NEW DEVELOPMENTS IN THE INVESTIGATION AND MANAGEMENT OF CHRONIC URTICARIA

Chronic urticaria is a challening condition that often defies explanation.

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Chronic urticaria (CU) remains a challenge for investigation and management. It is not unusual for patients with CU to undergo extensive laboratory and radio-logical investigation without much yield. Although antihistamines are widely regarded as first-line treatment for CU, many patients fail to respond (or respond incompletely). Some cases respond to corticosteroids but their use is limited by the potentially serious adverse effects associated with long-term use. This article reviews the recent advances in the investigation and management of CU, with particular focus on autoimmune urticaria.

The various types of chronic urticaria are listed in Table I.

Table I. **Types of CU**

- Chronic urticaria
  - Identifiable cause (5 - 10%)
  - Autoimmune urticaria (30 - 40%)
  - Chronic idiopathic urticaria (50%)
- Physical urticaria
  - Dermatographism
  - Cholinergic urticaria
  - Cold urticaria
  - Delayed pressure urticaria
  - Solar urticaria
- Urticarial vasculitis
- Mastocytosis
- Papular urticaria

One-third of patients with CU are believed to have autoantibodies to the high affinity receptor for IgE (FcεRI) and are considered to have autoimmune CU. An additional 30 - 50% of cases of CU have no identifiable cause. These patients traditionally are referred to as having chronic idiopathic urticaria (CIU). Some patients with CU might describe a number of factors that do not seem to be exclusive in causing urticaria but exacerbate or worsen the urticaria. Examples might include a physical trigger, such as prolonged pressure to the skin, a nonspecific releaser of histamine (e.g. a non-steroidal anti-inflammatory drug (NSAID)), or psychosocial stress. In this instance, avoidance of this specific exacerbating factor might be of some benefit, although little experimental evidence supports such a recommendation. If a patient has no clearly identifiable physical, cutaneous, or ingestant trigger, avoidance measures (see below) are unlikely to be of benefit.

AUTOIMMUNE CHRONIC URTICARIA

A growing body of evidence shows that 30 - 40% of adult patients with CU have an autoimmune basis for their condition, but few data are available in children.[1-6] A recently published study from Europe reported that the prevalence of autoimmune urticaria in children is at least 30%.[7] In a similar study on children with CU in Cape Town, anti-IgE receptor (FcεR1α) antibodies were found in 47% of patients. This subset of patients have autoantibodies directed against IgE or epitopes in the alpha chain of the IgE receptor (Fig. 1). Interaction between these antibodies and the IgE receptor/IgE itself causes histamine release, a reaction that has been shown to be dependent on complement.[8,9] Some adult patients with functional anti-FcεR1α autoantibodies also show evidence of thyroid autoimmunity;[10-13] however, the pathophysiological mechanism that may link these two entities is still unclear. As many as 12 - 14% of adults with CU have circulating antithyroid antibodies, which is considerably higher than the incidence seen in the normal population (5 - 6%). Most of these patients are female, and many have angioedema and urticaria. Although

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The diagnosis of autoimmune urticaria can often be suspected from a history of highly symptomatic, severe continuous wheeling linked with systemic features of malaise, indigestion, and feeling hot or cold.

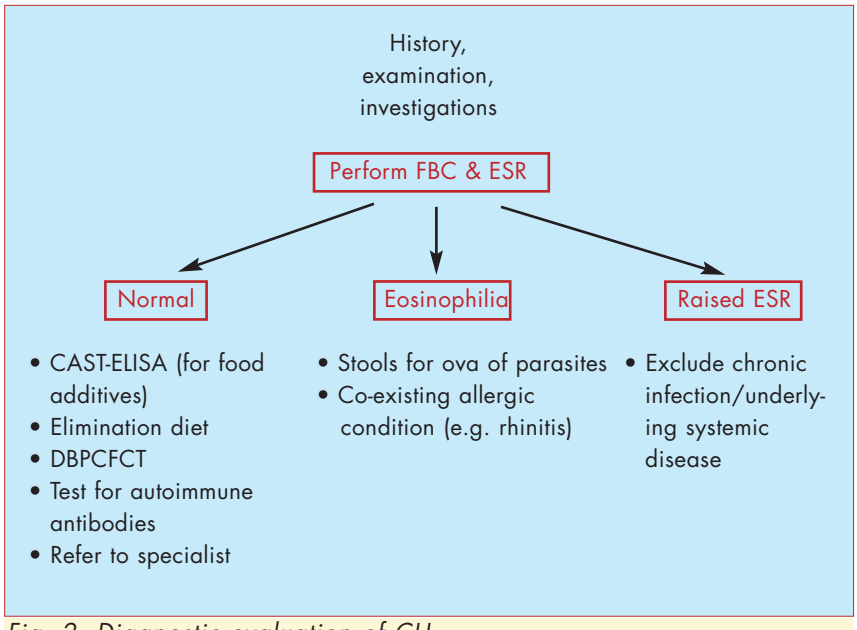

Fig. 2. Diagnostic evaluation of CU.

some of these patients have clear evidence of Hashimoto's thyroiditis, requiring treatment with thyroid hormone, many are euthyroid. No data are available in children with CU regarding the prevalence of thyroid autoantibodies.

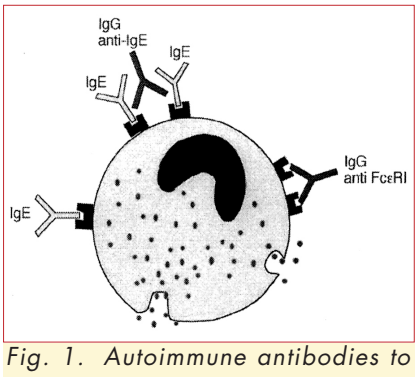

Fig. 1. Autoimmune antibodies to IgE/IgE receptor.

Clinical assessment in the diagnosis of autoimmune urticaria

The clinical presentation of patients with or without autoantibodies is surprisingly similar, although in adults, those with autoantibodies tend to have more severe disease.[14,15] Histological examination of spontaneous wheal biopsy specimens showed significantly greater numbers of neutrophils, activated eosinophils, and lymphocytes in lesions less than 4 hours or more than 12 hours old when compared with uninvolved skin. There is no important histological difference between patients with and without autoantibodies.[16] The lack of a clear clinical and histological separation between CU patients with and without autoantibodies indicates that the occurrence of skin mast cell degranulation may be more important in determining clinical presentation than its cause. Neverthe-less, it is possible that more patients would show functional autoantibodies than are currently recognised if more sensitive assays for their detection become available (see below). The diagnosis of autoimmune urticaria can often be suspected from a history of highly symptomatic, severe continuous wheeling linked with systemic features of malaise, indigestion, and feeling hot or cold. A past or family history of autoimmune disease, especially thyroiditis, can also be indicative.

Routine investigations might include a complete blood cell count, erythrocyte sedimentation rate, and thyroid autoantibodies in selected cases (Fig. 2).

Blood basophil enumeration and an autologous serum skin test (see below) are useful if facilities are available, but the diagnosis often has to be made on clinical suspicion and after exclusion of other recognisable patterns of urticaria, including patterns triggered by physical stimuli or those linked with drugs, infections, or dietary factors. CAST-ELISA, a commercially available, standardised, basophil-based assay, can be used to diagnose non-IgE-mediated reactions and food intolerance (non-immune reaction) in patients with CU. The CAST-ELISA allows the quantitative determination of sulphidoleukotriene (sLT) release after leucocyte stimulation with an allergen. The assay is performed in 3 steps:

- leucocyte isolation by dextran sedimentation
- simultaneous leucocyte priming and stimulation with allergen
- measurement of synthesised sulphidoleukotrienes, sLTC4 and its metabolites, sLTD4 and sLTE4 in an ELISA assay.

A wide variety of allergens, food additives and screening assays are commercially available for use in the CAST-ELISA (Table II). This test appears to be useful in evaluation of drug allergy and identification of food additives, colourants and preservatives. CAST-ELISA is not currently recommended as a first-line test for allergen-induced IgE-mediated reactions. More studies are required to determine the sensitivity, specificity and predictive value of this test, particularly in comparison with DBPCFC testing.

Basophil histamine-release assay

This test is currently the gold standard for detecting functional autoantibodies in the serum of patients with CU.[14-19] Most of the studies that support the concept of autoimmune urticaria have relied on the release of histamine from basophils of healthy donors as a marker of activation and degranulation. Assays for other products of degranulation, including leuoktriene C4 tryptase and TNF-ϐ have not been used, because histamine is the major mediator of most patterns of urticaria and is also relative-

ly simple and inexpensive to measure. For subgroups of patients, including those who are relatively unresponsive to antihistamines, assays for other mediators may be informative. The basophil histamine- release assay has several limitations: the assay is difficult to standardise because it requires fresh basophils from healthy donors and is time consuming. It is thus likely to remain confined to research centres and specialised laboratories.

Immunoassays

Immunoassays depend on the binding of autoantibody to a specific autoantigen (in this case, the soluble chain of FcεR1α or IgE) rather than the detection of a secreted mediator from the target cell (in this case, histamine) as evidence of functionality. Compara-tive studies have shown that positive detection of anti-FcεR1α by immunoblot does not correlate well with basophil histamine release.[9] The reasons for this are unclear, but false-positive results may relate to the aberrant binding of the autoantibody to carbohydrate moieties in the cloned autoantigen or to the non-complement fixing IgG_2 and IgG_4 subclasses that are detected by immunoassay. False-negative results could be caused by the insensitivity of Western blotting at the low concentrations of anti-FcεR1α present in sera of patients with CU. An ELISA would increase sensitivity and allow quantification of the autoantibody, but attempts to develop a suitable system for general use have been unsuccessful. The ELISA, published by Fiebiger *et al.*,[20] was a complex assay involving 2 reaction steps and using a human recombinant soluble FcεR1α that is generated by baculovirus-infected insect cells. This assay has not been repeated by other investigators. Horn *et al.*[21] subsequently compared two recombinant FcεR1α proteins that were produced similarly in insect cells or in mammalian Chinese hamster ovary (CHO) cells. They concluded that the CHO protein showed a superior biological activity for ELISA. They went on to show that similar levels of anti-FcεR1α could be detected in patients with CIU, patients with CU of other causes, and a small number of controls. There was no apparent relationship between the ELISA results and histamine-releasing activity. Future research should develop a sensitive ELISA that can distinguish pathogenic autoantibodies above background levels of natural autoantibody and that measures only functional anti-FcεR1α.

Autologous serum skin test (ASST)

The ASST remains the most accessible and useful test for demonstrating endogenous vasoactive factors in the blood of patients with ordinary urticaria. It is not a specific test for autoimmune urticaria. Although it has a reasonable sensitivity (about 70%) and specificity (about 80%) for basophil histamine release using the criteria described (a red serum-induced wheal with a diameter that is 1.5 mm or greater than the diameter of the oedema caused by an adjacent normal saline control injection at 30 minutes (Fig. 3a and 3b), it does not specifically imply mast cell degranulation or autoimmune stimulation as a cause of the wheal response.

The ASST offers a simple screening test for potentially relevant biological activity and may help to define a subgroup of patients with urticaria who are more likely to have an endogenous cause for their disease than do patients without a positive test.[22] The significance of a negative ASST remains less clear. Although it is unusual for patients with a negative ASST to show significant *in vitro* release of basophils, the histology of positive and negative ASSTs has shown marked neutrophil-rich infiltrates between 90 and 135 minutes, in contrast to injection of autologous serum in healthy controls in whom the serum response was similar to that seen with saline injection. The presence of this cellular infiltrate suggests that circulating proinflammatory factors may still be relevant in patients with chronic urticaria and negative ASSTs, but the role of histamine and other vasoactive mediators in the response is diminished. Various practical considerations may influence the outcome of the test, including the use of antihistamines within 3 days of the test, injection over the sites of recent wheals, and health and safety issues in relation to preparation of the serum. ASST is cheap, easy to perform and, if performed as appropriate, has good sensitivity and even better sensitivity at detecting autoantibodies in children. Therefore it can be used as a predictive clinical test to diagnose autoimmune urticaria, especially in situations where the basophil histamine- releasing test is not available.

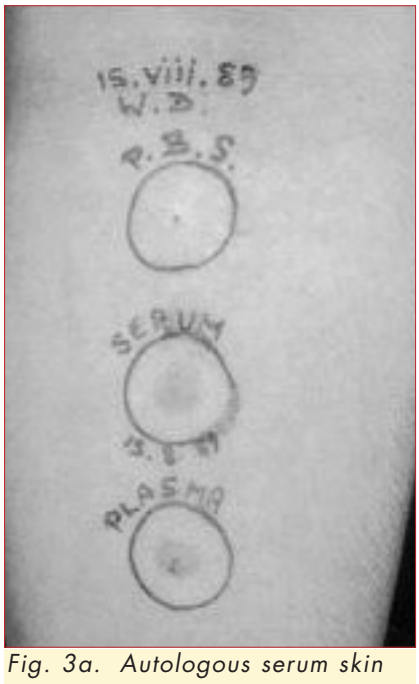

Fig. 3a. Autologous serum skin test (ASST).

Fig. 3b. Positive ASST.

Peripheral blood basophils

Peripheral blood basophils are reduced or absent in certain patients with CU with histamine-releasing autoantibodies.[23] Basopenia has proved to be a helpful clinical marker of autoimmune urticaria. However, there are no rapid and reliable techniques available at present for measuring small numbers of circulating basophils.

Table II. **Currently available CAST food additives**

Food Colourants Mix 1	Brilliant Black BN
Food Colourants Mix 2	Chromotrope B
Sodium benzoate	Cochineal
Sodium nitrite	Erythrosine
Sodium metabisulphite	Indigocarmine
Sodium salicylate	Patent Blue V
Tartrazine	Quinolene Yellow
Amarinth	Sunset Yellow FCF

Although the current gold standard of diagnosis hinges on functional release assays with basophils or mast cells, these investigations remain confined to a few research centres; in practice, the diagnosis of autoimmune urticaria relies primarily on clinical suspicion that is supported by tests when available.

MANAGEMENT OF CHRONIC URTICARIA

Avoidance of aggravating or trigger factors

A practical approach to treatment or CU is outlined in Tables III and IV.

Management should be directed at the cause of CU in the rare instance where one can be found. Aggravating factors that may be identified from the history (e.g. heat, tight clothing, stress, alcohol) and trigger stimuli for physical urticaria should be avoided if possible. Providing clear information and advice on preventive measures, such as covering exposed skin of patients with cold urticaria, and symptomatic measures, such as taking cool showers for cholinergic urticaria or rewarming in a hot bath for attacks of cold urticaria, can be helpful. Simple cooling lotions, such as 0.5 - 1.0% menthol in aqueous cream, are often helpful.

Some cases of urticaria may be caused exclusively by nonallergic triggers (some of which may cause direct release of histamine from skin mast cells). Examples of this type of trigger include aspirin and other NSAIDs[24] and opiates. If one of these agents is found to be a triggering factor, avoidance is prudent. Paracetamol is recommended as an alternative. It is also good practice to recommend avoidance of codeine and other opiates in view of the enhanced skin test reactions to codeine found in CU at the time of minor viral infections.

Angiotensin-converting enzyme (ACE) inhibitors should also be avoided in urticaria since angioedema and, rarely, urticaria are recognised adverse effects. Angioedema due to ACE inhibitors may present months after the onset of therapy.[25] Avoidance of foodstuffs that contain food colourants, preservatives and natural salicylates is advisable. Removal and reintroduction of food in an open fashion is commonly used to establish causality. If this approach is taken, patients should attempt to reintroduce suspected foods in an organised fashion to avoid lifetime use of an unnecessarily restricted diet. In select cases, a double-blind, placebo-controlled food challenge may be indicated. In patients with a history of significant angioedema or anaphylaxis, reintroduction should be done under the direct supervision of a doctor skilled in resuscitation techniques.

Treatment of underlying diseases

Urticaria rarely may be a manifestation of an underlying disease, and in these cases treatment of the underlying condition is warranted. Limited experimental evidence shows that treatment of underlying conditions lead to a clinical improvement of urticaria.

The best example of a systemic condition that commonly is associated with CU is Hashimoto's thyroiditis. Clinical experience has shown that treatment of

Table III. **Non-drug therapy of CU**

General advice
- Explanation and information
- Cooling lotions, e.g. calamine or 1.0% menthol in aqueous cream

Avoidance of aggravating factors
- Avoid aspirin, NSAIDs, codeine, morphine, ACE inhibitors
- Minimise stress, over-heating, alcohol
- Use an elimination diet
- When indicated by history, CAST-ELISA or blinded placebo-controlled challenge, e.g. food colourants and preservative avoidance

Treat underlying disease

Table IV. **Drug therapy of CU**

First line for all patients
- Non- or less- sedating H_1 antihistamine
  if little or no response
- Add sedating H_1 antihistamine at night
  if little or no response
- Add H_2 antagonist

↓

Second line – special indication
- Corticosteroids (for severe ordinary or delayed pressure urticaria)
  - short-term use only
  - alternate day regimen
- Other interventions (see text)

↓

Third line – specialist use only
- Immunomodulation (for severe autoimmune urticaria only)

Hashimoto's thyroiditis with thyroxine seems to lead to amelioration of CU in some patients. There have been a number of attempts to administer thyroxine to euthyroid patients with CU associated with antithyroid antibodies but the results have been variable. Leznoff *et al.*[12] treated 7 patients who had thyroid autoantibodies but were euthyroid with 0.2 mg/d of levothyroxine in an open-label, uncontrolled manner. Five patients showed improvement of their urticaria, but this finding generally was not seen until 2 months after beginning therapy. In a later study, Leznoff *et al.*[11] treated 46 patients with CU and thyroid autoimmunity (some of whom were euthyroid and others who were hypothyroid) with levothyroxine, but only 8 patients improved within 1 month. Two of these patients who improved initially had a recurrence of urticaria despite continuation of levothyroxine; however, 4 patients who improved, who had high thyroid autoantibody levels, had repeated remissions each time levothyroxine was started and repeated relapses when treatment was stopped. Rumbyrt *et al.*[26] had a better rate of success: all 7 euthyroid patients with CU and elevated levels of antithyroid antibodies reported resolution of symptoms within 4 weeks of starting thyroxine. Five of the 7 patients had a relapse of symptoms after discontinuing thyroxine and responded again when the medication was recommenced. There was no correlation between clinical response and change in antithyroid antibody levels, suggesting that the antithyroid antibodies themselves were not pathogenic. One patient in this study underwent a double-blind trial with thyroxine and placebo, in which the response to thyroxine was confirmed. These findings suggest that some patients with CU and thyroid autoimmunity may improve with thyroxine treatment, whereas others may fail the therapy. In patients who improve, the mechanism of action is not clear.

Hyperthyroid patients have no difference in response to histamine, codeine, and compound 48/80 compared with controls,[27] suggesting that thyroxine itself probably does not have direct effects on mast cell release or cutaneous response to histamine. Larger, double-blind, placebo-controlled trials are needed to clarify which patients, if any, respond to thyroxine.

Other underlying medical conditions that have been reported to be associated with urticaria are rarely seen as a cause of urticaria, and the evidence supporting these associations is less substantiated. Examples of other conditions include cryoglobulinaemia[28] and endocrine tumours.[29] A few reports have suggested that *Helicobacter pylori* might be associated with urticaria in some patients,[30-33] but the data are not strongly supported.

First-line drug therapies

Oral antihistamines are the mainstay of drug treatment for CU irrespective of the cause. The new-generation non-sedating or less-sedating antihistamines are preferred to the older antihistamines for initial treatment. They should be taken regularly for best disease control, although some patients prefer to take anithistamines intermittently (e.g. shortly before periods when they anticipate exacerbations of physical urticaria). Higher than recommended dosages or even twice daily dosing of the new antihistamines may be necessary to control urticaria in young children (< 2 years) because of shorter half-life. If possible, antihistamines should be avoided in pregnancy, especially during the first trimester. If an antihistamine must be prescribed during pregnancy, the consensus is that chlorpheniramine is relatively safe and is nonmutagenic.[34]

Addition of a sedating antihistamine at night, such as chlorpheniramine, hydroxyzine, or diphenhydramine, can be helpful when sleep is disturbed by itching that occurs predominantly at night. The use of a sedating antihistamine as monotherapy for CU is not recommended because of impairment of cognitive function and concentration.

H_2 receptors are found in large numbers in the stomach. For this reason, H_2 antagonists (e.g. ranitidine, cimetidine) primarily are used to inhibit gastric acid secretion; however, H_2 receptors also are present in the skin and may contribute to the cutaneous effects of histamine. The addition of an H_2 antagonist to an H_1 antagonist in treating CU can be more effective than an H_1 antagonist alone, as confirmed in small trials.[35-37] One of these studies found that 40 - 50% of patients had statistically significant improvement when cimetidine was added to hydroxyzine.[35] Other small trials have not seen this additive effect.[38] For some patients who experience this synergistic effect between certain H_1 and H_2 antagonists, the synergism may be caused by a pharmacokinetic effect, with the H_2 blocker leading to increased blood levels of the H_1 blocker;[39] this finding warrants further study. For dermatographism, a combination of chlorpheniramine and cimetidine was found to be superior to either agent alone in a small trial.[40]

Second-line drug therapies

Oral corticosteroids may occasionally be required in short tapering courses for severe exacerbations of CU that have not responded to full-dose antihistamines. They may be used for delayed pressure urticaria and urticarial vasculitis; these conditions respond poorly, if at all, to antihistamines. Oral corticosteroids may be justifiable for severe disease, especially autoimmune CU, although fairly high doses (≥ 30 mg prednisone daily) may be required. Long-term administration of corticosteroids should be avoided if possible as the likelihood of corticosteroid-induced side-effects increases with longer periods of treatment. Patients (or parents) should be advised of this possibility so that the risks and potential benefits can be considered carefully. Low-dose alternate-day regimens are preferred for medium- to long-term treatment with steroids.

Other interventions

Numerous other therapies have been reported for antihistamine-unresponsive CU although the quality of evidence for the intervention is often poor because of the small numbers studied. These include leukotriene receptor antagonists in aspirin-sensitive urticaria, nifedipine a calcium-channel blocker, for CU and sulfasalazine in delayed pressure urticaria.

Antileukotriene agents

Leukotriene C4 (LTC4) and leukotriene D4 (LTD4) are believed to play a role in the pathogenesis of urticaria. Studies have shown that the intradermal injection of LTC4, LTD4, and leukotriene E4 produces a wheal-and-flare reaction in normal subjects and in patients with CIU.[41,42] The sera from some patients with positive autologous serum skin tests have been shown to cause histamine release and *de novo* production of sulfidoleukotrienes *in vitro*.[43] Simons *et al.*[44] found that montelukast decreased the cutaneous response to intradermally injected LTD4, although montelukast was no more effective than placebo in

decreasing the early and late cutaneous response to intradermally injected histamine or allergen.

Case reports and small clinical studies have suggested that the antileukotriene agents may be effective in the treatment of urticaria.[45-51] There are also a few published reports of blinded, placebo-controlled trials of leukotriene receptor antagonists (LTRAs) in CU. In a double-blind, placebo-controlled, crossover study involving 52 patients with CU, Reimers *et al.*[52] found that zafirlukast was no more effective than placebo. Erbagci[53] found that montelukast was significantly more effective than placebo in a single-blind, crossover trial in 30 patients with refractory CIU. Nine of 11 patients who initially had a positive response to intradermal injection of autologous serum had a negative test after treatment with montelukast. Patients with aspirin-sensitive urticaria had good results with montelukast in this trial.

Although there have been some promising results with LTRAs in case reports and small trials, large-scale, double-blind, placebo-controlled trials are needed to confirm whether there is a significant role for LTRAs in the treatment of urticaria. Similarly, there have been no large-scale trials with the 5-lipoxygenase inhibitor zileuton, although its use would likely be limited because of the risk for hepatotoxicity.

Calcium-channel blockers

Limited evidence shows that the calcium-channel blocker nifedipine, at dosages of 10 mg twice daily to 20 mg 3 times daily and when used in combination with an H_1 antagonist, may have some added benefit in patients who have not responded to H_1 antagonists alone.[54] These agents rarely are used in clinical practice, however, perhaps because the clinical benefit is limited and significant side-effects, such as oedema, can occur.

Third-line therapies (immunomodulation)

Immunomodulating therapies that have been administered for CU include plasmapheresis, interferon α, intravenous immunoglobulins (IVIGs) and cyclosporine. Methotrexate, cyclophosphamide and azathioprine have also been used in some patients. Most early trials of immunomodulatory therapy stipulated that patients had to have some evidence of histamine-releasing autoantibodies to justify their recruitment into the studies (such as a positive ASST or *in vitro* evidence of functional autoantibodies). Because of the difficulty in proving autoimmunity as a cause of urticaria, it has become common practice to offer a trial of immunomodulation to patients with severe disabling chronic ordinary disease, particularly if they are corticosteroid dependent. Clinical experience suggests that good responses may be achieved with or without proof of functional autoantibodies, although it seems that patients with strongly positive basophil histamine release are more likely to respond well to cyclosporine.

Plasmapheresis

Only one open series of plasmapheresis for autoimmune urticaria has been reported.[55] Eight patients with severe CU and serum histamine-releasing activity were treated 3 times over 5 days (volume of plasma removed, 4.2 - 9.0 l). Two patients cleared for 8 and 4 weeks, 4 patients improved symptomatically for up to 2 months, but 2 patients showed only a slight benefit. The study showed that serum histamine-releasing activity could be involved in the pathogenesis of CU. It also demonstrated that the clinical improvement from removal of functional autoantibodies was short-lived because the autoantibodies reaccumulated afterward and that plasmapheresis as monotherapy was difficult to justify.

Interferon α

There have been 2 reports of interferon α (IFN α) treatment for CU. In the first report, patients with mastocytosis and several patterns of CU were treated with subcutaneous injections of IFN-α2a for at least 8 weeks.[56] The only patient with CIU failed to respond. Open administration of intramuscular IFN-α2a at 3 x 10^6 IU 3 times a week for at least 2 weeks in 8 patients with severe refractory CIU seemed to result in a 'good response' in 50% of patients, but this response was not maintained despite continuing treatment at the same dosage.[57] The authors of this report did not attempt to assess the patients for functional autoantibodies. The conclusion that can be drawn from these uncontrolled reports is that IFNα treatment of urticaria is unproven and probably should not be used at the present time.

Intravenous immunoglobulin

Pooled gammaglobulin containing predominantly IgG from multiple healthy donors has been used to treat a wide range of disorders, including idiopathic thrombocytopenic purpura and vasculitis. Ten patients with severe chronic autoimmune urticaria, evidenced by positive *in vitro* basophil histamine release, were treated over 5 days with 2g/kg IVIG.[58] Clinical benefit was noted in 9 patients. Two patients had prolonged complete remissions lasting at least 3 years, and 3 patients showed temporary complete remissions. The reduced urticarial activity corresponded with a reduction in the size of the ASST response in most patients. This encouraging open study has not been repeated or controlled, so it remains difficult to assess the likely benefits of IVIG. Further studies are needed to explore different dosing regimens.

Cyclosporine

Cyclosporine has been used widely off licence for treatment of severe CU over the past few years.[59-61] A randomised double-blind controlled study of patients with severe CU shows good evidence of efficacy.[62] All 30 patients had a positive ASST, and 14/27 patients tested had significant *in vitro* basophil histamine release. Patients were randomised to receive cyclosporine at 4 mg/kg/d or placebo for the first 4 weeks of treatment. Non-responders were offered open-label cyclosporine at the same dosage for another month. All patients took 20 mg/d of cetirizine throughout the treatment and follow-up period for a duration of up to 5 months. In the randomised phase of the study, the number of responders to cyclosporine was significantly greater than the number of responders to placebo. About two-thirds of the patients responded overall, with a reduction of their urticaria activity to less than 25% of baseline overall, but only 26% of responders remained clear or almost clear near the end of the study. Histamine-releasing activity of sera decreased significantly after cyclosporine treatment began, and 13 of the 18 responders showed significant *in vitro* histamine release. It is likely that the early response to cyclosporine seen in some subjects (within 48 hours) was a result of the sta-

bilising effects of the drug on basophils and most cells rather than the inhibition of functional autoantibodies, although the rate of autoantibody reduction was not assessed. Preliminary data from a multicentre study of cyclosporine given at 5 mg/kg/d for 2 weeks, 4 mg/kg/d for the next 2 weeks, and then 3 mg/kg/d for the remainder of the study confirmed a good therapeutic response and indicated that relapses were more frequent in patients treated for 8 weeks rather than 16 weeks.[63] Optimal treatment protocols with cyclosporine still need to be defined.

Methotrexate

There are rare case reports of the use of methotrexate in CU. Gach *et al.*[64] described its use in 2 patients with severe CU who were refractory to treatment with antihistamines and required chronic steroid therapy to control their symptoms. Neither patient had evidence of autoantibodies to the high-affinity IgE receptor using histamine-release assays. Significant clinical improvement was observed with 15 - 20 mg of methotrexate weekly. The potential toxicities of this agent need to be taken into account and make it unlikely that methotrexate will be used on a frequent basis in CU, especially in children.

Cyclophosphamide

Although cyclophosphamide has been used for the treatment of urticarial vasculitis, reports of its use in CU treatment are scarce. Bernstein *et al.*[65] reported a woman with severe autoimmune CU (established by a positive skin test to autologous serum) whose disease was unresponsive to most medications but could be controlled with prednisone at a dosage of 35 mg/d. She had developed steroid-related toxicity, so cyclophosphamide was started at an intravenous dose of 500 mg administered every 2 weeks and increased by 100 mg every 2 weeks until a maximum dose of 1 500 mg was achieved, which was continued every 4 weeks. She was able to slowly taper and discontinue prednisone, and the autologous serum skin test turned negative (suggesting that the cyclophosphamide may have eradicated B-cell clones that were producing autoantibodies to the high-affinity IgE receptor). She had some mild residual symptoms but did not require further steroid treatment. This study is the only known report of the use of this agent in CU. Because of its significant immunosuppressive properties, cyclophosphamide is unlikely to be used by most clinicians in CU, except in extreme cases.

Future directions and possibilities

As the treatment of allergic disease continues to advance, new agents may be discovered that are effective in the treatment of urticaria. Some of these agents may turn out to be more effective than existing therapies, whereas others may be equally effective but have a more desirable safety profile.

Anti-IgE monoclonal antibodies

Considerable evidence has accumulated to support the hypothesis that a large proportion of cases of CU are caused by an underlying autoimmune phenomenon. At least 30% of patients have a circulating autoantibody to the high-affinity IgE receptor, which is believed to be related to the ability of the serum to release histamine (and cause a positive autologous skin test). If these autoantibodies to the high-affinity IgE receptor are confirmed to be pathogenic in CU, specific targeting of this autoimmune process might be highly effective for the treatment of these patients. Treatment with omalizumab, a monoclonal antibody to IgE, has been shown to lead to decreased surface expression of the high-affinity IgE receptor on circulating basophils.[66] Whether this decreased expression would been seen on cutaneous mast cells is not known; if this effect were shown, one might hypothesise that omalizumab would be effective in patients who have the autoantibody to the high-affinity IgE receptor. No studies of the use of this drug for CU have been reported.

Specific targeting of autoantibodies to the IgE receptor

As further work is done to clarify the role of autoantibodies to the high-affinity IgE receptor of CU, other options for treatment may develop. If the autoantibodies are confirmed to be pathogenic, it may be possible to develop biological agents to specifically target these IgE receptor-specific antibodies. As the technology of biological therapy advances, this method may become feasible.

NATURAL HISTORY OF CU

The overall prognosis of CU in children is unknown but in adults it is good. Champion *et al.*[67] documented spontaneous resolution of a single continuous episode within 12 months in 50% of adult patients; 20% still had symptoms lasting 20 years. These rates of resolutions were significantly less in patients who had associated angioedema. Patients with autoantibodies seem to have worse disease but this finding is not dramatic.[14-16]

References available on request.

IN A NUTSHELL

Autoimmune urticaria, caused by autoantibodies to the high-affinity receptor for IgE or to IgE itself, occurs in 30 - 40% of patients with CU.

The diagnosis rests mainly on clinical suspicion in patients with the most severe presentations of CU and without any known cause or physical trigger.

Better laboratory assays (to detect these autoantibodies) need to be routinely available to facilitate diagnosis.

Currently, the new-generation antihistamines remain the mainstay of treatment for CU.

The use of immunomodulatory therapy may be beneficial for some patients with autoimmune urticaria.

With the ongoing development of novel agents for the treatment of allergic disease, perhaps new agents will be discovered that are highly effective for the treatment of CU and safe for long-term use.