

Advances in allergic skin diseases

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During the past year there have been significant advances in our understanding of the mechanisms underlying allergic skin diseases. This article reviews some of these advances in atopic dermatitis and urticaria. The introduction of a new class of topical anti-inflammatory medications, topical calcineurin inhibitors, has significantly increased our treatment options and led to a rethinking of potential management approaches in atopic dermatitis. (J Allergy Clin Immunol 2003;111:S805-12.)

Key words: *T cells, tacrolimus, pimecrolimus, atopic dermatitis, urticaria*

Atopic dermatitis (AD) and urticaria are commonly seen in clinical practice, and their mechanisms are actively being investigated.^{1,2} Recent interest in these allergic skin diseases has been sparked by reports of their increasing prevalence and the significant adverse impact that they can have on quality of life.^{3,4} The introduction of a new class of topical anti-inflammatory medications, topical calcineurin inhibitors, has significantly increased our treatment options and led to a rethinking of potential management approaches in AD.⁵ This review examines some of the recent advances in our understanding of these diseases and new treatment approaches that have been introduced (Table I).

ATOPIC DERMATITIS

Immune mechanisms

A variety of immune effector cells have been investigated for their potential roles in the pathogenesis of AD. In animal models of AD, T cells are critical to the evolution of eczematoid skin lesions.⁶ Activated T cells have been found to induce keratinocyte apoptosis, contributing to the spongiotic process found in acute AD.⁷ This process is mediated by T-cell-derived IFN- γ , which upregulates Fas on keratinocytes. The lethal hit is delivered to keratinocytes by membranous and soluble Fas-ligand produced by epidermotropic T cells.

There has been increasing interest in the unique properties of epidermal keratinocytes from patients with AD in augmenting atopic skin inflammation. In this regard, keratinocytes from patients with AD but not from those with psoriasis produce significantly higher levels of RANTES after stimulation with TNF- α and IFN- γ .⁸ AD keratinocytes but not nonatopic keratinocytes are also an

Abbreviations used

AD: Atopic dermatitis
CIU: Chronic idiopathic urticaria
CLA: Skin homing receptor
DBPCFC: Double-blind, placebo-controlled, food challenge
Fc ϵ RI: High-affinity IgE receptor
IVIg: Intravenous immunoglobulin

important source of thymic stromal lymphopoietin, which activates dendritic cells to prime naive T_H cells to produce IL-4, IL-13, and TNF- α .⁹ These observations may explain the link between scratching and the triggering of T_H2-mediated skin inflammation in AD.

Skin affected by AD contains an increased number of IgE-bearing Langerhans cells and inflammatory dendritic epidermal cells expressing the high-affinity receptor for IgE (Fc ϵ RI).¹⁰ These antigen-presenting cells play an important role in allergen presentation and development of naive T cells into T_H2 cells. The clinical importance of these cells is supported by the observation that the presence of Fc ϵ RI and IgE-bearing Langerhans cells is required to provoke eczematous skin lesions by application of aeroallergens on the skin of patients with atopic disease.¹¹ Downregulation of dendritic cell function has been found after treatment with topical tacrolimus or Chinese herbs.¹²⁻¹⁴

A potential link between antigen-presenting cells and immediate hypersensitivity reactions has been found. In this regard, total serum IgE levels are increased after epicutaneous sensitization in mast cell-deficient mice relative to wild-type mice.¹⁵ Furthermore, histamine downregulates IL-12 production by human monocyte-derived dendritic cells and may thereby enhance the development of T_H2 cells.¹⁶

There has been considerable interest in the molecules controlling infiltration of inflammatory cells into atopic skin.⁴ The CC chemokines, RANTES, monocyte chemoattractant protein 4, and eotaxin have been found to be increased in AD skin lesions and probably contribute to the chemotaxis of CC chemokine receptor 3-expressing eosinophils and T_H2 lymphocytes into the skin.^{17,18} Recent studies suggest that selective recruitment of CC chemokine receptor 4-expressing T_H2 cells into AD skin may also be mediated by the chemokines macrophage-derived chemokine and thymus and activation-regulated chemokine, which are increased in AD.¹⁹⁻²¹ Plasma levels of thymus and activation-regulated chemokine and macrophage-derived chemokine correlate significantly with disease activity of AD. IL-16, a chemoattractant for CD4⁺ T cells, is highly expressed in AD skin lesions and primarily found in CD1a⁺ Langerhans cells.²²

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0091-6749/2003 \$30.00 + 0

doi:10.1067/mai.2003.155

TABLE I. Major advances in allergic skin diseases

- Understanding is evolving regarding the role of keratinocytes and chemokines in the pathogenesis of AD.
- Deficiency of antimicrobial peptides may promote microbial infection in AD.
- Topical calcineurin inhibitors have been introduced for treatment of AD.
- In chronic urticaria, C5a contributes to the magnitude of histamine release from basophils stimulated with functional IgG antibody to the IgE receptor caused by the IgG alone.

Immunologic triggers

Foods. Double-blind, placebo-controlled, food challenge (DBPCFC) studies have demonstrated that food allergens induce skin rashes in nearly 40% of children with moderate to severe AD.²³ In mouse models of AD, oral sensitization with foods results in the elicitation of eczematous skin lesions on repeated oral food challenges.²⁴ Although egg, milk, wheat, soy, and peanut are the most common food allergens implicated in AD, other foods, including cooked potato, can exacerbate AD, and elimination of such food allergens from the diet results in improved disease control.^{25,26}

Although DBPCFCs are the criterion standard for diagnosis of food allergy, they are cumbersome to perform. Importantly, recent studies have demonstrated that quantitation of serum food-specific IgE is a useful test for diagnosing symptomatic allergy to certain foods such as egg, milk, peanut, and fish.²⁷ Furthermore, positive results of atopy patch tests to foods in combination with measurement of serum levels of specific IgE to foods has been advocated to further reduce the need for oral food challenges in children with AD.^{28,29} Further refinement of these techniques may facilitate the identification of foods that exacerbate AD. However, a recent report suggested that 10% of positive DBPCFC results were not IgE mediated. Therefore a high suspicion of food-related symptoms necessitates performance of DBPCFC even in the absence of positive results of skin prick testing or serum assay for specific IgE to foods.³⁰

Aeroallergens. Epicutaneous application of aeroallergens (eg, house dust mites, weeds, animal danders, and molds) by atopy patch test on uninvolved atopic skin elicits eczematoid reactions in a subset of patients with AD.³¹ This is likely to be an immune-mediated inflammatory reaction, because dust mites were recently found to have no direct proinflammatory effect on human keratinocytes.³² Several studies have reported that a combination of effective house dust mite reduction measures is associated with improvement of AD.³³ However, more recent studies have found that reduction of dust mite levels at home with mattress, duvet, and pillow encasings is not effective in reducing the symptoms of AD.³⁴ This suggests that reduction of allergens in other environments (such as work and school) may be necessary as well to gain control of allergic symptoms.

Autoantigens. Recent studies have found that most serum samples from patients with severe AD contain IgE

antibodies directed against human proteins.³⁵ These autoallergens are mainly intracellular proteins and have been detected in IgE immune complexes, suggesting that release of these autoallergens from damaged tissues could trigger inflammatory skin responses. This concept is supported by the observation that IgE autoallergen titers decrease with successful treatment of AD with cyclosporin.³⁶ These data suggest that although IgE immune responses are initiated by environmental allergens, allergic inflammation can be sustained by human endogenous antigens, particularly in severe AD.

Emotional stressors. Patients with AD often respond to stressful events with increased pruritus and scratching. Recent studies have demonstrated that stress can induce immunologic changes in patients with AD, including rises in the levels of eosinophils and natural killer cells.^{37,38} Interestingly, patients with psoriasis and healthy control subjects did not demonstrate such changes. Thus psychologic stress has different immunologic effects in patients with AD than in patients with psoriasis or healthy control subjects.

Microbes. It is well established that patients with AD have increased numbers of *Staphylococcus aureus* organisms on their skin lesions, and antibiotic therapy can be a useful adjunct in controlling their skin disease.³⁹ One strategy by which *S aureus* exacerbates or maintains skin inflammation in AD is by secreting superantigens, which stimulate marked activation of T cells, macrophages, and eosinophils.^{1,40} Furthermore, a recent study demonstrated that superantigens can induce glucocorticoid resistance of T cells and thus contribute to "difficult to manage" AD.⁴¹ Interestingly, this glucocorticoid-resistant effect of superantigens is selective, with superantigen-induced T-cell activation readily inhibited by FK-506.⁴²

Understanding the mechanisms for increased *S aureus* colonization and infection in AD has been an active area of investigation. In part, this is likely related to underlying AD inflammation. This surmise is supported by the observation that treatment with topical glucocorticoids or tacrolimus reduces *S aureus* counts on atopic skin.⁴³ Scratching probably enhances *S aureus* binding by disturbing the skin barrier and exposing extracellular matrix adhesions for *S aureus*, such as fibronectin and collagens. In studies of *S aureus* binding to skin lesions undergoing T_H1 versus T_H2 inflammatory responses, bacterial binding was significantly greater at skin sites with T_H2-mediated inflammation as a result of IL-4-induced expression of fibronectin.^{44,45} AD skin has also been found to be deficient in the production of keratinocyte-derived antimicrobial peptides needed for host defense against bacteria, fungi, and viruses.^{46,47} Thus once *S aureus* binds to AD skin, inadequate local host defense allows this microbe to colonize and predispose patients toward infection. Interestingly, T_H2 cytokines inhibit the expression of human β -defensin 2, one of the antimicrobial peptides deficient in atopic skin.⁴⁷

AD may be complicated by recurrent viral skin infections, such as herpes simplex and mollusca contagiosa. This may reflect defects in T_H1 cytokine generation and

cytotoxic T-cell function. This contention is supported by the recent observation that patients with AD have perforin hyperreleasability, which results in depletion of perforin granules (essential component of cytolytic machinery) within their cytotoxic T cells.⁴⁸ Monocytes from patients with AD have also been found to be deficient in generation of IL-18, an IFN- γ -inducing cytokine.⁴⁹ Of note, production of IFN- γ and IL-18 inhibits vaccinia-induced pock formation in mice.⁵⁰ These observations may therefore partially account for the increased susceptibility of patients with AD to eczema vaccinatum after exposure to the smallpox vaccine.⁵¹

Topical calcineurin inhibitors: A new class of anti-inflammatory agents

Tacrolimus. Topical application of FK-506 (tacrolimus), a calcineurin inhibitor that acts by binding with high affinity to the 12-kD macrophilin, has been successfully used in the treatment of AD.⁵² Tacrolimus inhibits the activation of a number of key cells involved in AD, including T cells, dendritic cells, mast cells, and keratinocytes.^{12,13} Multicenter, blinded, vehicle-controlled phase 3 trials with tacrolimus ointment (0.03% and 0.1%) have shown tacrolimus to be both effective and safe for both adults and children.⁵³ Local burning sensation has been the only common adverse event, and most patients have a reduction of pruritus within 3 days of initiation of therapy. Long-term studies with tacrolimus ointment have been performed in adults and children with demonstrated sustained efficacy and no significant side effects; for example, no increased skin infections have been observed. Tacrolimus ointment is not atrophogenic and is as efficacious as a midpotency topical corticosteroid.^{54,55}

Pimecrolimus. Ascomycin compounds, such as pimecrolimus, which has the same mechanism of action as tacrolimus, have been developed in topical and oral forms. Like tacrolimus, they inhibit T_H1 and T_H2 cytokine production, and they have also been shown to inhibit mediator release from mast cells and basophils.⁵⁶ Multicenter, blinded, vehicle-controlled phase 3 trials with pimecrolimus ointment (1%) have shown pimecrolimus to be both effective and safe for both adults and children with AD.⁵⁷ When used as maintenance therapy, topical 1% pimecrolimus cream has been found to reduce the number of flares related to AD and to reduce requirements for corticosteroid therapy.⁵⁸

The approval of topical preparations of the calcineurin inhibitors tacrolimus (Protopic) and pimecrolimus (Elidel) for the treatment of AD represents a significant advance in our management options for this chronic skin disease. However, we must still develop guidelines for use of topical corticosteroids versus calcineurin inhibitors in the management of AD. There are situations in which topical calcineurin inhibitors may be advantageous relative to topical corticosteroids. These would include treatment of patients who have poor responses to topical steroids, treatment of patients with steroid phobia, and the treatment of face and neck dermatitis, for

which ineffective, low-potency topical corticosteroids are usually used because of fears of steroid-induced skin atrophy. The potential use of topical calcineurin inhibitors as maintenance therapy is also intriguing for prevention of AD flares.⁵⁸ Although systemic absorptions of these compounds are low, however, there is a need for careful surveillance to rule out the possibility that local skin cancers and increased viral skin infections will appear when such agents are used long term.

A window of opportunity for prevention of respiratory allergy?

AD is frequently the first step in the atopic march toward respiratory allergy. Because there are no cures for asthma, the development of strategies to prevent respiratory allergy is important. Previous studies have demonstrated that the introduction of a histamine 1 receptor antagonist, such as cetirizine, in infants with AD could prevent asthma in at least a subset of patients with aeroallergen sensitization while the antihistamine was being administered.⁵⁹ Interestingly, an 18-month posttreatment follow-up study found that cetirizine compared with placebo truly delayed or prevented the development of asthma in a subgroup of infants with AD sensitized to grass pollen and, to a lesser extent, house dust mite.⁶⁰ Other studies have demonstrated that sensitization through the skin leads to high systemic allergen sensitization and can predispose toward the development of asthma.⁶¹ This raises the interesting possibility that effective control of skin disease in patients with AD may abort the development or reduce the severity of respiratory allergy later in childhood.

A number of studies have examined whether microbial products in early life reduce the risk of atopy.⁶² These studies suggest that reduced exposure to microbial products in early life may increase the prevalence of eczema and allergy.⁶³ The nature of the microbe may also be important; one report found that infants with AD were less often colonized with *Enterococcus* and *Bifidobacterium* organisms than were healthy infants but had higher counts of *Clostridium* and *S aureus* organisms in their intestinal flora.⁶⁴ These observations suggest that introduction of T_H1-polarizing microbial products may prevent or reverse the clinical symptoms of AD. In this regard, Arkwright et al⁶⁵ reported that intradermal administration of a killed *Mycobacterium vaccae* suspension was associated with improvement in AD relative to a control group. Gehring et al⁶⁶ also reported preliminary data suggesting that early exposure to environmental endotoxin decreases the risk of atopic eczema. Taken together, these studies suggest the possibility that T_H1-polarizing agents may be useful in the prevention or treatment of allergic disease.

URTICARIA AND ANGIOEDEMA

Immune mechanisms

A major advance in our understanding of chronic urticaria has been the demonstration of circulating IgG

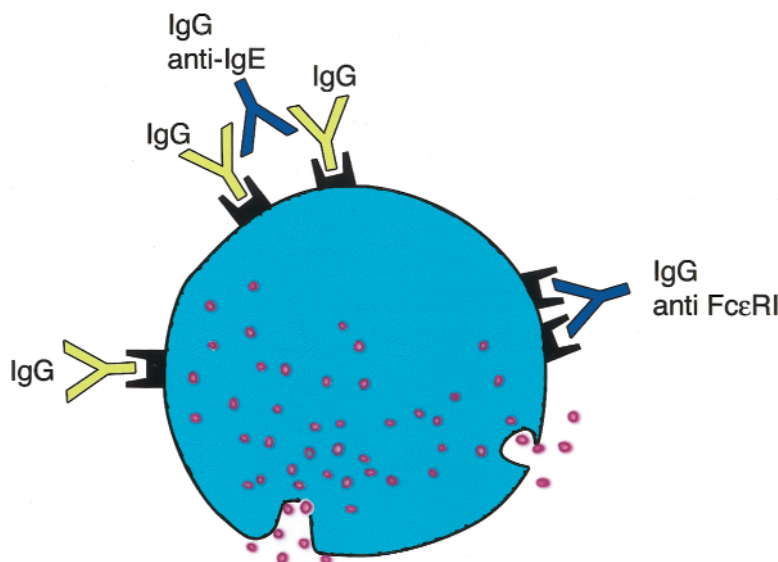


FIG 1. Functional autoantibodies of CIU. IgG anti-IgE antibodies combine with and cross-link adjacent receptor-bound IgE. IgG anti-FcεRI antibodies combine with and cross-link adjacent α -chains of FcεRI. Black notched membrane structures represent α -chain of FcεRI expressed on surface of dermal mast cell. From Greaves M. Chronic urticaria. *J Allergy Clin Immunol* 2000;105:664-72. Used with permission.

autoantibodies directed against the α -subunit of the high-affinity IgE receptor (FcεRI) or anti-IgE autoantibodies in a subset of patients with a diagnosis of chronic idiopathic urticaria (CIU, reviewed in by Greaves² and Kaplan⁶⁷; Fig 1). Approximately 30% to 40% of patients with chronic urticaria have anti-FcεRI α autoantibodies, and 10% have anti-IgE autoantibodies. Functionality of these autoantibodies has been demonstrated by in vitro release of histamine from basophils and dermal mast cells. Of note, patients with chronic urticaria with histamine-releasing autoantibodies have been shown to have more severe urticaria than have patients with chronic urticaria without such autoantibodies.⁶⁸ Although functional anti-FcεRI α autoantibodies were once thought to cause mast cell and basophil degranulation by direct ligation of the α -chain of FcεRI, these autoantibodies were subsequently shown to be primarily IgG1 and IgG3 complement-activating isotypes, suggesting a role for the complement pathway in the pathophysiology of a subset of chronic urticaria. A study by Kikuchi and Kaplan,⁶⁹ however, demonstrated that IgG autoantibodies could in fact directly activate basophils by interacting with the α -subunit of FcεRI but that histamine release was augmented by complement, and the percentage released varied significantly from patient to patient. More recently, Kikuchi and Kaplan⁷⁰ showed that complement activation liberates complement component C5a, which participates in mast cell activation in patients with chronic urticaria and functional anti-FcεRI α autoantibodies. These findings fit well with the observation that mast cells in the skin express receptor for C5a, whereas those in the lung do not do so.

Because of the heterogeneity of this population, Sabroe et al⁷¹ classified serum samples from patients with chron-

ic urticaria into five subgroups according to presence or absence of autoantibodies and functionality by means of Western blot analysis and serum-induced histamine release from basophils and dermal mast cells. Their classification also correlated autologous skin test reactivity with disease severity. Thus a serum sample could be classified as having immunoreactive histamine-releasing anti-FcεRI autoantibodies (26%), immunoreactive non-histamine-releasing anti-FcεRI autoantibodies (15%), anti-IgE-like autoantibodies (9%), mast cell-specific histamine-releasing factor, or no identifiable factor. Patients whose serum samples had histamine-releasing activity again were shown to have more severe disease than those patients without such activity. Furthermore, autologous skin test reactions correlated with presence of histamine-releasing anti-FcεRI autoantibodies. Specificity of functional autoantibodies for chronic urticaria was suggested by the lack of histamine release from basophils by serum samples from patients with dermatographism and cholinergic urticaria, except for 1 patient. Whether such classification will lead to further elucidation of underlying immune mechanisms and ultimately to more specific therapy remains to be determined.

Other autoimmune diseases, especially autoimmune thyroid disease, have been associated with chronic urticaria. Hashimoto thyroiditis has been associated with antimicrosomal or antithyroglobulin antibodies, and Graves' disease has been associated with anti-thyroid-stimulating hormone receptor antibodies, although a causal relationship of such antibodies with chronic urticaria has not been proved. A recent study reported the coexistence of chronic urticaria with anti-Fcε antibodies and Graves' disease (presumably mediated by anti-thyroid-stimulating hormone receptor antibodies) in a

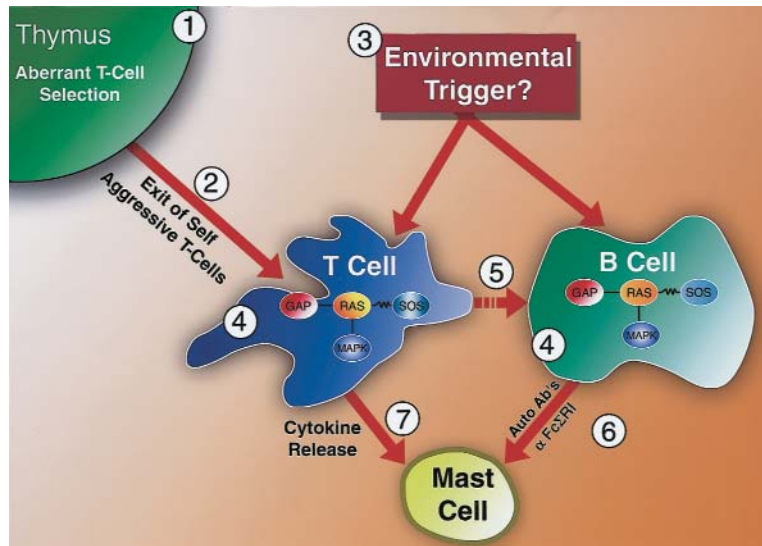


FIG 2. Aberrant regulation of the p21Ras pathway in lymphocytes of patients with CIU: possible mechanisms leading to autoimmune disease. Genetically determined aberrant p21Ras signaling interferes with thymic T-cell selection (1), leading to release of self-aggressive T cells (2). Alternatively, exposure to unknown environmental trigger (3) results in aberrant signaling in B and T cells (4) and disrupts immune balance. T-cell-assisted (5) production of anti-FcεRI autoantibodies (*Auto Ab's*) by B cells (6) and direct interaction of autoimmune T cells with mast cells (7) lead to autoimmune chronic urticaria. GAP, Guanosine triphosphatase-activating protein; MAPK, mitogen-activated protein kinase. From Confino-Cohen R, Aharoni D, Goldberg A, Gurevitch I, Buchs A, Weiss M, et al. Evidence for aberrant regulation of the p21Ras pathway in PBMCs of patients with chronic idiopathic urticaria. *J Allergy Clin Immunol* 2002;109:349-56. Used with permission.

female patient.⁷² Working with this proposed classification, however, Irani et al⁷² demonstrated histamine-releasing activity in the patient's serum, although whether this was mediated by specific anti-Fcε α autoantibodies remains uncertain. In addition, whether the two diseases and the autoantibodies are related remains unknown, because the patient had chronic urticaria for 28 years before the diagnosis of Graves' disease was made, and she continues to require treatment for her urticaria despite successful treatment of the thyroid disease. Another thyroid-related antibody previously reported in a single patient with chronic urticaria was anti-thyroid peroxidase IgE.⁷³ A more recent study of patients with chronic urticaria found evidence of anti-thyroid peroxidase IgG antibodies in some patients, but no anti-thyroid peroxidase IgE antibodies were found, suggesting that this is an unusual finding, and the clinical significance with respect to urticaria remains unproven.⁷⁴

Of note, approximately 50% to 60% of patients with chronic urticaria continue to have their disease classified as idiopathic, and further studies into underlying mechanisms are needed. One attempt at identifying mechanisms involved in the regulation and activation of immune cells in patients with CIU examined the expression, regulation, and function of the p21Ras pathway. The p21Ras protein is involved in T-cell receptor and IL-2 receptor activation and thus may play a critical role in immune responses. Confino-Cohen et al⁷⁵ found aberrant signaling through the p21Ras pathway in lymphocytes of patients with CIU. Confino-Cohen et al⁷⁵ speculated that such dysregulation may result in autoimmune urticaria (Fig 2).

In patients with milk-induced urticaria, a higher percentage of CD4⁺ T cells can be shown to express the skin homing receptor (CLA) than in patients with milk-induced gastrointestinal disease.⁷⁶ Similar results in patients with milk-induced AD were previously demonstrated.⁷⁷ These studies suggest that skin homing by lymphocytes expressing CLA occurs not only in milk-induced AD but also in milk-induced urticaria. However, whether CLA⁺ T cells play a pathogenic role in urticaria requires more definitive lesional biopsy studies. In addition, why some patients have AD develop and others have urticaria develop after allergen exposure remains a mystery.

Immunopathology

The histologic appearance of CIU lesions has been characterized as a nonnecrotizing perivascular infiltrate with T cells, monocytes, mast cells, and variable number of neutrophils and eosinophils.⁷⁸ However, the T cells have not been characterized by cytokine profile. With immunochemical methods and in situ hybridization, Ying et al⁷⁹ studied skin biopsy samples from patients with CIU and compared them with those from the allergen-induced skin late-phase reaction in atopic subjects. They found that the T cells from patients with CIU were characterized by a T helper 1/T helper 2 phenotype with cells positive for IFN-γ as well as IL-4 and IL-5 mRNA. This pattern is distinct from that seen in the allergen-induced late-phase reaction, where IFN-γ is not seen. Such differences are not surprising, because allergens do not appear to play a role in CIU, nor does complement C5a (as discussed previously), which is a chemotactic factor for neutrophils,

basophils, and eosinophils. Ying et al⁷⁹ also showed that indeed basophils are present in chronic urticaria lesions and thus could be targeted by anti-Fc ϵ RI α autoantibodies. In addition, their finding of diminished numbers of mast cells in lesional skin from patients with chronic urticaria may in fact reflect degranulation. Finally, the cytokine profiles of patients with chronic urticaria with and without circulating autoantibodies were found to be the same.

Treatment of urticaria and angioedema

Because of the complex immunopathology of skin lesions from patients with CIU, as discussed previously, it is not surprising that treatment with an antihistamine alone may not be effective. Indeed, Wedi et al⁸⁰ previously demonstrated leukotriene synthesis induced by serum samples from patients with positive results of autologous serum skin tests, and leukotriene receptor antagonists have been shown to be effective in treating urticaria of various origins, including those triggered by physical stimuli, allergens, and nonsteroidal anti-inflammatory drugs (as reviewed by Erbagci⁸¹). Of note, Grimm et al⁸² have demonstrated that in some aspirin-insensitive patients, selective cyclooxygenase-2 inhibitors may induce urticaria and angioedema, although they appear to be well tolerated with respect to aspirin-induced asthma.⁸³ Perez et al⁸⁴ demonstrated that montelukast pretreatment effectively blocked cutaneous reactions induced by nonsteroidal anti-inflammatory drugs, supporting a role for treatment with a leukotriene receptor antagonist for nonsteroidal anti-inflammatory drug-triggered urticaria and angioedema. More recently, Erbagci⁸¹ confirmed the beneficial role of montelukast given at 10 mg daily in a single-blind, placebo-controlled, crossover study of patients with refractory CIU, with decrease in urticaria activity scores and less need for antihistamine rescue therapy during treatment with the leukotriene receptor antagonist.

As discussed previously, pimecrolimus, a novel calcineurin inhibitor, has been shown to be effective as a topical nonsteroidal treatment for AD.^{57,58} In addition to its effects on T-cell-derived cytokines, Zuberbier et al⁵⁶ have shown that pimecrolimus can inhibit histamine release from mast cells and basophils *in vitro*, as well as mast cell tryptase and to some extent leukotriene C₄. Pimecrolimus was also more effective at blocking TNF- α release from mast cells than were cyclosporine and dexamethasone. An oral formulation of pimecrolimus is currently being studied in several inflammatory skin diseases and could in fact prove valuable in recalcitrant chronic urticaria, targeting the T cells as well as mast cells and basophils implicated in the immunopathology of the disease (as discussed previously).

Of interest, in a review of 256 patients with a diagnosis of common variable immunodeficiency, 6 patients had preceding chronic urticaria.⁸⁵ All 4 of the 6 patients treated with intravenous immunoglobulin (IVIg) had complete resolution of their urticaria. The autoantibody status of the reported patients was not determined, and IVIg has been reported to benefit patients with autoantibody-mediated chronic urticaria. However, immunomodulatory effects of

IVIg are usually seen with high-dose (1-2 g/kg) IVIg therapy, whereas presumably the patients with common variable immunodeficiency were treated with replacement doses (approximately 0.5 g/kg). Although it may not be worthwhile to screen all patients with chronic urticaria for common variable immunodeficiency, it certainly makes sense to measure serum immunoglobulin levels and specific antibody titers in those patients with chronic urticaria who have recurrent or unusual infections.

Finally, Zauli et al⁸⁶ have highlighted the need for physicians to recognize the association between angiotensin-converting enzyme inhibitor therapy and angioedema. Of interest, they chose to continue angiotensin-converting enzyme inhibitor therapy after myocardial infarction for patients who had angioedema develop, despite the possibility of more severe reactions, including life-threatening reaction treated with fresh-frozen plasma, as reported by Karim and Masood.⁸⁷

CONCLUSION

During the year in review, significant advances have been made in our understanding of mechanisms underlying allergic skin diseases. The evolving role of keratinocytes in the pathogenesis of atopic inflammation and the predisposition of patients with AD toward recurrent skin infections has been particularly noteworthy. In a subset of patients with chronic urticaria, histamine release by anti-Fc ϵ RI antibodies has been shown to be augmented by complement C5a. For most patients with CIU, however, underlying mechanisms remain to be explained. Of potentially greater importance has been the establishment of a new topical anti-inflammatory class of medications in the form of topical calcineurin inhibitors. These new medications, along with topical corticosteroids, provide the clinician with unprecedented flexibility in the management of skin inflammation. In the future it will be interesting to determine whether successful therapeutic intervention at the level of AD can interfere with evolution of the atopic march toward respiratory allergy.

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