Actinic Keratoses (AKs) are a relatively common premalignant inflammatory skin lesion, which affect a large proportion of individuals with light skin that has been exposed to sun and/or artificial UV radiation. Over a period of 10 years, a person with 8 AKs has a 6.1-10.2% chance of developing a squamous cell carcinoma.1

Risk factors for AKs include being:
• fair skinned
• male
• >50 years of age
• sensitive to the sun with poor ability to tan and frequent sunburns
• on a high fat diet
• immunosuppressed.2-6

AKs have a wide range of clinical presentations and there is no single therapy that treats the complete spectrum of pathologies and individuals. Current treatment options include cryosurgery, curettage, surgical excision, laser, chemical peels, photodynamic therapy (PDT), topical fluorouracil, and retinoids. Topical imiquimod has also been used experimentally.7 However, all these options have been associated with local discomfort and pain in some cases.8,9 Topical 3% diclofenac in 2.5% hyaluronic gel (Solaraze™, Bioglan Pharma) is a relatively new treatment that has been shown to be effective and well tolerated for the treatment of AKs.

**ABSTRACT**

Actinic Keratoses (AKs) are epidermal skin lesions that have the potential to develop into squamous cell carcinoma. Many of the treatment options available can cause discomfort, pain or skin irritation. Topical 3% diclofenac in 2.5% hyaluronic gel (Solaraze™, Bioglan Pharma) is a relatively new treatment that has been shown to be effective and well tolerated for the treatment of AKs.

KEY WORDS: actinic keratoses, diclofenac, hyaluronic acid

AKs have a wide range of clinical presentations and there is no single therapy that treats the complete spectrum of pathologies and individuals. Current treatment options include cryosurgery, curettage, surgical excision, laser, chemical peels, photodynamic therapy (PDT), topical fluorouracil, and retinoids. Topical imiquimod has also been used experimentally.3 However, all these options have been associated with local discomfort and pain in some cases.8,9 Topical 3% diclofenac in 2.5% hyaluronic acid (Solaraze®, Bioglan Pharma) is a new treatment for AKs that has been approved in the US, Canada and several countries in the European Union.

**Mechanism of Action**

Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) that is a potent inhibitor of inducible cyclo-oxygenase (COX-2), resulting in a reduction of
prostaglandin synthesis. Sun damage and AKs have been linked with raised prostaglandins in exposed skin.

Oral administration of this drug can result in adverse effects. However, when this gel is applied topically, diclofenac is absorbed into the epidermis, and studies indicate that systemic absorption is much lower than that occurring after oral daily dosing of this drug.

Clinical Trials

In an open-label study of 29 patients with mild to severe AKs, 1.0gm of the gel was applied twice daily for up to 180 days (the median was 62 days). At the end of the treatment, lesions were scored using visual and photographic assessment. There was a highly significant (p<0.001) improvement in lesions with 48% showing a complete response. Thirty days post treatment, 27 of the patients were reassessed and those who had a complete response rose to 81% with another four (15%) showing marked clinical improvement.

In a randomized double-blind, placebo controlled trial involving individuals with >5 AK lesions, adult patients received either 3% diclofenac gel in 2.5% hyaluronan gel or the gel vehicle as a placebo. They received 0.5gm b.i.d. for 90 days. Assessments were made at each visit and 1 month post-treatment, and included Target Lesion Number Score (TLNS), Cumulative Lesion Number Score (CLNS) and Global Improvement Indices (GII). At the follow-up visit, 50% of the patients using diclofenac showed complete resolution of all target lesions using TLNS compared to 20% in the placebo group (p<0.001). With regard to CLNS, 47% of patients applying diclofenac showed complete resolution compared to 19% in the placebo group (p<0.001) and the GII showed a 79% improvement in the diclofenac group vs. 45% in the placebo group (p<0.001).

Another multicenter, double-blind, placebo-controlled study of 195 patients received the same formulation of diclofenac, 0.5g or vehicle, twice daily for either 30 days or 60 days. While there was no statistical difference in complete responders in the 30 day treatment groups, significantly more patients given active treatment for 60 days had TLNS=0 (33% vs. 10%, p<0.05). With regard to CLNS, 31% of patients in the active group showed complete clearance vs. 8% for the placebo group (p<0.05). GII scores were also significantly better in the 60 day active treatment group (p<0.05).

In a randomized, double-blind, controlled trial, 150 patients were asked to apply diclofenac 3% gel twice daily as well as a sunscreen once daily for 24 weeks. The complete response rates were 29% for the active gel and 17% for the control gel. The difference was not statistically significant (p=0.14).

Furthermore, a high percentage of patients in both groups experienced a partial response to the treatment (38%) for the diclofenac group and 45% for the control group, but there was no significant difference in the spectrum of response between the two treatments (p=0.18). It should be noted

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Treatment</th>
<th>% Complete Response</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open label study</td>
<td>29</td>
<td>1.0gm applied b.i.d. for up to 180 days</td>
<td>81%*</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Randomized, double-blind, placebo controlled study</td>
<td>96</td>
<td>0.5gm b.i.d. vs. placebo for 90 days</td>
<td>50% (TLNS) vs. 20% placebo*</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Multicenter, double-blind, placebo-controlled</td>
<td>195</td>
<td>0.5gm b.i.d. vs. placebo for 30 or 60 days</td>
<td>30 days: 14% (TLNS) vs. 4% placebo</td>
<td>30 days: NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>60 days: 33% (TLNS) vs. 10% placebo*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14% (CLNS) vs. 4% placebo</td>
<td></td>
</tr>
<tr>
<td>Randomized, double-blind, controlled trial</td>
<td>150</td>
<td>Applied b.i.d. + sunscreen for 8-24 weeks</td>
<td>29% vs. 17% placebo</td>
<td>P=0.14</td>
</tr>
</tbody>
</table>

Table 1: Clinical trials results for diclofenac 3% in 2.5% hyaluronan gel

*Measured 30 days post-treatment
that the patients used sunscreens and there was no follow-up assessment 30 days post-treatment.

Adverse Events

Generally, adverse events have been mild-to-moderate in severity. The most commonly reported adverse events include: pruritus, application site reactions, dry skin, rash and erythema.

Conclusion

The primary cause of AKs is exposure to UV light. Wearing sun protective clothing, sunscreen and avoiding direct sunlight can help prevent them. However, for those patients who already have AKs, this new topical preparation provides an alternate therapeutic option. It has been shown to be effective, well-tolerated, and easy to administer.

References


Reviewers for 2003

During 2003, the reviewers noted below gave generously of their time and talents and completed manuscript reviews for the Skin Therapy Letter. On behalf of the Editorial Advisory Board and our readership, we thank them for their efforts.

Stuart Maddin, MD, FRCPC
Editor-In-Chief

Abdulmajeed Alajlar
Murad Alam
Hugo Degreef
Jeffery S. Dover
Jan Dutz

Bernard S. Goffe
Wayne Gulliver
Jason K. Rivers
D. Richard Thomas
Marni C. Wiseman

Go Online with


At last, a comprehensive website offering acne information for physicians and their patients.

Featuring content from
• Jerry K.L. Tan, MD
• Guy Webster, MD
• Marianne O’Donoghue, MD

Register today to receive updates about new online features!
Laser Treatment of Scars
E. L. Tanzi, MD and T. S. Alster, MD
Washington Institute of Dermatologic Laser Surgery, Washington, D.C., USA

ABSTRACT
Over the past decade, refinements in laser technology as well as advances in laser techniques have enabled dermatologic surgeons to define the most appropriate lasers to use for different scar types without the adverse sequelae and recurrence rates noted with older surgical revision techniques and continuous wave laser systems.

KEY WORDS: scars, laser, treatment, surgery

Scar Characteristics
Proper scar classification is important because differences in clinical scar characteristics determine the treatment protocol. Scar color, texture, and morphology, as well as previously applied treatments, will affect the laser parameters and number of treatments required for optimal improvement. See Table 1.

Hypertrophic scars are raised, firm, erythematous scars formed as the result of overzealous collagen synthesis coupled with limited collagen lysis during the remodeling phase of wound healing. The result is the formation of thick, hyalinized collagen bundles consisting of fibroblasts and fibrocytes. Despite the obvious tissue proliferation, hypertrophic scars remain within the confines of the original integument injury and may regress with time.

Keloids are raised, reddish-purple, nodular scars which, upon palpation, are firmer than hypertrophic scars. Keloids exhibit a prolonged, proliferative phase resulting in the appearance of thick hyalinized collagen bundles similar to those produced by hypertrophic scars, but extend beyond the margins of the inciting wound and do not regress over time. Although they can be seen in all skin types, keloids appear most frequently in patients with darker skin tones and are related to an inherited metabolic alteration in collagen.

Atrophic scars are dermal depressions most commonly caused by collagen destruction during the course of an inflammatory skin disease such as cystic acne or varicella. Scarring after inflammatory or cystic acne can manifest as atrophic, saucerized, ice pick, or boxcar scars. While ice pick and boxcar scars respond best to dermal filler augmentation or punch excision, atrophic scars usually respond well to laser therapy.

Laser Treatment for Hypertrophic Scars and Keloids
Progress in laser technology and refinements in technique have made laser therapy a preferred treatment choice for hypertrophic scars and keloids. Studies published using

<table>
<thead>
<tr>
<th>Scar Type</th>
<th>Clinical Characteristics</th>
<th>Preferred Laser Choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertrophic</td>
<td>Raised, pink-red, limited to site of original trauma</td>
<td>585nm PDL</td>
</tr>
<tr>
<td>Keloid</td>
<td>Raised, deep red-purple, extend beyond original traumatic border</td>
<td>585nm PDL</td>
</tr>
<tr>
<td>Atrophic</td>
<td>Saucer-like or ice-pick indentations</td>
<td>CO₂ (10,600nm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Er:YAG (2940nm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Long-pulsed diode (1450nm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Long-pulsed Nd:YAG (1320nm)</td>
</tr>
</tbody>
</table>

Table 1: Scar types and their preferred laser choice
the 585nm pulsed dye laser (PDL)\textsuperscript{5-7} have demonstrated striking improvements in scar erythema, pliability, bulk, and dysesthesia with minimal side-effects and treatment discomfort. These observations have been substantiated by skin surface textural analysis, erythema reflectance spectrometry readings, scar height measurements, and pliability scores.

Significant improvement in hypertrophic scars is generally noted within a couple of PDL treatments. (See Figures 1A, 1B) Although thick keloids may require the simultaneous use of intralosional corticosteroid or 5-fluorouracil injections to enhance clinical results, the adjunctive use of intralosional corticosteroids does not significantly enhance the clinical improvement seen after PDL treatment in all but the most symptomatic or proliferative hypertrophic scars.\textsuperscript{7}

Adjacent, non-overlapping laser pulses at fluences ranging 6.0-7.5J/cm\textsuperscript{2} (7mm spot) or 4.5-5.5J/cm\textsuperscript{2} (10mm spot) should be applied over the entire surface of the scar. Energy densities are decreased by 10\% in patients with darker skin phototypes or for scars in delicate locations (e.g., the anterior chest). With PDL irradiation, the patient experiences a snapping sensation similar to that of a rubberband. Post-treatment, a mild sunburn-like sensation is produced for 15-30 minutes that is generally well-tolerated; however, some patients may require application of an ice pack.

The most commonly experienced side-effect of 585nm PDL treatment is post-operative purpura, which can persist for several days. Swelling of treated skin may occur immediately after laser irradiation, but generally subsides within 48 hours. Strict sun precautions should be practiced between treatment sessions in order to avoid stimulating pigment production in the treated areas. Subsequent laser sessions should be postponed until any excess pigment has resolved, so that the presence of epidermal melanin does not compromise the effectiveness of the laser. Topical bleaching agents may be used to hasten pigment resolution. Treatments are typically delivered at 6-8 week intervals; however, longer treatment intervals may be necessary for adequate healing in those patients with darker skin phototypes who develop significant postoperative hyperpigmentation.

**Laser Treatment of Atrophic Scars**

**Ablative Laser Skin Resurfacing**

Facial atrophic scars can be safely and effectively resurfaced through the proper use of a high-energy, pulsed or scanned carbon dioxide (CO\textsubscript{2}) or Erbium-Yttrium-Aluminum-Garnet (Er:YAG) laser.\textsuperscript{2,3,8-11} These laser systems emit high energy densities within extremely short pulses that effect tissue vaporization with limited thermal conduction to non-targeted surrounding skin. Since each laser pass effects a predictable and reproducible amount of tissue vaporization and residual thermal damage, as much or as little tissue can be removed as required by the type of scar being treated.

Atrophic scar resurfacing with a CO\textsubscript{2} laser has effected scar improvements of 50\%-80\%.\textsuperscript{8-10} A predictable amount of epidermis and papillary dermis is vaporized by a typical CO\textsubscript{2} laser resurfacing procedure, with tissue vaporization depths of 20-60µm and zones of thermal necrosis ranging another 20-50µm. Immediate collagen shrinkage with subsequent collagen remodeling accounts for many of the clinical benefits observed after ablative laser skin resurfacing.

More recently, pulsed Er:YAG lasers have also been used for the treatment of atrophic scars.\textsuperscript{10,11} The short-pulsed Er:YAG laser was developed as a less aggressive alternative to CO\textsubscript{2} laser skin resurfacing. The 2940nm wavelength emitted by the Er:YAG laser corresponds to the peak absorption coefficient of water and is absorbed 12-18 times more efficiently by superficial, water-containing tissue than does the 10,600nm wavelength of the CO\textsubscript{2} laser. With a pulse duration of 250µsec, a typical short-pulsed Er:YAG laser ablates 10-20µm of tissue per pass at a fluence of 5J/cm\textsuperscript{2} and produces a residual zone of thermal

---

**Fig 1A**

Hypertrophic scars on upper lip before treatment

**Fig 1B**

Scar improvement seen after PDL treatment
injury not exceeding 15µm. The precise tissue ablation and limited residual thermal damage result in a faster postoperative recovery and improved side-effect profile as compared to CO₂ laser skin resurfacing.²,¹⁰ However, because of the limited zone of thermal injury, short-pulsed Er:YAG laser skin resurfacing is hindered by poor intraoperative hemostasis, limited collagen contraction, and substantially less impressive clinical results than with CO₂ laser skin resurfacing.

To overcome the limitations of short-pulsed Er:YAG laser skin resurfacing, “modulated” or “dual-mode” (short- and long-pulsed) Er:YAG systems have been developed that combine ablative and coagulative pulses to produce deeper tissue vaporization, greater contraction of collagen, and improved hemostasis. Studies have demonstrated significant clinical improvement in atrophic scars with these modulated laser systems.²,¹¹

Whether a CO₂ or modulated Er:YAG laser system is used to treat atrophic facial scars, the goal of treatment is to soften depressions and stimulate neocollagenesis in order to fill in the residual defects. (Figures 2A,B) For a small number of grouped scars, spot laser resurfacing may be a viable option. For more extensive and diffuse scarring, laser treatment should be performed with a scanning handpiece over the entire cosmetic unit in order to prevent obvious lines of demarcation between treated and untreated sites. With the CO₂ laser, a fluence of 300mJ is typically used to effect epidermal ablation with one pass. A dual-mode Er:YAG laser operated at a fluence of 22.5J/cm² achieves comparable results with a single pass. However, most atrophic scars will require multiple laser passes, regardless of the laser system used. Between each laser pass, the partially desiccated tissue must be completely removed with saline- or water-soaked gauze to prevent excessive thermal necrosis in residual tissue.

Side-effects and complications are potentially numerous after ablative laser scar resurfacing.²,⁸⁻¹¹ Expected side-effects in the immediate postoperative recovery period include intense erythema, edema, and serous discharge. The degree of erythema is directly correlated to the number of laser passes delivered, but typically improves spontaneously over time without requiring specific treatment. Other possible complications include infection, acne or milia formation, and dyspigmentation. Although laser skin resurfacing can be performed in darker-skinned patients, postinflammatory hyperpigmentation almost always occurs, typically within 3-4 weeks after treatment. This reaction pattern is temporary and its resolution can be hastened with topical bleaching and peeling agents; however, patients must be warned preoperatively that it may persist for several months. The Er:YAG laser is associated with a less complicated postoperative recovery period and less persistent hyperpigmentation than CO₂ laser skin resurfacing, which is of particular importance when treating patients with darker skin phototypes.¹¹ Rare but serious complications after ablative laser skin resurfacing include delayed-onset hypopigmentation, hypertrophic burn scars, disseminated infection, and ectropion.

**Nonablative Laser Skin Remodeling**

As a consequence of the risks associated with ablative laser skin resurfacing, great interest has been shown for less invasive methods to effectively treat atrophic facial scars. Several nonablative laser devices have demonstrated efficacy in the treatment of atrophic facial scars; however, the most popular and widely used are the 1320nm Neodymium:Yttrium-Aluminum-Garnet (Nd:YAG) and 1450nm diode lasers.¹²,¹³ Each system combines epidermal surface cooling with deeply penetrating wavelengths that selectively target water-containing tissue, thereby creating a selective thermal injury in the dermis without damage to the epidermis. Protocols for treatment often include three consecutive monthly laser treatment sessions with the greatest clinical improvement noted between 3 and 6 months after the final laser procedure.
Improvement of scars by 40-45% has been observed after either 1320nm Nd:YAG or 1450nm diode laser treatment, with results being substantiated by clinical assessments, patient satisfaction surveys, histologic evaluation, and skin surface texture (profilometry) measurements.\(^\text{12}\) (Figures 3A,B)

Side-effects and complications of nonablative laser treatment of atrophic facial scars are generally mild. Transient post-treatment erythema is observed in almost all patients, resolving within 24 hours. Blistering, crusting, and scarring are rare and although the risk of post-inflammatory hyperpigmentation is substantially reduced with nonablative laser treatment (compared to ablative CO\(_2\) or Er:YAG laser skin resurfacing), it is still possible—particularly in patients with darker skin phototypes.\(^\text{12}\) The post-inflammatory hyperpigmentation observed, however, is typically mild and resolves more quickly than that seen after ablative laser procedures.

Although a series of nonablative laser treatments can effect modest improvement in atrophic facial scars with minimal side-effects, the degree of clinical improvement does not equal that of ablative laser skin resurfacing. Therefore, it is critical to identify those patients best suited for non-ablative procedures in order to offer realistic clinical expectations and optimize patient satisfaction.

The newest approach in the treatment of acne and atrophic scarring includes the use of a nonablative radiofrequency device. Unlike a laser, which uses light energy to generate heat in targeted chromophores based on the theory of selective photothermolysis, radiofrequency technology produces an electric current that generates heat through resistance in the dermis and subcutaneous tissue, thus stimulating neocollagenesis and collagen remodeling. Preliminary studies\(^\text{14}\) demonstrate promise in the treatment of acne and, potentially, acne scarring. Further investigation is warranted to determine the role of this novel device in the treatment of atrophic facial scars.

References

### Update on Drugs

<table>
<thead>
<tr>
<th>Class</th>
<th>Name/Company</th>
<th>Approval Dates and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antipsoriatic Agent</strong></td>
<td>Efalizumab <em>RAPTIVA®</em> Genentech/XOMA/Serono Canada</td>
<td>The US FDA approved this biologic therapy in October 2003, for the treatment of chronic moderate-to-severe plaque psoriasis in adults ages 18 or older who are candidates for systemic therapy or phototherapy. Genentech and XOMA are collaborating on the development of <em>RAPTIVA®</em> in the US. Serono, Genentech’s marketing partner outside the US and Japan, is awaiting regulatory approval in Europe, Canada, Switzerland, Australia and New Zealand.</td>
</tr>
<tr>
<td><strong>HIV/AIDS</strong></td>
<td>TNX-355 Tanox</td>
<td>The US FDA granted fast track status in October 2003, to this humanized monoclonal antibody for the treatment of patients with HIV-1 infection who have failed or are failing antiretroviral therapy.</td>
</tr>
<tr>
<td><strong>Antibacterial Agent</strong></td>
<td>Ofloxacin Tablets Ranbaxy Pharmaceuticals</td>
<td>The Office of Generic Drugs of the US FDA approved new dosages for this antibiotic in September 2003. Ofloxacin 200mg, 300mg and 400mg were determined to be bioequivalent to Ortho McNeil’s Floxin® Tablets, 200mg, 300mg and 400mg respectively. This product is indicated for mild-to-moderate infections including uncomplicated skin and skin structure infections, chronic bronchitis, community-acquired pneumonia, acute and uncomplicated urethral and cervical gonorrhea among others.</td>
</tr>
<tr>
<td><strong>Antibacterial Agent</strong></td>
<td>Daptomycin for injection <em>Cubicin™</em> Cubist Pharmaceuticals</td>
<td>The US FDA approved this antibiotic in September 2003, for the treatment of complicated skin and skin structure infections caused by Gram-positive bacteria, including those caused by methicillin-resistant <em>Staphylococcus aureus</em> and methicillin-susceptive <em>S. pyogenes</em>, <em>S. Agalactiae</em>, <em>S. dysgalactiae</em> and the vancomycin-susceptible strains of <em>Enterococcus faecalis</em>. It is the first approved product in a new class of antibiotics called cyclic lipopeptide antibacterial agents.</td>
</tr>
</tbody>
</table>

### Drug News

| Anti-Acne Agent              | Phase III clinical trial results were reported in September 2003, for Actiza™ (Connetics Corp), an investigational new drug formulation of 1% clindamycin delivered in the Company’s proprietary Versafoam™ delivery system as a potential new topical treatment for acne. In a 12-week double-blind, active and placebo-controlled trial of 1,026 patients, Actiza™ was found to be not inferior to Clindagel® (clincamycin phosphate 1% topical gel, Galderma) as measured by the primary endpoints of Investigator’s Static Global Assessment and percent reduction in lesion counts from baseline to week 12. |
| Anti-Arthritic Agent         | In October 2003, Abbott Laboratories reported that a Phase III study has been initiated that will evaluate the potential of HUMIRA® (adalimumab) to improve signs and symptoms of psoriatic arthritis in adult patients with moderate-to-severe disease who have had inadequate response to disease modifying antirheumatic drugs. Patients in the trial will be randomized to receive HUMIRA® or placebo and responses will be measured by improvements in signs and symptoms as measured by American College of Rheumatology response scores. This study is in addition to the Phase III study in psoriatic arthritis initiated earlier in 2003. HUMIRA® is a human monoclonal antibody approved by the US FDA for reducing the signs and symptoms and inhibiting the progression of structural damage in adults with moderate-to-severe active rheumatoid arthritis. |