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Chronic Urticaria

Aetiology, Management and Current and Future Treatment Options

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Abstract

Chronic urticaria is a common condition that can be very disabling when severe. A cause for chronic idiopathic urticaria (CIU) is only infrequently identified. Potential causes include reactions to food and drugs, infections (rarely) and, apart from an increased incidence of thyroid disease, uncomplicated urticaria is not usually associated with underlying systemic disease or malignancy. About one-third of patients with CIU have circulating functional autoantibodies against the high affinity IgE receptor or against IgE, although it is not known why such antibodies are produced, or how the presence of such antibodies alters the course of the disease or response to treatment. There are only a few publications relating to childhood urticaria, but it is probably similar to the adult form, except that adult urticaria is more common.

The diagnosis is based on patient history and it is vital to spend time documenting this in detail. Extensive laboratory tests are not required in the vast majority of patients. Chronic urticaria resolves spontaneously in 30–55% of patients within 5 years, but it can persist for many years.

Treatment is aimed firstly at avoiding underlying causative or exacerbating factors. Histamine H_1 receptor antagonists remain the mainstay of oral treatment for all forms of urticaria. The newer low-sedating antihistamines desloratadine, fexofenadine, levocetirizine and mizolastine should be tried first. Sedating antihistamines have more adverse effects but are useful if symptoms are causing sleep disturbance. Low-dose dopexin is effective and especially suitable for patients with associated depression. There is controversy as to whether the addition of an histamine H_2 receptor antagonist or a leukotriene antagonist is helpful. For CIU, second-line agents include ciclosporin (cyclosporine) [which is effective in approximately 75% of patients], short courses of oral corticosteroids, intravenous immunoglobulins and plasmapheresis, although the last two were found to be beneficial in small trials only. Treatments for CIU with only limited or anecdotal supportive evidence include sulphasalazine, methotrexate, stanazol, rofecoxib and cyclophosphamide. The efficacy of photo(chemo)therapy is controversial.

Physical urticarias may respond to H_1 receptor antagonists, although in delayed pressure urticaria, and cold, solar and aquagenic urticaria, the response may be disappointing. Second-line agents for physical urticarias vary depending on the urticaria and most have limited supportive evidence.

The potential for spontaneous resolution, the variation in the disease activity and the unpredictable nature of the disease makes the efficacy of treatments difficult to assess.

Urticaria consists of recurrent wheals, which are usually itchy. Wheals are transient, and in most types of urticaria they last for less than 24 hours. Angioedema (angioneurotic oedema, giant oedema, Quinke's oedema) consists of swellings of the deep dermis and subcutaneous or submucosal tissues, which last for 24–72 hours. Angioedema may occur alone, but occurs often in patients with urticaria. Hereditary angioedema, contact urticaria and urticarial vasculitis are not included in this article.

1. Classification of Urticaria

Urticaria is usually classified as acute or chronic, depending on whether wheals occur repeatedly for less or more than 6 weeks, respectively.[1] Different types of urticaria can occur in the same patient.

Acute urticaria is idiopathic in >50% of patients, but can occur as a type I hypersensitivity reaction to food, wasp or bee stings, as an immunological response to blood products, infection or febrile illness, or as an adverse effect of drug therapy by various mechanisms, such as penicillin (probably type I hypersensitivity reaction), opiates and NSAIDs (here the mechanism is unclear, urticaria may result from direct mediator release from mast cells, but the drugs have also been described as 'pseudoallergens'[1]) and ACE inhibitors.[2]

Chronic urticaria can be physical or idiopathic. The physical urticarias are precipitated by specific physical stimuli, and include dermographism, cholinergic urticaria, delayed pressure urticaria, cold urticaria, solar urticaria, localised heat urticaria and vibration urticaria (see section 3.1).[1,3] Chronic idiopathic urticaria (CIU) is defined as the daily or almost daily occurrence of wheals for ≥6 weeks, where a predominant physical urticaria and urticarial vasculitis have been excluded. It has been shown that about one-third of patients with CIU have circulating functional autoantibodies to either the high affinity IgE receptor (FcεRI) or to IgE[4-8] (see section 3.8). In some patients, CIU is exacerbated by components of food, such as salicylates, benzoates, nitrites, etc., although the mechanism is unclear.[1]

2. Epidemiology

Urticaria and angioedema are common disorders, and 12–22% of the population are likely to have urticaria or angioedema at least once in their lifetime.[9-11] However, lower values of the prevalence of urticaria (<1%) were obtained from field studies of the general population,[12] prevalence values between 0.27% and 2.1% were calculated in family practices[12,13] and between 1% and 4% were found in patients consulting dermatological outpatient departments, whereas prevalence values >10% were identified in preselected patients in allergy or dermatology clinics.[12] The distribution of gender varies between different studies and in different types of urticaria, but there is generally a higher proportion of females, with 31–53% of patients being male.[12]

Acute urticaria is much more common than chronic urticaria, and indeed in 70% of the 79 patients who were seen in a university family practice centre between 1976 and 1983 the urticaria lasted for <6 weeks.[13]

3. Causes of Urticaria

It is often not possible to identify a cause for urticaria or angioedema. A causative factor is most commonly identified in acute cases, but even then in <50% of patients.

3.1 Physical Urticarias

In physical uricarias, specific physical stimuli reproducibly elicit wheals. Apart from delayed pressure urticaria, wheals usually occur within 15 minutes and last for <2 hours.[1,3] Physical urticarias were identified in 12–57% of patients with urticaria in different studies, each including 120–500 patients, performed between 1937 and 1985.[14] The incidence probably varied depending on the selected cohort and the referral pattern. In most cases it is not known why patients develop physical urticarias.

In dermographic urticaria the skin responds to stroking, friction, rubbing or scratching with rapidly appearing itchy, usually linear wheals. The prevalence of dermographism in the healthy population ranges from 1.4% to 5%.[15]

In delayed pressure urticaria swellings develop at sites of pressure against the skin. Delayed pressure urticaria differs from other physical urticarias in that wheals develop 30 minutes to 12 hours after the stimulus, may be tender or painful and may last for 24–72 hours.[15,16]

In patients with cholinergic urticaria, stimuli that raise the core temperature of the body, such as exercise, warmth, consuming spicy or hot food or drinks, or emotional stress, can elucidate 1–5mm pruritic pinpoint wheals on an erythematous base. In most patients wheals occur on the upper part of the

trunk and proximal limbs. This condition is usually mild, although angioedema can occur and exercise-induced anaphylaxis probably represents its extreme form. It is common and an overall prevalence of 11% was identified in high school and university students (15–35 years of age).[17]

In patients with cold urticaria, itching and wheals may occur after exposure to cold, especially a cold wind, cold rain or swimming in cold water. A few patients experience angioedema of the oral cavity and pharynx after consuming cold beverages or ice cream. Total body exposure to cold can cause generalised anaphylaxis, and drowning is a potential hazard for patients who swim in cold waters.[16] Patients with cold urticarias should inform their anaesthetist about their condition, especially if hypothermia is used during an operation. Ninety-six percent of the patients with cold urticaria have idiopathic cold urticaria.[18] Cold urticaria syndromes are rarely associated with underlying diseases, particularly those associated with cryoglobulins such as malignancies (especially lymphoma) or leukocytoclastic vasculitis, and infectious diseases.[19]

Solar urticaria can be provoked by UV light waves ranging between 280 and 760nm (UVB, UVA and visible light).[15] It is a rare condition. The differential diagnosis includes other photodermatoses such as polymorphous light eruption, photo-exacerbated diseases such as systemic lupus erythematosus (SLE) or porphyria, and drug-induced photoallergic reactions.[16] The hives are limited to the sun-exposed areas and are of variable size and shape.

Other rare forms of physical urticaria include aquagenic urticaria, which is precipitated by contact of the skin with water of any temperature, and localised heat urticaria, in which wheals occur on skin in direct contact with warm objects.

3.2 Adverse Drug Reactions

The antigenicity of a drug depends upon drug- and patient-specific factors, including the dose, duration, number of exposures, route of administration and chemical properties of a drug as well as the age, gender, atopy status and specific genetic polymorphisms of a patient. Drugs frequently responsible for urticaria and/or angioedema are antimicrobial agents (especially penicillin and sulphonamides), anti-inflammatory drugs and analgesics (aspirin [acetylsalicylic acid], NSAIDs, opiates), ACE inhibitors, blood products and blood substitutes.[20] Less commonly, urticaria and/or angioedema can be precipitated by anaesthetic muscle relaxants, sedatives and hypnotics, antiepileptic drugs, contraceptives, monoclonal antibodies and, very rarely, by antihistamines.[20] In a recent systematic review, including 3374 patients with chronic urticaria, an adverse drug reaction was the cause of urticaria in 148 patients (4.4%). In 59% (87 of 148 patients) analgesics were responsible.[21] This may make it difficult to recommend treatment for patients with urticaria who require analgesic agents. However, recent evidence would indicate that the cyclo-oxygenase (COX)-2 inhibitors, rofecoxib and celecoxib, appear to be relatively well tolerated in patients with a known adverse response to aspirin or NSAIDs.[22-24]

3.3 Adverse Food Reactions

The role of adverse food reactions is controversial. Reported frequencies range from 5% to 73%, probably depending on patient selection and variations in the method of detection (patient history, diet elimination, oral provocation, laboratory tests, double-blind placebo-controlled challenge).[25,26] The mechanisms involved in cutaneous adverse food reactions are IgE-mediated reactions (e.g. fish, crustaceans, nuts), reactions involving vasoactive amines (e.g. cheese, beer, wine) and pseudoallergic reactions (e.g. food additives, natural salicylates and benzoates in food).[27] In acute urticaria type I hypersensitivity (IgE-mediated) reactions are most commonly implicated, whereas in chronic urticaria other mechanisms are more likely to be involved.

3.4 Inhalants

Urticaria due to inhaled allergens is very rare. It can occur in sensitised patients, especially if exposed to aero-allergens in the workplace (e.g. flour, pharmaceutical or chemical industry, latex production or utilisation). However, the most common

clinical manifestations of an allergy to inhalants are asthma and rhinitis.[25]

3.5 Infections and Infestations

Bacterial infections are a very rare cause of urticaria.[28] More recently, infection with *Helicobacter pylori* has been suggested as a possible cause for chronic urticaria, but in most controlled prospective studies no relationship has been identified.[29-31] Viral infections, particularly upper respiratory tract infections in children, can precipitate an attack of acute urticaria or an exacerbation of chronic urticaria.[25] Hepatitis C virus has been associated with some cases of chronic urticaria in populations where the prevalence of hepatitis C infection is high, for example in Japan,[32] although the features of the rash that the investigators described in this study appeared to be more in keeping with urticarial vasculitis than with ordinary urticaria. No association between chronic urticaria and hepatitis C infection was found in France,[33] and at present there is no need for routine screening. The role of fungal infections, especially candida infections, is very controversial. Intestinal parasites are a very rare cause of urticaria in both developed and developing countries, and are mainly observed in patients travelling in or living in the (sub)tropics.

3.6 Internal Diseases

In the vast majority of patients with straightforward urticaria, no underlying internal disease will be found. However, we recently reviewed 29 studies describing 6462 patients with chronic urticaria and considerable differences in the incidence of identifiable underlying causative factors of any type (1–84%) were reported.[21] Some of the variation may relate to the proportion of different types of urticaria included, and on how each is defined. An internal disease was considered to be the cause in only 105 (1.6%) of patients. The following diseases were implicated: cutaneous vasculitis (60 patients), thyroid diseases (17 patients), SLE (seven patients), other connective tissue diseases (16 patients) and a paraproteinaemia (three patients).[21] There is also other evidence to support an association between CIU and thyroid disease.[34,35]

3.7 Malignancies

There is no evidence to support an association between malignancy and urticaria, except occasionally in urticarial vasculitis and, more frequently, in acquired C1 inhibitor deficiency. Therefore, an exhaustive search for underlying malignancy is not required in uncomplicated urticaria. In a large epidemiological study no association between chronic urticaria and malignancies was found.[36] Of 1155 patients with chronic urticaria, a malignancy was diagnosed in 36, whilst the expected number was 41. However, in the systematic review of 6462 patients, a relationship between malignancy and the onset of urticaria was described in ten patients: one each with acute myeloid leukaemia, breast cancer and renal cell carcinoma, four with polycythaemia rubra vera, and in two patients no tumour type was given.[21] However, acquired C1 inhibitor deficiency may be associated with lymphoproliferative disorders. In patients with such diseases a prevalence of 0.5% of symptomatic acquired C1 inhibitor deficiency, presenting as angioedema, was observed.[37]

3.8 Autoimmune Urticaria

The presence of circulating histamine-releasing factors was first indicated in patients with CIU by the observation that a wheal and flare response could occur after the intradermal injection of autologous serum.[38] This response can still be used to identify patients with such factors, and forms the basis of the autologous serum skin test.[39] Serum which could elicit an *in vivo* response was also found to release histamine from mast cells and basophils *in vitro*. Using histamine release assays, Western blot analysis and ELISA, these factors have been identified largely as circulating functional autoantibodies to either FcεRI or, less commonly, to IgE.[4-8] These autoantibodies are thought to occur in about one-third of patients with CIU. They have not been identified in patients with psoriasis, dermographism or cholinergic urticaria, or in healthy control subjects.[7,8,40] Anti-FcεRI autoantibodies have been

found in other autoimmune diseases, such as SLE or dermatomyositis, but autoantibodies in these other diseases do not release histamine from basophils or mast cells, and are of a different IgG isotype (mainly IgG2 and 4, rather than IgG1 and 3 complement-activating isotypes which are more commonly found in CIU).[8] Thus, functional autoantibodies appear to be specific to CIU. The finding that CIU has an autoimmune basis in some patients is supported by human lymphocyte antigen associations,[41] and the presence of autoimmune thyroid disease in some patients.[42,43] Using basophil histamine release assays to distinguish between patients with and without autoantibodies, patients with autoimmune CIU appeared to have rather more severe urticaria than those without, although the differences found were not great enough for them to be used to identify patients with autoantibodies.[40,44] Nettis et al.,[45] using the autologous serum skin test to identify patients with autoantibodies, found only an increased incidence of related angioedema. However, they also concluded that this test could not be used alone to identify patients with autoantibodies. Little difference was found between patients with and without autoantibodies in the cellular infiltrate of wheals.[46] To date, it is not known whether there is any difference between the two subtypes of CIU in response to treatment, although the autoimmune basis gives a theoretical reason to try immunosuppressants in patients with severe antihistamine-resistant disease. This is discussed further in sections 8.8–8.12.

4. Urticaria in Children

The classification of urticaria is the same in children as in adults. Acute urticaria is more common in children than in adults. The proportion of childhood urticaria described as chronic varies from 5% to 80%.[47-55] The variation in the reported frequency of chronic urticaria may be due to the geographic region, the kind of setting (primary, secondary or tertiary care), the definition of chronic urticaria or the referral pattern.

The cause of the urticaria has been reported as unknown in 8–71% of children.[47-54] Harris et al.[56] performed a retrospective study of 94 outpatients in the US; Volonakis et al.[57] prospectively investigated 226 outpatients in Greece. In these two studies of children with chronic urticaria, the cause of the urticaria was thought to be as follows: adverse food reactions (2–7%), adverse drug reaction (2%), physical urticaria (6–9%), infections and infestations (2–4%), connective tissue disease (3%) and unknown in 79–84% of patients. As in adults, a cause is more likely to be identified in acute rather than in chronic urticaria.

5. Diagnosis and Investigations

It is vital to take a detailed patient history, and this is often all that is required to make a diagnosis and manage the patient. Extensive laboratory tests are very rarely needed and only when indicated by the patient history.[58-62] If lesions are not visible during the visit it may be helpful to ask the patient to bring photographs.

The importance of a detailed history was emphasised in a prospective study of 220 patients with chronic urticaria. A comprehensive patient history was obtained by using a detailed questionnaire in combination with a complete blood count and erythrocyte sedimentation rate (ESR), and this was found to be almost as good in identifying a cause as a complete diagnostic evaluation (e.g. blood chemistry profiles, allergy tests, complement profiles, and screening for infections, autoimmune diseases and malignancies, physical examination, and provocation tests).[63] The questionnaire used is published and can be downloaded from the Internet.[64,65] Similarly, a systematic review of 6462 patients in 29 studies,[21] found no relationship between the number of identified diagnoses and the number of laboratory tests requested.

Clinical guidelines for the diagnosis and management of chronic urticaria are also presented in the systematic review by Kozel et al.,[21] and in other recent publications.[1,62,66,67] In acute urticaria, if the history indicates a type I hypersensitivity reaction, this can be confirmed by prick tests or laboratory radioallergosorbent tests. Routine tests are not recommended. When physical urticarias are suspect-

ed, appropriate provocation tests can be performed (table I).[3,15,16] In patients with CIU, we perform an ESR and full blood count with differential white cell count routinely, mainly because in one of the 350 patients we investigated, only an elevated ESR led to the detection of an internal disease.[63] Other investigators recommend no laboratory investigations in patients with mild disease and who respond to antihistamines.[62] Some investigators advise screening for thyroid autoimmunity and function in all patients with autoimmune CIU.[43] We recommend that thyroid function tests and tests for thyroid autoantibodies should only be performed if thyroid disease is suspected clinically. If a systemic disease is suspected, appropriate laboratory investigations (haematology, chemistry, serum immunoglobulins, complement levels, serum proteins and autoantibodies) should be performed, although these tests are rarely required in uncomplicated urticaria. In patients with angioedema without urticaria, complement C4 levels should be measured as a screening test for C1 inhibitor deficiency. The levels and function of C1 inhibitor can be measured if the C4 level is low.[62] However, in a recent report normal C4 levels were found in a patient with hereditary angioedema, and so some clinicians prefer to measure levels and function of C1 esterase inhibitor in all patients in whom this diagnosis is suspected.[68] If urticarial vasculitis is suspected a skin biopsy should be performed for histopathological evaluation, and if the diagnosis is confirmed further investigations are usually required, as detailed in other review articles.[66,69]

Table I. Provocation tests for physical urticarias[3,15,16]

Type of urticaria	Eliciting stimulus
Dermographism	Stroking of the skin (<36 g/mm^2)
Pressure urticaria	Locally applied weight for 20 minutes
Cholinergic urticaria	Physical exercise, hot bath
Cold urticaria	Cold contact (ice cube) for 20 minutes
Solar urticaria	Phototesting
Heat contact urticaria	Contact with heated object or water
Aquagenic urticaria	Contact with water of any temperature
Exercise anaphylaxis	Supervised exercise (± shortly after meal)

6. Natural Course

Information on the natural course of chronic urticaria is very important, since it frequently remits spontaneously, making it difficult to assess the efficacy of treatment.

There is little information available for children. In a study including 57 infants, three infants still had wheals after 1 year.[54] Harris et al.[56] followed 94 children prospectively and 58% were free of symptoms after 1 year. In a retrospective study of 123 children, 47% were free of symptoms after a mean follow-up period of 3.8 years (range 1–6.5 years). Physical urticarias had the worst prognosis in children.[48]

Seven studies provide data on the natural course of chronic urticaria in adults. In 500 patients with urticaria and/or angioedema, Urbach[70] found that urticaria went into remission within the following times: in 19% of patients in 3–12 months, in 20% in 1–5 years, in 4% in 6–10 years and in 1.5% in 11–20 years. Juhlin[71] reported that the median duration of attacks of chronic urticaria and/or angioedema was between 2 and 4 years. Quaranta et al.[72] investigated 86 patients with CIU over a 3-year period, of these 27 (31%) went into remission, 48 (56%) continued to have symptoms and in 11 (13%) patients the natural course was unknown. Important and detailed information about the natural course of chronic urticaria in a large group of patients was presented by Champion et al.[73] in 1969. In this study approximately 30–55% of patients with idiopathic urticaria and/or angioedema were free of symptoms after 1 year. The three most recent studies have investigated the natural course of chronic urticaria in tertiary care centres. In the first study, 544 of 950 patients, who were seen between 1968 and 1990, could be traced, of whom 372 completed the questionnaire.[74] The proportion of patients with all types of urticaria combined whose urticaria had cleared after 5 and 10 years was 29% and 44%, respectively. Thirty-four percent and 49% of patients with CIU (n = 153) were clear after 5 and 10 years, respectively. Thirty-six percent and 51% of patients with dermographism (n = 62), 32% and 36% of patients with cholinergic urticaria (n = 25),

28% and 48% of those with delayed pressure urticaria (n = 47) and 11% and 26% of patients with cold urticaria (n = 35) were clear of their urticaria after 5 and 10 years, respectively. It was also found that in patients with severe disease the duration of the disease tended to be longer.[74] In the second study, 220 patients with chronic urticaria were prospectively followed up for at least 1 year. After 1 year 47.4% of patients with CIU and/or angioedema (n = 78) were free of symptoms, and only 16.4% of the patients with physical urticaria (n = 73) were free of symptoms. Patients with identified causes, other than physical urticarias, were excluded.[75] In the third study, performed retrospectively, Beattie et al.[76] followed 60 of 87 patients with solar urticaria from 1975 to 2000. The probability of resolution after diagnosis was 12%, 26% and 36% after 5, 10 and 20 years, respectively.

7. Quality of Life

Urticaria varies in severity, but can cause significant disability. Various instruments have been used to assess patients with urticaria. The Dermatology Life Quality Index is a quickly self-completed questionnaire for routine daily clinical practice, consisting of ten items.[77] This questionnaire was used to assess 170 consecutive outpatients with different types of chronic urticaria.[78] The investigators found that patients with delayed pressure or cholinergic urticaria endured the largest impairment of quality of life, more than patients with CIU. The mean scores were comparable with those seen in outpatients with severe atopic dermatitis, and higher than in outpatients with psoriasis and vitiligo.[78] In an earlier study, using the Nottingham Health Profile and a disease-specific questionnaire, the investigators concluded that 142 outpatients with CIU with or without delayed pressure urticaria experienced quality-of-life impairment similar to that of patients with coronary artery disease.[79] Another study compared 21 patients with chronic urticaria, 27 patients with respiratory allergy and healthy subjects. They used two generic tools: the Short-Form 36 (SF-36), a health status questionnaire and SAT-P (a satisfaction profile). Patients with chronic urticaria had similar scores to patients with respiratory allergy, both of which were significantly higher than of healthy subjects.[80]

8. Treatment

This section is aimed at the treatment of CIU, although the details in sections 8.1 to 8.3 are relevant to all types of urticaria. Section 8.13 describes the treatment of physical urticarias.

8.1 Non-Drug Treatment

Patients should avoid known exacerbating factors such as food, alcohol or drugs, particularly aspirin and NSAIDs and possibly codeine. Cold cures, over-the-counter drugs and herbal remedies should be avoided until the presence of exacerbating agents has been excluded. A cool ambient temperature may help, since itching is often worse in the warmth. If physical urticarias are present then relevant physical factors should be avoided where possible, for example tight clothing should be avoided in delayed pressure urticaria. All patients should be reassured about the benign nature of the disease, the frequent absence of causative factors, the natural course of the disease and lack of curative therapy.

8.2 Topical Treatment

One percent or 2% menthol in aqueous cream may be helpful to reduce itching.[81] Potent topical corticosteroids reduce the number of mast cells in the skin and reduce wheal formation in dermographic patients,[82] but long-term use over large skin surface areas would be needed to treat urticaria, and hence topical corticosteroids are not clinically useful. Topical antihistamines and topical doxepin are not recommended because of the well known risk of sensitisation with a resultant type IV hypersensitivity reaction (contact dermatitis).[83]

8.3 Histamine H_1 Receptor Antagonists

Histamine H_1 receptor antagonists are the only drugs licensed for use in urticaria. They have been reported to produce a moderate or good response in 44–91% of patients with all types of urticaria[84,85] or

in 55% of patients with CIU.[86] H_1 receptor antagonists have also been shown to provide short- or long-term relief from itching in 94% of patients with CIU.[87] Thus, they should be used as first-line agents in the treatment of patients with urticaria of any type.

Low-sedating antihistamines (e.g. acrivastine, cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine or mizolastine) should be used initially to control daytime symptoms. Sedating antihistamines (e.g. hydroxyzine or chlorphenamine) have more adverse effects, and their use should be reserved for patients whose symptoms are not controlled by low-sedating antihistamines, especially if symptoms are causing sleep disturbance.[88,89] One of the authors (RA Sabroe) finds hydroxyzine 10–50mg at night the most useful of the sedating drugs.

Loratadine, cetirizine and acrivastine have been reviewed individually in *Drugs* previously,[90-94] and all of the low sedating antihistamines, except for desloratadine and levocetirizine, were reviewed and compared in *Drugs* in 1999 and 2001.[95,96] Most of these drugs were also reviewed and compared in urticaria, and cetirizine and mizolastine appeared to be the most effective in urticaria.[95,97] Astemizole and terfenadine have since been withdrawn from prescription in the UK and the US because of the potential for QT prolongation and torsades de points.

When one antihistamine is unhelpful it is usually worth trying a different one, and some clinicians combine two or more antihistamines at the same time. Some clinicians increase the dose of antihistamines, in young healthy adults, above those recommended by the manufacturers.[67] Indeed, although the recommended dose of cetirizine in adults and children over the age of 12 years is 10 mg/day in Europe, in Canada and the US a maximum of 20 mg/day may be prescribed.[95,97] In the US, Kaplan[98] recommends the following maximal dosages: 240 mg/day for fexofenadine and 20 mg/day for loratadine or cetirizine. However, if an increased dose is given, the patient should be warned that there may be a greater risk of sedation and of interaction with other drugs, particularly if these are also sedating, and such prescribing is entirely at the prescriber's own risk.

This article concentrates on the newer drugs, desloratadine, fexofenadine, levocetirizine and mizolastine.

8.3.1 Desloratadine

Desloratadine is the major orally active metabolite of loratadine, and was reviewed in *Drugs* in 2001 and 2003.[99,100] In CIU there appears to be an improvement in pruritus and total urticaria scores within the first day of treatment.[101,102] Desloratadine is metabolised by glucuronidation in the cytochrome P450 (CYP) system and its metabolites excreted equally in the urine and faeces.[103,104] It has a terminal half-life of 19–34.6 hours.[99]

Desloratadine is thought to have a low risk of adverse cardiovascular effects, and no significant effects on the ECG, including the corrected QT (QTc) interval, have been reported in clinical trials.[99,101-103,105] These reports also demonstrate that desloratadine has a safety profile similar to placebo.[99,101-103,105] However, it is of note that, in one study, loratadine was shown to have a minor effect on the K^+ channels associated with the cardiac toxicity of terfenadine, but only at very high doses which may not be clinically significant.[106]

Although there is the potential for interaction with drugs which alter the CYP enzyme system, such interactions do not, to date, appear to be of any significance.[103,105]

8.3.2 Fexofenadine

Fexofenadine is the active metabolite of terfenadine, and was reviewed in *Drugs* in 2000.[107] It reaches its peak concentration after 1–1.5 hours, undergoes very little metabolism and is excreted largely unchanged in the faeces. It has a half-life of 14 hours.

Fexofenadine does not appear to significantly block the K^+ channels associated with the cardiac toxicity of terfenadine.[108] Similarly, fexofenadine does not appear to have any adverse effects on the ECG, including the QTc interval, in clinical trials of up to 12 months,[107,109] and possible mild cardiac adverse effects were reported only very rarely in a

large post-marketing observational questionnaire study.[110] However, there is a single case report in which fexofenadine therapy was associated with QT lengthening and a life-threatening arrhythmia in a patient with pre-existing heart disease.[111] Although this may indicate risk in susceptible individuals, it may easily have been a coincidental finding. Overall, fexofenadine appears to have a very good safety profile, similar to that of placebo.[107,110,112,113]

Fexofenadine is dependent on transport proteins for absorption and elimination, and rifampicin and hypericum (St John's wort) have the potential to decrease the absorption of fexofenadine, whereas erythromycin and ketoconazole may increase absorption.[104] Although erythromycin and ketoconazole have been shown to increase plasma levels of fexofenadine, they still remained in the range achieved in clinical trials, and QTc intervals were not affected. Therefore, it would appear that such interactions are not clinically significant.[107,109] The absorption of fexofenadine is decreased by aluminium/magnesium-containing antacids if they are administered within 15 minutes of a fexofenadine dose.[104] Grapefruit juice has also been shown to reduce the absorption of fexofenadine.[114] Dose reduction is recommended in renal impairment.[104]

8.3.3 Levocetirizine

Levocetirizine is the active enantiomer of cetirizine, and is considered by the manufacturers to be pharmacologically equivalent to cetirizine at half of the dose.[115] In a detailed study of four healthy male volunteers, levocetirizine was rapidly and extensively absorbed, poorly metabolised, with no major active metabolite, and largely eliminated unchanged in the urine.[115] The data sheet indicates that peak plasma concentrations are achieved 0.9 hours after dose administration and that the rate, but not the extent, of absorption is reduced by food. The plasma half-life in adults is 7.9 ± 1.9 hours.[116]

The potential for cardiovascular adverse effects in humans has not been studied, but no effects on the QT interval were observed in dogs given levocetirizine.[116] However, cetirizine is thought to be free of cardiovascular adverse effects[96] and does not appear to interact with the K^+ channels associated with the cardiac toxicity of terfenadine.[106]

Drug interactions do not appear to have been studied specifically for levocetirizine, but cetirizine does not appear to have clinically relevant adverse interactions.[96] Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take levocetirizine, presumably because lactose monohydrate is an excipient. Dose reduction is recommended in renal impairment.[116]

8.3.4 Mizolastine

Mizolastine reaches its peak concentration after about 1 hour of administration. It undergoes extensive hepatic metabolism, has no major active metabolite and is largely excreted in the faeces. Its terminal elimination half-life is 7.3–17.1 hours.[117]

There was some concern about the cardiac safety of mizolastine, since one *in vitro* study demonstrated a potential for mizolastine to interact with the same K^+ channels associated with the cardiac toxicity of terfenadine and astemizole, but only in concentrations higher than those achieved *in vivo* by standard therapy.[118] However, in clinical studies mizolastine does not appear to have a significant effect on cardiac repolarisation and QTc interval,[117,119-121] even when used for up to 1 year in patients with CIU.[122]

Mizolastine is a relatively weak inhibitor of CYP, and may interact with other drugs which are metabolised by or interact with CYP, such as macrolide antibiotics or imidazole antifungals.[117] It may also interact with digoxin and theophylline.[117]

8.3.5 Comparative Studies of the Efficacy of the New H_1 Receptor Antagonists

All of the newer generation antihistamines have been shown to suppress cutaneous wheal and flare responses to histamine. Although all are useful clinically, ranked in order of their ability to suppress histamine-induced responses in healthy male volunteers, levocetirizine was the most potent drug, followed by fexofenadine, then mizolastine, and loratadine was the least effective, although it was still more effective than placebo.[123] In a similar double-blind, crossover, single-dose study, ceti-

rizine was the most effective drug, followed by mizolastine and terfenadine, then loratadine.[124] Similar results have been obtained in other studies. For example, cetirizine was more effective than mizolastine in suppressing wheal and flare responses at 24 hours,[125] and fexofenadine was more effective than loratadine, which in turn was more effective than chlorphenamine.[126]

Desloratadine, fexofenadine and mizolastine have been shown to be significantly more effective than placebo in CIU.[101,102,112,113,121] Fexofenadine has also been shown to improve quality of life and productivity in patients with CIU.[127] Few comparative studies including the newer antihistamines have been published, but mizolastine has been shown to be at least as effective as loratadine in CIU,[121,128] and cetirizine may have a therapeutic advantage over fexofenadine.[129]

Although studies of the use of levocetirizine in CIU have yet to be reported, in a single-dose comparison of cetirizine and levocetirizine both drugs produced roughly equal suppression of the wheal and flare response to histamine.[130] Thus, it is likely that levocetirizine will be shown to be effective, and it may prove to be one of the most effective antihistamines in CIU, like cetirizine.

8.3.6 CNS Effects of the New H_1 Receptor Antagonists

Although the risk of sedation with all of the newer generation of H_1 receptor antagonists is low compared with the first generation of drugs, loratadine and fexofenadine appear to have almost no sedative effects, whereas acrivastine and cetirizine may cause sedation in some individuals when given at recommended doses.[131,132] Controversy over the sedative effects of cetirizine has been reviewed previously.[96] Levocetirizine has been reported as having no effect on cognitive or psychomotor function in healthy volunteers,[133,134] but the data sheet indicates that slightly sedating adverse reactions such as somnolence, fatigue and asthenia occur more commonly than after placebo.[116] Additionally, the data sheet warns that in sensitive patients, the simultaneous administration of levocetirizine with alcohol or other CNS depressants may cause additional reduction in alertness and impairment of performance.[116]

8.3.7 Antihistamines in Pregnancy and Lactation

If possible, it is best to avoid all antihistamines in pregnancy, especially during the first trimester, although there is no reliable evidence to date that antihistamines are teratogenic. They should also be avoided towards the end of the third trimester because of the risk of neonatal seizures.[135]

In 1979, the US FDA established five categories (A to E) to describe the potential of a drug to cause adverse effects during pregnancy.[136] For drugs in category A, there is no evidence to support any adverse effect on the fetus. Unfortunately, no antihistamine meets the requirements for this category. For drugs in category B, studies show that either no adverse effect was found in animals and human studies were not performed or an adverse effect was found in animal studies, which was not confirmed in humans. Category B includes the sedating antihistamines clemastine, dexchlorpheniramine and diphenhydramine, and the low-sedating antihistamines cetirizine and loratadine.[136] The safe use of cetirizine (in only 39 exposed pregnancies) and loratadine (in 161 exposed pregnancies) has also been reported in recent prospective studies.[137-139] Similarly, a meta-analysis of 24 controlled studies using primarily first-generation antihistamines involved more than 200 000 women during 1960–91 and found no direct connection between the use of antihistamines in the first trimester of pregnancy and the rates of major fetal abnormalities.[140] However, in the manufacturer's data sheet, both loratadine and hydroxyzine are contraindicated during pregnancy.

The use of the sedating antihistamines in pregnancy has the advantage that their safety profile is known for a longer period, but they have more adverse effects than the low-sedating antihistamines, particularly sedation and performance impairment. Chlorphenamine and dexchlorpheniramine have been on the market for 50 years and, therefore, are favoured by some clinicians.[141] No adverse effect on pregnancy was demonstrated in animals receiving chlorphenamine.[136]

Antihistamines may appear in breast milk and may inhibit lactation, and so most manufacturers advise against their use in nursing mothers. Manufacturers warn of the possibility of 'CNS effects' on the nursing infant but do not give specific details, although these effects presumably include drowsiness and possibly also seizures.

8.3.8 Antihistamines in Childhood

All H_1 receptor antagonists can be used in children >12 years of age.[136] However, in younger children the recommended dose and minimum prescribing age vary in different countries and are currently changing. Therefore, the prescriber should refer to up-to-date local sources and drug data sheets. Currently, in the UK hydroxyzine can be used from the age of 6 months, and brompheniramine and chlorphenamine from the age of 1 year. In The Netherlands, dimetindene solution can be used in children of ≥1 month. Several other sedating antihistamines, and loratadine and cetirizine, can be used from the age of 2 years, although in the UK the latter is only licensed for hayfever in this age group. In the US, cetirizine may be used in children aged ≥6 months.[94] Desloratadine may be used in Europe from the age of 2 years.[100] The following are available in solution or elixir form in the UK: brompheniramine, cetirizine, chlorphenamine, clemastine, cyproheptadine, diphenhydramine, loratadine and promethazine.

8.4 H_2 Receptor Antagonists

The efficacy of H_2 receptor antagonists in the treatment of CIU is controversial. They have been studied mainly when given in combination with an H_1 receptor antagonist, and the outcome may depend on which H_1 and H_2 receptor antagonists are used, and on which type of urticaria is studied.

Significant improvement in symptoms compared with the use of an H_1 receptor antagonist alone has been reported with a combination of cimetidine and either hydroxyzine or chlorphenamine in CIU, and cimetidine and chlorphenamine in dermographism.[86,142-145] Similarly, itching in patients with chronic urticaria was found to be significantly less in patients taking a combination of ranitidine and terfenadine, than in those given terfenadine alone, whilst ranitidine alone had no effect.[146] One study supported a role for intramuscular cimetidine given alone in the treatment of acute urticaria.[147] In contrast, little or no additional benefit was obtained from the addition of cimetidine to chlorphenamine in CIU,[148] or ranitidine to cetirizine in dermographism.[149]

Some of the reported enhanced effects of combination therapy may be due to an increased serum concentration of the H_1 receptor antagonist. For example, cimetidine has been shown to increase the serum concentration of hydroxyzine and reduce its metabolism, but not to affect cetirizine, and in this study the combination of cimetidine and hydroxyzine enhanced wheal and flare suppression, but cimetidine and cetirizine did not.[150]

In practice, the authors often find that the addition of an H_2 receptor antagonist to an H_1 receptor antagonist is disappointing, but combinations may be worth trying in patients with urticaria poorly responsive to H_1 receptor antagonists alone.

8.5 Doxepin

Doxepin is a tricyclic antidepressant drug, but it also has very potent H_1 and H_2 receptor antagonist properties. Its use is not licensed in urticaria. However, it has been shown to be more effective and less sedating than diphenhydramine in the treatment of CIU,[151] as effective as mequitazine in CIU[152] and as effective with fewer adverse effects than hydroxyzine and cyproheptadine in idiopathic cold urticaria.[153] Only relatively low doses (10–50mg) are required. Doxepin is sedating and so is best taken at night. It interacts with the CYP system, and should not be used with drugs metabolised by or inhibiting this enzyme, such as imidazole antifungals, cimetidine or macrolides. Additionally, it should not be used with monoamine oxidase inhibitors or with drugs which can prolong QTc interval. One of the authors (RA Sabroe) finds this a very useful drug in patients with CIU, particularly if there is associated depression, since there is some evidence that the tricyclic antidepressants may have a mood elevating effect even at low dose.[154]

8.6 Leukotriene Antagonists

Leukotriene antagonists are licensed for use in asthma but not in urticaria. However, a number of case reports and small uncontrolled trials have indicated that they may be of benefit in some patients with urticaria of various types.[155-159] A single-blind, placebo-controlled, crossover study showed montelukast given in combination with cetirizine to be more effective than cetirizine alone, in 30 patients with refractory CIU.[160] However, in a double-blind trial in which cetirizine was given with either zafirlukast or placebo, only patients with antihistamine-resistant chronic urticaria with a positive autologous serum skin test benefited from the addition of zafirlukast.[161] Leukotriene antagonists may be most useful for patients with food additive or salicylate intolerance, as demonstrated in a double-blind study of 51 such patients.[162] However, a double-blind, placebo-controlled, crossover study of zafirlukast in 52 patients with chronic urticaria, showed that treatment with zafirlukast resulted in no significant benefit and no subgroup of responders was identified.[163] Additionally, a leukotriene antagonist caused an exacerbation of urticaria in two aspirin-sensitive patients[164] and precipitated urticaria in a patient given montelukast for asthma.[165] Thus, further work is required for the role of these drugs in urticaria to be established.

8.7 Corticosteroids

In patients with acute urticaria a short course of high-dose oral corticosteroids may shorten the duration of the episode. In one study, attacks stopped after 3 days in 94% of patients who received oral corticosteroids (prednisolone 50mg for 3 days) and a non-sedating antihistamine, but in only 66% of those who received the non-sedating antihistamine alone.[166]

Short tapering courses of oral corticosteroids may be helpful in antihistamine-resistant CIU in special circumstances where, for example, rapid control is needed to cover an important social or occupational event. Various regimens have been suggested in review articles, such as prednisolone 30 mg/day, slowly reduced to zero over a period of 10 days,[167] or prednisolone 40 mg/day, reduced by 5mg every 5 days to zero.[168] There is a tendency to use higher doses for more prolonged periods in the US, such as prednisolone 40mg every day, tapered to an alternate day schedule, for example 25mg every other day, and slowly tapered to zero over 3 months.[169] Systemic corticosteroids are best given as a single morning dose, and it is usually recommended that H_1 receptor antagonists should be continued.[168] A short course of oral corticosteroids may also be useful in antihistamine-resistant patients with severe intermittent facial angioedema which occurs only a few times a year, or for patients with urticarial vasculitis or severe delayed pressure urticaria.[62,170] In general, prolonged corticosteroid therapy should be avoided if at all possible, because it is likely to lead to significant systemic toxicity and the development of tolerance. However, if it is the only effective treatment, then it is best to use the lowest dose possible, carefully monitor for major adverse effects such as peptic ulcers, the risk of infections, diabetes mellitus, myopathy, cataracts and hypertension, and follow current guidelines for the prevention of osteoporosis and osteonecrosis.[171,172]

8.8 Ciclosporin and Tacrolimus

Ciclosporin (cyclosporine) 3–5 mg/kg has been shown to be effective in autoantibody (anti-FcεRIα)-positive and autoantibody-negative chronic urticaria when given for 1 month.[173,174] In a review article, Greaves[167] described his experience of using ciclosporin 3–4.5 mg/kg for up to 3 months. He reported that >75% of patients showed an excellent response and, of these, one-third remained in remission, one-third relapsed (but only mildly) and one-third relapsed to pre-treatment levels of disease activity.[167] During treatment with ciclosporin, H_1 receptor antagonists should usually be continued[168] and blood pressure and renal function should be monitored appropriately. The risk of maintaining the 'impossible to wean' patient on long-term ciclosporin is potentially considerable, as is the risk of rebound after discontinuation.[175]

In a recent review article, oral tacrolimus was reported to produce good to excellent results in a trial in patients with corticosteroid-dependent urticaria.[176] The overall study design and number of patients was not discussed, but doses of between 0.05 and 0.2 mg/kg/day in a twice-daily schedule were used. The need to monitor renal and liver function was emphasised, and it was recommended that blood levels of tacrolimus should be maintained below 20 μg/mL to prevent toxicity. Reported adverse effects in general appeared to be less than those for ciclosporin.[176]

8.9 Epinephrine

For patients with life-threatening episodes, such as attacks of tongue or laryngeal angioedema, anaphylaxis (such as exercise-induced anaphylaxis) or in patients with severe cold urticaria, emergency intramuscular epinephrine (adrenalin) may be required. A self-administered form (e.g. EpiPen®, Meridian Medical Techn. Inc., St Louis, MI, USA)[1] for intramuscular injection is available for adults and children. This can be reassuring for patients whose daily or holiday activities are limited by their disease. However, patients must be given adequate written instructions and proper demonstration at the time of the initial prescription and, possibly, repeatedly. Despite doing this, many patients will still be unable to use the syringe correctly.[177] Epinephrine should be used with caution in patients with hypertension and ischaemic heart disease, cerebrovascular disease and diabetes.[62] Fortunately, episodes of angioedema severe enough to warrant the prescription of self-administered epinephrine are unusual in CIU.

8.10 Intravenous Immunoglobulins

There is some evidence to support a role for intravenous immunoglobulins (IVIgs) in patients with severe disease that is unresponsive to conventional treatment. For example, in ten patients with severe CIU, IVIg 2 g/kg over 5 days produced clinical benefit in nine patients, and prolonged remission in three patients. All ten patients had circulating functional anti-FcεRI or anti-IgE autoantibodies.[178] In a single case report, low-dose IVIg 0.2 g/kg over 1 day was also helpful.[179] However, the effects may be short lived,[178,180] which raises the question as to whether repeated (e.g. monthly) infusions might be required, as in dermatomyositis.[181]

8.11 Plasmapheresis

In a single case series report, plasmapheresis was shown to be of at least temporary benefit in six of eight patients with severe treatment-resistant CIU, all with histamine-releasing activity (autoantibodies) in their serum.[182]

8.12 Other Treatments for Chronic Idiopathic Urticaria, with Limited Supportive Evidence

The successful use of sulfasalazine 500–4000 mg/day has been reported in three articles. These included three patients with CIU[183] and three patients with both CIU and delayed pressure urticaria.[184,185] All of these patients had severe corticosteroid-dependent urticaria.

Similarly, two patients with severe CIU and delayed pressure urticaria responded to methotrexate.[186]

One patient with severe corticosteroid-dependent CIU, with a positive autologous serum skin test, was shown to benefit from intravenous cyclophosphamide 500–1500mg every 2–4 weeks.[187] Another patient with acquired angioedema with autoantibodies against C1 inhibitor was previously successfully treated with cyclophosphamide by the same group.[188]

In a double-blind, placebo-controlled, randomised study of 58 patients with refractory chronic urticaria, stanozolol 2mg twice daily combined with cetirizine 10 mg/day was found to be more effective than cetirizine alone.[189] Previously, four patients with corticosteroid-dependent chronic urticaria had also been reported to improve with anabolic steroids.[190]

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Recently, two small studies have provided evidence for the use of the selective COX-2 inhibitor rofecoxib in CIU although, as with other NSAIDs, there is a risk of a serious, and in some cases dangerous, exacerbation of urticaria and/or angioedema and, rarely, of anaphylaxis.[191,192] However, of interest is the evidence that rofecoxib and celecoxib[24] may be well tolerated in patients with previous cutaneous reactions (urticaria and/or angioedema) to aspirin and/or NSAIDs.[22,23]

Some authors suggest the use of hydroxychloroquine, dapsone or colchicine in treatment-resistant CIU,[193,194] but, apart from one case report of the successful use of dapsone,[195] and a small open study on the use of hydroxychloroquine,[196] there is little published evidence to support their use in CIU.

Similarly, there is little data to support the use of psoralen UVA (PUVA) photochemotherapy or UVB phototherapy for chronic urticaria.[62] The efficacy of PUVA therapy was evaluated by Canadian dermatologists and allergists using a questionnaire, and it was ranked as neutral or ineffective.[197] However, recently, an uncontrolled retrospective study of narrow-band (TL-01) UVB phototherapy in 94 patients with antihistamine-resistant CIU was performed in Dundee, Scotland. The duration of the CIU ranged from 3 months to 20 years. Follow-up data after at least 1 year were available in 57 patients, 33% of whom were clear of symptoms, 46% felt that their condition had improved, and 21% felt that it was unchanged.[198]

8.13 Treatment of Physical Urticarias

It is usual practice to use H_1 receptor antagonists as first-line treatment in all types of urticaria (see section 8.3), although some types may be poorly responsive. Second-line treatments are often based on very little evidence, as discussed in this section.

Patients with dermographism often respond to antihistamines. The role of H_2 receptor antagonists is controversial (see section 8.4). However, in a study of 14 cases of severe antihistamine-resistant dermographism, PUVA therapy produced a temporary reduction in pruritus in five patients, but had no effect on wheal formation.[199] Similarly, in a study of 43 patients, UVB treatment induced remission or improvement in 39 patients, although 13 patients relapsed.[200]

In patients with delayed pressure urticaria antihistamines are often ineffective, and this condition may be persistent and extremely difficult to treat.[175,201] Oral corticosteroids (prednisone 10–30mg) may be helpful, but, as for CIU, long-term use is limited by adverse effects.[202,203] Potent topical corticosteroids (0.05% clobetasol) can reduce the clinical response to pressure on the skin, but are not practical for widespread or prolonged use.[204] Other therapies that have been used successfully and presented in case reports or in review articles include dapsone,[170,205] sulfasalazine 500–4000 mg/day (two patients)[185] and montelukast.[159,206] NSAIDs may suppress the painful sensation that may occur with the wheals of delayed pressure urticaria,[203] but can aggravate coexisting ordinary urticaria. In a double-blind, crossover trial of indometacin 25mg three times a day there was no improvement in experimentally induced delayed pressure urticaria wheals.[202] Similarly, colchicine given for 1 week had no therapeutic effect.[207] Recently, IVIgs were shown to induce remission or improve symptoms in five of eight patients with severe disease.[208]

Antihistamines are often helpful in suppressing cholinergic urticaria. Indeed, a double-blind, placebo-controlled study of cetirizine at doses of 10 or 20mg showed a highly significant improvement in 24 patients.[209] After provoking cholinergic urticaria some patients experience a refractory period of 8–24 hours. These patients can use physical exercise to suppress symptoms for a special event.[15] A double-blind, placebo-controlled study demonstrated the efficacy of a short course of danazol (400–600mg daily) in severely affected patients.[210]

Antihistamines are effective in many patients with idiopathic cold urticaria. Cinnarizine, doxepin, cyproheptadine, hydroxyzine, acrivastine, cetirizine and desloratidine[211] have been investigated; because of the lower risk of sedation with the last three antihistamines they are the first choice.[153,168,211] Ketotifen may also be helpful.[212] In severely affect-

ed patients, short-term treatment with oral corticosteroids (prednisone 20–25mg for 1–5 days) can be tried.[213] Alternatively, there are single case reports of patients responding to treatment with ciclosporin given over the winter months[214] or montelukast,[215] and in two patients a combination of zafirlukast with cetirizine appeared to be better than either drug alone.[216] Additionally, three members of a family with familial cold urticaria responded to stanozolol.[217] When pharmacological treatment fails, cold desensitisation can be tried, but only in highly motivated patients.[19] This time-consuming and unpleasant procedure often leads to noncompliance and anaphylaxis is a potential hazard.[218] Cold tolerance can rapidly disappear if patients do not maintain a daily schedule of cold immersion, again leaving the patient susceptible to a dangerous anaphylactic reaction.[19]

Patients with solar urticaria often respond poorly to antihistamines, although, as in other forms of urticaria, they remain the first treatment option.[219] In a recent study, 35% of the patients had a good response to antihistamines, 35% showed some improvement and 30% had no improvement.[76] In another study, cetirizine 10mg and terfenadine 60mg twice a day were compared in six patients. Four responded and in these patients both antihistamines appeared to be equally effective.[220] Doxepin may also be helpful.[221] Induction of tolerance by UVB, UVA or PUVA may be helpful in some patients, with total protection being achieved within a few weeks.[15] The main disadvantage of photo-(chemo)therapy is that the tolerance obtained often lasts for only a few days and so maintenance therapy is required with possible adverse effects (particularly skin cancer) in the long term.[219] Additionally, there is a risk of severe reactions, including anaphylaxis, particularly at the beginning of treatment.[222] Topical sunscreens with a high level of protection[76] and hydroxychloroquine are other treatment options,[15] although, as with oral β-carotene and oral corticosteroids, some clinicians find them of little value.[219] Ciclosporin[223] and plasmapheresis[224,225] have been shown to be effective in a small number of patients with severe solar urticaria.

8.14 Potential Future Treatments

These agents may have a role in the treatment of CIU in combination with antihistamines, or as corticosteroid-sparing agents, but little has been published on their use to date.

Zileuton, a 5-lipoxygenase inhibitor, reduces the generation of both leukotriene B4 (a stimulus for neutrophil migration) and leukotriene C4 (potent vasodilatory mediator). Its successful use has been reported in three patients with chronic urticaria, two of whom were aspirin sensitive.[226,227]

Rituximab is a monoclonal antibody that binds to the CD20 cell membrane protein found on the surface of most mature and malignant B lymphocytes.[228] The CD20 antigen appears to play a role in B-cell development and differentiation. Rituximab has been used successfully in the management of B-cell lymphoma, and autoimmune diseases such as SLE. Recently, a rapid response to rituximab of an episode of hypocomplementemic urticarial vasculitis with angioedema in a patient with SLE was reported.[228]

Mycophenolate mofetil and leflunomide are nonspecific immunomodulators that show promising effects in a variety of autoimmune (bullous autoimmune diseases, SLE) and inflammatory (psoriasis, atopic dermatitis, lichen planus) skin disorders,[228] and rheumatoid arthritis.[229,230]

Tumour necrosis factor (TNF)-α has an important role in the development and maintenance of inflammation. Two TNFα antagonists, infliximab and etanercept, have been licensed for the treatment of rheumatoid arthritis and Crohn's disease.[231] These drugs have been shown to significantly improve psoriasis in double-blind, randomised, placebo-controlled trials, and there are case reports of their successful use in scleroderma, SLE and cicatricial pemphigoid.[231] The finding that one-third of patients with CIU have circulating functional autoantibodies supports an autoimmune basis to the disease in some patients. Thus, it may be worth investi-

gating the use of these newer immunomodulatory agents in patients with severe CIU.

9. Conclusion

Although many patients with chronic urticaria have at least a partial response to H_1 receptor antagonists, a substantial proportion do not. However, antihistamines remain the only treatment licensed for use in urticaria and evidence-based data are sadly lacking for many of the other treatments. Patients with severe antihistamine resistant urticaria may be very disabled by their disease and treatment can pose a major challenge to the physician.

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