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The burden of chronic spontaneous urticaria: unsatisfactory treatment and healthcare resource utilization in France (the ASSURE-CSU study)

Background: Data on the clinical burden of chronic spontaneous urticaria (CSU) and economic consequences are lacking in France. **Objectives:** To characterize the clinical and economic burden of CSU in symptomatic patients despite treatment by analysing data of French patients from the ASSURE-CSU study. **Materials and methods:** ASSURE-CSU was an international observational study that included CSU patients with symptoms that lasted for 12 months or more despite treatment. Disease characteristics and healthcare resource use were obtained from medical records. Data on disease history, health-related quality of life (HR-QoL), and work productivity were collected from a patient survey. **Results:** A total of 101 patients were analysed (76.2% female; mean age: 48.9 years) with moderate to severe disease (UAS7 score ≥ 16) in 43.4% and angioedema in 72.3%. The mean (S.D.) total scores of Chronic Urticaria Quality of Life (CU-QoL) and Dermatology Life Quality Index (DLQI) were 37.7 (22.3) and 9.7 (6.9), respectively, thus indicating a significant impact of the disease on HR-QoL. Mean absenteeism and presenteeism were 6.4% and 20.8%, respectively, with a mean loss of work productivity estimated at 20.7%. The mean (S.D.) total direct cost of CSU was €2,397 per patient per year and was mainly driven by therapies (€1,435) and inpatient costs (€859). The indirect costs for four weeks were mainly presenteeism (€421) and loss of work productivity (€420). **Conclusion:** CSU significantly impairs HR-QoL, which increases with the severity of the disease. The direct and indirect costs for the management of symptomatic CSU are an important economic burden.

Key words: chronic spontaneous urticaria, chronic idiopathic urticaria, angioedema, health-related quality of life, health economics, observational study

Urticaria is an inflammatory skin disease characterized by itchy wheals, angioedema, or both [1]. Histamine and other inflammatory mediators and cytokines released by mast cells are responsible for sensory nerve activation, vasodilatation, and plasma extravasation [2]. Chronic spontaneous urticaria (CSU) is a specific type of urticaria, also known as chronic idiopathic urticaria, and is defined by the spontaneous appearance of symptoms over a period of six weeks or more [3]. There are limited data on the prevalence on CSU, but based on results from European studies, the prevalence is estimated at 0.5-1.0% [4]. According to recent international guidelines, the recommended first-line treatments are oral second-generation H1-antihistamines at licensed doses [3, 5]. If the response is insufficient within two weeks, then the dose may be increased up to four times the licensed dose. In the systematic review and meta-analysis of Guillén-Aguinaga *et al.*, 63.2% of non-respondent CSU patients improved after antihistamine up-dosing [6]. If this dose remains insufficient after four weeks, addition of another therapeutic class is recommended; montelukast, omalizumab or cyclosporine [3].

The negative consequences of CSU and other forms of chronic urticaria on health-related quality of life (HR-QoL) and on healthcare resource utilization have been reported in many studies [4, 7-11]. There is, however, a lack of real-life studies, in particular, for CSU patients who are refractory to treatment. A recent French observational study including 1,000 CSU patients reported a significant unmet medical need for CSU patients, even those with up-dosing of H1-antihistamines; 51.0% of patients had an insufficient response to H1-antihistamines at the licensed dose and 14.6% received a four-fold increased dose of whom 8.2% had an insufficient response [12]. The objective of the international ASSURE-CSU study was to describe the burden of CSU in real-world conditions [13, 14]. For this purpose, data on disease history, treatments, and disease activity, as well as consequences on HR-QoL, work productivity, healthcare resource utilization, and economic burden have been recorded in six European countries (including France) and Canada. The data from the ASSURE-CSU study offered the opportunity to obtain an overview of CSU in real-world conditions in France.

Patients and methods

Study design

ASSURE-CSU (ASsessment of the economic and humanistic burden of chronic Spontaneous/idiopathic URticaria patiEnts) was an international, observational, multicentre study performed in seven countries (The United Kingdom, Germany, Canada, France, Italy, Spain, and The Netherlands). The study protocol and the global results have been recently published [13, 14].

The objectives of this observational study were to assess the clinical and economic burden of CSU in symptomatic patients despite treatment. For this purpose, HR-QoL, healthcare resource utilization, absence from work, and productivity loss have been assessed. We present here, in detail, the outcomes of French CSU patients.

The study included retrospective patient medical record abstraction (12 months), a cross-sectional patient survey, and a seven-day patient diary to evaluate HR-QoL and productivity. The study procedures had no impact on the medical care delivered to patients.

Patients aged 18 years or older were included in urticaria specialty centres if they met the following criteria:

- a confirmed diagnosis of CSU, defined as the occurrence of spontaneous wheals and/or angioedema for at least six weeks without an obvious cause [15];
- at least one treatment course with an H1-antihistamine;
- symptoms for more than 12 months, occurring at least three days per week, and currently symptomatic despite treatment.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the local independent Ethics Committee. Written informed consent was obtained from each patient.

Data collected

Demographics, clinical data, and healthcare resource use were obtained from patients' medical records. Patients completed a survey in order to collect information on resource use, not reflected in medical records, and impact of the disease on patient-reported outcomes. The patient survey also recorded work days missed and productivity losses associated with CSU. The following patient-reported outcomes were completed:

- the Weekly Urticaria Activity Score (UAS7) is a two-item assessment of key urticaria symptoms (wheals and pruritus) assessed twice daily, with the average daily score summed over seven days. This provides an evaluation of disease activity and a change in score provides an evaluation of response to treatment [16]. The UAS7 provides an overall urticaria activity score of 0 to 42 with higher scores indicative of greater severity;
- the Chronic Urticaria Quality of Life Questionnaire (CU-QoL) is a 23-item instrument designed to measure urticaria-specific HR-QoL. Six dimensions are rated: pruritus, impact on life activities, sleep problems, limits, looks, and swelling. A total score and six domain scores are

reported on a scale of 0 to 100 with higher scores indicative of worse HR-QoL [17];

- the Angioedema Quality of Life Questionnaire (AE-QoL) is a 17-item instrument designed to measure the quality of life for patients with angioedema. Four domains are explored (functioning, fatigue/mood, fears/shame, and nutrition). The score of each domain and the total score vary from 0 (no alteration of quality of life) to 100 (maximal alteration);

- the Dermatology Life Quality Index (DLQI) is a dermatology-specific 10-item instrument, which assesses patients' perception of the impact of their skin disease on different aspects of their HR-QoL over the previous week. The items of the DLQI include symptoms and feelings, daily activities, leisure, work or school, personal relationships, and side effects of treatment. Each question is scored on a four-point Likert scale. Higher scores indicate greater impairment of patient's quality of life [18];

- the EuroQol 5 Dimensions 3 Levels (EQ-5D-3L) is a standardized measure of health status. It comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels: no problems, some problems and extreme problems. The responses are converted into a single utility index value: 1 represents full health and 0 represents death. In addition to the descriptive scale, the EQ-5D-3L includes a visual analogue scale (VAS) that corresponds to patient ratings of their current health (from 0 to 100, with 100 representing the best imaginable health state and 0 the worst imaginable health state);

- the productivity of employed subjects was assessed using the six-item Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI-SHP) version 2.0 [19]. The WPAI-SHP was administered at the completion of the seven-day diary. The WPAI-SHP has four subscales, which include "absenteeism", "presenteeism", "work productivity loss", and "activity impairment". The scores for these subscales are expressed as impairment percentages. Higher scores reflect greater impairment and less productivity.

Statistical analysis

The analysis was essentially descriptive and no formal hypothesis was tested. Mean values, standard deviations (S.D.), medians, and ranges were calculated for continuous variables whereas counts and percentages were calculated for categorical variables. Analyses were performed using SAS software version 9.3 or higher (SAS Institute, Inc., Cary, North Carolina, US).

For the direct cost calculations, costing algorithms were used to assign 2014 unit costs from published sources [20]. Indirect costs for workdays missed and lost productivity related to CSU were calculated by the human capital approach using specific average wage and hours worked per country [21].

Results

Characteristics of patients at inclusion

A total of 101 patients were enrolled in the French centres of the ASSURE-CSU study from September 2014 to March

Table 1. Characteristics of chronic spontaneous urticaria (CSU) patients at inclusion.

	<i>n</i> = 101
<i>Age (years)</i>	
Mean (S.D.)	48.9 (14.5)
Median (interquartile range)	49 (39-60)
Women, <i>n</i> (%)	77 (76.2)
<i>Disease duration from diagnosis to enrolment (months)</i>	
Mean (S.D.)	64.6 (82.0)
Median (interquartile range)	25.0 (12.4-79.4)
<i>Angioedema, n (%)</i>	
At any time	73 (72.3)
In the past 12 months	55/73 (75.3)
<i>CSU severity at diagnosis, n (%)</i>	
Mild	12 (11.9)
Moderate	31 (30.7)
Severe	49 (48.5)
Data not available	9 (8.9)
<i>UAS7 score at inclusion</i>	
Mean (S.D.)	16.1 (10.4)
<i>UAS7 score bands, n (%)</i>	
0-6	18 (19.6)
7-15	34 (37.0)
16-27	28 (30.4)
28-42	12 (13.0)

2015. A majority of patients were female (76.2%) with a mean age at enrolment of 48.9 years (*table 1*). The mean duration from diagnosis to enrolment was 64.6 months (median: 25 months). At the time of diagnosis, the severity of the CSU had been rated as moderate to severe by the physician for 79.2% of patients.

The most frequent comorbid conditions present at inclusion were allergic rhinitis (16.8%), asthma (11.9%), and Hashimoto's thyroiditis (10.9%) (*table 2*).

The mean (S.D.) UAS7 score was 16.1 (10.4) and 43.4% of patients had a score rated ≥ 16 by the patient in the prospective seven-day period after inclusion, thus indicating that the disease severity was moderate to severe.

Consequences of CSU on health-related quality of life and daily life

The mean (S.D.) total score of the CU-QoL questionnaire was 37.7 (22.3) (*table 3*). The most affected domains were "pruritus" (62.9), "sleep problems" (43.8), and "looks" (38.8). As expected, the impact on the urticaria-related quality of life increased with the UAS7 scores (*figure 1A*). Thus, patients with the highest UAS7 scores (28-42) achieved 84 for "pruritus" score.

The mean (S.D.) total score of the DLQI questionnaire was 9.7 (6.9) with 43.9% of patients achieving a DLQI score > 10 , indicating a very large to an extremely large effect of the skin disorder on quality of life (*table 3*). The most affected domains were "symptoms and feelings" (3.3), "daily activities" (2.1) (both scored from 0 to 6), and "work and school" (1.9) (scored from 0 to 3).

The mean (S.D.) EQ-5D-3L utility score was 0.62 (0.31) and mean (S.D.) score of VAS was 63.9 (22.8), thus indi-

Table 2. Comorbid conditions of chronic spontaneous urticaria (CSU) patients at inclusion.

	<i>n</i> = 101
<i>Allergy and atopy</i>	
Family history of allergic disease	18 (17.8)
Allergic rhinitis	17 (16.8)
Asthma	12 (11.9)
History of allergic disease	8 (7.9)
Hypersensitivity to NSAIDs	6 (5.9)
Atopic eczema	2 (2.0)
<i>Autoimmunity</i>	
Hashimoto's thyroiditis	11 (10.9)
Other autoimmune disease	3 (3.0)
Vitiligo	2 (2.0)
Diabetes mellitus type I	2 (2.0)
Lupus erythematosus	1 (1.0)
Rheumatoid arthritis	1 (1.0)
Myeloproliferative disease	1 (1.0)

Results are given as n (%). NSAIDs: non-steroidal anti-inflammatory drugs.

cating a significant impact of urticaria on health status. Patients most likely indicated moderate or extreme problems in the EQ-5D-3L domains "pain/discomfort" (79.8% of patients), "anxiety/depression" (71.4%), and "usual activities" (34.3%).

CSU patients with angioedema and impact on quality of life

CSU-associated angioedema episodes were reported in medical records for 73 patients (72.3%), including in the past 12 months for 55 (75.3%) of these patients. The mean (S.D.) number of episodes in the past 12 months was 28.7 (59.6) (median: 11.0). Among the 99 patients who completed the patient survey, 80 (80.8%) experienced angioedema, including 75 (75.8%) in the past 12 months. Among CSU patients who reported angioedema in the past four weeks (*n* = 50), angioedema significantly affected HR-QoL with respect to all domains of the AE-QoL questionnaire (mean total score: 56.1), in particular, "fears/shame" (70.8) and "fatigue/mood" (49.0) (*table 3*). The impact on these domains was higher for patients with higher UAS7 scores (*figure 1B*).

When patients with CSU-associated angioedema were asked to quantify their symptoms (from 0 to 10), the mean (S.D.) scores of intensity were 7.2 (2.2) for swelling, 7.5 (2.7) for itching, and 6.2 (3.4) for pain. When they experienced an angioedema episode, 54.7% reported that they took a medication prescribed by their physician, 25.3% applied ice to the affected areas, 17.3% went to the emergency department, and 6.7% took an over-the-counter medication, whereas 17.3% did nothing.

Consequences of CSU on professional life and work productivity

Among the 57 employed patients, nine (16.1%) missed at least one work hour due to CSU in the past seven days with a median number of hours missed of 3.5 (interquartile range:

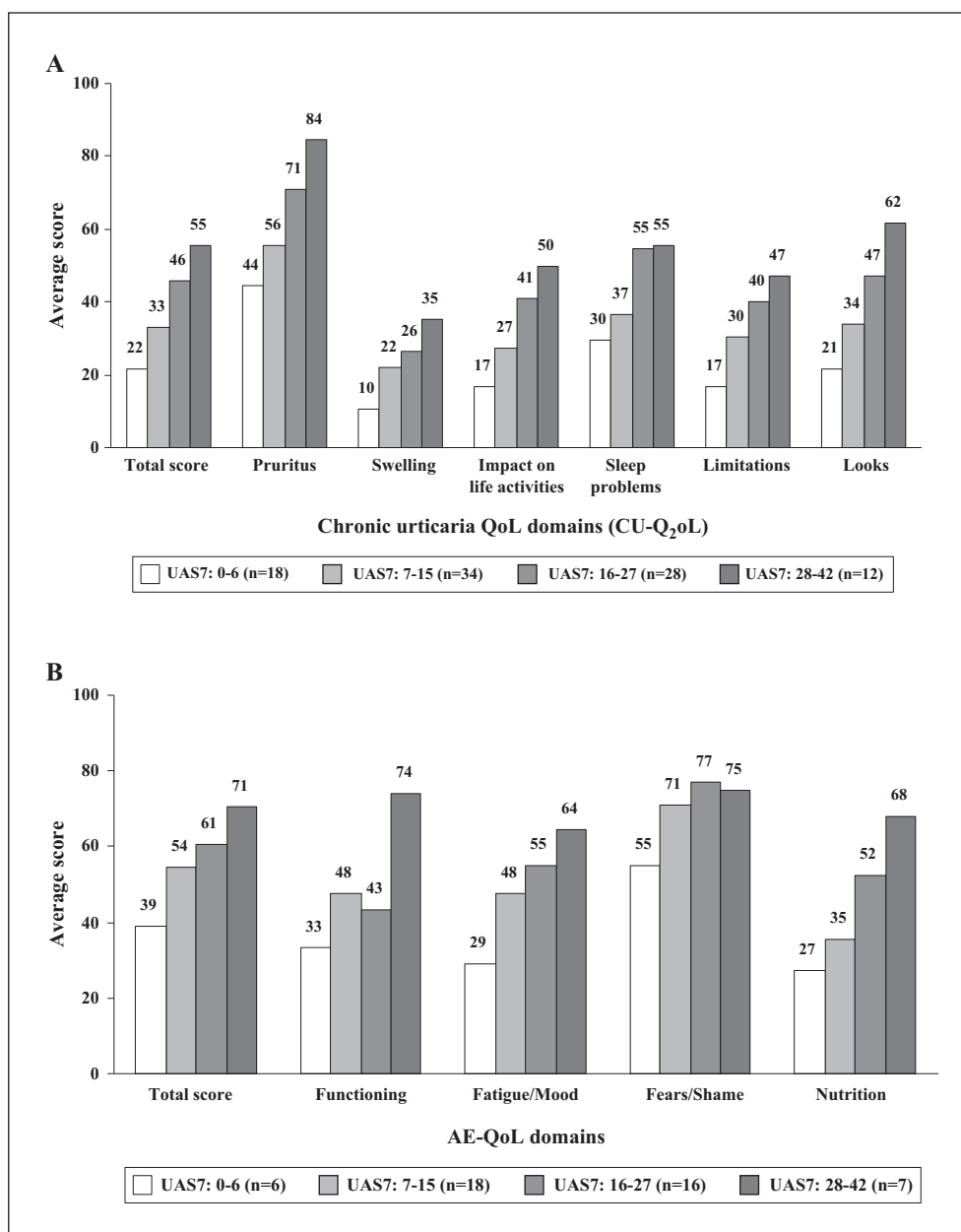


Figure 1. Impact of (A) chronic urticaria and (B) angioedema (for patients reporting angioedema) on quality of life over the past four weeks according to the severity of urticaria (UAS7 score).

2-35). During this period, mean (S.D.) absenteeism and presenteeism were 6.4% (23.1) and 20.8% (23.4), respectively. The consequence was a mean loss of work productivity estimated at 20.7% (24.2). Among the nine patients who missed at least one work hour, the main reasons were angioedema ($n = 5$) and itching ($n = 3$).

Treatment of CSU

Almost all patients (91.1%) received second-generation H1-antihistamines in the past 12 months, whereas 38.6% received leukotriene receptor antagonists (figure 2). Of note, about one patient out of four (26.7%) received sedative H1-antihistamines. Other treatments received for CSU in the past 12 months were oral corticosteroids (16.8%; median

duration: 108 days), immunosuppressants (14.9%), or anti-IgE (5.0%). Combinations of treatments were frequent: multiple H1-antihistamines (57.4%), H1-antihistamines plus any other class (27.7%), or H1-antihistamines plus leukotriene receptor antagonist (14.9%).

Use of healthcare resource related to CSU

At least one CSU-related visit to a healthcare professional was recorded in patient files in the past 12 months for 69.3% of patients, with a mean (S.D.) of 2.7 (2.4) visits. Among specialists, dermatologists (47.5% of patients) were the most frequently visited.

Admissions to the emergency room were reported for 15.8% of patients and inpatient hospital stays for 26.7%

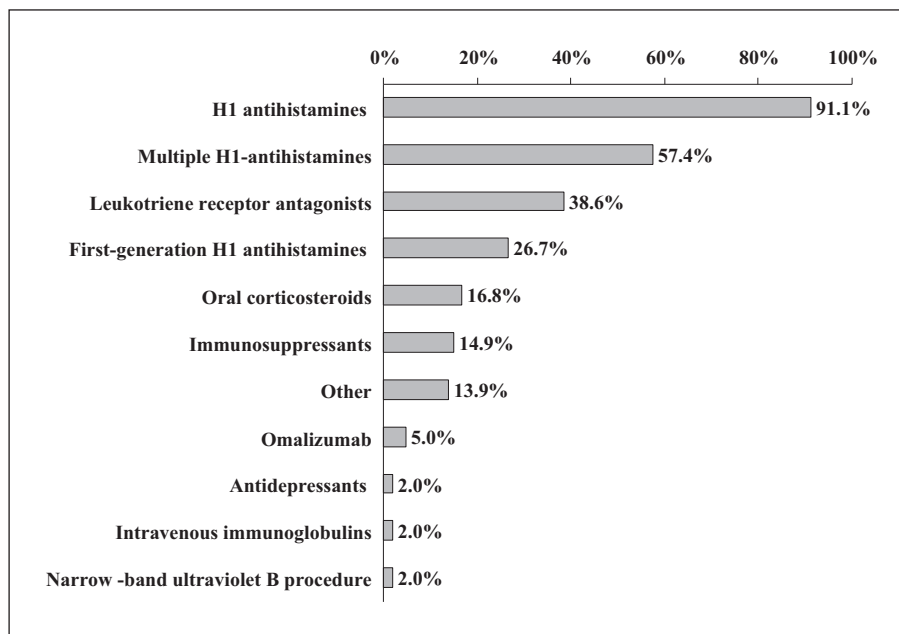


Figure 2. Percentages of French patients receiving chronic spontaneous urticaria (CSU)-related therapies in the past 12 months.

(with a mean total length of stay per admission of 2.3 [1.5] days); the most frequent reason for hospitalization was related to diagnostic testing (45.8%).

According to the patient survey, the most frequent health-care visits in the past three months were for family doctors (49.5% of patients; mean: 2.7 visits), dermatologists (22.2%; 2.1 visits), alternative medicine practitioners (22.2%; 3.8 visits), and allergists (19.2%; 1.6 visits).

Direct and indirect costs of CSU

Direct and indirect costs of CSU per patient and per year were calculated based on medical record abstraction (table 4). The mean (S.D.) total direct cost was €2,397 and was mainly driven by therapies (€1,435) and inpatient costs (€859).

The indirect costs over a four-week period were mainly driven by presenteeism (€421) and work productivity loss (€420).

Discussion

Our national analysis of the data from the international ASSURE-CSU study offers quantitative information on the burden of CSU in France in real-life conditions. This is, to our knowledge, the first study which reports both the impact of CSU on HR-QoL and the economic consequences of this debilitating skin disease in France. One of the strengths of the study is the recruitment of patients in urticaria specialty centres and the combination of data from medical records and data reflecting the perception of CSU by patients.

Demographics and characteristics of French patients included in our analysis were comparable to the data for the global cohort and from other studies [14, 22-25]. Comorbidities related to allergy and autoimmunity (asthma, allergic rhinitis, atopic dermatitis, and autoimmune dis-

eases) are frequently reported for CSU patients [26-29]. Thus, rates of allergic rhinitis as high as 40-50% have been reported in CSU patients [27, 28]. Only 16.8% of French patients had allergic rhinitis. This rate is, however, lower than the prevalence of allergic rhinitis in the French adult population [30]. The rate of Hashimoto's thyroiditis was clearly higher than the prevalence of this autoimmune disease in the French population (10.9%; in the global cohort: 6.7%). For the other allergic and autoimmune diseases, the numbers of patients were too low to compare. In the recent observational ETNA study performed in France based on 1,259 chronic urticaria patients (including 1,001 CSU patients), allergic rhinitis was reported in 23.7% of CSU patients and Hashimoto's thyroiditis in 3.5% [12].

The presence of angioedema has frequently a negative impact on QoL due to pain or alteration of the physical aspect related to oedema [31]. In the literature, rates of CSU-associated angioedema from 33% to 55% are reported [23-26, 32]. In the French cohort, 72.3% of patients had an angioedema reported in medical records, including 54.5% in the past 12 months. In the patient survey, 75.8% of patients reported having experienced angioedema in the past 12 months. These rates were higher than those reported in the global cohort (58.5% and 41.0% for medical records and 65.8% for the patient survey, respectively). The reasons for these higher rates of angioedema in French patients are unclear.

Almost half of the patients had moderate to severe CSU and all scores of HR-QoL (DLQI, CU-QoL, AE-QoL) were clearly impacted by skin disease; this impact increased with the severity of the disease. Overall, the QoL scores of the French cohort were comparable to the global cohort, except for the percentage of patients who reported moderate to extreme problems in the "anxiety/depression" dimension (EQ-5D-3L utility score), which was higher than that for French patients (71.4% versus 47.4% in the global cohort). Overall, almost all patients (>90%) received the recommended treatment for CSU, namely second-generation

Table 3. Impact of chronic spontaneous urticaria (CSU) on quality of life.

Items of quality of life	n = 99
<i>CU-Q_{2oL}</i>	
Overall score, mean (S.D.)	37.7 (22.3)
<i>Domains</i>	
Pruritus	62.9 (26.7)
Swelling	23.0 (26.7)
Impact on life activities	33.4 (26.4)
Sleep problems	43.8 (27.5)
Limitations	33.8 (26.4)
Looks	38.8 (26.9)
<i>DLQI^a</i>	
Total score, mean (S.D.)	9.7 (6.9)
<i>Total score bands, n (%)</i>	
No effect (0-1)	9 (9.2)
Small effect (2-5)	25 (25.5)
Moderate effect (6-10)	21 (21.4)
Very large effect (11-20)	34 (34.7)
Extremely large effect (21-30)	9 (9.2)
<i>Domains, mean (S.D.)</i>	
Symptoms and feelings	3.3 (1.7)
Daily activities	2.1 (1.9)
Leisure	1.7 (1.8)
Personal relationship	1.5 (1.7)
Work and school	1.9 (1.0)
Treatment	0.2 (0.6)
<i>EQ-5D-3L utility score</i>	
Overall score, mean (S.D.)	0.62 (0.31)
<i>Domains, patients with moderate or extreme problems, n (%)</i>	
Mobility	13 (13.5)
Self-care	2 (2.0)
Usual activities	34 (34.3)
Pain/Discomfort	79 (79.8)
Anxiety/depression	70 (71.4)
EQ-5D VAS, mean (S.D.), mm	63.9 (22.8)
<i>AE-QoL, mean (S.D.)^b</i>	
Total score	56.1 (21.8)
Functioning	47.4 (28.9)
Fatigue/mood	49.0 (27.0)
Fears/shame	70.8 (23.8)
Nutrition	45.3 (39.3)

VAS: visual analogue scale.

^a Domains of DLQI are scored from 0 to 6, except “work and school” and “treatment”, which are scored from 0 to 3.

^b For patients with angioedema (n = 50).

H1-antihistamines in the past 12 months. Of note, some patients received a treatment not recommended in CSU guidelines; first-generation H1-antihistamines (26.7%), oral corticosteroids (16.8%), and intravenous immunoglobulins (2.0%). Omalizumab (monoclonal anti-IgE) is a treatment recommended in the guidelines for CSU refractory to H1-antihistamines, as add-on therapy to second-generation H1-antihistamines [3]. In the past 12 months, 5.0% of patients were treated with omalizumab, but the more extensive indication of this product for CSU was approved by French authorities in October 2015, after the end of this study. Therefore, future studies will be use-

Table 4. Direct and indirect chronic spontaneous urticaria (CSU)-related costs per patient and per year in France in the past 12 months.

Items	Costs
<i>Total direct medical annual costs^a</i>	€2,397 (7,241)
Inpatient costs	€859 (2,305)
Emergency costs	€40 (109)
Routine visit cost	€46 (59)
Laboratory costs	€15 (34)
Therapies	€1,435 (5,727)
Other	€209 (452)
<i>Indirect costs over a 4-week period^b</i>	
Absenteeism	€130 (467)
Presenteeism	€421 (475)
Work productivity loss	€420 (490)

Results are given as mean (S.D.).

^a Calculated based on medical record abstraction.

^b Calculated from 7-day patient diary using WPAI-SHP version 2.0.

ful to evaluate the role of this new therapeutic class in CSU treatment.

The economic burden of CSU in France remains largely unexplored. A previous study more than 10 years ago evaluated the cost-effectiveness of a H1-antihistamine based on the results of two placebo-controlled trials [33]. Our approach was different since we evaluated the indirect and direct cost of patients engaged in real-world healthcare. Thus, we report that 15.8% of CSU patients were admitted to the emergency room and 26.7% were hospitalized (including for diagnostic testing) in the past 12 months. The CSU symptoms contributed to a significant loss of productivity, mainly due to presenteeism (one out of five patients was impaired at work). Overall, the burden of CSU for patients and society appears to be heavier than generally considered. Our results are in line with a French study that compared the impact of different skin diseases (chronic urticaria, psoriasis, and atopic dermatitis) on HR-QoL and concluded that severe impairment of chronic urticaria was often underestimated [34].

This study has some limitations. Only patients who were symptomatic for at least 12 months despite treatment were recruited. As a consequence, study patients were not representative of the general population of CSU patients. Another limitation was that the patient survey was dependent on patient memory. Nevertheless, biases related to indirect costs were limited since data necessary for calculating absenteeism, presenteeism, and work productivity loss were prospectively recorded after completion of a seven-day diary. For the retrospective medical record review, some data may have been missing in medical records. Since direct cost evaluations were based on medical records, the direct costs could have been underestimated.

In conclusion, CSU has significant impairment on HR-QoL which increases with the severity of the disease. The direct and indirect costs of symptomatic CSU are a significant economic burden. ■

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Ingelheim, Celgene, Galderma, Janssen, LEO Pharma, Lilly, MSD, Novartis, Pfizer, Regeneron, Roche; consultant receiving honoraria from Celgene, Galderma, LEO Pharma, Lilly, Novartis, Regeneron, Roche and Sanofi; speaker receiving honoraria from AbbVie, BMS, Celgene, Galderma, LEO Pharma, Lilly, Novartis, Roche and Sanofi. Abdallah Khemis: investigator in clinical trials from AbbVie, Amgen, BMS, Boehringer Ingelheim, Celgene, Cutanea, Dermira, Galderma, Janssen, LEO Pharma, Lilly, Merck, MSD, Novartis, Pfizer, Regeneron, Roche; consultant for Celgene, Isdin, Janssen, La Roche Posay, Novartis and Pfizer.

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Haijun Tian: employee of Novartis Pharmaceuticals Corporation and ownership of company stock.

Doreen McBride, Kelly Hollis and Shannon Hunter are employed by RTI Health Solutions, which provides consulting and other research services to pharmaceutical, device, governmental, and non-government organisations. In their salaried positions, they work with a variety of companies and organisations. They receive no payment or honoraria directly from these organisations for services rendered.

Laurent Martin, Audrey Lamirand, Sophie Le Guen, and Maria-Magdalena Balp are employees of Novartis.

Frédéric Bérard: investigator in clinical trials; consultant and speaker receiving honoraria from Novartis.

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