Introduction

Chronic urticaria is a common, mast-cell-driven disease characterized by recurring wheals, angioedema, or both, for more than six weeks [1, 2]. It is typically accompanied by itching or sometimes a burning sensation; angioedema can be painful instead of presenting with itching [1]. The lifetime prevalence of chronic urticaria in the five largest European countries has been estimated to be 0.63 % [3].

There are two types of urticaria, both of which impair quality of life considerably. Approximately two-thirds of patients suffer from chronic spontaneous urticaria (CSU) [4]. Its random occurrence is often perceived as an additional burden. The other type, chronic inducible urticaria (CIndU), is a response to certain triggers, and patients often undergo considerable efforts to avoid these. Both types can occur together.

A recent online survey of German patients [5] revealed that only 40 % of those who were symptomatic at the time were under a physician’s care. Among those who had chronic urticaria for more than 15 years, 74 % had given up seeing a doctor, and instead treated themselves or lived with the untreated condition. Other patients with chronic urticaria no longer consulted a doctor because they felt that the doctors were unable to help them. More than 50 % of patients reported insufficient or no control of the symptoms. Most of the surveyed patients were unsatisfied with their treatment [5].

The aim of this study was to evaluate guideline-based urticaria care, under real-life conditions at a specialized urticaria outpatient clinic, from the patient’s perspective. All observations concern the provision of care as a whole without separate evaluation of the three lines of treatment escalation. The primary objectives were to assess patient satisfaction,
treatment goals, self-treatment competence and knowledge concerning chronic urticaria, and to assess the factors that influence treatment satisfaction.

Materials and methods

Patients and inclusion criteria

Our study was conducted among patients at a specialized urticaria outpatient clinic at the University Hospital in Dresden, Germany, from April 2016 to August 2018. Adult patients were eligible if their symptoms had persisted for at least six months, if they had received medical care by another physician for at least three months, and if their urticaria had been treated with oral antihistamines. Patients were eligible even if they received further therapies in addition to the antihistamines. Patients provided written informed consent to participate in this study. Ethical approval was provided by the responsible committee (AZ EK 319082016) and the study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 1983.

Treatment

All patients had their medical history screened and were clinically examined by the same physician (KB); guideline-based laboratory analyses were performed according to the anamnesis. The patients received detailed individual and written information about their condition as well as a symptom diary. Treatment was performed according to the urticaria guidelines published by Zuberbier et al. (2014) [6] and patient preferences. Since all patients had been treated prior to the study without achieving sufficient disease control, they were transferred to a general practitioner or appropriate specialists to identify possible foci, based on anamnesis. A follow-up consultation was conducted within six to eight weeks and after six months. An additional consultation after three months was optional.

Therapy for each patient took into account etiology, previous treatment attempts, their results, and patient preferences. Each patient received a copy of their individual treatment plan. At the time of the consultation, if first-line treatment with modern, second-generation antihistamines was not yet exhausted, it was prescribed to the patient. The patients were instructed to escalate autonomously to second-line treatment (up to four-fold dosage of modern, second-generation antihistamines) if the symptoms persisted after two weeks of initiating the first-line treatment. Moreover, patients were advised to contact the study physician if their symptoms were not adequately controlled with the current treatment plan or when side effects occurred. If necessary, treatment escalation was continued up to third-line treatment with omalizumab, cyclosporin A, or montekulast.

Questionnaires and analyses

We applied all guideline-suggested instruments and a few additional instruments to assess disease activity, impact and control [1, 2]. The patients completed the questionnaires at baseline (visit 1), six months after the treatment (visit 3), and optionally after three months (visit 2). The five most important treatment goals were identified using a 15-item questionnaire (validated for psoriasis and atopic eczema) [7]. History of chronic urticaria and angioedema, quality of medical care, and treatment satisfaction were assessed using a self-developed questionnaire. At each visit, patients were administered the Urticaria Control Test (UCT) [8], Urticaria Activity Score over seven days for patients with CSU (UAS7) [9], and Angioedema Activity Score (AAS) [10]. They were also asked to complete appropriate quality of life instruments: The Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) [11], Angioedema Quality of Life Questionnaire (AE-QoL) [12], and Dermatology Life Quality Index (DLQI) [13]. In addition, we applied the work productivity and activity impairment (WPAI) questionnaire [14]. Data concerning comorbid atopic dermatitis, elevated total IgE, rhinoconjunctivitis allergica, thyroid diseases and type 1 allergies were collected during the consultation.

The following statistical tests were performed with IBM SPSS v25 (two-sided, α = 0.05):

- Change in UCT, UAS7, and treatment satisfaction from the baseline to visit 3 with the Wilcoxon test.
- Potential dichotomous factors influencing treatment satisfaction and UCT using the Mann-Whitney U test.
- Potential multicategory factors influencing treatment satisfaction and UCT with the Kruskal-Wallis test.
- Potential ordinal or metric factors influencing treatment satisfaction with Spearman’s correlation coefficient (r).
- Explorative stepwise regression analyses of potential factors influencing treatment satisfaction at visit 3; potential factors that were significant at α = 0.10 in a preceding bivariate analysis were included. Variables that were measured only in subgroups with certain diagnoses (UAS7, AAS, CU-Q2oL, AE-QoL) were excluded. In case of multicollinearity, only the variable with the strongest bivariate association was included.

Results

Patient characteristics

We included 87 patients who participated during the visits at the baseline and after six months. Sixty-two patients were also seen after three months. Most patients were females (64 %, n = 56). The patient’s mean age was 48 years.
(standard deviation [SD] 14.5 years) at the baseline visit and 40 years (SD 15.7 years, n = 79 [patients who completed this item]) at the onset of the disease. The patients had suffered from chronic urticaria for a mean duration of 6 years (SD 10.9 years), including possible remission periods.

**Diagnosis, etiology, and comorbid diseases**

The majority of patients had CSU (80 %, n = 70) and 32 % (n = 28) suffered from CIndU. Chronic urticaria was characterized by wheals alone (47 %, n = 41), histamine-induced angioedema alone (5 %, n = 4), or both (48 %, n = 42). The etiology was diverse (Table 1). In 50 % (n = 6) of the twelve cases with isolated CIndU, the etiology remained unknown. We observed five major comorbid diseases (Figure 1).

**Course of disease control, disease activity, and treatment satisfaction**

Disease control (UCT) rose significantly from visits 1 to 3 (P < 0.001) (Figure 2). However, no improvement was observed from visits 2 to 3. Of the 81 patients who completed the UCT, only 47 % (n = 38) achieved adequate control (UCT ≥ 12) (Table 2). At visit 3, chronic urticaria was sufficiently controlled in only 19 % (n = 5/27) of the patients with CIndU (with or without CSU). In contrast, 61 % (n = 33/54) of the patients without CIndU achieved adequate chronic urticaria control. At visit 3, UCT was significantly lower in men (mean UCT = 9.0) than in women (mean UCT = 12.5).

Etiology, including unknown etiology, and comorbid diseases were not associated with chronic urticaria control throughout the course of the study. UAS7 improved significantly from visits 1 to 3 (P = 0.003) (Figure 3; Table 3). AAS could not be evaluated because only a few patients completed this questionnaire. Overall treatment satisfaction on a 10-point visual analog scale rose significantly from a mean of 5.2 at visit 1 to 8.4 at visit 3 (P < 0.001) (Figure 4).

**Consultation frequency and self-management competence**

During the twelve months preceding the baseline visit, the patients had consulted a physician concerning their chronic urticaria for a mean number of 5.5 times (SD 3.5). Seventy-five percent of the patients (n = 55/73) found the consultation frequency adequate at the baseline compared to 91 % (69/76) after six months of treatment at our center. Twenty-eight patients contacted the study physician to arrange an additional consultation.

At the baseline, 71 % (n = 52/73) of the patients perceived that their physician treated them at least in part correctly, which increased to 87 % (n = 71/82) at visit 3.

A high percentage of patients (83 %, n = 65/78) already found at the baseline that their physician always or partially...
understood the problems associated with chronic urticaria. After six months, 93 % (n = 76/82) of the patients thought so. The proportion of patients who felt that they were informed adequately or better increased from 77 % (n = 61/79) to 91 % (n = 75/82) at visit 3.

At the baseline, 25 % (n = 19/76) of patients reported that they did not know how to adjust their treatment as a response to a worsening of symptoms. This proportion decreased to 11 % (n = 9/83) at visit 3.

**Treatment goals**

The questionnaire about treatment goals was completed in a formally correct way by only 36 patients. At the baseline, reducing itching and burning was among the five most important goals for 94 % (n = 34) of the patients. For many patients, the healing of all (67 %, n = 24) or all visible (50 %, n = 18) skin alterations, was one of the most important goals.

Avoiding strong adverse effects was important in 53 % (n = 19) of the patients, but only 11 % (n = 4) rated it as their most or second most important goal. The ratings remained unchanged during the study.

To achieve a decrease in the disease activity, many patients reported that they would accept more (70 %, n = 61) or longer (39 %, n = 34) consultations from a physician, and time-consuming therapeutic procedures (45 %, n = 39). Many patients were also willing to accept more complex skin care regimes (37 %, n = 32), more

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**Table 2** Proportion of patients with adequate control.

| Diagnosis      | Number (percent) of patients with UCT ≥ 12 | Visit 1 | Visit 2 | Visit 3 | P**  |
|----------------|-------------------------------------------|---------|---------|---------|------|
| Total          |                                           | 12/75 (16) | 26/56 (46) | 38/81 (47) | < 0.001 |
| CSU*           |                                           | 9/62 (15) | 25/48 (52) | 30/64 (47) | < 0.001 |
| CIndU*         |                                           | 3/26 (12) | 3/16 (19) | 5/27 (19) | 0.027 |
| No CIndU       |                                           | 9/49 (18) | 23/40 (58) | 33/54 (61) | < 0.001 |

*Multiple diagnoses were possible.

**2-sided Wilcoxon test for UCT change from visit 1 to 3.

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**Table 3** Course of CSU activity.

| UAS7 | Number (percent) of patients | Visit 1 | Visit 2 | Visit 3 |
|------|-----------------------------|---------|---------|---------|
| = 0  |                             | 6/46 (13) | 10/33 (30) | 10/43 (23) |
| ≤ 6  |                             | 9/46 (20) | 12/33 (36) | 16/43 (37) |

*Significant difference from visit 1 to 3.

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**Figure 3** Course of CSU activity. *Significant difference from visit 1 to 3.

**Figure 4** Course of patient satisfaction with treatment. *Significant difference from visit 1 to 3.
Factors affecting treatment satisfaction

In bivariate analyses, several variables were associated with treatment satisfaction at visit 3 (P < 0.10). Patients who gave better ratings for the physician’s competence and understanding or the provided information were generally more satisfied. Also, the patients’ treatment satisfaction at the baseline, better urticaria control, and higher self-treatment competence were associated with higher treatment satisfaction. Conversely, male patients, patients with an unknown etiology of chronic urticaria, patients who perceived that there were too few consultations, patients with CIndU, and patients suffering from itching, tight skin, or sleep disturbances were less satisfied. Also, an impairment of health-related quality of life (DLQI, CU-Q2oL, AE-QoL) or work productivity (WPAI), and high urticaria activity (UAS7) were associated with lower treatment satisfaction.

These variables were considered as factors for a regression model to explain treatment satisfaction at visit 3. After eliminating CSU-specific, angioedema-specific, or intercorrelated variables and performing the stepwise procedure of including variables, six of them remained significant independent factors (Figure 5).

Discussion

Our study shows that chronic urticaria control as well as treatment satisfaction improved significantly during six months of guideline-based therapy in patients who had received previous treatment with antihistamines without adequate effectiveness. However, only 47% of the patients achieved adequate urticaria control (UCT ≥ 12) during the course of the study. The German nationwide study AWARE [15], in comparison, achieved adequate disease control in 54% of the patients with CSU after six months. Nevertheless, the mean UCT was similar, with a median of 11 in our study and a mean of 11.1 (SD 4.0) in the AWARE study. Similar to the results of the AWARE study, we observed no improvement from three to six months [15]. Maurer et al. ascribed this to the lack of guideline-based treatment escalation. However, our patients were advised to escalate from first-line to second-line treatment autonomously where appropriate, or contact the study physician if their symptoms were not adequately controlled with the current treatment plan. Further research is required to determine why, for many patients, such protocol does not result in chronic urticaria control within six months.

Our data showed that prognosis was considerably worse in patients with CIndU, who comprised 22% in the AWARE study [15] and 32% in our sample. Accordingly, treatment satisfaction in these patients remained unchanged throughout the study. A likely cause for the lack of urticaria control is the low proportion of patients with a treatable underlying cause/comorbid disease and the limited licensed therapy options for CIndU. In cholinergic urticaria, only 38% of patients have been reported to experience good or very good symptom control with updosed second-generation antihistamines [16]. Continued research is required to establish further prognostic factors so that the patients can be comprehensively informed about the benefits they can expect from available treatments.

An exploratory regression analysis revealed six independent, significant factors influencing treatment satisfaction at the last study visit:

- Patients with better disease control were more satisfied. This is in line with the results in patients with atopic dermatitis [17]. In other diseases as well, self-assessed health status is one of the strongest determinants of treatment satisfaction [18]. DLQI as well as WPAI may also be important factors, but they could not be evaluated in the multivariate analysis due to their multicollinearity with disease control.
- Treatment satisfaction at baseline was an independent significant factor, suggesting that individual dispositions remain an important determinant of treatment satisfaction even when urticaria control and other factors are taken into account. We are unaware of studies that examine baseline
values as determinants of treatment satisfaction after the treatment. Future longitudinal studies should consider this factor in their regression models because it might be important as a mediator of other factors.

Sleep disturbances led the patients to be less satisfied. We found no information on this association in previous studies. It is known that chronic urticaria has a major impact on the quality of sleep, which might affect patient satisfaction [3, 19–23].

Irrespective of disease control, patients were more satisfied the more they were convinced that they were treated correctly. Similar results were found in a systematic review [18] and in previous studies [17, 24]. In patients with atopic dermatitis, professional competence and disease severity were independent determinants of treatment satisfaction [17]. In a survey of patients with hand eczema, professional competence was the only independent factor [24].

Men were less satisfied with the treatment than women. A systematic review found greatly differing results across studies, with seven (out of 109) articles showing that women were more satisfied with health services and six studies pointing to higher satisfaction scores in male patients [18]. In an internet survey of 321 German and French patients with urticaria, gender was not a significant factor for treatment satisfaction [25]. In patients with hand eczema [24] or atopic dermatitis [17], there were no associations between gender and treatment satisfaction. Contrary to our results, female patients with diabetes in Israel were found to be less satisfied with their treatment [26]. The association seems to be complex and has not been sufficiently explored.

Patients with CIndU (with or without CSU) were less satisfied with the treatment. While urticaria also remained worse in these patients, the association of CIndU and treatment satisfaction was not mediated by disease control. It was also not mediated by the patients’ assessment of the physician’s competence. We are unaware of any other study testing this factor. This association was possibly caused by disappointed expectations in the diagnostic and therapeutic options for CIndU.

Qualitative studies are required to explore the reasoning and preferences of patients with urticaria concerning their treatment.

In 33 % of the patients, laboratory diagnostics provided hints for a possible infectious etiology of chronic urticaria. Helicobacter pylori IgA or IgG was positive in 25 % of the patients. A higher prevalence was reported among the German general population in 2017 (35 %) [27] and among patients with chronic urticaria (47 %) in 1998 [28]. The differences might be due to a trend of decreasing Helicobacter pylori prevalence in Europe [27]. Yersinia IgA was positive in 21 % of our patients, which is within the scope of previous studies of patients with urticaria (5 %-47 %) [28, 29]. The anti-streptolysin O titer was elevated in 9 % of our patients, and was below the value reported in previous studies of chronic urticaria (10 %-37 %) [30]. Having signs of an infectious etiology was not associated with treatment satisfaction or UCT after six months of therapy.

Treatment goals in our sample of patients with chronic urticaria were similar to those reported for patients with atopic eczema [17] or hand eczema [24]. Compared to these conditions, patients with chronic urticaria valued the reduction of burning or itching the highest, even before the healing of skin signs. Emotional well-being was not rated quite as important by the patients with chronic urticaria compared to those with atopic eczema or hand eczema. A minority of patients with chronic urticaria primarily aimed for other goals, such as reducing the strong side effects of the treatment. These individual concerns should be addressed during consultations to enable patients to make informed decisions.

To the best of our knowledge, this is the first study to systematically examine the treatment satisfaction of patients with chronic urticaria over six months of treatment. All consultations at our center were performed by the same urticaria specialist, guaranteeing guideline-based therapy, and ensuring that the outcomes and associations were not due to varying physicians. Chronic urticaria control and treatment goals were assessed using validated questionnaires. However, there were some limitations. First, baseline questionnaires were handed to the patients at their first visit and were mostly completed at home. This may have led to confusion in some participants as to whether the questions referred to their first visit at the study center or to their previous physicians. While this makes it difficult to interpret some of the baseline results concerning patient satisfaction, it does not challenge our findings concerning its course or associations with other variables. Second, the questionnaire for treatment satisfaction, quality of care, and chronic urticaria was not validated. Third, the regression analysis was not designed to test a theory but to explore potential independent factors. In other studies, other variables, especially those that were associated with patient satisfaction in the bivariate analyses, may be independent factors.

Conclusions

Six months of guideline-based chronic urticaria therapy following insufficient previous treatment for a mean duration of six years with antihistamines (with or without additional urticaria treatments) significantly improved chronic urticaria control. Treatment satisfaction after six months was influenced by disease control, perceived competence of the physician, urticaria subtype, sleep disturbances, gender, and treatment satisfaction at the baseline. Adequate control
requires several consultations for many patients and is considerably harder to achieve for CIndU.

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