

SECTION 5

Treatment dilemmas in chronic urticaria

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Abstract

The European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA²LEN)/European Dermatology Forum (EDF)/World Allergy Organization (WAO) recently published updated recommendations for the classification, diagnosis and management of chronic urticaria (CU). This article discusses several case histories that provide examples of how these recommendations can be implemented in the treatment of CU in a variety of real-life patients.

Conflicts of interest

Gordon Sussman has acted as a consultant for Novartis and in the past three years has conducted studies for Novartis, CSL Behring, Merck and DBV Technologies; Margarida Gonçalo has acted as a consultant for Novartis; Mario Sánchez-Borges has participated in an advisory board for Genentech and has received speaker fees from Novartis.

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Introduction

The European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA²LEN)/European Dermatology Forum (EDF)/World Allergy Organization (WAO) recently published updated recommendations for the classification, diagnosis and management of chronic urticaria (CU).¹ These guidelines include a treatment algorithm for urticaria including recommended first-, second- and third-line options, with the main objective of therapy being complete symptom control (Fig. 1).¹ This article discusses several case histories that provide examples of how these recommendations can be implemented in the treatment of CU in a variety of real-life patients.

Patient with recurrent chronic spontaneous urticaria and severe angioedema

A 44-year-old male presented with a 2-year history of chronic spontaneous urticaria (CSU) (also called chronic idiopathic urticaria [CIU]). He presented with severe, disabling swelling and daily pruritic hives. He was treated with high-dose H₁-antihistamine (cetirizine 40 mg) without relief. The patient's CSU affected his ability to work and resulted in a poor quality of life. He required daily prednisone 30–40 mg for relief. A trial of omalizumab 150 mg was initiated (*in Canada the recommended*

dose is omalizumab 150 or 300 mg every 4 weeks; in the EU the recommended dose is omalizumab 300 mg every 4 weeks) and after two injections he was completely asymptomatic. He received omalizumab injections every 4 weeks for 9 months and prednisone was completely discontinued. Two months after stopping treatment, he developed urticaria together with severe angioedema of the hands (Fig. 2). Symptoms were managed by re-initiating omalizumab treatment, with a remarkable response (Fig. 2). This case raises the question of when to discontinue omalizumab treatment, as the timing of disease recurrence seems spontaneous. Practical considerations around omalizumab including optimal length of therapy, dosing and re-treatment have been assessed recently.^{2,3}

Patient with severe refractory chronic spontaneous urticaria

The patient is a 63-year-old male who has had severe refractory chronic spontaneous urticaria for over 16 years. His chronic urticaria interfered with all aspects of his life including his job, which required extensive travel, making treatment difficult. He was treated unsuccessfully with first-, second- and third-line medications including high-dose H₁-antihistamines (desloratadine 20 mg, diphenhydramine 200 mg, hydroxyzine 200 mg and cetirizine 40 mg), in addition to doxepin (100 mg),

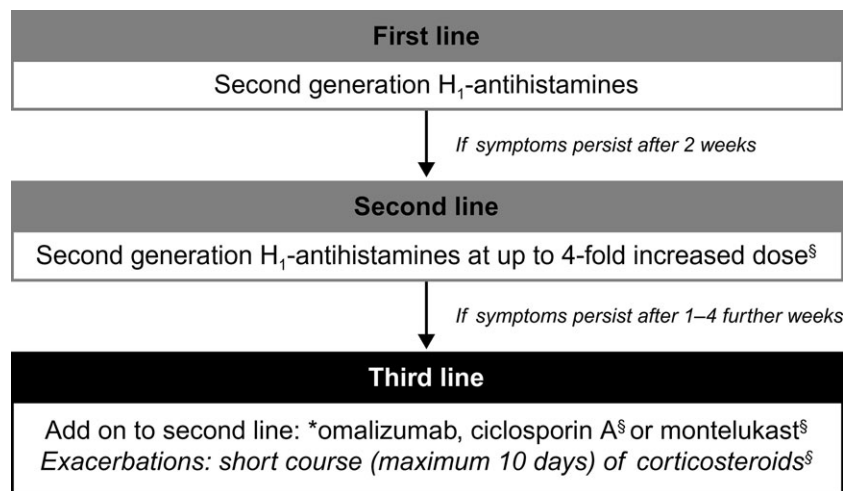


Figure 1 EAACI/GA²LEN/EDF/WAO 2013 urticaria guideline-recommended treatment algorithm.¹ *The order of third-line treatments does not reflect preference; [§]Not licensed for treatment in CSU. EAACI, European Academy of Allergy and Clinical Immunology; EDF, European Dermatology Forum; GA²LEN, Global Allergy and Asthma European Network; WAO, World Allergy Organization. Reproduced from Zuberbier *et al.* Allergy 2014;69(7):868–87.1 Copyright © 2015 Wiley, with permission.



Figure 2 Severe angioedema of the hands in a patient with urticaria before (left) and after (right) re-treatment with omalizumab (case provided by G. Sussman).

montelukast (10 mg), hydroxychloroquine (400 mg), ciclosporin (5 mg/kg) and intravenous gammaglobulin (which was stopped due to a severe adverse reaction). His symptoms were controlled only with prednisone (30–50 mg daily).

The patient received omalizumab (150 mg) and experienced remission within 1 week of the first injection (*in Canada the recommended dose is omalizumab 150 or 300 mg every 4 weeks; in the EU the recommended dose is omalizumab 300 mg every 4 weeks*). The patient initially responded to on-demand omalizumab treatment, often bridged with prednisone. However, he started to experience severe urticaria flares with this procedure. Therefore, omalizumab was increased to 300 mg per month, resulting in increased efficacy and excellent overall disease control. Prednisone use was significantly reduced and generally discontinued if he was able to keep on a 4-weekly treatment protocol.

Elderly patient with severe refractory chronic spontaneous urticaria

The patient is an elderly female who, at 61 years of age, first presented in 1997 with mild spontaneous urticaria and some lesions induced by physical pressure (delayed pressure urticaria) or exposure to NSAIDs (non-steroidal anti-inflammatory drugs). She has had good disease control with H₁-antihistamines and normal blood tests except for high anti-thyroperoxidase antibody levels [TPO] (>1800 UI/mL) but normal thyroid function. In 2000, her urticaria became severe with very large oedematous lesions (Fig. 3), almost daily angioedema and pressure-induced urticaria. She became resistant to H₁-antihistamines, and was treated with doxepin and short courses of corticosteroids. When she received treatment elsewhere she was given longer courses of corticosteroids, although this is not recommended by EAACI/GA²LEN/EDF/WAO urticaria guidelines.¹ In 2002/2003 she had



Figure 3 Severe refractory CSU in an elderly female patient (case provided by M. Gonalo).

daily urticaria, with some lesions lasting longer than 24 h, angioedema, but no systemic symptoms. She had a positive autologous serum skin test, elevated CRP (1.2 g/dL; $N < 0.5$) and normal C3 and C4. A skin biopsy showed oedema, and infiltration with many eosinophils, some neutrophils and absence of vasculitis (Fig. 4). Her diagnosis remained as autoimmune chronic spontaneous urticaria and the patient tried various add-on therapies (dissulone, colchicine, intravenous immunoglobulins, azathioprine, montelukast) to existing H₁-antihistamines plus corticosteroids, with no cessation of symptoms. Ciclosporin had a transient benefit but was stopped due to adverse reactions. Despite long-term treatment with low-dose oral corticosteroids

the patient still had severe urticaria, as determined by a weekly urticaria activity score (UAS7) >30 , with significant impact on her quality of life.

At 78 years of age, the patient was given omalizumab 150 mg every 4 weeks (*in the EU the recommended dose is omalizumab 300 mg every 4 weeks*). Her UAS7 decreased immediately, and corticosteroid and H₁-antihistamine treatment were discontinued. Both spontaneous lesions and pressure-induced urticaria resolved completely with omalizumab monotherapy. After 3 months, the monthly omalizumab dose was reduced to 75 mg with the patient's consent (*in the EU the recommended dose is omalizumab 300 mg every 4 weeks*). Efficacy was maintained for

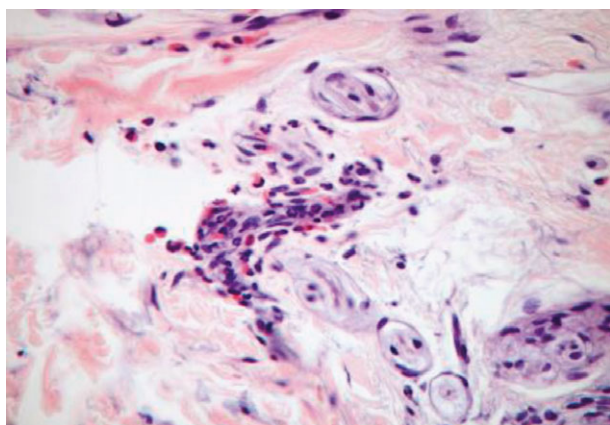


Figure 4 Skin biopsy of chronic urticaria in an elderly female, showing dermal perivascular infiltrate rich in eosinophils but no vasculitis (case provided by M. Gonalo).



Figure 5 Lip angioedema in a 70-year-old male after taking diclofenac (case provided by M. Snchez-Borges).



Figure 6 Lip angioedema in a 52-year-old male. Permission obtained from Korean Academy of Asthma, Allergy and Clinical Immunology and the Korean Academy of Pediatric Allergy and Respiratory Disease (Allergy, Asthma & Immunology Research). Sánchez-Borges M *et al.*¹²

3 months but when the dosing interval was increased to 5 weeks efficacy was poor. The patient responded once more when omalizumab dose was increased to 150 mg every 4–5 weeks. This patient was also able to undergo cataract surgery while receiving omalizumab treatment, with no additional treatment-related adverse events. This case supports the use of omalizumab in elderly patients, the importance of individualized treatment of chronic spontaneous urticaria with omalizumab in this population⁴, and confirms the efficacy of omalizumab also in delayed pressure urticaria.^{5,6}

CU exacerbated by concomitant medication – ASA/NSAID-exacerbated cutaneous disease

The patient is a 70-year-old male with recurring hives (mostly abdominal and on the forearms) for 3 years. He was admitted to the hospital for lip angioedema after taking diclofenac 2 h prior to the reaction (Fig. 5). Past medical history included a prostatectomy for benign hyperplasia, and disc herniation. Laboratory tests showed normal complement levels (C3, C4 and CH50). This patient has chronic urticaria/angioedema and aspirin hypersensitivity. Drugs causing non-allergic hypersensitivity reactions, namely NSAIDs, can not only elicit, but can also aggravate pre-existing CSU.⁷ The patient was diagnosed with ASA/NSAID-exacerbated cutaneous disease (AECD).

Exacerbation of CSU in patients with AECD is mediated by inhibition of cyclooxygenase [COX]-1.⁸ After a tolerance test, this patient was treated for pain and inflammation with celecoxib. Valdecoxib and rofecoxib were previously used in this setting but have since been withdrawn from the market because of rare, but serious, side-effects and increased prevalence of cardiovascular complications.⁹ It is recommended that a tolerance test is

performed prior to treatment with a COX-2 inhibitor (celecoxib or etoricoxib) and that classic NSAIDs are avoided in patients that are intolerant.⁸

CU exacerbated by concomitant medication – ACE inhibitor-induced angioedema

The patient was a 52-year-old male who was seen as an emergency case due to diffused facial and lip swelling (Fig 6). His medical history included hypertension, alcoholism and increased levels of aminotransferases due to alcohol-related liver damage. At the time of presentation he had been receiving aspirin, amlodipine and enalapril for hypertension, for the past 6 months. He was diagnosed with lip angioedema induced by the ACE inhibitor enalapril. The prevalence of ACE inhibitor-induced angioedema has been estimated to be approximately 30%, according to a multicentre study of patients who presented to an emergency department with angioedema.¹⁰ The postulated mediators of ACE inhibitor-induced angioedema are angiotensin 1, bradykinin and substance P.¹¹ In patients with enalapril-induced angioedema, hypertension can be treated with angiotensin receptor blockers and calcium antagonists. All ACE inhibitors should be avoided.

Summary

Current EAACI/GA²LEN/EDF/WAO urticaria guidelines include a treatment algorithm recommending first-, second- and third-line options, where the main aim of therapy is complete symptom control. In addition to the guideline-recommended third-line treatment options (omalizumab, ciclosporin, montelukast) several alternative therapies may be considered, although their use must always be carefully considered in relation to any patient comorbidities or complications.

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