Etanercept (Enbrel®)–An Update

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ABSTRACT

Etanercept is a tumor necrosis factor antagonist with anti-inflammatory effects. It is currently approved in the US for psoriasis, psoriatic arthritis, ankylosing spondylitis, rheumatoid arthritis and juvenile rheumatoid arthritis. Clinical trials have shown this agent to have an excellent safety profile and to be well tolerated by both adult and pediatric patients.

Key words: etanercept, Enbrel®, psoriatic arthritis, TNF-alpha, psoriasis

Etanercept (Enbrel®, Amgen) is a recombinant human protein with anti-inflammatory properties that was the first approved treatment for psoriatic arthritis by the US FDA in January 2002. It was approved by TPP Canada in January 2004 for the same indication. In May 2004, the US FDA approved this drug for the treatment of adult patients with chronic moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. In September 2004, the European Union approved it for the treatment of adult patients with moderate-to-severe plaque psoriasis who failed to respond to, or have a contraindication to, or are intolerant of other systemic therapies. Also in September 2004, the US FDA approved a new dosing form: a 50mg/ml prefilled syringe, which will allow most patients to take only one injection per week instead of two. Additional indications for etanercept include the treatment of rheumatoid and polyarticular-course juvenile rheumatoid arthritis (RA and JA respectively), and ankylosing spondylitis. In RA the clinical responses to etanercept have been maintained for up to 7 years in clinical trials. Tumor necrosis factor (TNF) is a proinflammatory cytokine that has been strongly implicated in the pathogenesis of psoriasis and psoriatic arthritis, and plays a key role in the activation of innate and acquired immune responses. An inappropriate production of this cytokine is seen in psoriasis and psoriatic arthritis, which can lead to chronic inflammation, tissue damage and excessive keratinocyte proliferation. The downstream effects of excessive TNF production on various cell types and the clinical manifestations relevant to psoriasis and psoriatic arthritis are summarized in Table 1. Currently there are three TNF-alpha inhibitors available in the US – one receptor fusion protein (etanercept), and two monoclonal antibodies (infliximab and adalimumab).

Mechanism of Action

Etanercept inhibits TNF activity by competitively binding to it and preventing interactions with its cell surface receptors. Elevated levels of TNF have been found in psoriatic skin lesions, and in synovial explants and fluid from patients with psoriatic arthritis. Furthermore, TNF levels in the serum of patients with plaque psoriasis, and in blister fluids of involved psoriatic skin have also been shown to be higher than in those of controls. These values were significantly correlated with the psoriasis area and severity index (PASI) scores, and TNF levels were reduced in association with clinical resolution after effective treatment.
The production of chemokines, and the expression of adhesion molecules by keratinocytes and vascular endothelial cells can be stimulated by TNF produced within psoriatic lesions. These signals then cause recruitment of additional inflammatory cells into the plaque. Krueger suggests that TNF may function as part of a positive feedback loop, which acts to amplify and sustain the inflammatory process within psoriatic plaques. Biologic responses that are induced or regulated by TNF are modulated by etanercept. It may, therefore, serve to reduce inflammation within plaques by breaking this cycle.

**Clinical Studies**

A 24-week, multicenter, double-blind, randomized, placebo-controlled, phase III trial studied etanercept as a monotherapy in moderate-to-severe psoriasis. Six-hundred-fifty-two patients with chronic, stable plaque psoriasis over ≥10% of their body surface area who had previously received or been candidates for phototherapy or systemic psoriasis therapy were enrolled. All systemic psoriasis therapies were discontinued within 4 weeks of the first dose of the study drug. Patients received 50mg etanercept subcutaneously (SC) twice weekly (n=164), 25mg etanercept SC twice weekly (n=162), 25mg etanercept SC once weekly (n=160), or placebo SC twice weekly (n=166). Forty-nine percent of patients in the 50mg etanercept twice weekly group achieved at least a 75% improvement in the PASI score (PASI 75) at 12 weeks, compared with 4% of placebo-treated patients (p<0.001). Efficacy continued to improve with longer treatment: 59% of the etanercept 50mg twice weekly patients reached PASI 75 at 24 weeks of treatment. Statistically significant improvements in patient global, physician global, and quality of life as assessed by the Dermatology Life Quality Index (DLQI) confirmed the efficacy of etanercept therapy. Etanercept was well tolerated.

In another phase III monotherapy trial, 46% of patients receiving etanercept 50mg twice weekly achieved PaSBI 75 at 12 weeks, compared with 3% of placebo-treated patients (p<0.0001). The majority of patients who achieved a PaSBI 75 in the 50mg biweekly arm continued treatment in an open-label extension where their etanercept dose was reduced to 25mg biweekly. At week 24, 77% had maintained their PaSBI 75 response using half of the original dose.

**Etanercept in Psoriatic Arthritis**

For adults with psoriatic arthritis and/or rheumatoid arthritis, the recommended dose of etanercept is 50mg administered SC once weekly using a 50mg/ml single-use pre-filled syringe. It may be used as monotherapy or concomitantly with methotrexate (MTX).

In a phase II, randomized, double-blind, placebo-controlled 12-week study, the efficacy and safety of 25mg twice-weekly subcutaneous injections of etanercept or placebo was assessed in 60 adult patients with psoriatic arthritis. The study endpoints for psoriatic arthritis included the proportion of patients who met the Psoriatic Arthritis Response Criteria (PsARC) and American College of Rheumatology 20%

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Action of TNF</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophage</td>
<td>• Increased proinflammatory cytokine production</td>
<td>• Increased inflammation</td>
</tr>
<tr>
<td></td>
<td>• Increased chemokine production</td>
<td>• Swelling of joints</td>
</tr>
<tr>
<td>Keratinocyte</td>
<td>• Increased proliferation</td>
<td>• Scale and thickness</td>
</tr>
<tr>
<td>Endothelial</td>
<td>• Increased expression of adhesion molecules</td>
<td>• Increased leukocyte infiltration into skin and joints</td>
</tr>
<tr>
<td></td>
<td>• Increased production of VEGF</td>
<td>• Increased angiogenesis and erythema</td>
</tr>
<tr>
<td></td>
<td>• Increased expression of adhesion molecules</td>
<td>• Auspitz sign</td>
</tr>
<tr>
<td>Hepatocyte</td>
<td>• Increased acute phase response</td>
<td>• Increased C-reactive protein</td>
</tr>
<tr>
<td>Synoviocyte (fibroblast-like)</td>
<td>• Increased metalloproteinase synthesis</td>
<td>• Articular cartilage degradation</td>
</tr>
<tr>
<td>T-lymphocyte</td>
<td>• Increased proinflammatory cytokine production</td>
<td>• Increased inflammation</td>
</tr>
<tr>
<td></td>
<td>• Increased nuclear transcription factor activation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• T cell activation</td>
<td></td>
</tr>
<tr>
<td>Dendritic cell</td>
<td>• Increased proinflammatory cytokine production</td>
<td>• Increased inflammation</td>
</tr>
<tr>
<td></td>
<td>• Dendritic cell maturation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Increased dendritic cell migration from skin to lymph nodes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• T-cell activation and differentiation</td>
<td></td>
</tr>
</tbody>
</table>

Table 1: Effects of Excessive TNF Production on Various Cell Types

criteria (ACR20) for improvement in the number of tender and swollen joints, as well as patient and physician assessments. The endpoints for psoriasis were a 75% improvement in the PASI score, and improvements in prospectively identified individual target lesions (≥2cm in diameter). The etanercept-treated group had statistically better outcomes for all clinical psoriatic arthritis endpoints. At 12 weeks, 87% of the etanercept-treated patients achieved the PsARC compared with 23% of patients receiving placebo (p<0.0001). The ACR20 was achieved by 73% of etanercept and 13% of placebo treated patients (p<0.0001).

Etanercept also improved the psoriasis skin lesions in this trial. The median target lesion response was 50% in the etanercept group compared with 0% in the placebo group (p=0.0004). There were 19 patients in each treatment group who met the criterion of ≥3% body surface involvement and were eligible for evaluation for psoriasis using the PASI score. At 12 weeks, 26% of the etanercept, and 0% of the placebo-treated patients had achieved a 75% improvement in the PASI (p=0.0154).

An open label extension of this study demonstrated that treatment with etanercept allowed statistically significant reduction of concomitant MTX and/or steroid doses, and discontinuation of MTX and/or steroids in 25% and 44% of patients respectively.

The results of this study were confirmed in a larger, 205 patient, multicenter, randomized, double-blind, placebo-controlled phase III trial of the efficacy and safety of etanercept in psoriatic arthritis. Arthritis was significantly improved with etanercept treatment. ACR 20 was achieved by 59% of the etanercept group and 15% of the placebo group at 12 weeks (p<0.0001). Significant improvement in arthritis was maintained with continued etanercept treatment through the end of the study at 24 weeks. Results from the subset of patients who were evaluated using PASI showed a median improvement of 47% in patients receiving etanercept while a median 0% improvement was seen in those receiving placebo (p<0.0001).

**Etanercept Administration**

Etanercept is supplied as a lyophilized powder (25mg to a vial) which requires reconstitution with sterile bacteriostatic water, which is also included. The administration is similar to that of insulin or SC methotrexate and can be easily taught to patients in a dermatology office setting. All patients are required to have regular follow-up visits while taking this medication. Etanercept is now also available as a 50mg/ml single-use prefilled syringe. Prior to therapy, lab work that includes a baseline HIV, hepatitis panel, tuberculin skin test, ANA, comprehensive metabolic panel, and a complete blood count is recommended. Thereafter, lab work may be done when deemed necessary. During therapy, patients are not allowed to be immunized with live virus vaccines. Etanercept may safely be given to patients who are already receiving MTX, as per the package insert. The cost for a 4-week supply of medication is approximately $1,100.00 USD.

**Safety**

Klareskog, et al. reported results of a long-term safety study of etanercept in 2,054 patients from North America and Europe. In the long-term follow-up group, the rates of infection requiring hospitalization or intravenous antibiotics were 0.04 events per patient-year, which is comparable to the rates seen in the placebo-control group during the double-blind portion of the trials.

However, it should be noted that postmarketing reports have included accounts of serious infections and sepsis, including fatalities with the use of etanercept. Even so, in the arthritis clinical trials, numerous patients were on concomitant methotrexate and/or prednisone without any increased risk of infection. Caution should be used when considering etanercept for patients with a history of recurring infections.

### Table 2: Adverse events occurring in at least 5% of patients in any treatment group.

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Placebo Group</th>
<th>Low-Dose Etanercept Group (25mg q.w.)</th>
<th>Medium-Dose Etanercept Group (25mg b.i.w.)</th>
<th>High-Dose Etanercept Group (50mg b.i.w.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=166)</td>
<td>(n=160)</td>
<td>(n=162)</td>
<td>(n=164)</td>
</tr>
<tr>
<td>Injection-site reaction</td>
<td>12 (7)</td>
<td>17 (11)</td>
<td>28 (17)</td>
<td>22 (13)</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (7)</td>
<td>5 (3)</td>
<td>19 (12)</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>19 (11)</td>
<td>16 (10)</td>
<td>15 (9)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Injection-site ecchymosis</td>
<td>6 (4)</td>
<td>11 (7)</td>
<td>4 (2)</td>
<td>8 (5)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>5 (3)</td>
<td>7 (4)</td>
<td>6 (4)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>4 (2)</td>
<td>3 (2)</td>
<td>6 (4)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Accidental injury</td>
<td>7 (4)</td>
<td>6 (4)</td>
<td>5 (3)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (1)</td>
<td>5 (3)</td>
<td>4 (2)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Rash</td>
<td>4 (2)</td>
<td>4 (3)</td>
<td>4 (2)</td>
<td>5 (3)</td>
</tr>
</tbody>
</table>

Table 2: Adverse events occurring in at least 5% of patients in any treatment group.
and etanercept should not be administered to patients with sepsis or active infections, including chronic or localized infections. Patients who are on concomitant immunosuppressive therapies, or patients who may be predisposed to infections may have a greater risk of infection when they are given etanercept. Patients who have had a significant exposure to varicella and have no immunity to this condition should temporarily discontinue etanercept, and prophylactic varicella zoster immune globulin should be considered. Rare reports of new onset or exacerbation of central nervous system demyelinating disorders, and pancytopenia in patients treated with etanercept have been noted by postmarketing surveillance. Consequently, caution should be exercised when considering the use of etanercept in patients with preexisting or recent-onset central demyelinating disorders. Discontinuation of etanercept therapy should be considered in patients with confirmed significant hematological abnormalities. Additionally, 11% of patients in clinical trials who were treated with etanercept developed a new positive ANA titer of 1:40 or greater, compared to 5% of patients who were in the placebo group. The development of anti-dsDNA antibodies was also higher in patients treated with etanercept when compared to those treated with placebo (15% and 4% respectively). Cases of drug-induced systemic lupus and subacute cutaneous lupus have been reported in the literature. After discontinuation of etanercept these conditions resolved. The US FDA pregnancy rating for etanercept is category B. However this rating was made based on results of developmental toxicity studies of etanercept performed in rats and rabbits. There have been no studies in pregnant women and, therefore, etanercept should be used during pregnancy only if clearly needed. It is not known if etanercept is excreted in human milk or absorbed systemically after ingestion. A decision to discontinue nursing or to discontinue etanercept should be made by nursing mothers.

Adverse Events
In controlled trials, the only adverse event that occurred significantly more frequently in patients treated with etanercept compared to placebo was mild-to-moderate injection-site reactions, e.g., erythema and/or itching, pain, or swelling (see Table 2). These reactions tended to occur in the first month, subsequently decreased in frequency, and did not generally result in discontinuation of the drug. Application of cool compresses and 1% hydrocortisone ointment are helpful to alleviate discomfort associated with injection-site reactions.

Conclusion
Clinical trials have demonstrated consistent efficacy for etanercept in the treatment of inflammatory diseases such as psoriasis, psoriatic arthritis, RA, and JRA, and research on the potential future use of this agent in other inflammatory diseases is ongoing. The rapid and significant clinical responses to etanercept highlight the central role of TNF in contributing to the pathology of these diseases, as well as etanercept’s potent inhibitory effects. Etanercept is well tolerated by both adult and pediatric patient populations, and long-term data on the use of etanercept have demonstrated an excellent safety profile.

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References

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ABSTRACT

Prednicarbate is a nonhalogenated corticosteroid that is used in the treatment of inflammatory skin diseases, for example atopic dermatitis. It has a favorable benefit-risk ratio, with an inflammatory action similar to that of a medium potency corticosteroid, but with a low potential to cause skin atrophy. Thus, prednicarbate may be a consideration in the treatment of atopic dermatitis in children, and other inflammatory disorders in children and adults.

Key Words: prednicarbate, corticosteroid, atopic dermatitis, inflammatory skin disease

Prednicarbate is a nonhalogenated, double-ester derivative of prednisolone. Modification to the prednisolone molecule has resulted in a molecule that causes the suppression of inflammation, but maintains low skin atrophy potential.12

Mechanism of Action

The anti-inflammation action of corticosteroids is associated with the inhibition of the IL-1 cytokine within keratinocytes.3,4 IL-1 is also found in fibroblasts, where it is responsible for proliferation, collagenase induction and IL-6 synthesis, which are related to skin thickness.4 Fibroblasts are important in wound healing and tissue repair.5 The primary mechanism of action of corticosteroids is the suppression of IL-1, which subsequently inhibits the cytokine in both keratinocytes and fibroblasts. The inhibition of IL-1 in keratinocytes results in anti-inflammatory effects, while in fibroblasts there is an atrophogenic effect. Prednicarbate has different effects on keratinocytes and fibroblasts. In keratinocytes, prednicarbate produces a high degree of suppression of IL-1 that is almost similar to that produced by betamethasone-17-valerate.5,6,7 In contrast, prednicarbate has only a minor effect on IL-1 and IL-6 suppression in fibroblasts; this results in a low potential to cause atrophy.5,6,7

Clinical Efficacy

Several German and Spanish studies have reported the effectiveness of prednicarbate in a variety of formulations at a strength of 0.25%, for the treatment of dermatitis.8

In two multicenter, randomized, double-blind, parallel group studies (see Table 1), Hanifin et al.9 compared prednicarbate 0.1% emollient cream with both the emollient cream vehicle and betamethasone valerate 0.1% cream in the treatment of patients with atopic dermatitis, where males were 12 years or older and females were 18 years or older. Treatments were applied twice daily for 21 days. Prednicarbate had significantly greater efficacy than the vehicle emollient, with greater improvement ratings of total key signs/symptoms at all return visits; significant improvement was recorded as early as day 8 (P≤0.05). Prednicarbate demonstrated at least equivalent or numerically higher clearing and mean percent improvements of signs and symptoms at return visits compared to betamethasone valerate. Prednicarbate had an overall improvement of 76.4% compared to the vehicle emollient (29.7%) and demonstrated similar efficacy to betamethasone valerate.9

Adverse Events

Prednicarbate has been associated with few adverse events; these include burning sensation, pruritus, drying, scaling, cracking, and pain, as well as dizziness, paresthesia, urticaria, folliculitis, and edema/rash.5,6 In a study where prednicarbate was applied to children (4 months to 12 years) twice daily for 21 days no suppression of the hypothalamic-pituitary-adrenal (HPA) axis was observed.9 The low atrophogenic potential of prednicarbate has been supported in several studies.1,4,6

Contact allergies to topical corticosteroids is also a concerning adverse event, particularly with long-term use. Corticosteroids have been ranked as the seventh most common allergen.11 Sensitivity to corticosteroids can be difficult to diagnose because the anti-inflammatory action of the corticosteroid can camouflage the allergic reaction to the corticosteroid itself.12 Corticosteroids may be classified into 4 groups (A-D) based on their allergenicity.12,13 Prednicarbate (in Group D) is a prodrug corticosteroid.12 It rapidly de-estersifies at position C21 to prednisolone-17-ethylcarbonate, which eventually metabolizes to prednisolone.12 The metabolites may exhibit allergenicity that is different from the parent molecule; furthermore, prednicarbate may cross-react with other corticosteroids.

In a study by Hanifin, et al.9 evaluating prednicarbate emollient cream 0.1% versus vehicle, safety data were available for 211 patients. Adverse effects thought to be related to the study drug were reported in 12 patients (prednicarbate group: 4, vehicle group: 8). In the prednicarbate group, the adverse effects included pruritus, burning sensation of skin, rash, contact dermatitis, and edema. Skin atrophy was recorded in three and one patients in the prednicarbate and vehicle groups, respectively. The presence of atrophy in the vehicle group may be explained by preexisting atrophy that may have been the result of previous topical corticosteroid usage. Therefore, it is difficult to ascertain whether atrophy in a patient is the result of
the current application of topical corticosteroid as opposed to previous topical corticosteroid use.

In the second Hanifin, et al.9 study comparing prednicarbate to betamethasone valerate, safety data are available for 200 patients. Adverse effects that were thought to be study drug related were seen in 7 and 5 patients in the prednicarbate and betamethasone valerate groups, respectively. The adverse effects in the prednicarbate group were burning sensation of the skin, rash, folliculitis, paresthesia and dizziness. None of the patients had skin atrophy.

**Indications**

In Canada and the United States, prednicarbate (0.1% emollient cream and 0.1% ointment) has been approved for the treatment of inflammatory and pruritic manifestations of acute and chronic corticosteroid-responsive dermatoses.14,15 It can be applied without occlusion twice daily for 2 weeks.14,15 The emollient cream has been approved for the use in adults and children over 1 year old, and the ointment has approval in the US for use in individuals 10 years and older.14,15 Prednicarbate should be used cautiously in children around the diaper area because the diaper and plastic pants may result in occlusion.

**Conclusion**

Prednicarbate has been demonstrated to be effective, with a high anti-inflammatory action and low potential for adverse events, particularly skin atrophy. This topical corticosteroid exhibits characteristics that may prove beneficial in the treatment of children and elderly patients, as well as adults who may require intermittent long-term treatment.

**Table 1:** Summary of the efficacy of prednicarbate emollient cream 0.1% compared with vehicle and betamethasone valerate cream 0.1%.9

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th></th>
<th>Study 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prednicarbate</td>
<td>Vehicle</td>
<td>Prednicarbate</td>
<td>Betamethasone Valerate</td>
</tr>
<tr>
<td>Number of subjects</td>
<td>98</td>
<td>86</td>
<td>89</td>
<td>92</td>
</tr>
<tr>
<td>% Improvement of total key signs/symptoms scores at endpoint</td>
<td>76.4%</td>
<td>29.7%</td>
<td>79.7%</td>
<td>75.8%</td>
</tr>
<tr>
<td>Global evaluation scores of cleared or excellent improvement at endpoint</td>
<td>72%</td>
<td>20%</td>
<td>Equally effective – scores were: prednicarbate=1.03 betamethasone valerate=1.00</td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>Pruritus, skin burning sensation, contact dermatitis, edema/rash, skin atrophy</td>
<td>Pruritus, skin burning sensation, dry skin, rash, pain, vasodilation, application-site reaction, discoloration, skin atrophy, striae</td>
<td>Dizziness, skin burning sensation, paresthesia, rash, folliculitis</td>
<td>Acne, furunculosis, rash, pustular rash</td>
</tr>
</tbody>
</table>

**References**


Continued on page 9
Nonablative laser and light sources have been widely used for the reduction of the visible signs of photoaging for several years. The benefits of nonablative treatment include quicker patient recovery time due to the absence of marked postoperative erythema, desquamation, and crusting. Moreover, the risks of unwanted pigmentary and textural abnormalities are much reduced in nonablative rejuvenation compared to ablative treatment.

The benefits of nonablative treatment are partially counterbalanced by its reduced efficacy relative to laser skin resurfacing. Among the novel methods for maximizing the efficacy of nonablative treatment is the concurrent use of a photosensitizing agent, such as 5-aminolevulinic acid (5-ALA).\(^1\)

### ABSTRACT

Photodynamic therapy (PDT) has been used for several years for the treatment of actinic keratoses and prevention of invasive nonmelanoma cancers. More recently, increasing physician expertise with the topical sensitizers and light sources employed in PDT has led to expanded applications, including its use for improvement of the visible signs of photoaging. Aesthetic treatment of photoaged skin with brief application of topical 5-aminolevulinic acid followed by well-tolerated light sources, such as intense pulsed light or pulsed-dye laser, can enhance the effectiveness of nonablative laser treatment without increasing adverse effects or downtime.

**Key Words:** photodynamic therapy, intense pulsed light, pulsed-dye laser, aminolevulinic acid, photoaging

### Treatment of Photoaging with Topical Aminolevulinic Acid and Light

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### 5-ALA and Light: Well-Tolerated Treatment of Actinic Keratoses and Photoaging

Originally developed to be used with red or blue light to treat superficial cutaneous malignancies and premalignant lesions (e.g., actinic keratoses), 5-ALA has recently been applied in combination with a variety of light sources, such as pulsed-dye laser and intense pulsed light, to increase the effectiveness of light treatment. This cosmetic use entails less intense 5-ALA pretreatment regimens and more well-tolerated light doses for activating the photosensitizer.

This so-called “photodynamic photorejuvenation” was discussed in the literature as early as 2002, when Ruiz-Rodriguez and colleagues\(^2\) treated 17 patients with a combination of actinic keratoses (AKs) and diffuse photodamage. They applied 20% 5-ALA mixed in an oil-in-water emulsion and under occlusion for 4 hours prior to treatment (0.2g/cm\(^2\)) with the pulsed light device (Epilight\(^6\), Lumenis), using a 615nm cutoff filter, total fluence of 40J/cm\(^2\) in double pulse mode of 4.0msec with 20msec interpulse delay.

Approximately \(\frac{3}{4}\) of the AKs and adjacent photodamaged skin resolved 1 month after the first treatments, and posttreatment erythema, edema, and crusting lasted up to 10 days. These results were extended by Alexiades-Armenakas and Geronemus,\(^1\) who showed that photodynamic treatment of AKs could be accomplished gently, not only with intense pulsed light (IPL), but also with 595nm pulsed-dye laser (PDL) (Vbeam\(^6\), Candela). The PDL offered the benefits of rapidity of treatment as well as the comfort and protective epidermal effects associated with cryogen spray cooling. The 5-ALA incubation times were as brief as 3 hours and nonpurpuric PDL settings (4-7.5J/cm\(^2\), pulse duration of 10ms, 10mm spot size, and 30ms cryogen spray with 30ms delay) were used. Minimal intraoperative stinging, burning, and pain were reported, and while there was some postoperative erythema, no purpura, crusting, or scarring was seen. While Alexiades-Armenakas and Geronemus were focused on the treatment of AKs, they demonstrated that laser and 5-ALA could be effectively used with virtually no downtime.

### 5-ALA and Light: Treatment of Photoaging Alone

Indeed, anecdotal use of IPL and PDL for improvement of the visible signs of aging has rapidly spread. Now the first discrete studies of this application are becoming available. Avram and Goldman\(^4\) retrospectively reviewed 17 patients treated with 5-ALA and IPL and found 55% improvement in telangiectasia, 48% improvement in pigmentary abnormalities, and 25% improvement in coarse skin texture, but minimal change in fine wrinkles. Low doses of 5-ALA and IPL permitted postoperative courses significant for only mild erythema and edema for 3-5 days. Separate preliminary studies by both Gold\(^4\) and Roe, et al.\(^4\) have also indicated treatment efficacy following short contact (30-60 minutes incubation) full-face incubation with 20% 5-ALA followed by treatment with IPL.
Recently, a prospective, randomized, controlled trial comparing efficacy and tolerability of 5-ALA followed by IPL treatment with IPL alone was performed by Dover, Bhatia, and Arndt (unpublished data, October 2004). A total of three split-face treatments were delivered to each of 20 patients, and these were followed by two whole-face IPL-only treatments, also 3 weeks apart. Prior to each of the first three treatments, one side of each patient’s face was precleansed with acetone and received topical 5-ALA solution for 45 minutes (+15 minutes). The 5-ALA solution was washed off before treatment was commenced with a 560-1200nm device (IPL™ Quantum SR, Lumenis Inc.) using the standard SR head on Program 1 (first pulse of 2.4ms, second pulse of 4.0ms, 14ms interpulse delay; fluence of 23-28J/cm²; epidermal cooling chiller tip on maximum). After each treatment, patients again washed their faces and applied a moisturizer containing an SPF 30 sunscreen. Assessment of outcomes was conducted using a comprehensive rating measure that evaluated global photodamage, fine lines, mottled pigmentation, tactile roughness, and sallowness, each on a 0-4 scale; measurements were obtained by a blinded rater before treatment and 4 weeks after the final treatment. The 5-ALA-IPL sides were associated with 80%-95% improvement on the various subscales compared to 20%-55% improvement for the 5-ALA-only sides. The greatest relative improvements in the 5-ALA-IPL sides were in mottled hyperpigmentation and global photaging, and to a lesser extent, in fine lines. Tactile roughness and sallowness did not appear to show greater improvement with 5-ALA-IPL treatment vs. IPL alone. Not only the independent rater, but also patients preferred the benefits of the combined 5-ALA-IPL treatment. Significantly, side-effects and tolerability did not differ between the IPL-only treated areas and the areas treated with 5-ALA-IPL.

General Treatment Guidelines
1. IPL (and other light sources, including PDL) can be used after pretreatment with 5-ALA to reduce the visible signs of photoaging.
2. Patients should be instructed that red/brown dyspigmentation and overall appearance are likely to improve significantly, and fine lines, to a lesser extent.
3. Pretreatment with acetone or alcohol is followed by short contact (approximately 1 hour) application of 20% 5-ALA. This is then thoroughly washed off before IPL treatment.
4. IPL or PDL treatment should be delivered at standard parameters.
5. After treatment, the treated area should again be washed off, and moisturizer and sunscreen applied.
6. Patients should be instructed to practice strict sun avoidance and sun protection for the remainder of the treatment day and the next day.
7. Additional treatments are delivered at 3-4 week intervals, with a standard regimen consisting of 3-6 treatments. While it appears from the Dover study that three combined 5-ALA-IPL treatments may produce results as good as or better than five IPL alone treatments, further study is necessary to confirm this finding.

Management of Undesired Effects
The 5-ALA-IPL or PDL treatment for photoaging is a safe treatment associated with patient comfort during treatment and rapid, uneventful recovery after treatment. There are two potential problems that can be easily detected and treated. Phototoxicity occurs when patients disregard instructions regarding post-treatment sun avoidance. The best treatment is prevention, including strict sun avoidance for 24 hours after treatment. If phototoxicity does occur, it presents as well-demarcated erythema and edema at the treated sites. Application of ice and topical corticosteroid ointments, rest, and the passing of time will aid in resolution of symptoms. The risk of superficial infection is very low. Patients with a history of recurrent cold sores may be given antiviral prophylaxis for herpes simplex prior to treatment. Superficial bacterial infections or impetigo may occur at extremely sun-damaged sites or at locations where the 5-ALA solution has not been completely washed off before IPL treatment. These are typically easily treated with topical antibiotics, such as mupirocin.

Conclusion
Topical 5-ALA enhances the efficacy of laser and light treatment of facial photoaging. While IPL devices have been used most often in this combination therapy, other lasers and light sources, including PDL, appear effective as well. Moreover, combination 5-ALA and light therapy does not add to recovery time or discomfort. Provided sun avoidance is practiced for a day following treatment, combination therapy, like laser or light alone, is associated with mild posttreatment erythema and edema, but no crusting or erosions. The new short-contact regimens of 5-ALA require pretreatment for 30-60 minutes, no longer than the duration of applications of topical anesthetics used for various cutaneous procedures. Finally, prepackaged 20% 5-ALA (Levulan® Kerastick®, DUSA Pharmaceuticals) does not require time-consuming preparation prior to application. In short, 5-ALA-light therapy is a further refinement of nonablative laser therapy that permits effective treatment of photoaging with minimization of post-treatment effects.

References
3. Enbrel® (etanercept) prescribing information. Immunex

5. Gold MH, Goldman MP. 5-aminolevulinic acid photodynamic therapy: where we have been and where we are going. Dermatol Surg 30(8):1077-83 (2004 Aug).


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15. Dermatop® Ointment (prednicarbate ointment 0.1%) and Dermatop® E Emollient Ointment (prednicarbate emollient cream 0.1%) Canadian package insert. Dermik Laboratories Canada, Inc. Mississauga, ON, Canada; November 15 2000.
<table>
<thead>
<tr>
<th>Class</th>
<th>Name/Company</th>
<th>Approval Dates and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsoriatic Agent</td>
<td>Efalizumab Raptiva® Serono</td>
<td>The European Medicines Agency (EMEA) approved this humanized therapeutic antibody in September 2004, for the treatment of moderate-to-severe chronic plaque psoriasis for which other systemic treatments or phototherapy have been inadequate or inappropriate.</td>
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<tr>
<td>Antihistamine</td>
<td>Desloratadine Syrup CLARINEX® Schering-Plough</td>
<td>The US FDA approved the use of this antihistamine in August 2004, for the relief of symptoms associated with seasonal allergic rhinitis in children &gt;2 years of age, and perennial allergic rhinitis and chronic idiopathic urticaria, or hives of unknown cause in children as young as 6 months of age. This product is expected to be available in the US during the first half of 2005.</td>
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<tr>
<td>Antifungal Agent</td>
<td>Posaconazole Oral Suspension Schering-Plough</td>
<td>The US FDA, in July 2004, accepted for review the NDA for this novel triazole agent for the treatment of invasive fungal infections, such as aspergillosis, fusariosis, and zygomycosis, in patients with refractory disease or who are intolerant to other therapy.</td>
</tr>
<tr>
<td>Antipsoriatic Agent</td>
<td>Etanercept Enbrel® Amgen/ Wyeth Pharmaceuticals</td>
<td>The US FDA approved a new dosing form in September 2004, for this biologic treatment. The new prefilled syringe, available for patient use in the 4th quarter 2004, will eliminate the need to mix the drug prior to injecting, and will allow most patients receiving this drug to take only one injection per week instead of the two 25mg injections currently used weekly by patients. Also in September, the EMEA approved this product for the treatment of adults with moderate-to-severe plaque psoriasis who failed to respond to, or have a contraindication to, or are intolerant of other systemic therapy.</td>
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**Drug News**

The US FDA is proposing to change the new and generic drug review processes by replacing “approvable letters” and “not approvable letters” with “complete response letters” that provide companies with specific information about what needs to be done before their drugs can be approved for marketing. This approach has been used by the FDA for biological drugs for some time and would be formalized for all drugs by this proposal. Under the new proposal, responses to “complete response letters” for new drug applications would be classified by what needs to be done to obtain marketing approval. More information is available online at: [http://www.fda.gov/OHRMS/DOCKETS/98fr/04n-0267-npr0001.pdf](http://www.fda.gov/OHRMS/DOCKETS/98fr/04n-0267-npr0001.pdf).

According to a recent article published in the journal *Cell*, researchers at Howard Hughes Medical Institute have isolated stem cells from the skin of mice and shown that they have the power to self-renew and differentiate into skin and functioning hair follicles when grafted onto mice. They conclude that the human equivalent of these stem cells, which scientists are also trying to isolate, could ultimately be used to regenerate skin and hair.