ORIGINAL ARTICLE

Low sensitivity of the pulse-controlled ergometry test as diagnostic tool for cholinergic urticaria

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Summary

Background. Cholinergic urticaria (CholU) is characterized by itchy wheals induced by physical exercise, yet validated tools for diagnosis and severity assessment remain limited. The Pulse-Controlled Ergometry (PCE) test and Cholinergic Urticaria Severity Index (CholUSI) were only evaluated in a limited number of patients. We aimed to evaluate the diagnostic value of the PCE test and CholUSI for monitoring CholU severity in an unselected CholU population. **Methods.** Retrospective study including all patients with a clinical diagnosis of CholU, based on exercise-induced wheals and pruritus by history and/or photo-documentation, between 2021 and 2024. Patient characteristics, urticaria control test (UCT), response to omalizumab, and outcome of CholUSI and PCE test (performed before initiation of additional treatment) were investigated. **Results.** Thirty-nine CholU patients (66.7% male, median age 25.0 years, mean UCT 2.0) were included. CholUSI showed a strong and statistically significant correlation with UCT ($p = -0.895$; $p < 0.01$) at baseline and follow-up. CholUSI improved significantly from baseline to end of treatment in patients treated with omalizumab (n=20) (CholUSI 17.5 *vs* 4.0, $p < 0.01$; UCT 2 *vs* 15.5, $p < 0.01$). The PCE test had a sensitivity of only 62.5% (n = 10/16, 95% CI 0.4-0.8). A positive PCE-test was associated with earlier sweating (5 *vs* 20 minutes, p=0.03) and higher disease severity by CholUSI (18.0 *vs* 14.5, $p < 0.01$). **Conclusions.** Our findings support the use of CholUSI as a practical and disease-specific tool

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for assessment of CholU severity and treatment response. However, the sensitivity of the PCE test was low, highlighting the need for improvement and further validation.

KEY WORDS

Cholinergic urticaria; chronic inducible urticaria; ergometry; diagnosis; disease severity.

IMPACT STATEMENT

CholUSI is a valuable tool for assessment of CholU-severity and treatment evaluation. However, PCE-test has low sensitivity, with a negative result associated with lower CholU-severity and later sweating.

Introduction

Cholinergic Urticaria (CholU) is a subtype of chronic inducible urticaria (CIndU), characterized by itchy, pinpoint short-lived wheals, which are triggered by physical exercise, passive warming, emotional stress, or the consumption of hot food or beverages(1,2). Diagnosis is based on patient history and photo-documentation of the typical wheals (2,3). According to the international guidelines provocation and threshold testing is recommended to confirm the diagnosis (2,3). The suggested test is a short exercise test, either on a stationary bicycle or treadmill, which is performed until sweating occurs and continued for up to 15 minutes, or until symptoms develop and considered positive if the typical wheals develop over 10 min(2). However, the guidelines do not provide a clear protocol on how to perform the exercise test, lacking specific instructions on maximum effort or intensity during the test, or whether this test should be pulse-controlled. Only few studies investigated the reliability of an exercise test in small populations (n=10-20) with varying results; 35-100% of patients tested positive(4–6). One of these, the pulse-controlled ergometry (PCE) test described by Altrichter et al. includes exercise for 30 minutes on a stationary bicycle with increasing the pulse rate by 15 beats every 5 minutes, followed by a 10-minute recovery period(6). The authors studied 10 patients with a history confirmed diagnosis of CholU and showed that all 10 patients developed wheals during PCE test, confirming the diagnosis and subsequently the reliability of PCE

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test. Overall, the PCE test and the other variants of provocation tests seem not frequently used in daily practice, nor in studies.

Once CholU is diagnosed, the most commonly used patient-reported outcome measure (PROM) to assess and monitor the severity of CholU is currently the Urticaria Control Test (UCT). This is a validated, universal, tool that assesses the level of disease control of non-specific chronic urticaria over the previous four weeks(7). Recently, the weekly Cholinergic Urticaria Activity Score (CholUAS7) is validated, measuring CholU-related daily itch and number of wheals summed up as week score(8). The CholU Severity Index (CholUSI) was previously described as score to assess disease severity(6,9) taking into account the frequency and severity of specific CholU symptoms and eliciting factors that are usually structurally evaluated in anamnesis of CholU. Since provocation testing cannot always be performed and does not discriminate severity very well an easy tool for measurement of CholU severity is needed in daily practice. However, the reliability of CholUSI is not investigated yet. The development and availability of new treatment options in chronic spontaneous urticaria(10–13) will also effect and improve treatment for CholU. Reliable and validated diagnostic criteria and disease severity scores are needed for responsible guidance of these potentially costly treatments.

The aim of this study is to investigate the value of the PCE test for diagnosing CholU and of CholUSI for monitoring of CholU severity in patients with a clinical diagnosis of CholU in daily practice.

Methods

Study design

All patients with a clinical diagnosis of cholinergic urticaria based on medical history, physical examination, and/or photo-documentation assessed by an experienced clinician between 2021 and 2023 at the department of Dermatology and Allergology at University Medical Center Utrecht, Netherlands were included. This study was approved by the Medical Ethic Review committee (METC-Utrecht no. 23U-0757) and informed consent was not required. Analyses were performed with pseudonymized data.

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Patient and disease characteristic, PCE test outcomes (itching, erythema, wheals, sweating and photo-documentation) and disease control (including effectivity of omalizumab treatment) evaluated by Urticaria Control Test (UCT) were retrospectively collected from electronic health records.

Treatment response to omalizumab was classified as "complete" (UCT = 16 or no symptoms), "good" (UCT 12–15 or minor symptoms), "partial" (UCT 3–11 and improvement ≥3, or insufficient improvement) or "no response" (UCT 0–11 and improvement of <3, no improvement) and was evaluated at end of treatment (Tend). Tend was defined as the timepoint of discontinuation of omalizumab or data lock.

CholUSI was investigated as tool for assessment of CholU disease severity and adapted from initial CholUSI (i-CholUSI) with high correlation between the two versions(6,9) (Pearson correlation r=0.93, P<0.01) (Supplemental table II). The CholUSI is calculated as follows:

1) Frequency of CholU (0-maximum 6 points): less than less than once a month=0; once a month=1; more than once a month=2; once a week=3; more than once a week=4; daily=5; more than once daily=6 points.

2) Eliciting factors (one point for each, maximum 6 points): intensive physical exercise, moderate physical exercise (walking, daily activities), hot bath/shower/sauna, emotional stress, hot food, other.

3) Duration of skin lesions (0–maximum 4 points): less than 5 min=0; 5–15 min=1; 15–30 min=2; 30–60 min=3; longer than 1h=4 points.

4) Itch during the events (0–maximum 3 points): none=0; low=1; medium=2; severe=3 points.

5) number of wheals (0-maximum 4 points): none=0; 1-10 wheals=1; 10-50 wheals=2; 50-100 wheals=3; >100 wheals=4 points.

Disease severity was ranked between 0 and 23 CholUSI points: <5 points: very mild CholU; 5–10 points: mild CholU; 11–16 points: moderate CholU; >16points: severe CholU.

See Supplemental Table II for details regarding the initial CholUSI.

PCE test was performed using a standardized local protocol based on the protocol described by Altrichter et al. (6); pulse-controlled ergometry for 30 minutes on a stationary bicycle, increasing the

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pulse rate by 15 beats every 5 minutes with ambient temperature of 20–22 degrees Celsius, followed by a 30-minute recovery period. Iodine and starch powder (according to Minor' sweat test(6,14)) was applied to the lower back to detect sweating. The time of the start of the sweating, presence of erythema, itching and wheals were recorded at 5-minute intervals. The test is considered positive for CholU if pinpoint-sized wheals are observed either during the exercise or during recovery period. Patients were instructed to discontinue antihistamines one to three days before the ergometry test. PCE-tests were performed before initiation of additional treatment including omalizumab.

Statistical analysis

Continuous variables are presented as means ± standard deviations (SD) or medians with interquartile ranges (IQR). Categorical variables are presented as a percentage. Chi-square test or unpaired t-test was used to compare the clinical characteristics. Sensitivity analysis of the PCE test was performed. Correlations were calculated using the Pearson correlation test. $P<0.05$ was considered a significant difference. Statistical analyses were performed in SPSS IBM SPSS Statistics 27 (IBM, Armonk, NY, U.S.A.)

Results

Characteristics of patients with CholU

Thirty-nine patients with clinical diagnosis of CholU (66.7% male, median age 25.0 years) within the study period were identified. These patients had poor CholU disease control (median UCT 2 (IQR 1-4.8)) and a mean disease duration of 4.2 years (SD 4.9), ranging from 3 months to 25 years. All patients had exercised-induced wheals and pruritus by history, including confirmation of typical wheals by photo-documentation in 70% of patients. The majority of patients (n=24, 61.5%) reported wheals within less than 15 minutes after starting exercise and reported more than 50 wheals (n=31; 79%) (details see Table I). In 22 patients, CholU was treated with omalizumab, of which 50% (n=11) had a complete or good response.

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Cholinergic Urticaria Severity Index (CholUSI) as tool for monitoring of CholU severity and treatment response

Median CholUSI was evaluated as tool for monitoring of CholU severity at first consultation (baseline) in all patients and was 17.0 points (IQR 15-18) (Table I), with 51.3% of patients (n=20/39) with CholUSI >16 indicating severe disease (Table II). In addition, CholUSI was evaluated as tool for assessment of treatment response in 22 patients treated with omalizumab. Median CholUSI decreased significantly from 17.5 (IQR 16.0-18.3) to 4.0 (IQR 0.0-15.0, $p<0.01$) at end of treatment (Figure I, Table II), while the median UCT significantly increased from 2 (IQR 1.0-4.8) to 15.5 (IQR 7-16, $p<0.01$) due to omalizumab treatment. Number of patients with CholUSI >16, indicating severe disease, decreased from 15 to 1 patient (Table II). In 11 patients (50%), complete/good response to omalizumab was reported with improvement of UCT from median 1.5 (IQR 0.8-3.3) to 16 (IQR 16-16, $p<0.01$) and of ChoUSI from median 16 to 0 ($p<0.01$) respectively. In contrast, in 11 patients with partial/no response, ChoUSI and UCT changed slightly (CholUSI 18.0 vs 15.5, $p=0.04$, UCT 2.0 vs 7.0, $p<0.01$).

The Pearson correlation between CholUSI and UCT was calculated among 39 patients with available UCT and/or CholUSI scores at baseline and during treatment. A total of 55 paired scores (UCT and CholUSI at the same timepoint) were obtained (baseline (n=20), 3 months (n=17) or end of treatment (n=18)) with a strong and statistically significant correlation ($r=-0.895$; $p<0.01$) (Supplemental Figure I).

Diagnostic value of the Pulse-Controlled Ergometry (PCE) test

Sixteen patients (81.3% male, median age 22.1 years, median UCT 2.0, median CholUSI 16.5 points) underwent a PCE test (Supplemental Table I). All patients had a very suggestive history of CholU, photo documentation in n=10 (62.5%) and did not show significant differences in CholU symptoms and severity compared to patients that did not undergo PCE test (Table I). Ten patients (62.5%)

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developed one or more wheals during the PCE test, indicating a positive PCE test, resulting in a sensitivity of 62.5% (95% CI 0.35-0.85).

The PCE test resulted in fewer wheals, a delayed onset of wheals and less frequent itching compared to symptoms reported by patient history. Only 5 patients (31.3%) developed more than 50 wheals due to PCE test, which is less than by history (n=11, 68.8%). Furthermore, wheals developed later during PCE test than reported by history; In 8 out of 10 patients with a positive PCE test (80.0%) wheals developed after 15 minutes or longer (range 5-36), with a median time of 27.5 minutes (IQR 22.5–36.0), while wheals were reported in less than 15 minutes by 11 patients (68.8%) by history. Beside a low sensitivity, these findings indicate that in patients with positive PCE test, the test was not able to reproduce the severity of CholU symptoms compared to symptoms in daily life.

Six patients did not show wheals upon PCE test, which was therefore interpreted negative according to guideline criteria, however of these 5 patients developed symptoms of pruritus during PCE test, with median onset time of 10.0 minutes (5.0-17.5). Additionally, 2 patients with a negative test developed erythema (Figure II, Supplemental Table I). Only one patient did not develop any symptoms during the PCE test. This shows that patients with a negative test experienced symptoms during the test, however not wheals.

Higher CholU severity and earlier sweating is associated with positive PCE test

We found that patients with a positive PCE test showed a significantly higher CholU severity (median CholUSI 18.0 (IQR 16.0-19.3)) compared to patients with a negative PCE test (median CholUSI 14.5 points (IQR 10.5-15.5), $p \leq 0.01$), mainly driven by lower number of wheals (median CholUSI 4 versus 3 points, $p \leq 0.01$) and shorter duration of wheals (median CholUSI 3 versus 1 points, p=0.Table S1). Of patients with positive PCE test, 50% (n=5) had severe CholU with CholUSI >16, while none of patients with negative PCE test.

Furthermore, patients with a positive PCE test showed earlier onset of sweating, compared to patients with a negative PCE test (median 5 minutes (IQR 5.0-10.0) versus 20 (IQR 7.5-25.0), p=0.03)

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(Figure II, Supplemental Table I). In patients with a positive test, wheals occurred median 21.0 minutes (IQR 15.0– 25.0) after onset of sweating.

Discussion

In this study, we investigated the diagnostic value of the pulse-controlled ergometry test (PCE), and CholUSI score for assessment and monitoring of disease severity. CholUSI showed a strong positive correlation with the UCT and was demonstrated very suitable to measure disease severity at baseline and at follow-up in patients treated with omalizumab. We found low sensitivity (62.5%) of the PCE test and showed a negative PCE test is associated with milder CholU and delayed sweating.

CholUSI is suitable for assessment of CholU severity and treatment response

CholUSI showed a strong correlation with UCT and was found to adequately monitor CholU over time and upon treatment response, which was not investigated before. We included "number of wheals" in CholUSI as it is a relevant and direct indicator of CholU severity. This is also supported by the finding that a higher number of wheals was identified as a main driver of significantly higher disease severity among patients with a positive PCE test.

CholUSI incorporates questions that are used in standard CholU anamnesis and can therefore be assessed easily and also retrospectively. Although the CholUSI is not yet validated, it has been used in several studies with varying patient numbers (n=10-30) to assess severity of CholU(6,9,15–17) in relation with other CholU specific outcomes as time to whealing during PCE provocation (15), impairment of sweating (16) or total IgE levels (17). However, these studies originate from one research group, so external validation was lacking.

At this moment, UCT and CholUAS7 are the only validated outcome measures for monitoring of CholU(8) in daily practice. UCT is a simple, short, monthly patient-reported score and widely used for monitoring of chronic urticaria but lacks CholU-specificity. CholUAS7 is a short, daily, patient-reported CholU-specific severity score(8), taking exercise exposure into account, however this score

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does not include specific eliciting factors or duration of wheals. As CholUAS7 is a daily score, there is a high risk of missing data. In addition, CholUAS7 might be complicated to calculate as days without exercise exposure need to be censored and left out the total weekly score. Concluding, CholUSI score is a CholU-specific easy-to-use tool, as it is based on readily available patient data including eliciting factors and duration of wheals, which are not included in the validated but non-CholU-specific UCT.

Low sensitivity of the pulse-controlled ergometry (PCE) test and its determinants

Evaluation of the PCE test showed a low sensitivity of 62.5%. This is unsatisfactory since the aim of this test is to confirm or exclude CholU diagnosis, especially in mild or uncertain clinical presentations, and it involves a considerable effort for patients and professionals. Despite using the same protocol, we could not confirm the high sensitivity of 100% found previously(6). However, low sensitivity of exercise provocation tests has been published previously. For instance, Komarow et al. found that 65% (n=13/20) of patients with CholU had a negative response to an exercise challenge test on a treadmill(4), indicating that CholU symptoms are difficult to reproduce during an exercise test. Overall, PCE test seems not appear to adequately reproduce the symptoms experienced by patients in their daily life. Its low sensitivity limits the clinical utility of the PCE test in daily practice. We found that the PCE test was not sufficient in diagnosing mild or moderate CholU, as a negative test result was associated with lower disease severity. Earlier studies did not show influence of CholU severity on provocation test outcome, however, these studies did not investigate complete and unselected daily practice populations as we did, and it cannot be excluded that these previous studies selected more severe cases. Lower disease severity might negatively affect the reproducibility of wheals during the PCE test, which is disadvantageous since a reliable diagnostic test is especially needed in patients with milder and possibly uncertain clinical presentation of CholU. Low PCE test sensitivity in these patients may contribute to underdiagnosing milder CholU with subsequent treatment retention. For patients with negative tests increasing exercise intensity during PCE test may improve diagnostic accuracy, which needs to be investigated in further studies.

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Importantly, patients with a negative PCE test did show symptoms i.e. pruritus and/or erythema but without wheals, even when having wheals documented in patient history, suggesting false-negative results, rather than cholinergic pruritus (CholP) or erythema (CholE)(18–20). Previous studies described that these conditions represent a spectrum of CholU and clinical manifestations of CholU were more wide-ranging and heterogenous than previously suspected(18–21).

We found that patients with a negative PCE test had a significantly longer time to sweating, which was not described previously. Sweat retention or impairment is common in CholU patients, especially in patients with longstanding and severe disease(6,16,22,23), however this was not observed in the present study. This suggests that variations in sweating might also contribute to the varying outcomes of provocation testing(16). Additionally, variations in temperature or other environmental factors during the test compared to real-life settings may also influence the outcome of exercise tests(5). Promoting earlier sweating during the test, by raising the room temperature, thicker and/or more layers of clothing, might improve diagnostic sensitivity.

PCE test might be overly controlled, too short, and pre-test triggers should be avoided

Exercise during the PCE test might be overly controlled and the intensity too gradually increased, which may not reflect the more variable and explosive exercise patients are exposed to at home/outside, and might even cause temporary desensitization, resulting in false-negative outcome (5,23). In case the PCE test is negative, a repeated provocation test without pulse-control may help better match real-life or sports exercise.

In addition, we showed that wheals can develop up to 35 minutes after start sweating, in contrast to 10 minutes in previous research(6), therefore an improvement to the PCE test is possibly to increase the duration of exercise to at least 35 minutes after start of sweating.

Notably, patients should be instructed to avoid any exposure to their trigger of symptoms, as physical exercise during the commute to the PCE test (e.g. walking stairs, cycling) and emotional stress before start of PCE test may contribute to a negative outcome. This idea is supported by previous research describing that there is a period of relative freedom for a few hours after an attack(24). Also, it is

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recommended that provocation testing should be carried out after at least 24 hours of the absence of symptoms (2).

Together this indicates that the diagnostic value of the PCE test could be improved by increasing exercise intensity, extending test duration, repeated testing and stimulating early sweating.

In conclusion, our findings support the use of the Cholinergic Urticaria Severity Index (CholUSI) as practical, disease-specific tool for monitoring of CholU-severity and treatment evaluation. The pulse-controlled ergometry (PCE) test showed a low sensitivity of 62.5% with risk of false-negative outcome, especially in patients with mild CholU. PCE test sensitivity might be improved by stimulating early sweating, higher exercise intensity, extending the test duration and repeated testing, which needs validation in future studies.

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Contributions:

JS: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing.

RS: Conceptualization, Supervision, Writing – review & editing.

HNL: Data curation, Formal Analysis, Writing – original draft.

ACK: Conceptualization, Resources, Supervision, Writing – review & editing.

HR: Conceptualization, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – review & editing.

Conflict of interest disclosures:

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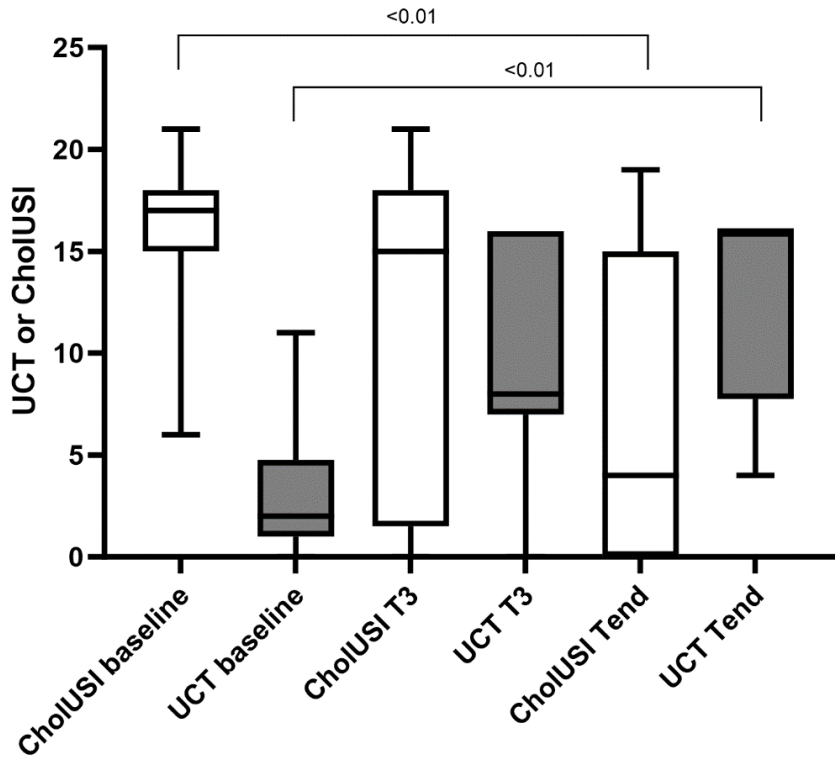
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Figure 1. Disease severity by CholUSI and urticaria control due to omalizumab treatment

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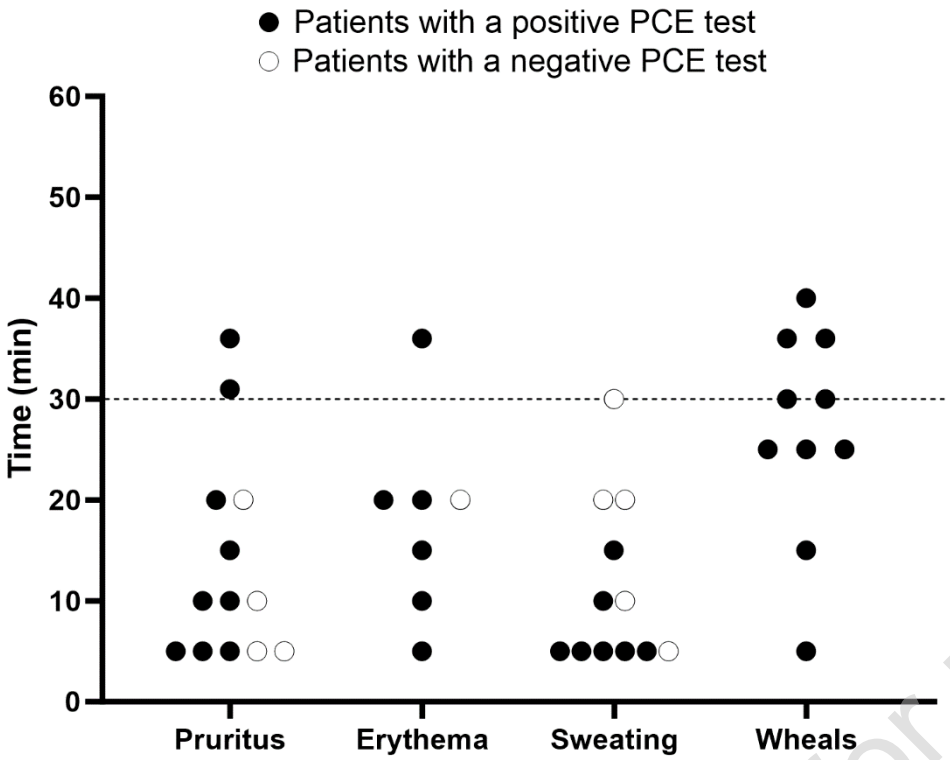


Legend

UCT (grey box) and CholUSI (white box) are assessed before initiation of omalizumab (baseline), after 3 months (T3) and end of treatment (Tend) with omalizumab (n=22)
Tend: the time of discontinuation of omalizumab or data lock

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Figure 2. Time to pruritus, erythema, sweating and wheals during PCE test



Legend:
The 30-minute exercise period and the following 30 minutes recovery period is divided by the dotted line. Patients with a positive test are shown in black dots and patients with a negative test in white dots.
Time of pruritus is missing of 1 patient with a positive test and 1 patient with a negative test.
Time of erythema is missing of 3 patients with a positive test and 1 patient with a negative test.
Time of sweating is missing of 1 patient with a positive test, and sweat test was not performed in 3 patients.

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Table I. Characteristics of patients with and without Pulse controlled ergometry (PCE) test

	Total N=39	PCE test N=16	No PCE test N=23	*P*
Patient characteristics				
Male, n (%)	26 (66.7)	13 (81.3)	13 (56.5)	0.107
Age, mean ±SD	25.0 ±10.5	22.1 ±7.5	27.1 ±12.0	0.152
Totaal IgE, mean ±SD	369.2 ±694.8[I]	435.6 ±742.1[II]	323.2 ±687.0[III]	0.719
Disease duration continuous, months, mean ±SD	50.1 ± 58.2	41.9 ±38.7	54.4 ±66.9	0.591
CU Comorbidity				0.368
- Wheals	7 (17.9)	1 (6.25)	6 (26.1)	
- Angio-edema	1 (2.6)	0 (0.0)	1 (4.3)	
CholU characteristics[a]				
History of symptoms				
- Wheals	39 (100.0)	16 (100.0)	23 (100.0)	-
- Pruritus	39 (100.0)	16 (100.0)	23 (100.0)	-
- Erythema [II]	11 (28.8) [IV]	7 (43.8) [V]	4 (17.4) [VI]	0.074
History of time to wheals, n (%)				0.698
- <5 minutes	16 (41.0)	8 (50.0)	8 (34.8)	
- 15 minutes	8 (20.5)	3 (18.8)	5 (21.7)	
- 30 minutes	1 (2.6)	0 (0.0)	1 (4.3)	
-1 hour	0 (0.0)	0 (0.0)	0 (0.0)	
- >2 hours	0 (0.0)	0 (0.0)	0 (0.0)	
- Unknown	14 (35.9)	5 (31.3)	9 (39.1)	
History of duration to wheals, n (%)				0.463
- <5 minutes	9 (23.1)	5 (31.3)	4 (17.4)	
- 15 minutes	4 (10.3)	2 (12.5)	2 (8.7)	
- 30 minutes	3 (7.7)	2 (12.5)	1 (4.3)	
-1 hour	11 (28.2)	4 (25.0)	7 (30.4)	
- >2 hours	7 (18.0)	2 (12.5)	5 (21.7)	
- Unknown	5 (12.8)	1 (6.3)	4 (17.4)	
History of number of wheals, n (%)				0.531
- 1-50	1 (2.6)	1 (6.3)	0 (0.0)	
- 50-100	10 (25.6)	3 (18.8)	7 (30.4)	
- >100	21 (53.8)	8 (50.0)	13 (56.5)	
- Unknown	6 (15.4)	3 (18.8)	3 (13.0)	
CholUSI score, median (IQR)	17.0 (15.0-18.0)	16.5 (15.0-18.8)	17.0 (15.0-18.0)	0.628
- Frequency of CholU symptoms	5.0 (4.0-5.0)	5.0 (3.3-5.0)	5.0 (5.0-5.0)	0.0.218
- Eliciting factors	3.0 (2.0-4.0)	3.5 (2.0-4.0)	3.0 (2.0-4.0)	0.274
- Duration of symptoms	2.0 (1.0-3.0)	2.0 (1.0-3.8)	3.0 (1.0-3.0)	0.637
- Itch severity	3.0 (3.0-3.0)	3.0 (3.0-3.0)	3.0 (3.0-3.0)	0.785
- Number of wheals	4.0 (3.0-4.0)	3.5 (3.0-4.0)	4.0 (3.0-4.0)	0.490
UCT, median (IQR)	2.0 (1.0-4.8) [VII]	2.0 (1.0-5.0) [VIII]	2.0 (1.0-4.5) [IX]	0.752
Confirmation of wheals by photo-documentation	27 (69.2)	10 (62.5)	17 (73.9)	0.447

Legend

[a] CholU characteristics at baseline

Missings: [I]N=17, [II]N=7, [III]N=10, [IV]N=27, [V]N=8, [VI]N=19, [VII]N=19, [VIII]N=9, [IX]N=10.

Abbreviations: CholUSI, Cholinergic Urticaria Severity Index; CU, chronic urticaria; IQR, interquartile range; PCE test, pulse-controlled ergometry test.

Table II. Categorized disease severity by CholUSI at baseline and follow-up

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	Baseline, n (%)[a]	Baseline omalizumab, n(%) [b]	3 months, n (%)[c]	End of treatment, n (%)[d]
Very mild (<5)	0 (0.0)	0 (0.0)	5 (27.8)	10 (52.6)
Mild (5-10)	1 (2.6)	0 (0.0)	3 (16.7)	2 (10.5)
Moderate (11-16)	18 (46.2)	7 (31.8)	4 (22.2)	4 (21.1)
Severe (>16)	20 (51.3)	15 (68.2)	6 (33.3)	3 (15.8)
Total	39 (100.0)	22 (100.0)	18 (100.0)	19 (100.0)

Legend:

Disease severity was based on CholUSI, and was ranked between 0 and 23 points: <5 points: very mild CholU; 5–10 points: mild CholU; 11–16 points: moderate CholU; >16points: severe CholU. Number of patients per CholUSI severity category is presented.

[a] At first visit

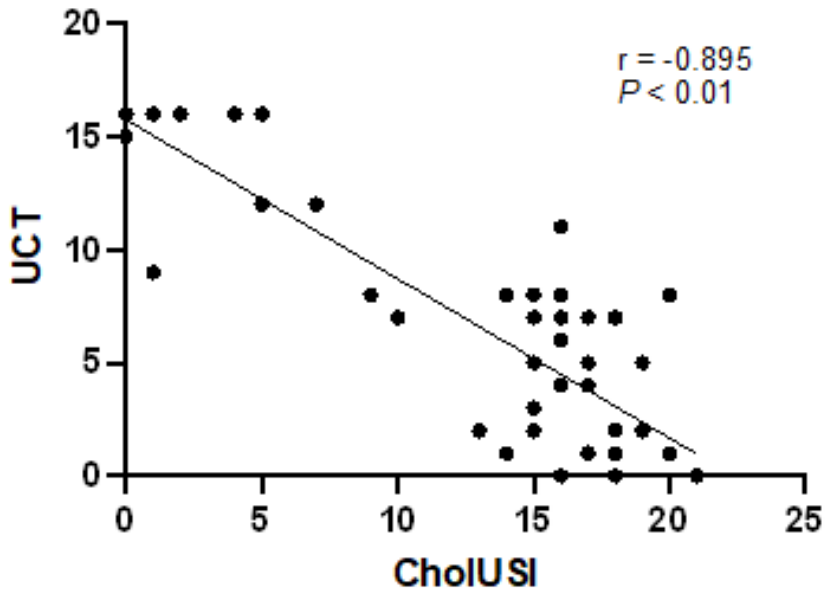
[b] Before start of omalizumab

[c] After 3 months of omalizumab treatment

[d] At time of discontinuation of omalizumab or datalock

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Supplemental Figure I. Pearson correlation of CholUSI and UCT



Legend

A total of 55 paired scores (UCT and CholUSI at the same timepoint) were obtained (baseline (n=20), 3 months (n=17) or end of treatment (n=18).

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Supplemental Table I: Comparison of patients with positive versus negative pulse-controlled ergometry

	Total N=16	Positive PCE test[a] N=10	Negative PCE test N=6	*P*
Patient characteristics				
Male, n (%)	13 (81.3)	7 (70.0%)	6 (100.0)	0.137
Age, mean ±SD	22.1 ±7.5	20.8 ±6.5	24.2 ±9.03	0.405
Disease duration, months, mean ±SD	41.9 ±38.7	40.0 ±33.0	44.8 ±51.5	0.862
Total IgE, mean ±SD	435.6 ±742.1	758.8 ±898.3	31.5 ±28.3	0.155
Main diagnosis, n (%)				-
- CindU	100 (100.0)	100 (100.0)	100 (100.0)	
- CSU	0 (0.0)	0 (0.0)	0 (0.0)	
Comorbidity, n (%)				0.691
- Wheals	1 (6.25)	0 (0.0)	1 (16.7)	
- Angio-edema	0 (0.0)	0 (0.0)	0 (0.0)	
CholU characteristics[b]				
History of symptoms, n (%)				
- Wheals	16 (100.0)	10 (100.0)	6 (100.0)	-
- Pruritus	16 (100.0)	10 (100.0)	6 (100.0)	-
- Erythema	7 (87.5)	5 (83.3)[I]	2 (100.0)[II]	0.504
History of time to wheals, n (%)				0.546
- <5 minutes	8 (50.0)	4 (40.0)	4 (66.7)	
- 15 minutes	3 (18.8)	2 (20.0)	1 (16.7)	
- 30 minutes	0 (0.0)	0 (0.0)	0 (0.0)	
- 1 hour	0 (0.0)	0 (0.0)	0 (0.0)	
- >2 hours	0 (0.0)	0 (0.0)	0 (0.0)	
- Unknown	5 (31.3)	4 (40.0)	1 (16.7)	
History of duration of wheals, n (%)				0.092
- <5 minutes	5 (31.3)	2 (20.0)	3 (50.0)	
- 15 minutes	2 (12.5)	0 (0.0)	2 (33.3)	
- 30 minutes	2 (12.5)	2 (20.0)	0 (0.0)	
- 1 hour	4 (25.0)	4 (40.0)	0 (0.0)	
- >2 hours	2 (12.5)	2 (20.0)	0 (0.0)	
- Unknown	1 (6.3)	0 (0.0)	1 (16.7)	
History of number of wheals, n (%)				0.167
- 1-10	0 (0.0)	0 (0.0)	0 (0.0)	
- 10-50	1 (6.3)	1 (10.0)	0 (0.0)	
- 50-100	3 (18.8)	1 (10.0)	2 (33.3)	
- >100	8 (50.0)	7 (70.0)	1 (16.7)	
- Unknown	3 (18.8)	1 (10.0)	2 (33.3)	
UCT (IQR)	2.0 (1.0-5.0)	2.0 (0.8-4.3)[III]	5.0 (5.0-5.0)[IV]	0.299
CholUSI based on history, median (IQR)	16.5 (15.0-18.8)	18.0 (16.0-19.3)	14.5 (10.5-15.5)	**0.002**
- Frequency of CholU symptoms	5.0 (4.0-5.0)	5.0 (4-5.3)	4.5 (3.0-5.0)	0.214
- Eliciting factors	3.5 (2.0-4.0)	4.0 (2.8-4.0)	2.5 (1.8-4.3)	0.409
- Duration of symptoms	2.0 (1.0-3.8)	3.0 (1.8-4.0)	1.0 (1.0-1.5)	**0.022**
- Pruritus severity	3.0 (3.0-3.0)	3.0 (3.0-3.0)	3.0 (2.8-3.0)	0.207
- Number of wheals	3.5 (3.0-4.0)	4.0 (3.8-4.0)	3.0 (2.0-3.0)	**0.000**
Confirmation of wheals by photo-documentation	10 (62.5)	7 (70.0)[V]	3 (50.0)[VI]	0.584

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CholU severity at baseline, based on CholUSI - Very mild - Mild - Moderate - Severe	 1 (6.3) 1 (6.3) 9 (56.3) 5 (31.3)	 0 (0.0) 0 (0.0) 5 (50.0) 5 (50.0)	 1 (16.7) 1 (16.7) 4 (66.7) 0 (0.0)	0.089
Pulse controlled ergometry test				
Symptoms, n (%) - Wheals - Pruritus - Erythema	 10 (62.5) 15 (93.8) 11 (68.8)	 10 (100.0) 10 (100.0) 9 (90.0)	 0 (0.0) 5 (83.3) 2 (33.3)	 **0.000** 0.182 **0.018**
Number of wheals, n (%) - 1-10 - 10-50 - 50-100 - >100 - Unknown	 2 (12.5) 2 (12.5) 2 (12.5) 3 (18.8) 7 (43.8)	 2 (0.0) 2 (20.0) 2 (20.0) 3 (30.0) 1 (10.0)	 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0)	0.000
Time to whealing, min, median (IQR)	27.5 (22.5-36.0)	27.5 (22.5-36.0)	-	-
Time to pruritus, min, median (IQR)	10.0 (5.0-20.0)	10.0 (5.0-25.5)[VII]	10.0 (5.0-17.5)[VIII]	0.427
Time to erythema, min, median (IQR)	10.0 (10.0-20.0	17.5 (8.8-24.0)[IX]	20.0 (20.0-20.0)[X]	0.817
Time to sweating, min, median (IQR)	7.5 (5.0-18.8)	5.0 (5.0-10.0)[XI]	20.0 (7.5-25.0)[XII]	**0.034**
Time between onset of sweating and whealing, median (IQR)	21.0 (15.0-25.0)	21.0 (15.0-25.0)[XIII]	-	-

Legend:

[a]A positive test is defined as observation of pinpoint-sized wheals during the exercise or during recovery period.

[b]CholU characteristics at baseline

p-values marked in bold were considered statistically significant

Missing data: [I]N=4, [II]N=4, [III]N=4, [IV]N=5, [V]N=2, [VI]N=2, [VII]N=1, [VIII]N=2, [IX]N=4 [X]N=5, [XI]N=3, [XII]N=1, [XIII]N=3

Abbreviations: CholUSI, Cholinergic Urticaria Severity Index; CU, chronic urticaria; IQR, interquartile range; PCE test, pulse-controlled ergometry test.

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Supplemental Table II. Items of CholUSI published by Altrichter et al (6) and adapted CholUSI

Legend: Changes are shown in grey

CholUSI		Points	Adapted CholUSI		Points
1) Frequency of CholU	Less than less than once a month	0	1) Frequency of CholU	Less than less than once a month	0
	Once a month	1		Once a month	1
	More than once a month	2		More than once a month	2
	Once a week	3		Once a week	3
	More than once a week	4		More than once a week	4
	Daily	5		Daily	5
	More than once daily	6		More than once daily	6
2) Eliciting factors	Physical exercise	1	2) Eliciting factors	Intensive physical exercise	1
				Moderate physical exercise (walking, daily activities)	1
	Hot Bath	1		Hot bath/shower/sauna	1
	Hot shower	1			
	Sauna	1			
	Emotional stress	1		Emotional stress	1
	Hot food	1		Hot food	1
	Other	1		Other	1
3) Duration of skin lesions	Less than 5 minutes	0	3) Duration of skin lesions	Less than 5 minutes	0
	5 to10 minutes	1		5 to15 minutes	1
	10 to 20 minutes	2		15 to 30 minutes	2
	20 to 30 minutes	3		30 to 60 minutes	3
	30 to 60 minutes	4		Longer than 1 hour	4
	Longer than 1 hour	5			
4) Itch during the events	None	0	4) Itch during the events	None	0
	Low	1		Low	1
	Medium	2		Medium	2
	Severe	3		Severe	3
			5) Number of wheals	None	0
				1 to 10 wheals	1
				10 to 50 wheals	2
				50 to 100 wheals	3
				More than 100 wheals	4
Total		21	Total		23

CholUSI by Altrichter: disease severity was ranked between 0 and 21 points: <5 points: very mild CholU; 5–9 points: mild CholU; 10–15 points: moderate CholU; >15points: severe CholU

Adapted CholUSI: disease severity was ranked between 0 and 23 points: <5 points: very mild CholU; 5–10 points: mild CholU; 11–16 points: moderate CholU; >16points: severe CholU

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