

Chronic idiopathic urticaria with functional autoantibodies: 12 years on

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Summary

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None declared.

It is now recognized that approximately one-third of patients with chronic idiopathic urticaria (CIU) have histamine-releasing autoantibodies directed against either the high-affinity IgE receptor or, less frequently, against IgE. However, there are several unsolved problems relating to the role of such autoantibodies in the disease. Additionally, it is not clear whether CIU with autoantibodies can be classified as an autoimmune disease. The detection of patients with autoantibodies also poses challenges. Firstly, the only *in vivo* method, the autologous serum skin test, is at best 80% sensitive and specific using *in vitro* basophil histamine release assays as the verum. Secondly, *in vitro* tests are only done in a small number of research laboratories, and are not widely commercially available, and thirdly, there is some divergence between results obtained by different methods (functional and immunoassays) used to detect patients with autoantibodies. The presence of autoantibodies may be important clinically in a small group of severely affected, treatment-resistant patients, where immunomodulatory treatments may be helpful.

Chronic idiopathic urticaria (CIU), or urticaria persisting for 6 weeks or more where a predominant physical urticaria has been excluded, has long been regarded by allergists and dermatologists alike as a 'heart sink' disease. The emergence in 1993^{1–3} of evidence that in up to 50% of patients the disease could be explained by an underlying autoimmune mechanism involving anti-high affinity IgE receptor (FcεRI) antibodies or, less frequently, anti-IgE antibodies was generally welcomed and the importance of these autoantibodies is now widely recognized.^{4,5} Even in 1993, the concept of autoimmune urticaria was not new. In 1983 Leznoff *et al.*⁶ suggested an autoimmune basis to the disease after the observation that there was an association between thyroid disease and CIU. In 1988 Gruber *et al.*⁷ detected anti-IgE antibodies in various types of urticaria, some of which appeared to be functional, and were the first to propose that these autoantibodies might be involved in the development of urticarial weals. In 1991 Grattan *et al.* provided evidence of histamine-releasing autoantibodies with properties of anti-IgE in sera from patients with CIU⁸ and later showed that these antibodies were predominantly anti-FcεRI autoantibodies.¹ Now, the presence and possible functional role of IgG autoantibodies directed against epitopes expressed on the α-chain of FcεRI or, less commonly, against IgE itself, in a subset of patients with CIU [CIU with autoantibodies (CIU Ab)] is generally acknowledged.^{1–5} Indeed, the presence of autoantibodies may make a subset of

CIU 'idiopathic' no longer, although we still do not know why some patients produce these autoantibodies.

The pie chart in Figure 1 illustrates the prevalence of autoantibodies in 78 patients with CIU. Of these, 26% had

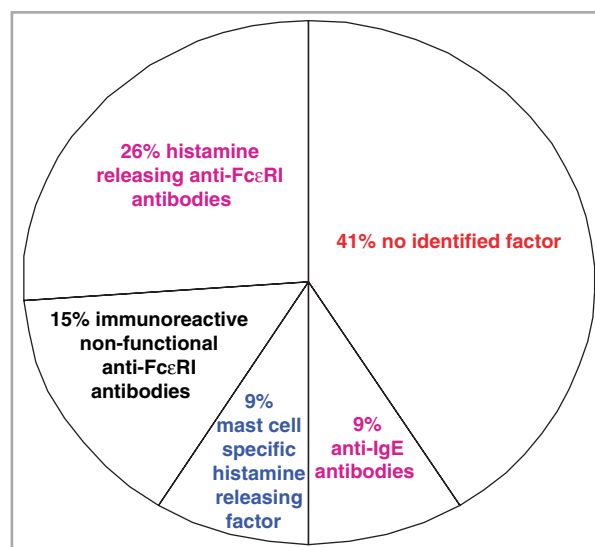


Fig 1. Pie chart showing the prevalence of autoantibodies in 78 patients with chronic idiopathic urticaria.⁹

histamine-releasing anti-FcεRI autoantibodies and 9% had anti-IgE autoantibodies.⁹ A recent study in children with CIU suggests a similar incidence.¹⁰ Patients with autoantibodies generally have more severe disease, and although H1 antihistamines have an important role in treatment, dosages above those licensed may be required and immunomodulatory treatment may be needed in selected cases.^{11,12}

However, there are several unsolved and challenging problems relating to the pathogenesis, investigation and management of CIU and the more important of these will be addressed briefly here.

Almost 50% of patients with chronic idiopathic urticaria have no detectable autoantibodies

Urticaria is mainly caused by dermal mast cell degranulation. The clinical and histological appearances of lesional skin in CIU are similar to those found in a late phase reaction.¹³ This would suggest the involvement of cytokines, chemokines and lipid mediators derived from mast cells, basophils and other incoming cells in the pathogenesis of weal formation and maintenance. In contrast, itching, the dominant symptom of urticaria, is likely to be due predominantly to mast cell- or basophil-derived histamine. This may explain the greater efficacy of H1 antihistamines in the suppression of itch than in the suppression of weal formation in urticaria. Any proposed mechanism has to account for these key pathological changes.

It is conceivable that autoantibodies against the high affinity IgE receptor occur in most or even all cases of CIU, but that our methods of detection lack the sensitivity necessary to identify them in at least 50% of patients. However, increasing the sensitivity of the *in vitro* basophil histamine release assay using interleukin (IL)-3 does not increase the proportion of positive sera – it does not convert negative into positive sera.¹⁴ Substituting human dermal mast cells for basophils has not, in our hands, resulted in increased serum positivity,⁹ although Asero *et al.*¹⁵ found that human dermal mast cells were more sensitive than human basophils.

The possibility that other circulating mediators besides autoantibodies might be causative in some patients also needs consideration. We previously reported that sera of about 5–10% of patients caused histamine release from dermal mast cells but not basophils (Fig. 1).^{9,16} This mast cell-specific >30-kDa histamine releasing factor, which was not an IgG, has been only partially characterized.¹⁷ Another candidate pathogenic factor might be histamine releasing factor, a cytokine produced by peripheral blood mononuclear cells, which enhances basophil histamine release, and modulates secretion of cytokines from human basophils, eosinophils and T cells.^{18–20}

That the primary abnormality in some patients with CIU might be cellular or subcellular rather than humoral also needs to be viewed. In this regard a recent report of aberrant regulation of the p21 Ras pathway in peripheral blood mononuclear cells of patients with CIU is of interest.²¹ The abnormalities were only present in patients with autoantibodies as indicated by a positive autologous serum skin test, and similar abnor-

malities were also found in type I diabetes mellitus and systemic lupus erythematosus. Therefore the authors concluded that these findings supported the proposed autoimmune basis of CIU Ab.

Immunoreactive but nonfunctional anti-FcεRI autoantibodies occur in some patients with chronic idiopathic urticaria, and also in patients with other diseases and healthy subjects

Nonfunctional anti-FcεRI autoantibodies have been detected by Western blot analysis or enzyme-linked immunosorbent assay in the serum of patients with a variety of autoimmune diseases such as dermatomyositis and pemphigus vulgaris, in a small proportion of patients with physical urticarias, as well as in patients with CIU.²² However, apart from being non-histamine releasing, such antibodies are predominantly of subtypes IgG2 and IgG4 in contrast to CIU Ab in which the histamine releasing autoantibody subtypes are predominantly IgG1 and IgG3.²² What it is about these anti-FcεRI autoantibodies which renders them inactive is unclear. Inability to activate complement may be important.^{23,24} Alternatively, epitopes exposed on the recombinant FcεRI used in immunoassays may not be available on *in vivo* receptors. Another interesting possibility is that these antibodies may coaggregate adjacent high affinity FcεRI and inhibitory low affinity FcγRII receptors leading to suppression of activation of mast cells and basophils.²⁵ However, antibodies of this specificity and action, although constructed in the laboratory, have yet to be demonstrated to occur naturally.

Horn *et al.*²⁶ have reported natural antibodies against FcεRIα in sera from healthy persons, and in multidonor intravenous immunoglobulin preparations. These natural antibodies may show histamine releasing activity provided target basophils have been incubated with IL-3 and have been lactic acid stripped to remove all IgE. Of interest, these autoantibodies were reported to be cross-reactive with tetanus toxoid, suggesting they might be a consequence of immunization. However, Kaplan⁵ was unable to absorb out anti-FcεRIα antibodies from positive sera or reduce histamine releasing activity using tetanus toxoid. These natural antibodies have only been identified by one group, and are as yet unexplained.

Is chronic idiopathic urticaria with functional anti-FcεRI or anti-IgE autoantibodies an autoimmune disease?

Rose and Bona²⁷ redefined the criteria for a disease to be categorized as autoimmune in 1993. Points in favour for CIU Ab include reproducibility of the autologous serum skin test through passive transfer of serum of affected patients into skin of healthy individuals;²⁸ correlation of functional autoantibody plasma levels with disease severity;²⁹ and disease remission following removal or suppression of the antibody.^{11,29}

Detection of autoantibodies provides only indirect proof of an autoimmune aetiology. However, apart from their ability

to release histamine from basophils and mast cells, there is other evidence to support the functionality of the autoantibodies detected in CIU. Although α -subunit epitope mapping has yet to be reported, reactivity of anti-Fc ϵ RI autoantibodies with the α -chain has been confirmed by inhibition studies utilizing recombinant α -chain. That more than one antigenic site is involved is suggested by the ability of lactic acid stripping, which removes IgE from donor basophils, to enhance binding by Fc ϵ RI autoantibodies from some but not all patients, this effect being reversed by subsequent saturation of basophils by IgE. These studies indicate that about 30% of the autoantibodies combine with epitope(s) located at the IgE binding site, the remainder reacting with epitopes elsewhere on the α -chain as basophil activation in these was unaffected by the presence or absence of IgE.^{1,9}

There is also circumstantial evidence to support an autoimmune basis to CIU, at least in the proportion of patients with autoantibodies. Firstly, there is the finding that HLA subtypes DRB1*04 (DR4) and DQB1*0302 (DQ8) are strongly associated with the subset of patients with autoantibodies.³⁰

Secondly, the association of CIU with autoimmune thyroid disease has long been recognized and a 'syndrome' of autoimmune thyroid disease and CIU proposed.⁶ Of 182 patients with CIU 36 were found to have thyroid microsomal autoantibodies and/or an abnormal plasma thyroid stimulating hormone level and there was marked cosegregation of these patients with those with a positive autologous serum skin test indicative of CIU Ab.³¹ Although these thyroid antibodies appear not to be pathogenic³² and most of these patients are euthyroid, L-thyroxine treatment has been claimed to be effective in suppressing urticaria in parallel with a decrease in antithyroid autoantibodies.³³

Thirdly, it was shown in the early 1970s that basophil histamine release was reduced in response to stimuli acting via IgE in patients with CIU. It has since been shown that this reduction in basophil releasability is most marked in patients with CIU Ab.³⁴ Basophils circulating in peripheral blood are exposed to autoantibodies and so this effect could be a consequence of desensitization of the Fc ϵ RI pathway.

However, the establishment of a disease as autoimmune in origin ideally requires construction of an animal model²⁷ and this has yet to be done in the case of CIU Ab.

The evidence summarized above, although incomplete, is in our view sufficiently persuasive that these functional autoantibodies are also pathogenic.

Does the presence of autoantibodies make any difference to individual patients?

A typical patient with CIU characteristically seeks advice from multiple professional sources, resulting in a file of unhelpful but expensive investigations and a trail of failed treatments. Demonstration of functional autoantibodies offers the patient a rational explanation for an unremitting, puzzling, distressing and sometimes frightening constellation of symptoms and signs.

In a small number of severely affected patients, making a diagnosis of CIU Ab also opens up the prospect of effective treatment by immunomodulatory therapies. These are reserved for patients with significant impairment of quality of life^{35–37} who have been poorly responsive to conventional measures. The effectiveness of ciclosporin in these patients has been confirmed in a randomized double-blind study.¹² The beneficial effects of intravenous immunoglobulin and plasmapheresis are supported by small open studies.^{11,29}

How are patients with chronic idiopathic urticaria with autoantibodies detected?

In vivo tests

Careful clinical and histological studies have failed to reveal diagnostically useful features which might help to distinguish between patients with CIU with and without autoantibodies.^{38,39} Accordingly, recourse has had to be made to using the autologous serum skin test as a screening test for CIU Ab.^{40,41} Briefly, 0.05 mL of serum obtained from the patient during a period of disease activity is injected intradermally into uninvolved skin of the flexor surface of the forearm (Fig. 2). Control intradermal injections of saline and histamine 10 μ g mL⁻¹ are made in adjacent sites. A positive response, read at 30 min, consists of a red weal of at least 1.5 mm greater in diameter than the saline-induced weal.⁴¹ Histological studies of positive autologous serum skin tests⁴² have reported a close resemblance to IgE-mediated late phase reactions. The sensitivity and specificity of this test for the detection of patients with CIU Ab is at best about 80% in each case, using the *in vitro* basophil histamine release assay as the verum. However, practice is needed for reproducibility, the test is time-consuming to perform, and results should be confirmed by *in vitro* testing using a functional assay. Test positivity has also been found to correlate with duration of attacks of CIU⁴³ and with disease severity,⁴⁴ although in the latter study the test was persistent in some patients even when the disease had gone into remission. Of interest, positive autologous serum skin test reactivity has been reported to correlate strongly with patients who have multiple intolerances to non-steroidal anti-inflammatory drugs,^{45–47} and in some cases may be related to the presence of *Helicobacter pylori* IgG antibodies.^{48,49} The relationship between *H. pylori* and CIU has been reviewed.⁵⁰

Confirmatory *in vitro* tests

As already indicated, immunoreactive but non-histamine releasing anti-Fc ϵ RI autoantibodies are detectable in sera from some patients with autoimmune connective tissue diseases and in a small proportion of patients with other types of urticaria. Therefore immunoassays for CIU Ab have been largely abandoned due to poor specificity. Instead, at present the most useful⁵¹ *in vitro* method for the diagnosis of CIU Ab is the demonstration of release of histamine (or other reactant) from



Fig 2. A positive autologous serum skin test.

target basophils or dermal mast cells. The human donor basophils used should be both lactic acid stripped to remove IgE for the detection of anti-FcεRI autoantibodies, and IgE sensitized for the detection of anti-IgE autoantibodies present in the serum of a minority of patients with CIU Ab. The assay can be made more sensitive by including IL-3 in the incubation medium.¹⁴ Dermal mast cells are usually obtained from fore-skin removed during circumcision.¹⁶ Some authors¹⁵ believe dermal mast cells are preferable to human basophils. Cells harvested from a rat basophil leukaemia cell line can also be used,³ beta-hexosaminidase being measured as an index of cell activation. Several laboratories now offer the basophil histamine release assay as a commercial service, and as IgG anti-FcεRI and anti-IgE autoantibodies are stable at room temperature, serum samples can be sent by post.

However, more convenient sensitive and specific screening methods for CIU Ab would be welcome and various approaches are currently being explored.

Potential future tests

That basopenia is a feature of CIU has long been recognized.⁵² Sabroe *et al.*³⁴ reported the near absence of circulating basophils in patients with autoantibodies, values in autoantibody-negative patients being nearer to normal. Histological studies of weals suggest that one reason for these low values may be sequestration of basophils within effected skin.^{13,53} Enumeration of blood basophils, possibly by an automated method,⁵⁴ might form the basis of a screening test for CIU Ab.

Recently an alternative screening test has been proposed based upon the observation that sera from autologous serum skin test-positive patients with CIU, when incubated with basophils from an atopic donor, cause CD63 expression on the target basophils.⁵⁵ Similarly, donor basophil CD203c expression appears to correlate with autologous serum skin test positivity.⁵⁶ Expression of these basophil activation markers can be detected using flow cytometry. This may be developed as a screening test for CIU Ab, but as yet still requires validation against the basophil histamine release assay.

Treatment of chronic idiopathic urticaria with autoantibodies

The treatment of CIU has recently been reviewed.^{4,57} After making the diagnosis of CIU,^{58,59} patients with CIU Ab should initially be treated in the same way as those without autoantibodies. This includes the use of low-sedation H1 antihistamines in licensed dosages. It is important to determine the periods of the day or night in which the patient is maximally symptomatic in order to fine-tune antihistamine therapy to the patient's individual requirements. Most patients experience maximum pruritus at night-time,³⁸ so a sedating antihistamine such as hydroxyzine 10–25 mg at night can be useful. However, the patient should be warned about impairment of cognitive function the following day even though there may be no overt symptoms of sedation. Drug therapy should always be accompanied by life-style advice, including avoidance of overtiredness, alcohol, drugs such as nonsteroidal anti-inflammatory drugs, and tight clothing. All too frequently patients fail to respond adequately to these measures. In this event dosages of low-sedation antihistamines above those licensed could be tried, e.g. fexofenadine 360 mg daily, a dosage which does not cause sedation.⁶⁰ Doxepin 10–30 mg can be used instead of night-time hydroxyzine. Doxepin, which is a powerful H1 antihistamine (775 times the affinity for the H1 receptor than diphenhydramine), in addition to its better known antidepressant actions, can be used cautiously even in the elderly. It is safe and effective, even in mild to moderate renal impairment, provided it is not withdrawn abruptly,⁶¹ and that it is not given in the presence of uncontrolled thyroid disease. It is metabolized via P450 and can prolong the QTc interval, so care should be taken when prescribing doxepin with other drugs. Early enthusiasm about the value of montelukast, a leukotriene antagonist, in chronic urticaria⁶² has not been born out by subsequent studies,⁶³ although it may be of

benefit in a small number of patients. Similarly, the use of H2 antagonists is only rarely helpful.

It is not uncommon to find patients to be well controlled most of the time by these measures, punctuated by occasional distressing flares due very often to personal, occupational or economic factors, or other previously described exacerbants.⁵⁷ These relapses are best controlled by brief courses of oral steroids. Prednisolone 30 mg daily for 5 days followed by tapering over 5–6 days is usually effective, after which the patient can continue regular antihistamines.

A minority of patients is unresponsive to these measures. Selected patients with a severely impaired quality of life, in whom more conservative measures have proved wanting, should be considered for immunomodulatory treatment.

Oral ciclosporin has been proven effective in a double-blind placebo-controlled trial in patients with autoantibodies detected by *in vivo* autologous serum skin tests,¹² and it has also been shown to be of benefit in patients both with and without autoantibodies in uncontrolled studies.^{64,65} Of interest, ciclosporin has also been shown to inhibit histamine release from basophils triggered *in vitro* by sera from patients with CIU known to have anti-FcεRI autoantibodies.⁶⁶ Given in dosages of 2.5–5 mg kg⁻¹ daily ciclosporin relieves pruritus within a few days, and is effective in suppressing weal formation in most patients. It is usually given for up to 3–4 months in the first instance in addition to antihistamine treatment as previously described. On withdrawing ciclosporin about one-third of patients remain in remission and one-third relapse but can readily be controlled by antihistamines in conventional dosage. In the remaining one-third, relapse of symptoms may prompt recontinuation of treatment (M.W. Greaves, unpublished data). In all patients prescription of this immunosuppressive is predicated on the assumption that renal function, serum lipids and blood pressure are satisfactory and these should be monitored throughout treatment. Patients with a history of cancer or precancerous conditions are unsuitable for this treatment. Other immunosuppressive measures which can be considered, and which have been shown to be helpful in small studies or case reports, include tacrolimus, intravenous immunoglobulin (0.4 g kg⁻¹ daily for 5 days), plasmapheresis, methotrexate and hydroxychloroquine.^{11,29,67–69} Most of the publications cited relate to patients with autoantibodies; however, the two cases reported as responding to methotrexate did not have autoantibodies, and there was no difference in the response to hydroxychloroquine between patients with positive or negative autologous serum prick tests. To date there have been very few publications comparing these treatments in patients with and without autoantibodies. A treatment flow chart summarizing the above is illustrated in Figure 3.

Conclusions

On current evidence the pathogenic role of anti-FcεRI and anti-IgE autoantibodies in CIU is probable, but several problems remain unsolved. CIU Ab fits many, but not all, of the

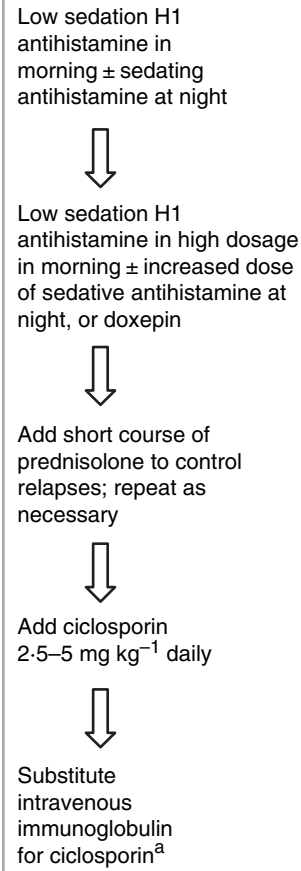


Fig 3. Suggested treatment stages for chronic idiopathic urticaria with autoantibodies. ^aOther immunomodulators which could be tried include methotrexate, systemic tacrolimus, or plasmapheresis.

criteria for autoimmune disease, but the pathogenic factor in patients without autoantibodies remains a mystery. Additionally, the detection of patients with autoantibodies remains a major stumbling block. The autologous serum skin test is characterized by moderate sensitivity and specificity, but it is an indicator of the presence of circulating vasoactive factors and not specifically autoantibodies. Functional *in vitro* tests suffer from variability between donor basophils or mast cells, and immunoassays detect autoantibodies which may or may not be functional, and so are less specific, and neither is readily available to the clinician. The development of reliable and easily accessible *in vitro* tests is badly needed. Finally, although theoretically patients with autoantibodies may respond better to immunomodulatory treatments, or to the removal of autoantibodies by plasmapheresis, there are as yet few comparative trials of these treatment modalities in patients with and without autoantibodies.

References

- 1 Hide M, Francis DM, Grattan CEH *et al*. Autoantibodies against the high-affinity IgE receptor as a cause of histamine release in chronic urticaria. *N Engl J Med* 1993; **328**:1599–604.

- 2 Fiebiger E, Maurer D, Holub H et al. Serum IgG autoantibodies directed against the α chain of Fc ϵ RI: a selective marker and pathogenetic factor for a distinct subset of chronic urticaria patients? *J Clin Invest* 1995; **96**:2606–12.
- 3 Tong LJ, Balakrishnan G, Kochan JP et al. Assessment of autoimmunity in patients with chronic urticaria. *J Allergy Clin Immunol* 1997; **99**:461–5.
- 4 Greaves MW. Chronic idiopathic urticaria. *Curr Opin Allergy Clin Immunol* 2003; **3**:363–8.
- 5 Kaplan AP. Chronic urticaria: pathogenesis and treatment. *J Allergy Clin Immunol* 2004; **114**:465–74.
- 6 Leznoff A, Josse RG, Denburg J et al. Association of chronic urticaria and angioedema with thyroid autoimmunity. *Arch Dermatol* 1983; **119**:636–40.
- 7 Gruber BL, Baeza ML, Marchese MJ et al. Prevalence and functional role of anti-IgE autoantibodies in urticarial syndromes. *J Invest Dermatol* 1988; **90**:213–17.
- 8 Grattan CEH, Francis DM, Hide M et al. Detection of circulating histamine releasing autoantibodies with functional properties of anti-IgE in chronic urticaria. *Clin Exp Allergy* 1991; **21**:695–704.
- 9 Sabroe RA, Fiebiger E, Francis DM et al. Classification of anti-Fc ϵ epsilonRI and anti-IgE autoantibodies in chronic idiopathic urticaria and correlation with disease severity. *J Allergy Clin Immunol* 2002; **110**:492–9.
- 10 Brunetti L, Francavilla R, Miniello VL et al. High prevalence of autoimmune urticaria in children with chronic urticaria. *J Allergy Clin Immunol* 2004; **114**:922–7.
- 11 O'Donnell BF, Barr RM, Kobza Black A et al. Intravenous immunoglobulin in autoimmune chronic urticaria. *Br J Dermatol* 1998; **138**:101–6.
- 12 Grattan CEH, O'Donnell BF, Francis DM et al. Randomized double-blind study of cyclosporin in chronic idiopathic urticaria. *Br J Dermatol* 2000; **143**:365–72.
- 13 Ying S, Kikuchi Y, Meng Q et al. TH1/TH2 cytokines and inflammatory cells in skin biopsy specimens from patients with chronic idiopathic urticaria: comparison with the allergen-induced late-phase cutaneous reaction. *J Allergy Clin Immunol* 2002; **109**:694–700.
- 14 Ferrer M, Luquin E, Kaplan AP. IL3 effect on basophils histamine release upon stimulation with chronic urticaria sera. *Allergy* 2003; **58**:802–7.
- 15 Asero R, Lorini M, Chong SU et al. Assessment of histamine-releasing activity of sera from patients with chronic urticaria showing positive autologous skin test on human basophils and mast cells. *Clin Exp Allergy* 2004; **34**:1111–14.
- 16 Niimi N, Francis DM, Kermani F et al. Dermal mast cell activation by autoantibodies against the high affinity IgE receptor in chronic urticaria. *J Invest Dermatol* 1996; **106**:1001–6.
- 17 Kermani F, Niimi N, Francis DM et al. Characterization of a novel mast cell-specific histamine releasing activity in chronic idiopathic urticaria (CIU). *J Invest Dermatol* 1995; **105**:452 (Abstract).
- 18 MacDonald SM, Rafnar T, Langdon J et al. Molecular identification of an IgE-dependent histamine-releasing factor. *Science* 1995; **269**:688–90.
- 19 Claveau J, Lavoie A, Brunet C et al. Chronic idiopathic urticaria: possible contribution of histamine-releasing factor to pathogenesis. *J Allergy Clin Immunol* 1993; **92**:132–7.
- 20 Vonakis BM, Sora R, Langdon JM et al. Inhibition of cytokine gene transcription by the human recombinant histamine-releasing factor in human T lymphocytes. *J Immunol* 2003; **171**:3742–50.
- 21 Confino-Cohen R, Aharoni D, Goldberg A 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.
- 22 Fiebiger E, Hammerschmid F, Stingl G et al. Anti-Fc ϵ RI α autoantibodies in autoimmune-mediated disorders. Identification of a structure–function relationship. *J Clin Invest* 1998; **101**:243–51.
- 23 Soundararajan S, Kikuchi Y, Joseph K et al. Functional assessment of pathogenic IgG subclasses in chronic autoimmune urticaria. *J Allergy Clin Immunol* 2005; **115**:815–21.
- 24 Ferrer M, Nakazawa K, Kaplan AP. Complement dependence of histamine release in chronic urticaria. *J Allergy Clin Immunol* 1999; **104**:169–72.
- 25 Tam SW, Demissie S, Thomas D et al. A bispecific antibody against human IgE and human Fc γ gammaRII that inhibits antigen-induced histamine release by human mast cells and basophils. *Allergy* 2004; **59**:772–80.
- 26 Horn MP, Pachlopnik JM, Vogel M et al. Conditional autoimmunity mediated by human natural anti-Fc(epsilon)RIalpha autoantibodies? *FASEB J* 2001; **15**:2268–74.
- 27 Rose NR, Bona C. Defining criteria for autoimmune diseases (Witebsky's postulates revisited). *Immunol Today* 1993; **14**:426–30.
- 28 Grattan CEH, Francis DM. Autoimmune urticaria. *Adv Dermatol* 1999; **15**:311–40.
- 29 Grattan CEH, Francis DM, Slater NGP et al. Plasmapheresis for severe, unremitting, chronic urticaria. *Lancet* 1992; **339**:1078–80.
- 30 O'Donnell BF, O'Neill CM, Francis DM et al. Human leucocyte antigen class II associations in chronic idiopathic urticaria. *Br J Dermatol* 1999; **140**:853–8.
- 31 O'Donnell BF, Francis DM, Swana GT et al. Thyroid autoimmunity in chronic urticaria. *Br J Dermatol* 2005; **153**:331–5.
- 32 Tedeschi A, Lorini M, Asero R. Anti-thyroid peroxidase IgE in patients with chronic urticaria. *J Allergy Clin Immunol* 2001; **108**:467–8.
- 33 Aversano M, Caiazzo P, Iorio G et al. Improvement of chronic idiopathic urticaria with L-thyroxine: a new TSH role in immune response? *Allergy* 2005; **60**:489–93.
- 34 Sabroe RA, Francis DM, Barr RM et al. Anti-Fc ϵ RI autoantibodies and basophil histamine releasability in chronic idiopathic urticaria. *J Allergy Clin Immunol* 1998; **102**:651–8.
- 35 O'Donnell BF, Lawlor F, Simpson J et al. The impact of chronic urticaria on the quality of life. *Br J Dermatol* 1997; **136**:197–201.
- 36 Poon E, Seed PT, Greaves MW et al. The extent and nature of disability in different urticarial conditions. *Br J Dermatol* 1999; **140**:667–71.
- 37 Grob JJ, Revuz J, Ortonne JP et al. Comparative study of the impact of chronic urticaria, psoriasis and atopic dermatitis on the quality of life. *Br J Dermatol* 2005; **152**:289–95.
- 38 Sabroe RA, Seed PT, Francis DM et al. Chronic idiopathic urticaria: comparison of the clinical features of patients with and without anti-Fc ϵ RI or anti-IgE autoantibodies. *J Am Acad Dermatol* 1999; **40**:443–50.
- 39 Sabroe RA, Poon E, Orchard GE et al. Cutaneous inflammatory cell infiltrate in chronic idiopathic urticaria: comparison of patients with and without anti-Fc ϵ RI or anti-IgE autoantibodies. *J Allergy Clin Immunol* 1999; **103**:484–93.
- 40 Grattan CEH, Wallington TB, Warin RP et al. A serological mediator in chronic idiopathic urticaria – a clinical, immunological and histological evaluation. *Br J Dermatol* 1986; **114**:583–90.
- 41 Sabroe RA, Grattan CEH, Francis DM et al. The autologous serum skin test: a screening test for autoantibodies in chronic idiopathic urticaria. *Br J Dermatol* 1999; **140**:446–52.
- 42 Grattan CEH, Boon AP, Eady RAJ et al. The pathology of the autologous serum skin test response in chronic urticaria resembles IgE-mediated late-phase reactions. *Int Arch Allergy Appl Immunol* 1990; **93**:198–204.

- 43 Toubi E, Kessel A, Avshovich N et al. Clinical and laboratory parameters in predicting chronic urticaria duration: a prospective study of 139 patients. *Allergy* 2004; **59**:869–73.
- 44 Fusari A, Colangelo C, Bonifazi F et al. The autologous serum skin test in the follow-up of patients with chronic urticaria. *Allergy* 2005; **60**:256–8.
- 45 Asero R, Tedeschi A, Lorini M. Autoreactivity is highly prevalent in patients with multiple intolerances to NSAIDs. *Ann Allergy Asthma Immunol* 2002; **88**:468–72.
- 46 Erbagci Z. Multiple NSAID intolerance in chronic idiopathic urticaria is correlated with delayed, pronounced and prolonged autoreactivity. *J Dermatol* 2004; **31**:376–82.
- 47 Asero R, Tedeschi A, Lorini M et al. Sera from patients with multiple drug allergy syndrome contain circulating histamine-releasing factors. *Int Arch Allergy Immunol* 2003; **131**:195–200.
- 48 Hizal M, Tuzun B, Wolf R et al. The relationship between *Helicobacter pylori* IgG antibody and autologous serum test in chronic urticaria. *Int J Dermatol* 2000; **39**:443–5.
- 49 Bakos N, Hillander M. Comparison of chronic autoimmune urticaria with chronic idiopathic urticaria. *Int J Dermatol* 2003; **42**:613–15.
- 50 Greaves MW. Chronic idiopathic urticaria (CIU) and *Helicobacter pylori* – not directly causative, but could there be a link? *ACI International* 2001; **13**:23–6.
- 51 Kikuchi Y, Kaplan AP. Mechanisms of autoimmune activation of basophils in chronic urticaria. *J Allergy Clin Immunol* 2001; **107**:1056–62.
- 52 Rorsman H. Basophilic leucopenia in different forms of urticaria. *Acta Allergologica* 1962; **XVII**:168–84.
- 53 Hoskin SL, Wilson SJ, Sabroe RA et al. Basophil infiltration of weals in chronic idiopathic urticaria. *J Allergy Clin Immunol* 2002; **109**:A229.
- 54 Grattan CEH, Dawn G, Gibbs S et al. Blood basophil numbers in chronic ordinary urticaria and healthy controls: diurnal variation, influence of loratadine and prednisolone and relationship to disease activity. *Clin Exp Allergy* 2003; **33**:337–41.
- 55 Gyimesi E, Sipka S, Danko K et al. Basophil CD63 expression assay on highly sensitized atopic donor leucocytes – a useful method in chronic autoimmune urticaria. *Br J Dermatol* 2004; **151**:388–96.
- 56 Yasnowsky KM, Schoen DJ, Vedanthan PK et al. Chronic urticaria sera increase basophil CD203c surface expression. *J Allergy Clin Immunol* 2005; **115**:S179 (Abstract).
- 57 Kozel MM, Sabroe RA. Chronic urticaria: aetiology, management and current and future treatment options. *Drugs* 2004; **64**:2515–36.
- 58 Bindeslev-Jensen C, Finzi A, Greaves MW et al. Chronic urticaria: diagnostic recommendations. *J Eur Acad Dermatol Venereol* 2000; **14**:175–80.
- 59 Zuberbier T, Greaves MW, Juhlin L et al. Definition, classification, and routine diagnosis of urticaria: a consensus report. *J Invest Dermatol Symp Proc* 2001; **6**:123–7.
- 60 Vermeeren A, O'Hanlon JF. Fexofenadine's effects, alone and with alcohol, on actual driving and psychomotor performance. *J Allergy Clin Immunol* 1998; **101**:306–11.
- 61 Goldsobel AB, Rohr AS, Siegel SC et al. Efficacy of doxepin in the treatment of chronic idiopathic urticaria. *J Allergy Clin Immunol* 1986; **78**:867–73.
- 62 Erbagci Z. The leukotriene receptor antagonist montelukast in the treatment of chronic idiopathic urticaria: a single-blind, placebo-controlled, crossover clinical study. *J Allergy Clin Immunol* 2002; **110**:484–8.
- 63 Di Lorenzo G, Pacor ML, Mansueto P et al. Randomized placebo-controlled trial comparing desloratadine and montelukast in monotherapy and desloratadine plus montelukast in combined therapy for chronic idiopathic urticaria. *J Allergy Clin Immunol* 2004; **114**:619–25.
- 64 Barlow RJ, Kobza Black A, Greaves MW. Treatment of severe, chronic urticaria with cyclosporin A. *Eur J Dermatol* 1993; **3**:273–5.
- 65 Toubi E, Blant A, Kessel A, Golan TD. Low-dose cyclosporin A in the treatment of severe chronic idiopathic urticaria. *Allergy* 1997; **52**:312–16.
- 66 Marsland AM, Soundararajan S, Joseph K et al. Effects of calcineurin inhibitors on an in vitro assay for chronic urticaria. *Clin Exp Allergy* 2005; **35**:554–9.
- 67 Kessel A, Bamberger E, Toubi E. Tacrolimus in the treatment of severe chronic idiopathic urticaria: an open-label prospective study. *J Am Acad Dermatol* 2005; **52**:145–8.
- 68 Gach JE, Sabroe RA, Greaves MW et al. Methotrexate-responsive chronic idiopathic urticaria: a report of two cases. *Br J Dermatol* 2001; **145**:340–3.
- 69 Reeves GE, Boyle MJ, Bonfield J et al. Impact of hydroxychloroquine therapy on chronic urticaria: chronic autoimmune urticaria study and evaluation. *Intern Med J* 2004; **34**:182–6.