

Nonclassical clinical indications for H₁-receptor antagonists in dermatology

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Allergy 1995; 50: 36–40. © Munksgaard 1995.

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Atopic dermatitis is a long-term inflammatory skin disease, the primary feature of which is extreme pruritus. It is characterized by a typical appearance which includes prurigo and lichenification associated with dry skin. Atopic dermatitis most commonly affects the antecubital and popliteal areas with involvement of the face, hands, and feet also. There is a pronounced tendency to itch, leading to plaques of thickened skin, and this is often exacerbated after emotional or environmental stress. The itching often results in difficulty in sleeping, and the resultant scratching can lead to infection by bacteria or herpes simplex virus (1). It affects 3–5% of the general population in industrialized countries, and the trend is toward an increase in the number of people affected. Atopic dermatitis is particularly common in childhood, and there is a tendency for the number of cases to decrease around 7–8 years of age. However, in some patients, symptoms may return at around the age of 12, and these often persist into adulthood, leading to chronicity. There does appear to be a genetic predisposition to the disease, because atopic dermatitis occurs more commonly in the children of atopic parents. Moreover, patients with this condition often have a history of other allergic disorders such as asthma, allergic rhinitis, or urticaria.

Patients with atopic dermatitis often have positive skin-prick tests to allergens, and IgE-mediated hypersensitivity reactions have been implicated in the pathogenesis of this disease, but the specific underlying cause remains unknown. The acute mast-cell-dependent early response is followed several hours later by the late-phase response, in which the eczematous lesions are infiltrated by proinflammatory leukocytes, which include T cells, antigen-presenting cells, and mast cells. Eosinophils are a prominent feature and are often accompanied by increased numbers of basophils (2, 3). Another aspect of this disorder is the presence of raised levels of histamine in the skin

lesions and in the serum of patients during acute exacerbations of the disease (4). Eosinophil blood counts are often elevated, and the degree of eosinophilia correlates with the severity of the disease (5, 6). Antigen challenge of patients by the skin-blister method has resulted in an increase in eosinophil numbers by up to 35 times (7), the peak of infiltration being observed at 18–24 h (8). Eosinophil granules contain several potent, toxic basic proteins, including major basic protein (MBP), eosinophil cationic protein (ECP), and eosinophil-derived neurotoxin (EDN). These cationic proteins have been implicated in the tissue damage associated with cutaneous inflammation.

Eosinophil degranulation has been demonstrated in the skin, and levels of these granule proteins can be detected in the blood of patients with atopic dermatitis. For example, ECP levels have been shown to be elevated in serum from patients with atopic dermatitis (9, 10), and the ECP serum level is related to the severity of the disease (11). Although the numbers of eosinophils are often elevated in the blood of patients with atopic dermatitis, it is difficult to detect their presence in skin lesions. However, immunohistochemical analysis can detect significant amounts of eosinophil-derived granule proteins such as MBP (12) and ECP (9), suggesting eosinophil disruption and loss of structural integrity in the skin of these patients. ECP is the more accurate measure of the presence of eosinophils in skin lesions because MBP is also found in basophils.

There are a number of regimens for the treatment of atopic dermatitis, but none are totally effective. Topical corticosteroids are widely used, and these are often combined with cream or ointment to deal with the problem of dry skin. The demonstrated presence of histamine in the lesions of patients with atopic dermatitis may be one reason for the efficacy of antihistamines in this condition. Older-generation antihistamines such as hydroxyzine or diphenhydramine have been fre-

quently prescribed to relieve itching and pruritus, but the main problem with these medications is sedation. This is a particularly important consideration with young people with atopic dermatitis, whose studies are often disrupted by sedation, especially at examination time. In these situations, the old sedating antihistamines had to be stopped temporarily and oral corticosteroids given. Today, the second-generation H₁-antagonists, which are almost devoid of sedative and anticholinergic side-effects, can be of use in atopic dermatitis, particularly those such as cetirizine which inhibit eosinophil accumulation (13). Various studies have compared the efficacy and safety of these medications in the treatment of atopic dermatitis.

One such study included 127 patients with atopic dermatitis who were treated for 4 weeks with cetirizine (10, 20, or 40 mg) or placebo (14). As compared with placebo, pruritus was significantly reduced by the 20- and 40-mg cetirizine treatments, while 40 mg also significantly reduced erythema, lichenification, lesion size, and total symptom score. Both patients and investigators expressed a preference for cetirizine 40 mg/day over the lower doses or placebo. Although cetirizine caused more sedation with increasing dosage, it was felt by these workers that the sedation observed was partly responsible for pruritus relief. However, the sedative side-effect could not account for all its other effects, such as skin-lesion healing. Furthermore, it should be noted that 40 mg daily of cetirizine is four times the recommended dose.

A double-blind, multicenter, placebo-controlled study over 4 weeks by Behrendt & Ring (15) compared cetirizine with terfenadine in 168 adult patients with atopic eczema. Cetirizine (10 mg twice daily) and terfenadine (60 mg twice daily) both gave a marked improvement in pruritus and in the extent and activity of skin lesions. In terms of efficacy, as assessed by both the investigators and patients, cetirizine was found to be superior to both terfenadine and placebo in relieving symptoms. One observation which was of particular interest in this study was the pronounced decrease in the number of blood eosinophils during treatment in the cetirizine group, but not in the terfenadine group. Whether this effect on eosinophil accumulation contributed to the clinical efficacy of cetirizine is not clear and requires further study.

An open multicenter study of 1465 patients treated with loratadine showed an effect on pruritus in 79% of the patients, an effect which was of the same magnitude as found with the old antihistamines (16). In 6–12-year-old children, mainly with atopic dermatitis, treatment with terfenadine or loratadine for 14 days decreased the pruritus in these patients by 58% and 54%, respectively (17).

Monroe compared hydroxyzine and loratadine in a placebo-controlled study of 41 patients with atopic dermatitis (18). Both drugs decreased pruritus. That less sedative antihistamines are better than placebo in relieving itching in patients with atopic dermatitis has been shown with loratadine and acrivastine (19, 20). Taking all clinical reports together, there is now evidence that the non- or less-sedative antihistamines can reduce pruritus in patients with atopic dermatitis.

Various forms of physical urticaria have been described which are triggered by stimuli such as mechanical trauma, light, heat, cold, or water. The second-generation antihistamines have proved useful in the treatment of the various forms of this condition with variable results, because not all patients benefit from treatment with these drugs (21–23). The removal or avoidance of the trigger stimulus remains the initial treatment for this condition.

Solar urticaria is an uncommon form of this disease which can be persistent and severely disabling. Treatment includes appropriate sunscreens, anti-malarials, plasmapheresis, or photodesensitization. In some patients, oral antihistamines might decrease the symptoms of solar urticaria, although, again, the use of the early agents was restricted by their sedative effects. Terfenadine and cetirizine have been shown to raise the threshold of sensitivity to a minimal photosensitivity dose (24, 25). The patients' exposure time to the sun after therapy was still limited to less than 30 min, and their sensitivity continued to impose severe restrictions on their lifestyle. These antihistamines seem therefore to be of limited clinical value in the treatment of solar urticaria.

Delayed pressure urticaria is another form of the disease which has been shown to respond to treatment with cetirizine. This condition is characterized by the development of painful wheals several hours after the application of pressure to the skin. The lesions, like those of chronic urticaria, also have a considerable infiltration of eosinophil leukocytes. It is a particularly difficult condition to treat and may require oral corticosteroid therapy. Kontou-Fili et al. (26) showed that cetirizine (30 mg daily) given for a period of 1 week to 11 patients significantly reduced the size and inflammation of wheals. Cold can also act as a stimulus for physical urticaria. Cetirizine given daily (10 mg) increased the time of cold exposure required to produce wheals in seven patients with primary acquired urticaria (27). Therapeutic doses of acrivastine or loratadine, ketotifen, and cyproheptadine had a similar effect (28, 29).

Mosquitoes are important vectors in the transmission of infectious diseases such as malaria and yellow fever. Even in countries where mosquitoes

are not disease carriers, their bites can cause severe cutaneous reactions. The female injects saliva into the skin as an anticoagulant before taking a blood meal. In man, particularly in sensitized subjects, the saliva can cause painful cutaneous reactions which vary from immediate, mild wheal-and-flare reactions to delayed papules, or, in extreme cases, to rare Arthus-type reactions with systemic effects. This problem is particularly acute in Scandinavian countries. Various topical treatments are available, but these have doubtful beneficial effect. Two studies have assessed the efficacy of cetirizine in the treatment of cutaneous reactions resulting from mosquito bites. In the first (30), 27 healthy adult volunteers were exposed to *Aedes aegypti* under laboratory conditions. Of these, 23 subjects showed a combination of immediate whealing and delayed bite papules. After exposure, IgG antibodies against a mosquito antigen could be found in approximately half of the subjects. In a double-blind, placebo-controlled study, cetirizine (10 mg) significantly decreased immediate whealing and pruritus, but had no effect on the delayed symptoms at either 12 or 24 h later. In a more recent study, the same group prophylactically treated 18 volunteers sensitive to mosquito bites with cetirizine (10 mg/daily) or placebo in a double-blind study (31). Adult subjects were selected who had suffered from large or intensively pruritic mosquito-bite lesions for at least two mosquito seasons. The subjects were then exposed to *Aedes communis* in the field on one exposure day in which they were bitten 8–12 h after the morning dose of cetirizine. Once again compared with placebo, cetirizine significantly decreased immediate whealing (by about 40%) and pruritus scores (by 67%). Interestingly, a clear-cut effect on the delayed (12- and 24-h) bite papules and pruritus was observed. The subjects in the latter study had a considerably delayed skin reactivity associated with a larger (about three times) diameter papule. Thus, prophylactically administered cetirizine may benefit both the early and delayed mosquito-bite symptoms in sensitive subjects.

In summary, the second-generation antihistamines are useful in the treatment of atopic dermatitis, although the number of studies to date remains small. Cetirizine is of particular interest because of its ability to inhibit both the early and late reaction and for its well-documented effect on eosinophil accumulation. Although the mechanism by which cetirizine inhibits eosinophil infiltration is not yet known, the available data suggest that this effect is independent of its H_1 activity. In skin conditions which are characterized by an increase in the extravasation of eosinophils into the tissues, the effect of cetirizine might be worth investiga-

tion. Studies have also shown cetirizine to be useful in various forms of urticaria and in treating the symptoms of cutaneous reactions to mosquito bites. It remains to be seen whether cetirizine's anti-inflammatory effects are responsible for its efficacy in these situations.

Round-table discussion

Simons: Atopic dermatitis is a long-term disorder, and yet the studies we see are of short duration, only 1–3 months at most, with very small numbers of patients. We need a long-term study which includes a large number of patients.

Juhlin: I agree. You also need the study to be carefully controlled. One other problem is the nature of atopic dermatitis, in that its severity varies with time; i.e., symptoms come and go to an extent. The patients may have a dry skin and need topical emollients and often topical steroids as rescue medication during a study, which of course would have to be taken into account.

Simons: I felt badly for the students with atopic dermatitis at the University of Uppsala. Did they try taking their first-generation antihistamines only at night?

Juhlin: Yes, but then they were tired the following morning, but with the less or non-sedating antihistamines they could easily follow the lectures and understand what the teacher said.

Simons: I think that everyone was surprised by the severity of some of the reactions to bites from mosquitoes. This is a big problem both in northern Europe and in the northern parts of North America at certain times of the year. H_1 -antagonists have proved to be very useful in the treatment of symptoms. We are in the process of studying this problem in our own unit. We have had no problem in recruiting volunteers because skin reactions to mosquito bites affect many people.

Meltzer: With regard to the Michel [J Allergy Clin Immunol 1988; 82: 101–9] and Charlesworth [J Allergy Clin Immunol 1989; 83: 905–12] studies in which eosinophil influx into the skin lesions was a feature, have ECP levels in the patients' blisters been measured as part of any study? It would be interesting to see whether there were any decreases following treatment; this might prove to be a useful marker of the effect of treatment. It would be nice if the fall in eosinophil numbers was accompanied by a drop in ECP levels.

Meltzer: I wonder whether ECP might also prove to be a useful marker in respiratory disease. For example, in asthma, if you were to do a study in which you gave them cetirizine, would you get a fall in ECP levels in the BAL [bronchoalveolar lavage fluid] or plasma? In a similar way, you could look at nasal washings from rhinitis patients. It might be a nice marker since we always have problems demonstrating a fall in actual eosinophil numbers.

Juhlin: The serum ECP level seems to be a good marker of disease severity as described by Czech et al. (11).

De Vos: Perhaps I can add something. We performed a bronchial provocation study in allergic asthmatic subjects and measured ECP in their plasma during the late asthmatic response. The placebo-treated group of patients had elevated levels of ECP in their plasma. In a parallel group treated with 15 mg cetirizine twice a day, there was no increase in plasma ECP levels. In this study, the late asthmatic response was slightly inhibited by cetirizine, but this was not significant.

Juhlin: What do you think is the cause of the decrease in ECP levels? Is it a direct effect on the eosinophils by cetirizine or because of an improvement in the disorder which results in a drop in ECP levels?

De Vos: We didn't show a decrease in ECP levels, but an absence of an increase. I think cetirizine acts on ECP levels by causing an overall improvement in the condition, rather than having a direct effect on the eosinophil.

Broide: Just a point regarding the interpretation of blood eosinophil numbers and ECP levels. If you antigen-challenge a patient with asthma and look at his eosinophil counts at 0, 4, and 24 h, you will see a fall in the eosinophil blood count as they traffic into the lung, and that would be anticipated. So you really do need a count from a placebo group or diluent challenge to make a valid comparison.

Juhlin: The advantage of ECP measurement is that it shows the ECP produced by eosinophils in the tissues, as well as of those in the circulation, which represent only a small portion of our total eosinophil population.

Rihoux: In one published study of the effect of ketotifen in atopic dermatitis, they showed what they called a normalization of blood eosinophils; i.e.,

there was an increase at the beginning of the study and this had normalized by its end. In the Ring study, we also showed that some patients presented with an initially high base-line eosinophil count. By the end of the study, we could only show a decrease in eosinophil numbers in these subjects.

Simons: I think that the fact that the discussion has moved away from atopic dermatitis to respiratory disease/allergy illustrates the lack of a really good knowledge base in atopic dermatitis. We really do need to have a lot more studies in this area.

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