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REVIEW ARTICLE

Stepping Down Treatment in Chronic Spontaneous Urticaria: What We Know and What We Don't Know

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Abstract

In chronic spontaneous urticaria (CSU), wheals, angioedema, or both appear spontaneously for > 6 weeks. Current recommended treatment options for urticaria target mast cell mediators such as histamine, or activators, such as autoantibodies. The goal of CSU treatment is to treat the disease until it is gone as effectively and safely as possible. As no cure is available for CSU as of now, the treatment is aimed at continuously suppressing disease activity, with complete control of the disease and a normalization of quality of life. To achieve this, pharmacological treatment should be continued until no longer needed. Treatment of CSU should follow the basic principles of treating as much as needed and as little as possible taking into consideration that the activity of the disease may vary. Since CSU is a disease with spontaneous remission, it is hard to tell, in patients with complete control and no signs or symptoms, when medication is no longer needed. The current international guideline for urticaria suggests that the treatment can be stepped down once a patient is free of signs and symptoms. Other reasons for stepping down the treatment of CSU patients include safety concerns or issues, pregnancy or wanting to become pregnant, and economic factors. As of now, it is unclear over which period, with what intervals and with which dosages CSU treatment should be stepped down. Guidance on this is needed for all recommended therapies: (i) standard-dosed second-generation H1-antihistamine (sgAH), (ii) higher than standard-dosed sgAH, (iii) standard-dosed omalizumab, (iv) higher than standard-dosed omalizumab, and (v) cyclosporine. However, there is a lack of controlled trials on the step down and discontinuation of these treatments. Here, we aim to provide a summary of what is known and what needs to be investigated in further studies, based on our own experience and real-world evidence.

1 Introduction and Background

Chronic spontaneous urticaria (CSU), a common disorder with a global prevalence of about 1%, is defined by the spontaneous occurrence of itchy wheals, angioedema or both, without any apparent reason, for > 6 weeks [1, 2].

In virtually all cases, CSU is a self-limiting disorder with spontaneous remission after 2–5 years, although about 20–50% of patients have CSU for > 5 years [3, 4].

Key Points

Chronic spontaneous urticaria (CSU) is a self-limited disease and good communication about duration and goals of treatment is necessary (as little as possible, as much as needed).

The decision to step down or stop treatment in CSU is mainly based on the score of the urticaria control test (UCT).

In patients with complete control, discontinuation/tapering of antihistamines should be considered after 3 months, and of omalizumab after 6–12 months.

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CSU is often debilitating, difficult to treat, and frustrating for both patients and physicians. More than half of patients have moderate-to-severe disease activity. CSU poses a substantial burden for patients, for example by markedly interfering with sleep and daily activities [5], thus impairing quality of life (QoL).

CSU is treated following recommendations from the international guideline on the management of urticaria [6]. According to these recommendations, treatment should be adjusted to the patient´s individual and specific needs, to provide complete control and protection from all signs and symptoms of CSU. In the newest update of this guideline, the *International EAACI/GA²LEN/EuroGuiDerm/APAAACI Urticaria Guideline*, this treatment strategy has been supplemented with an "as much as necessary and as little as possible" approach. The treatment is to be adjusted according to how well the disease is under control, based on the outcome of the urticaria control test (UCT) [6, 7].

Why should stepping down treatment be considered in CSU patients? There are many possible reasons, such as safety concerns or issues, pregnancy or wanting to become pregnant, and economic factors. The most common reason in CSU patients who achieve complete control and freedom of signs and symptoms, is to check for spontaneous remission. The longer patients who are using treatment are in full control of their disease and have no signs and symptoms of CSU, the higher the chance of spontaneous remission of their CSU. As there are currently no biomarkers for the occurrence of spontaneous remission in treated patients without signs and symptoms, the only way to determine whether or not patients still need their treatment is to discontinue it. There are, however, no guideline recommendations or data from controlled studies on when and how to do this. Step down strategies and protocols vary widely, and looking at their pros and cons as well as the challenges linked to different strategies for stepping down therapy is important. Based on our experience and a review of the recent literature, we herein discuss strategies for discontinuation of treatment in complete responders with CSU, trying to form a better understanding and give an outline on what we know and what we don´t know.

2 What are the Treatment Aims in Chronic Spontaneous Urticaria (CSU)?

The international urticaria guideline recommends, for CSU, to "treat the disease until it is gone". As CSU cannot be cured yet, this means two things: First, to aim for complete disease control and the absence of signs and symptoms by the use of prophylactic therapy. Second, to continue treatment and maintain complete response until spontaneous remission occurs. Why is complete control and freedom of signs and symptoms what we want to achieve for our patients with CSU? Patients with CSU can be severely impaired by their itchy wheals and angioedema, and they often are. They are also impaired by the unpredictability of their disease. Since new wheals and angioedema can occur at any time, patients live in constant fear of new attacks including the fear of suffocation. This adds to the physical, social and emotional impairment in CSU patients. Therefore, many patients develop depression and anxiety, which further impairs quality of life, mental health, and performance at work and school [8]. Having fewer wheals and angioedema translates to less impairment, but only complete control and total freedom from wheals and angioedema takes away the unpredictability of CSU and allows patients to plan and focus on their daily life without having to constantly worry that symptoms might appear again [9].

3 How Do We Assess Whether CSU Patients Achieve the Goals of Treatment?

As of now, there are no laboratory markers for disease activity or control, there are no objective measurements of itch, and wheals and angioedema are hard to assess objectively, due to their sudden, recurrent and fluctuating occurrence. Disease activity and control in CSU are therefore assessed with the help of various patient-reported outcome measures (PROMs, see Table 1). PROMs are questionnaires through which health outcomes are directly reported by the patients who experience them. In CSU, the urticaria control test (UCT) is the main PROM for use in routine clinical practice [6], and it should be used by all patients with CSU, but also by those with chronic inducible urticaria. The UCT is a simple four-item tool with questions on disease activity, disease control and quality of life during the past 4 weeks. A UCT version with a 7-day recall period is also available (UCT7). A score between 0 and 4 points is assigned to every answer option. Subsequently, the points for all four questions are summed up for the UCT score. The minimum and maximum UCT scores are 0 and 16 points, respectively, with 16 points indicating complete disease control. A UCT score of <12 points indicates poor disease control and the need for treatment step up. A UCT score of 12–15 points reflects well controlled disease and should prompt efforts to optimize the treatment until 16 points and complete control are achieved. Its retrospective approach and simple scoring system make the UCT an ideal instrument for the management of patients with chronic urticaria in clinical practice [10]. The UCT is widely available in many languages and included in the UCARE app for patients with CSU, and the chronic

Table 1 Patient-reported outcome measures to assess if CSU patients achieve complete control and freedom from signs and symptoms, the treatment aims in CSU

Name	Measures	Data collection	References
Urticaria Control Test (UCT)	Disease control	4-week recall period	[10]
Urticaria Activity Score (UAS/UAS7)	Disease activity	Daily documentation for 7 consecutive days	[12]
Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL)	Quality of life	2-week recall period	[13]
Angioedema Control Test (AECT)	Disease control	4-week or 3-month recall period	[20, 21]
Angioedema Activity Score (AAS)	Disease activity	Daily documentation for 28 consecutive days	[14]
Angioedema Quality of Life Questionnaire (AE-QoL)	Quality of life	4-week recall period	[22]

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urticaria self-evaluation app, CRUSE (https://cruse-control.com).

To assess CSU patients as accurately as possible, additional PROMs should be used. The urticaria activity score (UAS) measures CSU disease activity based on once-daily documentation of the numbers of wheals and itch severity [11]. The weekly UAS (UAS7) is the sum score of 7 consecutive days [12]. The CU-Q2oL (Chronic Urticaria Quality of Life Questionnaire) is used to measure the impact of CSU on quality of life and subjective wellbeing [13].

CSU patients can have wheals without angioedema, angioedema and wheals, or experience angioedema exclusively. Angioedema is characterized by suddenly occurring cutaneous and/or mucosal swellings [14]. More than half of CSU patients with wheals also have angioedema, and about 10% of CSU patients have angioedema but no wheals [3]. Patients with angioedema and wheals more often have a disease duration of > 1 year, compared with patients who exclusively develop wheals (64–70% vs 43–48%) [15, 16]. CSU patients with angioedema and without wheals appear to have an even longer disease duration [16–18]. Recent studies show that, in patients with CSU, angioedema may be underdiagnosed, with patients reporting it more often than their physicians (65·8% vs 41%) [19]. Taken together, this underlines the need to assess CSU patients for the presence, frequency, severity, and impact of angioedema. For this, angioedema-specific PROMs should be used.

Disease activity in CSU patients who exclusively or primarily develop angioedema is assessed with the Angioedema Control Test (AECT) [20, 21]. The AECT has four questions with five answer options each, addressing the frequency of angioedema, angioedema-related QoL impairment, unpredictability of angioedema attacks, and angioedema control with the current treatment approach. Like the UCT, the AECT is easy to administer, easy to complete, and easy to score, and it is included in CRUSE, which makes it an ideal assessment tool [20].

The Angioedema Activity Score (AAS) and the Angioedema Quality of Life Questionnaire (AE-QoL) are used as complimentary tools. The AAS is the first validated and reliable tool to determine disease activity in patients with recurrent angioedema (RA). AE-QoL is the first angioedema-specific QoL questionnaire [22].

4 Why and When Should Treatment Discontinuation Be Considered in CSU patients?

There are currently no reports of large and systematic studies on the duration of CSU treatment and reasons for stopping it. Such studies are currently under way, for example the UCARE DRUSOCU study, which assesses omalizumab drug survival in CSU. In our experience, reasons for stopping CSU treatment include safety concerns or issues, treatment burden, economic factors, patient requests to participate in a clinical trial, pregnancy or wanting to become pregnant, the onset of another disease or intake of a new treatment, and the hope that spontaneous remission has occurred.

4.1 The Role of Patient Concerns, Drug Safety, and Treatment Burden in CSU Treatment Discontinuation

Many CSU patients are worried about short- and long-term side effects when it comes to their medication, especially since they need to use it continuously over a long period of time, often many years. These concerns should be addressed by CSU-treating physicians. It is important to communicate to patients that antihistamines and omalizumab have been used for a long time, by many patients, and are generally considered to be safe, although side effects are possible. Long-term real-life studies on standard-dosed and higher than standard-dosed antihistamines and omalizumab should be performed to confirm and increase the confidence in the safety of these treatments and to address patients' concerns with real-world evidence. The fact that CSU treatment, albeit of long duration, is not for life, should be communicated to patients, as it can increase their willingness to use and stay on prophylactic treatment. The burden of treatment

of CSU with antihistamines or omalizumab is low, but not zero. Currently, it is unclear how often CSU treatment is stopped because of its burden or because of safety concerns or issues. From our experience, treatment burden and safety concerns or issues are rare causes of treatment discontinuation, although they can be important in some patients. When patients stop their treatment because of safety concerns or issues or because of the burden of treatment, they usually do this all at once, rather than by gradually decreasing the dose.

4.2 The Role of Economic Factors in the Discontinuation of CSU Treatment

The costs of CSU treatment are another important aspect to be considered. Treatment with omalizumab is expensive, even though it was demonstrated to be cost effective [23, 24]. Not every healthcare system has the capacity to carry those costs, especially for a longer period of time. The medical benefit must be in reasonable proportion to the costs. Patients on omalizumab treatment should, therefore, not receive further treatment after spontaneous remission has occurred. Since this can only be determined by stopping the treatment, protocols for discontinuation must balance the burden of relapse with the costs of treatment. In many countries, the decision on when and how to discontinue treatment in complete responders is that of the treating physician, as it should be. In some countries, however, the duration of omalizumab treatment is restricted by regulatory authorities, insurance companies, or the financial burden for patients who pay for treatment out of pocket.

4.3 The Role of Clinical Trials in the Discontinuation of Treatment

Over the past years, with several new treatments for CSU in development, we have seen increasing opportunities and patient interest in participating in clinical trials. The reasons for this are manifold and include incomplete response to current treatments, hope for receiving disease-modifying treatment, and the wish to help with the development of new and better treatments. Current treatment with omalizumab is an exclusion criterion for all ongoing and new clinical trials. This leads to patients requesting to stop their omalizumab treatment. When this happens, treatment is usually stopped immediately rather than tapered, in order to shorten the time to study participation.

4.4 The Role of Pregnancy and Wanting to Become Pregnant in the Discontinuation of Treatment

Most patients with CSU are female, and since the disease often occurs during the reproductive age, pregnancy is an important aspect to consider in the management of CSU [25]. Pregnancy is a common reason for the discontinuation of CSU treatment. The recent UCARE PREG-CU study [26] showed that more than 80% of CSU patients, when they decide to become pregnant, continue to use their medication. In contrast, two thirds of CSU patients who used regular treatment before pregnancy changed to another treatment or stopped their treatment altogether once the pregnancy began [26]. In our experience, fear of harming the unborn child is the main reason for this, although sgAHs and omalizumab are generally regarded as safe to use during pregnancy [27, 28]. Some women with CSU hope that their pregnancy will improve their urticaria, so that they no longer need treatment. In fact, the UCARE PREG-CU study demonstrated that chronic urticaria, during pregnancy, improves in about half of the patients [29]. Independent of the reason, when patients stop their treatment because they plan to become pregnant or because they are pregnant, they usually discontinue their medication all at once, rather than by tapering.

4.5 The Role of the Onset of Another Disease or Intake of a New Medication in the Discontinuation of Treatment

The onset of another disease, for example cancer, or the need for treatment of another disease, are rarely the reason for the discontinuation of CSU treatment, although they often cause concerns. Patients and physicians may think that the onset of another disease is caused by the CSU treatment received or that its continued use may negatively affect the newly diagnosed disease. Both are uncommon. None of our CSU patients treated with sgAHs or omalizumab, as of yet, discontinued their treatment because a new disease was diagnosed. Also, there are no reports that suggest that omalizumab is less safe or effective in CSU patients with comorbid malignancy. For now, the only contraindication to omalizumab is a history of hypersensitivity reactions to omalizumab [30], and in our experience and opinion, patients with comorbid malignancy can and should be considered for omalizumab treatment if needed.

The situation is similar when a new treatment needs to be started, especially a biologic treatment. Patients and physicians are often concerned that the current CSU treatment may interfere with the efficacy or safety of the new treatment needed, although this is usually unwarranted. None of our patients, as of now, discontinued their sgAH or omalizumab treatment, because another treatment had to be initiated. This includes other biologics [31–34].

4.6 The Role of Spontaneous Remission in the Discontinuation of Treatment

The most common reason for stepping down treatment in CSU patients is to check for spontaneous remission after

Table 2 Guideline-recommended treatment options for CSU

Drug	Pro	Con
Second-generation antihistamine	Low cost Worldwide availability (modern second-generation H1-antihistamines also exist in developing countries) Very good safety profile	Limited efficacy
Omalizumab	Very good safety profile Very good efficacy	High cost
Cyclosporine	Good efficacy	Medium to high cost Moderate safety profile

achieving complete control and freedom of signs and symptoms. There are currently no biomarkers for the occurrence of spontaneous remission in treated patients without signs and symptoms [35].

In some studies, but not others, higher rates of relapse were linked to long pre-treatment disease duration, being female, fast response to treatment, or high baseline disease activity [36–38]. While these markers may predict relapse on a group level, they are not useful for the prediction of relapse or for guiding stepping-down decisions for individual patients. Thus, whether or not patients still need their treatment can only be determined by stopping it [7]. Relapse after discontinuation of treatment is the rule rather than the exception. In a recent study, two thirds of patients who discontinued omalizumab experienced relapse [39]. In our personal experience, this rate is even higher.

5 How to Discontinue Treatment in CSU Patients with Complete Response

The decision to step down treatment and the choice of protocol for doing so are individual and require shared decision making. Interactive consultation should combine the physician's experience and expertise with the patient's needs and expectations. The overall disease experience differs from patient to patient. CSU patients with high pre-treatment disease activity, strong QoL impairment, and a long disease duration may prefer to delay discontinuation and to opt for a well-regulated stepping-down strategy over a longer period of time rather than stopping treatment abruptly. In our experience, this is often the case. Bringing patients' perspectives and needs into the decision on when and how to stop treatment can promote better patient understanding of the process, better risk perception, and more realistic expectations [40, 41].

Good communication is key. Patients need to understand that the reason for stopping their treatment is to see if the disease is still there. To this end, they should be encouraged to document their response to treatment discontinuation with the use of PROMs, for example with the help of the CRUSE app. Patients also need to understand, before the decision to stop the treatment is made, that the duration of their complete response does not affect the risk of relapse, as none of the current guideline-recommended treatments are considered to be disease-modifying. In one study [39], the rate of relapse was not different in patients who stopped omalizumab after 6 months or after 1 year of complete response. Most importantly, patients need to know that relapse is expected to happen after treatment discontinuation, with studies on omalizumab, for example, showing that the majority of patients will experience relapse after stopping it [42–44], even if the treatment is maintained for 1 year [43]. Patients need to understand that, in this case, they should resume treatment as early as possible and that they can expect retreatment to be effective and safe [42–46], even with multiple retreatment cycles [47]. Patients should also know that relapse of CSU after stopping omalizumab cannot be controlled with antihistamines and, therefore, re-treatment with omalizumab is needed. A process and protocol for retreatment after CSU relapse should be in place, for example by providing instructions and medication for restarting sgAH treatment or by scheduling an ad-hoc visit at short notice to re-initiate omalizumab treatment.

Stepping-down strategies differ across the five guideline-recommended treatment protocols. The latter include the use of a standard-dosed sgAH, the first-line treatment for CSU, stepping up the sgAH dose, omalizumab treatment at standard or higher than standard dose, and cyclosporine (Table 2).

5.1 How to Step Down and Discontinue Second-Generation H1-Antihistamine (sgAH) Treatment

In patients with complete response to daily treatment with a standard-dosed sgAH, discontinuation should be considered after 3–6 months of uninterrupted complete control and complete freedom of signs and symptoms. A standard-dosed sgAH is usually stopped all at once, but some patients benefit from taking their sgAH every other day for

1–2 weeks before they stop it for good. Re-treatment upon relapse should be maintained for 3–6 months of complete response before another attempt at treatment discontinuation is considered.

In patients who achieve complete response with a higher than standard-dose sgAH, we usually maintain that dose for 3 months before we consider reducing the dose. Dose reduction is highly individual, ranging from a reduction by one tablet every month to halving the dose every week. All step-down strategies have the common goal of finding the lowest sgAH dose that provides complete control and complete protection from CSU signs and symptoms. When the reduction of the sgAH dose results in relapse, patients are advised to recommence treatment with the last dose that provided complete response, which is then maintained until 3–6 months of continuous complete control and freedom from CSU signs and symptoms are achieved. Breakthrough wheals or angioedema that occur during this time prompt a reset (and possibly a dose escalation). After 3–6 months of complete response, patients are advised to try again to step down and eventually discontinue their sgAH treatment.

5.2 How to Step Down and Discontinue Omalizumab Treatment

When the recommended initial dose of omalizumab (i.e. 300 mg every 4 weeks [48]) results in complete response for at least 3 months, our first step-down measure is the reduction of concomitant sgAHs, which most patients use at higher than standard dose when they start omalizumab. Virtually all complete responders to omalizumab can discontinue their sgAH intake without losing complete control [49, 50]. This is usually done by reducing the sgAH by one tablet or half the dose every week, although some patients prefer to do this more slowly.

In patients with complete response to standard-dosed omalizumab monotherapy, we usually consider treatment step down and discontinuation after 1 year and virtually never before 6 months of complete response [28]. Importantly, breakthrough attacks during this year indicate that spontaneous remission has not yet occurred and these reset our 1-year timer. After 1 year of PROM-controlled complete response, we usually advise patients to increase their omalizumab injection intervals by one week. When this results in the reappearance of CSU signs and symptoms, patients are advised to continue treatment with the longest interval that had previously provided complete response, for 1 year, before step down and discontinuation is tried again. The vast majority of patients who can extend their omalizumab treatment interval to 8 weeks without relapse can stop their treatment for good [51–54]. This is supported by a recent study with 19 CSU patients with complete response to omalizumab treatment for at least 6 months, who extended their treatment interval by 1 week for each treatment and stopped omalizumab after reaching 8- to 9-week intervals [54]. Nine of these 19 patients were able to discontinue omalizumab this way, whereas the others relapsed after extending intervals to 5 or 6 weeks. Omalizumab can also be stopped all at once [55], and some patients prefer this. Based on published evidence and our clinical experience, both strategies are effective, and rates of relapse are similar. One of the benefits of the interval extension strategy is the minimization of time to retreatment in patients who show relapse [56]. More importantly, it can help patients identify their best (i.e. longest) individual injection intervals, which can be used for treatment continuation if needed. Stopping all at once, for some patients, is easier to manage than interval extension. Both strategies should see patients document their response to treatment discontinuation with the help of PROMs, so that retreatment can be started if needed.

How do we step down higher than standard-dosed omalizumab treatment? Here, the aim is to first reduce the dose of omalizumab to the standard dose. We advise our patients to try this after the use of higher than standard-dosed omalizumab has provided $\geq$ 3 months of complete control. To this end, patients on shorter than standard injection intervals extend their interval by 1 week at a time, until they reach the standard interval of 4 weeks. Patients who treat with 450 mg or 600 mg reduce the dose by 150 mg every 1–3 months, until they reach the standard dose of 300 mg. Patients who treat with 450 mg or 600 mg omalizumab every 2–3 weeks step down their treatment by dose reduction or interval extension, not both. Once the standard dose has been achieved while maintaining complete response, we proceed as outlined above.

5.3 How to Step Down and Discontinue Cyclosporine

In patients who use cyclosporine, with or without omalizumab, we step down cyclosporine after 6 months of maximum treatment. We stop cyclosporine by reducing the dose gradually or all at once, depending on individual patient needs and expectations. When cyclosporine is reduced gradually, we recommend to reduce by 1 mg/kg every 2 weeks.

6 Unmet Needs, Knowledge Gaps, Future Studies

As outlined above, there are many unmet needs and knowledge gaps when it comes to the discontinuation of CSU treatment. Further studies are needed to obtain the

evidence required to guide step-down decisions. Most importantly, we need to identify markers of spontaneous remission of CSU in patients with complete response to prophylactic treatment. In addition, we need to better characterize the benefits and challenges of stopping treatment all at once or by tapering, and the reasons for choosing either strategy. As the evidence and experience increase on when and how to discontinue CSU treatment, step-down recommendations should be included in future updates and revisions of the international urticaria guideline.

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