

Urticaria control test might misevaluate disease control in particular patients treated with omalizumab



Since its effectiveness in H_1 -antihistamine refractory chronic spontaneous urticaria (CSU) was shown, omalizumab has been increasingly used across the world. Omalizumab is licensed at a dose of 300 mg subcutaneously every 4 weeks in Turkey and in the European Union.^{1,2} The urticaria activity, control, and response to treatment should be assessed by a reliable and easily applicable tool during this 4-week interval. Urticaria activity score (UAS) and urticaria control test (UCT) are 2 well-developed and validated patient-reported outcome measures (PRO). Urticaria activity score is the gold standard tool to assess disease activity, and to better determine the frequently of fluctuating disease activity in CSU, it is recommended to collect and sum the data of 7 consequent days (UAS7).³ The UCT is a retrospective PRO with a recall period of 4 weeks and is suggested for assessing disease control. Even though both of these clinical measures have strengths and limitations,⁴ when compared, a strong and significant negative correlation was reported between UAS and UCT.⁵ Minimal important difference, which is defined as the smallest measured score change that is clinically meaningful to patients, was found to be 11 and 3 for the UAS7 and UCT, respectively.^{5,6}

Although both PROs are validated, used in several studies, and recommended by the European Academy of Allergology and Clinical Immunology, Global Allergy and Asthma European Network, European Dermatology Forum, World Allergy Organization guideline, in our clinical practice we noticed a discrepancy among UAS7 and UCT scores in patients who have symptomatic worsening toward the end of the 4-weekly intervals of omalizumab dosing. Thus, this retrospective study aims to investigate the effect of symptomatic fluctuations during the treatment interval on UCT scores in patients receiving omalizumab therapy.

At Erciyes University Allergy Clinic, UCT is used to determine the disease control and treatment response. In addition, all patients were advised to document UAS for 7 days both before and after all of the applications (UAS7-before and UAS7-after, respectively) to assess the maximum change in urticaria activity (Fig 1). Thus, on every application day, UAS7-before, UAS7-after, and UCT records of the previous treatment interval were obtained. UCT ≥ 12 , UAS7-before ≤ 6 , and UAS7-after ≤ 6 were accepted as well-controlled disease and UCT < 12 , UAS7-before > 6 , and UAS7-after > 6 were accepted as poorly controlled disease.

Sixty-two records from 28 CSU patients who had baseline UAS7 ≥ 16 , regularly documented UCT, UAS7-before, and UAS7-after scores, did not have accompanying chronic inducible urticaria, and had at least 3 doses of 300 mg/4 weeks omalizumab, were included. To make sure patients learned to score PROs correctly, we only selected PRO records after the 3rd omalizumab application for our analysis. Twenty-three of the patients (82%) were female, and mean age was 37 ± 9.4 years. Mean UCT, UAS7-before, and UAS7-after values of all 62 records were found 13.3 ± 2.5 (min: 4, max: 16), 6.8 ± 8.8 (min: 0, max: 38), and 3.3 ± 4.5 (min: 0, max: 21), respectively. There were 51 (82%) records with UCT ≥ 12 , 38 (61%) with UAS7-before ≤ 6 and 52 (84%) with UAS7-after ≤ 6 . Dual comparison of UAS7-before, UAS7-after, and UCT records showed a significant correlation (UAS7-before and UAS7-after $r = 0.455$ $P < .001$; UAS7-before and UCT $r = -0.63$, $P < .001$; UAS7-after and UCT $r = -0.539$, $P < .001$). Despite this significant correlation, when records of all UCT and UAS7-before scores were evaluated, 13 (26%)

of 51 records with UCT ≥ 12 were found at the same time scored as UAS7-before > 6 (Table 1). The changes in disease activity through the interval were significantly higher between the beginning and the end of these 13 results, compared with 38 results that had UCT ≥ 12 and UAS7-before ≤ 6 at the same time (9.6 ± 11.5 vs 0.16 ± 2 points difference between UAS7-before and UAS7-after; $P < .001$). When comparing the same 13 records with 11 records with UCT < 12 and UAS7-before > 6 , the mean difference between UAS7-after and UAS7-before scores showed no difference (9.6 ± 11.5 vs 8.1 ± 9.3 ; $P = 1$).

Our results showed that even with a strong correlation between UCT and UAS7-before scores, approximately a quarter of well-controlled patients, according to UCT, had poorly controlled disease with UAS7-before. Additionally, UAS was found to be increased 9.6 ± 11.5 points toward the end of the interval in these results. Both scoring systems were effective in identifying poorly controlled patients; however, our results may speculate that UCT may misevaluate the disease control in patients with symptomatic worsening toward the end of the interval.

The UAS is a valid “gold standard” tool for measuring and monitoring the disease activity in CSU.⁴ Because of the symptoms in CSU frequently fluctuate, documentation of the UAS at least for 4 consequent days was advised to measure the disease activity best.⁷ The current European Academy of Allergology and Clinical Immunology, Global Allergy and Asthma European Network, European Dermatology Forum, World Allergy Organization guideline suggests that UAS7 in routine clinical practice to determine disease activity and response to treatment.³ Currently, UAS7 is used in many different studies.

In the development and validation study of the UCT, investigators found a strong and highly significant correlation between UCT and UAS28 ($r = -0.750$; $P < .001$). They also showed a good linear trend with UCT and different control status measured by UAS28.⁵ We also found a high correlation between UAS14 (sum of UAS7-before and UAS7-after) and UCT scores ($r = -0.703$; $P < .001$). In their study, as far as we know, investigators did not evaluate the effect of fluctuations in the symptoms on UCT scores. Ferrer et al⁸ stated that definite characterization of fluctuations is important, because shortening of application intervals for omalizumab may be tried in patients with symptomatic worsening toward the end of the interval. Also, we previously showed that in these patients, 150 mg/2 weeks omalizumab may provide better symptom control than 300 mg/4 weeks.⁹

In the simplest form, UAS7 focuses on the severity of pruritus and wheal, whereas UCT questions the effect of urticaria on daily life. The discrepancy between UAS7-before and UCT scores in our study may suggest that every UAS7-proven symptomatic worsening would not mean a negative effect on daily life and disease control according to the patients. Also recently, Hawro et al⁶ found that the minimal important difference for UAS7 is 11. Therefore, our average 9.6-point increase toward the end of the interval may not be clinically meaningful to the patients. Recording patients' disease-specific quality of life is clearly important and should be evaluated together with measurements of urticaria activity and control. This approach may help clinicians to differentiate actual poorly controlled patient from well-controlled patients and to make correct treatment decisions.

Table 1

Mean Differences between UAS7-before and UAS7-after Scores for Well and Poorly Controlled Diseases Defined by UCT and UAS7-before

Mean difference between UAS7-before ^a and UAS7-after ^b			
	UAS7-before > 6 (poorly controlled)	UAS7-before ≤ 6 (well-controlled)	P value
UCT ≥ 12 (well-controlled)	9.6 ± 11.5* (n = 13)	0.16 ± 2 (n = 38)	<.001
UCT < 12 (poorly controlled)	8.1 ± 9.3* (n = 11)	(n = 0)	-

*P value = 1 when comparing these 2 results.

Abbreviation: UCT, urticaria control test.

^aUAS7-before: Urticaria activity score of the 7 days before the application of omalizumab.

^bUAS7-after: Urticaria activity score of the 7 days after the application of omalizumab.

Our study has limitations: First, it is a single-center study; second, its retrospective nature; and finally, we only included the patients with fully documented records, which may cause selection bias. Still, we showed that, in CSU, symptoms may still fluctuate even under omalizumab therapy; UCT may lack sensitivity to capture these fluctuations because of its 4-week evaluation period, and there might be discrepancy between UAS7 and UCT scores in patients with increasing symptoms toward the end of the interval. How much of these fluctuations in the symptoms, which can be captured more sensitively with UAS7, affect patients' well-being is not known and should be further investigated.

Murat Türk, MD
İnsu Yılmaz, MD

Division of Allergy and Clinical Immunology
Department of Chest Diseases
Erciyes University School of Medicine
Kayseri, Turkey
mrtrrk@gmail.com

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Measurement of exhaled nitric oxide in young children



Fractional exhaled nitric oxide (FeNO) is a direct marker of type 2 airway inflammation and aids in the diagnosis of asthma.^{1,2} FeNO is reproducible and easy to use in the clinic setting.^{3–5} The FeNO measurement technique is often easier for younger children to master than spirometry⁶ and much less invasive than sputum induction or bronchoscopy.^{7,8}

We assessed the ability of children 4 to 6 years of age to use a handheld, electrochemical, *in vitro* diagnostic device for measuring FeNO that operates using a 6-second exhalation mode or a 10-second exhalation mode (NIOX VERO, Circassia Pharmaceuticals Inc, Morrisville, North Carolina) and the degree of agreement between results obtained in each mode. This single-visit, point-of-care, clinical study was conducted at 4 centers across the United States (ClinicalTrials.gov Identifier: NCT02661984). Study participants were children who were considered healthy (ie, without pulmonary disease) or had a physician's diagnosis of asthma. Exclusions included pulmonary disease other than asthma, severe or uncontrolled asthma (defined as ≥2 exacerbations within the last year requiring systemic corticosteroids or ≥1 hospitalizations), acute asthma symptoms that required reliever inhaler use within 4 to 6 hours of FeNO measurements, acute respiratory illness, sinusitis, and inability to safely complete FeNO measurements.

FeNO was measured using a single-breath online method.⁹ Children were randomized to begin with 2 FeNO attempts using the 6-second mode followed by 2 FeNO attempts using the 10-second mode, or vice versa, until they achieved 2 successful FeNO measurements for both modes (4 successful FeNO measurements). Children used the same device for all measurement attempts and were allowed up to 12 attempts to obtain 2 successful measurements with both modes.

The primary objective was the degree of agreement between the 6- and 10-second modes assessed by weighted Deming regression analysis in children aged 4, 5, and 6 years with 2 successful FeNO measurements in both the 6- and 10-second modes (primary analysis population). Secondary end points included descriptive analysis of observed data for both exhalation modes (number of attempts and FeNO results), a comparison of FeNO results obtained with the 6-second mode vs the 10-second mode using a Bland-Altman plot, weighted Deming regression analysis of bias from the fitted regression line, repeatability (measured as the intra-subject SD) for both exhalation modes, and the percentage of children within tolerance limits.

A total of 105 children completed 1 FeNO measurement using either mode (n = 20 4-year-olds, 40 5-year-olds, and 45 6-year-olds) of whom 83 completed 1 FeNO measurement in both modes and 68 completed 2 successful FeNO measurements in both modes (n = 9 4-year-olds, 27 5-year-olds, and 32 6-year-olds). A total of 54 children were unsuccessful in completing any FeNO measurements (n = 28 4-year-olds, 17 5-year-olds, and 9 6-year-olds).

The primary analysis population (n = 68) was composed of 51.5% males, 60.3% children with asthma, 72.1% whites, and 51.5% randomized to the 6-second mode followed by 10-second mode. Weighted Deming regression analysis of the first FeNO result for

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