Can On-demand Non-sedating Antihistamines Improve Urticaria Symptoms? A Double-blind, Randomized, Single-dose Study

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Non-sedating H1-antihistamines are the recommended first-line treatment for chronic spontaneous urticaria. While efficacy studies usually apply continuous, daily treatment regimens, many patients take their medication on demand. In this randomized, double-blind trial we tested whether on-demand H1-antihistamine desloratadine in standard and higher doses is able to improve the resolution of existing wheals. Symptoms of 29 patients with chronic spontaneous urticaria were followed without treatment on one day and again on another day during the next 3 weeks after a single dose of either 5 mg or 20 mg desloratadine, using different objective measures. While the intervention with both doses of desloratadine was effective in terms of a reduction in hyperthermic skin area, there was no improvement in wheal area and wheal volume compared with no treatment. Wheal numbers were reduced after treatment with 20 mg, but not 5 mg, desloratadine. In conclusion, the beneficial effects of non-sedating H1-antihistamines given on demand appear to be low. Thus, a preventive treatment strategy should be preferred in chronic spontaneous urticaria. Key words: urticaria; antihistamines; clinical trial.

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Chronic spontaneous urticaria (CSU) is one of the most frequent skin disorders. It is characterized by a recurrent and spontaneous appearance of itchy wheals with or without angioedema, for 6 weeks or longer (1, 2). CSU often lasts for years, sometimes even decades, and has a substantial impact on patients’ quality of life (3–5). Urticaria symptoms are mediated mainly by the release of histamine from mast cells, which causes vasodilatation, extravasation, and subsequent development of wheal-and-flare type skin reactions (6). The current guidelines for management of urticaria strongly recommend non-sedating H1-antihistamines (nsAH) as the first-line symptomatic treatment for CSU, based on a large body of high-quality evidence (7).

CSU is a fluctuating disease and the severity of symptoms can change markedly from day to day. This may be one of the reasons why, in routine daily practice, many patients tend to perform on-demand, rather than continuous, daily, preventive treatment of their symptoms with H1-antihistamines. In allergic rhinitis, several studies point towards a better efficacy of modern non-sedating antihistamines if given continuously (8–10). The only study in CSU examining both treatment approaches was published by Grob and colleagues (11), who showed that daily treatment with desloratadine resulted in significantly better quality of life compared with on-demand therapy. While these studies indicate that the treatment schedule can generally have a major impact on the outcome of treatment, the results on the efficacy of on-demand nsAHs in CSU have not yet been independently confirmed. In addition, it has not been studied whether on-demand nsAHs in higher than standard doses might have a beneficial effect compared with standard doses. Increasing the nsAH to up to 4 times the standard dose is recommended by the current guidelines in all patients who cannot achieve symptom control with standard doses (7).

Desloratadine is a modern nsAH that has been shown to reduce pruritus and wheals and to improve quality of life in several studies at the standard 5 mg dose (12–17). In addition, in a study on patients with acquired cold urticaria, a preventive application of desloratadine at 4 times the standard dose was significantly more effective in reducing urticaria lesion severity compared with the standard 5 mg dose, without any increase in adverse events (18). Other studies also point towards a better efficacy of continuously applied high-dose nsAHs in CSU (19, 20). Most clinical trials rely on patient assessments of symptoms and quality of life over a period of outpatient treatment time. Although this is entirely appropriate, we designed the current clinical study to examine the efficacy of standard dose desloratadine (5 mg) and up-dosed desloratadine (20 mg) on existing wheals, under carefully monitored conditions, using the most technically reliable, objective measures. The aim of the study was to determine whether wheals in CSU can be actively reduced by on-demand treatment with a modern nsAH in guideline-suggested dosages. This
study simulates the treatment approach used by many patients: they wait with antihistamine treatment until wheals appear and then expect the wheals to disappear more rapidly than without treatment.

METHODS

Ethics

This study (clinicaltrials.gov identifier NCT00598611, EudraCT-No: 2006-001431-22) was approved by the Independent Ethics Committee of Berlin (Ethikkommission des Landes Berlin) and the Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM).

The study was conducted in accordance with the Declaration of Helsinki, guidelines from the International Conference on Harmonization (ICH) and Good Clinical Practice (GCP), and applicable national laws and regulations. All patients provided written informed consent to participate in the study.

Study setting and subjects

The study was performed at the Allergie-Centrum-Charité, a tertiary referral centre for allergies and urticaria. Outpatients, age range 18–75 years, were eligible for the study if: (i) they had moderate to severe CSU according to their clinical history, (ii) they exhibited spontaneous urticaria lesions at the second visit for a baseline assessment (as explained below), and (iii) they had a history of beneficial effect from antihistamine treatment. Exclusion criteria were: presence of acute urticaria/acute angioedema, intake of corticosteroids or other immunosuppressive therapy within 14 days prior to the beginning of the study, use of depot corticosteroids or chronic systemic corticosteroids within 21 days prior to the beginning of the study, presence of permanent severe diseases (especially those affecting the immune system), presence of galactose intolerance, lapp lactase deficiency or glucose galactose malabsorption, history of adverse reactions including hypersensitivity to desloratadine or loratadine, and intake of medication that could cause changes in QT interval (drugs listed on www.qtdrugs.org). In addition, patients were excluded if they met any criteria from a typical list of exclusion criteria for pharmacological studies: presence of a permanent gastrointestinal condition that may influence oral therapy, history or presence of epilepsy, significant neurologic disorders, cerebrovascular attacks or ischaemia, history or presence of myocardial infarction or cardiac arrhythmia that requires drug therapy, evidence of severe renal dysfunction, evidence of significant hepatic disease, presence of active cancer that requires chemotherapy, presence of alcohol abuse or drug addiction, participation in any clinical trial within 4 weeks prior to enrolment, pregnancy or breast-feeding, and existing or planned placement in an institution after ruling according to § 40 AMG (Arzneimittelgesetz).

The study had a target sample size of 30 patients. This was considered sufficient to adequately investigate the objectives of this study, based upon the investigator’s experience and previous studies on urticaria. Formally, our study had a power of 80% to detect effects of size 1.085 (quotient difference of means and standard deviation).

Study design

This was a randomized, double-blind, parallel group, single-dose study. The study-design is shown in Fig. 1. At visit 1, screening for eligibility was performed, and patients were requested to stop taking any antihistamines for the duration of the study, if possible. Rescue medication (cetirizine 10 mg, and additional clemastine 1 mg if required) was allowed for severe symptoms, but its use had to be documented by the patients and was reviewed. During the ensuing wash-out phase of 7–10 days, patients documented their symptoms with the 7 day Urticaria Activity Score (UAS) and a visual analogue scale (VAS). On days 7–10 of the screening phase patients were subjected to a standardized examination of urticaria symptoms for 5 h in case they developed skin lesions (Visit 2). All patients who completed this assessment successfully were randomized. Subsequently, at another day during any of the following 21 days, the study patients received a single-dose treatment with the study drug (desloratadine 5 mg or 20 mg) given that they again developed urticaria symptoms, and were subjected to the same standardized examination of symptoms for 5 h as before (Visit 3). The study drug was administered immediately after the first measurement of symptoms at Visit 3. Reasons for not randomizing screened patients were non-occurring symptoms during days 7–10 of the screening phase (13 patients, non-compliance regarding study procedures (3 patients), elevated liver enzymes (2 patients), intake of steroids after screening (1 patient) and withdrawal of written informed consent (1 patient). One of the patients showing non-compliance also did not develop any symptoms during days 7–10 of the screening period.

Visit 2 took place 7 days after visit 1, unless the patient showed no spontaneous urticaria lesions or had used rescue medication within the past 48 h, in which cases visit 2 could be rescheduled for up to 10 days after visit 1. During visit 2, all outcome measures (described below) were assessed over 5 h, as the “no treatment” control condition. Patients were then randomized (sequentially numbered) in a double-blind fashion, according to a computer-generated randomization scheme prepared by the Institute for Biostatistics and Clinical Epidemiology (Charité Berlin).

Visit 3 could take place anytime 1–21 days after visit 2, on condition that the participating patients exhibited spontaneous urticaria lesions on that day and had not used rescue medicine within the past 48 h. At visit 3, patients received the treatment drug (described below) according to their double-blind randomized assignment. All outcome measures were again assessed over 5 h.

Treatments

Patients received a single-dose treatment of desloratadine immediately after a first measurement of urticaria symptoms.
The UAS7 is a validated instrument for measuring urticaria activity and represents the 7 day cumulative score of the Urticaria Activity Score (UAS). It quantifies wheals (0–3 points) and itching (0–3 points). Accordingly, the minimum and maximum value of the 7 day cumulative score is 0 and 42, respectively.

### Table I. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Group A (5 mg desloratadine)</th>
<th>Group B (20 mg desloratadine)</th>
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<tbody>
<tr>
<td>Patients (n)</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Age, years, mean ± SD (range, median)</td>
<td>43.5 ± 12.9 (21–65, 42)</td>
<td>41.7 ± 11.3 (24–58, 42)</td>
</tr>
<tr>
<td>Gender ratio (F:M)</td>
<td>9:4</td>
<td>7:9</td>
</tr>
<tr>
<td>Body weight, kg, mean ± SD (range, median)</td>
<td>77.2 ± 20.4 (55–133, 70)</td>
<td>79.6 ± 9.8 (62–95, 70)</td>
</tr>
<tr>
<td>UAS7*, mean ± SD (range, median)</td>
<td>22.5 ± 11.7 (1–40, 24)</td>
<td>19.6 ± 9.0 (4–34, 18)</td>
</tr>
<tr>
<td>VAS value, mean ± SD (range, median)</td>
<td>4.1 ± 2.8 (0.5–8.4, 2.7)</td>
<td>3.6 ± 1.6 (0.6–6.5, 3.7)</td>
</tr>
</tbody>
</table>

*aThe UAS7 is a validated instrument for measuring urticaria activity and represents the 7 day cumulative score of the Urticaria Activity Score (UAS). It quantifies wheals (0–3 points) and itching (0–3 points). Accordingly, the minimum and maximum value of the 7 day cumulative score is 0 and 42, respectively.

*bThe visual analogue scale (VAS) assesses the severity of urticaria symptoms on a 10-cm unmarked line, where 0=no discomfort and 10=maximum discomfort.

The standard recommended dose of desloratadine is 5 mg. All patients received 4 identical pills out of sequentially numbered (randomization number) medication containers. Group A received 1 × 5 mg desloratadine and 3 × placebo; group B received 4 × 5 mg desloratadine. The placebo tablets and 5 mg desloratadine tablets looked identical; the identity of the tablets could be determined only through the randomization list.

### Outcome measures

All outcome variables were measured at visits 2 and 3, once per hour for 5 h. At visit 3, the first of these 5 hourly measurements was made just before the patient took the study treatment medications. The location of the body area measured depended on where lesions were occurring spontaneously in that patient during that visit. All outcome measures were performed in this body area.

The primary outcome measure was the area size of wheals (hyperthermic skin area) assessed by thermographic imaging. This method has been used in previous dermatology studies on antihistamines (22, 23). The area of all visible wheals was summed in the whole region of the body being assessed. Secondary outcome measures were the area size of wheals as assessed by digital time-lapse photography, the number of wheals, and the wheal volume of selected wheals. The area of all visible wheals on digital photographs was summed in the whole region of the body being assessed. The number of wheals was assessed by counting all visible wheals in the whole region of the body being assessed. The volume of a selected wheal in each patient was measured by 3D imaging (PRIMOS; GFM; Teltow, Germany), as previously explained in detail and validated (24). This volume measure was performed on only one selected wheal (in the region of the body being assessed) for each patient at each visit. Prerequisites for the selection of wheals were: (i) that they had to have a classical morphological appearance; and (ii) that their size fitted into the receptive field of the imaging device (30 × 40 mm). Usually, wheals with a diameter of 1–3 cm were selected.

For each outcome variable, the values after 5 h (t = 5 h) were computed as a percentage of the values at the beginning of the measurement (t = 0 h). These values mirror the spontaneous course without treatment (no treatment) or the treatment effect after 5 h. In addition, for each outcome variable, the measurements made each hour for 5 h were plotted and connected by a curve. The area under the curve (AUC) was then calculated, and this AUC was used as further data for that patient for that outcome variable. The AUC measurements summarize the therapeutic effect during the entire 5 h course of the treatment. All patients and clinical staff, for example study nurses and study physicians involved in the study, were blinded until the end of the trial (until all analyses of the outcome measures were completed and all data was entered in the study data bank).

### Statistical analysis

Descriptive statistics used means, medians, standard deviations and ranges. Comparisons between visit 2 (no treatment) and visit 3 (treatment) were performed separately for each study arm using the Wilcoxon signed-rank test. Furthermore, the 2 treatment arms (desloratadine 5 mg and 20 mg) were compared with each other for each outcome variable at visit 3 using the Mann–Whitney U test. The level of significance was 0.05 (2-sided). Commercially available software (SPSS for Windows, release 18) was used. The box plots show all data available for the indicated groups. Since data from all outcome measures were not available for no treatment and treatment in every patient, the number of patients included in the statistical comparisons may be slightly lower compared with those shown in the box plots (descriptive statistics).

### RESULTS

#### Subjects and disease severity

A total of 53 patients was screened, 34 were eligible and randomized, and 29 received treatment in the study (Fig. 1) between September 2007 and August 2009. The median (range) age was 42 years (age range 21–65 years). The severity of CSU was moderate to severe in most participants, but broad ranging. The median (range) UAS7 score was 21 (1–40). The median (range) VAS score was 3.6 (1–8), as shown in Table I. Rescue medication was used by 7 patients in group A (44 tablets) and 8 patients in group B (18 tablets). Since all rescue medication was used before the patients ever received the study medication (desloratadine), the amount of rescue medication only reflects the baseline condition of the patients, and does not reflect the efficacy or inefficacy of desloratadine in any way.

#### Primary outcome

The primary efficacy parameter of the study was the assessment of the reduction in size of spontaneous urticaria lesions by thermography (hyperthermic skin area) before and during treatment with study medication. Both 5 mg and 20 mg of desloratadine led to reduced total hyperthermic skin area 5 h after intake in relation to 0 h (baseline) (Fig. 2A). Among the patients in group A, the total hyperthermic skin area after 5 h was substantially reduced after 5 mg desloratadine treatment (median: 15.7%, mean: 25.4% at 5 h) compared with no treatment (median: 98.2%, mean: 240.2% at 5 h), and statistically this difference was significant (p = 0.036). Among the patients in group B, the total hyperthermic...
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Skin area was also markedly reduced 5 h after application of 20 mg desloratadine (median: 10.1%, mean: 24.8% at 5 h) compared with no treatment (median: 29.4%, mean: 58.4% at 5 h), but this difference just failed to reach significance ($p = 0.051$). It is likely that the contrasting outcome of these 2 comparisons occurred because the median total hyperthermic skin area of the patients in group A did not change during no treatment (visit 2), whereas the median total hyperthermic skin area of the patients in group B decreased (98.2% vs. 29.4%). A comparison of the reduction in the total hyperthermic skin area after 5 h in relation to baseline during active treatment with 5 mg desloratadine vs. treatment with 20 mg was neither clinically meaningful nor statistically significant. A comparison of the AUC between group A and B as well as between treatment and no treatment in each group showed similar results (data not shown).

Secondary outcomes

Additional parameters of efficacy were the assessment of the reduction in size of spontaneous urticaria lesions by planimetric analysis of digital time-lapse photography, volumetric analysis of selected wheals, and the evaluation of wheal numbers. Regarding wheal area measured by planimetric analysis of digital photographs, the reduction in the total wheal size was less pronounced compared with the thermographic assessment (Fig. 2B). Among the patients in group A and B, the total wheal area after 5 h seemed more reduced after 5 mg and 20 mg desloratadine (median: 50.6%, mean: 69.8%, and median: 40.3%, mean: 66.4%) than during no treatment (median: 77.5%, mean: 170.0%, and median: 76.1%, mean: 110.1%), but statistically, this difference was not significant ($p = 0.52$ and $p = 0.27$). A comparison of the reduction in the median total wheal area after 5 h in relation to baseline during treatment with 5 mg desloratadine vs. treatment with 20 mg was neither clinically meaningful nor statistically significant. A comparison of the AUC between group A and B as well as between treatment and no treatment in each group showed similar results (data not shown).

Regarding wheal volume, neither 5 mg desloratadine nor 20 mg desloratadine was any better than no treatment, and there was no difference between 5 mg and 20 mg (Fig. 3). It is important to keep in mind that the primary and secondary outcome of wheal area referred to the total area of wheals within a defined body region for the former; whereas wheal volume referred to the measurement of only one selected wheal.

Regarding the number of wheals, both 5 mg and 20 mg of desloratadine led to a reduction in the total wheal numbers 5 h after intake compared with 0 h (Fig. 4). Among the patients in group A, the total wheal number after 5 h seemed higher after treatment with 5 mg desloratadine (median: 26.7%, mean: 50.3% at 5 h) compared to no treatment (median: 10.0%, mean: 25.3% at 5 h), but statistically, this difference was not significant ($p = 0.10$). Among the patients in group B, the total wheal number after 5 h was significantly lower ($p < 0.05$) after active treatment with 20 mg desloratadine compared to no treatment.

Fig. 2. Wheal area assessment in the 2 study groups. Box and whisker plots show the effect of desloratadine (DL) 5 mg, DL 20 mg and no treatment on wheal area at $t = 5$ h (in percentage of the wheal area at $t = 0$ h in the same measurement). (A) Planimetric analysis of thermographic imaging. (B) Photographic imaging. The comparisons between wheal area at $t = 5$ h and wheal area at $t = 0$ h in the same measurement are indicated by $p$-value < 0.05 and $p$-value < 0.005 (paired analysis). All other comparisons are indicated by $p$-value < 0.05. No significant differences (n.s.) were found between treatments. Circles within the figures represent outliers. Extreme values of single patients not shown in the figures are: (A): Group A (no treatment): 1,354% and 358% and Group B (no treatment): 342%; (B): Group A (no treatment): 764% and 628%. Patient numbers are for (A): Group A (no treatment) $n = 9$, Group A (5 mg DL) $n = 12$, Group B (no treatment) $n = 14$, Group B (20 mg DL) $n = 12$. Patient numbers are for (B): Group A (no treatment) $n = 12$, Group A (5 mg DL) $n = 11$, Group B (no treatment) $n = 16$, Group B (20 mg DL) $n = 15$. 

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loratadine (median: 0.0%, mean: 30.0% at 5 h) than for no treatment (median: 100.0%, mean: 85.2% at 5 h). The direct comparison of treatment with 5 mg vs. 20 mg desloratadine on the number of wheals after 5 h failed to demonstrate significant differences (p = 0.40). In contrast, a comparison of the reduction in the total wheal number after 5 h during treatment with 5 mg desloratadine minus no treatment vs. treatment with 20 mg minus no treatment showed significant differences (p < 0.01). The relation between the AUC between group A and B as well as between treatment and no treatment in each group showed similar results (data not shown).

Safety
No adverse events were observed or reported after intake of the study drug during this study.

DISCUSSION

nsAHs at standard dose have been recommended by the recent guidelines as first-line treatment for CSU (7). They provide good relief of symptoms in less than half of all patients (25), while the others obtain inadequate or no response from this therapy. For these patients, the guidelines recommend increasing the dosage, up to 4 times the standard dose, as second-line treatment. While clinical trials examining the efficacy of H1-antihistamines usually apply continuous, daily treatment regimens, the situation in the real-life outpatient setting is different. Patients often tend to use their medication only in case symptoms appear rather than on a preventive basis. While, from a pharmacological perspective, a continuous, daily treatment schedule with H1-antihistamines can be expected to yield better efficacy due to their mode of action as an inverse agonist at the histamine receptor, there is, as yet, only limited evidence from clinical studies to support this assumption.

The current study was designed to determine whether desloratadine is objectively efficacious during on-demand application in CSU. In addition, it was tested, whether up-dosing in this setting provides additional benefit. Interestingly, only the results on the main outcome variable of wheal area measured by thermography (hyperthermic skin area) suggest that both doses of desloratadine would be an effective on-demand treatment.
for CSU. However, direct comparison of the 2 treatment arms failed to show a difference between 5 and 20 mg. Of the secondary outcome parameters, wheal numbers were reduced after treatment with 20 mg desloratadine but not after 5 mg compared with no treatment. The other outcome variables did not reveal any differences between treatment and no treatment.

Modern nsAHs are usually approved for the treatment of allergic rhinitis and urticaria. In allergic rhinitis, a continuous vs. an on-demand treatment scheme has already been examined in some studies. Most found a better efficacy of H<sub>1</sub>-antihistamines if given continuously (8–10). For example, Ciprandi et al. (8) demonstrated that patients treated with cetirizine continuously achieved better relief of symptoms and greater reduction in their nasal inflammatory infiltrate compared with patients treated on an on-demand basis. Canonica et al. (9) found an effect of levocetirizine for both treatment regimens. However, the continuous therapy showed better efficacy in the long-term. Interestingly, a single study of Dizdar et al. (26) also provided contrary results, i.e. failed to demonstrate superiori of a continuous, preventive application of desloratadine in 37 children with allergic rhinitis with or without intermittent asthma. These limited data led to the valid claim of Laekeman and co-workers (27) in their recent review on continuous vs. on-demand pharmacotherapy of alergic rhinitis, that more studies are needed to confirm the conclusion that continuous treatment is preferable. In CSU, we are aware of only one study comparing both treatment approaches: Grob et al. (11) were able to show that patients treated with desloratadine continuously experienced a significantly better quality of life and a lower mean number of days with moderate or severe pruritus compared with patients treated on demand. In contrast to our study, the treatment phase comprised 2 months.

The interpretation of studies in allergic rhinitis vs. urticaria has to take into account that the symptoms related to histamine receptor activation are different in both conditions. In rhinitis, one of the main features is the runny nose, where mucous glands of the nose are activated by histamine receptors. As soon as these are blocked, the active production of mucous is reduced after a short time. In contrast, the activation of endothelial histamine receptors in urticaria leads to an extravasation of fluid and cutaneous oedema. Thus, blocking of histamine receptors in urticaria can stop and prevent further extravasation of fluid, but is not expected to have a direct effect on existing oedema. Oedema is primarily reduced through the active transport of interstitial fluid via lymphatic vessels, which depends largely on the body area affected and its lymphatic vessel supply. Our findings support this notion and confirm that oedema reduction is largely histamine receptor-independent.

The results of our trial support and add to the findings reported by Grob et al. (11), which demonstrate that on-demand treatment in CSU is less effective than continuous daily intake of a standard-dose non-sedating antihistamine. In our study, neither the standard dose (5 mg) nor the higher dose (20 mg) of the same antihistamine used by Grob and co-workers, i.e. desloratadine, were convincingly effective in reducing already-existing wheals.

While this study has major strengths, e.g. it mimics the actual clinical situation of many patients and it concentrates on objective rather than subjective outcome parameters, it also has some limitations that should be kept in mind when interpreting the data. Firstly, only one nsAH was tested. Since it is known that different antihistamines exhibit different pharmacokinetic and pharmacodynamic properties, it cannot be excluded that the use of other antihistamines might have led to contrasting results. Secondly, disease activity may vary between different time-points in the same patient. This possibly affects treatment outcome. Thirdly, it was necessary to select an area of the body with well-established urticaria lesions for the measurements. It cannot be excluded that a greater effect of the study drug was present in other regions of the skin where the urticaria was earlier in evolution. Fourthly, a history of beneficial effect from H<sub>1</sub>-antihistamine treatment was an inclusion criterion. In this population it might be more difficult to demonstrate superiority of up-dosed nsAHs compared with a pre-selected population that is known to be resistant to standard dosed nsAHs. Fifthly, it is unclear if 5 h is sufficient time for following the wheals. Although this time-span was chosen based on the known time to maximum plasma concentrations for desloratadine (~3 h), it is also known that the drug is converted to active metabolites and a maximum efficacy at a later time-point cannot be fully excluded in our setting. Finally, the number of participants in this study was limited.

In summary, the results of this clinical trial demonstrate that the beneficial effects of H<sub>1</sub>-antihistamines on existing wheals (on-demand treatment) seem to be low, if not absent. As many patients with CSU still tend to use their medication only for on-demand treatment, the results of this study imply that a preventive rather than on-demand treatment strategy should be recommended to patients. Although we did not directly compare continuous vs. on-demand treatment, it is well-established by several randomized, double-blind, placebo-controlled clinical studies that H1-antihistamines are effective in chronic urticaria when given continuously. In addition, the results suggest that on-demand treatment does not appear to be a suitable approach to compare the efficacy of different therapeutic options in CSU. Hence studies using another design (preventive, continuous, daily treatment schedules and monitoring of symptoms over a longer period of time), should be preferred.
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