

SECTION 4

Management and treatment of chronic urticaria (CU)M. Maurer,^{1,*} M.K. Church,¹ M. Gonçalo,² G. Sussman³, M. Sánchez-Borges⁴¹Department of Dermatology and Allergy, Allergie-Centrum-Charité, Charité – Universitätsmedizin Berlin, Berlin, Germany²Clinic of Dermatology, University Hospital and Faculty of Medicine, University of Coimbra, Coimbra, Portugal³Division of Allergy and Clinical Immunology, St. Michael's Hospital and University of Toronto, Toronto, ON, Canada⁴Allergy and Clinical Immunology Department, Centro Médico-Docente La Trinidad, Caracas, Venezuela

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Received: 27 March 2015; Accepted: 14 April 2015

Abstract

Developments increasing our understanding of chronic urticaria have resulted in the simplification and improvement of available treatments. Currently, many treatments target mast cell mediators, but we can now disrupt mast cell activation with the anti-IgE antibody omalizumab, which has markedly advanced the treatment landscape for patients with difficult-to-treat urticaria. Current guidelines provide a framework for the management and treatment of patients with CU but, as each patient is different, knowledge and experience of specialist dermatologists and allergists are key to effective pharmacotherapy. This article reviews the different therapeutic options for patients with chronic spontaneous urticaria (also called chronic idiopathic urticaria) or chronic inducible urticaria and discusses management of special populations or special circumstances related to CU.

Conflicts of interest

Marcus Maurer is, or was recently, a speaker and/or advisor for FAES, Almirall Hermal, Genentech, GSK, Merckle Recordati, Novartis, Sanofi-Aventis MSD, Moxie, Takeda, Shire, UCB and Uriach. Martin Church has received lecture fees from Novartis. Margarida Gonçalo has acted as a consultant for Novartis. Gordon Sussman has acted as a consultant for Novartis and in the past 3 years has conducted studies for Novartis, CSL Behring, Merck and DBV Technologies. Mario Sánchez-Borges has participated in an advisory board for Genentech and has received speaker fees from Novartis.

Funding source

This supplement was funded by Novartis Pharma AG. It is a publication of the Novartis supported medical education meeting that took place in Prague in November 2014. The publication presents views of the authors and not Novartis.

How the pathogenesis of chronic urticaria has driven new treatment approaches

The pathogenesis of chronic urticaria (CU) is complex and not yet fully understood. However, central to our current understanding of this unpredictable disease is the activation and subsequent degranulation of mast cells in the skin.^{1,2} The symptoms of CU, i.e. itchy hives and/or angioedema, arise from the release of pro-inflammatory mediators from activated and degranulated cutaneous mast cells (Fig. 1).³ Mast cell degranulation can result from many different mechanisms of mast cell activation, including cross-linkage of immunoglobulin (Ig)E bound to the high-affinity IgE receptors (FcεRI) on the surface of mast cells.^{4–6} The release of histamine and other pro-inflammatory mediators from degranulated mast cells leads to hives and angioedema through increased capillary permeability and erythema, via vasodilation.^{3,7} The itch associated with hives is also induced by mast cell mediators, through stimulation of dermal sensory nerve fibres.^{3,7}

Evidence suggests that mast cells can exist within a spectrum of activation states, and that activation, priming and degranulation of mast cells are separate processes that can be triggered by a number of mechanisms.⁸ Furthermore, the degranulation of mast cells in CU can be due to different mechanisms in different patients.^{1,8} Up to 45% of patients with CU have IgG autoantibodies directed against either IgE (5–10%) or FcεRI (35–40%). These IgG autoantibodies can bind to and cross-link FcεRI on mast cells and basophils, resulting in their activation.^{1,8,9} This autoimmune characteristic of the disease is now regularly assessed by physicians, by means of the Autologous Serum Skin Test (ASST), to aid in specific diagnosis of autoimmune-related urticaria.^{2,10} Mast cell degranulation in CU may also result from infection-associated signals including complement components, autoallergens, neuropeptides and other unknown mechanisms. In addition to these, various other non-immunological factors can prime or trigger mast cells to induce inflam-

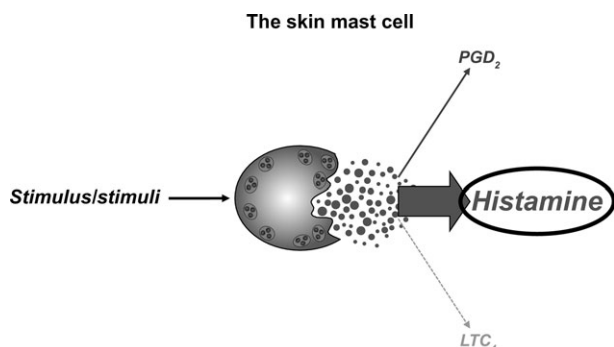


Figure 1 The basic mechanism of degranulation of the skin mast cell.

matory reactions, including physical stimuli such as heat or cold, or treatments such as non-steroidal anti-inflammatory drugs (NSAIDs).^{8,11,12}

The treatment of CU is similar to that of any other mast cell-dependent disease or allergic condition, namely to (i) avoid the cause or trigger/stimulus; (ii) reduce the release of mast cell mediators or the effects of these mediators on target organs with pharmacotherapy; and (iii) induce tolerance.² Guidelines from the European Academy of Allergy and Clinical Immunology (EAACI), Global Allergy and Asthma European Network (GA²LEN), European Dermatology Forum (EDF) and World Allergy Organization (WAO) recommend licensed doses of modern, second-generation, non-sedating H₁-antihistamines as first-line treatment; if symptoms persist after 2 weeks, dose escalation (up to four times) is advised (Fig. 2).²

The benefits of higher doses of non-sedating H₁-antihistamines have been well documented. For example, the efficacy of

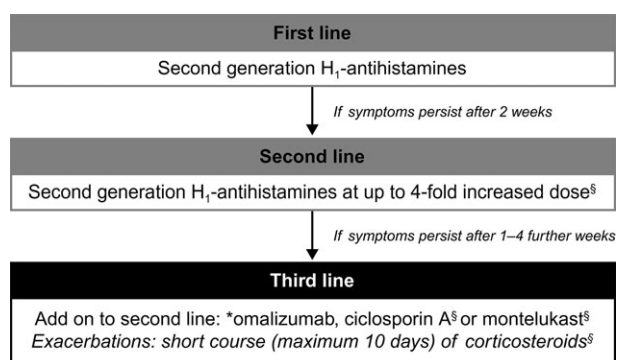


Figure 2 EAACI/GA²LEN/EDF/WAO-recommended treatment algorithm for urticaria. Reproduced from Zuberbier *et al.* Allergy 2014;69(7):868–87. Copyright ©, 2015 Wiley, with permission. *The order of third-line treatments does not reflect preference; [§]Not licensed for treatment in chronic spontaneous urticaria. EAACI, European Academy of Allergy and Clinical Immunology; EDF, European Dermatology Forum; GA²LEN, Global Allergy and Asthma European Network; WAO, World Allergy Organization.

higher doses of levocetirizine in patients with difficult-to-treat CU was demonstrated in a randomized, double-blind study, in which the proportion of symptom-free patients increased from 22% at week 1 to 55% at week 3 following a four-fold increase in the levocetirizine dose from 5 to 20 mg.¹³ Despite the increased dose, 45% of CU patients remained unresponsive to treatment. In those patients whose CU is inadequately controlled by licensed or higher doses of H₁-antihistamines, guidelines recommend the third-line addition of omalizumab, ciclosporin or the leukotriene receptor antagonist (LTRA) montelukast to existing H₁-antihistamine therapy (Fig. 2; more details on the selection of recommended third-line treatments can be found in the EAACI/GA²LEN/EDF/WAO urticaria guidelines).² Of the recommended third-line treatment options, omalizumab is the only option licensed for use as add-on therapy for the treatment of chronic spontaneous urticaria (CSU) (also called chronic idiopathic urticaria [CIU]). Although the efficacy and tolerability of omalizumab have been well established,^{14–16} its exact mechanism of action has yet to be confirmed.

Omalizumab is a humanized, monoclonal, anti-IgE antibody (rhuMab-E25) comprising a human IgG framework onto which are grafted the complementarity-determining regions from a murine anti-IgE antibody.¹⁷ Omalizumab binds to free IgE in the blood and interstitial space, forming biologically inactive IgE complexes that are unable to bind to FcεRI on the surface of mast cells and basophils.^{8,17} As such, omalizumab reduces the amount of free IgE, i.e. available to trigger mast cell and basophil degranulation and the subsequent inflammatory cascade. By forming inactive complexes with IgE, omalizumab can also indirectly bind and sequester free allergens and possibly autoallergens such as thyroperoxidase and double-stranded DNA, which can bind to the sequestered IgE.⁸ These may be the mechanisms for the rapid response (hours to days), i.e. seen in many cases of omalizumab treatment (M. K. Church, personal communication).^{8,18} There is also an important consequence of free IgE sequestration by omalizumab, which is the down-regulation of FcεRI on the surface of mast cells and basophils, and a subsequent reduced sensitivity and/or responsiveness of these cells to allergens or activating autoantibodies.^{8,19,20} This may be an explanation for the slower response (days to weeks), i.e. also seen in many cases of omalizumab treatment (M. K. Church, personal communication).^{8,18} Overall, the effect of omalizumab in urticaria is a downgrading of the IgE-FcεRI-mast cell axis and an increase in the threshold for mast cell activation.⁸ This decreased sensitivity and responsiveness of mast cells leads to increased stability and reduced degranulation, which ultimately culminates in reduced urticarial symptoms.^{8,19} Furthermore, omalizumab has been shown to also cause decreased release of inflammatory mediators and cytokines from basophils in the vasculature [e.g. interleukin (IL)-6 and tumour-necrosis factor (TNF) α] and decreased recruitment of other immune cells (e.g. T cells, macrophages, eosinophils), thus reducing local inflammation.⁸

The beneficial effects of omalizumab in CSU were demonstrated in several multicentre randomized controlled trials (X-CUISITE²¹, MYSTIQUE²², ASTERIA I¹⁶, ASTERIA II¹⁴ and GLACIAL¹⁵), and its efficacy and safety has been confirmed by small clinical and real-life studies^{18,23–25} and patient case reports.^{26–29} A retrospective, real-life study investigated optimal dosing, efficacy and safety of omalizumab and time to relapse following treatment discontinuation in 51 patients with CU.¹⁸ The study included 20 patients with CSU alone, 21 patients with chronic inducible urticaria (CINDU) and 10 patients with both CSU and CINDU. In addition to confirming the efficacy of omalizumab, results demonstrated its rapid onset of action, with complete remission seen in 12 of 21 (57%) patients with CSU within 1 week of treatment and in a further six patients (29%) within 4 weeks. The majority of CSU patients included in the study had complete remission with omalizumab 300 mg every 4 weeks.¹⁸ The same study group also assessed the response of patients who received omalizumab retreatment.³⁰ On re-initiating omalizumab, all patients reported a rapid and complete response after the first injection within the first 4 weeks.³⁰

Management of CU

General principles for the treatment of CU

With certain types of CU, a more definitive treatment may be possible, e.g. in cases of *Helicobacter pylori*-associated urticaria,³¹ or the development of CU signs and symptoms can be prevented by avoidance of eliciting triggers, e.g. cold in cold urticaria.² In CSU, it is notoriously difficult to eradicate underlying causes or target unspecific and unknown triggers; thus pharmacotherapy is key to effective treatment, with the aim being complete control of symptoms. Physicians should continue to treat the disease until the symptoms have subsided or until spontaneous remission of the disease occurs.²

First-generation, sedating H₁-antihistamines are not recommended for the treatment of CU.² Unfortunately, patients can now purchase sedating H₁-antihistamines, often without the guidance of pharmacists or physicians. Evidence has clearly shown that first-generation antihistamines cause significant drowsiness compared to modern, second-generation, non-sedating, non-impairing H₁-antihistamines. A study of patients allergic to ragweed showed that the sedating H₁-antihistamine, diphenhydramine, caused a significant impairment of simulated driving (comparable to patients who had received alcohol) when compared to the non-sedating H₁-antihistamine fexofenadine (Fig. 3a).³² Furthermore, despite their ability to cause drowsiness and potentially induce sleep, treatment with sedating H₁-antihistamines, can cause reduced quality of sleep with delayed and decreased periods of rapid-eye-movement (REM) sleep. Data also suggest that this poor quality sleep leads to after-effects the following day including drowsiness, impaired concentration and impaired memory.³³

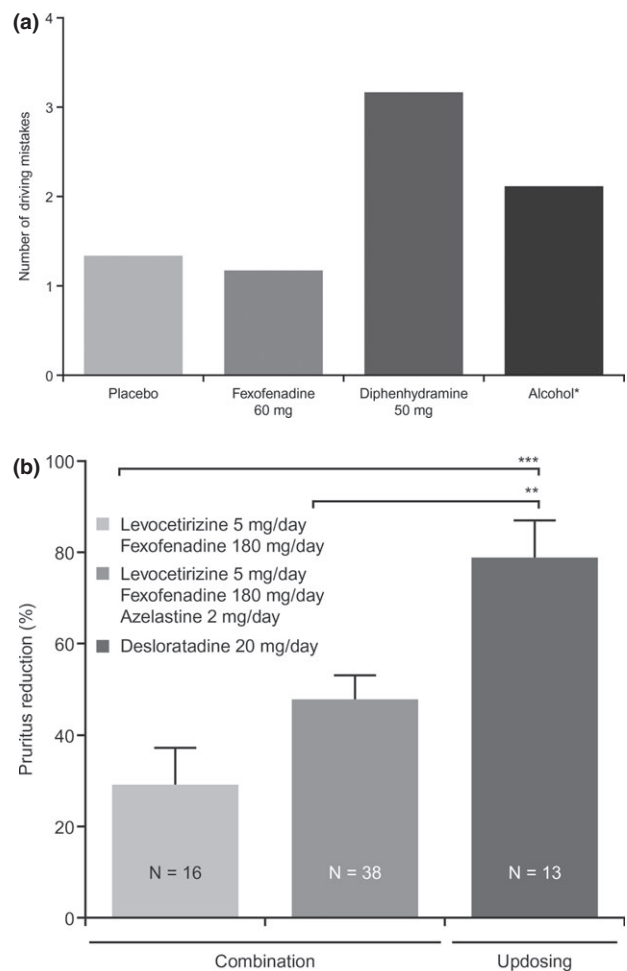


Figure 3 (a) First-generation sedating H₁-antihistamines led to more driving mistakes than alcohol, second-generation non-sedating H₁-antihistamines or placebo. From Annals of Internal Medicine, Weiler *et al.* Effects of fexofenadine, diphenhydramine, and alcohol on driving performance. A randomized, placebo-controlled trial in the Iowa driving simulator. Ann Intern Med 2000; 132(5): 354–63.³² Copyright © [2015]. American College of Physicians. All Rights Reserved. Reprinted with the permission of American College of Physicians, Inc.*Approximately 0.1% blood concentration. Alcohol given 1 h and antihistamine/placebo given 2.5 h prior to driving test. (b) High-dose (four times standard dose) monotherapy led to a significantly greater reduction in itch than combinations of two or three antihistamines (at twice the standard dose). With kind permission from Springer Science+Business Media: Schulz *et al.* [Antipruritic efficacy of a high-dosage antihistamine therapy. Results of a retrospectively analysed case series]. Hautarzt 2009;60(7):564–8.³⁴ ***P* < 0.01; ****P* < 0.005. nsAH, non-sedating antihistamine.

Use of higher doses of one non-sedating H₁-antihistamine is considered preferable to combinations of different non-sedating H₁-antihistamines at standard doses for the treatment of CU. A retrospective study of patients with chronic pruritus suggested that monotherapy with four times the standard dose of

desloratadine had a greater impact than combination of two or three antihistamines each at twice the standard dose (Fig. 3b).³⁴

General principles for the treatment of CSU

The aim for treatment of CSU is complete control of symptoms. Recommendations for the pharmacological treatment of CSU were described earlier (Fig. 2).² First- and second-line therapy with non-sedating H₁-antihistamines predominantly targets mast cell mediators. Third-line, add-on therapy includes omalizumab, ciclosporin and the LTRA montelukast. LTRAs, and potentially ciclosporin, also target mast cell mediators, although the specific mechanism of action of ciclosporin is unknown. We can disrupt mast cell activation by targeting the main mast cell-activating signal, IgE.⁸ IgE-induced mast cell activation is one of the crucial links between the cause and the symptoms of CSU, and anti-IgE therapy has dramatically improved the treatment of patients with long-term, refractory CSU.^{1,2,19}

Based on data from three phase III clinical trials (ASTERIA I, ASTERIA II and GLACIAL),^{14–16} involving over 900 patients with inadequately controlled CSU, omalizumab was approved in Europe as add-on therapy for the treatment of CSU in adult and adolescent (≥12 years) patients showing an inadequate response to H₁-antihistamine treatment, and has since been approved in many other countries.^{35,36} The treatment population in the phase III clinical trials were representative of the global, refractory CSU population. For example, in ASTERIA II,¹⁴ patients had a mean age of 42 years, 76% were female, 40% had angioedema, mean IgE levels were 179 IU/mL and the median duration of CSU was 3.3 years. Patients in ASTERIA II were randomized to omalizumab (75, 150 or 300 mg) or placebo every 4 weeks. After the first injection of omalizumab, particularly with the 300 mg dose, the hives score was rapidly and significantly reduced and this was maintained over the treatment duration (Fig. 4a). After treatment was discontinued, the symptoms returned to levels seen in the placebo group. There was also a significant increase in percentage of responders at week 12 (UAS7 score ≤6) with 150 or 300 mg omalizumab compared to placebo (Fig. 4b).

Consistent and significant relative reductions in itch, hives and overall Dermatology Life Quality Index (DLQI) scores were seen with omalizumab 300 mg vs. placebo in all three phase III trials, as well as significant increases in the percentage of responders at week 12 (UAS7 ≤ 6) (Table 1).^{14–16,37,38} Relative reductions were also seen with omalizumab vs. placebo in individual DLQI domain scores. Omalizumab (300 mg) showed a significant improvement compared to placebo in all three phase III trials in the *symptoms and feelings*, *daily activities*, *leisure* and *treatment* subdomains and a significant improvement vs. placebo in two of the trials in the *work and school* and *personal relationships* subdomains (Table 2).³⁹

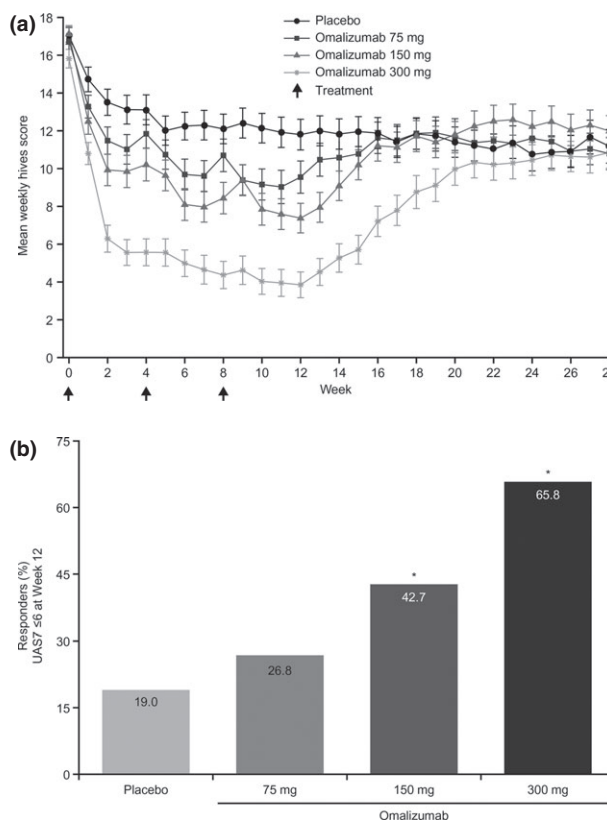


Figure 4 (a) Omalizumab treatment results in a rapid and significant decrease in the mean weekly hives score compared with placebo. (b) Omalizumab treatment results in a significantly increased proportion of responders (UAS7 ≤ 6) compared with placebo. From New England Journal of Medicine 2013: Maurer *et al.* Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med* 2013;368(10):924–35.¹⁴ Copyright © (2015) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. *Statistically significant ($P < 0.05$) vs. placebo.

Table 1 Summary of phase III data with omalizumab in chronic spontaneous urticaria: % reduction in itch, hives and overall DLQI score.

	ASTERIA I ¹⁶	ASTERIA II ¹⁴	GLACIAL ¹⁵
% Reduction*			
Itch Severity Score (ISS)	67	71	62
	$P < 0.0001$	$P < 0.001$	$P < 0.001$
Weekly Hives Score	67	74	62
	$P < 0.0001$	$P < 0.001$	$P < 0.001$
DLQI (overall score)	74	78	73
	$P < 0.0001$	$P < 0.001$	$P < 0.001$
Responder (%)			
UAS7 ≤ 6	52	66	52
	$P < 0.0001$	$P < 0.001$	$P < 0.001$

*From baseline to week 12 with omalizumab 300 mg.

P values are for absolute values relative to placebo and derived using ANCOVA t -test. DLQI, Dermatology Life Quality Index. UAS7, weekly Urticaria Activity Score.

Table 2 Summary of phase III data with omalizumab in chronic spontaneous urticaria: % reduction in DLQI sub-domain scores.

DLQI sub-domain (%)	ASTERIA I ¹⁶		ASTERIA II ¹⁴		GLACIAL ¹⁵
	150 mg	300 mg	150 mg	300 mg	300 mg
Overall	51*	74‡	66**	78‡	73‡
Symptoms and feelings	47*	70‡	60†	69‡	68‡
Daily activities	63*	79‡	69**	76‡	76‡
Leisure	69*	84†	62*	81†	76‡
Work and school	62*	82*	79*	86**	78**
Personal relationships	69*	84**	65*	84*	78†
Treatment	62*	85†	69*	85**	81†

P values are for absolute values relative to placebo and derived using ANCOVA *t*-test. DLQI, Dermatology Life Quality Index.

P* > 0.05; *P* ≤ 0.05; †*P* ≤ 0.001; ‡*P* < 0.0001.

Management of CINDU

General principle for the treatment of CINDU

The aim for treatment of CINDU is complete control of symptoms. Before the international urticaria guidelines were published,^{40,41} there was little consensus on effective treatments for CINDU and, as such, cocktails of antihistamines and/or beta-adrenergic agonists (e.g. terbutaline) were often prescribed.^{42,43} Due to a lack of controlled trials assessing efficacy of many treatment options for CINDU, physicians must rely on efficacy and tolerability data from single patient case studies or small-scale studies. Beyond first- and second-line options, treatment recommendations are also based on the experience and knowledge of dermatologists or allergists. Physicians can also measure the efficacy of treatments themselves by employing methods of threshold testing, which are routinely used for the diagnosis of many CINDUs (e.g. dermatographometer testing for symptomatic dermatographism⁴⁴ or the critical temperature threshold (CTT) test for cold urticaria).⁴⁵

It should be noted that the timeframe for treatment response is variable and not definitive; some patients may respond quicker than others. Also, certain treatments may not be available in all countries. Patients with CINDU who have a history of anaphylactic shock are recommended to always carry an emergency treatment kit containing an epinephrine autoinjector and non-sedating H₁-antihistamines.⁴⁶

Dermatographic urticaria

Dermatographic urticaria (symptomatic dermatographism or urticaria factitia) is the most common form of physical urticaria.⁴⁷ Given the potential for multiple CINDUs to occur in the same patient² and the ease of testing with a FricTest[®] device⁴⁴ or dermatographometer pen,^{48,49} all patients presenting with symptoms

of physical urticaria should be tested with a dermatographic challenge.

Prevention of dermatographic urticaria is almost impossible, as scratching (the key trigger for the development of symptoms) is a natural way to relieve pruritus (itch), one of the key symptoms of the disease, and even when not scratching it is difficult for patients to avoid mechanical irritation of the skin. Consequently, severe pruritus can have a detrimental impact on patients' quality of life.^{50,51} In some cases, basic daily activities, such as dressing or combing hair, can promote intense physical symptoms.²³ This can influence patients' choice of clothing, exercise, bathing regimens and behaviour.⁵² It is, however, possible to minimize skin irritation by choosing light clothing and by avoiding activities such as vigorous towelling.^{50,51} Skin hydration by emollients may also help prevent scratching due to dry skin.⁵³

Because of the difficulty of trigger avoidance, pharmacological treatment is very important for patients with dermatographic urticaria. Non-sedating H₁-antihistamines are the recommended first-line treatment of choice, and the dosage may be increased up to four-fold in those patients who are refractory to treatment with the licensed dose.⁵⁰

For those patients refractory to increased doses of non-sedating H₁-antihistamines, there are a number of additional therapeutic options, including LTRAs and narrow-band UVB, that have shown efficacy in individual trials or small studies; however, there is a lack of evidence from controlled clinical trials.^{50,51} There is conflicting evidence around the efficacy of corticosteroids in dermatographic urticaria, with only a few small patient case studies supporting their use as treatment modalities; as such, they are not recommended for routine use.^{51,54} Of all the physical urticarias, dermatographic urticaria has the strongest evidence base to support the efficacy of H₂-antihistamines, but even here the evidence is considered to be weak.^{2,55} Low-dose ciclosporin has also been shown to be effective in several patient case studies; in a case series of six patients with severe dermatographic urticaria, resistant to non-sedating H₁-antihistamines at higher doses, low-dose ciclosporin (starting dose ≥2.5 mg/kg/day) significantly improved symptoms in the four patients treated for ≥8 months.⁵¹

Omalizumab is currently being studied in a randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety in patients with dermatographic urticaria refractory to standard treatment.⁵⁶ Omalizumab has also been shown to be effective in the treatment of non-sedating H₁-antihistamine-refractory dermatographic urticaria in a number of individual cases and small studies (Table 3).

Acquired cold urticaria

Acquired cold urticaria can have a significant burden of disease for patients, depending on a number of factors such as the local climate and their personal threshold for cold urticaria. In fact, patients can have a CTT (e.g. ≥20°C), which can make it very

Table 3 Summary of data with omalizumab for the treatment of CINDU.

Urticaria type	References	Patient demographic		Previous treatment	Omalizumab dose	Improvement in symptoms
		Sex	Age			
Demographic urticaria (N = 7)	Metz <i>et al.</i> ³⁰	n/a	n/a	SD-H1-AH, HD-H1-AH, CS, Cic, Dapsone	150/225/300 mg every 2 or 4 weeks	Complete response (n = 6); significant improvement (n = 1).
Demographic urticaria (N = 1)	Krause <i>et al.</i> ²³	F	48	SD-H1-AH, HD-H1-AH, H2A, LTRA	300 mg every 2 weeks	Considerable reduction in hives and itch within first week of treatment, with complete remission of symptoms by week 4
Demographic urticaria (N = 3)	Metz <i>et al.</i> ³⁰	n/a	n/a	Yes	150–600 mg every 2 to 4 weeks	All patients displayed a rapid and complete response after the first injection.
Demographic urticaria, CSU and pressure urticaria (N = 1)	Vieira Dos Santos <i>et al.</i> ¹³²	F	37	SD-H1-AH, HD-H1-AH, LTRA, CS, Cic	150 mg every 4 weeks	The patient was treated for 2 years with no signs of symptoms until she became pregnant and stopped treatment. In the fourth month of pregnancy, when symptoms returned, omalizumab treatment was resumed, which resulted in complete remission.
Cold urticaria (N = 6)	Metz <i>et al.</i> ³⁰	n/a	n/a	SD-H1-AH, HD-H1-AH, CS, Cic, Dapsone	150/225/300 mg every 2 or 4 weeks	Complete response (n = 3); no significant improvement (n = 3).
Cold urticaria (N = 1)	Boyce <i>et al.</i> ¹⁵⁹	F	12	SD-H1-AH, HD-H1-AH, LTRA	375 mg every 2 weeks	A significant improvement in symptoms occurred after ~2 months of treatment, with complete resolution of symptoms after 5 months of treatment.
Cold urticaria (N = 1)	Metz <i>et al.</i> ²⁵	M	19	SD-H1-AH, HD-H1-AH	150 mg every 4 weeks	A single injection resulted in complete resolution of symptoms and reduction in critical temperature threshold from 16°C to <4°C.
Cold urticaria (N = 2)	Brodská <i>et al.</i> ¹⁶⁰	F	30/53	SD-H1-AH, HD-H1-AH, CS	300 mg every 4 weeks	Incomplete symptom control; long-lasting symptom control.
Cold urticaria (N = 6)	Sussman <i>et al.</i> ¹¹²	n/a	n/a	SD-H1-AH, HD-H1-AH	150/300 mg every 4 weeks	All patients became symptom-free.
Cholinergic urticaria (N = 8)	Metz <i>et al.</i> ³⁰	n/a	n/a	SD-H1-AH, HD-H1-AH, CS, Cic, Dapsone	150/225/300 mg every 2 or 4 weeks	Complete response (n = 5); significant improvement (n = 1); no significant improvement (n = 2).
Cholinergic urticaria (N = 1)	Metz <i>et al.</i> ²⁸	M	25	SD-H1-AH, HD-H1-AH, BB, LTRA	300 mg every 2 weeks	A significant improvement in symptoms was observed within 3 weeks of starting add-on treatment. After 11 weeks of treatment, concomitant medication could be stopped and normal activities could be resumed.
Cholinergic urticaria (N = 1)	Sabroe <i>et al.</i> ¹⁶¹	M	27	SD-H1-AH, HD-H1-AH	300 mg every 2 weeks	Patient remained refractory to omalizumab treatment.
Solar urticaria (N = 4)	Metz <i>et al.</i> ³⁰	n/a	n/a	SD-H1-AH, HD-H1-AH, CS, Cic, Dapsone	150/225/300 mg every 2 or 4 weeks	Complete response (n = 3); significant improvement (n = 1).
Solar urticaria (N = 2)	Metz <i>et al.</i> ²⁵	M/F	29/55	SD-H1-AH, HD-H1-AH	150/300 mg single injection	Complete resolution of symptoms
Solar urticaria (N = 1)	Güzelbey <i>et al.</i> ⁸⁶	F	52	SD-H1-AH, HD-H1-AH	150 mg every 4 weeks	A dramatic improvement in symptoms was seen after the first injection. An improvement in persistent, concurrent, respiratory symptoms was also noted and the patient was able to stop NS-AH medication.

Table 3 Continued

Urticaria type	References	Patient demographic		Previous treatment	Omalizumab dose	Improvement in symptoms
		Sex	Age			
Solar urticaria (N = 1)	Waibel <i>et al.</i> ¹⁶²	M	16	SD-H1-AH, HD-H1-AH	400 mg every 2 weeks	Repeat phototesting after 6 doses showed improvement with no immediate reaction in UV-A and UV-B spectrum (as was initially observed pre-treatment). However, erythema developed at all UV-A sites and some UV-B sites within 15 min of exposure.
Solar urticaria (N = 1)	Duchini <i>et al.</i> ⁸²	M	24	SD-H1-AH, HD-H1-AH, Doxepin	150 mg every 4 weeks	No change in phototesting was observed after three injections of omalizumab and no subjective improvement was reported after the fourth and final dose.
Delayed pressure urticaria (DPU) (N = 8)	Metz <i>et al.</i> ³⁰	n/a	n/a	SD-H1-AH, HD-H1-AH, CS, Cic, Dapsone	150/225/300 mg every 2 or 4 weeks	Complete response (n = 7); significant improvement (n = 1).
DPU (N = 1)	Bindsløv-Jensen and Skov ¹⁶³	F	39	SD-H1-AH, HD-H1-AH, Cic	150 mg every 2 weeks	Within 2 days of the first injection the patient had a complete resolution of DPU symptoms and maintained the response throughout treatment.
DPU (N = 1)	Metz <i>et al.</i> ²⁵	F	39	SD-H1-AH, HD-H1-AH	150 mg single injection	Complete resolution of symptoms.
DPU (N = 1)	Metz <i>et al.</i> ³⁰	n/a	n/a	SD-H1-AH, HD-H1-AH	150–600 mg every 2–4 weeks	All patients displayed a rapid and complete response after the first injection.

BB, beta blocker; CS, corticosteroids; Cic, ciclosporin; CINDU, chronic inducible urticaria; CSU, chronic spontaneous urticaria; F, female; H2A, H₂-antagonist; HD-H1-AH, High-dose H₁ anti-histamine; LTRA, leukotriene receptor antagonist; M, male; n/a, data not available; NS-AH, non-sedating antihistamine; SD-H1-AH, standard dose H₁-antihistamine.

difficult to spend time outdoors if they live in countries with cold climates.⁴⁵ Acquired cold urticaria can also be caused by cold wind, or cold food or drink. Patients with acquired cold urticaria can be at risk of anaphylaxis, especially when exposed to extensive cold contact (e.g. swimming) or following consumption of cold drinks which may cause local swelling with airway obstruction. Consequently, many patients are advised to carry an epinephrine autoinjector.^{57,58}

Cold tolerance induction can be achieved by gradually decreasing the temperature of showers, starting from above the CTT of the patient.⁵⁹ Tolerance is then maintained with daily cold showers.⁵⁰ Although there is some evidence to support the practice of tolerance induction in patients with acquired cold urticaria, due to the risk of anaphylaxis tolerance induction is not used by most physicians. If cold desensitization is used, patients must be monitored by their physicians during tolerance induction.⁵⁰

EAACI/GA²LEN/EDF/WAO-recommended first-line treatment with non-sedating H₁-antihistamines at standard doses can be effective for acquired cold urticaria and is supported by evidence from several controlled trials.^{2,40,58,60–62} However, patients who are refractory to standard doses may require an increase in dose of at least four-fold to achieve effective control of symptoms.^{45,58} There have been a number of studies focussing on up-dosing of non-sedating H₁-antihistamines. For example, it was shown that although bilastine can reduce CTT at standard doses, a four-fold increase in dose significantly improved its effectiveness (Fig. 5). This increase in dose and efficacy was without sedative effects.⁶³

Further treatment modalities such as ciclosporin, H₂-antihistamines, LTRAs, etanercept (anti-TNF) and anakinra

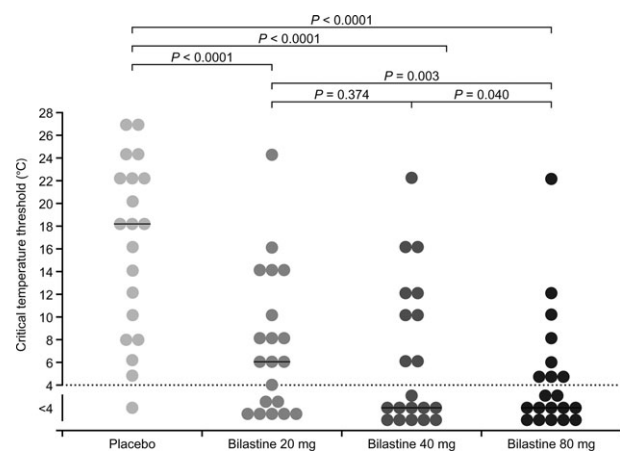


Figure 5 High-dose (four times standard dose) monotherapy with bilastine significantly reduces the critical temperature threshold in acquired cold urticaria. Reproduced from Krause *et al.* Allergy 2013;68(7):921–8.⁶³ Copyright © 2015 Wiley, with permission.

(anti-IL1) have all shown beneficial effects in cold urticaria and are supported by individual case studies or small group studies but lack evidence from controlled clinical trials.^{45,50,64,65} There is an increasing body of evidence for the use of omalizumab to treat cold urticaria, suggesting that thorough investigation is required to explore its potential benefit in this setting (Table 3). An ongoing double-blind, placebo-controlled study is assessing the effectiveness of omalizumab in patients with antihistamine-resistant cold contact urticaria (CUTEX; NCT01580592).

Cholinergic urticaria

Patients with cholinergic urticaria have a significant burden of disease, especially related to exercise, bathing and sexual activity.^{66,67} In some severe cases, patients with cholinergic urticaria are unable to undertake even mild exercise and are disabled because of their symptoms.⁶⁸

The most effective approach in the management of patients with cholinergic urticaria is avoidance of eliciting triggers. However, desensitization (through induced sweating or treatment with autologous sweat) may be useful in some patients.^{45,66,69} Pharmacotherapy for symptom relief may be achieved with non-sedating H₁-antihistamines at standard or higher doses, but most patients achieve only a partial response.⁵³ Other agents have shown varying efficacy in individual cases (e.g. the anticholinergic agent scopolamine, methantheliniumbromide⁷⁰, β_2 -adrenergic stimulants/blockers and botulinum toxin), but there is a low level of evidence associated with these treatments.^{69,71} Danazol has been shown to be effective for the treatment of cholinergic urticaria,⁷² although due to side-effects it is no longer recommended for routine use and may be more suitable for severe refractory cases.⁷³ To-date, there have been two reports published on cholinergic urticaria treated with omalizumab, with positive results^{18,28} (Fig. 6; Table 3) and a randomized controlled trial is ongoing (CUN-OMAL-UCOL; NCT02012387).

Solar urticaria

Patients with solar urticaria are often unable to spend time outdoors without triggering their symptoms. In a recent retrospective case series of 61 patients with solar urticaria, 95% of the patient cohort required <15 min of sun exposure to cause an urticarial response.⁷⁴ However, practically, patients cannot remain indoors, so UV-resistant clothing and the use of high-protection, broad-spectrum sunscreen is routinely recommended.⁷⁵

Induction of tolerance in solar urticaria through phototherapy has been reported to be effective;^{2,74,76} and rush therapy with UV-A (a rapid incremental phototherapy regimen) has also proven to be effective within 3 days.^{77,78} However, tolerance induction is transient, and patients require almost daily maintenance with UV-A exposure.^{2,76} These effects can reportedly be extended up to a week with pre-UV-A desensitization via PUV-A photochemotherapy (administration of psoralen before UV-A

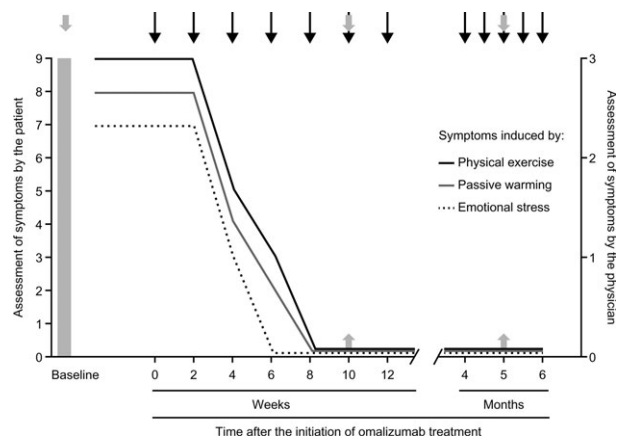


Figure 6 Omalizumab treatment results in a rapid and marked reduction in the symptoms of cholinergic urticaria. Reproduced from Metz *et al.* Allergy 2008;63(2):247–9.²⁸ Copyright © 2015 Wiley, with permission. Black arrows indicate treatment with omalizumab. Grey arrows indicate physical provocation tests assessed by the physician, horizontal bars represent the clinicians scoring of the severity of symptoms in the provocation test on a four-point quantitative scale (0–3+ s). Lines indicate the patients retrospective scoring of symptoms on a nine-point scale derived from adding individual scores for itch, wheals and reddening (0, none; 1, mild; 2, moderate; and 3, severe).

exposure), but continuous maintenance treatment is still required.^{76,79}

EAACI/GA²LEN/EDF/WAO guideline-recommend first-line treatment with non-sedating H₁-antihistamines at standard doses, which are effective at reducing itch and hives, but fail to prevent erythema. Therefore, second-line treatment at higher than standard doses may be required to provide symptom relief.^{53,80} Patients who respond to higher (two-fold or four-fold) doses of non-sedating H₁-antihistamines are able to continue natural exposure to UV light, allowing them to develop a natural desensitization.⁷⁴ A combination of therapeutic modalities and exposure prevention has demonstrated effective results. For example, a case series of three patients reported a synergistic benefit of broad-spectrum sunscreens and non-sedating H₁-antihistamines with a marked increase in tolerance to UV radiation compared with either treatment alone.⁸¹

Patients who are refractory to treatment with non-sedating H₁-antihistamines have a number of alternative therapeutic options. In addition to topical and systemic steroids, plasmapheresis and intravenous immunoglobulin (IVIG),^{50,53,82,83} anecdotal evidence supports the efficacy of LTRAs, chloroquine and an alpha-melanocyte-stimulating hormone analogue.^{50,75,83,84}

An antihistamine-refractory patient with solar urticaria has also been successfully treated with ciclosporin. The patient had been treated with PUV-A and chloroquine phosphate without success, and received ciclosporin at a dose of 4.5 mg/kg/day.

They showed decreased light sensitivity to UV-A, UV-B and visible light following ciclosporin treatment and, as a result, could be out in the sun for at least 1 h with minimal urticarial flares. Two weeks after ciclosporin therapy was discontinued, symptoms returned.⁸⁵

The successful use of omalizumab has also been reported in patients with solar urticaria^{18,86} (Table 3).

Delayed pressure urticaria

Despite a wealth of case reports and anecdotal evidence supporting efficacy claims for a number of different therapies, delayed pressure urticaria (DPU) remains a difficult-to-treat disorder with no broadly effective treatment.^{87–89} Management of DPU begins by explaining to the patient the fluctuating nature of the condition, and the association of pressure and delayed onset of swelling.⁸⁹ Patients may have to modify their behaviour, particularly physical activity, and may be advised to wear looser clothing and footwear.⁸⁹

Non-sedating H₁-antihistamines, at higher than licensed doses, may be used to reduce the frequency and severity of swelling, particularly in those patients with concomitant CSU and/or angioedema.^{2,50,89} However, in patients with DPU, the response to non-sedating H₁-antihistamines is generally poor and treatment guideline recommendations are based on low-grade evidence.^{2,87} Combination therapy (consisting of the non-sedating H₁-antihistamine desloratadine in association with montelukast) assessed in a small randomized controlled trial of 36 patients with DPU, significantly improved patients' symptoms.⁹⁰

Patients with DPU may respond to oral corticosteroids, but long-term use is not recommended because of the risk of serious adverse effects due to the high doses that are often required. Short-course oral corticosteroids may be considered in patients refractory to non-sedating H₁-antihistamines, especially if rapid symptomatic relief is required.^{50,89,91} There is little evidence for alternative treatment options. Case reports and small studies indicate that chloroquine, LTRAs, oral coumarins (warfarin, nicoumalone), anti-TNF α or monotherapy with dapsone or sulfasalazine can be effective.^{87,88,90,92–94} IVIG can also be beneficial in chronic DPU, but may itself severely impair quality of life.^{89,95}

There is mixed evidence to support the use of NSAIDs in DPU,^{89,91} which can themselves often be a triggering factor in CSU associated with DPU. Methotrexate was shown to be an effective treatment option in some patients with steroid-dependent CU; a retrospective case review of three patients with CU and DPU reported a marked symptomatic benefit in one (15 mg, once weekly), some benefit in another (25 mg, once weekly), and no benefit in the third patient (25 mg, once weekly). A steroid-sparing effect was seen in the patient with a good response to methotrexate; the frequency of corticosteroid dosing could be reduced from twice weekly to twice monthly.⁹⁶ There are only two patients with DPU reported to have been

treated with omalizumab in the literature. In both patients, omalizumab was shown to be effective (Table 3).

Management of special populations

Current EAACI/GA²LEN/EDF/WAO guidelines for the diagnosis, management and treatment of urticaria include recommendations for special populations, specifically children, the elderly and pregnant or lactating women.² The guidelines suggest using the same differential diagnoses, diagnosis and treatment algorithm and treatment recommendations as for adults but with consideration of factors such as age, dosage and availability of child-friendly formulae.²

Children

Urticaria in children is common, but correct diagnosis of the specific urticarial subtype can be challenging.^{97,98} While urticaria can occur in all age groups, it is acute spontaneous urticaria or recurrent urticaria, as opposed to CU, that most commonly affects infants and young children (Fig. 7 a,b).⁹⁹ There are a number of triggers associated with acute urticaria in children: physical stimuli (such as cold temperatures), contact with chemicals, viral infections (such as measles) and allergic reactions to food and/or drugs.^{99–101} Of these, the most common trigger is thought to be infections.¹⁰⁰ Interestingly, evidence suggests that 20–30% of children with acute urticaria (the majority caused by infection) go on to develop CU.¹⁰² When CU does occur in children, its underlying causes do not appear to differ from those seen in adults, although subtle differences in clinical characteristics have been suggested, including shorter time to remission, less frequent occurrences of angioedema and a reduced gender bias towards females. Further epidemiological studies are required to evaluate differences between these two populations.^{2,99,103,104} Diagnosis based on complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate and clinical history is essential in children to eliminate juvenile



Figure 7 (a, b) Examples of the symptoms of urticaria as seen in children (case provided by M. Gonçalves).

idiopathic arthritis or hereditary auto-inflammatory syndromes (e.g. chronic infantile neurological cutaneous articular syndrome or familial cold auto-inflammatory syndrome), which can all present with urticarial-like lesions.²

Regarding the management and treatment of children with CU, the EAACI/GA²LEN/EDF/WAO guidelines discourage the use of sedating H₁-antihistamines.² This is particularly important, as children are more sensitive to higher doses of sedating H₁-antihistamines than adults and consequently are more likely to experience side-effects.¹⁰⁵ Second-generation, non-sedating H₁-antihistamines are therefore recommended as first-line therapy, followed by weight-adjusted up-dosing if symptoms persist after 2 weeks. Choice of non-sedating H₁-antihistamine in very young children will largely depend on its availability as an oral solution.² Only those non-sedating H₁-antihistamines with proven efficacy and safety (at higher doses) in paediatric patients should be used; e.g. cetirizine, desloratadine, levocetirizine and loratadine.¹⁰⁶ The guidelines suggest that all subsequent treatment steps should be based on individual patients. Short courses of corticosteroids (maximum of 10 days) may be necessary during an exacerbation, but caution is advised due to adverse effects, including growth suppression, which is particularly relevant in children.¹⁰⁷

Options for third-line, add-on therapy are as per adult recommendations and include the LTRA montelukast, ciclosporin and omalizumab.² Despite data being available (albeit conflicting) on the efficacy of montelukast in adults with CU, there are relatively few published studies to assess its effectiveness in children. However, it is well tolerated with an acceptable safety profile and is licensed for use in children from the age of 6 years for the treatment of asthma.^{108,109}

A number of studies in children have shown ciclosporin to be effective in treating symptoms of CU.^{110,111} In a small retrospective study of seven children aged 9–16 who were refractory to high-dose H₁-antihistamines and corticosteroids, all seven children had resolution of their CU symptoms following treatment with ciclosporin, six within 1–4 weeks of treatment and one within 8 weeks.¹¹⁰ However, due to its side-effects, the authors caution that ciclosporin should be reserved for children whose CU is resistant to conventional measures and that serum concentrations of ciclosporin should be carefully monitored as well as regular assessment of renal and hepatic function.¹¹⁰

Omalizumab is approved as add-on therapy for CSU in adolescent patients (aged ≥12 years) with an inadequate response to H₁-antihistamine treatment and is also licensed for children aged ≥6 years with severe-persistent allergic asthma.³⁶ Its efficacy and safety have been demonstrated in small case studies in children with CU aged <12 years,^{112,113} including a recent case of an 11-year-old boy with severe, ciclosporin-resistant CU in whom an immediate and definitive response was reported following a single injection of omalizumab 300 mg.²⁶

The elderly

Treatment of elderly patients (>65 years of age) with CU should follow standard guideline recommendations. Second-generation, non-sedating H₁-antihistamines are recommended as first-line therapy and, particularly in elderly patients, first-generation antihistamines are to be avoided.² There are no reports concerning particular safety precautions when using the presently available second-generation antihistamines in this age group and there are no published pharmacokinetic studies for most antihistamines in this population. However, since many elderly patients have comorbidities and are receiving concomitant medications, it may be necessary to consider their hepatic and/or renal function, which may impact the efficacy or safety of medication.¹¹⁴ Potential drug–drug interactions are now of less concern as astemizole and terfenadine are no longer in use.¹¹⁵ However, due to a lower clearance rate of loratadine in elderly patients (compared to the normal patient population)¹¹⁶ and with significant hepatic metabolism of loratadine and desloratadine¹¹⁷ the use of these antihistamines in patients with hepatic insufficiency or renal impairment is not recommended (M. Gonçalo, personal communication). There may also be safety issues with the use of systemic corticosteroids and ciclosporin, particularly in elderly patients with hypertension and a low glomerular filtration rate.¹¹⁸ No safety concerns have been reported with omalizumab or montelukast in elderly patients with CU (M. Gonçalo, personal communication).

Pregnant and lactating women

Evidence suggests that the symptoms and progression of CU can be affected by pregnancy. Some patients with refractory urticaria have been reported to have spontaneous resolution of symptoms upon becoming pregnant and a return of symptoms following delivery. Conversely, some other patients with CU have reported intense flares of urticaria during pregnancy (M. Gonçalo, personal communication).¹¹⁹ Although it is best practice to avoid therapy during pregnancy, current evidence suggests that, for those patients who do experience flare-ups, certain treatments can be given without risk of embryotoxic or teratogenic adverse effects. Differential diagnosis is important as other conditions can present with more persistent, urticaria-like hives (such as the urticarial dermatoses of pregnancy).¹²⁰

First-generation, sedating H₁-antihistamines should be avoided in pregnant women, due to the sedative effects. Second-generation, non-sedating H₁-antihistamines should be the first-line treatment of choice, as they have been considered to have an acceptable risk, and are classified as pregnancy category B ('Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women').¹²¹ Furthermore, in lactating women, a small number of studies have shown that non-sedating H₁-antihistamines are almost completely cleared from breast milk.^{122,123} With respect to potential drug-exposure in (breastfeeding)

infants, loratadine and cetirizine are the preferred choice for lactating, as well as pregnant women. Furthermore, the related antihistamines, desloratadine and levocetirizine can also be recommended.^{124–128}

Use of corticosteroids in the first trimester of pregnancy is not advisable due to the possible increased risk of cleft palate, and ciclosporin use in pregnant women should be considered with extreme caution due to potential adverse embryotoxic and teratogenic effects.^{78,129,130} Published evidence on the use of montelukast during pregnancy suggests that there is no increased risk of major malformations above the baseline rate in the general population; however, one study reported a significantly lower birth weight of babies whose mothers had been treated with montelukast.¹³¹ Further clinical studies are required to be able to fully evaluate the efficacy and safety of montelukast in pregnant women.

There is little published data on the safety of omalizumab in pregnant women with CU, apart from one case study;¹³² however, the EXPECT pregnancy registry, in patients with severe allergic asthma treated with omalizumab, has assessed outcomes from 169 pregnant women treated with omalizumab. No apparent increase or patterns in major anomalies were observed.¹³³ This is supported by recent real-life evidence in two patients with severe asthma who were treated with omalizumab whilst pregnant. In both cases treatment with omalizumab did not affect their pregnancies or newborn babies.¹³⁴

Management of special situations

The diagnosis and treatment of patients in special situations, such as those with hypersensitivity to drugs, is a topic, i.e. frequently discussed amongst physicians, specialist dermatologists and allergists. Recommendations from the EAACI/GA²LEN/EDF/WAO guidelines suggest that if drugs are the suspected cause of urticaria, they should be discontinued or replaced by a drug of a different class (assuming pharmacological treatment is essential).² They also note that drugs can often exacerbate pre-existing urticaria; therefore, removal of the drug in such cases may not always resolve symptoms and further testing may be required to evaluate the actual trigger/cause. The following sections focus on acute urticaria caused by drug-hypersensitivity, in particular that caused by the use of NSAIDs or angiotensin-converting enzyme inhibitors (ACEi).

Urticaria and NSAIDs

It is well established that aspirin and other NSAIDs can induce acute urticaria. NSAID hypersensitivity is either termed NSAID-induced urticaria/angioedema, if it has no underlying chronic disease, or NSAID-exacerbated cutaneous disease (NECD) if associated with CU.¹³⁵ Depending on the subtype of CU, it is thought that up to 50% of patients experience exacerbations associated with NSAID treatment.^{136–138} Recent data illustrate subtle differences in the manifestation of symptoms in patients

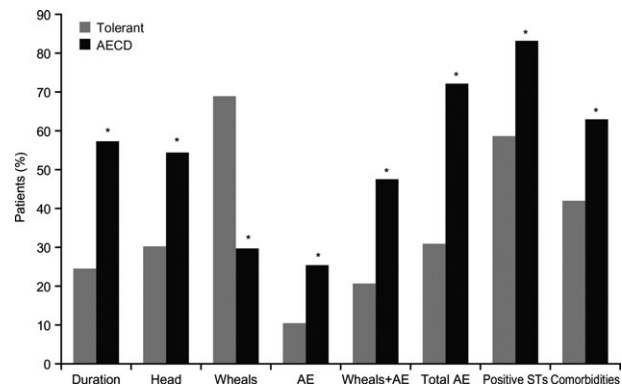


Figure 8 Chronic urticaria symptom manifestation in patients with aspirin-exacerbated cutaneous disease (AECD) compared with patients who are tolerant to treatment with aspirin. * $P \leq 0.05$. AE, angioedema; ST, skin (prick) tests.

with NECD and those with CU who are tolerant to NSAIDs; these data suggest that NECD could be classified as a sub-phenotype of CU (Fig. 8).¹³⁹ However, clinically, exacerbations manifest as hives or angioedema 0.5–6 h after drug ingestion; i.e. there is a strong resemblance to the clinical symptoms presented by patients with CSU (Fig. 9 a–c) (M. Sánchez-Borges, personal communication).^{135,138} The prevalence of NECD is increased in those patients with active urticaria and is thought to be dose-dependent.¹³⁵ Furthermore, patients are often young women suffering from dysmenorrhoea, who use NSAIDs for analgesia and consequently develop acute monthly episodes of NECD (M. Sánchez-Borges, personal communication). Oral provocation testing to confirm diagnosis can be performed with one tenth the starting dose of NSAID, increasing every 2 h until symptoms occur or therapeutic dose is achieved.¹³⁵

Although NECD exacerbations can be induced by different drugs, a common physiological mechanism is thought to be involved, i.e. the inhibition of cyclooxygenase (COX-1).¹³⁵ Furthermore, raised basal levels of leukotriene E4 can be found in the urine of these patients, and these have been shown to increase further after treatment with aspirin. Importantly, this increase is not seen in those patients with CU who are aspirin tolerant.¹⁴⁰ Management of patients with NECD is primarily through the avoidance of COX-1 inhibitors, and the use of COX-2 inhibitors. Paracetamol is generally well tolerated at standard doses, although tolerance testing is recommended for higher doses, as they can also cause hypersensitivity reactions (these patients may represent a distinct subset of NECD patients characterized by a different mechanism).^{135,141}

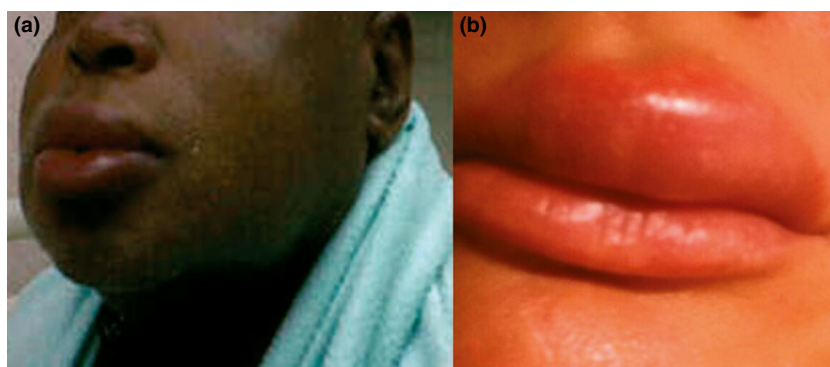
Angioedema and ACEi

Angiotensin-converting enzyme inhibitors are indicated for the treatment of various cardiovascular diseases, including hypertension and heart failure. There are a number of different ACEi, but

Figure 9 Examples of wheals (hives) (a) and angioedema (b, c) seen in patients with non-steroidal anti-inflammatory drugs-exacerbated cutaneous disease (case provided by M. Sánchez-Borges).



Figure 10 (a,b) Examples of angioedema triggered by treatment with angiotensin-converting enzyme inhibitors (ACEi) (case provided by M. Sánchez-Borges).



hypersensitivity to one particular type should be considered as hypersensitivity to the overall drug class, and patients should therefore avoid using all ACEi as a precaution. A study of 12 557 patients with hypertension estimated the incidence of angioedema due to a common ACEi (enalapril) to be 0.68%.¹⁴² However, general prevalence of ACEi-induced angioedema is thought to be between 0.1% and 6%, depending on the study and the particular drug.¹⁴³ In the US, incidence is higher in African-Americans compared with Caucasians, smokers compared with non-smokers and women compared with men.^{143,144} Clinical risk factors are obesity, sleep apnoea, immunosuppression, recent initiation of treatment, upper airway surgery/trauma and concomitant use of NSAIDs or some hypoglycaemics (such as sitagliptin).^{145,146} Clinically, ACEi-induced angioedema affects the orofacial and/or perioral area and/or upper airways most frequently (Fig. 10 a,b).¹⁴⁷ Approximately 30% of all cases of angioedema that present at the emergency department are ACEi induced¹⁴⁸ and up to 40% of cases can be life threatening (M. Sánchez-Borges, personal communication).¹⁴⁶

The pathogenesis of ACEi-induced angioedema is not yet fully elucidated, but current understanding suggests that ACEi affect a number of pathways related to vasopermeability and vasodilation. Primarily, ACEi prevent the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor. Secondary effects of ACEi are to prevent the degradation of bradykinin (BK) and substance P (SP) and cause local accumulation, and subsequent vasodilation. Increased vascular permeability with resulting extravasation, is then thought to cause the angioedema.¹⁴⁷

The ACEi-induced angioedema should be suspected in every hypertensive patient over the age of 40, who has been prescribed ACEi and presents with angioedema. However, a thorough patient history is important when diagnosing this condition, as there are a number of other types of BK-induced angioedema including: type I- and type II-hereditary angioedema with C1-inhibitor deficiency, acquired angioedema with C1 deficiency and hereditary oestrogen-related-type III angioedema.¹⁴⁹ ACEi are contraindicated in such patients with hereditary or acquired-C1-esterase inhibitor deficiency.¹⁵⁰ It is important for physicians

to establish if patients are taking any concurrent medication. A study of patients with ACEi-induced angioedema showed that approximately 50% were prescribed concomitant aspirin or NSAIDs.¹⁴⁶

With regard to management of patients with ACEi-induced angioedema, treating the angioedema is the main priority. C1-inhibitor concentrate has been shown to be effective for the treatment of ACEi-induced angioedema and is available in a number of countries.^{151–153} Icatibant, a BK receptor antagonist has also been shown to be effective in a series of patient cases and also a randomized clinical trial.^{154–156} Recently, results from a phase II clinical study of the efficacy and safety of ecallantide for use in ACEi-induced angioedema in an emergency department setting were reported.¹⁵⁷ A secondary concern is the continued treatment of hypertension. Angiotensin receptor antagonists are recommended in this setting because they rarely induce angioedema.¹⁵⁸ Patients should be periodically monitored during treatment.

Summary

Advances in understanding of the pathophysiology of CU have helped drive the development of new or improved treatment approaches. With all CU subtypes, the aim of therapy is to treat the patient until the symptoms have subsided. EAACI/GA²LEN/WAO/EDF urticaria guidelines provide a framework for the management and treatment of patients with CU. Non-sedating H₁-antihistamines, recommended in the first- or second-line, target mast cell mediators. An important development was the ability to disrupt mast cell activation with the anti-IgE antibody omalizumab, recommended third line as add-on therapy. Omalizumab has markedly changed the treatment landscape for patients with difficult-to-treat urticaria and, although its mechanism of action is not fully understood, its rapid effects have been demonstrated in a number of different CU subtypes.

As each patient case is different, the knowledge and experience of specialist dermatologists and allergists is an invaluable addition to the direction provided by treatment guidelines and is key to effective pharmacotherapy. Importantly, physicians should be aware of potential differential diagnoses and factors to consider when evaluating the needs of some special populations, or in certain special situations, to enable them to make informed assessments and treatment decisions. A broader understanding of the CU landscape, taking into account data from smaller real-life studies and case series in addition to large randomized trials, should improve the management of this disease and lead to better prospects for all who suffer with CU.

Acknowledgements

Editorial assistance was provided by Alex Goonesinghe, a professional medical writer contracted to CircleScience, an Ashfield Company, part of UDG Healthcare plc. Writing support was funded by Novartis Pharma AG.

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