Acitretin (SORIATANE®, Roche Pharmaceuticals) is an aromatic retinoid, effective in the treatment of severe psoriasis. This study highlights data from two existing clinical trials to capture PASI 50 and PASI 75 responder rates which represent a common metric used in current psoriasis clinical trials. A review of pharmacokinetics, safety and a discussion of relapse rate establish acitretin as an efficacious, convenient, oral treatment for initial and maintenance therapy of severe psoriasis.

Key Words: acitretin, aromatic retinoid, psoriasis, PASI

Acitretin (SORIATANE®) is an aromatic retinoid which is used in the symptomatic treatment of severe psoriasis.

Mechanism of action

The efficacy of acitretin in psoriasis is mainly explained by the fact that this compound acts on a pathological epidermis to reduce proliferation and stimulate differentiation. It also decreases inflammation in the epidermis and dermis by interfering with various cytokines. However, in contrast to other systemic anti-psoriatic drugs, acitretin is neither cytotoxic nor immunosuppressive.

The cellular mechanisms underlying the pharmacological effects of acitretin are not well characterized. Acitretin appears to interfere with the intracellular metabolism of natural retinoids. It also competes with retinoic acid for CRABP (Cellular Retinoic Acid Binding Protein) binding and activates retinoic acid nuclear receptors (RARs).

Pharmacokinetics

Acitretin exists in the form of 10mg and 25mg capsules, administered once daily during a meal, since the concomitant intake with food increases the bioavailability of the drug. After treatment discontinuation, the terminal elimination half-life of acitretin is approximately 50 hours and that of its 13-cis isomer around 90 hours. This is much shorter than that of its more lipophilic ester, etretinate, which has been previously marketed for the same indications.

However, measurable levels of etretinate, have been detected in plasma samples of some patients taking acitretin. Experimental data indicate that etretinate is formed when acitretin is taken concomitantly with ethanol. This has been confirmed in a clinical study. No etretinate was found in patients who reported that they never drink alcohol while it was detected in all patients with an average weekly alcohol consumption of more than 200g ethanol (this corresponds to around 15 pints of beer or glasses of wine).
For the treatment of psoriasis

The recommended initial dose for acitretin therapy is 25-30mg/day. Maintenance doses of 25-50mg/day may be given after initial response to treatment (12-16 weeks). The maintenance dose should be based on clinical efficacy and tolerability. The best clinical responses are obtained in localized or generalized (Zumbusch type) pustular psoriasis and in erythrodermic psoriasis. Acitretin markedly improves plaque-type psoriasis and complete remission is obtained in around one-third of patients.

In some patients, an initial worsening of the disease may be observed with an increase in erythema and in the extent of lesions. A therapeutic scheme that initially uses low doses and is progressively increased (up to 50mg/day) seems to avoid this undesirable effect and may allow optimization of the therapeutic effect. After 12-16 weeks initial therapy, efficacy can be safely maintained in a long term treatment with acitretin.

PASI 50 and PASI 75 response rates

Acitretin has been shown in extensive clinical trials to be effective in the treatment of severe psoriasis. In clinical trials, the efficacy of psoriasis therapy is typically measured using the Psoriasis Area Severity Index (PASI), which quantifies the severity of a patient’s condition based on both the percentage of body surface area affected and the lesion severity. PASI 50 and PASI 75, which refer to the percentage of patients achieving a 50% or 75% improvement in baseline PASI score, are increasingly used as efficacy endpoints.

A retrospective analysis was undertaken to determine PASI 50 and PASI 75 response rates for two previously published acitretin clinical trials, study A3 and study B4. In both studies, efficacy was measured by PASI scores and Physician’s Global Assessment (PGA) at the end of treatment.

In study A3, a multicenter Canadian trial, a total of 63 patients (42 men, 21 women) with severe psoriasis were enrolled. Treatment with acitretin was initiated at 50 mg/day for 4 weeks, followed by dosage adjustment according to therapeutic response for up to 12 months. After 12 weeks of treatment, PASI 50 response rate was 66% and PASI 75 response rate was 34%. For the 37 patients who completed the 12-month course of therapy, 89% were found to be PASI 50 responders, and 78.4% PASI 75 responders. Among the 63 patients enrolled, 76% achieved a PASI 50 response and 46% a PASI 75 response by the end of treatment (average duration: 267 days; mean daily dose: 41mg). PGA evaluations found 52.4% of patients to show “marked improvement”, 31.7% “moderate or slight improvement” or “no change or worsening”.

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<tr>
<th>Week</th>
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<tr>
<td>End of Treatment</td>
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<td>63</td>
</tr>
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Figure 1: Patients with PASI 50 and PASI 75 (Study A3)
Of the patients showing “marked improvement”, 79% were PASI 75 responders.

Study B was a multicenter, double-blind trial comparing acitretin and etretinate that was conducted in the four European Nordic countries. Treatment for the acitretin group consisted of 4 weeks of therapy at 40mg/day followed by an 8-week phase of dosage adjustment according to therapeutic response. A total of 127 patients received acitretin (median daily dose: 40 mg) and 41 patients received etretinate (median daily dose: 49.7mg). After 8 weeks of treatment, PASI 50 and 75 response rates were 57% and 24% for acitretin, and 40% and 17% for etretinate, respectively. In patients who completed the 12 week treatment, PASI 50 and PASI 75 response rates were 85% and 52% for acitretin, and 80% and 45% for etretinate, respectively.

The high percentage of patients achieving a 50% or 75% reduction in PASI score during treatment with acitretin confirms the therapeutic efficacy of this drug. Although responder rates were slightly higher in study B than in study A at week 12, responder rates at the end of treatment were found to be similar in both trials, with around 75% of patients showing a PASI 50 response rate, and 50% demonstrating a PASI 75 response rate.

**Relapse rate**

The differences in the duration of response between various psoriasis therapies is not well established, since the definitions of relapse used in various clinical studies differ. In a double-blind study comparing acitretin with etretinate, patients were followed for 6-months after a 12-week treatment course. Relapse was defined as a marked or continuous deterioration of psoriasis that has required an active specific treatment, as judged by the physician or requested by the patient. At the end of the 6-month follow up period, 59% of acitretin and 53% of etretinate treated patients did not relapse.

**Contraindications**

There is an extremely high risk that major fetal abnormalities will occur if pregnancy occurs during treatment with acitretin. Effective contraceptive measures must be used for at least one month before starting treatment, during treatment and for at least 3 years after discontinuation of treatment. This post-therapy contraception period is based on the potential formation of etretinate in presence of alcohol (see pharmacology).

**Adverse events**

**Mucocutaneous reactions**

Undesirable dose-related effects on the skin and mucous membranes are almost always observed during treatment with acitretin. Dry lips (or cheilitis) is the earliest and most frequent sign appearing after treatment starts. Other reactions frequently observed include xerosis of the skin, pruritus, peeling of the palms and soles, epistaxis,
Nonablative Laser and Light Therapy: An Approach to Patient and Device Selection

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ABSTRACT

Nonablative laser and light therapy is a relatively novel modality for the improvement of the visual appearance of photodamaged, scarred, and injured skin. A number of different wavelengths and devices have been purported to be efficacious for the delivery of nonablative therapy. Among the features that can be addressed are red spots and telangiectasia, pigmentation and lentigines, and fine rhytides. A major attraction of nonablative therapy is the very limited downtime after each treatment. Patients can continue their daily routines while benefiting from the cumulative effects of skin rejuvenation.

Key Words: photodamage, nonablative therapy

What is Nonablative Laser and Light Therapy?

Nonablative laser and light treatments (other equivalent terms include subsurface resurfacing, photorejuvenation, and laser toning) have been used for several years for the aesthetic improvement of photoaged skin, particularly of the face. These treatments provide an alternative to traditional full-face laser resurfacing, an ablative modality in which carbon dioxide and/or erbium:YAG lasers are used to remove the entire epidermis and portions of the dermis. Ablative resurfacing improves skin roughness, fine and moderately deep facial wrinkles, and dyspigmentation by replacing the damaged epidermis and superficial dermis with a new papillary dermis and overlying epidermis. While results in expert hands are impressive, patients undergo an unpleasant healing period of 1-2 weeks during which time there is swelling, oozing and crusting, as well as discomfort. All nonablative treatments improve skin texture and tone, some improve wrinkles or surface irregularities including scarring, and some additionally address dyspigmentation and/or erythema and telangiectasia. The epidermis is not visibly disrupted in nonablative treatment. Nonablative resurfacing is attractive to physicians and patients alike because, contrary to ablative resurfacing, there is little if any downtime.

What are the Available Nonablative Devices?

Based on the work of Zelickson and Kilmer¹ the pulsed dye laser was initially found to induce dermal fibroblasts to produce a zone of new collagen within the papillary dermis after one or two purpuric treatments to photoaged periocular skin. Since then it has been determined that a significant number of wavelengths of both visible and infrared radiation applied to the skin have the ability to induce this very same change. It remains to be determined which of the different wavelengths is most effective at inducing this change.

Numerous laser and light devices,² including the KTP laser (532nm), pulsed dye laser (585nm, 595nm), intense pulsed light (IPL) devices (515-1200nm), Nd:YAG lasers (1064nm Q-switched, 1064nm long-pulse, 1319nm, 1320nm), diode lasers (980nm, 1450nm), Er:Glass laser (1540nm) and light emitting diodes have been adapted to be effective in, or specifically developed for, nonablative resurfacing. The mid-infrared devices, including 1320, 1450, and 1540nm devices, appear most effective for wrinkle and acne scar reduction. Red color and vascular lesions are best addressed by vascular-selective devices, such as the KTP, pulsed-dye, and long pulsed Nd:YAG lasers. The KTP also has efficacy for pigmentation as does the Q-switched Nd:YAG laser, but IPL devices, by virtue of their broad emission spectrum, appear the most effective for simultaneous treatment of both red and brown patches.

Clinical Efficacy: Does Nonablative Therapy Work?

Clinical evaluations of this therapeutic intervention have routinely relied on patient and treating physician evaluations and before and after photographs. To assure some degree of standardization in the evaluation process, images have been rated by double-blinded observers, and these ratings supplemented by more objective noninvasive texture measurement such as profilometry, ultrasound, and the PRIMOS (Phaseshift Rapid In-Vivo Measurement of Skin, GF Mestechnik, Teltow, Germany) 3-dimensional in vivo skin imaging system.³ Differences between before
and after results can be subtle and not always seen easily, even in side-by-side photographic comparisons. However, the popularity of these treatments among patients and physicians strongly suggests that differences, while not always easy to quantify, are likely real.

**Tissue Effects: How and Where Does Nonablative Therapy Work?**

For nonablative therapy, an epidermal surface temperature of 40-48º C is ideal since this correlates with a dermal temperature of 55 to 65º C, which is required for collagen denaturation. Recently, there has been some attempt to define the mechanisms underlying the clinical results observed with nonablative resurfacing. Most invasive investigations of nonablative resurfacing have compared the histology of preoperative and postoperative biopsies. A very few investigators have employed in situ hybridization to dissect what is occurring at the mRNA level; however, this work has been limited in scope. In histologic analyses, dermal thickening interpreted as “increased” and “organized” horizontally arrayed bundles of normal collagen fibers in the papillary dermis may in fact be a vestige of trauma and inflammation caused during remodeling after thermal or light injury to the dermis. Whether the alterations produced by nonablative laser are as persistent as typical photodamage, and the extent to which they are comparable to photodamage, is not known. However, the lasers used for nonablative resurfacing do not emit at ultraviolet wavelengths, and at present there is no evidence to indicate that nonablative laser treatments are deleterious.

**Patient Selection and Education**

Deciding which patients are best suited for nonablative rejuvenation depends in part on understanding what they want so that it can be determined if nonablative therapy is likely to provide these results. Good candidates for nonablative resurfacing tend to be relatively young, usually 25-65 years of age, and have minimal sagging of the face. Patients should understand that skin texture will improve and fine lines in particular will be softened, not eradicated. Cumulative aesthetic benefits from nonablative resurfacing are similar in type though less in magnitude than the results of ablative resurfacing. Additionally, since changes will occur gradually, typically after three to six or more treatments, those receiving nonablative treatments should not expect dramatic results immediately.

Patients who want to minimize treatment discomfort and downtime tend to appreciate nonablative treatments. These treatments are variably painful. The infrared sources are the most painful of these non-ablative procedures and usually require topical anesthesia for the procedures to be tolerable. Mild erythema and edema do occur following each treatment, but these sequelae remit within minutes to a few hours or may be concealed with cosmetics. Intense treatments can elicit moderate erythema and edema, which may peak 1-2 days after treatment and tend to subside a day or two later. In general, it is important to distinguish between the infrared nonablative devices (1320nm, 1450nm, 1540nm) on the one hand, and pulsed dye lasers, IPLs, and 532 and 1064nm Nd:YAG lasers on the other. Infrared lasers, while uncomfortable, are associated with only a few hours of redness and swelling, while side-effects and longer duration tissue effects are routine with the other devices.

Dark-skinned patients or those with a tendency to develop hyperpigmentation after skin injury can often safely undergo nonablative infrared therapy. These lasers are less prone to pigmentary complications, and patient skin color is less important when using these. With the non-infrared devices, treating tan patients is more risky, and skin color problems after treatment, more likely. Although recent evidence indicates that, in most cases, dark-skinned and Asian patients seldom develop pigmenetary abnormalities after nonablative treatment, the risk of hyperpigmentation and hypopigmentation in such patients is still greater than in lighter-skinned patients.

After nonablative treatment, little if any post treatment care is required. Unusually stringent sun protection is not necessary after nonablative therapy although patients should refrain from active sun-seeking behaviors for a few days thereafter.

Patients who prefer to continue to receive maintenance therapy for the texture and color of their facial skin will often be satisfied with nonablative resurfacing. After the standard course of three to six nonablative facial treatments separated by 3-4 week intervals, treatments can be continued indefinitely on a 3 to 4 times/year basis. Some patients may choose to receive subsequent treatment courses on different devices to obtain cumulative benefits.

Lasers and light sources should be chosen so that the features most bothersome to the patient are best addressed. Most devices are relatively specific, in that they are better for some purposes.

1. Wrinkle or acne scars are best treated with mid-infrared lasers. While acne scarring does not respond very well even to ablative resurfacing, there are some surprising results indicating that nonablative therapy may have significant efficacy for this purpose. There is
also evidence to indicate that low energy pulsed dye (NLite) laser can alleviate depressed scars.

2. Red color is best treated with vascular-selective KTP, long pulsed Nd:YAG and pulsed-dye lasers and IPL.

3. Brown color is best treated with pigment-selective KTP, Nd:YAG and Q-switched lasers, and IPL.

4. Texture and color, including red and brown color, can be collectively modestly improved by many different devices. IPL is a particularly effective multipurpose modality, and the infrared lasers are notable in their inability to effectively treat color.

In general, the less specific the patient objective, the greater the likelihood of satisfaction with nonablative therapy. Thus, patients who want removal of a particular feature, like redness or brown spots, or a particular wrinkle, tend to be less pleased after treatment than those interested in overall facial skin rejuvenation. Specific complaints are better treated with a laser device and setting specific for that indication (e.g., a Q-switched laser for lentigines, or a pulsed-dye laser with purpura for a spider angioma).

**Specific Features of Nonablative Devices**

**KTP or frequency-doubled Nd:YAG laser (532nm)**

*Good for red, brown, texture*

The KTP laser has traditionally been used for the treatment of small-caliber focal facial telangiectasia and lentigines. Combined treatment with 532nm KTP and 1064nm Nd:YAG lasers has been shown to provide synergistic benefits.\(^5\) When used with newer large spot sizes and scanner heads, the 532nm laser can be used to nonablatively resurface the entire face rather than just fine vessels.

**Pulsed-dye laser (585nm, 595nm)**

*Good for red and texture*

The pulsed-dye laser, a workhorse in the treatment of facial telangiectasia, diffuse erythema, and other superficial vascular lesions, has also been used with intralesional steroids for the treatment of keloids and hypertrophic scars. Recently, low energy pulsed-dye lasers (e.g., “NLite”), as well as long-pulse pulsed-dye lasers (e.g., pulse durations of 10-40msec) have also been studied. Anecdotal findings have suggested that not only scars, but also minor skin texture irregularities improve after repeated laser applications.\(^6\) This smoothing effect, coupled with marked reduction in diffuse erythema, may be achievable by multiple treatments with purpura-free, long-pulsed, pulsed-dye lasers. One recent study shows that the low energy pulsed-dye device successfully induces modest improvements in skin texture.\(^7\) Others have reported efficacy for amelioration of acne scarring as well.\(^8\)

**Intense-pulsed light device (500-1200nm)**

*Good for red, brown and texture*

Intense pulsed light devices have been used for the treatment of telangiectasia and erythema, reduction of lentigines, and softening of facial lines and creases. The multiple skin improving functions of intense pulsed light have made it a favorite modality for nonablative therapy. While the degree of improvement of fine lines may be less remarkable, significant simultaneous improvement in brown spots and redness is conducive to overall patient satisfaction. At least five manufacturers now actively market IPL devices in the US, and further research on refining this modality is proceeding briskly.

**Nd:YAG laser (1064nm)**

*Good for brown and texture*

The Q-switched Nd:YAG laser was developed for the treatment of skin pigments, including those present in lentigines and tattoos, but has been used by some practitioners for nonablative resurfacing referred to as “laser toning.” The long pulse 1064nm Nd:YAG laser is primarily a vascular device but has been increasingly used for nonablative treatment.

**Mid-infrared lasers (1320nm Nd:YAG, 1450nm diode, 1540nm Er:Glass)**

*Best for texture, wrinkles and texture*

*Do not help color*

This class of lasers has been used to treat periocular and perioral fine rhytides, with the former tending to respond better. They are less effective at treating pigmentation and vascular lesions. The 1450nm laser has also been used for the nonablative treatment of acne via partial necrosis of sebaceous glands. Mid-infrared devices, like the 1064nm Nd:YAG, can induce serious eye damage in patients and operators if adequate eye protection is not used. Pain during treatment is common, and can be somewhat mitigated with topical anesthesia.

**Future Directions for Nonablative Therapy**

New machines may provide more specific improvements of greater absolute magnitude. As the mechanisms underlying nonablative therapy are better understood, these treatments may be adapted to exploit these biochemical and physical changes.\(^9\)

Also, combined rejuvenation regimens that incorporate nonablative resurfacing will likely be further perfected. Botulinum toxin and soft-tissue augmentation materials are already being used on the upper and lower face, respectively, to improve lines of negative facial expression and hence
conjunctivitis and hair loss. All these reactions are dose-dependent and rapidly reversible after drug discontinuation.

**Systemic toxic effects**
The most common clinical adverse effects include headache, arthralgia, myalgia, and fatigue. Skeletal changes after long-term use have been attributed to retinoids. However, a prospective study has failed to document new spurs or other bone changes. Transitory abnormal elevations in liver enzymes are reported in approximately 33% of patients in US trials. Serum lipid changes (increase in triglycerides, in VLDL and LDL) are common.

**Conclusion**

Acitretin (SORIATANE®) is a convenient oral treatment of severe psoriasis, with a well-established efficacy and safety profile. Due to its long-term safety, acitretin can be used both as an initial and a maintenance treatment.

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**References**

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<td><strong>Antiviral Agents</strong></td>
<td>Valacyclovir&lt;br&gt;Valtrex® Caplets&lt;br&gt;GlaxoSmithKline</td>
<td>The US FDA approved a supplemental new drug application in April 2003, for the suppression of recurrent genital herpes in HIV-infected individuals. This is the first and only anti-viral approved in the US for suppression of recurrent genital herpes outbreaks in HIV infected individuals.</td>
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<td><strong>Antiviral Agents</strong></td>
<td>HPV DNA Test&lt;br&gt;HC2 High Risk HPV DNA Test&lt;br&gt;Digene</td>
<td>The US FDA approved expanded use in March 2003, for this laboratory test to detect the presence in women of human papillomavirus (HPV). This test was initially approved in March 2000 for testing women who had abnormal Pap test results. The new indication allows the test to be used for screening in conjunction with the Pap test of women over the age of 30 for HPV infection.</td>
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<td><strong>Antifungal Agents</strong></td>
<td>Ciclopirox&lt;br&gt;Loprox® 1% Shampoo&lt;br&gt;Medicis</td>
<td>The US FDA gave marketing approval for this antifungal shampoo in March 2003, for the treatment of seborrheic dermatitis of the scalp.</td>
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<td><strong>Enzyme Replacement Therapy</strong></td>
<td>Agalsidase Beta&lt;br&gt;Fabrazyme®&lt;br&gt;Genzyme General</td>
<td>The US FDA granted marketing approval for this enzyme replacement therapy in April 2003, for the treatment fo Fabry Disease, a rare and potentially fatal inherited disorder.</td>
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| **Cosmetics** | According to a study recently published in Photodermatology, Photoimmunology & Photomedicine,* topical glycolic acid, an ingredient commonly found in cosmetics, increases the skin’s sensitivity to photodamage by ultraviolet light. The backs of 29 Caucasian subjects were treated, once daily, 6 days/week with either 10% glycolic acid (with a pH of 3.5) or placebo in a randomized double-blinded study. At the end of 4 weeks, sites within each treated area were exposed to 1.5 minimal erythema dose (MED) of UV light, which was determined on previously untreated skin. They found that glycolic acid caused enhanced sensitivity to UV light measured as increased sunburn cells (SBCs) and lowered MEDs. There were no differences in SBCs or MEDs a week after treatments were discontinued. 

| **Psoriatic Arthritis** | Hungarian researchers reported* that tests used to measure rheumatoid arthritis also prove useful for measuring disease activity in their study of 38 patients with psoriatic arthritis or with peripheral arthritis who were studied before beginning drug therapy and again a year after treatment. Assessments included extended and reduced tender and swollen joint counts, Ritchie articular index, Health Assessment Questionnaire, erythrocyte sedimentation rate, morning stiffness, and both patient and assessor’s global assessment. 