for 2 years, no more SCCs. However, no patient wants to suffer from this type of reaction. But the final results are that if you're treating AKs and *in situ* SCCs, you need high-dose ALA/PDT, you need incubation times and you need sun exposure afterward.

Roy Geronemus, M.D.: I think the panelists have prematurely judged ALA/PDT for skin cancer. I'd like to just raise the possibility, not with any definitive proof as of yet, that perhaps ALA-PDT can be used for invasive skin cancer — basal cell and perhaps even squamous cell carcinoma.

There's very preliminary data coming out of Boston University. I've seen some very impressive results from using intra-lesional PDT, where Levulan is being injected — drawn up from the Kerastick — and injected into the tumor and then activated through a variety of different light sources. I just want to raise the issue that it's something that should be considered over the long term. ■

- Next, apply the Levulan liberally for 30 to 60 minutes and then wash it off with soap and water or alcohol prior to application of the light or laser source.
- Match the light source with the condition you're treating. If you're treating somebody who has actinic damage, for example, the recommended light source is Blue-U light. If you're treating acne or acne rosacea, choose a pulsed dye laser. If you're treating someone's photodamage, consider selecting an IPL device.

- Post-treatment, use a good physical sunblock, advise patients to avoid direct sunlight and bright light exposure for 24 to 48 hours, and use moisturizers as needed.
- The society recommends that the typical number of treatments patients undergo should range from two to five treatments, 2 to 4 weeks apart. Based on the patient's response, vary incubation times and the light devices you select.

Challenges for the Future

By Rox Anderson, M.D.

I think that we still have a lot to learn about the photochemistry of ALA/PDT.

First of all, each of the conditions we're treating have different anatomic levels of depth. *With regard to the depth of the treatment, there are two parameters.*

1. It's well known that the topical application gives you a gradient of the drug with depth. So if you do a short contact time, you're not going to penetrate the skin deeply enough to treat invasive squamous cell carcinomas and nodular basal cells and so forth.
2. The second parameter with regard to depth is, of course, the choice of the wavelength of light. If you want to treat a deeper lesion, or let's say the sebaceous component of acne, you really must use high-dose ALA, a long contact time, and high-dose red light. This information has been confirmed by numerous studies done on tumors throughout the past decade or so in Europe.

Another interesting point to consider is based on a number of well-controlled studies that have been conducted in Japan using oral ALA to treat acne. Researchers there have attained very good results with this method. It's interesting that in this country we really have stayed away from oral ALA.

My challenge is to industry. I think we have a clear development pathway that one could take to optimize the light sources and delivery systems for ALA. It will take a lot of work, but it can be done and it would give us some sort of feedback so that as clinicians we won't have to make so many guesses as to which therapy protocols will work best. We should consider developing ways to produce high-dose PDT results but cause the selective elimination of conversion of ALA to protoporphyrin 9 in the epidermis so as to eliminate excess pain for patients. ■

What's the Bottom Line?

With good clinical judgment, obtaining reproducible results with ALA/PDT is possible. The main goals to work toward are standardizing treatments, coordinating our research efforts and continuing to share the results. With more clinical experience we will attain reproducible, more predictable results with ALA/PDT for a variety of conditions. ■

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Treatment Options for Vascular Lesions

What new findings and technologies have contributed to current treatment strategies.

By Jerome M. Garden, M.D., Emil A. Tanghetti, M.D.,
J. Stuart Nelson, M.D., Ph.D., Martin C. Mihm, Jr., M.D.

Vascular lesions take many different shapes and are known by various names (e.g., telangiectasia, hemangiomas, rosacea, and port wine stains). This article will look at what new methods of treatment are available to dermatologists for tackling these skin abnormalities, with a particular focus on hemangiomas and port wine stains.

General Treatment Strategies

Common treatment strategies for vascular lesions include intense pulsed light (IPL), laser therapy or a combination of the two. In 1999, Angermeier conducted a study of 200 patients who had facial telangiectasia, facial hemangiomas, port wine stains and rosacea. He administered one to four treatments of IPL and 174 patients achieved 75% to 100% clearance at 2 months.¹

Emil A. Tanghetti, M.D., treated 25 facial telangiectasia patients using a combination of the pulsed dye laser and the long-pulsed Nd:YAG laser. Parameters were pulsed dye laser at first, 10 mm, 7-10 J/cm², 10-40 ms, followed by the long pulsed Nd:YAG laser with a delay typically of about 50 ms between the pulsed dye and the Nd:YAG. In this study, 75% of the patients achieved clearance with up to two treatments, whereas 25% achieved 50% to 75% clearance.

The Nd:YAG energies used in this study were lower than we'd use if we were treating with the Nd:YAG alone. The challenge is to optimize and apply these parameters to the heterogeneous group of vascular lesions.

IPL tends to work well for broad areas, diffuse lesions, lesions that are mixed vascular and pigmented and for mixed depth/diameter lesions. Consider using laser treatment options when you are faced with single or multiple single lesions, larger diameter vessels or vessels of great depth.

What are the Controversies?

1. How important is the discovery of mutations in the Tie-2 receptor?
2. What is pulse photo tomography, and could it be important to future treatment of vascular lesions?
3. Does one type of treatment offer the best overall results?

Let's take a closer look at treatment strategies directed specifically at hemangiomas and port wine stains.

Basic Science Advances

Hemangiomas. A recent study by Ritter² found that there is a high expression in proliferating hemangiomas of indolamine 23 dioxygenase (IDO), which is a T-cell toxin that is not expressed in the regressing lesion. It seems that the T-cells have something to do with regression, and we increasingly believe that immunological activities are involved in the regression of hemangiomas. The insulin-like growth factor 2 is also highly expressed.

With regard to immune reaction, the use of imiquimod has become quite widespread. And there is now a report by Sidbury on the mechanism of action.³ Two things about involution: There's decreased tumor proliferation and increased tumor apoptosis. We're hearing reports of responsive hemangiomas to imiquimod. This response is apparently due, in part, to endothelial cell destruction.

With regard to angiogenesis, it is clear that vascular endothelial growth factor (VEGF) is highly expressive in proliferating hemangiomas. VEGF does not allow lymphocytes to travel and stick to



Port wine stain on the neck before treatment (A) and after treatment (B) with a pulsed dye laser.

Photos courtesy of Roy Geronemus, M.D.

the walls of vessels, but fibroblast growth factors does. VEGF disappears in the regressing lesion virtually completely. Fibroblast growth factor is expressed in the regressing lesion, which would also speak to possibly supporting another argument for an immune-type of response as being partly induced by inflammation, as lymphocytes can better traffic in the hemangioma.

There is increasing evidence that estrogens will act in a synergistic manner with VEGF, so it is possible that tamoxifen or some drug analog may have a role in the regression of hemangiomas, especially as a topical agent.

The most important molecular finding this year was reported by Barnes from Judah Folkman's group in December 2005 in the proceedings of the National Academy of Sciences.⁴ She described a study of genes in hemangiomas and placental cells and other tissues and found them to be virtually identical. Research is now shifting to focus on placental devolution, which may provide clues to the devolution of a hemangioma. This finding supported a hypothesis put forth by Paula North, M.D., and Martin C. Mihm, Jr., M.D., in 2000.⁵

An important observation has surfaced with regard to vascular malformation research: the detection of a mutation of three amino acids in the Tie-2 receptor. The Tie-2 receptor, when mutated, acts as a phosphorylated kinase and continues to lead in the production of transcription factors. A block to that factor may be useful in controlling these lesions, and COX2 antagonists seem

to block this receptor and may be useful in treating these lesions.

A variety of studies (none of which are highly conclusive) have concluded that there is a definite relationship between the Eph-2 receptor and the formation of arterial venous malformations. This receptor is highly expressed in some arterial venous malformations. The Eph-2 receptor and its ligand are responsible for the identity of the artery to be identified and to be differentiated from a vein. So advances in the immune angiogenesis and molecular research opens a door for us to understand therapy better. For many of the different types of pathology you can use all of the available devices as long as you know how to use them correctly.

Port wine stains. The big problem with the port wine stain is the unpredictable nature of the lesion. You can give two children five treatments and in one, the lesion is almost completely gone, and in the other, the lesion has significantly persisted. One of the significant reasons for this unpredictability is the tremendous blood vessel heterogeneity. Port wine stains vary in color and anatomic location. Considering the complex vascular heterogeneity of these lesions, it really isn't a surprise that lasers don't do particularly well.

A lot of work is going on to develop diagnostic imaging and a technology called pulse photo tomography attempts to acquire an infrared image of the blood vessels, how deep they are, what the diameter is, how hot they get in response to pulsed laser therapy. If we selected optimal laser parameters would port wine stain therapy improve?

Interestingly, revascularization of port wine stains does occur in response to treatment. But the real question is, "Does the PDL treatment lead to the development of these tortuous new types of capillaries, or are we actually seeing reformation of existing capillaries that are underneath the skin?"

Why are these lesions so difficult to treat? The vast majority of port wine stains don't respond to laser therapy because of the heterogeneity of these different types of lesions. The laser is doing what it's supposed to do, so we should start focusing on the port wine stain healing response after the laser treatment. Can this port wine stain healing response somehow be modulated?

We're probably not going to be able to treat port wine stains with just visible light because it doesn't penetrate deeply enough. And we probably can't resolve them with the deeper wavelengths because they're too unpredictable and you can't always do it safely.

For port wine stains resistant to PDL, multiple passing with both PDL and IPL, in combination with the deeper lasers such as 1064 nm is a good approach.

When you're using a combination approach or just using Nd:YAG alone and you see the immediate graying or even a tan-gold color to the skin, you're cooked. So what you want to see is just a little

bit of purpura, and you want to see the second pulse magnify that purpura, but you don't want to see a gray or gold-brown color.

Remember that these lesions re-populate the vascular channels from below, so it's important that you destroy the deeper vessels. And if you have the channels still available and you have not altered the collagen framework of the vessel wall, then the cells will still re-populate.

We know little about mixing inhibitors (basically drug therapy) along with various lasers. We've artificially segregated medical therapy for these vascular lesions from the physical modalities, and they belong together. For instance, if you could inhibit VEGF in post-PDL or Nd:YAG laser treatment, you might speed up response to therapy. Patients who have platelet abnormalities (either ITP or thrombocytopenia) don't respond at all, but you transfuse their platelets and get the platelet concentration up, they will begin to respond. So it's clear that there's something in platelets and aggregation and growth factors that's doing the job for the treatment of port wine stains.

Treatment Pearls

No one form of treatment exists that effectively treats all vascular lesions. And not everyone even agrees on the best treatment modality for specific lesion type. The following are some helpful tips to keep in mind when treating patients for vascular lesions.

Have respect for 1064 nm and take the minimalist approach. It really can cook the tissue, so to look for these endpoints as we do with the PDL is dangerous because once you've reached that endpoint many times it's already too late for the patient. It's a wonderful tool, but it's also dangerous.

Commonalities between PDL and Nd:YAG. You can use the Nd:YAG clinically like a PDL. Your endpoint is purpura. Without adequate cooking, you have epidermal damage because when you have graying it's too much. Many practitioners have not experienced ulceration with the Nd:YAG and are therefore comfortable using it on infants. And you use it just as you would a PDL (with the same endpoints), only for a different indication.

How do you explain the time factor when you're doing sequential pulsing with pulsed dye and Nd:YAG lasers? It depends on the type of lesion with which you're dealing. If you're talking about a high-flow lesion such as the nasal vessels, you want to put the pulses close together because the chromophore you generate, whether it's a clot or methemoglobin, only lasts a short period of time. So putting these about 50 ms apart makes sense. (Don't put them there simultaneously, otherwise you may introduce too much heat into the tissue.) On the other hand, if you put them too close together with a bleb port wine stain, then you don't give the lesion enough time to cool off. So you want to have it hundreds of milliseconds apart, 1 to 2 seconds would be

fine. It would behoove all practitioners to learn what energies are produced by two wavelengths and how to put them together. It's difficult, but it's possible.

Avoid overtreating. When treating vascular lesions, be careful not to over treat because you will get a much bigger reaction. Taking a second pass or using a different wavelength is an opportunity to better treat some vascular lesions. Some practitioners double hit or pulse stack with the V-Beam laser. If taking this approach, consider starting out a bit higher, then drop down a bit and hit with a second pass to target the methemoglobin. It's important to remember that for anything that depends on thrombus formation, take your patients off aspirin because you will diminish their effect.

Depth of wavelengths. Both 1064 nm and 755 nm are longer wavelengths than other light sources, but because the 755 nm is absorbed so well by deoxyhemoglobin, it doesn't go as deep as the 1064 nm. The 532 nm is absorbed nicely, much more than 1064 nm. And with the 532 nm, unfortunately, you have absorption in melanin. With 1064 nm, you get more volumetric heating. For 1064 nm, consider longer-pulse duration and low energies. For some of these patients, it makes sense to use less 1064 nm and more 532 nm.

Treating arteries vs. veins. The Nd:YAG laser 1064 nm is selective for arteries, not veins. The alexandrite, on the other hand, should be selected for veins, not arteries. The Synergy device (Cryosure) is a prototype that's recently been introduced. It has one platform, two laser heads, one power supply and the ability to discharge 595 nm first, then a 1064 nm with a delay. One hand-piece, one fiber, and cooling is done by Zimmer air cooling. With the combined 595 nm/1064 nm you can get by with a much lower dose of 1064 nm to get efficacy. So the concerns of scarring are not likely to happen if used properly here. Another point of interest with this particular device is that the purpura is short-lived (about 2 days), and we are seeing considerable clearing early on.

What the Studies Say

A 2002 study comparing the effectiveness of 585 nm vs. 595 nm PDL treatment of port wine stains with cryogen found that the 585 nm works better than the 595 nm for most port wine stains.⁶ The 595 nm would probably work better for patients who have larger, thicker vessels, but Jerome M. Garden, M.D., presented a study at an American Society for Laser Medicine and Surgery national meeting that looked at multiple wavelengths on the same patients and found that some areas seemed to work better with 593 nm and others seemed to work better with 597 nm. These vascular malformations cause such a complex lesion that it's hard to just pick one wavelength. A system that offered multiple settings would be ideal.



Telangiectasia treated with the two laser wavelengths (532 nm/KTP and 1064 nm/Nd:YAG) of the Gemini.
Photos provided by Laserscope, courtesy of E. Victor Ross, M.D.

We still need a better understanding of the best approach for treating various vascular lesions. Manufacturers and researchers must work together to continue expanding our options. ■

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A 2001 study found that 17% of the treated patients who were resistant to PDL had a 50% improvement by using the 532 nm, but they had a significant amount of scarring (7% scarred, versus 4% in the PDL group).⁷ Another similar study in 2003 used cooling and compared KTP to PDL.⁸ The study investigators found similar clearance and again high scarring. They concluded that PDL was the treatment of choice.

Lastly, a study by Yang, et al. evaluated the use of 1064 nm for minimum purpura doses and its effectiveness relative to the pulsed dye laser.⁹ They found that you can use 1064 nm if you stay below the purpura, but the PDL still worked better than the low-pulse Nd:YAG. They also found that because 1064 nm goes deeper, you can use it to reduce the hypertrophic lesions. They had some epidermal necrosis and were able to go deeper in this.

Challenges Remain

Certainly, some distinct advantages could exist when using PDT to treat vascular lesions because you can use low-end energy light, which may help us with some of the decreasing angiogenesis that can occur. One problem with lasers is that we can't always get those small vessels that we should be able to get with photodynamic therapy. You have to design the PDT carefully so you can get the vessels you want but not get total destruction and cause a big ulceration.

Attacking Acne with Lasers and Light Sources

Many options exist, but do they work?

By E. Victor Ross, Jr., M.D., Jeffrey S. Orringer, M.D.,
Brian D. Zelickson, M.D., and David J. Goldberg, M.D.

The treatment of acne by laser- and light-based technologies, as well as radiofrequency (RF) technologies, is controversial because we can treat a great majority of acne cases with topical and oral medications. However, problems (e.g., adverse effects, antibiotic resistance, increasing concern about oral isotretinoin) exist with traditional acne therapy, and for a subset of patients, laser- or light-based acne therapy can provide relief either as a monotherapy or by augmenting traditional therapy. We will review the various forms of acne treatment and discuss the pros and cons of each. For a quick comparison of available treatment options, see the sidebar on page 19.

Browsing the Options

Some physicians have all of their patients initially undergo standard topical and/or oral acne therapy before even discussing lasers and light sources. Patients who fail antibiotic therapy and are unwilling or unable to tolerate isotretinoin (Accutane) may be good candidates for light.

Other physicians use lasers and light sources in combination with standard therapy initially because many patients are already undergoing standard therapy. Visible light by itself is helpful for slightly speeding treatment in patients who have mild acne. Certainly, lasers and light sources are not typical stand-alone therapies in many practices. There are four basic acne treatment categories:

1. Visible lasers and light sources. All of these visible light sources work on the basis of endogenous porphyrins, whether it's at the red LED at the top, the pulsed dye laser in the middle or the intense pulsed light (IPL) at the bottom. They all work the same way.

What are the Controversies?

- 1. Can alternative therapies, such as laser- and light-based technologies, radiofrequency and ALA/PDT work as well to treat acne as traditional therapies?**
- 2. Should we abandon testing these therapies and just stick with the tried-and-true traditional therapies for acne?**
- 3. Which of these therapies appears most promising?**
- 4. What are the next steps for testing alternative treatments for acne?**

Several recent studies, including two by Monica Elman, examine this treatment option and its effect on endogenous porphyrin and acne.^{1,2} At 4 weeks, the results actually tend to be better as compared to oral antibiotics and topical therapy.

After 12 weeks, however, we have to start questioning how effective these modalities really are. With higher fluences, these lasers may decrease acne through vascular destruction.

Photopneumatic Therapy is a new therapy that, according to Aesthera Corp. of Pleasanton, Calif., uses a revolutionary combination of pneumatic energy and broadband light to treat unsightly veins as well as unwanted hair and pigment.

2. Infrared heat technology. Whether the mid-infrared devices or the amount of polar radiofrequency (RF) or light and bipolar RF, everybody goes to Dr. Ross's work, which is

always the best on this technology.³⁻⁵ Histology has been done with Smoothbeam, but the results are basically the same as with the Cooltouch. They provide better results than do the visible lasers and light sources alone. We tend to use infrared lasers for refractory and inflammatory acne only, although it seems to help in patients who have some mild textural changes as well. However, these technologies tend to hurt more.

Standard Treatment Options

Topical

- antibiotics
- retinoids
- exfoliants

Systemic

- antibiotics
- hormones
- retinoids

Light-based Options

- Photodynamic therapy (PDT) with endogenous photosensitizer Blue, Red and UV light
- Thermal targeting of the sebaceous gland
- PDT with exogenous photosensitizer

Mid-infrared lasers are great for treating adult acne — and patients in their 20s and 30s who have smoldering acne, some scarring and textural change, particularly women, do incredibly well.

3. PDT. Potential phototoxicity occurs with PDT and topical topical 5-aminolevulinic acid (ALA) adds to the expense. Any visible laser or light source can be used with ALA.

4. Home units. We can probably spare patients from some antibiotic and isotretinoin use with home units. With one device on the market now (Zeno Zit Zapper), the patient touches the acne with the device, it warms up, and 4 to 5 days later, the pimple is gone. How well do they really work? Does it matter? The problem is the variable duration of the effect. Drug-type studies (rather than 3-month studies) are necessary for these devices.

Should we be using a combination of light in the prescription pad? Does light have a medication-sparing role? There's a niche of patients for which this works well, but for the average patient who presents to a hospital-based residency program and wants to get acne treatments, light treatment might not be the first-line therapy. The following section will explore light-based treatments in more detail.

Light-Based Treatments

The foundation of acne treatment with light-based devices lies in the understanding of the anatomy of acne, as well as its pathophysiology. Light-based acne treatments fall into the following five broad categories:

1. Low-level, visible light. Used to presumably excite endogenous porphyrins produced by *Propionibacterium acnes*. (This category does not include technologies that require the application of a pro-drug such as ALA.) The strategy with this technique is to have patients sit under a 400–700 nm light source for several minutes exposed to power densities that are incapable of achieving significant temperature elevations. The advantages of low-fluence pulsed dye laser (PDL), low-fluence IPL or low-power density continuous wave sources is that they are typically painless and easy to perform.

PDL treatments are thought to act locally. Lasering the skin in one area doesn't seem to have a profound effect on what's going on in another. Acne is a clinically dynamic condition.

2. Aminolevulinic acid. ALA is used as an adjunct to the previously mentioned light sources. The solution is typically applied for between 30 minutes and 2 hours before light treatment. Different modalities have been attempted to increase the penetration of the drug (e.g., microdermabrasion before application of the cream, using different devices such as the Vibraderm to accelerate penetration of the solution). After application, irradiation is performed with one of the aforementioned light sources. With low-power continuous wave sources, the application has been similar to that provided without ALA. (Doses of light may be reduced.) Fluences with IPL or PDL are typically less than those without ALA.

3. Green-yellow light sources and near-infrared light sources. This approach is simple to use and the goal is to either heat the vasculature and/or the sebaceous glands. These photothermal effects presumably would decrease the vascularity associated with rosacea. Many people have reported or noticed reduced acne severity after treatment with traditional PDL, IPL or KTP ("long-pulsed" frequency doubled Nd:YAG) lasers.

4. Mid-infrared lasers. The three standard wavelengths in this range (1320, 1450 and 1540 nm) have all been applied to acne with variable success. It is likely that the main targets of these treatments are the acro- and infra-infundibulum. Although sebaceous glands might be heated to some degree by all three wavelengths, it is unlikely that with typical settings, the heating would be severe enough to cause any permanent sebaceous gland damage.

5. Radiofrequency (RF) devices. This type of treatment uses radiofrequency energy to strengthen and organize collagen fibers in the skin and is especially useful in the treatment of acne scars, although not enough studies have been conducted for this indication. One advantage to RF treatments is that there is a minimal recovery time, with only mild swelling lasting from 3–7 days.

Some patients claim to see improvement from 1–3 months after treatment with effects lasting as long as 5–10 years.

It is not known which device offers the most effective treatment for acne. From a theoretical perspective, several proposed mechanisms explain how these various devices may work to improve acne. Examining these potential mechanisms of action may offer us at least some clue as to which ones hold the most promise.

Potential Mechanisms

We know that multiple different wavelengths may be absorbed by endogenous porphyrins in *P. acnes*, leading to the destruction of the bacteria. However, no study to date has demonstrated eradication of *P. acnes* as the result of light therapy. By definition, we would expect that the results would be relatively short-lived and that ongoing therapy would be necessary to maintain results. Also, devices that depend on this particular mechanism would likely improve only inflammatory acne based on the role that high intralesional bacterial counts play in the etiology of this particular sub-type of acne.

Alternatively, infrared lasers and RF devices are thought to potentially improve acne by causing a non-specific thermal injury that includes the sebaceous glands. On this basis, both inflammatory and non-inflammatory acne lesions could potentially be improved. Studies that have included histology, including Smoothbeam studies, have shown there are some resulting structural alterations in sebaceous glands. What's unclear is whether or not a functional change in the sebaceous gland may result, which would provide the potential at least for longer-lasting affects.

However, we may not yet have a complete picture of all the true mechanisms involved with PDT for acne. Most people believe that acne is multifactorial and volatile, which make it difficult to conduct successful studies. Consequently, there is a paucity of randomized, controlled studies of efficacy.

Finding Proof

Although many studies have been conducted, most investigations of light treatment of acne are suboptimal. Typical study deficiencies include the lack of a split-face design, lack of long follow-up periods, no controls and too few subjects. Studies will help us all understand the role of lasers in the treatment of acne more thoroughly. The first step is to prove that the device actually provides a statistically significant benefit, and the way to do this is through prospective randomized studies with meaningful controls. There are numerous pilot studies in the literature that examine various devices for acne, but they're rarely followed up with the larger controlled series.

In many ways, split-face study protocol provides the purest

control possible and is quite feasible to perform, even from a patient acceptance perspective. It's vital that investigators who are doing the actual clinical assessments are blinded as to the treatment to eliminate even the potential for certain forms of bias. Unfortunately, many of the reports to date in this area are difficult to interpret because subjects have been allowed to remain on other anti-acne treatments during these studies. It seems to me that to establish the efficacy of a treatment for acne, we should first try to fully assess its individual impact. Once that's established, we may then begin to sort out how it fits in other treatments.

Michael Gold conducted a study that evaluated blue light versus topical clindamycin, and he saw better effect with blue light (a 34% decrease in acne and lesions as compared to 14% for topical 1% clindamycin).⁶

Where Do We Go From Here?

In terms of where we are with current laser and light therapy in the treatment of acne, endogenous porphyrins, blue light, KTP laser and pulsed dye lasers are all temporary. You can reduce the *P. acnes* count and patients get temporary remission, and I think it's useful if someone wants to be cleared up right away, but they need to know they're not going to have any long-term remission from this. So it's good in pregnant patients where you can't use other topical systemic therapy, and it's good for that quick fix, but not a long-term remission. We really need to target the sebaceous gland, and right now, we have two ways of doing so: PDT and options such as mid-infrared lasers.

Unfortunately, many parents are refusing to let their children be treated with isotretinoin because of all of the press about

Comparison of Treatment Options

	Medical	Light	Laser	PDT
FDA Cleared	+	+	+	-
Standard of care	+	-	-	-
Pain	-	+	+	-/+
Systemic side effects	+	-	-	-
Local side effects	-	-	-/+	-/++
Cost	-	-/+	++	+
Ease of use (PT)	+/-	-	--	-/+
Ease of use (MD)	++	+	-	-/+
MD \$ incentive	-	+	++	++
Efficacy	++	-	+	+/?

depression, etc. Isotretinoin is actually a safe drug and it's proven to be effective. We have nothing like it in terms of systemic therapy and no laser treatment is as good as this therapy. That said, the value of using laser and light devices to treat active acne is often emphasized because scarring from previous acne may be concurrently treated. While the degree of efficacy of such devices in the treatment of atrophic acne scarring is still debatable, from a conceptual standpoint, it is a bit troublesome that

The value of using laser and light devices to treat active acne is often emphasized because scarring from previous acne may be concurrently treated.

regarding scarring we invoke a mechanism that includes a pro-inflammatory response leading to wound healing, while with the same devices regarding active acne we often propose an anti-inflammatory effect.

Relatively encouraging evidence exists for the possible role of PDT for acne. ALA is preferentially taken up by the sebaceous glands, so this would tend to restrict the thermal damage to the intended target of the light-based acne therapy. There's good *in vitro* evidence of enhanced bacterial killing with the use of ALA prior to blue light exposure, for example.

While there are several mechanistic reasons to believe that a number of these devices may be worthwhile in the treatment of acne to varying degrees, solid evidence is still lagging behind claims of efficacy, and no one device has become a part of first-line standard acne therapy. ■

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Ablative vs. Non-Ablative Skin Rejuvenation: Is There a Middle Ground?

Experts discuss results with Fraxel and plasma skin regeneration technologies.

By Suzanne L. Kilmer, M.D., Robert A. Weiss, M.D.,
Robert G. Geronemus, M.D., and Dieter Manstein, M.D.

While many effective ablative and non-ablative technologies currently exist for skin rejuvenation, we are constantly searching for a technology that will offer greater results with fewer treatments and less downtime.

There is no question that ablative procedures produce great results for skin rejuvenation. However, as we know, this approach creates a fairly significant wound and requires significant downtime for patients.

And, while many doctors are happy with the efficacy of available non-ablative procedures and the fact that they cause little to no downtime, some patients want more noticeable results with fewer treatments.

So, is there a middle ground? The evolving technologies of fractional resurfacing and plasma skin regeneration (PSR) appear to bring us a step closer to results similar to ablative procedures with downtime that can be as minimal as we see with non-ablative techniques. Here's what we've found so far using these new technologies.

Plasma Skin Regeneration

We're starting to see good results with PSR — a rapid treatment taking 15 minutes to treat the entire face. Patients undergoing PSR need pain medication including a topical anesthetic plus hydrocodone and acetaminophen as well as diazepam. Patients rarely require pain medication after the procedure.

This technology uses plasma, a high-energy source, to deposit heat into the skin. The Portrait PSR technology delivers millisecond pulses of nitrogen plasma to the skin's surface. The plasma, which is generated in the handpiece, is an ionized gas that transfers its energy directly to the skin. PSR treatment

What are the Controversies?

- 1. Are the results from Fraxel and PSR much different from non-ablative procedures?**
- 2. Are these technologies ready to be used in everyday practice?**

doesn't immediately ablate the skin; it leaves the skin intact for the first few days until around day 4 through 7 when the skin begins to desquamate. Higher energy treatments result in more immediate desquamation. Similar to a chemical peel, patients will have browned skin in the first couple of days. Patients look their worst between 2 and 5 days post treatment, and then they improve. PSR creates a deeper dermal effect than a chemical peel does. PSR won't give you as much tightening as CO₂ or erbium laser resurfacing, but it will offer more tightening than a chemical peel. It is kind of like a chemical peel with an added thermal benefit.

Another benefit is that the improvement seen after treatment sessions with PSR continues with time. The treatment has less risk, less downtime and is better tolerated than deep phenol peels. Because PSR produces some tightening without risk to melanocytes, patients infrequently experience hypopigmentation. There have been some reports of mild hyperpigmentation, but so far there has been no reported cases of patients who have had permanent depigmentation. It is important to pay close attention when performing the procedure to make sure you get complete coverage, because it can be difficult to see what you have and haven't treated.



This patient underwent fractional resurfacing with the Fraxel laser for acne scarring. The photo at left depicts the patient before treatment. At right is an image of the patient's acne scars after undergoing five treatments over a 3-month span.

Photos courtesy of Roy Geronemus, M.D.

Resurfacing with the Fraxel Laser

Fractional laser resurfacing also offers a “gentle” resurfacing option with very promising results and very little downtime. With fractional resurfacing, multiple microthermal injuries are applied

What is really unique about fractional resurfacing is how quickly the epidermis repairs itself. This rapid epidermal repair occurs by lateral keratinocyte migration. Basically, untreated areas bridge the gap between areas of treated tissue, resulting in rapid re-epithelialization. The microthermal zones are close enough together that the wound healing gradually spreads throughout the skin.

Treatment generally involves topical anesthesia and forced air cooling during the procedure for patient comfort and tolerability. Patient acceptance has been high.

Fractional resurfacing is user-dependent. When different dermatologists take the handpiece and go over paper, the pattern is going to be different depending on how much pressure is placed on the device. So, needless to say, there is a learning curve involved with using this device — practice is needed. Fractional resurfacing is safe if you stay within the recommended range of parameters and avoid multiple passes within small areas. Avoid too many passes and avoid using energy higher than 20 milliJoules. Multiple passes within a short time interval can cause bulk heating, which can result in hypertrophic scarring. Limit passes to no more than eight at higher energies. Most treatments can be done in about six passes. Bronzing indicates the need to decrease the number of passes.

Short-term side effects of Fraxel can include edema, erythema and some pruritus for a few days.¹ There are no reports of scarring, hypopigmentation or post-inflammatory

Fractional resurfacing is safe if you stay within the recommended range of parameters and avoid multiple passes within small areas. Avoid too many passes and avoid using energy higher than 20 milliJoules.

to the skin. Fraxel's microthermal zones go fairly deep into the tissue (200 to 500 μm), are relatively narrow, and can be delivered to the skin in such a way that there's no ablation of the skin surface. There is deep thermal injury, but because each thermal zone is so small, about 100 μm in diameter, this therapy is considered to be non-ablative.



This patient underwent plasma skin resurfacing (PSR), which is a minimum downtime procedure. At left is the patient depicted at baseline. At right is the patient 3 months after the procedure.

Photos courtesy of Suzanne Kilmer, M.D.

hyperpigmentation in patients with Fitzpatrick skin types I to IV, although darker skin types can experience some temporary hyperpigmentation.

Indications for Fractional Resurfacing

There are many applications for fractional resurfacing. We can treat photodamage, acne scars, surgical scars, melasma and traumatic scars. We're also finding that we can treat hyper and hypopigmentation if we change the parameters of the Fraxel laser. The parameters are still evolving, and we need different settings for different problems (treating scars is much different than trying to get epidermal turnover for melasma).

Overall, we see good results with photorejuvenation with improvement of dyschromia and of skin quality and texture. Fine lines have been observed to improve under the eyes. Melasma has been noted to improve, as has vitiligo. Poikiloderma and small vessels also respond well to this treatment. For most of these conditions, we need to treat patients four to five times to see significant results.

This technology also enables us to treat multiple actinic keratoses diffusely over the skin surface rapidly. Fraxel has become the treatment of choice for acne scarring, which requires several treatment sessions.

Most experts agree that the typical protocol for treating acne with the Fraxel laser is about five treatment session, spaced 2 to

4 weeks apart at setting of 8 to 10 J/cm² with a microthermal zone density of 250. Each treatment session requires approximately eight passes.

Practitioners have used the PRIMOS device, which is a 3-D profiling system that measures skin texture changes, to measure the results with acne scars. In one study of 60 acne scars in 12 patients, researchers noted an average improvement of 40%, which compares favorably to any resurfacing procedure and nicely to any other non-ablative procedure.

Researchers have been able to see improvement of acne scars immediately with the Fraxel. The short-term edema is replaced by rejuvenation in the dermis that occurs and persists over time. This is different than what is seen with other acne scar treatments, which show gradual improvement for 6 months after the last treatment.

Researchers have also been investigating a different type of beam, a smaller focus beam, which provides a shorter, but wider microthermal zone. This beam has been used for the improvement of pigmentation and superficial scars.

Combining Fraxel and PSR

When trying to treat deeper lines, which the Fraxel is not able to treat completely, PSR is great complementary treatment. Researchers are using the two technologies together in a synergistic fashion, which allows a rather nice response that compares favorably to non-ablative treatments in terms of efficacy and



The top and middle photos depict untreated skin (left photos) and skin after 1 week and four treatment sessions (right photos). The histologic slide depicts the vertical controlled zones of denatured collagen in the dermis 16 days post-treatment.

Photos courtesy of Richard Fitzpatrick, M.D.

but further studies need to be done to show optimization and comparison with competitive technologies.

Fraxel compares favorably to ablative procedures, except for treatment of deeper lines and in terms of skin tightening. It appears to produce better results for skin rejuvenation than non-ablative treatments. In terms of post-operative downtime, the concerns with the Fraxel are minimal.

Side effects of edema and wounding are significantly less with Fraxel than with ablative treatments. For example, when treating a patient with a CO₂ laser, you can see the ablation and the wounding immediately following resurfacing. With fractional resurfacing, one-day post-treatment you may see some mild edema under the eyes and some mild redness that persists for a few days.

With PSR, after about three low-energy treatments, patients can experience some mild exfoliation of the skin, just a mild peel. There is a slight exfoliation of the skin for 2 days after three simple treatments involving topical anesthesia. Higher fluences result in more exfoliation that takes 5 to 7 days to heal.

So, is there a middle ground? Both PSR and fractional resurfacing offer something that's in between ablative and non-ablative resurfacing options. At this point, they are promising technologies that offer a "middle-ground" option. ■

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favorably to ablative treatments in terms of the fact it is something safer and with much less downtime.

Comparing the Procedures

There's no question that ablative resurfacing is an outstanding procedure, which produced excellent results. Unfortunately, the side effects and downtime resulting from this treatment make it an option that many patients will not choose.

Fractional resurfacing involves minimal downtime and is safe and effective for collagen remodeling, dyspigmentation and eliminating telangiectasia. It's promising for a variety of applications,

The Future of Hair Removal Technology

Have we reached the end of the development line?

By Melanie C. Grossman, M.D., Christine Dierickx, M.D., and R. Rox Anderson, M.D.

The first report of hair removal with lasers was presented at the American Society for Laser Medicine and Surgery in 1995. In the early days of laser hair removal technology, all we had available to us the Q-switched Nd:YAG with a carbon suspension (Thermalase Softlight), and the long-pulsed ruby laser also appeared promising. Some physicians also tested 5-aminolevulinic acid (ALA) photodynamic therapy (PDT).

The long-pulsed ruby laser turned out to be the most effective technology for attaining long-term hair loss. Subsequently, many different lasers (e.g., the millisecond-pulsed alexandrite and diode lasers and the long-pulsed Nd:YAG) were modeled after that technology.

Now even more hair removal devices are on the market. Initially, we were only able to treat light-skinned, dark-haired patients. The evolution of the technology has allowed us to treat darker-skinned patients effectively, but we are still unable to successfully remove white hair. Blond hair and thin hair in dark-skinned individuals also continue to present a challenge.

New devices are readily available and treatments have and will continue to become less expensive and faster. But the important questions to ask are: What structures are these technologies targeting to remove hair? How far have we come with removing unwanted hair? Is there still room to improve the technology, or are we at the end of the development line? This article addresses these and other relevant issues.

What Limitations Affect Outcomes?

We still have many questions to answer when we discuss limitations to hair removal efficacy. For example, are some areas of the body more susceptible to hair removal? The skin on the back is thicker, so does that mean we need to target structures that

are located more deeply in the skin? Or, does it not even make a difference whether the amount of light delivered to the actual targets varies? What should our ultimate target be when perform-

What are the Controversies?

- 1. Are we targeting the most effective structures for attaining long-term hair removal?**
- 2. Is anything being tested that's effective for treating patients who don't respond to hair removal techniques?**
- 3. Will home-based hair removal eliminate the need for in-office procedures?**

ing hair removal with lasers or light devices? Should we target stem cells, which are located in the bulge? Or, should we really focus on the hair matrix and the hair bulb, which are located at the end of the hair follicle? Or, should our main target be the vessels in the papilla?

Then, if we finally determine the best target, what should we do to this target? Should we destroy it completely? Should we destroy it partially and miniaturize the hair? Or, should we also destroy the perifollicular tissue immediately around it? We just don't know.

One of the options for improving hair removal technologies is to try to optimize the light delivery to the target, whatever that target might be. There are two options for doing so:

- 1. *Selectively increase the light delivery to the target alone.*** (We can increase the power density at a selected depth, where it's estimated the target resides.)



The photo on left shows a patient with excessive back hair. The photo on the right shows what they are looked like after treatment with _____. Photos provided by Laserscope.

2. Increase the light delivery to the follicle and perifollicular area and damage the entire follicular structure.

Some companies are trying to get the skin closer to the light device and deliver four to five times more energy to the whole follicle. Time will tell if this will increase efficacy.

The identity of the target aside, how far have we come with hair removal technology, and is there room for improvement?

Is There Still Room for Improvement?

Is the science of hair removal at a plateau? Have we reached the end of the development line?

We still need to develop an effective technology for eliminating white hair. Another limitation is hair color, which is melanin-dependent. We could use an exogenous chromophore such as the photosensitizer ALA. Early on, carbon particles were experimented with, as well as different hair dyes and liposome melanin such as Meladine. They produced disappointing results. However, ALA-PDT may provide the answer to effectively treating white or blond hair, but more studies are needed.

One area in which the technology has greatly improved is in the incidence of long-term hyperpigmentation. The use of longer pulse widths and longer wavelengths have allowed for the treatment of somewhat darker skin without this adverse effect, but problems still exist when focusing on the darkest complexions, despite improved technology.

Limitations of efficacy are evident. When we remove hair, we see that after a single treatment, we are only able to obtain permanent hair loss about 20% to 40% of the time. With each additional treatment given at the right time in the hair growth phase, we get an additional loss of 20% to 40%, so we need several treatments to achieve complete, long-term hair loss.

Some investigators have been working on selective delivery of dyes into follicles with microspheres. With an optimal size of 1.5 μm , they were able to deliver 55% selectively to the follicles up to a depth of more than 2300 μm . Using these microspheres with a dye to selectively deliver energy to the follicles seems promising.

Side Effects and Non-Responders

The more we attempt to remove hair, the more side effects we see. For example, in the typical young female patient who has fine fuzz on the cheeks, vellus hairs convert to terminal hairs with the use of a low-dose 1064 nm laser. This conversion also happens in other areas. Hair stimulation is sometimes an undesirable effect of treatment and it's a problem. It would be interesting to see if we could turn this "side effect" to our advantage, seeing as many people are eager to grow more hair. However, at this point, we don't understand what's going on.

Some patients, despite having dark hair and fair skin, are non-responders. These patients only represent a small percentage of the population, but they are also a noteworthy focus for future studies and technologies.

Other challenges to effective hair removal include the following.

- **Using exogenous dyes.** The photothermal targeting of melanin has been fairly successful, while attempts to replace melanin with exogenous dyes have failed repeatedly. The problem could be that we're not getting enough of the dye inside the follicle. Hopefully, we'll find some success with exogenous dye targeting in the future.

- **Exploring photodynamic therapy with ALA.** ALA/PDT is quite effective and is hair-color independent. Unlike laser hair removal, where you target melanin, ALA/PDT is highly selective



At left is the patient before laser hair removal. At right is the patient after three treatments (1 month apart) with the Nd:YAG (1064 nm) laser at a fluence of 40 J/cm² and a pulse width of 40 ms. *Photos courtesy of Heather Woolery-Lloyd, M.D.*

for the growth phase, or anagen phase, of the follicle. High-dose ALA/PDT kills nearly 100% of anagen hairs.

To attain a high efficacy with ALA, we need to use red light at high doses. In one study on PDT for hirsutism,¹ researchers tested 10% and 20% ALA exposed to light from a 630-nm argon pumped dye laser at fluences of 100 J/cm² and 200 J/cm². Patients in this study were treated 3 hours after ALA was applied to wax-epilated skin at all doses and, on one site, 3 hours after ALA was applied to shaven skin.

Researchers found that for both the epilated and shaven groups, the combination of 20% ALA at 3 hours with occlusion and 200 J/cm² of red light was most effective. Also, researchers found that while prior to this treatment, protoporphyrin IX fluorescence was seen within follicles and throughout the dermis, after treatment there was follicular and epidermal damage with sparing of the the adjacent dermis.

On the Horizon

The methods of hair removal we currently use may work well in practice, but we don't know much about cumulative effects. That's why it's important for companies to continue offering newer, better devices and technologies.

One major new development in the area of hair removal is the availability of home-use devices. We all knew from the beginning that laser hair removal or intense pulsed light hair removal could induce temporary hair loss and permanent hair reduction, but we were not concerned with temporary hair loss, as this is quite easy to achieve. We wanted to focus on permanent hair reduction, which led to the development of home devices that can safely and effectively stun the hair. Patients want to manage their hair removal issues in the privacy of their own homes. With

home-use devices, which induce temporary hair diminution, patients can repeat the procedure whenever they want.

We have not reached the end of the development line as far as hair removal goes. Companies are constantly tweaking and improving their products and we are getting closer to more permanent solutions. ■

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Patients want to manage their hair removal issues by themselves and in the privacy of their own homes.

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Safety vs. Efficacy

How is it that safe, yet sometimes ineffective, dermatologic devices receive approval from the FDA?

By Richard Felten, Mitchell Levinson,
and Eric F. Bernstein, M.D.

Just because a product is cleared by the FDA does not necessarily mean that the safety and efficacy have been demonstrated in a clinical trial. This true statement has, no doubt, been the source of bewilderment and, possibly, anger for many dermatologists.

How can this be possible?

What are the Controversies?

- 1. How do ineffective devices get an FDA stamp of approval?**
- 2. Why are indications for devices often much different than the mechanisms of action of the devices?**

Device Approval Process in a Nutshell

First, it helps to understand some of the basics of how devices are approved. To obtain FDA approval for a technology-based medical device, companies must travel down one of the following two common clearance routes:

1. *Pre-Market Approval (PMA)/Product Development Protocol (PDP)*. This route is for Class III devices, and devices that have a higher-risk profile or do not have a legally marketed predicate device to which a technological and specification comparison can be made under the Pre-Market Notification program.

2. *510(k) Pre-Market Notification*. During this process, the burden is on the company to demonstrate substantial equivalence

to a legally marketed device. This route is the most common clearance pathway for getting devices to market.

The Approval Process in More Detail

The traditional 510(k) approval process does not require a device manufacturer to perform clinical trials with the device. Under this type of approval, a company must compare its device's materials, technological characteristics, function, and the indications for use to the predicate device. The predicate device is considered the first device approved in a specific category (e.g., the carbon dioxide [CO₂] laser is the predicate for all wrinkle-removal devices). So companies with laser and light devices seeking approval for the indication of wrinkle removal must compare their devices to the CO₂ laser.

For example, say a company is seeking approval for a new intense pulsed light (IPL) system that is similar to other IPL systems that are legally marketed in the United States. To attain 510(k) approval for the new IPL system, the manufacturer could compare the energy per square centimeter and the device's wavelength to the predicate device.

However, if a company wants to make a device that is technologically different but has a similar clinical effect to a predicate device, then it must compare the effect(s) of the new device with the predicate device — not just compare the technological characteristics. To do this, a company must conduct a clinical trial to demonstrate that the safety and effectiveness of the device are substantially equivalent to the predicate device.

Conflicts with Indications and Usage

It is common for dermatologic device indications to conflict with how they are used. For example, the Thermage Thermacool

radiofrequency device is cleared for wrinkle reduction, yet the mechanism of action of the device is tissue tightening, which is the technology discussed when the company describes how its device achieves wrinkle reduction.

So, why is this? This is a discussion that goes back almost as long as wrinkle removal devices have been approved by the FDA, said Richard Felten, Senior Reviewer and Photobiologist with the General Surgical Devices Branch of the FDA.

"What we've told most companies is in your promotional advertisement, if you very clearly state at the beginning what the device is cleared for, then you may talk about how the device achieves that endpoint.

"So, for example, Coherent Medical, which was the first company to get clearance for a wrinkle removal, included comments in its promotional advertisement about collagen formation. We said 'go ahead, you can do that. You can talk about how you're altering collagen. But you can't claim you have a device that alters collagen. You have a device that fixes wrinkles,'" explained Mr. Felten.

"The agency very actively goes after any company that promotes its device for skin tightening, photorejuvenation or anti-aging in the indication," Mr. Felten added.

What Information Should You Get from Device Manufacturers?

As was already stated, you can't assume that the safety and efficacy of a device have been demonstrated in a clinical trial just because the device was approved by the FDA. So, where do you find the information you need about a device?

First and foremost, ask manufacturers what data were provided in order to secure the FDA clearance for the device.

Second, insist on other proof sources: Clinical studies, peer-reviewed articles, other supporting scientific proof to demonstrate to you before you buy into a new technology.

However, as several dermatologists noted, having access to this information is often difficult and impossible.

According to one conference attendee, Emil Tanghetti, M.D., who is a Clinical Professor at the University of California Davis, "Those of us in the field find that safety and efficacy aren't necessarily mutually exclusive," he explained. "We're trying to find out if a device is efficacious, but we're really not helped because often the P-values don't make much sense, and sometimes they're not even available with some of the devices. If we rest upon some of the Phase IV studies in the device industry, we can't even halfway believe them. How can the FDA help us?" Dr. Tanghetti asked.

"Historically," explained Mr. Felten, "Congress never intended the pre-market notification regulation, the 510(k), to exist beyond

Are Companies Required to Report Side Effects After a Device is on the Market?

Q. What is the responsibility of device manufacturers after a device has been cleared by the FDA and is on the market? Is industry obligated to report side effects and complications? Also, what is the obligation of physicians to report complications that they encounter?

A. According to Mr. Richard Felten, Senior Reviewer and Photobiologist with the General Surgical Devices Branch of the FDA, Medwatch requires that industry report all adverse events that potentially could cause injury to patients.

Companies do not need to report a device failure if, for example, an inconsequential event took place such as a light bulb burned out. However, for example, if the fiber optics break and patients were burned, then that must be reported to us for evaluation. Industry must also keep records, which are reviewed during FDA inspections.

"It's frustrating to us at the FDA that practitioners don't always tell us about adverse events," explained Mr. Felten. "I think that this happens because practitioners are so used to expecting things to happen that some events aren't viewed as potential injuries. We estimate that at the FDA we see only about 10% of the actual adverse event reports due to us," Mr. Felten added.

"The other problem is that in many cases practitioners might be using a device off-label, so it could put a company in a bad quandary when asked for advice in solving the problem," explained Mr. Felten. "By law, the company can't tell you how to fix the problem because it doesn't have approval for that use; therefore, they can't talk about it because, by providing instructions for use, they can be viewed as no promoting the device for this off-label use." ■

How Big is the Device Market?

In 2004, it was \$100 billion in annual sales. This works out to be about five-fold smaller than the pharmaceutical industry, which was around \$500 billion per year in the same time period.

The thoughts are that drugs have profit margins that are 90% to 95%. Of that, 15% of sales go into research and development. Clinical trials for pharmaceutical companies are also much more costly and take longer to complete.

In the device market, the profit margins are typically 60% to 80%, or less (all devices, not just lasers). In addition, about 6% of sales is allocated for research and development, and the clinical trials for devices are much less costly and time-consuming when compared with the pharmaceutical industry. ■

Eric Bernstein, M.D.

Obvious solutions would be for Congress to change the law and require that device manufacturers can only receive FDA approval through the PMA process and not the 510(k), although Mr. Felten conceded that this probably wouldn't happen within the next few years. Another option would be for practitioners to work together and require that companies publish studies about devices in peer-reviewed journals.

Either way, a concentrated effort and change in thinking will be necessary. ■

Richard Felten is Senior Reviewer and Photobiologist with the General Surgical Devices Branch of the FDA.

Mitch Levinson is from the Thermage Corporation.

Eric Bernstein, M.D., is volunteer faculty at the University of Pennsylvania in the Department of Dermatology as a Clinical Associate Professor. Dr. Bernstein is also Director of the Laser Surgery and Cosmetic Dermatology Centers in Marlton, NJ; and Bryn Mawr, PA.

the first year or two of the law. Congress really wanted devices to look like drugs and everything to go to market through PMAs.

"What happened instead, and I'll use lasers as the best example because they've been around the longest, is that when lasers went from only CO₂ lasers to including the addition of Nd: YAG lasers, a decision was made about the intended use of the devices," said Mr. Felten. "At that time, it was decided that lasers be treated with the intended use of cutting tissue. It was agreed upon to let the physicians decide how or what they were going to cut, just as we do with scalpels. So, the clinical trial data that have been used to get most new lasers to the market is more focused on: *Can the physician actually cut what he wants to cut? And then, does the device enable him to cut as safely as he had before the device existed?*"

Can the Problem Be Solved?

The best way to solve this problem would be for companies to publish the clinical data used to gain FDA PMA approval or 510(k) clearance. Yet, there's no FDA requirement for that. In addition, sometimes companies won't release the information because it's considered proprietary data.

Hot Topics

Controversies, trends and debates in dermatology

Saphenous Vein Treatment with 1320-nm Laser

Girish S. Munavalli, M.D., M.H.S.

We routinely treat many conditions in our offices and for these, we typically turn to the same options. However, it's important to keep aware of new options. We need to look at upcoming technologies with an open mind, and recognize that they may be more functional and more beneficial to patients, that they may decrease morbidity, and may be as good as or better than the gold standard.

For example, saphenous reflux is common in general dermatology offices. For years, we've had many options, including vein stripping and ligation, and more recently, diode lasers. And now, we have an even newer treatment option.

In 2004, the first mid-infrared 1320-nm laser (CoolTouch CTEV) was FDA approved for endovenous treatment of the greater saphenous vein. This laser targets water as the chromophore, resulting in a shorter absorption length compared to diode lasers. It actually uses the wavelength to heat the vessel wall directly, creating collagen contraction and occluding the vein, and it is not dependent on hemoglobin.

In *ex-vivo* studies, we've shown that contraction can result in vessel obliteration. In more than 180 treatments, we have had good success rates with this treatment. Patients in studies in Germany have shown much less morbidity with this treatment compared to hemoglobin-dependent devices. With a single needle puncture and a 4- to 5-minute procedure, you can eliminate veins. ■

Dr. Munavalli is in practice at the Maryland Laser, Skin and Vein Institute in Hunt Valley, MD.

Alternative to Liposuction

Elizabeth Tanzi, M.D.

If you're looking for a non-invasive alternative to liposuction, then consider the VelaSmooth device for your patients. I explain to patients that they'll need 8 to 10 sessions of this treatment (two treatments per week for about 4 to 5 weeks) to get temporary improvement of the look of their cellulite. Maintenance treatments, anywhere from once a month to every 3 months, depending on the patient, are often necessary. I don't perform the treatment if a patient has elevated expectations of what the VelaSmooth can do. It's a temporary improvement of the look of cellulite. It is not a cure.

I have to do a lot of re-education in my practice. Patients come in with unrealistic expectations, saying that they read about the treatment in a beauty magazine and thought it was great.

I have also had a number of dermatologists ask me what kind of results I really see and if the device lives up to the marketing. I tell them exactly what I tell the patients.

There are quite a few patients who decide not to go through with the treatment after I discuss it with them. But, if patients are willing to accept the limitations of the treatment, I treat them and the majority of patients are happy. ■

Dr. Tanzi is the Co-Director of the Washington Institute of Dermatologic Laser Surgery in Washington, D.C. She is Clinical Instructor of Dermatology at Johns Hopkins University School of Medicine.

Compounding: Buyer Beware

D. Geoffrey Shulman, M.D., F.R.C.P.C.

DUSA Pharmaceuticals offers the only FDA-approved aminolevulinic acid (ALA) (Levulan Kerastick). To obtain this FDA approval, we passed stringent reviews, pre-clinical, clinical trials and ongoing inspection of our products and facilities. There is no such thing as a FDA-approved generic ALA, and compounded ALA is not generic ALA. Compounded ALA is not reviewed, inspected, approved or monitored by the FDA for quality control, composition, concentration, stability or manufacturing standards.

I'm a dermatologist. I know there's a good use for compounding pharmacies, but when an FDA-approved product is available, the use of a non-FDA approved ALA for photodynamic therapy (PDT) involves a number of potential risks.

Risks for Patients. When you use a product with unproven safety and efficacy, you put patients at risk of phototoxic reactions.

Medical-Legal Risks. If you use a compounded product and a patient gets a severe phototoxic reaction, medical malpractice issues come into play. Insurance may not cover use of a compounded product when an FDA-approved product is available. Also, if someone has a Medicare audit and they're using a J-code for the approved Levulan but using a different product, he may be violating federal law. In extreme cases, such those where fake Botox was being used in Florida, doctors' licenses were suspended. In some cases, licenses were suspended just for using unapproved product even when there was no harm to patients.

Patent Violation Risks. DUSA has many patents related to ALA/PDT in our products. We actually are in litigation with the compounding firm. Doctors using compounded ALA for a patented use are liable for patent infringement as well.

Ethical Issues. DUSA, in contrast to compounding firms, has invested tens of millions of dollars and many years of effort and hard work to develop ALA-PDT for dermatology. And we need tens of millions more to do all the research required for all of these indications, such as hair removal. We'll continue to spend millions more to develop new indications while manufacturing Levulan at FDA-quality standards. Dermatologists can benefit by supporting companies that invest back into the field of dermatology. This is an issue that affects many companies in this field. ■

Dr. Shulman is a dermatologist and Chairman and CEO of DUSA Pharmaceuticals.

Tattoo Law Project

Maurice Adatto, M.D.

Should there be a federal law regulating the main aspects of tattooing, piercing and permanent makeup practices? By 2006, Switzerland will likely have such a law in place. The goal of this proposed law is to protect the customers as well as the professionals in these fields. The law will state that all tattoo professionals belong to a recognized association, be at least 18 years old, have at least 5 years experience and have a post-graduate education in this area.

The law will regulate hygiene issues and the toxicology of tattoo pigments. It will also force customers to be forthcoming about any contraindications they may have to be tattooed or pierced.

But will this law help protect customers or professionals? Questions still remain with regard to this law. It's not clear how it will be enforced or which federal department will enforce it. ■

Dr. Adatto is President of the European Society for Laser Dermatology and Medical Director of the Skinpulse Dermatology Centre in Geneva, Switzerland.

Defining Dermatology Terms: Q&A

Richard Felten: I've been attending dermatology meetings for the last 10 years, and I've been doing most of the FDA reviews of devices used in dermatology for the same period of time. I continue to hear about skin tightening, skin toning and photorejuvenation. I've discussed with companies how to make measurements for skin tightening, but I can't figure out how to make a measurement that the FDA can evaluate. There's not a laser on the market that has a clearance for any of these terms. What do the experts believe these terms mean?

R. Rox Anderson, M.D.: The tightening of skin is measurable. We've done studies where you put little micro-tattoos on the face, measure the skin area, and actually show that there's less skin area among the tattoos. You do have to remove the tattoos at the end of the study.

Mr. Felten: I agree that you can use the microdots to make measurements. We've actually seen this in a couple of presentations that have come to us at the FDA. But we've asked the question: How did you ensure that you could reproducibly identify

Ocular Safety

Brian Biesman, M.D.

Using appropriate eye protection, including goggles, is important when working with lasers, but just putting on a pair of goggles does not in and of itself assure you of safety from the devices. Every patient has different facial anatomy. Some eyes are more prominent. Some patients have very small, thin faces, and the goggles hang over the edge, whereas other people have larger faces and accommodate the goggles more effectively.

A lot of doctors use goggles incorrectly. Depending on what you're doing, if you're really working far away from the eyes or using a wavelength that isn't particularly dangerous, that might be okay. But if you're working anywhere around the eye, you can have a false sense of security if your eye protection is inappropriately placed.

When using lasers, especially the 1064 nm laser and the 810 nm diode, in the peri-orbital region to treat between the eyebrows for a "unibrow" or under the eyebrows, my advice with regard to these devices is do so at your own risk. These wavelengths are very dangerous to the eye. If you're going to treat in

those areas, you need to have a cornea-protective lens behind the lids. And, again, you must make sure that that lens is sufficient in size to protect the globe adequately. ■

Dr. Biesman is an ophthalmologist in practice in Nashville, TN.

When using lasers, especially the 1064 nm laser and the 810 nm diode, in the peri-orbital region to treat between the eyebrows for a "unibrow" or under the eyebrows, do so at your own risk.

those areas? If the dots are getting closer together, you're trying to make some kind of measurement orientation. How much error do you have in the person making those measurements just by doing the measurements over and over again, or if there's a change in contour and you get tightening or toning, does that change the orientation? Are the measurements really changing or does the skin just look tighter? I agree you can do it, but we have yet to see these measurements come in to us in a way that has convinced us, or maybe nobody has done a good study yet to show the reproducibility of it.

Robert Weiss, M.D.: I think we have a fairly good definition of photorejuvenation. If you read most of the papers about rejuvenation, it's pretty clear that we're talking about reduction of telangiectasias, reduction or blending of dyspigmentation. We're talking about textural smoothing, and histologically, that's defined with a reduction in the elastosis.

Jeffrey S. Dover, M.D.: I believe the FDA, however, looks at reduction of brown pigmentation and reduction of wrinkling, but

this generic term "rejuvenation" means so many things to so many people that it would be impossible to approve a device for an indication of photorejuvenation.

Mr. Felten: You're right. We've cleared wrinkles as a special thing because we have a standard we use, which is the Fitzpatrick Scale. For telangiectasia claims, we've allowed companies to show us that first you can see the blood vessel and after treatment you can see it go away. For change in pigmentation, again, we've allowed companies to show that treatment lightens color. We did the same thing with tattoos a long time ago — companies could show us changes in color. But when people say photorejuvenation, I'm not sure that's something you can show.

Many companies seem to want to use that as a claim, but while I'm sure you can look at patients you treat and say they look better or younger, we can't simply look at a picture and identify that. We can identify the telangiectasia, the melasma, the port wine stains, the spider veins, the pigment change. It's that generic term of photorejuvenation that we would like to have someone show us how to measure. ■

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