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The Treatment of Atopic Dermatitis and Other Dermatoses with Leukotriene Antagonists

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ABSTRACT

Atopic dermatitis (AD) is a chronically relapsing eczematous disorder of the skin that occurs in persons of all ages but is more common in children. AD is associated with other atopic diseases such as allergic rhinoconjunctivitis or bronchial asthma. Nearly 80% of children with AD eventually develop allergic rhinitis or asthma. AD can be classified as "mixed" (cases associated with respiratory allergies) and "pure". Pure AD has "intrinsic" and "extrinsic" variants. In the extrinsic type, interleukin-4 is secreted by T-cells isolated from spontaneous lesions and skin-derived T-lymphocytes express more IL-13. Due to the different immunopathogenesis, it has been suggested that antileukotriene agents may be more successful in the treatment of the extrinsic subgroup. Leukotrienes (LTs) are a class of potent biological inflammatory mediators derived from arachidonic acid through the 5-lipoxygenase pathway. There is evidence of enhanced LT production in the pathogenesis of AD. Evidence in the literature provides a pathophysiological rationale for the use of cysLT receptor blockers in the treatment of AD. However, the exact mechanism of action of leukotriene receptor antagonists in AD is not known. In small clinical and case studies, montelukast was found to be a safe and effective alternative or steroid-sparing therapy in the management of patients with atopic dermatitis.

KEY WORDS: atopic dermatitis, dermatoses, leukotriene antagonists

Atopic Dermatitis

Atopic dermatitis (AD) is a chronically relapsing eczematous disorder of the skin that occurs in persons of all ages but is more common in children. AD has been reported to affect more than 10% of children in most countries.¹ Approximately 60-70% of those with mild to severe dermatitis will continue to experience symptoms into adulthood.² The condition is characterized by intense pruritus and a course marked by exacerbations and remissions. Patients with AD may have disrupted sleep with consequent daytime fatigue and compromised school and work quality.³ Skin hydration, avoidance of irritants, antihistamines, topical corticosteroids and newer topical immunomodulators are the mainstay of therapy for AD. However, AD is usually refractory to treatment and the local and systemic side effects of topical steroids are widely recognized. AD is associated with other atopic diseases such as allergic rhinoconjunctivitis or bronchial asthma.⁴ Nearly 80% of children with AD eventually develop allergic rhinitis or asthma.⁵ It is estimated that in the U.S, \$364 million is spent annually on the treatment of childhood AD.⁶

Immunologic Abnormalities in AD

An understanding of the immunologic basis of AD is necessary for the development of novel approaches to treating this disease. A recent review by Leung⁵ summarized the following

immunologic findings. Most patients with AD have elevated numbers of circulating eosinophils and increased immunoglobulin E (IgE) levels. This is caused by T-cell dysfunction. An increased frequency of Th2 cells that produce increased IL-4, IL-5 and IL-13 has been demonstrated in the peripheral blood of patients with AD. Factors contributing to Th2 cell development in AD include cytokines, genetic differences in cytokine (IL-4) production, pharmacologic factors (monocytes with increase CAMP phosphodiesterase activity) and antigen presenting cells (increased IgE-bearing Langerhans' cells with a role in cutaneous allergen presentation to Th2 cells).

IL-4 and IL-13 are the only cytokines that promote an increase in IgE production at the level of germline transcription. IL-5 induces eosinophilopoiesis, activation and chemotaxis.⁷ Eosinophils secrete cytokines and mediators that injure tissue via reactive O₂ intermediates and the release of toxic granule proteins.⁸ Eosinophil granule proteins are increased in AD sera and correlate with disease activity.⁹ Urinary eosinophil protein X has also been found to correlate with AD disease activity.¹⁰

Furthermore, AD can be classified as "mixed" (cases associated with respiratory allergies) and "pure". Pure AD has "intrinsic" and "extrinsic variants. Patients with the intrinsic or "non-allergic" form of AD have no associated respiratory diseases, such as bronchial asthma or allergic rhinitis, show normal total serum IgE levels, no specific IgE, and negative atopy patch tests.¹¹ In the extrinsic type, 1) interleukin-4 is secreted by T-cells isolated from spontaneous lesions, 2) the atopy patch test is positive; and 3) skin-derived T-lymphocytes express more IL-13 than T cells from the intrinsic type.¹² Due to the different immunopathogenesis, it has been suggested that antileukotriene agents may be more successful in the treatment of the extrinsic subgroup.¹³

There are pathogenic mechanisms that are central to both AD and asthma. An exaggerated inflammatory response (including increased production of IgE and eosinophilia) to environmental triggers, including irritants and allergens is characteristic of both AD and asthma.¹⁴ Total IgE levels are elevated in both AD and asthma. Genetic studies have demonstrated common chromosomal linkages between AD and asthma.¹²

Leukotrienes and AD

Leukotrienes (LTs) are a class of potent biological inflammatory mediators derived from arachidonic acid through the 5-lipoxygenase pathway¹⁵ (Fig. 1) Leukotrienes are divided into two groups according to their chemical structure: those with a sulphur linkage (cysteinyl LTs: LTC₄, LTD₄, LTE₄), and those that do not (LTB₄). Eosinophils, basophils and mast cells are the most important sources of LTs.⁴ Epidermal cells are able to transform neutrophil derived LTA₄ into LTB₄ and LTC₄.¹⁶ Thus the epidermis can also contribute significantly to LT synthesis. It has been shown that cysteinyl leukotrienes (cysLTs) mediate asthma and allergic rhinitis and when the LT receptors are antagonized, symptoms resolve.^{17,18}

Leukotrienes are important proinflammatory mediators that are capable of inducing airway smooth muscle constriction, airway hyperresponsiveness, eosinophil migration, vascular permeability, edema, and chemotaxis.¹⁹ A role for LTs in AD has been suggested in the literature. There is evidence of enhanced LT production in the pathogenesis of AD. The cysteinyl LTs increase vascular permeability and dilate skin blood vessels.²⁰ LTC₄ has been found in the skin of AD patients using the suction blister technique.²¹ Patients with AD have activated circulating basophils and increased basophil releasability of LTC₄.²² Cysteinyl LT release from basophils and eosinophils isolated from AD patients is increased compared to healthy controls.¹² Enhanced spontaneous and stimulated releasability of LTC₄ from leukocytes of patients with AD compared with normal controls has been reported.²³ Increased production of LTs has been reported in the skin of atopic patients after allergen specific challenge.¹² There is conflicting evidence in the literature on urinary LTE₄ levels, an index of whole-body cysteinyl LT production *in vivo*. LTE₄ is a stable urinary metabolite of LTC₄ and LTD₄.⁴ Sansom, et al.²⁴ found that urinary LTE levels in seven AD patients were not significantly different during or after an acute exacerbation when compared with the normal range. However, another study demonstrated mean urinary LTE₄ levels in 20 patients with AD were significantly higher than in 17 healthy volunteers, and a significant correlation between urinary LTE₄ and total serum IgE levels in AD patients was observed.²⁵

Leukotriene receptor blockers and AD

There are at least two types of LT receptors: cysLT1 and cysLT2. Montelukast (Singulair[®], Merk-Frosst), zafirlukast (Accolate[®], Zeneca), and pranlukast (Ultair[®], SmithKline Beecham) are LT receptor antagonists that demonstrate high-affinity binding to the cysLT1 receptor. Montelukast is currently indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older and for the relief of symptoms

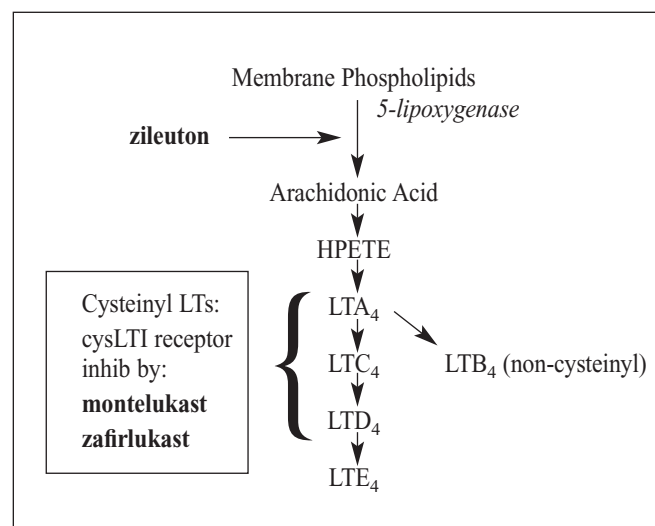


Fig. 1: Leukotriene synthesis inhibitors

of seasonal allergic rhinitis in adults and pediatric patients 2 years of age and older. Montelukast is generally a safe drug during long term treatment; side effects are minimal.²⁶ Asthma and allergic rhinitis have numerous pathophysiological elements in common with AD, and together these three diseases are referred to as the “atopic triad”. As outlined above there are pathogenic mechanisms that are central to both AD and asthma. Therefore scientific inquiry into the use of leukotriene receptor blockers in the treatment of AD is warranted.

Evidence in the literature provides a pathophysiological rationale for the use of cysLT receptor blockers in the treatment of AD however the exact mechanism of action of leukotriene receptor antagonists in AD is not known. Intradermal LTD₄ causes a wheal-and-flare response that could be blocked by a LTD₄ antagonist.²⁷ Montelukast has been shown to decrease eosinophils by 15%.²⁸ LTD₄ stimulates proliferation of eosinophil hematopoietic progenitor cells, and this increase can be suppressed by Montelukast.²⁹ Zafirlukast has been shown to inhibit LTD₄ and histamine mediated cutaneous vascular permeability.³⁰ In 16 AD adults treated with montelukast, there was a significant reduction in eosinophilic cationic protein and eosinophilic protein X levels compared to their baseline.³¹

Leukotriene Receptor Blockers and Other Skin Conditions

Leukotriene receptor antagonists have also been studied in chronic urticaria. Chronic urticaria (CU) may manifest as a reaction to a known cause such as cold, pressure, food additives or nonsteroidal anti-inflammatory drugs. In some patients there is no specific causative agent, this is referred to as chronic idiopathic urticaria (CIU). H1-receptor antagonists are the major class of therapeutic agents used in the management of urticaria. Nevertheless, CU is often difficult to treat and may not be controlled by antihistamines alone. Like AD, there is pharmacological plausibility of LTRAs effectiveness in the treatment of CIU and CU. Though the pathogenic mechanisms can vary, the final common pathway for lesion induction in most cases is cutaneous mast cell activation with release of histamine and other vasoactive or proinflammatory mediators.³² While histamine is considered to be the principle mediator in immediate urticarial responses, a late-phase reaction caused by substances such as LTs seem to prolong the inflammatory process in some types of urticaria.^{33,34} The prevalence of aspirin sensitivity among patients with CU is estimated to be between 20-30%.³⁵ The

Author(s), Date	Method	Duration	Subjects	Intervention	Outcomes Measured	Results
Carrucci et al. (1998) ⁵⁰	Case series	Variable Approx. 2 weeks	4	Zafirlukast 20mg BID	Extent of erythematous dermatitis	All experienced alleviation of symptoms
Zabawski E. (1999) ⁵¹	Case series	Variable 2-6 weeks	5 subjects 8-57 yr with severe AD	Zafirlukast 20mg BID	Variable Pruritus, lichenification, erythema, reduction in topical corticosteroid	All 5 patients experienced clinical improvement. No adverse side effects were reported
Pei, A.Y. (2001) ⁵²	Randomized double-blind placebo-controlled crossover study	12 weeks	15 subjects age 6-16 yr mod-severe AD	Montelukast 5mg OD vs. placebo	Impact of eczema on daily living (subjective) Disease extent, severity (objective)	Statistically significant improvement in severity of AD in patients on active treatment compared with placebo (p<0.05)
Yanase, D and David-Bajar, K. (2001) ⁵³	Randomized double-blind, placebo-controlled, crossover study	8 weeks	8 subjects adult (male and female) with AD	Montelukast 10mg OD vs. placebo Continuous adjunctive treatment: emollients, antihistamines, weak topical corticosteroids	Clinical severity scores (6 signs of AD)	Improvement in: • Scaling/dryness (p=0.003) • Lichenification (p=0.009) • Induration (p=0.016) • Erythema (p=0.024) • Erosions (p=0.027)
Kagi (2001) ⁴	Case Series	8 months	4 subjects with AD refractory to treatment.	Montelukast 10 mg OD	Extent of dermatitis (pruritus, skin changes), amount of topical steroids needed.	Significant improvement in pruritus and skin changes in both the treatment and control group. No significant difference in extent of dermatitis between the treatment and control group.
Capella, GL. (2001) ³¹	Randomized, single-blind study	6 weeks	32 subjects adults with AD	Montelukast 10 mg OD (n=16) vs. combined regimen (n=16) (oral cetirizine and clarythromycin topical corticosteroids and hydrating preparations.	SCORAD (objective +subjective assessment of severity of AD), eosinophilic cationic protein (ECP), eosinophilic protein X (EPX).	Similar SCORAD reductions in both groups. (p<0.05) ECP, EPX levels significantly reduced within each group. (p<0.05)
Eustachio et al. (2002) ⁵⁴	Randomized double-blind study	6 weeks	20 males Age range: 18-28 yr. Severe AD (SCORAD index)	Montelukast 10 mg OD (n=10) vs. placebo (n=10) No other treatment for AD allowed.	SCORAD index (objective and subjective criteria).	Significant reduction in disease activity (measured by SCORAD index) in the montelukast group compared with placebo group. (p<0.02)

Table 1: Clinical evidence supporting the use of montelukast and zafirlukast in patients with AD

pathogenesis of aspirin sensitivity likely involves the inhibition of cyclooxygenase by aspirin, thus altering the balance of arachidonic acid metabolites, leading to an increase in leukotriene LTB₄, C₄, D₄ and E₄.³⁶ It is postulated that due to this imbalance, patients with aspirin sensitivity and CU may be more likely to respond to LTRAs than those without this particular sensitivity.³³

There is evidence from anecdotal case reports^{33,37-43} and controlled trials^{29,44,45} of improvement in CU and CIU with LTRA treatment including montelukast and zafirlukast. Nevertheless, montelukast was not found to be more effective than placebo in decreasing the early and late cutaneous allergic responses.⁴⁶ Low doses of pranlukast have been reported to cause provocation of aspirin sensitive urticaria in two patients.⁴⁷ More experimental research and long term clinical studies are required to determine the role of LTs in the pathogenesis and treatment of CU and CIU.

Leukotriene Synthesis Inhibitors

Zileuton (Zylflo[®], Abbott Laboratories) is an inhibitor of the 5-lipoxygenase enzyme, which prevents the production of not only the cysteinyl leukotrienes but also of LTB₄ (see Fig. 1).

The production of other metabolites in the arachidonic acid cascade including 5-HETE and 5-oxo-EETE will be blocked. This is important in AD since LTB₄ and 5-oxo-EETE are chemoattractants for eosinophils,⁴⁸ which as outlined above are implicated in the pathophysiology of AD. In a prospective open-label pilot study, six female subjects with severe AD received 600mg zileuton QID for 6 weeks.⁴⁹ All six patients experienced a significant reduction in disease dissatisfaction (p=0.03). There was no significant difference in the subjective report of pruritus. Objective skin scores (based on erythema of 20 different body parts) were conducted by a physician prior to and following treatment and a significant decrease was found (p=0.03).

Future directions

There currently is no cure for AD. All of our current management strategies aim to control the symptoms of this immunocutaneous dysfunction. Montelukast might be a safe and effective alternative or steroid-sparing therapy in the management of patients with AD. In four randomized controlled trials^{28,52-54} with a total of 75 subjects, three of the trials found significant improvement of AD with montelukast treatment⁵²⁻⁵⁴ and one found no significant difference from placebo.³¹ There are three case series with a total of 13 patients that report improvement in AD with zafirlukast^{50,51} and montelukast.⁴ Long-term, larger double-blind placebo controlled studies are needed to determine the role of LTs in the pathogenesis of AD, to confirm the efficacy of leukotriene receptor inhibitors, and to determine the optimal timing and dosing for the treatment of AD.

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Chemical Peels

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ABSTRACT

With so many new peel preparations on the market today, the dermatologist must ask himself basic questions concerning the products. The most important question is directed to the medical literature rather than the advertising or marketing campaign so common among market-driven cosmetic products. Since all peeling agents—superficial, medium depth and deep—are derived from basic chemicals known to cause exfoliation, destruction and/or inflammation of skin in a controlled manner, the clinician must ask what is new and better about the product. Peeling agents, regardless of their “proprietary” new name, fall into chemical families. The clinical evaluation of these generic agents is well documented in our literature as to efficacy, technical care and safety. In addition, combinations of peeling agents have been presented in the dermatologic cosmetic literature with scientific clinical trials and histology. These include: 1) The Gordon-Baker phenol peel; 2) Combination medium depth peeling; 3) Glycolic acid formulations. It is the responsibility of the dermatologic surgeon to be in control of his chemicals and his products. It is thus necessary for him to understand all the products and the peel formulation and be sure it has undergone the test of objective scientific study with clear clinical evaluations and histology. Only then will we truly know the effectiveness of the agents we are using for exfoliating and resurfacing.

KEY WORDS: *chemical peels, photoaging*

The explosion of interest in chemical peeling and laser resurfacing on the part of dermatologists has paralleled the general public's interest in acquiring a youthful appearance by rehabilitating the photoaged skin. Advertising has further heightened the public's interest for cosmetic agents, over the counter chemicals and treatment programs that have entered the general market of products meant to rejuvenate skin and erase the marks of sun damage and age. Patients have tried most of these OTC home do-it-yourself programs and by the time they consult their dermatologist, they are ready for a more definitive procedure performed with either chemical peeling or laser resurfacing. It is the obligation of the physician to analyze the patient's skin type and the degree of photoaging skin, and thus prescribe the correct facial rejuvenation procedure. This should be the procedure or combination of procedures that will give the greatest benefit for the least risk factors and morbidity. Chemical peeling has been the tried and true basic procedure.

The approach to peeling photoaging skin has expanded beyond a one-stage procedure to now include preparatory medical therapy and post-treatment cosmeceutical topical therapy to maintain results and prevent further photodamage. It is up to the physician to fully understand the nature of skin and sun damage, protective techniques available, and active agents that work as cosmeceutical preparations. Having available multiple procedures to solve these problems will make his patients better candidates for the right procedure to restore and rehabilitate their skin.

Chemical peeling involves the application of a chemical exfoliant to wound the epidermis and dermis for the removal of superficial lesions and improve the texture of skin. Various acidic and basic chemical agents are used to produce the varying effects of light-to-

medium-to-deep chemical peels through differences in their ability to destroy skin. The level of penetration, destruction and inflammation determines the level of peeling. The stimulation of epidermal growth through the removal of the stratum corneum without necrosis consists of light superficial peel. Through exfoliation, it thickens the epidermis with qualitative regenerative changes. Destruction of the epidermis defines a full superficial chemical peel inducing the regeneration of the epidermis. Further destruction of the epidermis and induction of inflammation within the papillary dermis constitutes a medium-depth peel. Then, further inflammatory response in the deep reticular dermis induces new collagen production and ground substances which constitutes a deep chemical peel.¹ These have now been well classified and usage has been categorized for various degenerative conditions associated with photoaging skin based on levels of penetration. The dermatologist, thus, has tools capable of solving problems that may be mild, moderate or severe with agents that are very superficial, superficial, medium-depth, and deep peeling chemicals.

Indications and Patient Selection

Analyzing the patient with photoaging skin must take into account skin color and skin type as well as degree of photoaging. Pigmentary risks are generally not a great problem with very superficial and superficial pigment chemical peeling, but may become a significant problem with medium and deep chemical peeling. It can also be a significant risk when regional areas such as lips and eyelids are deep peeled, creating a significant color change in these cosmetic units from the rest of the face. The physician must inform the patient of this and other potential problems, especially if the skin type is III through VI. He must justify whether the benefits of the procedure

outweigh these risks and, in addition, plan for the appropriate techniques to prevent these unwanted changes in color.

The Glogau system classifies severity of photodamage, taking into account the degree of epidermal and dermal degenerative effects.² The categorization is I through IV, ranging from mild, moderate, advanced and severe photodamaged skin. These categories are devised to project which patients need therapeutic intervention. Category I or minimal degree photodamage can be treated with light chemical peeling and medial treatment. Category II and III would entail medium-depth chemical peeling while category IV would need deep peeling or resurfacing plus cosmetic surgical intervention for gravitational changes.

The peeling agent is a chemical escharotic that damages the skin in a therapeutic manner. It is important that the physician understand the patient's skin and its ability to withstand this damage. The epidermis and stratum corneum have a barrier function against noxious chemicals and some skin types withstand the damage to a greater degree than others, while particular skin disorders have a greater tendency to produce side-effects and complications from chemical peels, due to poor barrier function or exaggerated inflammatory reactions. Patients with extensive photodamage may require stronger peeling agents and repeated applications of medium-depth peeling solutions to obtain therapeutic results. It is for this reason a careful evaluation of skin types and problems must be assessed.

Herpes simplex can be a post-operative problem with significant morbidity. Patients susceptible should be pre-treated with antiherpetic agents such as acyclovir or valacyclovir to prevent herpetic activation. These patients can be identified in the pre-operative consultation and placed on appropriate therapy at the time of the chemical peel. All anti-herpetic agents act by inhibiting viral replication in the intact epidermal cell. The significance of this in peeling is that the skin must be reepithelialized before the agent has its full effect. Thus, the antiviral agent must be continued in deep chemical peeling for the entire two weeks, or in medium-depth peeling for at least ten days.³

Medium-depth chemical peeling

Medium-depth chemical peeling is defined as controlled damage from a chemical agent to the epidermis and papillary dermis resulting in specific regenerative changes that can be performed in a single setting. Agents currently used include combination products—Jessner's solution, 70% glycolic acid, and solid carbon dioxide with 35% trichloroacetic acid. The benchmark for this level peel was 50% trichloroacetic acid. It has traditionally achieved acceptable results in ameliorating fine wrinkles, actinic changes, and preneoplasia. However, since TCA itself is an agent more likely to be fraught with complications, especially scarring, in strengths of 50% or higher, it has fallen out of favor as a single agent chemical peel.⁴ It is for this reason that the combination products along with a 35%

TCA formula have been found equally effective in producing this level of control damage without the risk of side-effects.

Brody first developed the use of solid CO₂ applied with acetone to the skin as a freezing technique prior to the application of 35% trichloroacetic acid. The preliminary freezing appears to break the epidermal barrier for a more even and complete penetration of the 35% trichloroacetic acid.⁵

Monheit then demonstrated the use of Jessner's solution prior to the application of 35% trichloroacetic acid. The Jessner's solution was found effective in destroying the epidermal barrier by breaking up individual epidermal cells. This also allows a deeper penetration of the 35% TCA and a more even application of the peeling solution.⁶ Similarly, Coleman has demonstrated the use of 70% glycolic acid prior to the application of 35% trichloroacetic acid. Its effect has been very similar to that of Jessner's solution.⁷

All three combinations have proven to be as effective as the use of 50% trichloroacetic acid with a greater safety margin. The application of acid and resultant frosting are better controlled with the combination so that the "hot spots" with higher concentrations of TCA can be controlled, creating an even peel with less incidence of dyschromias and scarring. The combination peel produces an even, uniform peel. The Monheit version of the Jessner's solution—35% TCA peel is a relatively simple and safe combination. The technique is used for mild-to-moderate photoaging including pigmentary changes, lentigines, epidermal growths, dyschromias, and rhytids. It is a single procedure with a healing time of 7-10 days. It is useful also to remove diffuse actinic keratoses as an alternative to chemical exfoliation with topical 5-fluorouracil chemotherapy. Topical chemotherapy is applied for 3 weeks creating erythema, scabs and crusts for up to 6 weeks. The combination peel will produce similar therapeutic benefits within 10 days of healing. It thus reduces the morbidity significantly and gives the cosmetic benefits of improved photoaging skin.

The procedure is usually performed with mild preoperative sedation and nonsteroidal anti-inflammatory agents. The patient is told that the peeling agent will sting and burn temporarily and aspirin is given before the peel and continued through the first twenty-four hours if the patient can tolerate the medication. Its inflammatory effect is especially helpful in reducing swelling and relieving pain. If given before surgery, it may be all the patient requires during the postoperative phase.

Vigorous cleaning and degreasing is necessary for even penetration of the solution. The face is scrubbed gently with Ingasam (Septisol[®], Vestal Laboratories) 4" x 4" gauze pads and water, then rinsed and dried. Next, an acetone preparation is applied to remove residual oils and debris. The skin is essentially debrided of stratum corneum and excessive scale. A thorough degreasing is necessary for an even penetrant peel.

After thorough cleaning, the Jessner's solution is applied with either cotton-tip applicators or 2" x 2" gauze. The Jessner's solution is applied evenly with usually one or two coats to achieve a light but even frosting. The frosting achieved with Jessner's solution is much lighter than that produced by TCA and the patient is usually uncomfortable, feeling only heat. A mild erythema appears with a faint tinge of splotchy frosting over the face.

The TCA is painted evenly with one to four cotton-tipped applicators that can be applied over different areas with light or heavier doses of the acid. Four cotton-tipped applicators are applied in broad strokes over the forehead and also on the medial cheeks. Two mildly soaked cotton-tipped applicators can be used across the lips and chin, and one damp cotton-tipped applicator on the eyelids. Thus, the dosage of application is technique dependent on the amount used and the number of cotton-tipped applicators applied. The cotton-tipped applicator is useful in quantitating the amount of peel solution to be applied.

The white frost from the TCA application appears complete on the treated area within 30 seconds to 2 minutes. Even application should eliminate the need to go over areas a second or a third time, but if frosting is incomplete or uneven, the solution should be reapplied. TCA takes longer to frost than Baker's formula or straight phenol, but a shorter period of time than the superficial peeling agents do. The surgeon should wait at least 3-4 minutes after the application of TCA to ensure the frosting has reached its peak. He then can document the completeness of a frosted cosmetic unit and touch up the area as needed. Areas of poor frosting should be retreated carefully with a thin application of TCA. The physician should achieve a level II to level III frosting. Level I frosting is erythema with a stringy or blotchy frosting, seen with light chemical peels. Level II frosting is defined as white-coated frosting with erythema showing through. A level III frosting, which is associated with penetration through the papillary dermis, is a solid white enamel frosting with little or no background of erythema.⁸ A deeper level III frosting should be restricted only to areas of heavy actinic damage and thicker skin. Most medium-depth chemical peels use a level II frosting and this is especially true over eyelids and areas of sensitive skin. Those areas with a greater tendency to scar formation, such as the zygomatic arch, the bony prominences of the jaw line, and chin, should only receive up to a level II frosting. Overcoating trichloroacetic acid will increase its penetration so that a second or third application will drive the acid further into the dermis, creating a deeper peel. One must be careful in overcoating only areas in which the take up was not adequate or the skin is much thicker.

Anatomic areas of the face are peeled sequentially from forehead to temple to cheeks and finally to the lips and eyelids. The white frosting indicates keratocoagulation or protein denaturation of keratin and at that point the reaction is complete. Careful feathering of the solution into the hairline and around the rim of the jaw and brow conceals the line demarcation between peeled and nonpeeled

areas. The perioral area has rhytids that require a complete and even application of solution over the lip skin to the vermillion.

Eyelid skin must be treated delicately and carefully. A semidry applicator should be used to carry the solution within 2-3mm of the lid margin. The patient should be positioned with the head elevated at 30 degrees and the eyelids closed. Excess peel solution on the cotton tip should be drained gently on the bottom before application. The applicator is then rolled gently on the lids and periorbital skin. Never leave excess peel solution on the lids because the solution can roll into the eyes. Dry the tears with a cotton-tipped applicator during peeling because they may pull peel solution to the puncta and eye by capillary attraction. The solution should be diluted immediately with cool saline compresses at the conclusion of the peel.

The Jessner's-TCA peel procedure is as follows:

1. The skin should be cleaned thoroughly with Septisol® to remove oils.
2. Acetone or acetone alcohol is used to further debride oil and scale from the surface of the skin.
3. Jessner's solution is applied.
4. Thirty-five percent TCA is applied until a light frost appears.
5. Cool saline compresses are applied to dilute the solution.
6. The peel will heal with 0.25% acetic acid soaks and a mild emollient cream.

There is an immediate burning sensation as the peel solution is applied, but this subsides as frosting is completed. Cool saline compresses offer symptomatic relief for a peeled area as the solution is applied to other areas.

Postoperatively, edema, erythema, and desquamation are expected. With periorbital peels and even forehead peels, eyelid edema can occur and may be enough to close the lids. For the first 24 hours, the patient is instructed to soak four times a day with a 0.25% acetic acid compress made of 1 tablespoon white vinegar in 1 pint of warm water. A bland emollient is applied to the desquamating areas after soaks. After 24 hours, the patient can shower and clean gently with a mild nondetergent cleanser. The erythema intensifies as desquamation becomes complete within 4-5 days. Thus, healing is completed within 1 week to 10 days. At the end of 1 week, the bright red color has faded to pink and has the appearance of a sunburn. This can be covered by cosmetics and will fade fully within 2-3 weeks.

The medium-depth peel is dependent on three components for therapeutic effect: (1) degreasing, (2) Jessner's solution, and (3) 35% TCA. The amount of each agent applied creates the intensity and thus the effectiveness of this peel. The variables can be adjusted according to the patient's skin type and the areas of the face being treated. It is thus the workhorse of peeling and resurfacing in my practice as it can be individualized for most patients we see.

For a patient in which there is advanced photoaging changes such as crow's feet and rhytides in the periorbital and/or perioral area with

medium-depth changes on the remaining face, a medium-depth peel can be used to integrate these procedures together. That is, laser resurfacing or deep chemical peeling can be performed over the periorbital and perioral areas that have more advanced photoaging changes, while the medium-depth chemical peel is used for the rest of the face. This will blend the facial skin as a unit so that the therapeutic textural and color changes will not be restricted to one area. The patients requiring laser resurfacing in a localized cosmetic unit will have the remaining areas of their face blended with this medium-depth chemical peel. Patients having laser resurfacing or deep peeling to the perioral or periorbital areas alone develop a pseudo hypopigmentation that is a noticeable deformity. The patient requiring laser resurfacing at a localized cosmetic unit will have the remaining areas of their face blended with this medium-depth peel. The alternative—a full-face deep peel or laser resurfacing has an increased morbidity, longer healing and risk of scarring over areas such as the lateral jaw line, malar eminences, and forehead. If deep resurfacing is needed only over localized areas such as perioral or periorbital face, a blending medium-depth peel does reduce morbidity and healing time.¹⁰

Deep chemical peeling

Glogau Level III and IV photodamage requires deep chemical peeling. This entails the use of either trichloroacetic acid above 50%, or the Gordon-Baker phenol peel. Laser resurfacing can also be used to reliably reach this level of damage. TCA above 45% has been found to be unreliable and dangerous with a high incidence of scarring and postoperative complications. For this reason, it is not included as a preferred treatment method for deep chemical peeling. The Baker-Gordon phenol peel has been used successfully for over 40 years for deep chemical peeling and produces reliable results. It is a labor-intensive procedure that must be taken seriously as all major surgical procedures are.

The patient requires preoperative sedation with an intravenous line and preoperative IV hydration. Usually a liter of fluid is given preoperatively and in addition, a liter of fluid is given during the procedure. This is helpful in decreasing the phenol concentration from the serum. For this reason, one must be concerned with phenol absorption through the skin and the resultant serum concentration of phenol through cutaneous absorption. Methods to limit this include:

1. IV hydration prior to the procedure and during the peel to flush the phenolic products through the serum.
2. Extending the time of application for a full-face peel over one and one-half hours. Baker's solution is applied to each cosmetic unit with a fifteen-minute wait in between each unit. That is, the forehead, cheeks, chin, lips, and eyelids are each given a fifteen-minute period of time for a total of an hour to an hour and a half for the procedure.

3. All patients are monitored and if there is any electrocardiographic abnormality, i.e., PVC or PAC, the procedure is stopped and the patient is watched carefully for other signs of toxicity.

4. Many physicians believe that O₂ given during the procedure can be helpful in preventing arrhythmic complications.

5. Any patient with a history of cardioarrhythmia, hepatic or renal compromise, or on medications that give a propensity for arrhythmias, should not undergo the Baker-Gordon phenol peel.¹⁰

The patient undergoing deep chemical peeling must recognize the significant risk factors, the increased morbidity, and possible complications involved in this procedure so that the benefits can be weighed positively against these particular factors. In the hands of those that do this technique regularly, it is a reliable and safe method of rejuvenating advanced to severe photoaged skin including deeper perioral rhytids, periorbital rhytids and crow's feet, forehead lines and wrinkles, as well as the other textural and lesional changes associated with the more severe photoaging process.

There are two methods for deep chemical peeling: Baker's formula phenol unoccluded, and Baker's formula phenol occluded with tape. Occlusion is accomplished with the application of waterproof zinc oxide tape such as inch Curity[®] tape. The tape is placed directly after the phenol is applied to each individual cosmetic unit. Tape occlusion increases the penetration of the Baker's phenol solution and is particularly helpful for deeply lined "weather-beaten" faces. A taped Baker's formula phenol peel creates the deepest damage in mid-reticular dermis and this form of chemical peeling should only be performed by the most knowledgeable and experienced cosmetic surgeons who understand the risks of over penetration and deep damage to the reticular dermis. The unoccluded technique as modified by McCollough involves more skin cleansing and application of more peel solution. On the whole, this technique does not produce as deep a peel as the occluded method.

The Baker-Gordon formula for this peel was first described in 1961, and since then has been used successfully for over 25 years. The Baker-Gordon formula of phenol penetrates further into the dermis than full-strength undiluted phenol because full-strength phenol allegedly causes an immediate coagulation of epidermal keratin proteins and self blocks further penetration. Dilution to approximately 50-55% in the Baker-Gordon formula causes keratolysis and keratocoagulation resulting in greater penetration. The liquid soap, Septisol[®], is a surfactant that reduces skin tension allowing a more even penetration. Croton oil is a vesicant and epidermolytic agent that enhances phenol absorption. The freshly prepared formula is not miscible, but rather is a suspension and must be stirred in a clear glass medicine cup immediately before application to the patient. Though the mixture can be stored in an amber glass bottle for short periods, this is usually unnecessary and should be reformulated on a regular basis.

The four stages of wound healing are apparent after a deep chemical peel. They include: (1) inflammation, (2) coagulation, (3) reepithelialization, and (4) fibroplasia. At the conclusion of the chemical peel, the inflammatory phase has already begun with a brawny, dusky erythema that will progress over the first 12 hours. This is an accentuation of the pigmented lesions on the skin as the coagulation phase separates the epidermis producing serum exudation, crusting, and pyoderma. It is during this phase that it is important to use debriding soaks and compresses as well as occlusive salves. These will remove the sloughed, necrotic epidermis and prevent the serum exudate from hardening as crust and scab. I prefer the use of 10% acetic acid soaks found in the vinegar/water preparation (1 teaspoon white vinegar, 1 pint warm water), as it is antibacterial, especially against *Pseudomonas* and gram negatives. In addition, the mildly acidic nature of the solution is physiologic for the healing granulation tissue, and mildly debriding, as it will dissolve and cleanse the necrotic material and serum. I prefer to use bland emollients and salves such as Vaseline® petrolatum, Eucerin®, or Aquaphor®, as the skin can be monitored carefully day by day for potential complications.

Reepithelialization begins on day 3 and continues until day 10-14. Occlusive salves promote faster reepithelialization and less tendency for delayed healing, which may occur with dry crusting. The final stage of wound healing—fibroplasia, will continue well beyond the initial closure of the peeled wound and continues with neoangiogenesis and new collagen formation for 3 or 4 months. Prolonged erythema may last 2-4 months in unusual cases of sensitive skin or with contact dermatitis. New collagen formation can continue to improve texture and rhytides for a period up to 4 months during this last phase of fibroplasia.

Complications

Many of the complications seen in peeling can be recognized early on during healing stages. The cosmetic surgeon should be well acquainted with the normal appearance of a healing wound and its time frame for both medium and deep peeling. Prolongation of the granulation tissue phase beyond 1 week to 10 days may indicate delayed wound healing. This could be the result of viral, bacterial, or fungal infections, contact dermatitis interfering with wound healing, or other systemic factors. A red flag should alert the physician to carefully investigate and institute prompt treatment to forestall potential irreparable damage that may result in scarring.

Complications can be caused either intraoperatively or postoperatively. The two inherent errors that lead to intraoperative complications are (1) incorrect peel pharmacology and (2) accidental solution misplacement. It is the physician's responsibility to know that the solution and its concentration is correct. Trichloroacetic acid concentrations should be measured weight by volume as this is the standard for measuring depth of peel. Glycolic acid and lactic acid solutions as well as Jessner's solution must be checked for expiration

date as the potency decreases with time. Alcohol or water absorption may inappropriately increase the potency, so one must assure that the shelf life is appropriate. The peel solution should be applied with cotton-tipped applicators and in medium and deep peels, it is best to pour the peel solution in a secondary container rather than apply the solution spun around the neck of the bottle. Intact crystals may give the solution a higher concentration of solution as it is taken directly from its container. One should be careful to apply the solution to its appropriate location and not to pass the wet cotton-tipped applicator directly over the central face where a drop may inadvertently get on sensitive areas such as the eyes. Saline and bicarbonate of soda should be available to dilute TCA or neutralize glycolic acid if inappropriately placed in the wrong area. Likewise, mineral oil should be present for Baker's phenol peels. Postoperative complications can result from local infection or contact dermatitis. The best deterrent for local infection is the continuous use of soaks to debride crusting and necrotic material. Strep and staph infection can occur under biosynthetic membranes or thick occlusive ointments. The use of 10% acetic acid soaks seems to deter this as well as the judicious removal of the ointment with each soak. *Staphylococcus*, *E. coli*, or even *Pseudomonas* may result from improper care during healing and should be treated promptly with the appropriate oral antibiotic.

Frequent postoperative visits are necessary to recognize the early onset of a bacterial infection. It may present itself as delayed wound healing, ulcerations, build up of necrotic material with excessive scabbing, crusting, purulent drainage, and odor. Early recognition and institution of appropriate antibiotics will prevent the spread of infection, heal the skin, and prevent scarring.

Herpes simplex infection is the result of reactivation of the herpes simplex virus on the face and most commonly on the perioral area. A history of previous HSV infection should necessitate the use of prophylactic oral antiviral medications. Patients with a positive history can be treated with 400mg of acyclovir three times a day beginning on the day of the peel and continuing for 7-14 days, depending on whether it is a medium-depth or deep chemical peel. I prefer to treat all patients with antiviral agents regardless of a positive history as many patients do not remember prior herpes simplex infection that may have occurred years ago. The mechanism of action of all antiviral agents is to inhibit viral replication in the intact epidermal cell. This would mean that the drug would not have an inhibitory effect until the skin is reepithelialized, which is 7-10 days in medium and deep peels. In the past, these agents were discontinued at 5 days and in treated patients, clinical infection became apparent in 7-10 days. Active herpetic infections can easily be treated with antiviral agents and caught early, they usually do not scar.

Delayed wound healing and persistent erythema are signs that the peel is not healing normally. The cosmetic surgeon must know the normal time table for each of the healing events so that he may

recognize when healing is delayed or the erythema is not fading adequately. Delayed wound healing may respond to physician debridement if an infection is present. It will respond to corticosteroids, if it's due to contact allergic or contact irritant dermatitis along with the change of the offending contact agent, or protection with a biosynthetic membrane such as Flexzan® (Bertek Pharmaceuticals) or Vigilon (Bard Medical). When this diagnosis is made, these patients must be followed daily with dressing changes and a close watch on the healing skin.

Persistent erythema is a syndrome where the skin remains erythematous beyond what is normal for the individual peel. A superficial peel loses its erythema in 3-5 days, a medium-depth peel within 15-30 days, and a deep chemical peel within 60-90 days. Erythema and/or pruritus beyond this period of time is considered abnormal and fits this syndrome. It may be contact dermatitis, contact sensitization, reexacerbation of prior skin disease, or a genetic susceptibility to erythema. It, though, is a red flag that also indicates a sign of potential scarring. Erythema is the result of the angiogenic factors stimulating vasodilation which indicates the phase of fibroplasia is being stimulated for a prolonged period of time. For this reason, it can be accompanied by skin thickening and scarring. It should be treated promptly and appropriately with topical steroids, systemic steroids, intralesional steroids if thickening is occurring, and skin protection which would eliminate the factors of irritancy and allergy. If thickening or scarring becomes evident, other measures that be helpful include the daily use of silicone sheeting and the dye pulsed vascular laser to treat the vascular factors. With prompt intervention, scarring in many cases can be averted.

Conclusion

The physician has the responsibility of choosing the correct modality to treat skin conditions such as photoaging skin, scars, dyschromias, and the removal of skin growths. There are many agents available including the three levels of chemical peels reviewed. It is the responsibility of the physician to have thorough knowledge of all of these tools to give each patient the correct treatment his condition warrants.

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Update on Drugs

Class	Name/Company	Approval Dates and Comments
<i>Antihistamines</i>	Loratadine <i>CLARITIN Hives Relief Tablets</i> Schering-Plough	The US FDA approved this once-daily formulation in November 2003, for the OTC relief of itching due to hives. This product is the first and only FDA-approved, non-drowsy antihistamine to offer OTC itch relief to adults and children >6 years of age who suffer from hives. The US FDA's decision was contingent upon the results of label comprehension studies fielded by Schering-Plough to demonstrate that the label could be properly understood by consumers. Marketing is expected to begin in February 2004.
<i>Antiviral Agent</i>	Docosanol 10% cream AVANIR Pharmaceuticals	The Swedish Medical Products Agency approved this product in November 2003, for marketing as a non-prescription, OTC topical treatment for cold sore infections. Sweden will act as AVANIR's Reference Member State for the mutual recognition process within Europe. Docosanol is marketed as Abreva® by GlaxoSmithKline in the US.
<i>Cosmetic Treatment</i>	Hyaluronic Acid <i>Restylane™</i> Q-Med AB	The US FDA General and Plastic Surgery Devices Advisory Panel recommended approval of this biodegradable gel in November 2003, for the nonsurgical use through injections for patients wishing to smooth wrinkles, sculpt lips and shape facial contours.
<i>Cosmetic Treatment</i>	Hylan-B Gel <i>Hylaform®</i> Inamed/Genzyme	The US FDA General and Plastic Surgery Devices Advisory Panel recommended approval with conditions of Genzyme's Pre-Market Approval application to market this hyaluronic acid-based cosmetic dermal filler for the treatment of soft tissue contour deficiencies such as wrinkles.
<i>HIV/AIDS</i>	Fosamprenavir calcium <i>Lexiva®</i> GlaxoSmithKline	The US FDA approved this new protease inhibitor (PI) in October 2003, for the treatment for HIV infection in adults in combination with other antiretroviral medications. GSK cautions that the following should be considered when initiating therapy: the PI-experienced patient study was not large enough to reach a definitive conclusion that Lexiva® and lopinavir/ritonavir are clinically equivalent. Once daily administration of Lexiva® plus ritonavir is not recommended for PI-experienced patients.
Drug News		
<i>Drug Warning</i>	The US FDA informed physicians in October 2003, that it has received more than 50 reports of adverse events, including some deaths, associated with Cordis Corporation's Cypher Coronary Stent. Symptoms include pain, rash, respiratory alterations, hives, itching, fever, and blood pressure changes. Cordis considers these to be possible hypersensitivity reactions. The cause of these adverse events has not yet been determined.	
<i>Neurotoxin</i>	Enrollment began in November 2003, for the first clinical trial to compare the effectiveness and patient satisfaction of BOTOX® Cosmetic with three cosmetic creams: StriVectin-SD®, HydroDerm®, and WrinkleRelax®, for patients with moderate-to-severe glabellar lines. The trial will be conducted by Dr. Kenneth Beer, who is a board-certified cosmetic dermatologist and clinical instructor of dermatology at the University of Miami. BOTOX® Cosmetic was approved by the US FDA in April 2002, while none of the creams have been approved.	

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