Recent Advances in Dermatology

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Chapter 3

Update on the management of chronic urticaria

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INTRODUCTION

Chronic urticaria (CU) is a disease characterised by the development of itchy weals, angioedema, or both for more than 6 weeks. It is mediated by mast cell degranulation, which can be immunological or nonimmunological, leading to release of proinflammatory mediators including histamine [1]. It comprises several subtypes which are classified according to clinical pattern rather than etiology. The latter remains poorly understood in general despite abundant literature on the role of functional autoantibodies in the pathogenesis of the disease in more than a third of patients. The disease can cause significant disability affecting an individual's quality of life (QoL) and has a high economic burden with considerable health care costs [1]. Antihistamines have long been the mainstay, and at standard dose, the only licensed treatment for CU until the advent of omalizumab. This has encouraged a new interest in CU, not only because of its efficacy but also as it shed new insights into the pathophysiology of the disease and increased interest in research in the field. There is a sizable medical literature on the treatment of various subtypes of urticaria. This chapter will only cover current evidence-based management of the disease.

DISEASE TERMINOLOGY AND CLASSIFICATION

Chronic urticaria is divided into two main types. Chronic spontaneous urticaria (CSU) is characterised by the spontaneous appearance of weals and/or angioedema lasting for 24–48 hours. It is a relatively common disease with a point prevalence of 0.5–1% and a female predominance [2]. The inducible urticaria subtypes are each triggered by a specific and reproducible stimulus and resolve in less than 2 hours with the exception of delayed pressure urticaria. It is not uncommon for CSU and chronic inducible urticaria to overlap in some patients (**Figure 3.1**). Although the terms CSU and chronic idiopathic urticaria (CIU) are still used interchangeably in the medical literature, there has been an emphasis

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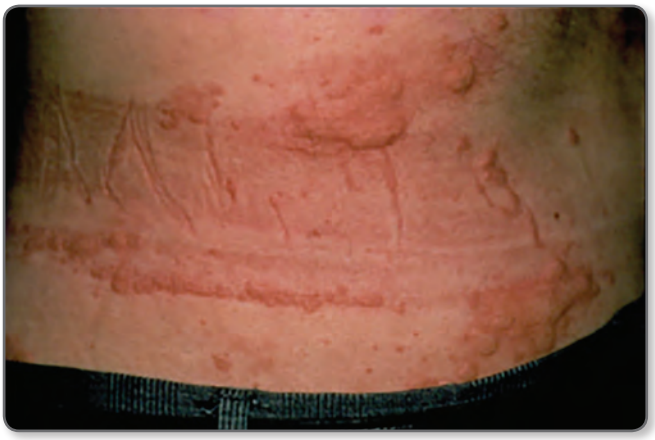

Figure 3.1 Chronic spontaneous urticaria and delayed pressure urticaria overlap.

in the latest urticaria consensus meeting on adopting the term CSU to refer to the disease [3]. CSU encompasses both chronic idiopathic and chronic autoimmune urticarias. Chronic inducible urticaria is further divided into subtypes, each a disease entity on its own (**Table 3.1**). It is important to differentiate urticaria from other medical conditions where weals, angioedema, or both can occur as a symptom like the autoinflammatory syndromes and from diseases that have been associated with urticaria for historical reasons like maculopapular cutaneous mastocytosis (urticaria pigmentosa) [1].

CHRONIC URTICARIA DIAGNOSIS AND ASSESSMENT TOOLS

The diagnosis of CSU is mostly based on a good medical history. Skin examination can be normal on clinical presentation due to the recurring nature of the disease. Unless suggested otherwise by the history and/or physical examination, no specific laboratory investigations are needed in the evaluation of CSU, as it is unlikely to identify an underlying etiology. Some clinicians measure the level of thyroid autoantibodies to identify circumstantial evidence for autoimmunity as an underlying cause for CSU. In addition, their presence could indicate a poorer disease prognosis with a longer course and more severe symptoms [4]. The diagnosis of an inducible urticaria is also based on a detailed medical history but should always be confirmed by a challenge test that aims to induce the rash by reproducing the stimulus that triggers it. The test should also help determine trigger thresholds, which provide objective measures for assessing disease severity and response to treatment [1].

Objective assessment tools have been developed to assess disease severity and its impact on QoL. These are also important to monitor patients while on treatment. The dermatology life quality index (DLQI) questionnaire is still widely used to measure the impact of the disease on patients' QoL although a disease-specific tool known as chronic urticaria quality of life questionnaire (CU-Q2oL) has proven to be superior and more sensitive [5]. As for disease severity, the urticaria activity score (UAS) is now a validated test that combines the daily number of weals and pruritus severity scores to create a daily score ranging from 0 to 6. The sum of UAS scores over 7 consecutive days (UAS7) has been used as an endpoint in many trials assessing the efficacy of omalizumab in CSU and is

Table 3.1. Current classification of chronic urticaria

Chronic spontaneous urticaria	Chronic inducible urticaria (known trigger)
No known eliciting factor	Symptomatic dermographism (mechanical shearing pressure) Delayed pressure urticaria (vertical pressure) Solar urticaria (ultraviolet and/or visible light) Heat urticaria (localised heat contact) Cold urticaria (cold contact) Vibratory angioedema (vibratory force) Cholinergic urticaria (change in core body temperature) Contact urticaria (contact with causal substance) Aquagenic urticaria (water contact)

now commonly used in clinical practice[5]. More recently, a new tool, the angioedema activity score (AAS), has been developed to assess disease activity in patients with recurrent angioedema, which is not assessed by the UAS [6].

CHRONIC URTICARIA TREATMENT

The management of CU is mostly pharmacological and aims at controlling the symptoms of the disease including pruritus as well as improving the QoL. In CSU, certain lifestyle modifications like heat and alcohol avoidance can be beneficial in some patients but mostly when combined with medical treatment. Avoiding the culprit trigger can alleviate an inducible urticaria but this is often a practical challenge. The most recent European guidelines for the management of urticaria have focused on evidence-based treatment options. These include H1-antihistamines as a mainstay therapy, to be supplemented with ciclosporin, omalizumab, or montelukast in case of antihistamine failure. Medications like H2-antihistamines, dapsone, and methotrexate, although still widely used in clinical practice, are no longer endorsed by these guidelines due to lack of trial evidence. Most of these therapies appear to work in CU by mechanisms that are yet to be elucidated. It is recommended to monitor the disease response to any of the above therapies by using the objective assessment tools and to stop the treatment when symptoms have settled to establish whether the disease has gone into spontaneous remission. Treatment can be restarted when the condition relapses. Indeed, it is reported that 80% of CSU patients become symptom-free after just 1 year of disease activity [2].

ANTIHISTAMINES

Antihistamines have been used in the treatment of urticaria since the 1950s and remain the mainstay of treatment. There is a long-standing experience among medical practitioners in the use of sedating H1-antihistamines but concern about their safety emerged over the past few decades in relation to sedation, especially with updosing. Most current guidelines recommend against their use [7]. Nonsedating H1-antihistamines (2nd generation) are first-line treatment for CU. They have all been shown to be effective in controlling the symptoms of urticaria but none stands out as the most effective [8]. For years, they have been, at the standard dose, the only licensed treatment for CU, until omalizumab was licensed in 2014 as well. Studies have shown they are often significantly

more effective at higher doses in both the spontaneous and inducible types of CU. The current European guidelines propose up-dosing H1-antihistamines up to 4 times the licensed dose, if necessary, before considering other treatment options, and there is real world evidence to show this practice is safe. Most studies have evaluated the updosing of a single antihistamine and hence the guidelines recommend this approach over combining different H1-antihistamines. However, studies have shown that up to one-third of patients show resistance to antihistamine therapy [9].

OMALIZUMAB

Omalizumab is a humanised anti-IgE monoclonal antibody. It has been intensively studied in the field of allergic asthma for which it is a licensed treatment. Although the specific mechanism of action of omalizumab in CU is still unknown, it is thought to increase mast cell stability by sequestering free IgE and subsequently down-regulating membrane bound FcεRI [10]. Several multicentre randomised controlled trials have demonstrated the efficacy and safety of omalizumab in CSU irrespective of autoimmune status and background therapy for the disease. Overall, the use of omalizumab at a dose of 300 mg demonstrated the best results in controlling CSU symptoms and improving QoL [11–14]. Omalizumab appears to be effective not only in reducing pruritus and number of weals but also in alleviating angioedema when it is a component of CSU [15,16]. It is the only licensed treatment for H1-antihistamine resistant CSU patients. A real-world retrospective study of CSU patient cohorts treated with omalizumab and ciclosporin showed better outcomes and improved QoL with omalizumab [17]. The practice of prescribing omalizumab is different among various centres in the world. In the UK, the National Institute for Health and Care Excellence (NICE) recommends omalizumab as an add-on therapy for treating severe CSU in adults and young people aged 12 years and above. Patients should demonstrate inadequate response to H1-antihistamines with montelukast (UAS7 scores ≥28) to be eligible for therapy. Omalizumab is administered as a 300-mg subcutaneous injection every 4 weeks for a total of 6 months. According to NICE guidance, omalizumab should be stopped before or at the fourth dose if CSU has not responded to treatment. At the end of a 6 months treatment cycle, omalizumab is also stopped to re-assess disease activity and can be restarted if the disease relapses. Patients should be monitored for signs of anaphylaxis following each injection although no confirmed cases have been reported in CSU patients to date. Therapy is monitored using objective disease assessment tools (UAS7 and DLQI) and there is no need for baseline or monitoring biochemical tests [18]. More studies are needed to establish the mechanism of action and optimum treatment duration of omalizumab in CSU. Although not licensed for inducible urticaria, there are several case reports/series on efficacy of omalizumab in various subtypes of inducible urticaria [19,20]. Omalizumab has been observed to be effective and safe in children as young as 2 and in pregnant woman but the data is based on individual case reports/series and its use in such settings is only recommended when the expected benefit outweighs any potential risk [20–22].

CICLOSPORIN

Ciclosporin is so far the best-studied immune modulator in the treatment of CSU. There is strong evidence-based data to support its efficacy, in daily doses ranging between 3–5 mg/kg, in the treatment of recalcitrant disease, usually as add on-therapy

to H1-antihistamines [23,24]. Its long-term use is limited by its potentially serious side effects including increased serum creatinine and hypertension. Patients should be closely monitored accordingly. Most of these effects are dose-related and reversible on discontinuation of therapy and it appears that a lower dose of the drug (2–3 mg/kg/day) is better tolerated while still effective in CSU. In addition, long-term use of ciclosporin in transplant recipients has been associated with an increased risk of malignancy [25]. Ciclosporin has been shown to be more effective in patients with positive basophil histamine release assay, which is used as a marker for autoimmune urticarial [26]. In general however, phenotyping patients is not required before treatment.

MONTELUKAST

Montelukast is a leukotriene receptor antagonist. In the UK, it is licensed in the prophylactic treatment of asthma and to relieve symptoms of seasonal allergic rhinitis in patients with asthma. There is evidence to support its added therapeutic benefit in the treatment of CSU when used in combination with H1-antihistamines but not when used as monotherapy [27]. A therapeutic response is usually expected in the first 3 weeks of treatment beyond which therapy should be discontinued if the disease remains symptomatic [28]. It is recommended as add-on therapy if antihistamine monotherapy fails in the US guidelines whereas the European guidelines advocate its use only when up-dosing antihistamines has failed. There are anecdotal reports about its efficacy, along with H1-antistamines, in the treatment of some types of inducible urticaria with most evidence for delayed pressure urticaria [29].

ORAL CORTICOSTEROIDS

The efficacy of systemic corticosteroids in the treatment of different types of CU is well established and they are included in CU treatment algorithms of international guidelines. However, there is only one retrospective study on their use in CU, which might explain why there is no widely agreed therapeutic regime of their use to treat the disease [30]. The current European guidelines recommend a short course (maximum of 10 days) of oral corticosteroids to control acute flares of CU despite treatment with first, second, or third line agents. As such, corticosteroids continue to play an important role in the management of CU but are regarded a rescue rather than mainstay treatment.

FUTURE PERSPECTIVES

There have been important changes in the management of CU over the last decade. There is general agreement among CU experts to use a more specific terminology and to simplify the classification of the disease. New disease assessment tools are now widely used. These not only provide an objective way of assessing disease severity but also emphasize the importance of considering the disease' significant impact on QoL. The most recent guidelines have focused on simple stepwise therapeutic algorithms with evidence-based and safer treatment options. However, there remain unmet needs in the management of CU. Real-world data has demonstrated heterogeneity in patients' response to various treatments implying different phenotypes for the disease. This is still poorly understood and more evidence is required to shed light on this observation and eventually help

us better understand the pathophysiology of the disease. It has been suggested that identification of potential biomarkers to monitor CSU activity and response to treatment would help clinicians predict disease outcomes and propose more specific treatment algorithms [31].

Key points for clinical practice

- Chronic spontaneous urticaria (CSU) is the most common type of chronic urticaria.
- Although the pathophysiology of CSU remains poorly understood, there have been major advances in the management of the disease over the past few years.
- Omalizumab is now licensed for the treatment of CSU and appears to be a more effective and safer treatment than immunosuppressive therapies.

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