**Summary** Recent studies have shown a correlation between an increased number of mast cells in patients with atopic dermatitis (AD) resulting in raised plasma levels of nerve growth factor (NGF), pointing to a possible key role of their interaction in the pathogenesis of AD. It is well known that mast cells synthesize, store and release NGF. Mast cells and NGF both appear to be involved in tissue inflammation and neuroimmune interactions, with NGF acting as a general “alert” molecule capable of recruiting and priming both local tissue and systemic defense processes following stressful events. Also, NGF has been demonstrated to increase mast cell histamine content and intracellular tryptase activity in a dose- and time-dependent fashion. Endogenous aliamides are capable of down-regulating mastocyte reactivity by their action through the vanilloid (VR1) receptors, and keratinocytes, and through the CB1 and CB2 cannabinoid receptors linked to G-protein, also expressed by sensitive nerve endings, macrophages, and epithelial cells. Therefore, aliamide action should be regarded as a multifaceted mechanism interfering with the inflammatory process occurring in AD further beyond the known and controversial anti-histamine pharmacologic effect. In this regard, the reduction of mast cell degranulation by adelmidrol, as demonstrated by in vitro and in vivo investigations in animals, would interfere with the release of other inflammatory mediators, including NGF. Based on these considerations, a pilot study aimed to assess the efficacy and safety of twice daily application of a topical emulsion containing adelmidrol 2%, a novel aliamide, in a series of 20 patients (11 male and 9 female, mean age 8 (range 3-16) years) affected by mild AD was performed. Complete resolution with no side effects was observed in 16 (80%) patients after 4 weeks of treatment, with no relapses at 8-week follow up. Six patches in six subjects with multiple lesions that had not been treated and served as controls showed no improvement. Controlled clinical studies in larger series are warranted to confirm the efficacy of aliamide in the management of AD.

**Key Words:** atopic dermatitis, mast cells, aliamides

**Introduction**

Atopic dermatitis (AD) is a chronic inflammatory skin disorder associated with cutaneous hyperreactivity to environmental triggers. Its cause is believed to be multifactorial. The clinical AD phenotype is the result of the interaction between susceptibility genes, environmental influences, a defective skin barrier function, and an altered immune response (1). Mast cells also play a pathogenetic role in AD. They are abundantly localized in the dermis close to the epidermis and blood vessels, where they play a pivotal role in hypersensitivity responses by releasing histamine and...
other mediators causing pruritus. Moreover, they may stimulate neoangiogenesis, and contribute to maintaining chronic inflammation by enhancing transportation through the new vessels of complement components and antibodies, together with inflammatory cells (2).

AD in pediatric patients is particularly problematic, as children are more susceptible to entering the itch-scratch cycle, where constant scratching of the skin exacerbates the condition. Addressing the itch is of primary concern to patients and their caregivers, who are often distressed by the child’s symptoms. Therapy of mild AD is based on the use of topical corticosteroids, non-steroidal anti-inflammatory agents, topical immunomodulators, and the regular daily use of emollients. Topical corticosteroids are associated with side effects, and patients and physicians would prefer to avoid their extended usage if possible. A non-steroidal method of managing patients with AD would therefore be welcome. This is particularly true in children, who are more susceptible to potential systemic adverse effects of topical corticosteroids.

In the past few years, a novel mechanism of local modulation of mast cell function by specific endocannabinoids belonging to the class of aliamides, known as “autacoid local inflammation antagonism” (ALIA), has been elucidated (3).

Based on these considerations, a pilot study aimed to assess the efficacy and safety of a topical emulsion containing adelmidrol 2% (Table 1), a novel aliamide, in the treatment of mild AD in pediatric subjects, was performed at our Department.

**PATIENTS AND METHODS**

Twenty patients (11 male and nine female), mean age 8 (range 3-16) years, affected by mild AD were enrolled. Inclusion criteria were: male or female children and adolescents aged between 2 and 16 years, diagnosed with mild AD at study entry according to Hanifin and Rajka criteria (4) and based on the Investigator Global Assessment (IGA) score (5). Exclusion criteria were: moderate to severe AD, presence of severe excoriation, coexistence of skin disorders other than AD, including active bacterial, fungal or viral skin infections, use of other topical or systemic treatments for AD in the 4 weeks prior to baseline. Following informed consent signed by both parents, participants were instructed to apply the study drug twice daily for 4 weeks. Six areas in six subjects with multiple lesions were not treated and served as controls. Efficacy was assessed by objectively recording the degree of erythema and infiltration according to the IGA score and the patient assessment of pruritus relief at subsequent visits.

**RESULTS**

Improvement of erythema and pruritus was evident in 12 (60%) patients soon after 10-15 days of treatment. Clinical resolution was observed in 16 (80%) patients after 4 weeks of treatment (Figs. 1 and 2), with no relapses at a 4-week follow up. Untreated lesions showed no improvement. No treatment-related side effects were observed in any subject during the study.

**DISCUSSION AND CONCLUSION**

The role of histamine release in the pathogenesis of pruritus in AD and evidence for the beneficial use of antihistamines is still a matter of speculation (6). Recent studies have shown a correlation between an increased number of mast cells in patients with AD resulting in raised plasma levels of histamine. As a result, the use of antihistamines for the treatment of AD has become more popular. However, the side effects of antihistamines can be significant, especially in children. Therefore, alternative therapies that do not involve the use of systemic medications are desirable.

**Table 1. Main ingredients of the tested emulsion**

<table>
<thead>
<tr>
<th>Ingredient</th>
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<tbody>
<tr>
<td>Adelmidrol</td>
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<tr>
<td>Hyaluronic acid</td>
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<tr>
<td>Phytosphingosine</td>
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<tr>
<td>Sodium pyroglutamate</td>
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<td>Trans-2-dodecenedioic acid</td>
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**Figure 1.** Nummular lesion on the left cheek of a 6-year-old child before (a) and after (b) treatment with topical adelmidrol 2% cream for 4 weeks.
nerve growth factor (NGF), pointing to a possible key role of their interaction in the pathogenesis of AD (7-9). It is well known that mast cells synthesize, store and release NGF (10). Mast cells and NGF both appear to be involved in tissue inflammation and neuroimmune interactions, with NGF acting as a general “alert” molecule capable of recruiting and priming both local tissue and systemic defense processes following stressful events (11). Also, NGF has been demonstrated to increase mast cell histamine content and intracellular tryptase activity in a dose- and time-dependent fashion, leading to mast cell hyperactivity, enhanced degranulation, and boost in the release of proinflammatory mediators causing erythema, edema and pruritus.

Aliamides are a new class of pharmacological agents that possess a peculiar mechanism of action that does not simply rely on histamine antagonism. Endogenous aliamides are capable of down-regulating mastocyte reactivity by their action through the vanilloid (VR1) receptors, non-selective cationic canals also expressed by type C nerve endings, and keratinocytes, and through the CB1 and CB2 cannabinoid receptors linked to G-protein (12), also expressed by sensitive nerve endings, macrophages, and epithelial cells (13).

Therefore, aliamide action should be regarded as a multifaceted mechanism interfering with the inflammatory process occurring in AD further beyond the known and controversial anti-histamine pharmacological effect. In this regard, the reduction of mast cell degranulation by adelmidrol, as demonstrated by in vitro (3) and in vivo investigations in animals (3), would interfere with the release of other inflammatory mediators, including NGF. This would explain the mechanism of action of adelmidrol cream in our series of patients affected by mild AD.

The positive clinical response, with complete clearing of treated lesions in 80% of patients, suggests that this new topical agent may represent a promising tool for the management of this disorder (14). Controlled clinical studies in larger series are warranted to confirm the efficacy of aliamides in the management of AD.

References


For Sun tanned, healthy skin - Nivea cream and Nivea oil; year 1935. (from the collection of Mr. Zlatko Puntijar)