

Omalizumab in patients with chronic spontaneous urticaria nonresponsive to H1-antihistamine treatment: results of the phase IV open-label SUNRISE study*

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Summary

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Conflicts of interest

The following conflicts of interest are declared: F.B.: AbbVie, Janssen, Novartis, Roche (grants/research support); AbbVie, Novartis, Sanofi (honoraria, advisory board, or consulting fees). M.C.F.l.e.B.: Novartis (congress registration fees and accommodation). L.B.: Novartis (consultant and lecturer). Z.R.: Novartis Pharma (investigator, speaker and advisory board member). A.B.: Sanofi, Novartis, Biogen, Genevri, La Roche Posay (invitation to a congress or protocols or expert meetings or conferences). F.C.: AbbVie, Celgene, Janssen, LEO Pharma, Novartis, Pfizer (has performed clinical research and received honoraria). B.M.: Novartis (honoraria, advisory board). B.P., I.K. and H.G.: Novartis Pharma (employees). J.P.L.: AbbVie, Boehringer, Celgene, Galderma, Janssen, Lilly, Merck, Novartis, Regeneron Pharmaceuticals Inc., Roche (grants/research support); AbbVie, Celgene, Galderma, Lilly,

Background Omalizumab is approved as an add-on therapy for the treatment of chronic spontaneous urticaria (CSU) in patients with inadequate response to H1-antihistamine treatment. The urticaria control test (UCT) is a reliable, concise tool developed as an alternative to the 7-day urticaria activity score (UAS7) – the standard for CSU disease activity assessment.

Objectives This prospective, open-label, phase IV study evaluated the efficacy and safety of omalizumab in French adult patients with CSU nonresponsive to H1-antihistamine treatment.

Materials and methods Patients [$n = 136$; stratified 1 : 2 (with angio-oedema : without angio-oedema)] received omalizumab 300 mg subcutaneously every 4 weeks for 12 weeks. Study assessments included UCT, UAS7, angio-oedema activity score and D-dimer levels (exploratory objective).

Results At Week 12, 74.6% of the patients achieved disease control [UCT score ≥ 12 (primary endpoint)] and 67.7% of patients showed well-controlled disease (UAS7 ≤ 6). There was a strong negative correlation between UCT score and UAS7 at Week 12 (Spearman's correlation coefficient -0.839). Mean plasma D-dimer concentration was elevated at baseline ($1002.1 \text{ ng mL}^{-1}$) and decreased notably at Week 8 (455 ng mL^{-1}). Among the nine patients with a very high baseline D-dimer concentration ($> 3000 \text{ ng mL}^{-1}$), eight were responders (UAS7 ≤ 6) at Week 12.

Conclusions Omalizumab was efficacious in patients with CSU nonresponsive to H1-antihistamines. The UCT was a reliable tool for disease assessment and the scores correlated well with UAS7. This study does not support the usefulness of D-dimer to monitor long-term disease prognosis in adult urticaria; however, it may indicate patients who respond to omalizumab.

What's already known about this topic?

- Omalizumab is recommended as the third-line treatment for chronic spontaneous urticaria (CSU), as an add-on to H1-antihistamines.

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- The urticaria control test (UCT) is a recently validated tool for disease control assessment in patients with CSU.
- Elevated plasma levels of D-dimer observed in some patients with CSU suggests a potential role of D-dimer as a biomarker in CSU treatment response and prognosis.

What does this study add?

- Omalizumab controlled symptoms and improved quality of life in French patients with moderate-to-severe CSU.
- UCT was a reliable tool for the assessment of urticaria control.
- D-dimers are elevated in some patients with CSU and change in response to treatment with omalizumab.
- This study does not support the usefulness of D-dimer to monitor long-term disease prognosis in adult urticaria; however, it may indicate patients who respond to omalizumab.

Chronic spontaneous urticaria (CSU) is characterized by the spontaneous occurrence of transient, itchy recurrent wheals that persist for at least 6 weeks, with or without angioedema.¹ CSU has an estimated point prevalence of approximately 0.5–1%.² Its etiology and pathogenesis has not been completely understood and several causative factors, including autoimmune processes, have been hypothesized.^{3,4} Recent evidence suggests a possible involvement of the coagulation cascade in the pathogenesis of CSU as elevated plasma levels of thrombin and D-dimer were observed in some patients.^{5–7}

CSU is a debilitating disease that can severely impact patients' quality of life (QoL).^{8,9} International guidelines recommend second-generation H1-antihistamines at licensed doses as first-line therapy and to progressively increase the dosage up to fourfold, in case of nonresponse.¹⁰ However, in about 10% of patients, H1-antihistamines fail to achieve symptom control even at higher doses and the patient requires additional medication.⁹ Omalizumab, a humanized anti-immunoglobulin E (anti-IgE) monoclonal antibody, is recommended as the third-line treatment for CSU, as an add-on to H1-antihistamines. Omalizumab binds to the Fc region of free IgE and prevents it from binding to its high-affinity receptor (FcεR1) on mast cells and basophils.¹¹ The safety and efficacy of omalizumab in the treatment of CSU were established in three phase III studies in patients with H1-antihistamine-refractory moderate-to-severe CSU.^{12–14}

In these pivotal studies, disease activity was assessed using the 7-day urticaria activity score (UAS7) as recommended by international guidelines.¹⁰ The UAS7 is a unified and simple score that combines daily weal count and pruritus intensity. Although UAS7 is a useful and widely used tool, it has some limitations in that it is prospective, does not cover angioedema and is difficult to evaluate if the patient forgets to complete the diary on a daily basis.¹⁵

Hence, the urticaria control test (UCT), a reliable and brief tool, was developed to overcome the limitations of UAS7. The UCT is the first validated and reliable patient-reported outcome (PRO) tool that retrospectively measures disease control in patients with all types of chronic urticaria and through its

clear threshold of ≥ 12 for well-controlled disease helps treatment decisions. Unlike UAS7, UCT has a 4-week recall period and is independent of any previous patient presentations.¹⁵

The SUNRISE study was conducted to evaluate the efficacy of subcutaneous (s.c.) omalizumab 300 mg every 4 weeks in French adult patients with CSU who had an inadequate response to H1-antihistamine treatment. The recently validated UCT was used to assess disease activity for the first time in this prospective clinical study. Additionally, the present study explored the relation between plasma D-dimer concentrations and disease activity in patients with CSU.

Materials and methods

Study design and participants

SUNRISE (trial registration: EudraCT no. 2014-005424-97) was a prospective, open-label, single-arm, nonrandomized, multicentre (30 centres), phase IV study conducted in France. The study comprised a screening period, a 12-week treatment period and an extension period (Fig. 1). Patients included in the study were aged between 18 and 75 years and met all the following criteria prior to enrolment: a diagnosis of CSU for ≥ 6 months with an inadequate response to non-sedating H1-antihistamines as evidenced by the presence of hives associated with itching for at least six consecutive weeks at any time before enrolment despite current use of H1-antihistamines; a UAS7 ≥ 16 (equivalent to moderate-to-severe CSU symptoms) and a UCT score < 8 . Exclusion criteria included body weight < 40 kg (minimum age at inclusion, 18 years); a clearly defined underlying cause for chronic urticaria (e.g. physical urticaria); use of any H2-antihistamine or leukotriene receptor antagonist within 7 days preceding the screening; presence of other diseases with similar signs of urticaria or angioedema; evidence of parasitic infection and concomitant use of ciclosporin or any other immunosuppressive agent within 30 days prior to screening. The detailed exclusion criteria and the list of prohibited medications are provided in Supplementary Appendix S1 (see Supporting Information).

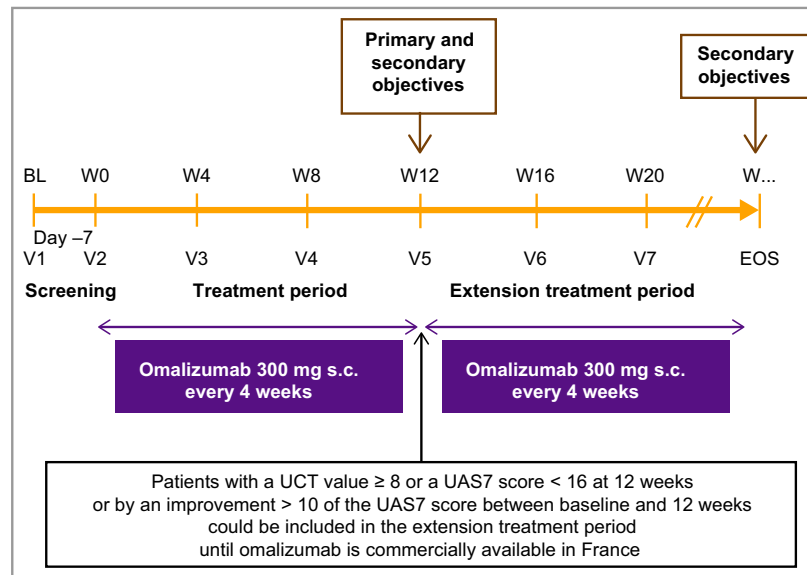


Fig 1. Study design. BL, baseline; EOS, end of study; s.c., subcutaneous; UAS7, 7-day urticaria activity score; UCT, urticaria control test; V, visit; W, week.

Enrolled patients were stratified 1 : 2 (with angioedema : without angioedema) to represent general CSU epidemiology. All patients received three s.c. injections of omalizumab 300 mg (two injections of 150 mg each in the deltoid region of the left and right arm or in the thigh) at 4-week intervals at the study centre. Patients who had an adequate response to omalizumab at Week 12 (defined as UCT ≥ 8 or a UAS7 < 16 at 12 weeks or an improvement > 10 points on the UAS7 between baseline and 12 weeks) were allowed to continue treatment during the extension period (up to commercial availability of omalizumab in France: 3 Nov 2015).

All patients provided written informed consent. The study protocol and all amendments were reviewed and approved by an Independent Ethics Committee. The study was conducted according to the ethical principles of the Declaration of Helsinki.

Study objectives

The primary objective of the study was to evaluate the proportion of patients with a UCT score ≥ 12 (indicating a well-controlled urticaria) at Week 12. The secondary and exploratory objectives have been described in Supplementary Appendix S2 (see Supporting Information).

Study assessments

All the PRO tools used by the patients were available in a French version. The use of the available French version of the UCT was permitted with fees to Moxie GmbH, Berlin, Germany, owners of the rights, for this study. The UCT was completed by the patients at baseline and prior to administration of the study drug at Weeks 4, 8 and 12. The UCT score was derived from four questions, each with five answer options

(scored 0–4 points), where low points indicated high disease activity and poor disease control (see Supplementary Appendix S3, Supporting Information, for the UCT questionnaire). The minimum and maximum UCT scores were 0 and 16, respectively, with 16 indicating complete disease control. Patients completed a diary that covered the UAS7 and angioedema activity score (AAS; in case of angioedema), once daily. The diary was given to patients on Day -7, and complete diary information was collected for the seven consecutive days prior to the baseline visit and at Weeks 4, 8 and 12. The QoL assessments were performed at baseline and prior to administration of the study drug at Weeks 4, 8 and 12. See Supplementary Appendix S4 for details on UAS7, AAS, Dermatology Life Quality Index (DLQI), chronic urticaria QoL (CU-QoL) and angioedema QoL (AE-QoL) assessments; see Supporting Information.

The D-dimer concentration was determined at baseline and Weeks 4 and 8. Blood levels of prothrombin factors 1 and 2, hypersensitive C-reactive protein, and factors VIIa and XIIa were also assessed. Safety assessments consisted of collecting all adverse events (AEs) and serious AEs along with their severity and relationship to the study drug.

Statistical analysis

The sample size was based on the proportion of patients with a UCT score ≥ 12 for the full analysis set (FAS), assuming a mean UCT score of 14 with a SD of 3, which corresponds to an expected true proportion of 74.8% of patients achieving disease control at 12 weeks. Based on a 95% confidence interval (CI), 110 patients were needed to achieve a disease control success rate in the 66.6–82.9% range. Based on an assumption that 10% of patients would not contribute values to the primary evaluation, 126 patients were planned to be enrolled. All efficacy analyses were performed using a two-sided test at 5%

significance level. The primary analysis variable was the proportion of patients achieving disease control (UCT score ≥ 12).

The proportion of patients achieving disease control at Week 12 was calculated and presented with corresponding 95% CIs using the Clopper-Pearson method (exact binomial). Success of disease control was considered to have been achieved if the observed proportion of patients achieving disease control at Week 12 fell within the 66.6–82.9% range. Missing UCT scores at Week 12 were imputed using the last-observation-carried-forward method. The correlation between D-dimer concentration at baseline and the UCT score and UAS7 at Week 8 was presented using Spearman's rank correlation coefficient and scatter plots. The FAS, which included all patients who provided signed informed consent and received at least one dose of omalizumab, was used to analyse the efficacy and safety data.

Results

Of the 156 patients screened, 136 were enrolled and received at least one dose of omalizumab; 124 patients completed the core period of 12 weeks, and 12 patients discontinued the study (Fig. 2). The most common reason for discontinuation was protocol deviation ($n = 6$, 4.4%, Fig. 2). The mean ($\pm$ SD) age of the study population was 44.4 ± 12.7 years and women comprised 77.9% of this population (Table 1). The median (range) number of previous CSU medications was 2.0 (1–5) (Table 2); the most frequent were H1-antihistamines and antileukotrienes. During the study, 50.7% of patients used at least one concomitant medication for CSU. The most common category of concomitant medications (taken by 59.6% of patients) was second-generation antihistamines (Table 3).

Urticaria control test score and 7-day urticaria activity score

The primary endpoint of disease control (UCT score ≥ 12 at Week 12) was achieved by 74.6% (95% CI 66.4–81.7) of

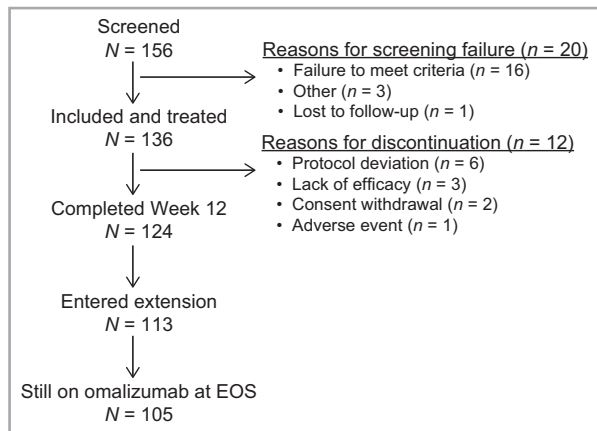


Fig 2. Patient disposition. EOS, end of study.

Table 1 Patient baseline demographic and clinical characteristics

Population characteristics	Study population (N = 136)
Age, mean (SD), years	44.4 (12.7)
Sex, female, n (%)	106 (77.9)
BMI, mean (SD), kg m ⁻²	26.5 (5.01)
Duration since onset of CSU symptoms, mean (SD), years	6.4 (7.9)
Duration since diagnosis of CSU, mean (SD), years	4.7 (6.2)
Patients with weals during the last 6 months, n (%)	129 (94.9)
Patients with angioedema during the last 6 months, n (%)	83 (61.0)
Duration of angioedema, mean (SD), h	19.6 (24.96)
UAS7 score, mean (SD)	29.7 (6.98)
UCT score, mean (SD)	3.3 (2.4)
AE-QoL total score, mean (SD) ^a	57.9 (22.5)

AE-QoL, angioedema quality of life; BMI, body mass index; CSU, chronic spontaneous urticaria; UAS7, 7-day urticaria activity score; UCT, urticaria control test. ^aAssessed in patients with angioedema.

Table 2 Medication history at baseline

Prior CSU treatment	Study population (N = 136) ^a
Previous number of CSU medications, median (min, max)	2.0 (1.0, 5.0)
Previous medications taken:	
H1-antihistamines 1×	34 (25.0)
H1-antihistamines 2×	34 (25.0)
H1-antihistamines 3×	25 (18.4)
H1-antihistamines 4×	86 (63.2)
H2-antihistamines	5 (3.7)
Antileukotriene	52 (38.2)
Oral corticosteroids	26 (19.1)
Doxepin	1 (0.7)
Ciclosporin	6 (4.4)
Methotrexate	3 (2.2)
Hydroxychloroquine	1 (0.7)
Dapsone	1 (0.7)
Anti-IgE	4 (2.9)
Colchicine	2 (1.5)
Tranexamic acid	2 (1.5)

CSU, chronic spontaneous urticaria; IgE, immunoglobulin E. ^aAll values are n (%) unless otherwise specified. Percentages are based on the total number of patients in the full analysis set.

patients (Fig. 3). There was a significant increase in the UCT score from baseline to Week 12, with a mean increase of 9.6 ± 4.95 points ($P < 0.0001$) indicating a better disease control (Fig. 4). The increase in the UCT score was comparable between patients with and without angioedema. A total of 67.7% of patients (95% CI 58.8–75.7) achieved a UAS7 ≤ 6 at Week 12 (Fig. 3), with no major differences between patients with and without angioedema. There was a significant

improvement in UAS7 from baseline to Week 12 (-22.9 ± 11.67 points, $P < 0.0001$), signifying the efficacy of omalizumab treatment in patients with CSU. The decrease

Table 3 Concomitant medications used for CSU during the study

	Study population (N = 136)
Any concomitant medications for CSU, n (%)	69 (50.7)
Second-generation H1-antihistamines	77 (56.6)
First-generation H1-antihistamines	13 (9.6)
Betamethasone	1 (0.7)
Alprazolam	1 (0.7)
Paracetamol	1 (0.7)
Ibuprofen	1 (0.7)
Hydroxychloroquine	1 (0.7)

A patient with multiple occurrences within an ATC class is counted only once. A medication/therapy can appear with more than one ATC class. One patient might have taken more than one medication. ATC, anatomical therapeutic chemical; CSU, chronic spontaneous urticaria

in the UAS7 was comparable between patients with and without angioedema (Fig. 4).

There was a strong negative correlation between the UCT score and UAS7 at Week 12 (Spearman's correlation coefficient -0.839 ; Fig. 5a). Overall, in 87.3% of patients, both UCT score and UAS7 varied in a coherent and consistent manner ($UCT \geq 12$ and $UAS7 \leq 6$ or $UCT < 12$ and $UAS7 > 6$), reinforcing the association between the two scores (Fig. 5b).

D-dimer and other biomarkers

The mean plasma concentration of D-dimer was high at baseline [$1002.1 \text{ ng mL}^{-1}$ (normal levels $< 500 \text{ ng mL}^{-1}$)]^{16,17} and decreased notably with omalizumab treatment at Week 4 (506.4 ng mL^{-1}) and Week 8 (455 ng mL^{-1}) (Fig. 6). The reduction in plasma D-dimer levels with omalizumab was observed both in patients with and without angioedema at baseline (Fig. 6). There was a weak positive correlation of UCT score at Week 12 with baseline D-dimer concentration (Spearman's correlation coefficient 0.059) and a weak negative

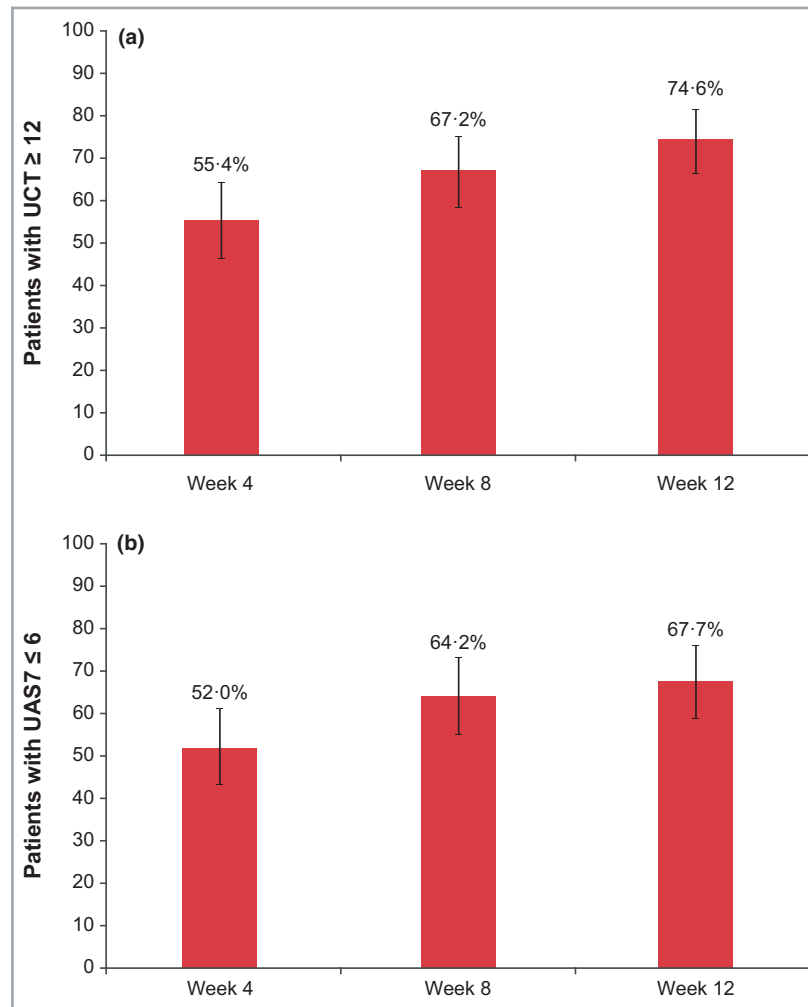


Fig 3. Proportion of patients with well-controlled urticaria at Week 12 (a) UCT score ≥ 12 and (b) UAS7 ≤ 6 . UAS, 7-day urticaria activity score; UCT, urticaria control test. Error bars represent the confidence interval. UAS, 7-day urticaria activity score; UCT, urticaria control test.

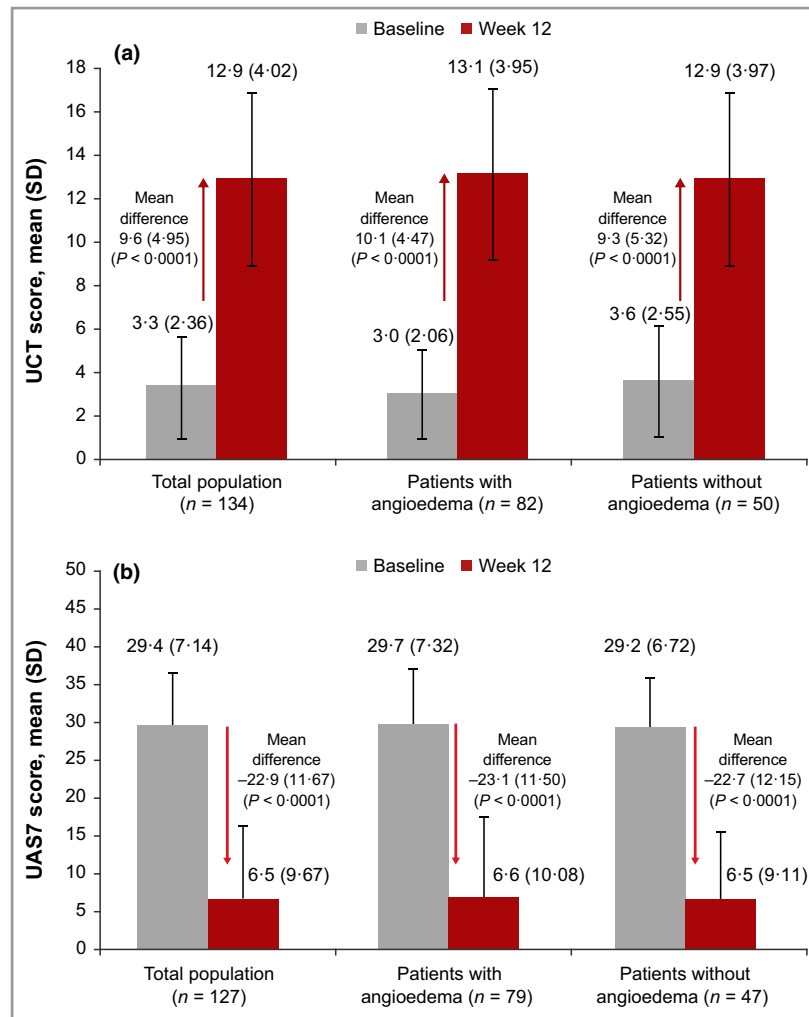


Fig 4. Change in UCT score and UAS7 depending on angioedema status from baseline to Week 12. (a) UCT; (b) UAS7. UAS7, 7-day urticaria activity score; UCT, urticaria control test. Error bars represent the SD.

correlation of UAS7 at Week 12 with baseline D-dimer concentration (Spearman's correlation coefficient -0.108) (Fig. 7). Ten patients had a very high baseline D-dimer level ($> 3000 \text{ ng mL}^{-1}$), in five of those the D-dimer levels were normalized with treatment at Week 8. At Week 12, eight patients had a UAS7 ≤ 6 and seven of nine patients, who had a UCT score available at Week 12, achieved a UCT score ≥ 12 .

No meaningful correlation with PROs was demonstrated for the other biomarkers.

Quality of life

There was a notable improvement in the QoL of patients with CSU after 12 weeks of omalizumab treatment. Although patients with angioedema had higher CU-QoL and DLQI scores at baseline than those without angioedema, the improvement in scores was similar in both groups at Week 12 (Table 4) after treatment with omalizumab. The UCT score was negatively correlated with CU-QoL and DLQI scores at Week 12 (Table 5).

Angioedema-related assessments

In patients with angioedema, the total AE-QoL score decreased and the AAS improved from baseline to Week 12 with omalizumab (both $P < 0.0001$; Table 4). The UCT score was negatively correlated with AE-QoL and AAS at Week 12 (Table 5).

Safety

The mean duration of exposure to omalizumab during the core treatment period was 11.93 ± 1.72 (range 4.1–14.1) weeks. Most patients (93.4%) received a total of three injections as the approved dose of 300 mg was administered s.c. every 4 weeks over a period of 3 months, and the mean cumulative dose was $869.12 \pm 122.63 \text{ mg}$. The mean duration of exposure to omalizumab was 19.11 ± 5.46 (range 4.1–29.1) weeks from baseline up to the end of the study. No death or episode of anaphylactic shock were reported during the study. A total of five

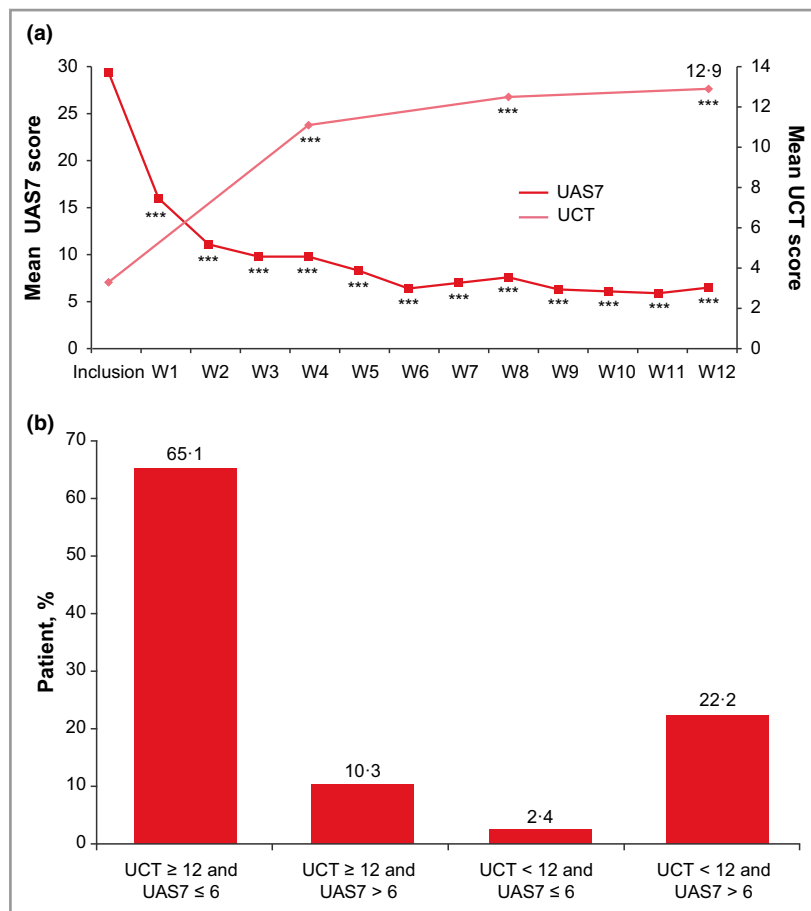


Fig 5. Variations in UCT score and UAS7 and their correlation. (a) Improvement of disease control (UCT) vs. improvement of disease activity (UAS7); strong negative correlation between the UCT score and UAS7 at Week 12 (Spearman's correlation coefficient -0.839). (b) Distribution of patients according to UCT score and UAS7 at Week 12. *** $p < 0.0001$ vs. baseline at all time points. UAS7, 7-day urticaria activity score; UCT, urticaria control test; W, week.

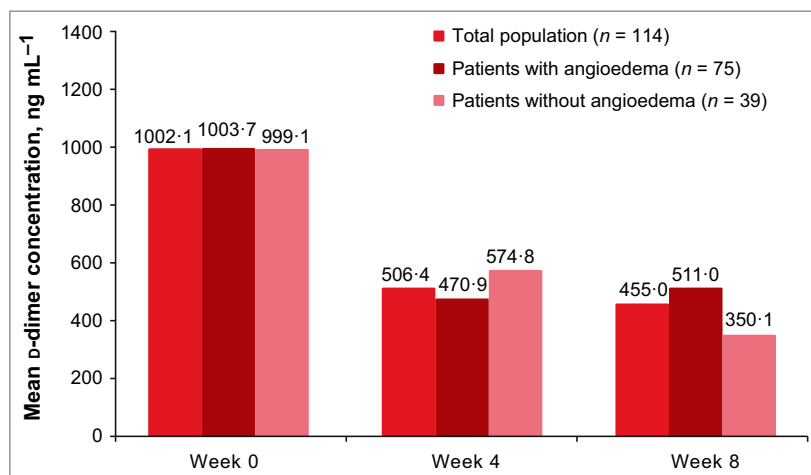


Fig 6. Change in D-dimer concentration after 8 weeks of treatment with omalizumab.

patients reported seven serious AEs which included pneumonia, cervical vertebral fracture, fractured sacrum, ligament sprain, obesity, bladder dilatation and pharyngeal oedema.

During the 12 weeks of treatment, 66.2% of patients experienced at least one AE and 36.8% of patients experienced at least one treatment-related AE. The most common

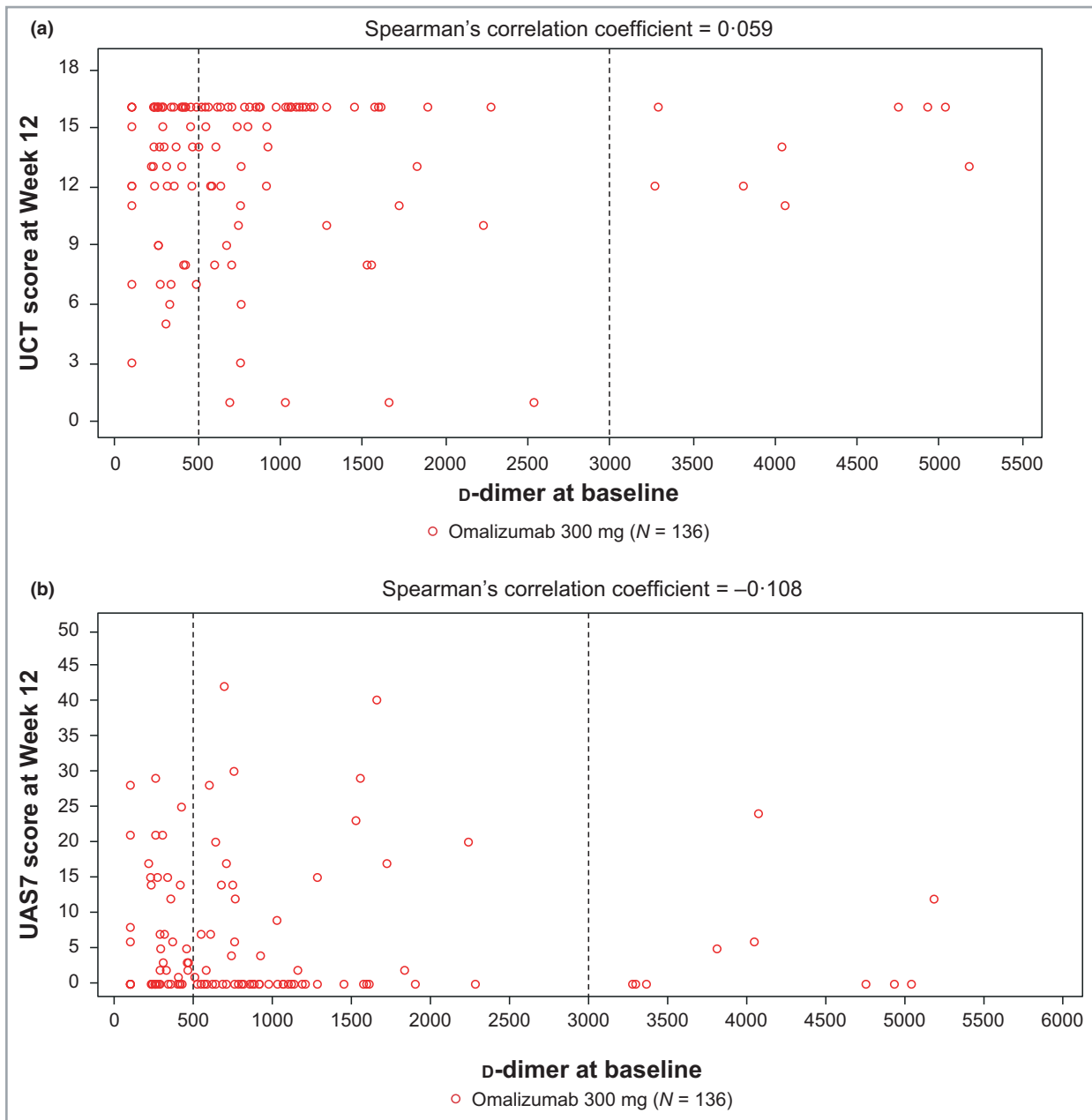


Fig 7. Correlation between D-dimer concentration and UCT score and UAS7 at baseline and Week 12. UAS7, 7-day urticaria activity score; UCT, urticaria control test. Vertical lines indicate the cut-off points. Normal D-dimer values < 500 ng mL⁻¹. Of the 10 patients with very high D-dimer levels (> 3000 ng mL⁻¹) at baseline, one patient did not have UCT levels captured at Week 12.

treatment-emergent AEs were headache (15.4%), asthenia (14.7%) and arthralgia (7.4%) (Table 6).

Discussion

The results of the SUNRISE study confirm the efficacy of omalizumab 300 mg s.c. in controlling the symptoms and in improving the QoL in French patients with moderate-to-severe CSU nonresponsive to H1-antihistamine treatment. Indeed, two-thirds of our patients achieved a UAS7 ≤ 6 at Week 12 of omalizumab treatment, indicative of well-controlled disease,

which is comparable with the data observed in the three pivotal studies (52–66% of patients with a UAS7 ≤ 6).^{12–14}

SUNRISE is the first prospective study that investigated the utility of the UCT in patients with CSU treated with omalizumab. Overall, 74.6% of patients in our study achieved a UCT score ≥ 12 with omalizumab treatment. Our results confirm that the UCT is a reliable tool to measure disease control, consistent with the findings from a previous study from Thailand in 169 patients with chronic urticaria.¹⁸ Urticaria symptoms vary greatly from one day to another, and the disease condition at the time of presentation to the physician is rarely

Table 4 Change in QoL and angioedema assessment parameters after 12 weeks of treatment

Variable	Baseline, mean (SD)	Week 12, mean (SD)	Change from baseline at Week 12, mean (SD)	P-value
With angioedema, n = 83				
CU-QoL	68.9 (15.64)	32.5 (13.33)	−36.4 (18.04) ^b	< 0.0001
DLQI	14.2 (5.39)	2.4 (3.95)		< 0.0001
AAS ^a	32.7 (27.21)	3.7 (10.40)	−29.0 (28.02)	< 0.0001
AE-QoL (total score) ^a	57.88 (22.47)	16.4 (20.07)	−41.48 (25.20)	< 0.0001
Without angioedema, n = 51				
CU-QoL	62.4 (17.76)	33.3 (13.32)	−29.1 (18.74) ^b	< 0.0001
DLQI	13.2 (6.67)	2.7 (5.12)		< 0.0001

AAS, angioedema activity score; AE-QoL, angioedema QoL; CU-QoL, chronic urticaria QoL; DLQI, Dermatology Life Quality Index; QoL, quality of life. ^aAssessed in patients with angioedema. ^bAbsolute change from baseline at Week 12 was not calculated for DLQI

Table 5 Correlation of UCT score with other scores

Variable	Absolute values at Week 12, mean (SD)	Spearman's correlation coefficient vs. UCT
UCT	12.9 (4.02)	1
UAS7	6.5 (9.67)	−0.839
CU-QoL	32.8 (13.28)	−0.800
DLQI	2.5 (4.42)	−0.894
AAS ^a	3.7 (10.4)	−0.615
AE-QoL (total score) ^a	16.4 (20.07)	−0.666

AAS, angioedema activity score; AE-QoL, angioedema QoL; CU-QoL, chronic urticaria QoL; DLQI, Dermatology Life Quality Index; QoL, quality of life; UAS7, 7-day urticaria activity score; UCT, urticaria control test. ^aAssessed in patients with angioedema.

representative of actual disease status.¹⁵ Therefore, it is important to have retrospective, easy-to-use PRO tools such as the UCT.

Taken together, the UAS7 and UCT scores confirm the efficacy of omalizumab in these patients with moderate-to-severe CSU nonresponsive to H1-antihistamines. Interestingly, a significant negative correlation was observed between the UCT score and UAS7, with a consistent variation between the two scores in a majority of patients, reinforcing the correlation between the two.

Another interesting finding is that omalizumab was equally efficacious in patients with or without angioedema as shown by the comparable change in UCT score and UAS7 in both groups at Week 12. Angioedema is fairly common in patients with CSU (33–67%); it adversely affects the patient's QoL and is also associated with increased disease duration and worse prognosis.² In the present study, 61% of patients had angioedema at baseline with an increased AE-QoL total score, which significantly decreased at Week 12 along with the AAS. These results are in line with the findings of the X-ACT study, which showed the efficacy of omalizumab in patients with moderate-to-severe CSU symptoms and angioedema nonresponsive to

Table 6 Summary of treatment-emergent AEs up to Week 12 (safety set)

AEs	Omalizumab 300 mg (N = 136) n (%)
Patients with at least one AE	90 (66.2)
Patients with at least one serious AE	5 (3.7)
Treatment discontinuation due to AE	3 (2.2)
Arrhythmia	1 (0.7)
Pneumonia	1 (0.7)
Pharyngeal oedema	1 (0.7)
Hypertension	1 (0.7)
Death	0
Treatment-emergent AEs experienced by ≥ 3% of patients	
Headache	21 (15.4)
Asthenia	20 (14.7)
Arthralgia	10 (7.4)
Weight increased	6 (4.4)
Alopecia	5 (3.7)
Nausea	5 (3.7)

AEs were coded using MedDRA v18.1. AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities.

high doses of antihistamine treatment.¹⁹ In addition, as expected, our patients had a severe QoL impairment at baseline as evidenced by the high CU-QoL, DLQI and AE-QoL scores. Treatment with omalizumab for 12 weeks resulted in a significant improvement of all QoL scores. Moreover, these scores negatively correlated with the UCT scores, further confirming the reliability of the UCT. Overall, these results from the SUNRISE study suggest that UCT can be used as an alternative to UAS7, for example, in new patients or in those who did not fill in their UAS7 before the consultation and in patients with angioedema whose disease activity cannot be measured by UAS7.

Several pathways have been suggested to explain omalizumab's mechanism of action in urticaria; however, the mechanism is not yet fully understood. The major effect of omalizumab in patients with CSU is considered to result from

the downregulation of high-affinity IgE receptors on mast cells and basophils, leading to a reduction in the release of inflammatory mediators from these cells.^{20,21} The 2017 study by Deza *et al.* demonstrated downregulation of FcεRI, a high-affinity IgE receptor, with omalizumab treatment.²² Other effects, including those on the coagulation cascade leading to a marked reduction in D-dimer plasma levels, have also been suggested.^{7,23} Furthermore, high D-dimer levels have been found to be associated with poor response to antihistamines and ciclosporin in patients with CSU.⁷

Recently, Asero *et al.* observed elevated baseline D-dimer levels in 59% of patients with severe CSU, and a dramatic decrease in the levels in some patients who responded to omalizumab treatment, suggesting a possible effect of omalizumab on coagulation activation and fibrin degradation in a subset of patients with CSU.⁷ Consistent with the published literature, elevated baseline D-dimer levels were observed in patients from the SUNRISE study. A fast normalization in plasma D-dimer levels was observed with omalizumab as early as Week 4, with a further decrease until Week 8. There was no meaningful correlation between Week 12 UCT or UAS7 scores and baseline D-dimer concentrations. However, in a small subset of patients (10 of 136) with very high baseline D-dimer levels ($> 3000 \text{ ng mL}^{-1}$), most had disease control at Week 12. Future studies may help us to better understand the link between D-dimer and clinical response with omalizumab.

This study has some limitations including its open-label nature and lack of a control group. Although H1-antihistamine treatment was to be at a stable dose for the duration of the treatment period per protocol, patients had the option to decrease the dosage if needed. As any change in dose was not actively monitored, we cannot conclude on the adaptation of the H1-antihistamine following improvement in urticaria. Moreover, the study was conducted only in France, possibly limiting the generalizability of the results. Overall, these data further confirm the efficacy of omalizumab in patients with CSU with inadequate response to H1-antihistamine treatment and highlight the reliability of the UCT as a disease control tool in these patients. Omalizumab was well tolerated, and the safety results were consistent with the established safety profile.

The use of the UCT should be recommended in routine clinical practice in order to assess efficacy and response to any urticaria treatment. Results demonstrate that D-dimers are elevated in some patients and change in response to treatment. This study does not support the usefulness of D-dimer as a marker of disease activity in adult urticaria; however, it may represent a useful tool to indicate patients who respond to omalizumab.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1. Eligibility criteria.

Appendix S2. Secondary and exploratory objectives.

Appendix S3. Urticaria Control Test questionnaire.

Appendix S4. Patient-reported outcome and quality-of-life assessment scores.

Supporting Information

Appendix S1

Eligibility criteria

Inclusion criteria

1. Male or female patients aged between 18 and 75 years
2. Diagnosis of chronic spontaneous urticarial (CSU) for ≥ 6 months and an inadequate response to non-sedating H1-antihistamines at the time of the request, as defined by the following:
 - The presence of itch and hives for >6 consecutive weeks at any time prior to enrolment, despite current use of H1-antihistamine therapy during this time period
 - Weekly urticaria activity score (UAS7) (range 0 to 42) ≥ 16 and urticaria control test (UCT) score (range 0 to 16) < 8 prior to enrolment (Day 1)
3. Patients must document current use of an H1-antihistamine for CSU on the day of the initial visit and on Day 1
4. Patients must be willing and able to complete a daily symptom diary (paper) for the duration of the study
5. Patients must be willing to give written informed consent, adhere to the visit schedules and meet the clinical requirements

Exclusion criteria

1. Treatment with an investigational agent within 30 days before enrolment
2. Body weight less than 40 kg
3. Clearly defined underlying aetiology for chronic urticaria (CU) other than CSU (main manifestation being physical urticaria). This included the following urticaria types: acute, solar, cholinergic, heat, cold, aquagenic, delayed pressure or contact urticaria, or skin disease that includes urticarial plaques (other than CSU) such as bullous pemphigoid, dermatitis herpetiformis
4. The following diseases with similar symptoms of urticaria or angioedema: urticarial vasculitis, urticaria pigmentosa, erythema multiform, mastocytosis, hereditary or acquired angioedema, lymphoma, leukaemia and generalised cancer
5. Evidence of parasitic infection defined as having the following 3 characteristics:
 - Risk factors for parasitic disease (living in an endemic area, chronic gastrointestinal symptoms, travel within the last 6 months to an endemic area and/or chronic immunosuppression)
 - AND
 - An absolute eosinophil count more than twice the upper limit of normal (ULN)
 - AND

- Evidence of parasitic colonisation or infection in stool evaluation for ova and parasites; note that stool ova and parasite evaluation was only conducted in patients with both risk factors and an eosinophil count more than twice the ULN
6. Patients with current malignancy, history of malignancy, or currently under work-up for suspected malignancy except non-melanoma skin cancer that has been treated or excised and is considered resolved
 7. Concomitant use of cyclosporine or any other immunosuppressive agent
 8. Hypersensitivity to omalizumab or any component of the formulation
 9. History of anaphylactic shock
 10. Presence of clinically significant cardiovascular, neurological, psychiatric, metabolic or other pathological conditions that could compromise the safety of the patients
 11. Medical examination or laboratory findings that suggest the possibility of decompensation of co-existing conditions. Any items that were cause for uncertainty must be reviewed with the attending physician
 12. Inability or unwillingness to comply with the visits and follow-up procedures
 13. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of the study treatment and for 16 weeks after stopping the treatment.
 14. Routine (daily or every other day for 5 or more consecutive days) doses of the following medications within 30 days prior to Day -7: systemic or cutaneous (topical) corticosteroids (prescription or over the counter), hydroxychloroquine, methotrexate, cyclosporine or cyclophosphamide
 15. Intravenous (i.v.) immunoglobulin (Ig) G or plasmapheresis within 30 days prior to Day -7
 16. Regular (daily/every other day) doxepin (oral) use within 14 days prior to Day -7
 17. Any H2-antihistamine use within 7 days prior to Day -7
 18. Any leukotriene receptor antagonist (LTRA; montelukast or zafirlukast) within 7 days prior to Day -7

Appendix S2

Secondary objectives

- To evaluate the proportion of patients with UAS7 ≤ 6 (patients achieving disease control) at Week 12, in adult patients with CSU, with or without the presence of angioedema
- To assess the CSU disease activity at Week 12 using the UAS7 with or without the presence of angioedema
- To assess the control of CSU at Week 12 and every 4 weeks (q4w) until the end of study (EOS) visit for patients in the extension period phase using the UCT score, with or without the presence of angioedema
- To assess the quality of life (QoL) at Week 12 using the chronic urticaria quality of life (CU-QoL) questionnaire, the angioedema quality of life (AE-QoL) questionnaire and the Dermatology Life Quality Index (DLQI)
- To assess the angioedema activity at Week 12 using the angioedema activity score (AAS)

Exploratory objectives

- To assess the correlation between CSU disease control (UCT) and disease activity (UAS7 and AAS) and QoL (CU-QoL, AE-QoL and DLQI) measures at Week 12
- To explore the evolution of D-dimer concentration at Week 4 and Week 8
- To explore the D-dimer concentration at the same time points based on the presence or absence of angioedema
- To explore the correlation between D-dimer concentration and CSU disease control (UCT) at Week 8
- To explore the correlation between D-dimer concentration and disease activity (UAS7) at Week 8

Appendix S3

Urticaria Control Test

Patient name: _____

Date (dd mm yyyy): ____ ____ ____

Date of birth (dd mm yyyy): ____ ____ ____

Instructions: You have urticaria. The following questions should help us understand your current health situation. Please read through each question carefully and choose an answer from the five options that *best fits* your situation. Please limit yourself to the last four weeks. Please don't think about the questions for a long time, and do remember to answer all questions and to provide only one answer to each question

1. How much have you suffered from the **physical symptoms of urticarial (itch, hives (welts) and/or swelling** in the last four weeks?
☐ very much ☐ much ☐ somewhat ☐ a little ☐ not at all
2. How much was your **quality of life** affected by the urticarial in the last 4 weeks?
☐ very much ☐ much ☐ somewhat ☐ a little ☐ not at all
3. How often was the **treatment** for your urticarial in the last 4 weeks **not enough** to control your urticarial symptoms?
☐ very often ☐ often ☐ sometimes ☐ seldom ☐ not at all
4. **Overall**, how well have you had your urticarial **under control** in the last 4 weeks?
☐ Not at all ☐ a little ☐ somewhat ☐ well ☐ very well

Each UCT question has 5 answer options (scored with 0–4 points). Low points indicate high disease activity and low (poor) disease control. The minimum and the maximum UCT scores are 0 and 16, with 16 indicating complete disease control (UCT ≥ 12 indicates well controlled CU). A permission for use of the French version of UCT was obtained from Moxie GmbH, Berlin, Germany; owners of the right, after the payment of appropriate fees.

Appendix S4

Patient-reported outcome (PRO) and QoL assessment scores

All the PROs used by patients were available as a French version.

Urticaria activity score (UAS)

UAS is a simple scoring system, which captures the intensity of pruritus and the number of hives. Daily intensity of pruritus (range: 0 [none] to 3 [severe]) and number of hives ratings (range: 0 [none] to 3 [more than 12 hives]) are summed to obtain a daily UAS score (range: 0–6 points/day). Daily UAS scores are summed over a week to obtain the UAS7 (range: 0–42).

Angioedema activity score (AAS)

AAS is a validated, easy-to-use tool designed to be used by patients for daily documentation of their swelling episodes, including their duration, severity and impact on daily functioning and appearance. Its objective is to determine disease activity in patients with recurrent angioedema, independent of its underlying causes. The AAS consists of 5 questions (score 0 to 3 each) as well as an opening question (no score). The scores are summed up to obtain an AAS day sum score (range: 0 to 15), an AAS week sum score (range: 0 to 105) and an AAS 4-week sum score (range: 0 to 420).

Dermatology Life Quality Index (DLQI)

The DLQI is a 10-item dermatology-specific PRO instrument used by the patients to rate their dermatology symptoms as well as the impact of their skin condition on various aspects of their lives. The score is calculated across the following domains: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. An overall score is then computed by summing the score of each question (scored 0–3 points) resulting in a minimum of 0 and a maximum of 30. The higher the score, more the QoL was impaired. The minimally important difference of the overall DLQI score for patients with CSU has been estimated to be 2.24 to 3.10.

Chronic urticaria quality of life questionnaire (CU-QoL)

The CU-QoL consists of 6 domains (pruritus, swelling, impact on life activities, sleep problems, limits and looks) and each domain consists of several items. Each item is scored from 1 to 5 (score 5 = most affected, score 1 = not affected). A total score including all 23 items is then calculated.

Angioedema quality of life questionnaire (AE-QoL)

The AE-QoL is a short, validated and reliable instrument and the only angioedema-specific QoL questionnaire that is widely used to determine QoL impairment in all patients with recurrent angioedema, independent of its underlying causes. It is a 17-item questionnaire with a recall period of 4 weeks. The total AE-QoL score has a range of 0 to 100, as well as scores (0 to 100) for each of the following 4 domains: functioning, fatigue/mood, fears/shame and food.

remains a challenge. Not only do these patients present more frequently with multiple, disseminated lesions and field cancerization compared with patients who are immunocompetent; they are also less likely to experience spontaneous or therapy-induced regression, and the risk that their AK lesions will progress, both in terms of quantity and pathology, is higher.^{2,3}

Multiple treatment options are available to target AK lesions and fields,⁴ and drawing upon the best evidence to develop a comprehensive management strategy is crucial. Although the goals of AK treatment in organ transplant recipients (OTRs) do not generally differ from those in immunocompetent patients, it is important to consider that some treatments may be less effective or have a different safety profile in OTRs as a result of their immune-related mechanism of action. Considering the large number of OTRs and other people who are chronically immunosuppressed,⁵ the interesting and comprehensive systematic review⁶ included in this issue of the *BJD* is of great value.

In their systematic assessment of evidence from randomized trials of treatments for AKs in OTRs, Heppt et al.⁶ found that photodynamic therapy was the intervention most frequently investigated and associated with the highest rates of complete clearance and reduction in lesion counts. Of note is that the largest study included by the authors assessed photodynamic therapy vs. cryotherapy and found comparable rates of lesion clearance. Given that cryotherapy is easy to use and inexpensive, this is an important finding.

However, drawing conclusions about which treatment is best for AKs in OTRs is difficult for several reasons: the methodological quality of the studies included by the authors and small sample sizes limit the generalizability of the findings, and the heterogeneity of the participants and variety of outcomes make comparing results between studies difficult. Moreover, data on short-term results are of questionable value when evaluating treatments for a population in which the risk of recurrence and progression of AK lesions is high.

Heppt et al. sensibly begin the discussion of their findings by noting that 'there is surprisingly little evidence'.⁶ Indeed, further research is needed on the treatment of AKs in OTRs. Short-term efficacy cannot serve as the basis to define preferred treatment options, particularly in this population. Future trials should assess long-term outcomes and provide evidence on whether treatments can help prevent invasive squamous cell carcinoma.⁷ OTRs with AKs often require large areas to be treated, and this need has not yet been met, whether in terms of evidence or approved treatment options. A comprehensive approach to treating AKs in OTRs will continue to rely on combining the available evidence with expert consensus and indirect evidence from studies on immunocompetent patients.

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Conflicts of interest

None to declare.

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Omalizumab: living up to PROMises

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Linked Article: Bérard et al. *Br J Dermatol* 2019; **180**:56–66.

Since 2014, when omalizumab was approved as a treatment for chronic spontaneous urticaria (CSU) refractory to standard treatments, we, as physicians, have become confident with its use in our daily practice.¹ The efficacy of omalizumab in CSU is well supported by evidence-based medicine² and consensus has been reached that it is the drug of choice once a high dose of second-generation antihistamines fails to control the activity of the disease.³ In this issue of the *BJD*, the results of the phase IV SUNRISE study provide further reassurance of the safety and effectiveness of this agent.⁴

The prospective study design employs two patient-reported outcome measures (PROMs): the urticaria activity score 7 (UAS7) and the urticaria control test (UCT). The UAS7 was used in the phase III studies of omalizumab, and is a validated measure of CSU disease activity.⁵ The UCT is now recommended as a validated tool to measure control of CSU.⁶ UCT has the advantage that it can be answered during the medical consultation. Also, UCT is valid for measurement of disease control in chronic inducible urticaria, which is concomitantly present with CSU in about 20% of patients.⁷ The authors are to be applauded for the incorporation of two PROMs into the study, which simultaneously allow the physician to define response to treatment, while also encouraging the patient to assume an active role in disease monitoring and management. Whether to use one or other of the PROMs mentioned (UAS7 and UCT), or both together, as robust measures of treatment response in a clinical setting is a point for further discussion among experts.

A further point of clinical importance raised by this prospective study is the observation of increased levels of D-dimer in patients with more active CSU, supporting the theory of tissue involvement in the coagulation cascade and fibrinolysis. As was reported in trials of treatment of CSU with antihistamines and ciclosporin A, the SUNRISE study shows a normalization of D-dimer values with successful treatment with omalizumab. Although multicentre prospective studies would be required, measurement of D-dimer has the potential to become a useful biomarker in CSU.⁸

This study provides further encouragement to physicians involved in the management of CSU and chronic inducible urticaria to adopt evidence-based guidance on therapy, and objective assessment of outcomes using PROMs. Reducing the burden of CSU in our patient populations depends upon it.

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Conflicts of interest

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Tofacitinib: a new oral Janus kinase inhibitor for psoriasis

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Linked Article: Strober et al. *Br J Dermatol* 2019; **180**:67–75.

Psoriasis is a chronic disorder that has a significant impact on patient's quality of life.¹ There are now many effective therapeutic agents including: tumour necrosis factor inhibitors, interleukin (IL)-12/23 inhibitors, IL-23 inhibitors, IL-17A inhibitors and phosphodiesterase type 4 inhibitors. Tofacitinib is a new class of oral medication operating through the Janus kinase (JAK) pathway and has been previously approved for use in rheumatoid arthritis, ulcerative colitis and psoriatic arthritis.

Strober et al. conducted a pooled analysis across five randomized controlled trials and one open-label extension study examining the risk–benefit profile of tofacitinib in patients with moderate-to-severe plaque psoriasis that is reported in this issue.² Their analysis used the co-primary end points of Physician's Global Assessment of clear/minimal and a 75% reduction in baseline Psoriasis Area and Severity Index (PASI 75). There were three comparison groups: tofacitinib 5 mg orally twice daily, tofacitinib 10 mg orally twice daily and placebo followed up to 16 weeks. Their analysis demonstrated a PASI 75 of 43.1%, 59.4% and 8.9%, respectively ($P < 0.001$), suggesting a reasonable level of efficacy, especially for the higher dose group. They demonstrated an acceptable safety profile with overall adverse events in 54.0% in the tofacitinib 5 mg twice daily group, 58.9% in the tofacitinib 10 mg twice daily group and 50.4% who received placebo.