Eur J Dermatol 2019; 29(1): 49-54

Gérard GUILLET[1]
Pierre-André BÉCHEREL[2]
Pauline PRALONG[3]
Marielle DELBARRE[4]
Omar OUTTAS[5]
Laurent MARTIN[6]
Berengère PELVET[6]
Hakam GHARBI[6]
Françoise GIORDANO-LABADIE[7]

[1] Dermato-Allergology Department, CHRU Poitiers, Poitiers,
[2] Dermatology Department, Private Hospital, Antony,
[3] Dermatology and Allergology Department, CHU Grenoble, La Tronche,
[4] Dermatology office, Compiègne,
[5] Dermatology office, Montluçon,
[6] Novartis Pharma SAS, Rueil-Malmaison,
[7] Dermatology Department, Larrey Hospital, CHU Toulouse, Toulouse, France

Reprints: G. Guillet
<gmguillet@wanadoo.fr>

Article accepted on 08/09/2018

The burden of chronic urticaria: French baseline data from the international real-life AWARE study

Background: The AWARE study is an ongoing international study of patients with chronic urticaria refractory to H1-antihistamines. The aim of this study is to evaluate the burden of disease and the use of healthcare resources in real-life conditions. *Objectives:* To analyse the baseline data of French patients included in the AWARE study. *Materials & Methods:* AWARE is a prospective, non-interventional, international study that includes adult patients who have had chronic urticaria, refractory to at least one H1-antihistamine, for at least two months. *Results:* Ninety-four patients (mean age: 47.9 years; 71.3% women) with chronic urticaria (50.0% spontaneous only, 9.6% inducible only, and 40.4% both) were included in French centres. The median duration from diagnosis was three years and angioedema was present in 31.5% of patients for the past six months. In 63.8% of cases, the patients received at least one treatment for urticaria (H1-antihistamine for 66.0%). Chronic urticaria was poorly controlled (UCT score <12) in 88.9% of patients and quality of life was severely impaired (mean DLQI score: 8.6). The use of healthcare resources was significant with frequent visits to general practitioners (80.8% of patients; mean: 8.1 visits). However, more than half of patients had not previously consulted a dermatologist. *Conclusion:* These baseline data of French patients in the AWARE study show that patients suffering from chronic urticaria, refractory to H1-antihistamines for a median of three years, are insufficiently treated and that their quality of life is impaired. Despite the significant use of healthcare resources, access to specialised consultations remains insufficient.

Key words: chronic spontaneous urticaria, chronic inducible urticaria, angioedema, H1-antihistamines, quality of life

Chronic urticaria is a frequent inflammatory skin disorder characterized by the intermittent occurrence of itchy and evanescent wheals lasting for more than six weeks [1]. Based on recent European studies, the prevalence of chronic urticaria is reported to be 0.5-1% [2]. The wheals are associated with angioedema in 33% to 55% of patients [3-7]. Angioedema can sometimes be painful [8].

Chronic urticaria can be spontaneous (due to unknown causes), induced by physical triggers (*e.g.* cholinergic, cold, heat, delayed-pressure, solar, and dermographic urticaria) or occur after contact through immunological or non-immunological mechanisms [9]. Spontaneous and inducible urticaria can coexist in the same patient [8].

In order to control the symptoms of chronic urticaria, international guidelines published in 2014 recommend, as first-line treatment, the use of an oral second-generation (non-sedating) H1-antihistamine at licensed doses [1, 10]. If the response is insufficient within two weeks, the doses can be increased up to four times. If the response remains inadequate after an additional one to four weeks, additional treatment with montelukast, omalizumab or cyclosporine is recommended [1].

The impact of chronic urticaria on patient quality of life and healthcare consumption has been reported in many studies [2, 11-15]. However, these data were obtained from specialised centres whose patients were frequently severely ill, thus limiting the interpretation of results. The burden of chronic urticaria remains unknown due to the lack of real-life data. The AWARE (A World-wide Antihistamine-Refractory chronic urticaria patient Evaluation) study is an international study designed to prospectively evaluate disease burden, treatment schedules, and use of clinical resources for patients with chronic urticaria refractory to H1-antihistamine. Here, we report the baseline data of the patients included in the French centres.

Patients and methods

Type of study and objectives

AWARE is an international (12 European countries) non-interventional study that includes adult patients (≥ 18 years) with a confirmed diagnosis of chronic urticaria (for at least two months), which is refractory to at least one H1-antihistamine.

doi:10.1684/ejd.2018.3495

To cite this article: Guillet G, Bécherel PA, Pralong P, Delbarre M, Outtas O, Martin L, Pelvet B, Gharbi H, Giordano-Labadie F. The burden of chronic urticaria: French baseline data from the international real-life AWARE study. *Eur J Dermatol* 2019; 29(1): 49-54 doi:10.1684/ejd.2018.3495

At the inclusion visit, a retrospective record of data from the previous 12 months was documented and a prospective two-year follow-up was subsequently initiated.
Before inclusion in the study, the patients received from the physician written information on the objective of the study and the conditions for participation. Written informed consent was obtained from each patient.
The primary objective of the study is to correlate patient-reported outcomes (recorded prospectively) with the different therapeutic options that have been prescribed. The objective of the interim analysis reported in the present article is to document patient characteristics, pharmacological treatments, burden of chronic urticaria, and consumption of healthcare resources in the French cohort.

Data collected and patient-related outcome

Data recorded at the initial visit (upon inclusion in the study) included demographics, history, and characteristics of the disease (time of diagnosis, type of chronic urticaria, presence and duration of angioedema, presence and duration of wheals, comorbidities, pharmacological treatment, and utilisation of healthcare resources related to chronic urticaria during the previous year).
Questionnaires assessing both the impact on quality of life and disease activity were completed at each visit in order to evaluate:

– Patient satisfaction with current treatment using a visual analogue scale (VAS) graded from 0 (not at all satisfied) to 10 (very satisfied).
– The control of urticaria (over the last four weeks) using the Urticaria Control Test (UCT); a retrospective four-item questionnaire. The total score varies from 0 (uncontrolled disease) to 16 (completely controlled disease).
– Patient quality of life using the Dermatology Life Quality Index (DLQI); a 10-item questionnaire that evaluates the impact of a skin disease on daily life over the last seven days according to different domains (Symptoms and Feelings, Daily activities, Leisure, Work and School, Personal relationships, and Treatment). The total score varies from 0 (no effect at all on patient life) to 30 (extremely large effect on patient life).
– The quality of life in patients with angioedema using the Angioedema Quality of Life Questionnaire (AE-QoL). This includes 17 questions covering four domains (Function, Fatigue/Mood, Fears/Shame, and Nutrition). The score for each domain and the total score vary from 0 (no impairment of quality of life) to 100 (maximal alteration of quality of life).

Statistical analysis

Statistical analysis was only descriptive and no hypothesis was tested. Data were analysed using SAS software version 9.2 (SAS Institute; Cary, North Carolina, USA).

Results

Patient demographics and disease characteristics at baseline

Ninety-four patients with chronic urticaria for at least two months and unresponsive to H1-antihistamines were included in 25 French centres (following consultation with 15 hospital dermatologists for chronic urticaria and 10 private practice dermatologists) from February 2015 to July 2015. All patients met the selection criteria.
The mean age of patients was 47.9 years and 71.3% were women (*table 1*). The median duration of the disease from diagnosis was three years; 50.0% of patients had spontaneous urticaria only, 9.6% had inducible urticaria only, and 40.4% had both.
Wheals were present within the last six months in 78.9% of patients and for most patients (80.3%), their individual duration did not exceed 24 hours (*table 1*). Angioedema was present within the last six months in 31.5% of cases with a mean total duration of 23.8 days; intensity was severe in 17.9% of patients, moderate in 50.0%, slight in 25.0%, and negligible in 7.1%.
The most frequent types of inducible chronic urticaria were dermographism (26.6%) and delayed-pressure urticaria (16.0%) (*table 2*).
The most frequent comorbidities were allergic rhinitis (19.1%), arterial hypertension (12.8%), and anxiety (11.7%) (*figure 1*).

Table 1. Patient demographics and disease characteristics at baseline.

	***n* = 94**
Age (years)	
Mean (SD)	47.9 (15.3)
Median (interquartile range)	48.0 (37.0-60.0)
Women, *n* (%)	67 (71.3)
BMI (kg/m^2)	
Mean (SD)	25.4 (4.5)
Median (interquartile range)	24.8 (22.0-27.7)
Duration (years) from diagnosis	
Mean (SD)	6.6 (8.8)
Median (interquartile range)	3.0 (1.0-8.0)
Presence of wheals within the last 6 months, *n* (%)	71 (78.9)
Mean duration of wheals, *n* (%)	
≤ 24 hours	57 (80.3)
> 24 hours	14 (19.7)
Angioedema within the last 6 months, *n* (%)	29 (31.5)
Total duration (days) of angioedema, mean (SD)	23.8 (32.0)

BMI: body mass index.

Table 2. Types of chronic urticaria.

	***n* = 94**
Type of urticaria	
Chronic spontaneous urticaria (CSU) only	47 (50.0)
Chronic inducible urticaria (CIndU) only	9 (9.6)
Both CSU and CIndU	38 (40.4)
Types of CIndU[a]	
Dermographism	25 (26.6)
Delayed-pressure urticaria	15 (16.0)
Cholinergic urticaria	9 (9.6)
Cold urticaria	4 (4.3)

Results are presented as n (%). [a]Several answers were possible.

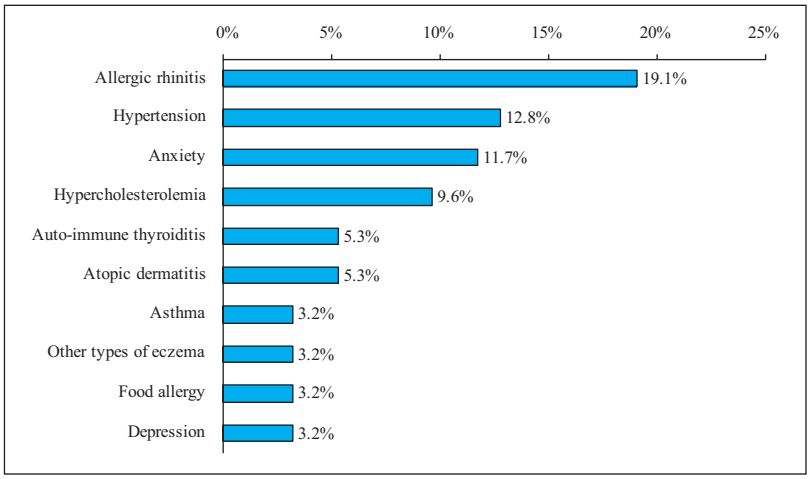

Figure 1. Comorbidities at baseline.

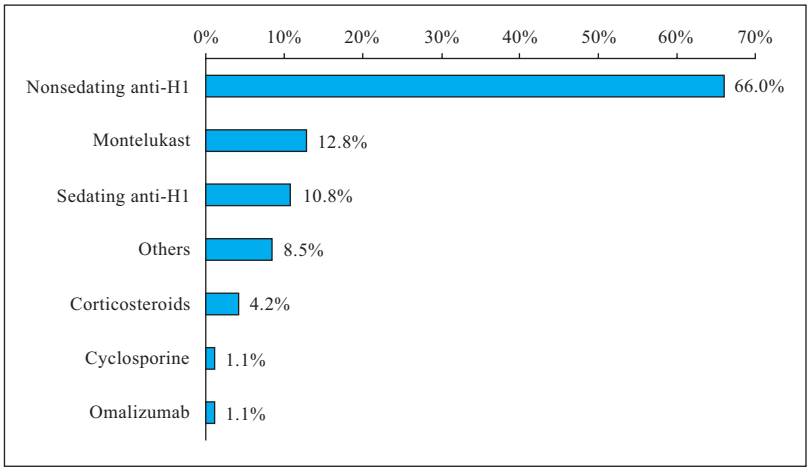

Figure 2. Baseline treatment for chronic urticaria (60/94 patients had at least one treatment).

Drug regimens and utilisation of healthcare resources

Sixty out of 94 patients (63.8%) were receiving at least one treatment for urticaria at the inclusion visit. The most frequent treatments were non-sedating H1-antihistamines (66.0%), montelukast (12.8%), and sedating H1-antihistamines (10.8%) (*figure 2*).
Between the onset of symptoms and the inclusion visit, 80.8% of patients visited a general practitioner, with a mean of 8.1 visits (*table 3*). About a quarter of patients were admitted to an emergency department (with a mean of 3.6 admissions). Only 43.8% of patients visited a dermatologist or an allergologist, and 24.7% visited a specialised urticaria centre.

The burden of disease: disease severity and quality of life

The mean (SD) UCT score was 6.4 (3.6) and 88.9% of patients had an UCT score < 12, indicating insufficiently controlled urticaria for most patients (*table 4*). These results are consistent with the mean score of satisfaction with the treatment assessed using the VAS that was only 4.7 (10 being maximal satisfaction).
The mean DLQI score was 8.6 with a "moderate effect on patient life" (score: 6-10) for 31.8% of patients, a "very large effect on patient life" (score: 11-20) for 33.0%, and an "extremely large effect on patient life" (score: 21-30) for 2.3% [16]. In patients with angioedema, the domains, Fatigue/Mood and Fears/Shame (questionnaire AE-QoL), were the most impaired due to angioedema symptoms (*table 4*).
Sick leave related to urticaria was reported in 11.0% of patients (with a mean duration of 2.2 weeks).

Discussion

Once fully analysed, the prospective international AWARE study will provide us with valuable real-life data on H1-antihistamine-refractory chronic urticaria. These data will help us to correlate the evolution of chronic urticaria with the different treatments. The interim analyses reported in

Table 3. Utilisation of healthcare resources related to chronic urticaria.

	Patients with at least one visit (n = 73) n **(%)**	**Number of visits Mean (SD)**
General practitioner	59 (80.8)	8.1 (9.5)
Dermatologist/allergologist	32 (43.8)	4.9 (7.7)
Specialised urticaria centre	18 (24.7)	4.1 (3.4)
Emergency department	18 (24.7)	3.6 (3.0)
Pharmacist	13 (17.8)	41.8 (108.2)
Hospitalisation	7 (9.6)	1.8 (1.0)
Alternative medicines	5 (6.8)	3.2 (2.3)
Dentist	4 (5.5)	6.3 (4.7)
Ear-nose-throat specialist	1 (1.4)	1
Others	8 (11.0)	6.0 (7.0)

Table 4. Patient-reported outcomes at baseline.

Type of evaluation	n[a]	**Scores**
UCT score[b]	90	
Mean (SD)		6.4 (3.6)
Ranges, n (%)		
UCT < 12		80 (88.9)
UCT ≥ 12		10 (11.1)
Patient satisfaction with treatment (VAS)[c], mean (SD)	89	4.7 (2.9)
DLQI score[d]	88	
Mean (SD)		8.6 (5.7)
DLQI ranges, n (%)		
0-1 (no effect at all on patient life)		9 (10.2)
2-5 (small effect on patient life)		20 (22.7)
6-10 (moderate effect on patient life)		28 (31.8)
11-20 (very large effect on patient life)		29 (33.0)
21-30 (extremely large effect on patient life)		2 (2.3)
AE-QoL score[e], mean (SD)		
Function	37	31.9 (26.8)
Fatigue/Mood	39	42.1 (28.6)
Fears/Shame	38	43.5 (32.7)
Nutrition	38	26.6 (31.1)
Total	39	38.0 (25.4)

AE-QoL: Angioedema Quality of Life Questionnaire; DLQI: Dermatology Life Quality Index; UCT: Urticaria Control Test; VAS: Visual Analogue Scale.[a]Number of patients with available data.[b]Score from 0 (uncontrolled disease) to 16 (completely controlled disease).[c]Score from 0 (not at all satisfied) to 10 (very satisfied).[d]Score from 0 (no effect at all on patient life) to 30 (extremely large effect on patient life).[e]The score for each domain and the total score varied from 0 (no impairment of quality of life) to 100 (maximum effect on quality of life); this questionnaire was only for patients with angioedema.

this article relate to baseline data of the French cohort. Inclusion criteria were not restrictive, allowing an overview of the characteristics of chronic urticaria, its impact on quality of life, therapeutic management, and utilisation of healthcare resources.

The baseline characteristics of the French patients are consistent with the data from other studies [2-7, 10, 12, 17] as well as baseline characteristics of the German and Scandinavian patients of the AWARE study [18, 19]. Our patients had a mean age of 47.9 years and there was a majority of women (71.3%); the median BMI (close to 25 kg/m^2) indicates that a large proportion of patients were overweight.

In the German and Scandinavian patients of the AWARE study, 20.2% and 24.0% had chronic urticaria that was both spontaneous and inducible, respectively [18, 19]. In our cohort, this percentage was higher, with 40.4% of the French patients showing an association with both types of chronic urticaria.

Angioedema frequently has a negative impact on patient quality of life because of the associated pain and alteration of physical appearance [20]. Moreover, the anxiety resulting from angioedema frequently leads to admission to an emergency department where this disorder is often ill-diagnosed. Based on our analysis, angioedema was reported in about a third of patients, which is comparable to the results of the German and Scandinavian patients of the AWARE study (46.1% and 32.9%, respectively) [18, 19], as well as other studies in which angioedema rates varied

from 33% to 55% [3–7]. In French patients, angioedema appeared to negatively impact quality of life, as assessed by the AE-QoL score, more particularly for the domains, Fatigue/Mood and Fears/Shame.

Chronic urticaria is frequently associated with atopic disorders (asthma, allergic rhinitis, and atopic dermatitis) or auto-immune diseases [3, 21-23]. Thus, some studies have reported that up to 40-50% of patients with chronic urticaria also had allergic rhinitis [21, 22], whereas only 19.1% of our patients reported allergic rhinitis (18.2% of the German patients and 16.5% of the Scandinavian patients of the AWARE study). These results are comparable to the prevalence of allergic rhinitis in the French adult population and do not suggest an increased prevalence in this cohort [24]. Due to the low sample size, the results for the other allergic and auto-immune disorders are only described descriptively. However, the prevalence of asthma in the French patients (3.2%) is lower than that in the German (12.0%) and Scandinavian patients (19.6%) [18, 19].

Psychiatric disorders such as anxiety and depression are classically associated with chronic urticaria; 25 to 30% of patients suffer from anxiety and 11 to 21% from depressive disorders [2, 25-28]. In our French cohort, psychiatric disorders were reported with lower rates; 11.7% for anxiety disorders and 3.2% for depressive disorders. Psychiatric disorders were reported also at relatively low rates in the German (9.5% for anxiety and 4.7% for depression) and Scandinavian patients (3.2% and 4.4%, respectively) in the AWARE study. According to the German authors, the rates reported in their cohort were slightly higher than the prevalence in the general German population [18]. However, it is difficult to draw any conclusions because the prevalence of psychiatric disorders is highly dependent on definition and methods of evaluation. Thus, the AWARE study did not include psychometric scales for the measure of anxiety and depression, but relied only on reports from patients and dermatologists within a non-interventional setting.

At the inclusion visit, only 63.8% of patients were receiving pharmacological treatment for urticaria and half of them were taking non-sedating H1-antihistamines. Dose escalation of antihistamines and treatment combinations were not analysed in this baseline report and will be further analysed during the prospective follow-up phase.

Chronic urticaria was insufficiently controlled in almost nine patients out of 10 (88.9% with UCT <12) and patient satisfaction with the treatment was low (4.7 on the VAS scale). These results are comparable with the German (75% and 5.4, respectively) and Scandinavian (75.6% and 6.1, respectively) patients in the AWARE study. It is noteworthy that we used the UCT rather than the Urticaria Activity Score (UAS) given that it is a retrospective and easy-to-use patient-reported outcome; the UCT allows a more global evaluation that takes into account angioedema status.

The quality of life scales (DLQI and AE-QoL for angioedema) provided evidence of the negative impact of inadequately treated chronic urticaria. The impaired quality of life was nevertheless limited as shown by the mean total score of DLQI (8.6) which was comparable to the scores reported for German (8.3) and Scandinavian (7.7) patients. However, a significant proportion of the lives of patients was heavily disturbed by this insufficiently controlled disease that had a median duration of three years from diagnosis; for 33.0% of patients, chronic urticaria had a "very large effect on patient life" (score: 11-20) and for 2.3%, an "extremely large effect on patient life" (score: 21-30). In addition, the insufficient control of chronic urticaria was responsible for frequent admissions to emergency departments (24.7% of patients from the onset of symptoms; 3.6 admissions on average) and visits to the general practitioner (80.8%; 8.1 consultations on average). These data confirm that patients with chronic urticaria use a significant level of healthcare resources, as recently demonstrated by the survey of Balp *et al.* in five European countries [11, 12]. We note, however, that a majority of patients in our cohort did not benefit from a visit to a dermatologist/allergologist or to a specialised urticaria centre, although the disease had a median duration of three years.

The main limitations of this study are common to all non-interventional studies with patient-related outcomes and retrospective data based on patient recall. Another limitation is the study sample size that made the subgroup analysis for infrequent events, such as associated disorders, difficult. Despite these limitations, there is an overall consistency between the main results and those from other published AWARE studies and other studies with French patients [29, 30].

In conclusion, the baseline data of the French cohort of the AWARE study provides evidence that most patients suffering from H1-antihistamine-refractory chronic urticaria for a median of three years are insufficiently treated and dissatisfied with their treatment. Despite their impaired quality of life and significant healthcare resource utilisation, access to specialised consultations for patients remains low. The prospective data from the AWARE study will provide an initial analysis and allow for a comparison of the different therapeutic options and their impact on symptoms and quality of life at the end of the two-year follow-up period. ■

Disclosure. *Conflicts of interest: G. Guillet received research funding from Novartis for this study; F. Giordano-Labadie received research funding for a study from Novartis and is scientific advisor for Novartis; P.A. Bécherel provides consulting services for Novartis; P. Pralong received funding for participation in a congress and two oral communications for meetings organized and funded by Novartis; M. Delbarre et O. Outtas received research funding from Novartis for this study; L. Martin, B. Pelvet and H. Gharbi are employees of Novartis. Acknowledgments: Novartis Pharma SAS funded this study. We thank the following physicians who included and followed patients: Dr Pierre-André Bécherel, Pr Christophe Bedane, Pr Frédéric Berard, Dr Isaac Bodokh, Dr Diana Valentina Bumbea, Pr Frédéric Cambazard, Dr Muriel Campourcy, Dr Marielle Debons, Dr Marielle Delbarre, Dr Fanny Fichel, Pr Gérard Guillet, Dr Anne Grange-Prunier, Dr Matthieu Greco, Pr Jean-Philippe Lacour, Dr Omar Outtas, Dr Yves LE Corre, Pr Carle Paul, Dr Laurent Peyret, Dr Christine Pieto Le Corvaisier, Dr Pauline Pralong, Dr Nadia Raison-Peyron, Dr Mireille Ruer-Mulard, Dr Sandrine Sierra-Fortuny, Pr Delphine Staumont-Salle, Dr Catherine Tremeau-Martinage; and also all patients who participated in the study in France. We thank C2R (Paris, France) for its contribution for conducting this study and Francis Beauvais (Sèvres, France) for medical writing and editorial assistance.*

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