Swiss Expert Opinion on the Management of Chronic Spontaneous Urticaria

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Report

This article presents the current Swiss recommendations concerning the evaluation and treatment of chronic spontaneous urticaria. These recommendations are based upon International Guidelines[3] and on the personal experiences in daily clinical practice of the participating experts. These recommendations reflect the opinions of the experts and have been compiled during an Advisory Board meeting organised by Novartis Pharma Schweiz AG.
Twelve participants attended the board meeting, hence a consensus was reached with 10 votes. If not stated otherwise, the recommendations reflect the consensus of opinion arrived at by the participants.

Introduction

According to the updated international guidelines, urticaria is characterised by a sudden appearance of wheals, angioedema or both[3]. Urticaria can be classified as acute and chronic urticaria (CU; >6 weeks), with CU being further subclassified as chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CINDU). CSU is the spontaneous development of symptoms without any apparent trigger. It includes patients with known causes such as autoreactivity, infections, intolerance reactions to drugs, food or additives as well as patients with unknown causes of their urticaria[3]. CSU has a high overall impact on quality of life (QoL) comparable to other dermatological conditions such as psoriasis[7]. Further, there is a high socioeconomic impact arising from both the direct costs (e.g. medication or healthcare visits) and indirect costs (e.g. absence or reduced efficiency at work) associated with the condition[6].

Diagnosis and diagnostic tests recommended for CSU[3]

The first step in diagnosing is a thorough examination of the patient's history including the time-of-onset, frequency, duration, concomitant symptoms, causative/provoking factors, concomitant diseases and previous therapy. Diagnosis is recommended to be performed in accordance with international guidelines[3] Figure 1 illustrates a simplified version of the internationally recommended guidelines. Urticaria can be associated with angioedema which should be diagnosed and treated concomitantly. Other forms of angioedema such as bradykinin-associated angioedema (e.g. hereditary angioedema) or drug-induced angioedema [ACE-Inhibitors, sartans, gliptens] usually present without associated urticaria and are therefore not considered here [3].

- Check for clinical characteristics of urticaria: wheals with a duration of less than 24 hours, no epidermal component, no postlesional marks
- Check for urticarial dermographism
- Differential blood count and BSG or CRP
- Determine thyroid autoantibodies (anti-thyreoperoxidase (TPO), anti-thyreoglobulin (TAK),Thyreotropin-Rezeptor-Autoantikörper (TRAK) and TSH basal level (detection of thyroid dysfunction)

Extended Diagnostic tests[3]
In general, extended diagnostic procedures and the evaluation of possible causes are only recommended if so indicated by the symptoms (e.g. fever, arthralgia, malaise) and patient history. Currently, there is no strong evidence to include all of

the tests listed below in a routine CSU diagnostic work-up. The recommendations as to what extent the tests should be applied varies among experts. Hence there was no clear consensus regarding for the following list of tests. In individual cases these tests may however be of use (Table 1).

Management of CSU

1. General aspects
Once diagnosis is concluded, the board recommends the treatment of CSU according to the escalation algorithm proposed by the international guidelines (Figure 2)[3].
Discontinuation of possible triggering factors:

- e.g. medications (such as aspirin (above 100mg/day) and NSAIDs; if suggested by clinical history)
- Food containing histamine and biogenic amines, if suggested by history in severe cases

Considering that urticarial symptoms change frequently in intensity, the overall disease activity can be measured by advising patients to document 24-hour self-evaluation scores once daily for several days. International guidelines recommend assessing the disease activity in CSU using the urticaria activity score 7 (UAS7, Figure 3), a unified and simple scoring system that has been validated[3]. The UAS7 is based on the assessment of key urticaria symptoms (wheals and pruritus) over a period of 7 days and is suitable for the evaluation of disease activity by urticarial patients and their treating physicians (Figure 3). Such an assessment of disease activity may be of particular importance when treating by means of third line therapies, such as Omalizumab, as it guarantees somewhat objective and patient reported monitoring of the control of the disease.

2. Therapy of CSU with antihistamines
Most symptoms of urticaria are mediated by the actions of histamine on H1-receptors located on endothelial cells (the wheal) and on sensory nerves (neurogenic flare and pruritus). Thus, continuous treatment with H1-antihistamines is of eminent importance in the treatment of urticaria (safety data are available for using these drugs continuously over several years). The continuous use of H1-antihistamines in chronic urticaria is supported by the results of clinical trials and by the mechanism of action of these drugs[12]. H1-antihistamines are inverse agonists with preferential affinity for the inactive state of the histamine H1-receptor, which is stabilised in this conformation. Second generation H1-antihistamines are preferred because of their increased benefit/risk ratio, e.g.they are non-/less sedative. If AH single dose per day does not sufficiently control CSU, H1-antihistamines AH up-dosing up to the four-fold dose is recommended (see Figure 2). Note: although well-established as treatment regiment, up-dosing of H1 antihistamines up to four-fold represents an off-label treatment and should therefore only take place after informing the patient about the possible risks. In individual cases, switching to another H1-antihistamine can be tried in order to optimise the response

3. Therapy of CSU with Xolair® (Omalizumab)
CSU is mediated by mast cells that upon activation degranulate and release inflammatory mediators, including histamine, that cause the clinical signs and symptoms [5]. In addition to intrinsic factors within the mast cells and non-immunologic factors such as components of the complement system and neuropeptides, two main immunologic mechanisms seem to be important for the pathogenesis of CSU: 1. The priming of mast cells by monomeric IgE without FceRI cross-linking, and 2. Autoreactive antibodies that are either IgE type or IgG targeting IgE and its high affinity receptor FceRI[5].
Omalizumab is a recombinant, humanised, monoclonal, anti-IgE antibody that targets the C3 domain of the Fc region of IgE, and thus may neutralise free IgE[8,6]. The exact mechanism by which Omalizumab acts upon CSU needs to be expanded upon. By decreasing free IgE levels in the blood and tissues, Omalizumab might reduce the priming and activation of mast cells. Impeding IgE and FceRI engagement is suggested in order to result in an increase in the mediator release threshold and thus a decrease in mast cell sensitivity to various stimuli. Moreover, in CSU, Omalizumab may target autoreactive IgE antibodies and prohibit their binding to the FceRI receptor. In the case of autoreactive IgG antibodies against IgE or FceRI, Omalizumab is assumed to reduce IgE binding to its receptor with subsequent downregulation of FceRI expression on mast cells [5]. Furthermore, by affecting IgE+ B cells, Omalizumab is thought to reduce the production of IgE[10]. Recently, Omalizumab at high concentrations was reported to accelerate the dissociation of preformed IgE-FcεRI complexes on the surfaces of allergic effector cells[11]. Omalizumab has proven to be efficacious and well-tolerated in the treatment of CSU.

Table 1: Extended diagnostic tests for CSU and differential diagnoses

Physical test	based on specific history (cold, heat, and pressure tests, exercise)
Tests for infectious diseases	e.g. Helicobacter pylori if GI symptoms (breath or stool test), search for parasites if history of travelling or blood eosinphilia
Autologous serum skin test / basophil activation test	May be useful for the detection of auto-reactivity
Skin prick test, specific IgE	to detect type I allergy if there I the suspicion of a specific allergen
Tryptase	If relevant based upon clinical symptoms (e.g. repeated anaphylaxis, signs of mastocytosis)
Autoantibodies	as a 3rd level investigation in CU > 6 months and not responding to usual treatment and/or with leading symptoms such as symptoms of the gastrointestinal tract or neurological system • anti-nuclear antibodies, if there is a suspicion of associated autoimmune diseases (such as joint pain, fever, vasculitis)
Skin biopsy of lesional skin	If there is a suspicion of vasculitis and if wheals last longer than 24 hours, for conventional histology (H&E) and additional direct immunofluorescence analysis (immunoglobulins and C3)

Indication of Omalizumab in CSU (according to Swissmedic)[1]

Additional therapy for adults and children (starting at 12 years old) with persistent* chronic spontaneous urticaria (CSU), which could not be controlled by H1-antihistamine therapy, and for which an evaluation by a physician familiar with this clinical picture did not find any other underlying disease[1].

Limitations to health insurance coverage (according to BAG)[2]

CSU in adults and children (from 12 years of age) with inadequate response to treatment with H1-antihistamines, with the prerequisite that treatment by a medical consultant for allergies and clinical immunology, or dermatology and venereology, was prescribed[2].

* In the pre-approval studies, patients were examined for whom the duration of the CSU disease was 6 months to 66 years, averaging 6 years[1].

CSU patient qualifying for Omalizumab

- Moderate to severe CSU (optionally based on UAS7 score) with an impact upon quality of life
- Pre-existing duration of more than 3 months, earlier in severe cases
- Inadequate response to H1-AH (not controlled by 2x and subsequent 4x dosage) or intolerance to >2x H1-AH and montelukast (optional and not licensed in CH)

Dosage and administration

Omalizumab is available in a 150 mg vial for injection. The lyophilised product dissolves within 15-20 minutes. The fully reconstituted product is administered by means of a subcutaneous injection in the outer surface of the upper arm.

The recommended dose is usually 300 mg every 4 weeks[1, 2].

In individual cases (e.g. no angioedema), the therapy can be started with an initial dose of 150 mg; if free of symptoms/sufficient improvement after 2 weeks, continue with 150 mg, otherwise increase the dose to 300 mg every 4 weeks.
The treating physician should review the necessity of continuing the therapy at regular intervals during the first 3 months: Re-evaluation at latest after 3 months (3 injections).

Concomitant, duration of, and repeated Therapy

Concomitant therapy: Therapy with H1-AH +/- montelukast can be continued until a satisfactory response is achieved with Omalizumab. With partial response, H1-AH +/- montelukast can be further administered.
For patients with systemic corticosteroid or cyclosporine: Steroids have to be tapered off depending upon the dosage and length of time administered, cyclosporine can be stopped immediately. No wash-out is necessary between steroids/cyclosporin and Omalizumab.

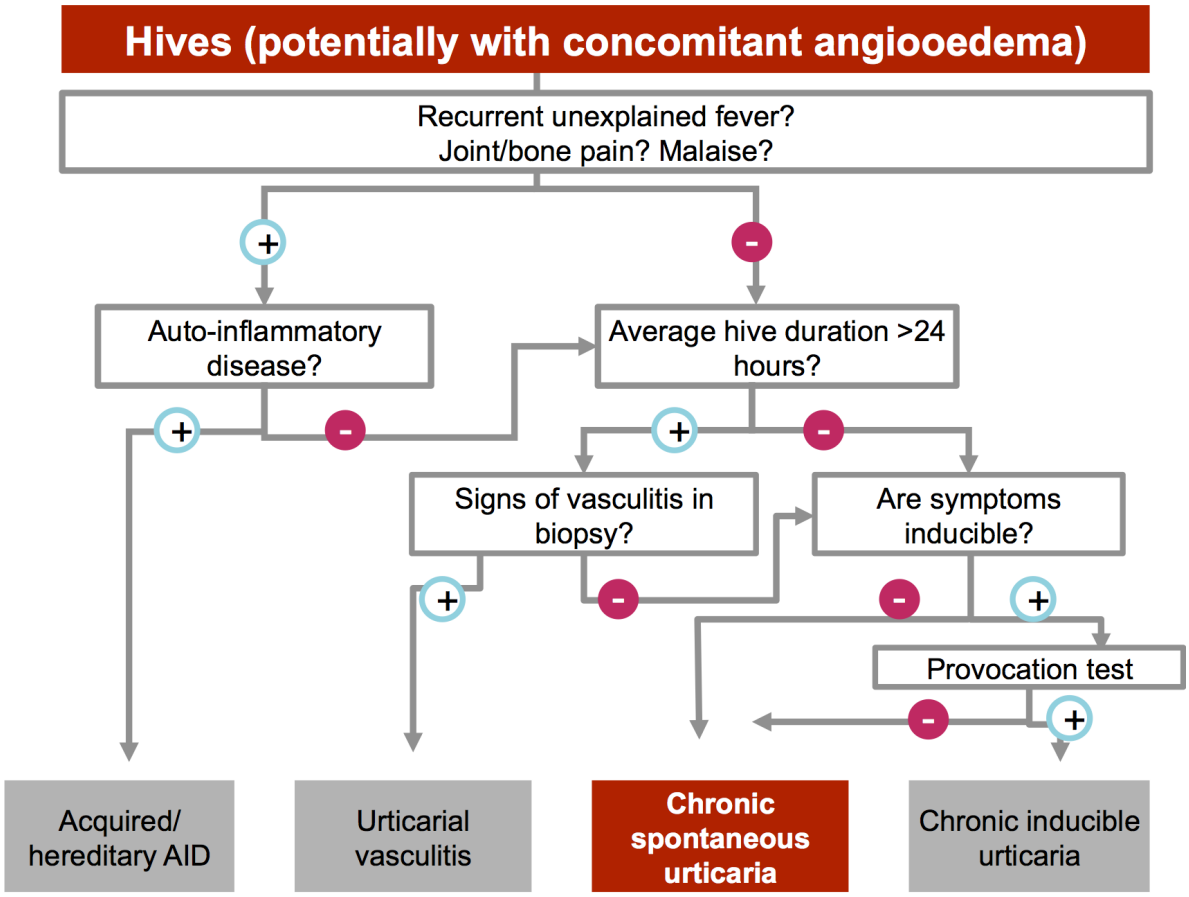

Figure 1: Diagnosis algorithm for urticaria according to the 2013 EAACI/GA2LEN/EDF/WAO guidelines3
Abbreviations: AID = auto-inflammatory disease; EAACI = European Academy of Allergy and Clinical Immunology; GA²LEN = Global Allergy and Asthma European Network; EDF = European Dermatology Forum; WAO = World Allergy Organization.

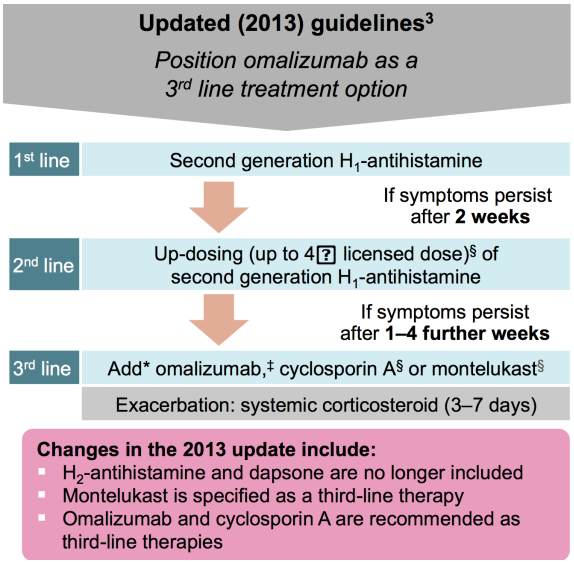

Figure 2: Step-wise therapy recommendations according to severity3
***the order of third-line treatments does not reflect preference; ‡Licensed in Europe and the US; §Not licensed.**
Abbreviations: EAACI = European Academy of Allergy and Clinical Immunology; GA2LEN = Global Allergy and Asthma European Network; EDF = European Dermatology Forum; WAO = World Allergy Organization.

Therapy duration: knowledge from clinical studies concerning the indication of CSU and regarding treatment lasting more than 6 months is limited[1]. The treating physician should review the necessity of continuing the therapy at regular intervals[1].

In the case of insufficient response (optional, "UAS7" and ">15" or ">=16") after 3 months:
- discontinue Omalizumab and reconsider diagnosis.

In the case of sufficient response (optional, UAS >6 to <16) and/or angiooedema after 3 months:
- Continue with 300 mg every 4 weeks
- Reduce interval to 3 weeks, if symptoms improve upon injection but recur after 2- 3 weeks (note: requires approval by the insurance)
- Re-evaluation after another 3 months
- Further continuation with 300 mg possible (individual benefit/risk evaluation)

In the case of a very good response (optional UAS 0 or =<6) after 3-6 months:
- dosage reduction to 150 mg
- or stepwise increase of intervals to 6-8 weeks
- or if free of symptoms, discontinue Omalizumab

Re-treatment: In the case of relapse (optional UAS7 ">15" or ">=16")
- Start again (see above proposal)

Contraindications: Hypersensitivity to the active substance or other ingredients of the medication[1]

Adverse effects, precautions
- Nasopharyngitis
- Sinusitis
- Headaches
- Arthralgia
- Allergic reactions, anaphylaxis[1]
  - in pivotal phase III CSU studies (ASTERIA I, ASTERIA II, GLACIAL), no cases of anaphylaxis attributed to omalizumab were reported [16,17,18].
  - Immunogenicity (low antibody titer to Xolair in approximately 1/1,843 (<0.1%) of patients treated with Xolair)[1]
- Note: while monitoring patients, be prepared to treat anaphylaxis according to the guidelines and have appropriate equipment available [9]
- Monitoring after an injection of Xolair:
  - After the 1st injection: 60 minutes
  - Follow-up injections: 30 minutes [9]

In the case of accompanying allergic asthma/IgE-mediated diseases: 2 hours for the first three injections[13-15]

Evaluation before and during therapy with Xolair® (Omalizumab)

Medical history/symptoms
- Current serious infections, parasitic (worm) infections1
- Cerebrovascular diseases (mainly observed with severe allergic asthma)[1].
- Pregnancy: Omalizumab has not been tested in pregnant women. Some evidence regarding safety is provided by an asthma registry of Omalizumab patients[4]. Omalizumab is not however currently recommended to be used during pregnancy unless clearly necessary[1].
- Lactation: The passage of Omalizumab into the breast milk of lactating women has not been studied. If the treatment of the mother is clearly indicated, weaning is advised[1].
- Neoplasia: The rate of malignancies occurring under Omalizumab therapy is comparable to that of the general population. In the case of active malignancy contact an oncologist[1].

Laboratory: No tests are necessary before the injection of Omalizumab. In particular, determining the total IgE is not necessary before therapy and is not a suitable activity parameter.

Evaluation of the therapy

Usage of UAS7 (optional) to assess the course of the urticaria. Alternatively or parallel to the UAS7 score, use a visual analogue scale to determine disease activity.
Patient information: aha patient brochure.

For further information, please also consult the prescribing information.

In conclusion, CSU is a common, debilitating disease with a high impact on quality of life. It is often resistant to standard therapy. Second generation H1 antihistamines are used as first-line therapy. If standard dosing is not effective, increasing the dosage up to four- fold (second-line) is recommended. Omalizumab is indicated as an add-on third line therapy in adults and children (from 12 years of age) with refractory CSU and inadequate response to treatment with H1-antihistamines. It has proven to be effective, well- tolerated and to

significantly improve the quality of life of patients with CSU. Future studies are needed in order to optimise long-term treatment strategies and to specify which patients would particularly benefit from treatment with Omalizumab.

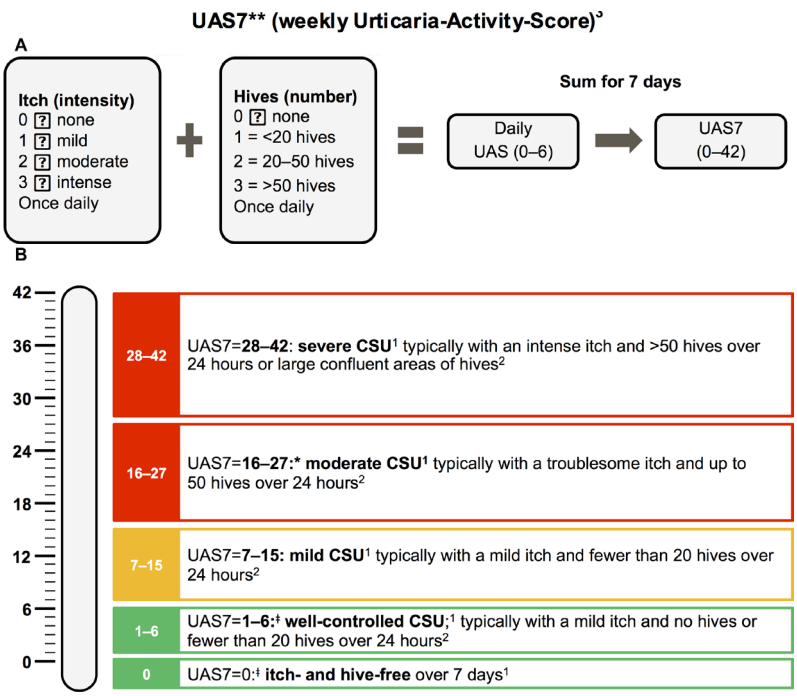

Figure 3: The UAS7 (weekly Urticaria-Activity-Score) is a measure of CSU severity over 7 days [3]

A) Weekly ISS is the sum of daily ISS over 7 days (scale 0–21). Weekly number of hives score is the sum of the daily number of hives score over 7 days (scale 0–21). UAS7 is a composite score of the weekly ISS and weekly number of hives score (scale 0–42).

B) Based on the measured UAS7 score the degree of CSU symptom severity can be determined. During CSU therapy reaching an UAS7 <6 is advisable with an overall goal of reaching complete control of symptoms (UAS7 = 0).3

****As recommended in the 2013 urticaria EAACI/GA2LEN/EDF/WAO guidelines: UAS7 = weekly Urticaria Activity Score; ISS = Itch Severity Score;**

***UAS7≥16 was an inclusion criterion for Phase III clinical trials of Omalizumab in patients with refractory CSU; UAS7≤6 (well controlled disease) and UAS7=0 (complete response) were key secondary endpoints in these trials;**

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Declaration of conflicts of interest

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Individual COI by each coauthor can be provided on request.

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