Desloratadine for the Treatment of Chronic Urticaria

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ABSTRACT

Chronic urticaria is a common dermatologic condition that is idiopathic in most cases. Antihistamines are the mainstays of treatment for this condition. The newer, second and third generation antihistamines are the preferred agents because of their improved safety profile and comparable efficacy to the first generation antihistamines. Desloratadine is a new non-sedating H1-receptor antagonist. Based on clinical studies, desloratadine is a valuable new addition to the available treatment options and should be considered as a first-line therapy for patients with chronic urticaria.

Key Words: desloratadine, chronic urticaria

Desloratadine is a new selective H1-receptor antagonist and is the primary active metabolite of loratadine (Claritin®, Schering-Plough). It has been approved for use in many countries throughout the world and is sold as Clarinex® in the US, and as Aervis® in Canada. In Europe it is being marketed as Neoclarityn™ and Aervis™. During the first quarter of 2002, it received US FDA approval for the relief of both nasal and non-nasal symptoms of allergic rhinitis (seasonal and perennial) in patients ≥12 years of age. Additionally, it is indicated for the symptomatic relief of pruritus and the reduction in the number and size of hives in patients ≥12 years of age with chronic idiopathic urticaria.

Urticaria

Urticaria is a cutaneous reaction pattern characterized by pruritic, transient, erythematous papules and wheals often with central clearing. It results from the transudation of fluid from the cutaneous vasculature. Numerous factors both immunologic and non-immunologic, including autoantibodies, can cause mast cell activation and the release of mediators capable of causing vascular permeability, and thus, hives. Histamine is the best documented of these mediators. Numerous etiologies exist for urticaria including: drugs, foods, infections, contactants, internal diseases, psychogenic factors, genetic factors and physical factors (pressure, cold, heat, etc.). Urticaria is classified as acute or chronic depending on whether its duration is > 6 weeks. The cause of acute urticaria is usually detectable. In chronic urticaria, most cases (90-95%) are idiopathic.

Mechanism of Action and Pharmacology

Desloratadine, is a selective H1-receptor antagonist. It is approximately 10-20 times more potent in H1-receptor binding than loratadine in vitro, and has 2.5-4 times more antihistaminic potency in animals,1,2 and has no significant cholinergic or H2-receptor affinity. Furthermore, desloratadine does not penetrate the blood-brain barrier in animal studies, a fact that has been confirmed by the lack of sedation or cognitive impairment in clinical trials.

In vitro studies have shown that desloratadine also possesses anti-allergic and anti-inflammatory activity. This product inhibits the release by mast cells and basophils of histamine and other inflammatory mediators.3,4 In addition, it inhibits cytokines, and the induction of cell adhesion molecules, as well as reducing eosinophil chemotaxis and activation.5,6,7 Although these in vitro effects do not necessarily translate into in vivo effects, these added properties may result in improved clinical responses.
Pharmacokinetics and Drug Interactions

Desloratadine is rapidly absorbed, has dose-proportional pharmacokinetics, and a half-life of 27 hours. The absorption of desloratadine is not affected by food, and the metabolism and elimination are not significantly affected by the subject’s age or sex. Metabolism of desloratadine does not involve the cytochrome P450 system or the p-glycoprotein transport system. Results of electrocardiographic studies have revealed no clinically relevant interactions between desloratadine and erythromycin, ketoconazole or grapefruit juice.8

Clinical Trials

The efficacy and safety of desloratadine 5mg, once daily was studied in two randomized, double-blind, placebo-controlled, clinical trials of six weeks’ duration involving 416 patients, 12-84 years of age with chronic idiopathic urticaria.9,10 The primary efficacy variable, i.e., the mean improvement from baseline in pruritus over the first week of treatment, was significantly greater in the desloratadine group (47.9%) than in the placebo group (21.9%; p<.001). All secondary efficacy parameters, i.e., total symptom scores (pruritus, number and size of hives), quality of life measures (interference with sleep and daily activities), showed that desloratadine was significantly better than placebo at all time points from day 2 of treatment until the end of the study at 6 weeks.

The study showed statistically significant improvement after dosing that lasted for the entire 24-hour period after each dose (see Table 1). The safety profile of desloratadine was excellent with the overall adverse event profile, including somnolence, similar to placebo (see Table 2).

Conclusion

Clinical trials have demonstrated that desloratadine has a superior efficacy and similar safety profile to placebo in the treatment of patients with chronic idiopathic urticaria. Once-daily dosing provided rapid, prolonged benefits in objective and subjective disease and quality of life measures. Desloratadine’s effectiveness was maintained for the full 24 hours after each dosing, as well as throughout the 6 week study. Further active comparator studies will determine whether desloratadine’s potent H1-antihistaminic properties combined with potential anti--

Continued on page 5
Allergic Contact Dermatitis in Children: A Practical Approach to Management

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ABSTRACT

Allergic contact dermatitis (ACD) may account for at least 20% of all childhood dermatitis. Clinically, its morphology is identical to other forms of dermatitis in acute, subacute, and chronic forms. A persistent or unusual and localized pattern is often the key to diagnosis. Treatment has centered around the use of corticosteroids, with the adjunct of antihistamines, wet dressings, and emollients for alleviation of symptoms. The newer topical immunosuppressives, tacrolimus and pimecrolimus, may also hold promise as alternative therapies, although they have not been well-studied in this regard. Allergen identification, sometimes through patch testing, and allergen avoidance are the keys to preventing recurrences of this disease.

Key Words: allergic contact dermatitis, allergen, childhood dermatitis

Allergic contact dermatitis (ACD) is an acquired, inflammatory reaction of the skin that requires absorption of an antigen from the skin surface and recruitment of previously sensitized, antigen-specific T lymphocytes into the skin. An intact immune system is required for the development of ACD, which occurs in two phases. The sensitization phase begins with initial exposure to the antigen. Contact antigens are usually low molecular weight substances that penetrate the outer layer of the skin and are taken up by Langerhans cells (LC). After processing the antigen and migrating to regional lymph nodes, LCs present the antigen to T lymphocytes. These antigen-specific T lymphocytes undergo clonal expansion, creating a pool of cells with immune memory that can generate an immune response upon re-exposure to the allergen. In this elicitation phase, the sensitized T lymphocytes proliferate and release inflammatory mediators, producing a localized dermatitis. The resulting dermatitis develops in 12-24 hours after allergen exposure, peaks in 3-5 days and may last 3-4 weeks, if untreated.1-3 The potency of the allergen determines the number of exposures necessary for this process to occur. A strong antigen such as poison ivy requires only one exposure, while weaker antigens require numerous exposures over weeks to years. Once sensitization occurs, however, it is thought to be long lived.1-3

The exact incidence and prevalence of ACD in children is not known.4 According to Weston,5 ACD may account for up to 20% of all cases of childhood dermatitis, but when considering that in endemic areas nearly all individuals are sensitized to poison ivy, this estimate may be higher. It was previously believed that ACD was rare in children, possibly due to a less mature immune system. Case reports, however, have described ACD in children as young as 1 week old,6,7 and recent studies of asymptomatic children have shown that 13-25% are sensitized to common contact allergens, with sensitization commonly beginning as early as 6 months of age.8-10

Contact allergens are found in both the natural and man-made environment, of which the most common is urushiol, a pentadecylcatechol found in plants of the Toxicodendron species, such as poison ivy, poison oak, and poison sumac. Other common childhood contact allergens include nickel, neomycin, chromates, thimerosal, Balsam of Peru, formaldehyde and related preservatives, colophony, p-Tert-butylphenol formaldehyde resin, lanolin, and several others.8-10

Clinical features

ACD presents as pruritic dermatitis, localized to the site of allergen contact. Acute ACD to potent allergens is characterized by erythema and edema with vesicles or bullae that often rupture, leaving a crust. More commonly, a subacute or chronic dermatitis, characterized by lichenification, erythema and scaling, is produced by less potent antigens. A more generalized dermatitis, termed autoeczematization, may develop distal to the original site of contact ≥1 week after the appearance of the initial, localized dermatitis.

Because the clinical morphology of ACD is identical to other forms of dermatitis, such as irritant or atopic dermatitis (AD), a history of allergen exposure and the pattern of the eruption are important keys in making the correct diagnosis. Patterns of dermatitis that are suggestive of ACD include persistent, localized dermatitis, dermatitis that has not responded as expected to therapy, and dermatitis in an unusual pattern or distribution. Its location is often a clue to the offending allergen.11

Treatment

The treatment of ACD has not changed dramatically over the years and still involves two main principles: 1) the dermatitis must be treated; and 2) the allergen must be identified and avoided in order to prevent recurrence of the disease.

Acute ACD is best controlled with corticosteroids (CSs) (see Table 1). Through various mechanisms, CSs decrease
Table 1: Therapy of Childhood ACD

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<td>Acute ACD</td>
<td>Prednisone (&gt;10% BSA)</td>
<td>Antihistamines:</td>
<td>Allergen</td>
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<td></td>
<td>Medium/medium-high potency</td>
<td>-Hydroxyzine</td>
<td>avoidance</td>
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<td>topical CS (&lt;10% BSA):</td>
<td>-Diphenhydramine</td>
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<td>-Fluocinolone 0.025%</td>
<td>Wet dressings</td>
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<td>-Triamcinolone 0.1%</td>
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<td>-Mometasone 0.1%</td>
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<td>Subacute/Chronic ACD</td>
<td>Medium potency topical CS</td>
<td>Tacrolimus</td>
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<td>Emollients</td>
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Table 1: Therapy of Childhood ACD

the production of cytokines and halt lymphocyte proliferation, limiting the inflammatory response to contact allergens.\textsuperscript{12} If the dermatitis involves more than 10% of the skin surface, systemic steroids are indicated. A single morning dose of prednisone (1-2mg/kg) for 7-10 days, followed by a taper over the text 7-10 days is usually sufficient. Localized eruptions may be treated with steroid ointments of moderate potency applied twice daily for 2-3 weeks. For both topical and systemic therapy, continuing the treatment for 2-3 weeks is necessary, as stopping it too quickly may cause rebound dermatitis.

In addition to CSs, other treatments aimed at alleviating associated symptoms such as burning or pruritus may be beneficial. Sedating antihistamines such as diphenhydramine or hydroxyzine decrease itching and allow the patient to sleep through the night. As an alternative to standard dosing, we have found a single dose of hydroxyzine 1-2mg/kg given 30 minutes – 1 hour before bedtime to be effective in this regard. Wet dressings are also soothing and additionally help to debride crusts. Slightly dampened cotton garments are worn over the affected area and covered with a dry garment. The patient may use these dressings overnight or change them every 8 hours during the day.\textsuperscript{13}

Subacute and chronic ACD is often the result of repeated exposures to modest or weak contact allergens, making treatment challenging. Systemic CSs are effective at suppressing chronic dermatitis, but their use should be avoided in this condition as their potential side-effects outweigh the benefits of the long course of therapy likely to be required.\textsuperscript{12} Depending on the part of the body affected, low or medium potency topical steroids applied twice daily are a more reasonable alternative. Appropriate long-term use of these medications does not cause hypothalamic-pituitary-adrenal suppression in infants and children,\textsuperscript{14} although localized side-effects such as atrophy are possible. Recently, two macrolide immunosuppressants have emerged as potential alternatives to CSs in the treatment of ACD. Tacrolimus is used systemically to prevent organ rejection after transplantation. It inhibits calcineurin, thereby halting the transcription of IL-2, decreasing the responsiveness of T lymphocytes to antigenic stimuli.\textsuperscript{15} As a topical ointment in 2 concentrations (Protopic\textsuperscript{®} 0.03% and 0.1%, Fujisawa), it is approved for the treatment of AD, but only the 0.03% version is recommended for use in children aged 2 to 15 years. Topical tacrolimus can inhibit the inflammatory reaction in both pig and human models of ACD,\textsuperscript{16,17} but its efficacy as a treatment for ACD has not been well studied.

Pimecrolimus (SDZ ASM 981), an ascomycin analog, down-regulates the production of various cytokines that are released due to antigen-specific stimulation of immune-memory T cells.\textsuperscript{18} A 1% cream (Elidel\textsuperscript{®}, Norvartis) is approved in the US for the treatment of mild-to-moderate AD in children 2 years and older. In a recent report, 0.1% SDZ ASM 981 cream was as effective as topical clobetasol-17-propionate in inhibiting the development of ACD in a pig model.\textsuperscript{19} Additionally, 0.6% SDZ ASM 981 cream was as effective as 0.1% betamethasone-17-valerate in the treatment of experimentally-produced nickel ACD in 66 volunteers.\textsuperscript{20}

The T cell-specific mechanisms of action of tacrolimus and pimecrolimus are highly applicable to ACD. It is important to point out, however, that inhibiting the development of ACD in controlled situations does not necessarily correlate with effective treatment of clinically apparent disease. Further studies are needed to clarify the clinical efficacy of these medications for the treatment of ACD. We currently recommend that they be considered as alternatives to CS.

Identifying the offending allergen is important, as allergen avoidance is the key to prevention of recurrent disease. This may be done by history alone, but patch testing may be necessary to identify specific antigens.\textsuperscript{21} Once the allergen is known, the patient should be given educational information regarding potential sources. Avoidance may involve placing a barrier between the allergen and the skin.
Examples include wearing long pants when out in the woods to prevent rhus dermatitis, and using nail enamel or a cloth patch to cover the exposed portions of metal fasteners in a person allergic to nickel.

**Conclusion**
ACD is an acquired, immune-mediated dermatitis that is common in children. Clinicians should be familiar with recognizing common patterns consistent with ACD. While CSs have been the mainstay of therapy, other topical immunosuppressives hold promise as alternative treatments. Allergen identification and avoidance is crucial in preventing future recurrences of the disease.

**References**

**Continued from page 2**

allergic and anti-inflammatory effects make it superior to other current treatment options. At this time, desloratadine should be considered one of the preferred first-line treatments for patients with chronic idiopathic urticaria.

**References**
Dear Reader,

Starting with the next issue, the Skin Therapy Letter will include a regular section devoted to dermatologic surgery. Entitled “Advances in Dermatologic Surgery,” this section will highlight evolving clinical topics in laser, cosmetic, oncologic, and reconstructive surgery. Prominent practitioners will share their expertise in simple, concise language. The goal will be to impart practical tips about procedural indications, benefits and limitations, patient selection, and treatment technique. We hope that despite the brevity of the articles, the emphasis on new developments will provide value to novice readers as well as to more experienced cosmetic dermatologists and dermatologic surgeons.

Jeffrey S. Dover, MD and Murad Alam, MD

**Update on Drugs**

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<th>Class</th>
<th>Name/Company</th>
<th>Approval Dates and Comments</th>
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<tbody>
<tr>
<td><strong>Antifungal Agent</strong></td>
<td><strong>Ketoconazole</strong></td>
<td><strong>Ketoderm®</strong> Cream 2% OptimaPharma TP - Canada approved this topical antifungal agent in April 2002, for the treatment of fungal infections of the skin. It is a prescription product that is bioequivalent to Nizoral® Cream (McNeil Consumer Products).</td>
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<td><strong>Benzoyl Peroxide, Clindamycin</strong></td>
<td><strong>DUAC®</strong> Topical Gel Stiefel Laboratories The US FDA approved this anti-acne agent in August 2002, for the treatment of acne vulgaris.</td>
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<td><strong>Antiviral Agent</strong></td>
<td><strong>Trans-Ver-Sal® Wart Removal Patch</strong> Bradley Pharmaceuticals The Swedish Medical Products Agency approved this product in June 2002. Sweden is the first EU member country to market this wart removal patch under the new EU regulations.</td>
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<td><strong>HIV/AIDS</strong></td>
<td><strong>Rubitecan</strong></td>
<td><strong>Orathec®</strong> SuperGen The US FDA issued orphan-drug designation in July 2002, for the treatment of pediatric patients infected with HIV and AIDS.</td>
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<td><strong>Antihistamine</strong></td>
<td><strong>Loratidine</strong></td>
<td><strong>Claritin®</strong> 10mg Tablets Schering-Plough KK The Ministry of Health, Labor and Welfare (MHLW) in Japan approved this antihistamine in July 2002, for the treatment of allergic rhinitis, chronic idiopathic urticaria and itching associated with skin diseases in adults and children 15 years and older.</td>
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<td><strong>Smoking and Basal Cell Carcinoma</strong></td>
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**Drug News**

**Smoking and Basal Cell Carcinoma**

Smoking can play a key role in the differentiation of basal cell carcinoma (BCC) toward its sclerosing form, according to a recent article in the *International Journal of Dermatology*. In a retrospective study of 34 patients with morpheaform BCC, and 50 patients with solid BCC, Erbagci and Erkilic investigated the possible roles of smoking and occupational UV exposure in the development of morpheaform BCC, through the quantification of peritumoral mast cells. Increased mast cell indices were associated with smoking (p=0.003), but not with UV exposure (p>0.05).


**Actinic Keratosis Agent**

In May 2002, SkyPharma PLC transferred all rights to market Solaraze® in Europe to Shire Pharmaceuticals. This product is a topical therapy for actinic keratosis that has been approved for marketing in several European countries including the UK, Germany and Sweden.